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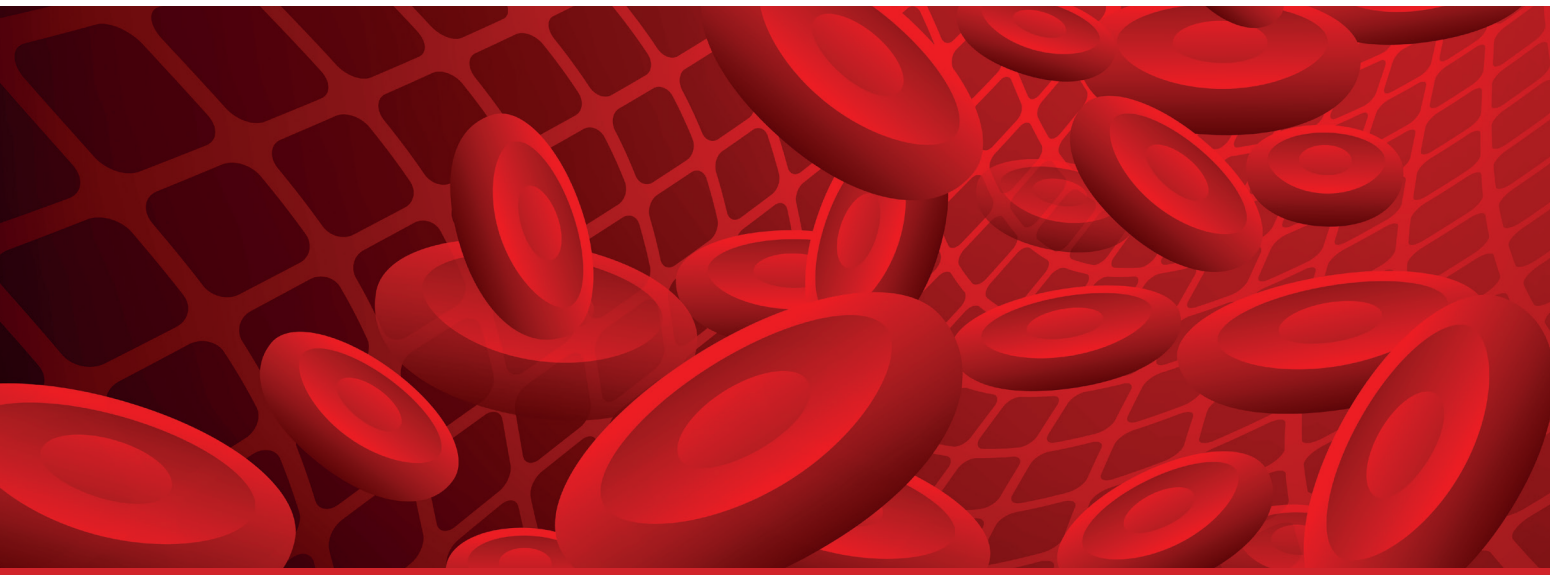

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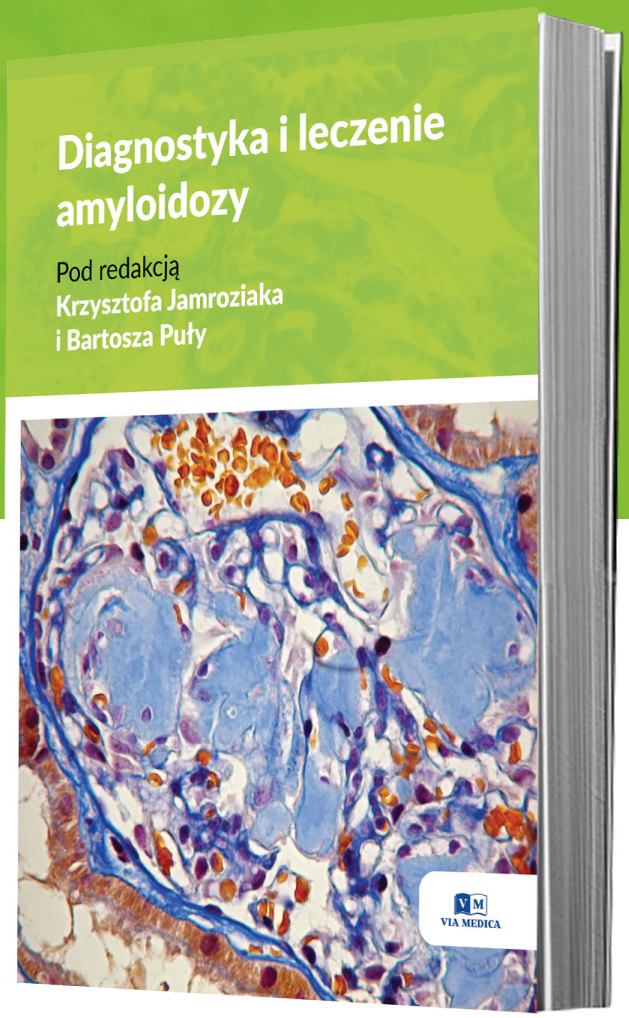

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OBITUARY

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Prof. dr hab. n. med. Piotr Paweł Smolewski 25 December 1960–19 March 2023

Tadeusz Robak, Agnieszka Wierzbowska, Euzebiusz Krykowski

Department of Hematology, Medical University of Lodz, Łódź, Poland

Professor Piotr Smolewski, MD, PhD, died suddenly aged 62 on 19 March 2023 at his home in Lodz. He was born in Lodz on 25 December 1960, and his whole professional life was devoted to medicine in this city. In 1985, he graduated from the Faculty of Medicine at the Medical Academy of Lodz. At the same Faculty, he received his Doctor of Medicine degree in 1991 and Habilitation degree in 2002. In 2007, the President of the Republic of Poland awarded him the academic title of Professor of Medical and Health Sciences.

Professor Smolewski was a specialist in Internal Medicine and Hematology. He held many positions at the Medical University of Lodz. He was the Head of the Department of Experimental Hematology which he co-founded in 2008. Moreover, he acted as the Vice-Dean for Teaching at the Faculty of Nursing and Midwifery, and was the Regional Consultant in Hematology for the Lodz Voivodeship. Professor Smolewski participated in a number of foreign research internships, the most important of which was his double stay at the Brander Cancer Research Institute, New York Medical College, New York, USA, as part of a grant from the US National Health Institute. He cooperated there with the world-renowned scientist of Polish origin, and co-inventor of new research methods in flow cytometry, Professor Zbigniew Darżynkiewicz. The knowledge and experience gained at this Research Institute enabled him to further develop this diagnostic and research method back in Poland and to create the Cytometry Laboratory in our Department.

In recognition of his achievements, Professor Smolewski was elected President of the Polish Society of Cytometry. He published several hundred original and review papers, including 158 indexed in the PubMed database. Publications to which he contributed included the most prominent scientific journals, including the 'New England Journal of Medicine', 'The Lancet Haematology' and 'Cancers'. Their leading topics concerned lymphoid malignancies, flow and scanning cytometry methods, prognostic factors in cancerous blood diseases, caspase inhibitors, activity and mechanisms of action of new anticancer drugs, as well as apoptosis and cell cycle disorders in cancer. Professor Piotr Smolewski was a world-class expert in the field of cytometry, authoring applications of laser scanning cytometry in the study of apoptosis and other aspects of cell biology. He developed a new method for nucleolus assay, cell nucleolar morphometry, a technique for staining cells and tissues for use in space,

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a method of so-called differential fluorescence, and a technique for applying fluorogenic caspase inhibitors as markers.

Professor Piotr Smolewski was the supervisor of several doctoral and dozens of Master's theses in nursing, midwifery and medical analytics. He was also the supervisor of one habilitation dissertation, a reviewer of many doctoral and habilitation dissertations, and the supervisor of specialization in Family Medicine for a number of primary care doctors. Moreover, he was the supervisor of specialization in internal medicine and hematology and a teacher of many doctors, nurses, midwives, pharmacists and medical analysts.

For his scientific, teaching and organizational activities, he was awarded the Medal of the 65th Anniversary of Medical Higher Education in Lodz, the Golden Cross of Merit, and many awards from the Rector of the Medical University of Lodz and Poland's Minister of Health.

Professor Piotr Smolewski was an outstanding physician and scientist, a respected academic, a boss adored by his colleagues, and a good man. He passed away suddenly leaving his wife Elisabeth, his son Paul and daughter-in-law Julia in deep sorrow and grief. He was buried at St Adalbert's Roman Catholic Cemetery in Lodz, Poland.

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EDITORIAL

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Inspiration from Annual Meeting of European Society for Blood and Marrow Transplantation

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The European Society for Blood and Marrow Transplantation (EBMT) is the largest scientific society in the field of hematopoietic cell transplantation and cellular therapy. Scientists, physicians, nurses, data managers, pharmacists, psychologists, statisticians, quality officers, patients and their families from more than 100 countries all over the world attend the Annual Meeting. The 49th such event took place in Paris between 22–26 April 2023, with more than 5,500 attendees.

Over 200 sessions were organized including scientific, educational, administrative, and business meetings. Over 1,150 abstracts were submitted for physicians and nurses, with 200 presented orally and 950 as e-posters.

The EBMT's Annual Meeting is a very important scientific event. All the most significant achievements in the field of hematopoietic cell transplantation and cellular therapy are presented, and new trends are explored.

The two most prestigious prizes awarded at the 2023 meeting were:

- The Van Bekkum Award: Ingvar Floisand et al., 'Vedolizumab for prophylaxis of lower gastrointestinal acute graft-versus-host disease after allogeneic hematopoietic stem-cell transplantation from unrelated donors: a phase III, randomized, double-blind, placebo-controlled, multicenter study';
- The Basic Science Award: Erik Thiele Orberg et al., 'Bacteriophage-modulated production of intestinal interferon inducing metabolites is associated with protection in allogeneic stem cell transplantation patients'.

The six highest-scoring abstracts presented at the Presidential Symposium this year were the following:

1. Per Ljungman et al. 'Improved outcomes over time and higher mortality in CMV seropositive allogeneic stem cell transplantation patients with COVID-19: an IDWP study from the EBMT registry';
2. Emily Liang et al. 'Factors associated with duration of response after CD19 CAR T-cell therapy for relapsed/ /refractory CLL: 5-year follow-up update';
3. Spyrou N. et al. 'An early endpoint for acute graft versus host disease clinical trials';
4. Joseph McGuirk et al. 'CTX110 allogeneic CRISPR-CAS9-engineered CAR T-cells in patients with relapsed or refractory large B-cell lymphoma: results from phase I dose escalation carbon study';
5. Franco Locatelli et al. 'Efficacy and safety of a single dose of exagamglogene autotemcel for transfusion-dependent β-thalassemia and severe sickle cell disease';
6. Rodríguez-Otero P. et al. 'Idecabtagene vicleucel versus standard regimens in patients with triple-class-exposed relapsed and refractory multiple myeloma: KARMMA-3, a phase III randomized controlled trial'.

Poland, with 21 transplant centers accredited with the EBMT, is the 8th largest country in the society. Currently, there are 620 EBMT centers which are located in 55 countries, and the top 10 countries represent 445 centers i.e. 71% of the total. At the 49th EBMT Annual Meeting, Polish scientists presented or co-authored 16 original studies selected for verbal presentation, plus many e-poster presentations. This is proof of high activity, both at national and international level, which is continuously evolving [1–5]. Polish physicians are active in most of the EBMT Working Parties.

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References
1. Snowden JA, Styczyński J, Snarski E, et al. Hematopoietic stem cell transplantation in autoimmune diseases: update from the EBMT Autoimmune Diseases Working Party with special reference to Poland. Acta Haematol Pol. 2021; 52(4): 217–224, doi: 10.5603/AHP.2021.0043.
2. Goldman-Mazur S, Vesole DH, Jurczyszyn A. Clinical implications of cytogenetic and molecular aberrations in multiple myeloma. Acta Haematol Pol. 2021; 52(1): 18–28, doi: 10.5603/AHP.2021.0004.
3. Gil L, Grajek M. Artificial intelligence and chimeric antigen receptor T-cell therapy. Acta Haematol Pol. 2022; 53(3): 176–179, doi: 10.5603/AHP.a2022.0019.
4. Antoniewicz-Papis J, Brojer E, Fabijańska-Mitek J, et al. Current status and achievements of Polish transfusion medicine. Acta Haematol Pol. 2021; 52(3): 147–162, doi: 10.5603/AHP.2021.0031.
5. Giebel S, Basak G, Bieniaszewska M, et al. Current status and achievements of Polish haemato-oncology. Acta Haematol Pol. 2021; 52(1): 4–17, doi: 10.5603/AHP.2021.0003.

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REVIEW ARTICLE

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Zanubrutinib: novel therapeutic option for treatment of B-cell neoplasms

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Abstract

Bruton's tyrosine kinase (BTK) is a part of the B-cell receptor (BCR) signaling pathway. Activation of the BCR appears crucial for normal B cells as it regulates proliferation, differentiation, adhesion, survival, and apoptosis. Such signaling is also vital for malignant B cells, since many of them show constitutive activation of the BCR pathway. The development of ibrutinib, a best-in-class BTK inhibitor, has led to a new direction in the treatment of B-cell malignancies. Further studies have enabled the development of more potent and more selective BTK inhibitors, such as zanubrutinib. These novel agents were designed primarily to reduce adverse effects such as diarrhea, atrial fibrillation, rash, or hemorrhagic complications. Compelling data from clinical studies that have verified its efficacy and safety has allowed the approval of zanubrutinib in hematological malignancies such as mantle cell lymphoma, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, and marginal zone lymphoma.

Key words: ibrutinib, zanubrutinib, CLL, non-Hodgkin's lymphoma, Bruton's tyrosine kinase

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Introduction

Targeted immunotherapy has been a significant milestone in the treatment of cancer. A boom starting in the 1990s brought innovations also to the field of hematology, especially when rituximab, the first anti-tumor monoclonal antibody (mAb) bondable to CD20 antigen, was approved for clinical use in 1997 [1]. Considered to be the biggest breakthrough in treating B-cell malignancies for over half of a century [2], rituximab became a prototype of new generations of more effective compounds, as many patients are refractory to rituximab [3–5]. Antitumor antibodies bondable to cluster of differentiation (CD) antigens are the most popular so far, but not the only, targeted drugs for B-cell malignancies. Representatives of other classes, including inhibitors of immune checkpoints (nivolumab [6], pembrolizumab [7]), methyltransferase inhibitors (tazemetostat [8]), phosphatidylinositol-3 kinase (PI3K) inhibitors [9], spleen kinase (Syk) inhibitors [10], and some like proteasome inhibitor bortezomib [11], nuclear export inhibitor selinexor [12], and specimens based on chimeric antigenic T-cell receptor (CAR-T) technology [13–16], are undergoing clinical trials or have already been approved in clinics. Into the quickly evolving landscape of anti-B cell therapeutics, a new class of drugs, Bruton's tyrosine kinase (BTK) inhibitors, has emerged as a 'rising star' to

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be used either alone or in combination with acknowledged immunotherapeutics.

Overexpression or disturbances in the activation of protein kinases involved in cellular proliferation and migration are among the key mechanisms of neoplasia development [17, 18]. Furthermore, hereditary mutations in genes encoding particular protein kinases are associated with the initiation, promotion, progression, and relapse of various neoplasms [19]. Extensive studies into the role of protein kinases in neoplastic diseases have led to the development of drugs that specifically inhibit signals transduced by these enzymes. Such compounds usually have a relatively low molecular weight compared to immunotherapeutics, and some of them can be administered orally. Their introduction is considered to be another milestone in both oncology and hematology [20].

BTK is a non-receptor kinase engaged in signal transduction following the binding of a specific ligand to the B-cell receptor (BCR). Activation of the BCR pathway is critical for normal B-cell maturation, proliferation, differentiation, and migration [21], although downstream events of this cascade also provide anti-apoptotic and proliferative signals for neoplastic cells. BCR signaling in normal and malignant cells, with an emphasis on the role of BTK, was recently reviewed by Efremov et al. [22]. Briefly, binding of antigen to receptor antibody triggers re-organization of the cytoskeleton and assembly of local BCR units into clusters. This rearrangement initiates the pathway, which leads to the formation of a multiprotein complex called the 'BCR signalosome'. Within the signalosome, the lipid kinase PI3Kδ becomes activated and phosphorylates the membrane phospholipid phosphatidylinositol-4,5-bisphosphate (PIP2). Phosphorylated PIP2 (now termed PIP3) forms a docking site for another pool of adaptor molecules and kinases, including BTK. Phosphorylation of BTK by SRC-family kinases and subsequent autophosphorylation turns on the activity of BTK. Downstream effects of BTK activation include dephosphorylation of the transcription factor NFAT, which is then translocated from cytosol to the nucleus and binds promotor regions of genes pivotal for B cell fate [23].

The other, canonical effect of BTK activation is the nuclear translocation of a transcription factor known as NFκB. Besides the canonical signaling through the BCR receptor, many constituents of this pathway are engaged in crosstalk with elements of parallel signaling cascades [24, 25], which often occur in a cell-specific manner and an inducible fashion [26].

Role and status of BCR signaling in B-cell malignancies

The ability to pass the signal through BCR indicates a proper rearrangement of heavy and light chain genes, the assembly of functional receptors, and the appearance of specific antigens demanding a humoral adaptive response, i.e. activation, proliferation, and differentiation of normal B cells. Moreover, downstream elements of the cascade bias cellular mechanisms of self-control into anti-apoptotic scenarios [27]. This is the putative reason why numerous B-cell malignancies, including chronic lymphocytic leukemia (CLL), Burkitt lymphoma, mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and Waldenström's macroglobulinemia (WM), exhibit activated status of the BCR pathway [22].

However, the drivers of the pathway and mutational background/context may be different to those observed in normal B cells. Certain diseases such as CLL are characterized by tumor cells which bear a subset of identical BCRs on their surface [28, 29]. Interestingly, these variants of BCR are rarely identified in normal B cells, and this observation suggests that binding to certain antigens may be supportive of the survival of CLL cells. Indeed, antibodies produced by these CLL clones bind to ubiquitous antigens [22, 30–33]. This ensures continuous, or very frequent, activation of BCR in CLL cells and seems to be crucial for the maintenance of anti-apoptotic proteome [34]. A similar scheme of BCR activation has been reported for DLBCL cells, although they additionally exhibit a mutation in CD79B, which protects from the internalization of BCR by a negative feedback loop [35].

Different mechanisms of BCR activation are characteristic of follicular lymphoma. Somatic mutations of these tumor cells often add glycosylation sites in BCR chains, resulting in the exposure of mannose residues. The chronic activation of BCR is then supported by interactions with macrophages and dendritic cells expressing high levels of mannose-binding lectin DC-SIGN [36]. Constitutive activation of BCR pathway elements is often reported in MCL [37], and the correlation between disease occurrence and bacterial infections putatively resulting in notorious stimulation of BCR by bacterial antigens has been reported in MZL [22].

The abovementioned all point towards a critical role of BCR signaling in B cell-derived lymphatic disorders and posit elements of this cascade, including BTK, as a reliable molecular target.

Ibrutinib: first generation BTK inhibitor

Ibrutinib was the first BTK inhibitor approved by the US Food and Drug Administration (FDA) in 2013 for treating relapsed-refractory (R/R) MCL [38]. MCL affects mostly older men, and it is usually diagnosed at stages III or IV, which significantly limits the number of available therapeutic options. Ibrutinib's approval was granted after publishing the results of the clinical trial PCYC-1104 [39]. Patients involved in this study received a median of three prior therapies followed by a daily oral dose of 560 mg ibrutinib. 75 of

111 patients (68%) responded to the therapy, including 21% complete response (CR) and 47% partial response (PR). Secondary end-points, namely duration of response (DOR) and progression-free survival (PFS), were 15.3 months and 13.9 months, respectively (medians). Median overall survival (OS) was not reached, and that estimated at 18 months was 58% [39]. Two further studies on ibrutinib as a single agent for treating R/R MCL (the SPARK phase II study, n = 120 and the RAY phase III study, n = 139 in the ibrutinib arm), revealed similar outcomes: overall response rates (ORR) were 63% and 72%, median PFS was 10.5 and 14.6 months, and OS at 18 months was 58% and 61%, respectively [40].

Other clinical trials have assessed the efficacy of ibrutinib's combination with approved immunotherapeutics (reviewed in [41]). ORR as high as 88% (including 44% CR) was reported for R/R MCL patients treated with ibrutinib + rituximab [42]. Even more encouraging results, such as 94% ORR (76% CR), were achieved when a combination of ibrutinib + rituximab + bendamustine was used [43]. Notably, equally promising data has been preliminarily reported for combinations of ibrutinib + rituximab (98% ORR, 60% CR) [44], ibrutinib + obinutuzumab + venetoclax (100% ORR, 47% CR) [45], and ibrutinib + rituximab followed by short-course R-HCVAD (rituximab plus hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone)/methotrexate (MTX) (100% ORR, 90% CR) [46], when used as a frontline MCL therapy. Further clinical studies have led to ibrutinib's approval for CLL [47], WM [48], and MZL [49]. Promising results were also obtained in a trial testing ibrutinib's combination with lenalidomide and rituximab for the treatment of R/R DLBCL [50].

The clinical approval of ibrutinib was a breakthrough, not only due to its efficacy against lymphoproliferative diseases, but also to the decreased risk of side effects. Previous treatment regimens applied in B-cell malignancies contained chemotherapeutic components like chlorambucil, fludarabine and cyclophosphamide, which rendered patients subjected to such treatment to a high risk of early bone marrow suppression and of late onset myelodysplasia. The introduction of BTK inhibitors in monotherapy, or combined with other agents, brings nearer the prospect of chemo-free therapies.

Why are next generation BTK inhibitors necessary?

Despite the clinical success of ibrutinib, some patients experience adverse effects (AEs) which can eventually enforce discontinuation of therapy. Typical AEs associated with ibrutinib are different than those observed in acknowledged chemotherapy regimens and are therefore considered to be class-specific ones [51]. Rates of discontinuation due to AE vary between trials/diagnoses. In MZL, such discontinuation accounts for 17% of patients, whereas serious AEs of any grade occurred in 44% of patients. Pneumonia grade ≥3 was the most common severe side effect, reported in 8% of the cohort [49]. Serious AEs occurred in 42% of CLL patients receiving single-agent ibrutinib, becoming the reason for discontinuation in 4% of patients, and fatal in another 4% [47]. In this study, out of 81 cases of serious AE, 46 accounted for infections and 13 for cardiac disorders, including atrial fibrillation.

A separate study analyzed the prevalence of atrial fibrillation in a retrospective follow-up analysis of CLL patients receiving ibrutinib. Atrial fibrillation was found in 6.1% of individuals without a prior history of this disorder [52]. Other AEs of grade ≥3 reported in the CLL clinical trial were pyrexia, diarrhea, fatigue, nausea, anemia, neutropenia, thrombocytopenia, arthralgia, dyspnea, stomatitis, and sinusitis. Another clinical study on ibrutinib in R/R CLL and small lymphocytic lymphoma (SLL) patients of the high risk associated with del(17p) showed a discontinuation rate due to AEs of 15% (22 of 144 patients) and fatality in two patients, although an extended analysis reported death due to AEs in 18 patients [53]. In the R/R MCL study, 7% of patients discontinued ibrutinib and 3% died from AEs, whereas diarrhea, neutropenia, thrombocytopenia, fatigue and dyspnea, but not upper respiratory tract infection, were the most common AEs of grade ≥3 [39]. The occurrence of thrombocytopenia but also direct activity on the signaling pathway in platelets predisposes to bleeding and hemorrhage, which is especially noticeable in head-to-head clinical trials comparing the effect of ibrutinib and chemo plus immunotherapeutics (reviewed in [54]). Some of these AEs, including diarrhea, bleeding, and atrial fibrillation, are attributed to off-target effects [55]. Ibrutinib covalently and irreversibly binds cysteine 481 in the ATP-binding pocket of BTK [38]. However, many other kinases share a similar molecular architecture of this functional site as that of BTK, e.g. interleukin-2-inducible T-cell kinase (ITK), Tec protein tyrosine kinase (TEC), bone marrow tyrosine kinase gene in chromosome X (BMX), and epidermal growth factor receptor (EGFR) (reviewed in [54, 56]). Kaptein et al. [57] assessed the specificity of ibrutinib in terms of kinase inhibition (excluding BTK) and, by the application of KinomeScan technology, found that the activity of 9.4% of human wild-type kinases was inhibited by more than 65% at a 1 μM concentration. They also provided IC_{50} values from biochemical assays showing non-specific inhibition of particular kinases. The IC_{50} value for BTK was 1.5 nM, whereas those for TEC, ITK, BMX, and EGFR were 10 nM, 4.9 nM, 0.8 nM, and 5.3 nM, respectively. Importantly, functional impairment of these kinases is thought to be associated with diarrhea, dysfunction of antibody-dependent cellular cytotoxicity (ADCC) mechanism, dysfunction of platelets, and the risk of bleeding [38, 58, 59].

Next generation irreversible BTK inhibitors

Selective BTK inhibitors were developed mainly with the aim of reducing significant AEs occurring during ibrutinib therapy while maintaining high efficacy in the treatment of B-cell malignancies. Apart from zanubrutinib, other selective irreversible BTK inhibitors have been approved or are under investigation. The first approved second-generation agent was acalabrutinib (approved for MCL in 2017 [60], which due to increased selectivity compared to ibrutinib, e.g. lack of TEC, ITK and HER 2 inhibition, presented fewer or no AEs such as bleeding or atrial fibrillation [61].

Although there is limited data regarding a direct comparison between acalabrutinib and zanubrutinib in terms of efficacy and safety, recent findings from the ongoing BGB-3111-215 trial (NCT04116437) showed that zanubrutinib could prove beneficial to many patients with B-cell neoplasms who had to discontinue acalabrutinib because of AEs. In patients intolerant to acalabrutinib who received zanubrutinib, 75% of acalabrutinib AEs of any grade did not occur during zanubrutinib therapy, and no acalabrutinib AEs recurred at a high severity [62].

Other important irreversible BTK inhibitors already approved for B-cell malignancies are tirabrutinib (CNS lymphoma, WM, CLL) and orelabrutinib EGFR, BMX, TEC (MCL, CLL, SLL). Studies on these molecules have also shown improved selectivity against potential off-target enzymes, e.g. BMX, EGFR, TEC, and ITK [63, 64]. Clinical trials have led to the approval of these drugs for treating various hematological malignancies, including CNS lymphoma (in the case of tirabrutinib) [65].

Many irreversible BTK inhibitors, such as evobrutinib, spebrutinib, remibrutinib, tolebrutinib and olmutinib, are currently under pre-clinical and clinical investigation. So far, the results are promising and support the continued investigation of these molecules, which may, in the future, contribute to approval for the treatment of autoimmune disorders (e.g. SLE, arthritis, Sjogren's syndrome) and cancers, such as non-small cell lung cancer [65].

Reversible BTK inhibitors

Another important issue is resistance to BTK inhibitors, whose mechanism of action relies on covalent and irreversible binding to cysteine 481. Substitution of cysteine with serine, despite being conservative in terms of amino acid homology, precludes effective inhibition of BTK by either ibrutinib or zanubrutinib. Such C481S mutation is often manifested in CLL patients receiving prolonged treatment, and is believed to stem from the selection and expansion of rare clones of tumor cells already present in patients before treatment initiation [66].

The novel, reversible inhibitors of BTK, such as vecabrutinib (SNS-062) [67], pirtobrutinib (LOXO-305) [68], and nemtabrutinib (ARQ-531, MK-1026) [69] have been shown to effectively diminish the activity of the C481S variant in preclinical testing. Their selectivity, safety, tolerability, pharmacokinetics, and efficacy are now being assessed in clinical trials [70]. At this stage, the evidence suggests that these novel agents may provide clinical benefit for patients with CLL or MCL who are resistant to ibrutinib [71, 72].

Advantages of zanubrutinib over ibrutinib in biochemical and mechanistic context

Zanubrutinib is a novel irreversible BTK inhibitor developed as a therapeutic agent dedicated to the treatment of B-cell lymphoproliferative diseases. Initial studies have shown potent on-target activity against BTK comparable to that of ibrutinib, but with higher selectivity and an excellent pharmacodynamic profile *in vivo* [73]. KinomeScan analyses have revealed a halving in the percentage of non-BTK kinase inhibition by zanubriutinib compared to ibrutinib (4.3% vs. 9.4%, respectively) [57]. Importantly, off-target effects of zanubrutinib toward vital tyrosine kinases such as EGFR, human epidermal growth factor receptor (2HER2), HER4, ITK, Janus kinase 3 (JAK3), and TEC are considerably lower than ibrutinib [55, 57]. The effective inhibitory concentrations depended on the assay, and the average IC_{50} values reported for EGRF, ITK, JAK3, HER2, and TEC were respectively 8, 26, 51, 70, and 2.4-fold higher for zanubrutinib than for ibrutinib. Such characteristics may result in more favorable pharmacodynamics, as well as limited AEs, such as diarrhea, rash, atrial fibrillation, bleeding, and fatigue. Dobue et al. analyzed the effect of BTK inhibitors on thrombus formation, and found that pretreatment of mice with ibrutinib, but not zanubrutinib, resulted in either *in vitro* reduction of platelets' adhesion to immobilized type I collagen, von Willebrand factor (vWF), and fibrinogen, or thrombus formation *in vivo* [74]. The same conclusions were drawn from experiments performed on platelets collected from ibrutinib-treated CLL patients, who formed smaller thrombi than those collected from zanubrutinib-treated patients or healthy controls. Such results show a lower incidence of zanubrutinib-related bleeding and underline zanubrutinib's advantage over ibrutinib in patients receiving anticoagulants [75].

The relative sparing of ITK by zanubrutinib could result in less interference with the tumor-clearing mechanism of anti-CD20 antibody-induced antibody-dependent cytotoxicity (ADCC), resulting in enhanced efficacy when combined with obinutuzumab [76]. Another advantage of zanubrutinib includes favorable drug-drug interaction characteristics that allow co-administration with azole antifungals, proton pump inhibitors, and vitamin K antagonists [76, 77]. Moreover, according to preclinical trials, zanubrutinib has better bioavailability when administered orally [55].

Better selectivity and bioavailability of zanubrutinib should be mirrored in fewer AEs in patients and comparable on-target activity should make it as effective as the parental molecule. Such a thesis is being verified in clinical trials, which assess safety and efficacy, as well as a head-to-head comparison with ibrutinib.

Clinical trials of zanubrutinib

Ongoing and completed clinical trials of zanubrutinib in B-cell malignancies are set out in Table I [78–86]. Here, we provide a more detailed description of studies concerning MCL, CLL/SLL, and WM.

Mantle cell lymphoma

In the clinical trial NCT02343120, 62 individuals with a variety of non-Hodgkin lymphoma (NHL) types were assessed. ORR was 58.1% among all patients, 60.9% among 46 patients with aggressive NHLs — DLBCL or MCL, and 50% among 16 patients with indolent lymphomas (FL or MZL). CR ratios were 12.9%, 15.2%, and 6.3% respectively and PR ratios were 45.2%, 45.7%, and 43.8% respectively [87]. In the BGB-3111-AU-003 study among 37 previously treated patients with MCL, ORR was 86.5%, CR was 29.7% and PR was 56.8%. The median duration of response was 17.1 months [79]. In the single-arm, open, phase II trial NCT03206970, zanubrutinib was effective in patients with MCL who had been given at least one prior line of treatment, particularly CHOP/CHOP-R (cyclophosphamide, doxorubicin, oncovin, prednisone, and rituximab). Among 86 patients evaluated, ORR was 84%, CR was 59%, and PR was 24%. The median duration of treatment was 19.5 months, whereas the median PFS was 16.7 months [78]. Independent review committee (IRC) evaluated the response, based on the Lugano 2014 classification [88]. Compelling results of zanubrutinib clinical trials in patients previously treated for MCL led to FDA approval in November 2019. Zanubritinib is currently indicated for the treatment of adult patients with MCL who have received at least one prior therapy. The recommended dosage in this indication is 160 mg twice daily, or 320 mg once daily, until the progression of the disease or unacceptable toxicity.

Chronic lymphocytic leukemia/ /small lymphocytic lymphoma

In the non-randomized arm of the international, open, phase III clinical trial SEQUOIA, comparing zanubrutinib to bendamustine plus rituximab among 90 previously untreated patients with CLL/SLL and del(17p) present, ORR was 92.2% [80]. In another cohort trial, NCT02343120, ORR was 96.7% among all 120 patients with CLL/SLL and 93.8% in patients with del(17p) at median follow-up (MFU) of 26.4 months. ORR was comparable in both previously untreated patients and those with relapsed/refractory

Table I. List of clinical trials of zanubrutinib in B-cell malignancies

Disease	Trial	Phase	N (population tested)	ORR [%]	CR [%]	PR [%]	PR-L [%]	DOR [median in months]	PFS [median in months]	MFU [months]	VGPR [%]	VGPR or CR [%]	MR [%]	2y PFS [%]
MCL	NCT03206970 [78]	II	86	83.7	68,6			19.5	22.1	18.4				
	NCT02343120 [79]	I/II	37	86.5	29,7	56.8				17.1				
CLL/SLL	NCT03336333 (SEQUOIA) [80]	III	90	92.2	0	75.6	16.7			7				
	NCT03734016 (ALPINE) [81, 82]	III	66 — TN = 16	94	6									
			R/R = 50		2									
	NCT02343120 [83]	I/II	120	96.7 (all) 93.8 [del(17p)]						26.4				
WM	NCT02343120 [84]	I/II	73 — TN = 24	100	0	54.2				23.5	33.3	33.3	12.5	91.5
			R/R = 49	93.9	2	28.6				35.8	49	51	14.3	76.2
	BGB-3111-302 (ASPEN) [85]	III	102 — TN = 19	95	0	47		NE	NE	19.4	26	26	74	
			R/R = 83	94	0	49		NE	NE		29	29	78	
MZL	BGB-3111–214; NCT03846427 (MAGNOLIA) [86]	II	68	68.2	17	28		NE	NE	15.7				

ORR — overall response rate; CR — complete response; PR — partial response; PR-L — partial response with lymphocytosis; DOR — duration of response; PFS — progression-free survival; MFU — median follow-up; VGPR — very good partial response; MR — minimal response; MCL — mantle cell lymphoma; CLL/SLL — chronic lymphocytic leukemia/small lymphocytic lymphoma; TN — treatment-naive; R/R — relapsed/refractory; WM — Waldenström's macroglobulinemia; NE — not estimable; MZL — marginal zone lymphoma

disease (RR CLL/SLL) [83]. Long-term follow-up of zanubrutinib monotherapy in treatment-naïve CLL/SLL patients with del(17p) proved the durability of responses in this high-risk cohort, with an estimated 18-month PFS of 88.6% and an estimated 18-month OS of 95.1%. Zanubrutinib was generally well tolerated, with low rates of discontinuation due to AEs. These findings support the potential utility of zanubrutinib in the frontline management of patients with the high-risk [del(17p) positive] disease [89].

The ongoing ALPINE study has been comparing zanubrutinib to ibrutinib in relapsed/refractory CLL/SLL. This is the first head-to-head comparison of the efficacy and safety of these two compounds in a randomized trial [81, 82]. Thus far, zanubrutinib has been shown to be superior to ibrutinib with respect to PFS and OS. Zanubrutinib has also caused fewer AEs leading to discontinuation or death than ibrutinib. Also, the risk of atrial fibrillation or grade 3 infection was lower with zanubrutinib. The risk of cardiovascular AEs, such as hypertension, was very similar between the zanubrutinib (16.7%) and ibrutinib arms (16.4%). Overall, zanubrutinib in the ALPINE trial seems to have a favorable benefit-risk profile compared to ibrutinib in patients with R/R CLL/SLL [86, 90]. In a phase I trial (NCT02343120) zanubrutinib has demonstrated encouraging activity in CLL/SLL patients, with a low incidence of major toxicities. Among 78 efficacy-evaluable CLL/SLL patients, the overall response rate was 96.2% (95% confidence interval, 89.2–99.2). The estimated progression-free survival at 12 months was 100% [55]. Grade 3/4 AEs reported included neutropenia (6.4% of patients), anemia (2.1%), pneumonia (2.1%), and hypertension (2.1%). One patient had febrile neutropenia (grade 3), and one patient had disseminated herpes zoster infection (grade 3). Atrial fibrillation (grade 2) occurred in one patient with a history of hypertension and hyperlipidemia. Only one patient with CLL/SLL (receiving concomitant aspirin) experienced major hemorrhage (grade 3 subcutaneous hemorrhage). Concomitant antiplatelets (aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs) and anticoagulants (unfractionated or low-molecular-weight heparin, direct thrombin inhibitors, or warfarin) were used by 16.0% and 8.5% of patients, respectively. The exposure-adjusted incidence rate for grade 3 petechiae/purpura/contusions was 0.086 per 100 person-months. There were no deaths in the CLL/SLL cohort [55].

A 4-year follow-up of the phase I/II AU-003 study evaluated long-term tolerability and efficacy of zanubrutinib in CLL/SLL patients. In treatment-naïve patients, ORR was 100%, and in R/R CLL/SLL it was 95%. Complete response was observed in 18.7% of patients. At three years, 85.7% of patients had ongoing response. AEs leading to discontinuation of therapy were uncommon, and the incidence of AF, major hemorrhage or grade ≥3 infection decreased. This study showed that, with durable efficacy and acceptable tolerability, zanubrutinib can provide long-term clinical benefits for patients with CLL/SLL.

Waldenström's macroglobulinemia

Clinical trial NCT02343120 evaluated the safety, tolerability, pharmacokinetic profile, and effectiveness of zanubrutinib. Among 73 individuals with WM (24 previously untreated, and 49 with relapsing/refractory disease), long-term zanubrutinib treatment resulted in an overall response rate of 96% and a very good partial response (VGPR)/CR rate of 45%, which increased over time: 20.5% at six months, 32.9% at 12 months, and 43.8% at 24 months. The estimated 3-year progression-free survival rate was 80.5%, and the overall survival rate was 84.8% [84]. In the ASPEN study, a randomized phase III trial, zanubrutinib was head-to-head compared with ibrutinib in symptomatic WM [85]. Zanubrutinib was associated with fewer major hemorrhages than ibrutinib (0.3 vs. 0.6 events/100 person-months). Ibrutinib patients experienced a ~10-fold higher incidence of atrial fibrillation/flutter (1.0 vs. 0.1 events/100 person-months) and an approximately doubled frequency of hypertension on an exposure-adjusted basis (1.2 vs. 0.7 events/100 person-months). The frequency of diarrhea among zanubrutinib patients in the study was half that reported among ibrutinib patients (1.3 and 2.6 events per 100 person-months, respectively), probably explained by the less potent inhibition of epidermal growth factor receptor by zanubrutinib. Grade 3 neutropenia was more common among zanubrutinib patients (29% vs. 13%). Both agents inhibit BTK in neutrophil precursors by similar mechanisms, so higher rates of severe neutropenia among zanubrutinib patients may be a function of its greater bioavailability. However, the higher incidence of neutropenia did not result in a higher infection incidence compared to that of ibrutinib. Paradoxically, the incidence of some respiratory tract infections (mostly pneumonia) was higher among ibrutinib recipients. More ibrutinib than zanubrutinib patients required dose reductions for AEs (23% vs. 14%, respectively. Treatment with zanubrutinib was associated with fewer discontinuations than treatment with ibrutinib (4% vs. 9%, respectively), and fewer deaths were attributed to AEs (1% vs. 4%). A lower proportion of zanubrutinib-treated patients experienced an AE that led to dose reductions (13.9% vs. 23.5%) or doses being withheld (46.5% vs. 56.1%) [85]. Data from real-life studies of zanubrutinib in WM is still limited. However, results provided by Itchaki et al. [91] from their retrospective multi-center study seem to be consistent with clinical studies, with an 83% ORR and a 23% rate of grade ≥3 AEs.

Recent case studies indicate that zanubrutinib is effective in the treatment of Bing-Neel syndrome, an extremely rare complication of WM characterized by infiltration of the central nervous system by clonal lymphoplasmocytes, sometimes accompanied by hyperglobulinemia in the cerebrospinal fluid [92].

Marginal zone lymphoma

The phase II MAGNOLIA trial (BGB-3111–214; NCT03846427), conducted in 2020 in nine countries, evaluated the efficacy and safety profiles of zanubrutinib in patients with relapsed/refractory marginal zone lymphoma. The study included 68 R/R MZL patients who had previously received at least one line of therapy with a CD20-directed agent. After a median follow-up of 15.7 months, ORR was 68.2% and CR was 25.8%. The estimated DOR rate at 12 months after the first response was 93%. At a median follow-up, 40 (89%) of the 45 patients who responded were free from progression or death. The response to treatment varied between MZL subtypes (nodal, extranodal, splenic, unknown). Zanubrutinib in R/R MCL patients was generally well tolerated. Most AEs that occurred were in grades 1 or 2. The most common AEs were infections (45.6%), diarrhea (22.1%), contusion (20.6%), constipation (14.7%), and pyrexia (13.2%). A total of four patients developed COVID pneumonia during the investigations, being fatal in two cases. However, these cases were assessed to not have been related to zanubrutinib. Bleeding occurred in 36.6% of subjects, but no patient experienced a major hemorrhage [93].

In September 2021, due to its high efficacy and a favorable safety profile, zanubrutinib was approved by the FDA for adult patients with relapsed or refractory marginal zone lymphoma who had received at least one anti-CD20-based regimen [94].

Current position of BTK inhibitors and zanubrutinib in treatment of B-cell malignancies

The position of BTK inhibitors in the treatment of B-cell malignancies is not yet completely established. However, in CLL, BTK inhibitors have emerged as the most successful therapeutic approach inhibiting signals transmission from the B-cell receptor into the cell. The critical role of the B-cell receptor for CLL cells has been one of the major discoveries of the last two decades, improving outcomes in CLL patients, including those with unmutated immunoglobulin heavy-chain variable region gene and with p53 deletion/mutation. This explains the expansion of FDA approval of ibrutinib to the frontline treatment of all adult patients with CLL in April 2020 based on the results of the E1912 trial [95], and acalabrutinib in November 2019 based on the results of two phase III randomized trials — ELEVATE-TN and ASCEND [96, 97]. Also, early administration of zanubrutinib has led to higher overall response rates and greater durability of therapeutic benefit [98].

In our opinion, BTK inhibitors are also changing the treatment paradigm for MCL [70], which remains incurable, and patients will ultimately relapse with shortened remission durations with each successive therapy. As yet, BTK inhibitors are only approved for second-line MCL: ibrutinib in 2013, acalabrutinib in 2017 and zanubrutinib in 2019, but clinical trials in untreated MCL patients are ongoing with very promising results [99]. BTK inhibition has changed the treatment landscape of WM. Ibrutinib has resulted in deep and durable responses both as an upfront and as a salvage treatment, whereas zanubrutinib has resulted in similar antitumor activity, including deep and durable responses, but with a low discontinuation rate due to treatment-related toxicity [85].

Considering the similar efficacy of different BTK inhibitors, the choice between them mainly depends on their toxicities. Acalabrutinib and zanubrutinib, recently approved in China for patients with relapsed/refractory CLL, appear to have a more favorable toxicity profile compared to ibrutinib, especially cardiovascular, making them particularly interesting agents in the current treatment of patients with CLL. In our opinion, they have become the BTK inhibitors of choice for CLL and MCL treatment.

The second important issue is to establish whether BTK inhibitors should be used in monotherapy or alongside anti-CD20 monoclonal antibodies or bcl-2 inhibitors. The bcl-2 inhibitor venetoclax, given for a fixed period of time together with an anti-CD20 antibody, is a valid option for CLL patients. Among patients with untreated CLL and coexisting conditions, venetoclax + obinutuzumab has been associated with longer progression-free survival than chlorambucil + obinutuzumab [100]. Several clinical trials [101–103] are now reviewing ways to incorporate venetoclax into the treatment with BTK inhibitors, but it remains an unanswered question as to within which setting this strategy would work best. In MCL, BTK inhibitors should be combined with other agents to improve treatment outcomes. The combination of obinutuzumab, ibrutinib, and venetoclax provides high response rates, including at the molecular level, in relapsed and untreated MCL patients [99]. In WM, it is unclear whether BTK inhibitors should be combined with other agents [104].

The third unresolved issue is how to sequence BTK and bcl-2 inhibitors. In CLL, there is no randomized trial comparing BTK inhibitors given continuously to bcl-2 inhibitors given for a limited time, so it is very difficult to decide which is the better approach. Obviously, limited-time treatment has some advantages over continuous treatment. It should be stressed however, that the greatest benefit from venetoclax is for patients who achieve MRD negativity, whereas MRD in continuous treatment with BTK inhibitors, in our opinion, is not the treatment goal. We also think that patients with 17p deletion seem to-have better outcomes on BTK inhibitors than bcl-2 inhibitors. Most of the patients who come off the BTK inhibitor move to venetoclax. It is unclear whether a patient could be successfully transferred from venetoclax to a BTK inhibitor. There is no prospective data in that setting, but in our experience, and looking at data from retrospective studies, it seems that

most patients who are treated with venetoclax in any line of therapy, who then relapse either on or after venetoclax, can be successfully rescued with a BTK inhibitor. Patients with CLL who are resistant to BTK-inhibitors and venetoclax should be referred to novel treatments such as CAR-T cell therapy. Interestingly, BTK inhibitors can improve the efficacy of CAR-T cells [105]. In MCL, we believe that combined therapy of BTK inhibitors with bcl-2 inhibitors and anti-CD20 antibodies will soon become a standard first--line treatment. Relapsing patients should be referred for CAR-T cell therapy, which has recently been reported to induce durable remissions in most patients with relapsed or refractory MCL [16].

Conclusions

Bruton's tyrosine kinase inhibitors have already become an acknowledged element of the treatment for lymphoproliferative neoplasms. Ibrutinib, the best-in-class BTK inhibitor, has so far been the most evaluated and has been most widely used in numerous indications. Its efficacy and relatively good safety profile are well-proven. However, the incidence of serious AEs such as atrial fibrillation and hemorrhagic complications has led to the development of novel agents with reduced off-target effects.

Zanubrutinib, a second-generation BTK inhibitor, exhibits higher selectivity against BTK than ibrutinib, and appears to have a more favorable toxicity profile, especially regarding cardiovascular AEs, primarily atrial fibrillation. Clinical studies have already led to the approval of zanubrutinib in WM, MZL and CLL/SLL.

Nonetheless, further studies of zanubrutinib, both in monotherapy and in combination with other agents, are necessary to extend the scope of potential indications and evaluate its long-term safety profile. Longer follow-ups, more clinical experience, and comparative trials should help answer the question as to whether zanubrutinib could become the first-line treatment for a variety of lymphoproliferative neoplasms.

Authors' contributions

All authors were engaged in the preparation and writing of the manuscript, and all agreed on the final version.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Maloney DG, Grillo-López AJ, White CA, et al. IDEC-C2B8 (rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low--grade non-Hodgkin's lymphoma. Blood. 1997; 90(6): 2188–2195, doi: 10.1182/blood.v90.6.2188.2188_2188_2195.
2. Murawski N, Pfreundschuh M. New drugs for aggressive B-cell and T-cell lymphomas. Lancet Oncol. 2010; 11(11): 1074–1085, doi: 10.1016/s1470-2045(10)70210-2.
3. Czuczman MS, Fayad L, Delwail V, et al. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. Blood. 2012; 119(16): 3698–3704, doi: 10.1182/blood-2011-09-378323.
4. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. N Engl J Med. 2017; 377(14): 1331–1344, doi: 10.1056/NEJMoa1614598, indexed in Pubmed: 28976863.
5. Okroj M, Österborg A, Blom AM. Effector mechanisms of anti-CD20 monoclonal antibodies in B cell malignancies. Cancer Treat Rev. 2013; 39(6): 632–639, doi: 10.1016/j.ctrv.2012.10.008, indexed in Pubmed: 23219151.
6. Ansell SM, Minnema MC, Johnson P, et al. Nivolumab for relapsed/ /refractory diffuse large B-cell lymphoma in patients ineligible for or having failed autologous transplantation: a single-arm, phase II study. J Clin Oncol. 2019; 37(6): 481–489, doi: 10.1200/JCO.18.00766, indexed in Pubmed: 30620669.
7. Armand P, Shipp MA, Ribrag V, et al. Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol. 2016; 34(31): 3733–3739, doi: 10.1200/JCO.2016.67.3467, indexed in Pubmed: 27354476.
8. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020; 21(11): 1433–1442, doi: 10.1016/S1470-2045(20)30441-1, indexed in Pubmed: 33035457.
9. Lenz G, Hawkes E, Verhoef G, et al. Single-agent activity of phosphatidylinositol 3-kinase inhibition with copanlisib in patients with molecularly defined relapsed or refractory diffuse large B-cell lymphoma. Leukemia. 2020; 34(8): 2184–2197, doi: 10.1038/s41375-020-0743-y, indexed in Pubmed: 32060403.
10. Liu D, Mamorska-Dyga A. Syk inhibitors in clinical development for hematological malignancies. J Hematol Oncol. 2017; 10(1): 145, doi: 10.1186/s13045-017-0512-1, indexed in Pubmed: 28754125.
11. Hambley B, Caimi PF, William BM. Bortezomib for the treatment of mantle cell lymphoma: an update. Ther Adv Hematol. 2016; 7(4): 196–208, doi: 10.1177/2040620716648566, indexed in Pubmed: 27493710.
12. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol. 2020; 7(7): e511–e522, doi: 10.1016/S2352-3026(20)30120-4, indexed in Pubmed: 32589977.

13. Chavez JC, Bachmeier C, Kharfan-Dabaja MA. CAR T-cell therapy for B-cell lymphomas: clinical trial results of available products. Ther Adv Hematol. 2019; 10: 2040620719841581, doi: 10.1177/2040620719841581, indexed in Pubmed: 31019670.
14. Schuster SJ, Bishop MR, Tam CS, et al. JULIET Investigators. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019; 380(1): 45–56, doi: 10.1056/NEJMoa1804980, indexed in Pubmed: 30501490.
15. Neelapu SS, Jacobson CA, Ghobadi A, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017; 377(26): 2531–2544, doi: 10.1056/NEJMoa1707447, indexed in Pubmed: 29226797.
16. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020; 382(14): 1331–1342, doi: 10.1056/NEJMoa1914347, indexed in Pubmed: 32242358.
17. Maurer G, Tarkowski B, Baccarini M. Raf kinases in cancer-roles and therapeutic opportunities. Oncogene. 2011; 30(32): 3477–3488, doi: 10.1038/onc.2011.160, indexed in Pubmed: 21577205.
18. Torkamani A, Schork NJ. Prediction of cancer driver mutations in protein kinases. Cancer Res. 2008; 68(6): 1675–1682, doi: 10.1158/0008-5472.CAN-07-5283, indexed in Pubmed: 18339846.
19. Bhullar KS, Lagarón NO, McGowan EM, et al. Kinase-targeted cancer therapies: progress, challenges and future directions. Mol Cancer. 2018; 17(1): 48, doi: 10.1186/s12943-018-0804-2, indexed in Pubmed: 29455673.
20. Cuellar S, Vozniak M, Rhodes J, et al. BCR-ABL1 tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. J Oncol Pharm Pract. 2018; 24(6): 433–452, doi: 10.1177/1078155217710553, indexed in Pubmed: 28580869.
21. Wu J, Liu C, Tsui ST, et al. Second-generation inhibitors of Bruton tyrosine kinase. J Hematol Oncol. 2016; 9(1): 80, doi: 10.1186/s13045-016-0313-y, indexed in Pubmed: 27590878.
22. Efremov DG, Turkalj S, Laurenti L. Mechanisms of B cell receptor activation and responses to B cell receptor inhibitors in B cell malignancies. Cancers (Basel). 2020; 12(6), doi: 10.3390/cancers12061396, indexed in Pubmed: 32481736.
23. Maguire O, Tornatore KM, O'Loughlin KL, et al. Nuclear translocation of nuclear factor of activated T cells (NFAT) as a quantitative pharmacodynamic parameter for tacrolimus. Cytometry A. 2013; 83(12): 1096–1104, doi: 10.1002/cyto.a.22401, indexed in Pubmed: 24136923.
24. Erdmann T, Klener P, Lynch JT, et al. Sensitivity to PI3K and AKT inhibitors is mediated by divergent molecular mechanisms in subtypes of DLBCL. Blood. 2017; 130(3): 310–322, doi: 10.1182/blood-2016-12-758599, indexed in Pubmed: 28202458.
25. Suthers AN, Sarantopoulos S. TLR7/TLR9- and B cell receptor-signaling crosstalk: promotion of potentially dangerous B cells. Front Immunol. 2017; 8: 775, doi: 10.3389/fimmu.2017.00775, indexed in Pubmed: 28751890.
26. Lindvall J, Islam TC. Interaction of Btk and Akt in B cell signaling. Biochem Biophys Res Commun. 2002; 293(5): 1319–1326, doi: 10.1016/S0006-291X(02)00382-0, indexed in Pubmed: 12054657.
27. Berry CT, Liu X, Myles A, et al. BCR-induced Ca signals dynamically tune survival, metabolic reprogramming, and proliferation of naive B cells. Cell Rep. 2020; 31(2): 107474, doi: 10.1016/j.celrep.2020.03.038, indexed in Pubmed: 32294437.
28. Tobin G, Thunberg U, Karlsson K, et al. Subsets with restricted immunoglobulin gene rearrangement features indicate a role for antigen selection in the development of chronic lymphocytic leukemia. Blood. 2004; 104(9): 2879–2885, doi: 10.1182/blood-2004-01-0132, indexed in Pubmed: 15217826.
29. Agathangelidis A, Darzentas N, Hadzidimitriou A, et al. Stereotyped B-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies. Blood. 2012; 119(19): 4467–4475, doi: 10.1182/blood-2011-11-393694, indexed in Pubmed: 22415752.
30. Chu CC, Catera R, Hatzi K, et al. Chronic lymphocytic leukemia antibodies with a common stereotypic rearrangement recognize nonmuscle myosin heavy chain IIA. Blood. 2008; 112(13): 5122–5129, doi: 10.1182/blood-2008-06-162024, indexed in Pubmed: 18812466.
31. Hoogeboom R, van Kessel KPM, Hochstenbach F, et al. A mutated B cell chronic lymphocytic leukemia subset that recognizes and responds to fungi. J Exp Med. 2013; 210(1): 59–70, doi: 10.1084/jem.20121801, indexed in Pubmed: 23296468.
32. Lanemo Myhrinder A, Hellqvist E, Sidorova E, et al. A new perspective: molecular motifs on oxidized LDL, apoptotic cells, and bacteria are targets for chronic lymphocytic leukemia antibodies. Blood. 2008; 111(7): 3838–3848, doi: 10.1182/blood-2007-11-125450, indexed in Pubmed: 18223168.
33. Steininger C, Widhopf GF, Ghia EM, et al. Recombinant antibodies encoded by IGHV1-69 react with pUL32, a phosphoprotein of cytomegalovirus and B-cell superantigen. Blood. 2012; 119(10): 2293–2301, doi: 10.1182/blood-2011-08-374058, indexed in Pubmed: 22234695.
34. Gobessi S, Laurenti L, Longo PG, et al. Inhibition of constitutive and BCR-induced Syk activation downregulates Mcl-1 and induces apoptosis in chronic lymphocytic leukemia B cells. Leukemia. 2009; 23(4): 686–697, doi: 10.1038/leu.2008.346, indexed in Pubmed: 19092849.
35. Young RM, Wu T, Schmitz R, et al. Survival of human lymphoma cells requires B-cell receptor engagement by self-antigens. Proc Natl Acad Sci USA. 2015; 112(44): 13447–13454, doi: 10.1073/pnas.1514944112, indexed in Pubmed: 26483459.
36. Amin R, Mourcin F, Uhel F, et al. DC-SIGN-expressing macrophages trigger activation of mannosylated IgM B-cell receptor in follicular lymphoma. Blood. 2015; 126(16): 1911–1920, doi: 10.1182/blood-2015-04-640912, indexed in Pubmed: 26272216.
37. Pighi C, Gu TL, Dalai I, et al. Phospho-proteomic analysis of mantle cell lymphoma cells suggests a pro-survival role of B-cell receptor signaling. Cell Oncol (Dordr). 2011; 34(2): 141–153, doi: 10.1007/s13402-011-0019-7, indexed in Pubmed: 21394647.
38. Wen T, Wang J, Shi Y, et al. Inhibitors targeting Bruton's tyrosine kinase in cancers: drug development advances. Leukemia. 2020; 35(2): 312–332, doi: 10.1038/s41375-020-01072-6.
39. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013; 369(6): 507–516, doi: 10.1056/NEJMoa1306220, indexed in Pubmed: 23782157.
40. Rule S, Dreyling M, Goy A, et al. Outcomes in 370 patients with mantle cell lymphoma treated with ibrutinib: a pooled analysis from three open-label studies. Br J Haematol. 2017; 179(3): 430–438, doi: 10.1111/bjh.14870, indexed in Pubmed: 28832957.
41. Ruan J, Yamshon S, van Besien K, et al. An update on options of therapy for aggressive mantle cell lymphoma. Leuk Lymphoma. 2020; 61(9): 2036–2049, doi: 10.1080/10428194.2020.1755860, indexed in Pubmed: 32336184.

42. Wang ML, Lee H, Chuang H, et al. Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: a single-centre, open-label, phase 2 trial. Lancet Oncol. 2016; 17(1): 48–56, doi: 10.1016/S1470-2045(15)00438-6, indexed in Pubmed: 26640039.
43. Maddocks K, Christian B, Jaglowski S, et al. A phase 1/1b study of rituximab, bendamustine, and ibrutinib in patients with untreated and relapsed/refractory non-Hodgkin lymphoma. Blood. 2015; 125(2): 242–248, doi: 10.1182/blood-2014-08-597914, indexed in Pubmed: 25355819.
44. Jain P, Lee H, Steiner R, et al. Frontline treatment with ibrutinib with rituximab (IR) combination is highly effective in elderly (≥65 years) patients with mantle cell lymphoma (MCL) — results from a phase II trial. Blood. 2019; 134(Suppl_1): 3988–3988, doi: 10.1182/blood-2019-125800.
45. Le Gouill S, Morschhauser F, Bouabdallah K, et al. Ibrutinib, venetoclax plus obinutuzumab in newly diagnosed mantle cell lymphoma patients. Blood. 2019; 134(Suppl_1): 1530–1530, doi: 10.1182/blood-2019-125681.
46. Wang ML, Jain P, Lee HJu, et al. Frontline treatment with ibrutinib plus rituximab (IR) followed by short course R-HyperCVAD/MTX is extremely potent and safe in patients (age ≤ 65 years) with mantle cell lymphoma (MCL) — results of phase-II WINDOW-1 clinical trial. Blood. 2019; 134(Supplement_1): 3987–3987, doi: 10.1182/blood-2019-126044.
47. Byrd JC, Brown JR, O'Brien S, et al. RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014; 371(3): 213–223, doi: 10.1056/NEJMoa1400376, indexed in Pubmed: 24881631.
48. Treon SP, Tripsas CK, Meid K, et al. Ibrutinib in previously treated Waldenström's macroglobulinemia. N Engl J Med. 2015; 372(15): 1430–1440, doi: 10.1056/NEJMoa1501548, indexed in Pubmed: 25853747.
49. Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. Blood. 2017; 129(16): 2224–2232, doi: 10.1182/blood-2016-10-747345, indexed in Pubmed: 28167659.
50. Goy A, Ramchandren R, Ghosh N, et al. Ibrutinib plus lenalidomide and rituximab has promising activity in relapsed/refractory non-germinal center B-cell-like DLBCL. Blood. 2019; 134(13): 1024–1036, doi: 10.1182/blood.2018891598, indexed in Pubmed: 31331917.
51. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. Haematologica. 2018; 103(5): 874–879, doi: 10.3324/haematol.2017.182907, indexed in Pubmed: 29419429.
52. Shanafelt TD, Parikh SA, Noseworthy PA, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL). Leuk Lymphoma. 2017; 58(7): 1630–1639, doi: 10.1080/10428194.2016.1257795 , indexed in Pubmed: 27885886.
53. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016; 17(10): 1409–1418, doi: 10.1016/S1470-2045(16)30212-1, indexed in Pubmed: 27637985.
54. Shatzel JJ, Olson SR, Tao DL, et al. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017; 15(5): 835–847, doi: 10.1111/jth.13651, indexed in Pubmed: 28182323.
55. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood. 2019; 134(11): 851–859, doi: 10.1182/blood.2019001160, indexed in Pubmed: 31340982.
56. Paydas S. Management of adverse effects/toxicity of ibrutinib. Crit Rev Oncol Hematol. 2019; 136: 56–63, doi: 10.1016/j.critrevonc.2019.02.001, indexed in Pubmed: 30878129.
57. Kaptein A, Bruin Gde, Hoek MEv, et al. Potency and selectivity of BTK inhibitors in clinical development for B-cell malignancies. Blood. 2018; 132(Suppl 1): 1871–1871, doi: 10.1182/blood-2018-99-109973.
58. Lynch TJ, Kim EdS, Eaby B, et al. Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: an evolving paradigm in clinical management. Oncologist. 2007; 12(5): 610–621, doi: 10.1634/theoncologist.12-5-610, indexed in Pubmed: 17522250.
59. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl Acad Sci USA. 2010; 107(29): 13075–13080, doi: 10.1073/pnas.1004594107, indexed in Pubmed: 20615965.
60. Markham A, Dhillon S. Acalabrutinib: first global approval. Drugs. 2018; 78(1): 139–145, doi: 10.1007/s40265-017-0852-8, indexed in Pubmed: 29209955.
61. Estupiñán HY, Berglöf A, Zain R, et al. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. Front Cell Dev Biol. 2021; 9: 630942, doi: 10.3389/fcell.2021.630942, indexed in Pubmed: 33777941.
62. Shadman M, Flinn I, Kingsley E, et al. Zanubrutinib in acalabrutinib-intolerant patients (pts) with B-cell malignancies. Blood. 2022; 140(Suppl 1): 3655–3657, doi: 10.1182/blood-2022-159726.
63. Liclican A, Serafini L, Xing W, et al. Biochemical characterization of tirabrutinib and other irreversible inhibitors of Bruton's tyrosine kinase reveals differences in on — and off — target inhibition. Biochim Biophys Acta Gen Subj. 2020; 1864(4): 129531, doi: 10.1016/j.bbagen.2020.129531, indexed in Pubmed: 31953125.
64. Zhang B, Zhao R, Liang R, et al. Abstract CT132: Orelabrutinib, a potent and selective Bruton's tyrosine kinase inhibitor with superior safety profile and excellent PK/PD properties. Cancer Res. 2020; 80(16_Suppl): CT132–CT132, doi: 10.1158/1538-7445.am2020-ct132.
65. Tasso B, Spallarossa A, Russo E, et al. The development of BTK inhibitors: a five-year update. Molecules. 2021; 26(23), doi: 10.3390/molecules26237411, indexed in Pubmed: 34885993.
66. Burger JA, Landau DA, Taylor-Weiner A, et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. Nat Commun. 2016; 7: 11589, doi: 10.1038/ncomms11589, indexed in Pubmed: 27199251.
67. Fabian CA, Reiff SD, Guinn D, et al. Abstract 1207: SNS-062 demonstrates efficacy in chronic lymphocytic leukemia in vitro and inhibits C481S mutated Bruton tyrosine kinase. Cancer Res. 2017; 77(13_Suppl): 1207–1207, doi: 10.1158/1538-7445.am2017-1207.
68. Naeem AS, Nguy WI, Tyekucheva S, et al. LOXO-305: targeting C481S Bruton tyrosine kinase in patients with ibrutinib-resistant CLL. Blood. 2019; 134(Suppl_1): 478–478, doi: 10.1182/blood-2019-124362.
69. Reiff SD, Mantel R, Smith LL, et al. The BTK inhibitor ARQ 531 targets ibrutinib-resistant CLL and Richter transformation. Cancer Discov. 2018; 8(10): 1300–1315, doi: 10.1158/2159-8290.CD-17-1409, indexed in Pubmed: 30093506.

70. Bond DA, Woyach JA. Targeting BTK in CLL: beyond ibrutinib. Curr Hematol Malig Rep. 2019; 14(3): 197–205, doi: 10.1007/s11899-019-00512-0, indexed in Pubmed: 31028669.
71. Alu A, Lei H, Han X, et al. BTK inhibitors in the treatment of hematological malignancies and inflammatory diseases: mechanisms and clinical studies. J Hematol Oncol. 2022; 15(1): 138, doi: 10.1186/s13045-022-01353-w, indexed in Pubmed: 36183125.
72. Gu D, Tang H, Wu J, et al. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. J Hematol Oncol. 2021; 14(1): 40, doi: 10.1186/s13045-021-01049-7, indexed in Pubmed: 33676527.
73. Guo Y, Liu Ye, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. J Med Chem. 2019; 62(17): 7923–7940, doi: 10.1021/acs.jmedchem.9b00687, indexed in Pubmed: 31381333.
74. Dobie G, Kuriri FA, Omar MMA, et al. Ibrutinib, but not zanubrutinib, induces platelet receptor shedding of GPIb-IX-V complex and integrin αIIbβ3 in mice and humans. Blood Adv. 2019; 3(24): 4298–4311, doi: 10.1182/bloodadvances.2019000640, indexed in Pubmed: 31869418.
75. Lipsky AH, Farooqui MZH, Tian X, et al. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. Haematologica. 2015; 100(12): 1571–1578, doi: 10.3324/haematol.2015.126672, indexed in Pubmed: 26430171.
76. Tam CS, Quach H, Nicol A, et al. Zanubrutinib (BGB-3111) plus obinutuzumab in patients with chronic lymphocytic leukemia and follicular lymphoma. Blood Adv. 2020; 4(19): 4802–4811, doi: 10.1182/bloodadvances.2020002183, indexed in Pubmed: 33022066.
77. Mu S, Tang Z, Novotny W, et al. Effect of rifampin and itraconazole on the pharmacokinetics of zanubrutinib (a Bruton's tyrosine kinase inhibitor) in Asian and non-Asian healthy subjects. Cancer Chemother Pharmacol. 2020; 85(2): 391–399, doi: 10.1007/s00280-019-04015-w, indexed in Pubmed: 31875923.
78. Song Y, Zhou K, Zou D, et al. Treatment of patients with relapsed or refractory mantle-cell lymphoma with zanubrutinib, a selective inhibitor of Bruton's tyrosine kinase. Clin Cancer Res. 2020; 26(16): 4216–4224, doi: 10.1158/1078-0432.CCR-19-3703, indexed in Pubmed: 32461234.
79. Tam CS, Wang M, Simpson D, et al. Updated safety and efficacy data in the phase 1 trial of the patients with mantle cell lymphoma (MCL) treated with the Bruton Tyrosine Kinase (BTK) inhibitor zanubrutinib (BGB-3111). Hematological Oncology. 2019; 37(Suppl 2): 245–247, doi: 10.1002/hon.55_2630.
80. Tam CS, Robak T, Ghia P, et al. Efficacy and safety of zanubrutinib in patients with treatment-naive chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): initial results from arm C of the SEQUOIA (BGB-3111-304) trial. Blood. 2019; 134(Suppl_1): 499–499, doi: 10.1182/blood-2019-125394.
81. Hillmen P, Brown J, Byrd J, et al. ALPINE: phase III zanubrutinib (BGB-3111) versus ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). J Clin Oncol. 2019; 37(15_Suppl): TPS7572–TPS7572, doi: 10.1200/jco.2019.37.15_suppl.tps7572.
82. Hillmen P, Brown J, Byrd J, et al. ALPINE: phase 3 trial of zanubrutinib (BGB-3111) vs ibrutinib in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Blood. 2019; 134(Suppl_1): 4307–4307, doi: 10.1182/blood-2019-124213.
83. Cull G, Simpson D, Opat S, et al. Treatment with the Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) demonstrates high overall response rate and durable responses in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): updated results from a phase 1/2 trial. Blood. 2019; 134(Suppl_1): 500–500, doi: 10.1182/blood-2019-125483.
84. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. Blood. 2020; 136(18): 2027–2037, doi: 10.1182/blood.2020006449, indexed in Pubmed: 32698195.
85. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. Blood. 2020; 136(18): 2038–2050, doi: 10.1182/blood.2020006844, indexed in Pubmed: 32731259.
86. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: interim analysis of a randomized phase III trial. J Clin Oncol. 2023; 41(5): 1035–1045, doi: 10.1200/JCO.22.00510, indexed in Pubmed: 36395435.
87. Tam CS, Simpson D, Opat S, et al. Safety and activity of the highly specific BTK inhibitor BGB-3111 in patients with indolent and aggressive non Hodgkin's lymphoma. Blood. 2017; 130: 152, doi: 10.1182/blood.V130.Suppl_1.152.152.
88. Cheson BD, Fisher RI, Barrington SF, et al. Alliance, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, Italian Lymphoma Foundation, European Organisation for Research, Treatment of Cancer/Dutch Hemato-Oncology Group, Grupo Español de Médula Ósea, German High-Grade Lymphoma Study Group, German Hodgkin's Study Group, Japanese Lymphorra Study Group, Lymphoma Study Association, NCIC Clinical Trials Group, Nordic Lymphoma Study Group, Southwest Oncology Group, United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32(27): 3059–3068, doi: 10.1200/JCO.2013.54.8800, indexed in Pubmed: 25113753.
89. Brown JR, Robak T, Ghia P, et al. Efficacy and safety of zanubrutinib in patients with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with del(17p): follow-up results from arm C of the SEQUOIA (BGB-3111-304) Trial. Blood. 2020; 136(Suppl 1): 11–12, doi: 10.1182/blood-2020-134280.
90. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023; 388(4): 319–332, doi: 10.1056/nejmoa2211582.
91. Itchaki G, Benjamini O, Levi M, et al. "Real-life" data of zanubrutinib in patients with Waldenström macroglobulinemia — a multi-center retrospective study. Blood. 2022; 140(Suppl 1): 11981–11982, doi: 10.1182/blood-2022-163009.
92. Wong J, Cher L, Griffiths J, et al. Efficacy of canubrutinib in the treatment of Bing-Neel syndrome. Hemasphere. 2018; 2(6): e155, doi: 10.1097/HS9.0000000000000155, indexed in Pubmed: 31723793.
93. Opat S, Tedeschi A, Linton K, et al. The MAGNOLIA trial: zanubrutinib, a next-generation Bruton tyrosine kinase inhibitor, demonstrates safety and efficacy in relapsed/refractory marginal zone lymphoma. Clin Cancer Res. 2021; 27(23): 6323–6332, doi: 10.1158/1078-0432.CCR-21-1704, indexed in Pubmed: 34526366.
94. Opat S, Tedeschi A, Hu B, et al. Long-term efficacy and safety of zanubrutinib in patients with relapsed/refractory (R/R) marginal

zone lymphoma (MZL): final analysis of the MAGNOLIA (BGB-3111-214) trial. Blood. 2022; 140(Suppl 1): 573–576, doi: 10.1182/blood-2022-163371.
95. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. N Engl J Med. 2019; 381(5): 432–443, doi: 10.1056/NEJMoa1817073, indexed in Pubmed: 31365801.
96. Sharman JP, Egyed M, Jurczak W, et al. Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzmab for treatment-naive chronic lymphocytic leukaemia (ELEVATE TN): a randomised, controlled, phase 3 trial. Lancet. 2020; 395(10232): 1278–1291, doi: 10.1016/S0140-6736(20)30262-2, indexed in Pubmed: 32305093.
97. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol. 2020; 38(25): 2849–2861, doi: 10.1200/JCO.19.03355, indexed in Pubmed: 32459600.
98. Xu W, Yang S, Tam C, et al. Earlier use of zanubrutinib monotherapy in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma is associated with greater efficacy: a pooled analysis from 3 studies. Blood. 2020; 136(Suppl 1): 36–37, doi: 10.1182/blood-2020-136236.
99. Le Gouill S, Morschhauser F, Chiron D, et al. Ibrutinib, obinutuzumab, and venetoclax in relapsed and untreated patients with mantle cell lymphoma: a phase 1/2 trial. Blood. 2021; 137(7): 877–887, doi: 10.1182/blood.2020008727, indexed in Pubmed: 33181832.
100. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. N Engl J Med. 2019; 380(23): 2225–2236, doi: 10.1056/NEJMoa1815281, indexed in Pubmed: 31166681.
101. Woyach JA, Blachly JS, Rogers KA, et al. Acalabrutinib in combination with venetoclax and obinutuzumab or rituximab in patients with treatment-naïve or relapsed/refractory chroniclymphocytic leukemia. Blood. 2020; 136(Suppl 1): 16–18, doi: 10.1182/blood-2020-136317.
102. Davids MS, Lampson BL, Tyekucheva S, et al. Updated safety and efficacy results from a phase 2 study of acalabrutinib, venetoclax and obinutuzumab (AVO) for frontline treatment of chronic lymphocytic leukemia (CLL). Blood. 2020; 136(Suppl 1): 20–21, doi: 10.1182/blood-2020-139864.
103. Tam CS, Flinn IW, Tedeschi A, et al. Zanubrutinib in combination with venetoclax for patients with treatment-naïve chronic lymphocytic leukemia or small lymphocytic lymphoma and del(17p): arm D of the SEQUOIA (BGB-3111-304) trial. Blood. 2020; 136(Supplement 1): 24–25, doi: 10.1182/blood-2020-134179.
104. Ntanasis-Stathopoulos I, Gavriatopoulou M, Fotiou D, et al. Current and novel BTK inhibitors in Waldenström's macroglobulinemia. Ther Adv Hematol. 2021; 12: 2040620721989586, doi: 10.1177/2040620721989586, indexed in Pubmed: 33613931.
105. Wierda WG, Dorritie KA, Munoz J, et al. Transcend CLL 004: phase 1 cohort of lisocabtagene maraleucel (liso-cel) in combination with ibrutinib for patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Blood. 2020; 136(Suppl 1): 39–40, doi: 10.1182/blood-2020-140622.

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Antibiotic prophylaxis: a chance to reduce infections during childhood leukemia treatment

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Abstract

The curability of childhood leukemia has significantly increased in recent years. The 5-year survival rate for children with acute lymphoblastic leukemia (ALL) now exceeds 90%, and is 65–70% for acute myeloblastic leukemia (AML) patients. Improvements in supportive care, better understanding of biological features of leukemia cells, better recognition of high-risk children, and optimization of treatment regimens through national and international collaboration have led to tremendous progress.

However, the most common and serious complications during antileukemic treatment are infections, mainly bacterial. Literature data shows that antibiotic prophylaxis reduces bacteremia and improves outcomes of adult patients during aggressive chemotherapy. However, the use of antibiotic prophylaxis in pediatric cancer is still controversial. There is a lack of evidence regarding its effectiveness and the best choice of antibiotic. In this review, we summarize the current knowledge on antibiotic prophylaxis in children with leukemia undergoing intensive chemotherapy, considering also antibiotic efficacy and resistance.

Key words: leukemia, antibiotic prophylaxis, children, levofloxacin, ciprofloxacin, moxifloxacin

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Introduction

The curability of childhood leukemia has significantly increased in recent years. The 5-year survival rate for children with acute lymphoblastic leukemia (ALL) now exceeds 90%, and is 65–70% for acute myeloblastic leukemia (AML) patients. Improvements in supportive care, better understanding of biological features of leukemia cells, better recognition of high-risk children, and optimization of treatment regimens through national and international collaboration, have led to tremendous progress [1–5].

However, despite the improvement in cure rates, the most common and serious complications during antileukemic treatment are infections, mainly bacterial [6–9]. Many studies show that Gram-positive bacteria are a significant etiological factor causing infections during ALL and AML treatment in children [10–14]. The most common complications related to infections are infections of the bloodstream, upper respiratory tract, gastrointestinal tract, and ear. Infections interrupt leukemia treatment and prolong hospitalization [15].

Treatment-related mortality is estimated to be 2–4% in current ALL trials, with infections accounting for the majority of deaths [9, 16]. Mortality ranges from 3% to 15% in patients treated for AML [17]. An increased risk of infection during chemotherapy is associated with the use of

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central catheters, prolonged neutropenia, the coexistence of Down's syndrome, female gender, young age, and also Caucasian race [9, 11, 15, 16, 18, 19].

Literature data shows that antibiotic prophylaxis reduces bacteremia and improves outcomes of adult patients during aggressive chemotherapy [20]. In 2016, the guidelines drawn up by the National Comprehensive Cancer Network (NCCN), which were approved in hematological malignancies, recommended fluoroquinolones prophylaxis for adult patients [21]. The use of antibiotic prophylaxis in pediatric cancer is still controversial, and there is a lack of clear evidence of its effectiveness and the best choice of antibiotic [22]. The 8th European Conference on Infections in Leukemia (ECIL-8) did not support routine antibiotic prophylaxis in patients with acute leukemias [23]. Empirical antibiotic therapy is a standard procedure in the treatment of children and adults, in the case of neutropenia at the beginning of fever or other infection-related symptoms [24–26].

However, many studies have shown that the prophylactic use of levofloxacin in patients with ALL and AML has resulted in a significant reduction in bacteremia [22, 27]. On the other hand, increasing bacterial resistance is a major concern with prophylaxis [28–31]. The introduction of antibiotic prophylaxis is associated with an increased risk of fluoroquinolone-resistant Gram-negative strains development, which has been demonstrated among patients receiving fluoroquinolone prophylaxis [28, 32]. The choice of antibiotic prophylaxis ought to be considered with local epidemiology-resistance patterns [33]. Additionally, potential adverse effects of antibiotic prophylaxis use, including drug toxicities, invasive fungal disease (IFD) and *Clostridioides difficile* (*C. difficile)* infection, have been described [34]. In this context, it is important to mention musculoskeletal negative side effects, which were observed one year after levofloxacin administration in children and have been described in a few studies [35, 36]. These negative side effects are discussed in the following sections.

In this review, we summarize the current knowledge of antibiotic prophylaxis in children with acute leukemias undergoing intensive chemotherapy, antibiotic efficacy and resistance.

Efficacy of antibiotic prophylaxis during leukemia treatment

Levofloxacin prophylaxis

Fluoroquinolones, as broad-spectrum antibiotics, are a significant class of antibacterial agents. Quinolones inhibit DNA synthesis by blocking the activity of DNA gyrase and topoisomerase IV. DNA gyrase is an enzyme which cannot be found in eukaryotic cells and it is a significant factor for bacterial growth. Levofloxacin, which is classified as the third-generation fluoroquinolone, shows stronger activity against Gram-positive strains than the second-generation group that includes ciprofloxacin [37]. Wolf et al. [22] described the efficacy of levofloxacin prophylaxis use during the induction phase in newly diagnosed patients with acute lymphoblastic leukemia between October 2007 and January 2016. A total of 344 pediatric patients participated in this study. Sixty-nine of those patients received the above-mentioned broad-spectrum antibiotic, and 102 of them received other antibiotics such as ciprofloxacin, cefepime and vancomycin. The remaining 173 patients received no antibiotic prophylaxis. The dose of antibiotic and the exposure duration were selected individually. This single-center cohort trial showed decreased episodes of fever, enterocolitis, bacteremia and general infections, including *Clostridium difficile* (*C. difficile)* infections, thanks to the use of levofloxacin during induction therapy. Children who received levofloxacin prophylaxis had a risk of bacterial infections that was more than halved compared to the group of patients who did not receive prophylaxis (15.9% vs. 37%) [22]. In the study by Sulis et al. [38], 230 patients, aged 1–21, with newly diagnosed ALL, received fluoroquinolones prophylaxis during induction chemotherapy. Children enrolled in that trial were receiving oral or intravenous levofloxacin or moxifloxacin. Therapy was applied to patients without fever. For patients who developed fever, the antibiotic was changed to a broad spectrum one and was administered intravenously. The results were compared to the other ALL Consortium Protocol 05-001 Dana-Farber Cancer Institute. The study showed a remarkable reduction of bacteremia incidents (10.9 vs. 24.4), especially those caused by Gram-negative strains, in pediatric patients undergoing the induction phase. The scientists noticed a significant reduction of infection frequency caused by *Streptocccus viridans* (*S. viridans*) and *Staphylococcus aureus* (*S. aureus*) [38].

In another trial by Alexander et al. [27], patients aged six months to 21 years with AML or relapsed ALL were randomly assigned to one of two groups. One group received levofloxacin prophylaxis (n = 100), while the other received no antibiotics (n = 100). Patients aged six months to five years received a dose of 10 mg/kg of levofloxacin twice a day, whereas patients older than five years received the same dose, but only once a day. The antibiotic was administered orally, or when this was not possible intravenously, on the first or third day of chemotherapy during two cycles. The percentage of bacteremia was much lower in the levofloxacin prophylaxis group of patients (21.9% vs. 43.4%), and there was a lower risk of neutropenia and fever (71.2% vs. 82.1%). Despite the positive effects of this antibiotic, a large number of infections were still observed — *S. viridans* and Gram-negative bacteremia. No influence on the risk of infection frequency caused by the mentioned pathogens suggests a dependence on the spectrum of activity or a lower absorption of the antibiotic by the oral administration. A significant conclusion of the study is that the use

of antibiotic was not associated with an increased risk of musculoskeletal toxic effects, IFD or *C. difficile* infection in the levofloxacin prophylaxis group of patients [27]. Moreover, in the study of Bradley et al. [36], the risk of cartilage injury caused by levofloxacin appears to be uncommon, and musculoskeletal events are clinically undetectable after five years of therapy or are reversible. An American retrospective cohort study conducted for four years enrolled patients aged 6 months to 21 years with AML and relapsed ALL. The pre-implementation group contained 63 patients, and the post-implementation group, in which patients were receiving levofloxacin prophylaxis, contained 72 patients. The main goal of this trial was to examine the influence on the bloodstream infection (BSI) risk and central line associated bloodstream infections (CLABSI), as a result of implementing levofloxacin prophylaxis. The authors reported that bacteremia cases caused by Gram-negative microorganisms significantly decreased in patients in the post-implementation group. Researchers observed more frequent BSI incidents due to levofloxacin-resistant Gram-negative strains presence. Therefore, it is important to pay attention to this possible problem, which is resistance, in the future [39]. The use of antibiotic prophylaxis brings on current-period expense, which is drug cost and antimicrobial resistance caused by the routine introduction of antibiotics [3, 40]. A cost-utility analysis by Maser et al. checked the cost-effectiveness of using levofloxacin prophylaxis and analyzed the influence on quality-adjusted life-years (QALY). In this evaluation, the researchers compared the estimated cost of the levofloxacin prophylaxis to no prophylaxis in pediatric patients with relapsed ALL or AML receiving chemotherapy. They showed that levofloxacin prophylaxis effects cost savings. The estimated cost associated with the use of levofloxacin prophylaxis was lower vs. no antibiotic prophylaxis, and also a small profit in QALY was noticed. This analysis revealed a satisfactory cost/benefit ratio analyzing 99.2% of the iterations [3]. A summary of the main levofloxacin prophylaxis use results is set out in Table I below.

Ciprofloxacin prophylaxis

Ciprofloxacin is a second-generation class and one of the most-frequently used quinolones, obtained by a fluoridation of the quinolone structure [37]. This substance is also a broad-spectrum antibiotic, which shows the most potent activity against Gram-negative strains of all the fluoroquinolones [41]. In a single-center cohort study, Yeh et al. conducted a trial on 113 children with ALL and 36 with AML from January 2010 to December 2012. Patients received ciprofloxacin orally twice a day at a dose of 300 mg/m^2 in the case of neutropenia without fever, and when was expected more than seven days of neutropenia during intensive treatment. The research showed less frequent episodes of febrile neutropenia, and also a lower frequency of bacteremia during the ciprofloxacin prophylaxis period. There were 24 episodes of febrile neutropenia altogether in the ciprofloxacin prophylaxis period, compared to 96 episodes in the preprophylaxis period in a group of ALL patients. Similar results were obtained in AML patients. The authors also mentioned that this study was too short to draw any definite conclusions on any effect on the development of microbiological resistance [4].

In the Laoprasopwattana et al. [48] double-blind, randomized study of 95 patients (aged 0.25–18 years) with lymphoma and ALL, 45 of them received ciprofloxacin and 50 of them received a placebo therapy. The study was conducted from April 2007 to May 2010. Children were receiving either 20 mg/kg/day ciprofloxacin prophylaxis orally or a placebo. Additionally, rectal swab cultures were taken, to check if the applied antibiotic had an influence on increasing resistance. Prophylaxis was started within five days after the first day of chemotherapy, and lasted until the fever had increased to more than 38.5°C once or to 38°C twice or until adverse effects of ciprofloxacin were present, such as rash, arthropathy or when the patient had an absolute neutrophil count of 1,000/μL after two weeks of applied treatment. A significant difference was observed in the proportion of those who developed fever (50% in the ciprofloxacin group vs. 73% in the placebo group) in patients who underwent induction prophylaxis, but not consolidation (in the whole group of 71 patients who had been diagnosed with neutropenia). Regarding negative side effects, both groups of patients developed similar adverse effects related to the underlying disease (arthritis) and caused by chemotherapy-related nausea. One patient developed a maculopapular rash after the first day of ciprofloxacin treatment that was directly linked to the administration of the antibiotic. More importantly, in all three cases of bacteremia, the causative strains were sensitive to ciprofloxacin [48].

In a further single-center retrospective study conducted between October 2002 and October 2008, 103 patients with AML were divided into groups and received cefepime or vancomycin, oral ciprofloxacin, cephalosporin, or cefepime with ciprofloxacin administered orally at a dose of 250 mg/m^2 twice a day. A control group received only oral cephalosporin or no prophylaxis. The average age at diagnosis was 8.7 years. The main positive effect of prophylaxis was a reduction in infection episodes and a lower frequency of bacteremia caused by *S. viridans* but without a significant effect on the occurrence of febrile neutropenia [7]. In one of the American studies, 45 pediatric patients with de novo and relapsed AML (35 vs. 10) were enrolled. The patients were treated using ciprofloxacin prophylaxis. Patients were infused with ciprofloxacin intravenously at a dose of 15 mg/kg twice daily in every chemotherapy cycle. The control group underwent no prophylaxis. The authors observed a reduction in bacteremia caused by Gram-negative strains (13.4% with no prophylaxis vs. 4.7% with ciprofloxacin prophylaxis), with no change in the

Table I. Comparison of efficacy of levofloxacin, ciprofloxacin and moxifloxacin prophylaxis in patients with acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML)

Antibiotic prophylaxis	Number of patients	Age range [years]	Type of leukemia	Article type	Main results	References
Levofloxacin	344	3–11.9	ALL	Retrospective cohort study	Decreased episodes of fever, enterocolitis, bacteremia	Wolf et al. 2017 [22]
Levofloxacin, moxifloxacin	230	1–21	ALL	Randomized study	Bacteremia reduction, especially caused by Gram-negative strains strains	Sulis et al. 2018 [38]
Levofloxacin	200	3–16	AML, ALL	Randomized study	Lower risk of bacteremia, neutropenia and fever	Alexander et al. 2018 [27]
Levofloxacin	135	0.5–21	AML, ALL	Retrospective cohort study	Lower bacteremia caused by Gram--negative microorganisms	Davis et al. 2022 [39]
Ciprofloxacin	149	0.2–18	ALL, AML	Single-center cohort study	Less frequent episodes of febrile neutropenia, lower frequency of bacteremia	Yeh et al. 2014 [42]
Ciprofloxacin	140	0.25–18	ALL	Double-blind, randomized study	Lower frequency of fever episodes	Laoprasopwattana et al. 2013 [48]
Ciprofloxacin	103	<1–21	AML	Single-center retrospective study	Reduction in infections and lower frequency of bacteremia caused by *Streptococcus viridans*, but with no significant effect on occurrence of febrile neutropenia	Inaba et al. 2014 [7]
Ciprofloxacin	45	3.3–15.4	AML	Retrospective observational study	Reduction in bacteremia caused by Gram-negative strains	Felsenstein et al. 2014 [43]
Ciprofloxacin	69	0–13	ALL	Retrospective study	Lower frequency of bacteremia, especially Gram-negative strains	Yousef et al. 2004 [44]
Moxifloxacin, levofloxacin	85	≥18	AML, ALL	Single-center cohort study	Similar numbers of neutropenia episodes in both types of prophylaxis, higher rates of Gram-negative infections in moxifloxacin group than in levofloxacin	Lee et al. 2018 [47]

frequency of febrile neutropenia, the number of infectious episodes and mortality. The authors suggested that this substance, as a supportive care component, should be further investigated [43]. Another retrospective study was conducted on 69 patients with newly diagnosed acute lymphoblastic leukemia at the age of 0–13 who received ciprofloxacin prophylaxis during delayed intensification. The study was conducted between 1997 and 2000 and the patients received 25 mg/kg of ciprofloxacin twice a day. The patients were receiving antibiotic prophylaxis during delayed intensification no. 1 (5 week of chemotherapy), no. 2 (20 week) and no. 3 (35–42 weeks). The patients were receiving antibiotic prophylaxis during delayed intensification no. 1 (5 week of chemotherapy), no. 2 (20 week) and no. 3 (35–42 weeks). An oral antibiotic was given for 9.21 days (mean) in delayed intensification no. 1 and no. 2. In no. 3 ciprofloxacin prophylaxis was administered for 28 days. Ciprofloxacin prophylaxis reduced duration of hospitalization in no. 1 and no. 2 while in no. 3 both the rate and duration of hospitalization were reduced. A lower frequency of bacteremia was noted especially considering Gram-negative strains [44]. A summary of the main ciprofloxacin prophylaxis use results is set out in Table I.

Moxifloxacin prophylaxis

The fourth-generation of quinolones class consists of moxifloxacin. Compared to levofloxacin and ciprofloxacin antibiotics, moxifloxacin is a rarely used fluoroquinolone, but is more potent against anaerobic and Gram-positive bacteria [45, 46]. A few studies have shown the benefits of moxifloxacin prophylaxis use during leukemia treatment in adult patients, as described by Lee et al. [47], who in

a single-center cohort analysis enrolled 85 patients with ALL and AML (16 vs. 69), mostly during the induction phase, who received moxifloxacin (40 patients) or levofloxacin (45 patients) prophylaxis. Patients aged 18 and older were included in the trial from July 2012 to October 2014 and they received 500 mg/day of levofloxacin or 400 mg/day of moxifloxacin. The authors focused on the frequency of febrile neutropenia cases, number of infections and infection-related mortality, when comparing the use of moxifloxacin to levofloxacin. Among the moxifloxacin group, 22 patients experienced neutropenia episodes compared to 30 patients within the levofloxacin group, which suggested similar frequency rates of febrile neutropenia. Furthermore, the duration of neutropenia ≥10 days was a high-risk factor for febrile neutropenia despite the use of fluoroquinolone prophylaxis. However, no differences in the frequency of infections or the mortality rate were noted in both groups in the hospital. The authors observed higher rates of Gram-negative infections in the moxifloxacin group (25% vs. 10%) than the levofloxacin group [47]. A summary of the main moxifloxacin prophylaxis use results is set out in Table I.

Conclusions

The main challenge during leukemia treatment is an increased risk of infection incidents, mainly bacterial, which can lead to treatment failure. Several studies have shown that the prophylactic use of fluoroquinolones reduces bacteremia episodes during the treatment of ALL and AML in children. Despite potential negative side effects and antibiotic resistance related to fluoroquinolone prophylaxis, numerous benefits appear to outweigh the disadvantages. For this reason, it may be used as a potent treatment agent in the future and be introduced to the standard treatment of ALL and AML. Larger, randomized trials are needed to confirm the long-term effectiveness of these antibiotics.

Authors' contributions

JZ, ML — conceptualization. JZ, NZ, WM — methodology. NZ, WM, ML — writing, original draft preparation. JZ, ML — review and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Malard F, Mohty M. Acute lymphoblastic leukaemia Lancet. 2020; 395: 1146–62.
2. Rubnitz JE, Kaspers GJL. How I treat pediatric acute myeloid leukemia. Blood. 2021; 138: 1009–18.
3. Maser B, Pelland-Marcotte MC, Alexander S, et al. Levofloxacin prophylaxis in hospitalized children with leukemia: a cost-utility analysis. Pediatr Blood Cancer. 2020; 67(10): e28643, doi: 10.1002/pbc.28643, indexed in Pubmed: 32785971.
4. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. Haematologica. 2020; 105(11): 2524–2539, doi: 10.3324/haematol.2020.247031, indexed in Pubmed: 33054110.
5. Kuhlen M, Klusmann JH, Hoell JI. Molecular approaches to treating pediatric leukemias. Front Pediatr. 2019; 7: 368, doi: 10.3389/fped.2019.00368, indexed in Pubmed: 31555628.
6. Sung L, Aplenc R, Alonzo TA, et al. Effectiveness of supportive care measures to reduce infections in pediatric AML: a report from the Children's Oncology Group. Blood. 2013; 121(18): 3573–3577, doi: 10.1182/blood-2013-01-476614, indexed in Pubmed: 23471307.
7. Inaba H, Gaur AH, Cao X, et al. Feasibility, efficacy, and adverse effects of outpatient antibacterial prophylaxis in children with acute myeloid leukemia. Cancer. 2014; 120(13): 1985–1992, doi: 10.1002/cncr.28688, indexed in Pubmed: 24677028.
8. Sung L, Buxton A, Gamis A, et al. Infections and association with different intensity of chemotherapy in children with acute myeloid leukemia. Cancer. 2009; 115(5): 1100–1108, doi: 10.1002/cncr.24107, indexed in Pubmed: 19156894.
9. O'Connor D, Bate J, Wade R, et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths on UKALL2003. Blood. 2014; 124(7): 1056–1061, doi: 10.1182/blood-2014-03-560847, indexed in Pubmed: 24904116.
10. Sung L, Lange BJ, Gerbing RB, et al. Microbiologically documented infections and infection-related mortality in children with acute myeloid leukemia. Blood. 2007; 110(10): 3532–3539, doi: 10.1182/blood-2007-05-091942, indexed in Pubmed: 17660380.
11. Zawitkowska J, Drabko K, Szmydki-Baran A, et al. Infectious profile in children with ALL during chemotherapy: a report of study group for infections. J Infect Chemother. 2019; 25(10): 774–779, doi: 10.1016/j.jiac.2019.04.005, indexed in Pubmed: 31101529.
12. Bochennek K, Hassler A, Perner C, et al. Infectious complications in children with acute myeloid leukemia: decreased mortality in multicenter trial AML-BFM 2004. Blood Cancer J. 2016; 6(1): e382, doi: 10.1038/bcj.2015.110, indexed in Pubmed: 26771808.
13. Lehrnbecher T, Varwig D, Kaiser J, et al. Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93. Leukemia. 2004; 18(1): 72–77, doi: 10.1038/sj.leu.2403188, indexed in Pubmed: 14586478.
14. Johannsen KH, Handrup MM, Lausen B, et al. High frequency of streptococcal bacteraemia during childhood AML therapy irrespective of dose of cytarabine. Pediatr Blood Cancer. 2013; 60(7): 1154–1160, doi: 10.1002/pbc.24448, indexed in Pubmed: 23281248.

15. Inaba H, Pei D, Wolf J, et al. Infection-related complications during treatment for childhood acute lymphoblastic leukemia. Ann Oncol. 2017; 28(2): 386–392, doi: 10.1093/annonc/mdw557, indexed in Pubmed: 28426102.
16. Christensen MS, Heyman M, Möttönen M, et al. Nordic Society of Paediatric Haematology and Oncology (NOPHO). Treatment-related death in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992-2001. Br J Haematol. 2005; 131(1): 50–58, doi: 10.1111/j.1365-2141.2005.05736.x, indexed in Pubmed: 16173962.
17. Klein K, van Litsenburg RRL, de Haas V, et al. Causes of early death and treatment-related death in newly diagnosed pediatric acute myeloid leukemia: Recent experiences of the Dutch Childhood Oncology Group. Pediatr Blood Cancer. 2020; 67(4): e28099, doi: 10.1002/pbc.28099, indexed in Pubmed: 31872548.
18. Afzal S, Ethier MC, Dupuis LL, et al. Risk factors for infection-related outcomes during induction therapy for childhood acute lymphoblastic leukemia. Pediatr Infect Dis J. 2009; 28(12): 1064–1068, doi: 10.1097/INF.0b013e3181aa6eae, indexed in Pubmed: 19773675.
19. Rogers AEJ, Eisenman KM, Dolan SA, et al. Risk factors for bacteremia and central line-associated blood stream infections in children with acute myelogenous leukemia: A single-institution report. Pediatr Blood Cancer. 2017; 64(3), doi: 10.1002/pbc.26254, indexed in Pubmed: 27616655.
20. Gafter-Gvili A, Fraser A, Paul M, et al. Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev. 2005; 1(4): CD004386, doi: 10.1002/14651858.CD004386.pub2, indexed in Pubmed: 16235360.
21. Baden LR, Swaminathan S, Angarone M, et al. Prevention and treatment of cancer-related infections, version 2.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016; 14(7): 882–913, doi: 10.6004/jnccn.2016.0093, indexed in Pubmed: 27407129.
22. Wolf J, Tang Li, Flynn PM, et al. Levofloxacin prophylaxis during induction therapy for pediatric acute lymphoblastic leukemia. Clin Infect Dis. 2017; 65(11): 1790–1798, doi: 10.1093/cid/cix644, indexed in Pubmed: 29020310.
23. Lehrnbecher T, Averbuch D, Castagnola E, et al. 8th European Conference on Infections in Leukaemia: 2020 guidelines for the diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or post-haematopoietic cell transplantation. Lancet Oncol. 2021; 22(6): e254–e269, doi: 10.1016/S1470-2045(20)30723-3, indexed in Pubmed: 33811813.
24. Lehrnbecher T, Robinson P, Fisher B, et al. International Pediatric Fever and Neutropenia Guideline Panel. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. J Clin Oncol. 2012; 30(35): 4427–4438, doi: 10.1200/JCO.2012.42.7161, indexed in Pubmed: 22987086.
25. Lehrnbecher T, Robinson P, Fisher B, et al. Guideline for the management of fever and neutropenia in children with cancer and hematopoietic stem-cell transplantation recipients: 2017 update. J Clin Oncol. 2017; 35(18): 2082–2094, doi: 10.1200/JCO.2016.71.7017, indexed in Pubmed: 28459614.
26. Averbuch D, Orasch C, Cordonnier C, et al. ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN. European guidelines for empirical antibacterial therapy for febrile neutropenic patients in the era of growing resistance: summary of the 2011 4th European Conference on Infections in Leukemia. Haematologica. 2013; 98(12): 1826–1835, doi: 10.3324/haematol.2013.091025, indexed in Pubmed: 24323983.
27. Alexander S, Fisher BT, Gaur AH, et al. Effect of levofloxacin prophylaxis on bacteremia in children with acute leukemia or undergoing hematopoietic stem cell transplantation: a randomized clinical trial. JAMA. 2018; 320(10): 995–1004, doi: 10.1001/jama.2018.12512, indexed in Pubmed: 30208456.
28. Castagnola E, Haupt R, Micozzi A, et al. Differences in the proportions of fluoroquinolone-resistant Gram-negative bacteria isolated from bacteraemic children with cancer in two Italian centres. Clin Microbiol Infect. 2005; 11(6): 505–507, doi: 10.1111/j.1469-0691.2005.01114.x, indexed in Pubmed: 15882204.
29. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Infectious Diseases Society of America, Infectious Diseases Society of Americaa. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2011; 52(4): 427–431, doi: 10.1093/cid/ciq147, indexed in Pubmed: 21205990.
30. Mikulska M, Averbuch D, Tissot F, et al. European Conference on Infections in Leukemia (ECIL). Fluoroquinolone prophylaxis in haematological cancer patients with neutropenia: ECIL critical appraisal of previous guidelines. J Infect. 2018; 76(1): 20–37, doi: 10.1016/j.jinf.2017.10.009, indexed in Pubmed: 29079323.
31. Lehrnbecher T, Sung L. Anti-infective prophylaxis in pediatric patients with acute myeloid leukemia. Expert Rev Hematol. 2014; 7(6): 819–830, doi: 10.1586/17474086.2014.965140, indexed in Pubmed: 25359519.
32. Bucaneve G, Micozzi A, Menichetti F, et al. Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) Infection Program. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med. 2005; 353(10): 977–987, doi: 10.1056/NEJMoa044097, indexed in Pubmed: 16148283.
33. Miedema KGE, Winter RH, Ammann RA, et al. Bacteria causing bacteremia in pediatric cancer patients presenting with febrile neutropenia–species distribution and susceptibility patterns. Support Care Cancer. 2013; 21(9): 2417–2426, doi: 10.1007/s00520-013-1797-4, indexed in Pubmed: 23579946.
34. Alexander S, Nieder M, Zerr DM, et al. Prevention of bacterial infection in pediatric oncology: what do we know, what can we learn? Pediatr Blood Cancer. 2012; 59(1): 16–20, doi: 10.1002/pbc.23416, indexed in Pubmed: 22102612.
35. Noel GJ, Bradley JS, Kauffman RE, et al. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J. 2007; 26(10): 879–891, doi: 10.1097/INF.0b013e3180cbd382, indexed in Pubmed: 17901792.
36. Bradley JS, Kauffman RE, Balis DA, et al. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Pediatrics. 2014; 134(1): e146–e153, doi: 10.1542/peds.2013-3636, indexed in Pubmed: 24918220.
37. Fàbrega A, Madurga S, Giralt E, et al. Mechanism of action of and resistance to quinolones. Microb Biotechnol. 2009; 2(1): 40–61, doi: 10.1111/j.1751-7915.2008.00063.x, indexed in Pubmed: 21261881.
38. Sulis ML, Blonquist TM, Stevenson KE, et al. Effectiveness of antibacterial prophylaxis during induction chemotherapy in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2018; 65(5): e26952, doi: 10.1002/pbc.26952, indexed in Pubmed: 29319209.
39. Davis A, Stevens AM, Brackett J, et al. Levofloxacin prophylaxis for pediatric leukemia patients: Longitudinal follow-up for impact on health care-associated infections. Pediatr Blood Cancer. 2022; 69(7): e29525, doi: 10.1002/pbc.29525, indexed in Pubmed: 35029328.

40. Shrestha P, Cooper BS, Coast J, et al. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. Antimicrob Resist Infect Control. 2018; 7: 98, doi: 10.1186/s13756-018-0384-3, indexed in Pubmed: 30116525.
41. LeBel M. Ciprofloxacin: chemistry, mechanism of action, resistance, antimicrobial spectrum, pharmacokinetics, clinical trials, and adverse reactions. Pharmacotherapy. 1988; 8(1): 3–33, doi: 10.1002/j.1875-9114.1988.tb04058.x, indexed in Pubmed: 2836821.
42. Yeh TC, Liu HC, Hou JY, et al. Severe infections in children with acute leukemia undergoing intensive chemotherapy can successfully be prevented by ciprofloxacin, voriconazole, or micafungin prophylaxis. Cancer. 2014; 120(8): 1255–1262, doi: 10.1002/cncr.28524, indexed in Pubmed: 24415457.
43. Felsenstein S, Orgel E, Rushing T, et al. Clinical and microbiologic outcomes of quinolone prophylaxis in children with acute myeloid leukemia. Pediatr Infect Dis J. 2015; 34(4): e78–e84, doi: 10.1097/INF.0000000000000591, indexed in Pubmed: 25764103.
44. Yousef AA, Fryer CJH, Chedid FD, et al. A pilot study of prophylactic ciprofloxacin during delayed intensification in children with acute lymphoblastic leukemia. Pediatr Blood Cancer. 2004; 43(6): 637–643, doi: 10.1002/pbc.20065, indexed in Pubmed: 15390313.
45. Guan Y, Liu Y. Meta-analysis on effectiveness and safety of moxifloxacin in treatment of multidrug resistant tuberculosis in adults. Medicine (Baltimore). 2020; 99(25): e20648, doi: 10.1097/MD.0000000000020648, indexed in Pubmed: 32569195.
46. Principe L, Sanson G, Luzzati R, et al. Time to reconsider moxifloxacin anti-anaerobic activity? J Chemother. 2022 [Epub ahead of print]: 1–2, doi: 10.1080/1120009X.2022.2106637, indexed in Pubmed: 35947127.
47. Lee P, Knoebel RW, Pisano J, et al. Moxifloxacin versus levofloxacin for antibacterial prophylaxis in acute leukemia patients. J Oncol Pharm Pract. 2019; 25(3): 758–761, doi: 10.1177/1078155217752074, indexed in Pubmed: 29310512.
48. Laoprasopwattana K, Khwanna T, Suwankeeree P, et al. Ciprofloxacin reduces occurrence of fever in children with acute leukemia who develop neutropenia during chemotherapy. Pediatr Infect Dis J. 2013; 32(3): e94–e98, doi: 10.1097/INF.0b013e3182793610, indexed in Pubmed: 23080291.

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REVIEW ARTICLE

VIA MEDICA

Association between tumor markers and anemia: a short review

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Abstract

Tumor markers are a group of molecules used to diagnose certain diseases, including cancer. These molecules can alter cellular pathways, including those associated with some anemias, by expressing or influencing certain cellular mediators. The present study is based on data obtained from the PubMed database (1970–2019) using the key words 'tumor markers', 'anemia' and 'iron'. We found that some tumor markers can affect hepcidin expression and iron uptake by altering cell pathways. Several other tumor markers also increase in some anemias, so that they can sometimes be used to diagnose and confirm the type of anemia. The role of some tumor markers remains unclear despite the increase in some anemias. In general, some tumor markers are involved in the pathophysiology of a number of anemias or help diagnose anemia. However, studies of the role of tumor markers in the diagnosis, development or progression of anemias have been very limited.

Key words: tumor markers, anemia, iron, hepcidin

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Introduction

Tumor markers refer to a group of molecules that help to detect cancer and predict how cancers behave in the body [1, 2]. These molecules have impacts not only in terms of disease diagnosis in asymptomatic patients, but also in differential diagnosis in patients with symptoms [2, 3]. In fact, genetic changes in tumor cells affect the gene expression pattern of cells and surrounding tissues and lead to the formation of some tumor markers. However, only a small number of tumor markers are used for disease diagnosis [4, 5]. Furthermore, these genetic alterations affect parts of cellular pathways via expressing certain proteins or cellular mediators [6]. Given that the pathophysiology of anemia is cell-dependent, it is possible that a group of tumor markers could cause and promote anemia. In this study, we aimed to investigate the role of tumor markers in the formation and progression of anemia.

Cancer antigen 15-3

Pernicious anemia is an autoimmune disorder characterized by gastric atrophy, decreased gastric acid and pepsinogen secretion, increased serum gastrin concentration, and malabsorption of vitamin B12. The detection of tumor markers in serum represents a useful tool in the diagnosis and follow-up

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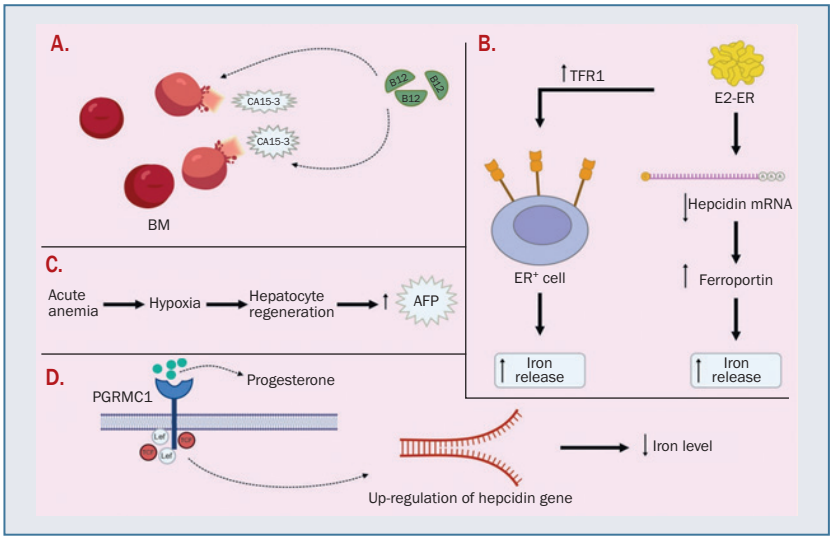

Figure 1. Role of tumor markers in some anemias: **A.** Decrease of B12 vitamin causes increase of cancer antigen (Ca) 15-3; **B.** 17β-estradiol-estrogen receptor (E2-ER) complex increases iron release to circulation by an increase of transferrin receptor-1 (TFR1) expression in ER+ cells, also E2-ER complex increases ferroportin activity and iron release by suppression of estrogen responsive element region (ERE) in promoter of hepcidin gene; **C.** Acute anemia with creation of hypoxia affects hepatocyte regeneration and leads to increase of alpha-fetoprotein (AFP); **D.** Progesterone-progesterone receptor membrane component 1 (PGRMC1) complex can reduce iron levels through SFK (Src family kinases) pathway and with help of T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) by increasing hepcidin gene expression

of malignant gastrointestinal disorders [7, 8]. Cancer antigen 15-3 (CA 15-3) tumor marker has long been used as a proven test for the diagnosis, as well as the staging, of adenocarcinomas, especially breast cancers. Studies have shown that there is an increase in CA 15-3 levels in the serum of most pernicious patients and this is not related to the *Helicobacter pylori* infection. Screening of megaloblastic anemia patients' serum has shown an unexpected increase in CA 15-3 that is not associated with the presence or progression of breast cancer [9, 10]. Elevated CA 15-3 levels in both gastrectomy patients with a limited portion of normal gastric mucosa, and in non-gastrectomy patients with atrophic mucosa, suggest that this finding is associated with cobalamin deficiency, but not gastric disease. The association between levels of CA 15-3 and serum hemoglobin, lactate dehydrogenase (LDH) and B12 vitamin suggests that accelerated production of CA 15-3 may be consistent with the severity of megaloblastic anemia.

The increase in CA 15-3 levels in bone marrow supernatants suggests megaloblastic bone marrow as the site of increased CA 15-3 production. Thus, the increase in serum CA 15-3 levels in patients with megaloblastic anemia is probably due to B12 deficiency, which is secreted by apoptotic megaloblastic erythroblasts (Figure 1A, Table I). This increase does not appear to be related to breast cancer or other cancers [11].

Alpha-fetoprotein

Alpha-fetoprotein (AFP) is a tumor-related embryonic protein that is classified as an 'oncofetal' protein due to its dual role in tumor and embryonic activity. Physiologically, different AFP isoforms can act as a tumor regulator (growth enhancer or inhibitor) [12].

Much of the growth regulation is mediated by receptor-mediated endocytosis, in which an AFP-cell surface receptor complex is located inside the tumor [13, 14].

Adult liver oval cells appear to be the only source of AFP synthesis/secretion, and there is almost no AFP storage in liver parenchymal cells [15]. Studies have shown that patients with the bilateral mutation *FANCD1/BRCA2* had higher serum AFP levels than patients with other Fanconi anemia (FA) genotypes. In this study, patients had a steady increase in AFP levels for one year after hematopoietic cell transplantation (HSC), with the exception of one patient who returned to normal after one year. A percentage of patients with normal levels of normal AFP showed an increase in the level of this factor after one year of HSC. However, the absence of high AFP does not rule out FA, and all patients still need diagnostic chromosomal fragility testing [16].

Hypoxic status due to acute anemia may affect liver cell regeneration and lead to increased AFP synthesis because shortly after acute bleeding, a moderate increase in serum AFP is observed in these patients (Figure 1C, Table I). Therefore, an increase in serum AFP is important in patients with severe anemia without liver cell damage [17].

Calcitonin

The physiological role of gastrin has been suggested as a hormonal mediator of calcitonin secretion in the intestine

Table I. Role of tumor markers in anemia

Tumor marker	Role	Ref.
Cancer antigen (CA) 15-3	B12 deficiency increases serum levels of CA-15.3 in patients with megaloblastic anemia secreted by megaloblastic apoptotic erythroblasts	[11]
Alpha-fetoprotein (AFP)	Hypoxic status due to acute anemia may affect liver cell regeneration and lead to increased AFP synthesis; some studies have shown that patients with bilateral mutation *FANCD1/ /BRCA2* had higher serum AFP levels than patients with other Fanconi anemia genotypes	[16, 17]
Calcitonin	An increase in calcitonin has been reported in some people with pernicious anemia, but exact information on cause is not yet available	[22, 23]
Estrogen receptor	Estrogen-estrogen receptor (E2-ER) complex participates in iron metabolism by acting on hepcidin and ferroportin	[33]
Progesterone receptor membrane component 1 (PGRMC1)	Progesterone-PGRMC1 complex can reduce iron levels by increasing hepcidin expression	[36, 37]

[18]. Intravenous or intramuscular injection of pentagastrin (synthetic human gastrin-17) increases serum calcitonin concentrations in animals. No precise information is available on the ability of pentagastrin to stimulate calcitonin secretion in humans. *In vivo* injection of pentagastrin increases both serum and urine calcitonin by two to three times. Patients with pernicious anemia (PA) have high levels of endogenous gastrin, possibly due to achloridria (the absence of hydrochloric acid in gastric secretions) [19, 20]. In contrast, in another study, an increase in serum calcitonin was observed in 25% of patients with PA and no association with serum gastrin levels was shown. However, such an association may be complex because calcitonin reduces gastric acid and serum gastrin. Even so, no explanation is apparent for the increase in calcitonin concentration, and the main regulator of calcitonin secretion is still unknown [21]. Some studies have shown that in long-term hypergastrinemic conditions, such as PA for duodenal ulcers, there is no change in the normal fasting level of serum calcitonin, while in some other studies, calcitonin levels have increased in some patients with PA. A study examining the relationship between serum gastrin concentration and serum calcitonin in patients with PA (Table 1) and healthy individuals showed that patients with PA have normal serum calcitonin concentrations despite very high serum gastrin levels [22, 23].

Increases in serum calcitonin concentrations after food stimulation have been reported in animals and patients with duodenal ulcers, possibly due to increased serum gastrin concentrations. In normal people, no increase in calcitonin has been observed after eating. In one study, there was a transient increase in serum calcitonin in five PA patients 5–10 minutes after a meal, whereas in healthy subjects, no increase was observed. The reason for the initial increase in serum calcitonin in some PA patients is unknown, but it is probably not due to gastrin, because the increase in serum calcitonin started before any increase in serum gastrin [24].

Estrogen receptor

Estrogen receptor (ER) is one of the markers that is used as a measure in breast cancer. ER is known as a tumor marker and is used to determine prognosis and treatment goals for breast cancer [25]. Estrogen as a sex hormone plays an important role in reproductive development and female characteristics. Evidence suggests that estrogen also has an important role in the development and growth of breast cancer [26]. 17β-estradiol (E2), the most active form of estrogen, is expressed highly in young women, while iron level (Fe) is low ain this group, but the opposite is the case in older postmenopausal women, since they usually have low E2 and high iron levels, which could indicate the possible role played by E2 in iron level alteration [27, 28]. Hepcidin as an iron-regulating peptide hormone inhibits iron entry into the plasma by the degradation of the iron exporter ferroportin [29]. Studies have shown that hepcidin mRNA in human liver HuH7 and HepG2 cells is suppressed by E2 treatment through binding E2 to ER. Suppression of hepcidin by E2-ER complex acts directly on the estrogen-responsive element region (ERE) in the promoter of the hepcidin gene [27, 30, 31]. With decreased hepcidin levels, ferroportin activity increases, and subsequently iron release escalates (Figure 1B). Also tissue iron decreases due to its over excretion. E2-ER complex also increases the expression of transferrin receptor-1 (TfR1) in ER+ MCF-7 cells that were treated with E2, which leads to rises in the amounts of iron released (Figure 1B) [30, 32]. Studies have shown that the G-coupled protein 30 (GPR30)–bone morphologic protein 6 (BMP6) pathway, which is separate from the ER-mediated signaling pathway, is involved in E2-induced hepcidin expression in mice. As an estrogen membrane receptor, GPR30 regulates iron metabolism through affecting hepatic hepcidin expression. As a result of this regulation, ferroportin is upregulated in the duodenum and hepcidin mRNA expression is decreased in HepG2 cells, and subsequently iron release

increases [33]. Accordingly, estrogen participates in iron metabolism by acting on hepcidin and ferroprotein (Table I).

The interaction of the E2-ER complex with iron metabolism at the systemic level is still not fully understood. Although various factors can play a role in iron level alteration in women, the role of estrogen and its receptor is a possible factor. According to animal studies, it seems that ER as a tumor marker plays a role in iron metabolism by affecting the expression of hepcidin and subsequently ferroportin. Confirming the role of ER in iron metabolism will require more extensive studies in the future.

Progesterone receptor membrane component 1

Progesterone receptor membrane component 1 (PGRMC1) has been linked to multiple cancers, such as breast cancer [34]. PGRMC1 is a small hemoprotein that can play a role in the differentiation of the erythroid lineage. PGRMC1 has a single transmembrane domain and a heme-binding site. Increased progesterone by binding to PGRMC1 can reduce iron levels through the Src family kinases (SFK) pathway also, with the help of T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors, via more expression of hepcidin gene (Figure 1D) [35]. Hepcidin can deliver heme to ferrochelatase (FECH) and apo-hemoprotein. In addition, hepcidin with PGRMC1 can be introduced as a chaperone and regulator for FECH.

PGRMC1 can also act as a sensor to regulate heme production. This hemoprotein directly coordinates FECH activity with stabilizing or destabilizing mitochondrial heme contents. Therefore, progesterone can reduce iron levels by increasing hepcidin expression during binding to PGRMC1 [36, 37].

Conclusions

Tumor markers are a group of molecules that are used to diagnose certain diseases. Some tumor markers can affect iron uptake and metabolism or play a role in the identification, development, and progression of some anemias. Elevated CA 15-3 levels are probably associated with vitamin B12 deficiency and megaloblastic anemia. Checking AFP levels can help diagnose Fanconi anemia. An increase in calcitonin has been reported in some people with PA but exact information on the cause is not yet available. E2-ER can increase iron exportation to blood circulation by affecting and suppressing hepcidin, whereas progesterone — PGRMC1 decreases iron levels by increasing hepcidin expression. So far, limited studies have been conducted on the relationship between tumor marker levels and types of anemia, which limits our knowledge in this area. Therefore, further studies on this topic are needed.

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Authors' contributions

MJ conceived manuscript and revised it. NS, BM and MA wrote manuscript and prepared figure.

Conflict of interest

The authors declare no conflict of interest.

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Data availability

All data has been included in manuscript and will be made available upon publication.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Duffy MJ. Clinical uses of tumor markers: a critical review. Crit Rev Clin Lab Sci. 2008; 38(3): 225–262, doi: 10.1080/20014091084218.
2. Duffy MJ. Tumor markers in clinical practice: a review focusing on common solid cancers. Med Princ Pract. 2013; 22(1): 4–11, doi: 10.1159/000338393, indexed in Pubmed: 22584792.
3. Bevilacqua V, Chan MK, Chen Y, et al. Pediatric population reference value distributions for cancer biomarkers and covariate-stratified reference intervals in the CALIPER cohort. Clin Chem. 2014; 60(12): 1532–1542, doi: 10.1373/clinchem.2014.229799, indexed in Pubmed: 25261558.
4. Diamandis EP, Fritche HA, Lilja H, et al (ed). Tumor markers: physiology, pathobiology, technology, and clinical applications. AACC Press, Washington, DC 2002.
5. Sharma S. Tumor markers in clinical practice: general principles and guidelines. Indian J Med Paediatr Oncol. 2009; 30(1): 1–8, doi: 10.4103/0971-5851.56328, indexed in Pubmed: 20668599.
6. Yao F, Zhang C, Du W, et al. Identification of gene-expression signatures and protein markers for breast cancer grading and staging. PLoS One. 2015; 10(9): e0138213, doi: 10.1371/journal.pone.0138213, indexed in Pubmed: 26375396.
7. Bidart JM, Thuillier F, Augereau C, et al. Kinetics of serum tumor marker concentrations and usefulness in clinical monitoring. Clin Chem. 1999; 45(10): 1695–1707, indexed in Pubmed: 10508114.
8. Karlson BM, Ekbom A, Wacholder S, et al. Cancer of the upper gastrointestinal tract among patients with pernicious anemia: a case-cohort study. Scand J Gastroenterol. 2000; 35(8): 847–851, doi: 10.1080/003655200750023228, indexed in Pubmed: 10994624.

9. Cheung KL, Graves CR, Robertson JF. Tumour marker measurements in the diagnosis and monitoring of breast cancer. Cancer Treat Rev. 2000; 26(2): 91–102, doi: 10.1053/ctrv.1999.0151, indexed in Pubmed: 10772967.
10. Zimmerman RL, Fogt F, Goonewardene S. Diagnostic value of a second generation CA 15-3 antibody to detect adenocarcinoma in body cavity effusions. Cancer. 2000; 90(4): 230–234, doi: 10.1002/1097-0142(20000825)90:4<230::aid-cncr5>3.0.co;2-6, indexed in Pubmed: 10966563.
11. Symeonidis A, Kouraklis-Symeonidis A, Apostolopoulos D, et al. Increased serum CA-15.3 levels in patients with megaloblastic anemia due to vitamin B12 deficiency. Oncology. 2005; 67(5-6): 359–367, doi: 10.1159/000082919.
12. Mizejewski GJ. alpha-fetoprotein as a biologic response modifier: relevance to domain and subdomain structure. Proc Soc Exp Biol Med. 1997; 215(4): 333–362, doi: 10.3181/00379727-215-44143, indexed in Pubmed: 9270717.
13. Mizejewski GJ. Review of the adenocarcinoma cell surface receptor for human alpha-fetoprotein; proposed identification of a widespread mucin as the tumor cell receptor. Tumour Biol. 2013; 34(3): 1317–1336, doi: 10.1007/s13277-013-0704-4, indexed in Pubmed: 23446764.
14. Mizejewski GJ. The alpha-fetoprotein third domain receptor binding fragment: in search of scavenger and associated receptor targets. J Drug Target. 2015; 23(6): 538–551, doi: 10.3109/1061186X.2015.1015538, indexed in Pubmed: 25766080.
15. Sell S. Heterogeneity of alpha-fetoprotein (AFP) and albumin containing cells in normal and pathological permissive states for AFP production: AFP containing cells induced in adult rats recapitulate the appearance of AFP containing hepatocytes in fetal rats. Oncodev Biol Med. 1980; 1(2): 93–105, indexed in Pubmed: 6169057.
16. Salem B, Mitchell R, DeFor TE, et al. Elevations in serum alpha fetoprotein levels in patients with Fanconi anaemia. Br J Haematol. 2019; 184(6): 1032–1035, doi: 10.1111/bjh.15223, indexed in Pubmed: 29676781.
17. Masahiro F, Haruto U. Elevation of serum alpha-fetoprotein in anemic patients. Clin Chim Acta. 1981; 113(1): 7–11, doi: 10.1016/0009-8981(81)90434-4.
18. Becker KL, Silva OL, Cyrus J, et al. Hypercalcitonemia in pernicious anemia. Experientia. 1980; 36(11): 1330–1331, doi: 10.1007/BF01969618, indexed in Pubmed: 7449924.
19. McGuigan JE, Trudeau WL. Serum gastrin concentrations in pernicious anemia. N Engl J Med. 1970; 282(7): 358–361, doi: 10.1056/NEJM197002122820703, indexed in Pubmed: 5411129.
20. Thrall JH. Parathormone and calcitonin radioimmunoassay in various medical and osteoarticular disorders. P. Franchimont and G. Heynen. Philadelphia, Lippincott, 1976, 134 pp, $15.00. JNM. 1976; 17(12): 1118.
21. Franchimont P, Heynen G. Parathormone and calcitonin radioimmunoassay in various medical and osteoarticular disorders. Lippincott Williams & Wilkins, Philadelphia 1976.
22. Brandsborg M, Nielsen HE, Brandsborg O, et al. The role of serum gastrin in the secretion of calcitonin: studies in patients with pernicious anaemia and in healthy subjects. Scand J Gastroenterol. 1980; 15(1): 23–28, doi: 10.3109/00365528009181426, indexed in Pubmed: 7367817.
23. Deftos LJ, Roos BA, Bronzert D, et al. Immunochemical heterogeneity of calcitonin in plasma. J Clin Endocrinol Metab. 1975; 40(3): 409–412, doi: 10.1210/jcem-40-3-409, indexed in Pubmed: 163843.
24. Nozaki K, Noda S, Obi S, et al. Secretion of gastrin and calcitonin after ingestion of meat extract in patients with peptic ulcer. Endocrinol Jpn. 1976; 23(1): 83–86, doi: 10.1507/endocrj1954.23.83, indexed in Pubmed: 945157.
25. Lindström LS, Karlsson E, Wilking UM, et al. Clinically used breast cancer markers such as estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 are unstable throughout tumor progression. J Clin Oncol. 2012; 30(21): 2601–2608, doi: 10.1200/JCO.2011.37.2482, indexed in Pubmed: 22711854.
26. Bhardwaj P, Au CC, Benito-Martin A, et al. Estrogens and breast cancer: mechanisms involved in obesity-related development, growth and progression. J Steroid Biochem Mol Biol. 2019; 189: 161–170, doi: 10.1016/j.jsbmb.2019.03.002, indexed in Pubmed: 30851382.
27. Jian J, Pelle E, Huang X. Iron and menoause: does increased iron affect the health of ostmenoausal women? Mary Ann Liebert, Inc., New Rochelle, NY 2009.
28. Miller EM. Hormone replacement therapy affects iron status more than endometrial bleeding in older US women: A role for estrogen in iron homeostasis? Maturitas. 2016; 88: 46–51, doi: 10.1016/j.maturitas.2016.03.014, indexed in Pubmed: 27105697.
29. Ganz T, Nemeth E. Hepcidin and iron homeostasis. Biochim Biophys Acta. 2012; 1823(9): 1434–1443, doi: 10.1016/j.bbamcr.2012.01.014, indexed in Pubmed: 22306005.
30. Yang Q, Jian J, Katz S, et al. 17β-estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site. Endocrinology. 2012; 153(7): 3170–3178, doi: 10.1210/en.2011-2045, indexed in Pubmed: 22535765.
31. Hilton HN, Clarke CL, Graham JD. Estrogen and progesterone signalling in the normal breast and its implications for cancer development. Mol Cell Endocrinol. 2018; 466: 2–14, doi: 10.1016/j.mce.2017.08.011, indexed in Pubmed: 28851667.
32. Dai J, Jian J, Bosland M, et al. Roles of hormone replacement therapy and iron in proliferation of breast epithelial cells with different estrogen and progesterone receptor status. Breast. 2008; 17(2): 172–179, doi: 10.1016/j.breast.2007.08.009, indexed in Pubmed: 17928227.
33. Ikeda Y, Tajima S, Izawa-Ishizawa Y, et al. Estrogen regulates hepcidin expression via GPR30-BMP6-dependent signaling in hepatocytes. PLoS One. 2012; 7(7): e40465, doi: 10.1371/journal.pone.0040465, indexed in Pubmed: 22792339.
34. Pedroza DA, Rajamanickam V, Subramani R, et al. Progesterone receptor membrane component 1 promotes the growth of breast cancers by altering the phosphoproteome and augmenting EGFR/PI3K/AKT signalling. Br J Cancer. 2020; 123(8): 1326–1335, doi: 10.1038/s41416-020-0992-6, indexed in Pubmed: 32704174.
35. Piel RB, Shiferaw MT, Vashisht AA, et al. A novel role for progesterone receptor membrane component 1 (PGRMC1): a partner and regulator of ferrochelatase. Biochemistry. 2016; 55(37): 5204–5217, doi: 10.1021/acs.biochem.6b00756, indexed in Pubmed: 27599036.
36. Li X, Rhee DK, Malhotra R, et al. Progesterone receptor membrane component-1 regulates hepcidin biosynthesis. J Clin Invest. 2016; 126(1): 389–401, doi: 10.1172/JCI83831, indexed in Pubmed: 26657863.
37. Zhao N, Zhang AS, Enns CA. Iron regulation by hepcidin. J Clin Invest. 2013; 123(6): 2337–2343, doi: 10.1172/JCI67225, indexed in Pubmed: 23722909.

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Prognostic impact of lipid profile in adult Egyptian acute leukemia patients

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Abstract

Introduction: Acute leukemia is a malignant disorder which results from clonal proliferation of lymphoid and myeloid blast cells. Several studies have reported changes in lipid metabolism at the time of diagnosis of leukemia. Although investigators have reported decreased total cholesterol, decreased high-density lipoprotein, and elevated triglyceride (TG) in leukemic patients, there is a lack of agreement about these changes among different types of leukemia and between children and adult patients, in addition to different data about their impacts on prognosis. In this study, lipid profile has been examined at the time of diagnosis of acute leukemia in order to correlate it with response to therapy.

Material and methods: This is a prospective study carried out at the Oncology Center at Mansoura University, Egypt between 2018 and 2019. Fifty patients newly diagnosed with *de novo* acute leukemia were included. Thirty-four patients were diagnosed with acute myeloid leukemia (AML) (68%), while 16 patients were diagnosed with acute lymphoblastic leukemia (ALL) (32%). Lipid profile and body mass index (BMI) data was obtained.

Results: Overweight/obese patients showed a more statistically significant association with female patients than with male patients ($p = 0.009$). By comparing the lipid profile between overweight/obese patients and other patients, there was no statistically significant association. 76.7% of AML patients were overweight or obese ($p = 0.015$), and 81.3% of ALL patients showed hypertriglyceridemia ($p = 0.014$). There was no statistically significant association between lipid profile and complete response (CR) rate; however, there was a marginally significant association between non-CR rate and overweight and obese patients ($p = 0.051$). In addition, there was no impact of BMI or lipid profile on overall survival among acute leukemia patients.

Conclusions: Female, and acute myeloid leukemia, patients were more commonly associated with overweight and obesity, and high TG level was found to be associated with acute lymphoid leukemia. Changes in lipid profile showed no impact on complete response rate or on overall survival in acute leukemia patients.

Key words: acute leukemia, AML, ALL, TG, CR

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Introduction

An association between hypocholesterolemia and various malignant tumors such as colon, pancreatic, ovarian, and lung cancer has been determined [1]. In addition, alterations in lipid profile in hematological malignancies including leukemia have been demonstrated in the course of disease and treatment. Acute leukemia is a neoplastic transformation where there is proliferation of hematopoietic progenitor cells in the bone marrow, blood and extramedullary sites. Several studies have reported changes in the lipid's metabolism at the time of a diagnosis of leukemia. Although investigators have reported decreased total cholesterol (TC), decreased high-density lipoprotein (HDL), and elevated triglyceride (TG) in leukemic patients, there is uncertainty about these changes regarding different types of leukemia and differences between children and adults [2]. Some studies have demonstrated that lipid profile in patients with leukemia can be considered as a possible prognostic factor, and might be used as a simple test to follow the response to chemotherapy [3–5]. This study was carried out to evaluate the lipid profile among Egyptian patients who had been diagnosed with acute myeloid and lymphoid leukemia, at the time of their diagnosis and the impacts on their prognosis.

Material and methods

This is a prospective study conducted on patients with acute leukemia admitted to the Oncology Center at Mansoura University, Egypt in 2018 and 2019.

A total of 50 adult patients (25 males and 25 females), diagnosed with *de novo* acute leukemia on the basis of peripheral blood morphology, bone marrow (BM), and flow cytometry,were included. Immunophenotyping (Coulter Epics XL Flow Cytometer PN 42372238 B, Coulter Corporation, Miami, FL, USA) was used to confirm the diagnosis; Cyt. MPO, CD13, CD33, and CD117 were the primary panel for myeloid lineage, CD14, CD36, and CD11b for M4 and M5, CD61 and glycophorin A for M6, and CD41 and CD42 for M7. CD20, CD10, CD79a, CD3, CD5, CD7, and TDT were the panel for lymphoid lineage.

Blood specimens for lipid profile assessment were collected after a conclusive diagnosis, and segregated serum was kept in a freezer for lipid testing. Blood specimens were collected without anticoagulant and serum was separated from red blood cells (RBCs) by centrifugation. Triglyceride and total cholesterol were determined using laboratory kits. Direct analysis of high-density lipoprotein cholesterol (HDL-C) was done using kits (ELITECH, France). LDL-cholesterol direct SL kits also from ELITECH were used for direct analysis of low-density lipoprotein cholesterol (LDL-C). All measurements were done by an open system HITACHI 902 autoanalyzer automatically.

All patients received intensive induction therapy (there was no control group): cytarabine 100 mg/m^2/day for 5–7 days intravenous (i.v.) continuous infusion and doxorubicin 30 mg/m^2 for 2–3 days i.v. for acute myeloid leukemia (AML), Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) or augmented BFM (Berlin–Frankfurt–Münster) for acute lymphoblastic leukemia (ALL) [max. chemotherapy dosage not exceeding surface area (SA) = 2]. Patients were classified according to their body mass index (BMI) as overweight and obese patients (29 patients), or others (16).

The study design was approved by The Institutional Review Board of the Faculty of Medicine, Mansoura University, Egypt (code number: R.19.09.607)

Statistical analysis

Data was analyzed using SPSS (Statistical Package for Social Scientists) 16. A two-tailed p value of <0.05 was considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean and standard deviation or the median and range was used. An association between categorical variables was tested by a Chi square test, or by Fishers exact test if the assumptions of Chi square were violated. Survival and relapse-free survival analyses were calculated using the Kaplan-Meier method. Comparisons of survival were performed using a log-rank test.

Results

This prospective study analyzed 50 *de novo* acute leukemia patients [25 (50%) males, and 25 (50%) females]. Mean age was 39.5 years (range 16–69). 34 (68%) patients were AML, and 16 (32%) were ALL. Five patients (10%) had diabetes, and eight (16%) had hypertension. In the ALL patients, t(9;22) was done in four patients [positive in one (25%) and negative in three (75%)], and 11q23 re-arrangement was done in four patients (negative in all). In the AML patients, inv(16) was done in 12 patients [positive in three (25%) and negative in nine (75%)], t(8;21) was done in 11 patients [positive in two (18.2%) and negative in nine (81.8%)], and t(15;17) was done in three AML (M3) patients [positive in all (100%)]. 29 (58%) patients were overweight or obese based on their body mass index (BMI). Basic data is set out in Table I.

Overweight/obese patients showed a statistically more significant association with female patients than male patients (65.5%, p = 0.009). Female patients were statistically significantly associated with high cholesterol level (64%, p = 0.048), low HDL level (60%, p = 0.023), and elevated LDL level (60%, p = 0.047) (Table II).

Table I. Descriptive data of acute leukemia patients

Variables		No	[%]
Gender	M:F	25:25	50:50
Leukemia type	AML	34	68
	ALL	16	32
CBC and PB	WBC	66.5	0.6–498
	Hb	8.5	3.8–13.6
	PLT	56.3	5–296
	Blast cells	69.3	20–100
BMI	Overweight + obese	29	58
	Others	16	32
	Missing	5	10
TG level	Hypertriglyceridemic	28	56
	Normal	22	44
Cholesterol level	Hypercholesterolemic	25	50
	Normal	25	50
HDL level	Low level (risky)	22	44
	Normal	28	56
LDL level	Elevated	23	46
	Normal	27	54
Total cholesterol/HDL ratio	High risk	21	42
	Normal and borderline	29	58

M — male; F — female; AML — acute myeloid leukemia; ALL — acute lymphoblastic leukemia; CBC — complete blood count; PB — peripheral blood; WBC — white blood cells; Hb — hemoglobin; PLT — platelets; BMI — body mass index; TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

Table II. Comparative lipid profile pattern regarding gender in all 50 patients

Variables		Male	Female	*p*
BMI*	Overweight/obese	10 (34.5%)	19 (65.5%)	0.009
	Others	12 (75%)	4 (25%)	
TG level	Hypertriglyceridemic	14 (56%)	14 (56%)	1
	Normal	11 (44%)	11 (44%)	
Cholesterol level	Hypercholesterolemic	9 (36%)	16 (64%)	0.048
	Normal	16 (64%)	9 (36%)	
HDL level	Low level (risky)	7 (28%)	15 (60%)	0.023
	Normal	18 (72%)	10 (40%)	
LDL level	Elevated	8 (32%)	15 (60%)	0.047
	Normal	17 (68%)	10 (40%)	

*50 cases included in analysis, except for body mass index (BMI) where only 45 cases included (five missed BMIs); TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

Table III. Comparative lipid profile pattern regarding body mass index in 45 patients

Variables		Overweight/obese	Others	*p*
TG level	Hypertriglyceridemic	15 (51.7%)	10 (62.5%)	0.48
	Normal	14 (48.3%)	6 (37.5%)	
Cholesterol level	Hypercholesterolemic	12 (41.4%)	9 (56.3%)	0.33
	Normal	17 (58.6%)	7 (43.8%)	
HDL level	Low level (risky)	14 (48.3%)	7 (43.8%)	0.77
	Normal	15 (51.7%)	9 (56.3%)	
LDL level	Elevated	11 (37.9%)	8 (50%)	0.43
	Normal	18 (62.1%)	8 (50%)	

TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

In comparing the lipid profile between overweight/obese patients and other patients, there was no statistically significant association (Table III).

76.7% of AML patients were overweight or obese (p = = 0.015), while 81.3% of ALL patients showed hypertriglyceridemia (p = 0.014) (Table IV).

There was no statistically significant association between lipid profile and complete response (CR) rate, although there was a marginally significant association between non-CR rate and overweight and obese patients (p = 0.051) (Table V). In addition, there was no impact of BMI or lipid profile on overall survival among acute leukemia patients.

Discussion

The high rate of expansion and metabolism in cancer cells associated with decreased intracellular cholesterol and other lipids may lead to LDL receptor overexpression. For example, in myeloblast cells, LDL uptake can increase by up to 100-fold. Many attempts have been made to evaluate the correlation between serum lipids in leukemic patients and disease activity and response to chemotherapy [3, 6].

Epidemiological data suggests a significant association between increased BMI and hematological neoplasms [7]. Several large studies have revealed an association between a high incidence of leukemia and being overweight, and suggested that obesity is a poor prognostic factor for leukemia [8, 9]. In our study, 76.7% of AML patients were overweight or obese, as opposed to 40% of ALL patients (p = 0.015).

Our data showed that female patients were significantly overweight/obese (p = 0.009), and were more associated with increased TC level (p = 0.048), low HDL level (p = 0.023),

Table IV. Comparative lipid profile between acute leukemia patients

Variables		ALL	AML	*p*
BMI*	Overweight/ /obese	6 (40%)	23 (76.7%)	0.015
	Others	9 (60%)	7 (23.3%)	
TG level	Hypertrigly-ceridemic	13 (81.2%)	15 (44.1%)	0.014
	Normal	3 (18.8%)	19 (55.9%)	
Choleste-rol level	Hyperchole-sterolemic	10 (62.5%)	15 (44.1%)	0.2
	Normal	6 (37.5%)	19 (55.9%)	
HDL level	Low level (risky)	7 (43.8%)	15 (44.1%)	0.9
	Normal	9 (56.2%)	19 (55.9%)	
LDL level	Elevated	9 (56.2%)	14 (41.2%)	0.32
	Normal	7 (43.8%)	20 (58.8%)	
Total cho-lesterol/ /HDL ratio	High risk	8 (50%)	13 (38.2%)	0.75
	Normal and borderline	8 (50%)	21 (61.8%)	

*50 cases included in analysis, except for body mass index (BMI) where only 45 cases included (five missed BMIs); ALL — acute lymphoblastic leukemia; AML — acute myeloid leukemia; TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

Table V. Impact of body mass index (BMI) and lipid profile on complete response rate among acute leukemia patients

Variables		CR	Non-CR	*p*
BMI*	Overweight/ /obese	13 (52%)	16 (80%)	0.051
	Others	12 (48%)	4 (20%)	
TG level	Hypertrigly-ceridemic	17 (65.4%)	11 (45.8%)	0.16
	Normal	9 (34.6%)	13 (54.2%)	
Chole-sterol level	Hyperchole-sterolemic	11 (42.3%)	14 (58.3%)	0.25
	Normal	15 (57.7%)	10 (41.7%)	
HDL level	Low level (risky)	10 (38.5%)	12 (50%)	0.41
	Normal	16 (61.5%)	12 (50%)	
LDL level	Elevated	10 (38.5%)	13 (54.2%)	0.26
	Normal	16 (61.5%)	11 (45.8%)	

*50 cases included in analysis, except for body mass index (BMI) where only 45 cases included (five missed BMIs); CR — complete response; TG — triglycerides; HDL — high-density lipoproteins; LDL — low-density lipoproteins

and elevated LDL level ($p = 0.047$) than male patients. This data accords with that of Mehrabani et al. [9] who found that the incidence of obesity and overweight was higher in females than in males, and of Safford et al. [10] who found that females have higher TC and LDL levels than males.

In comparing the lipid profile in overweight/obese patients to that of others, no significant difference was found. 81.3% of ALL cases were associated with hypertriglyceridemia compared to 44.1% of AML cases ($p = 0.014$). Babu et al. [11] demonstrated that only TC and LDL cholesterol showed significant differences between obese and non-obese individuals, and other parameters like HDL and TG did not show any significant difference.

On the other hand, Einollahi et al. [12] reported hypertriglyceridemia and a decline in TC, HDL and LDL among leukemic patients. Also, similar results have been observed by Naik et al. [8] (in 55 leukemic patients) and Tao et al. [13] (in 86 ALL patients).

As regards response rate and BMI, 80% of patients who did not achieve complete response were obese or overweight ($p = 0.051$), which aligns with Orgel et al. [14] who found that obesity was associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia, and with Elazab et al. [15] who reported that overweight and obesity were associated with decreased complete response rates in adult AML patients ($p = 0.004$).

Targeting the metabolic profiles in leukemia cells could improve the outcome of leukemia patients. Statins possess several anti-leukemia effects such as apoptosis, anti-proliferation, and autophagy. Preliminary data has suggested that statins have anti-leukemia activities [16–18]. Two clinical trials have further revealed that statins can improve the efficacy of standard therapy in AML [19, 20].

Conclusions

Female, and acute myeloid leukemia, patients were more commonly associated with overweight and obesity, and a high TG level was found to be associated with acute lymphoid leukemia. Changes in lipid profile showed no impact on the complete response rate in acute leukemia patients. However, 80% of patients who did not achieve complete response were obese or overweight.

Further studies are needed to understand the correlations between metabolic profile and leukemia to help in developing new therapeutic approaches.

Authors' contributions

SE-A, FEIG — data collection and statistical analysis. SE-A, FEIG, TEA, MME, MAG — scientific writing. SA, MA — laboratory analysis. TEA, SA, MA, MME, MAG, FEIG, SE-A — article review.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Fiorenza AM, Branchi A, Sommariva D. Serum lipoprotein profile in patients with cancer. A comparison with non-cancer subjects. Int J Clin Lab Res. 2000; 30(3): 141–145, doi: 10.1007/s005990070013, indexed in Pubmed: 11196072.
2. Halton JM, Nazir DJ, McQueen MJ, et al. Blood lipid profiles in children with acute lymphoblastic leukemia. Cancer. 1998; 83(2): 379–384, indexed in Pubmed: 9669823.
3. Ghalaut VS, Pahwa MB, Ghalaut PS. Alteration in lipid profile in patients of chronic myeloid leukemia before and after chemotherapy. Clin Chim Acta. 2006; 366(1-2): 239–242, doi: 10.1016/j.cca.2005.10.022, indexed in Pubmed: 16386722.
4. Gokhale CD, Udipi SA, Ambaye RY, et al. Post-therapy profile of serum total cholesterol, retinol and zinc in pediatric acute lymphoblastic leukemia and non-Hodgkin's lymphoma. J Am Coll Nutr. 2007; 26(1): 49–56, doi: 10.1080/07315724.2007.10719585, indexed in Pubmed: 17353583.
5. Zalewska-Szewczyk B, Matusiak I, Wyka K, et al. [Changes in the lipid profile in children with acute lymphoblastic leukaemia — the influence of the disease and its treatment]. Med Wieku Rozwoj. 2008; 12(4 Pt 2): 1035–1040, indexed in Pubmed: 19531822.
6. Spiegel RJ, Schaefer EJ, Magrath IT, et al. Plasma lipid alterations in leukemia and lymphoma. Am J Med. 1982; 72(5): 775–782, doi: 10.1016/0002-9343(82)90543-5, indexed in Pubmed: 7081275.
7. Lichtman MA. Obesity and the risk for a hematological malignancy: leukemia, lymphoma, or myeloma. Oncologist. 2010; 15(10): 1083–1101, doi: 10.1634/theoncologist.2010-0206.
8. Naik PP, Ghadge MS, Raste AS. Lipid profile in leukemia and Hodgkin's disease. Indian J Clin Biochem. 2006; 21(2): 100–102, doi: 10.1007/BF02912921, indexed in Pubmed: 23105623.
9. Mehrabani J, Ganjifar ZK. Overweight and obesity: a brief challenge on prevalence, complications and physical activity among men and women. Women's Health. 2018; 7(1), doi: 10.15406/mojwh.2018.07.00161.
10. Safford MM, Gamboa CM, Durant RW, et al. Race-sex differences in the management of hyperlipidemia: the REasons for Geographic and Racial Differences in Stroke study. Am J Prev Med. 2015; 48(5): 520–527, doi: 10.1016/j.amepre.2014.10.025, indexed in Pubmed: 25891050.
11. Babu SV, Jagadeesan A, Ramalingam J. A comparative study of lipid profile in obese and nonobese men attending master health checkup. Indian J Med. 2017; 21(2): 73–75, doi: 10.5005/jp-journals-10054-0024.
12. Einollahi N, Alizadeh S, Nabatchian F, et al. Serum lipid profile alterations in acute leukemia before and after chemotherapy. IJBC. 2013; 6(1): 3–9.
13. Tao LJ, Qin YQ. [Alteration of serum lipids in patients with acute leukemia and its clinical significance]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2002; 10(4): 371–372, indexed in Pubmed: 12513777.
14. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood. 2014; 124(26): 3932–3938, doi: 10.1182/blood-2014-08-595389, indexed in Pubmed: 25349177.
15. Elazab A, Denewer M, Mabed M. PB1818: Influence of body mass index on the outcome in patients with acute myeloid leukemia. HemaSphere. 2022; 6(Suppl): 1698–1699, doi: 10.1097/01.hs9.0000850124.98624.52.
16. Li HY, Appelbaum FR, Willman CL, et al. Cholesterol-modulating agents kill acute myeloid leukemia cells and sensitize them to therapeutics by blocking adaptive cholesterol responses. Blood. 2003; 101(9): 3628–3634, doi: 10.1182/blood-2002-07-2283, indexed in Pubmed: 12506040.
17. van der Weide K, de Jonge-Peeters SD, Kuipers F, et al. Combining simvastatin with the farnesyltransferase inhibitor tipifarnib results in an enhanced cytotoxic effect in a subset of primary CD34+ acute myeloid leukemia samples. Clin Cancer Res. 2009; 15(9): 3076–3083, doi: 10.1158/1078-0432.CCR-08-3004, indexed in Pubmed: 19383813.
18. Minden MD, Dimitroulakos J, Nohynek D, et al. Lovastatin induced control of blast cell growth in an elderly patient with acute myeloblastic leukemia. Leuk Lymphoma. 2001; 40(5-6): 659–662, doi: 10.3109/10428190109097663, indexed in Pubmed: 11426537.
19. Advani AS, McDonough S, Copelan E, et al. SWOG0919: a phase 2 study of idarubicin and cytarabine in combination with pravastatin for relapsed acute myeloid leukaemia. Br J Haematol. 2014; 167(2): 233–237, doi: 10.1111/bjh.13035, indexed in Pubmed: 25039477.
20. Kornblau SM, Banker DE, Stirewalt D, et al. Blockade of adaptive defensive changes in cholesterol uptake and synthesis in AML by the addition of pravastatin to idarubicin + high-dose Ara-C: a phase 1 study. Blood. 2007; 109(7): 2999–3006, doi: 10.1182/blood-2006-08-044446, indexed in Pubmed: 17158228.

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ORIGINAL RESEARCH ARTICLE

VIA MEDICA

SARS-CoV-2 infection in patients with multiple myeloma: survey in 23 centers across Europe and USA

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Abstract

Introduction: Despite several studies, the impact of coronavirus disease 2019 on patients with multiple myeloma remains uncertain.

Material and methods: We performed a survey that covered the period of the first and second waves of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in 23 centers inseven countries. Out of 352 patients with myeloma and SARS-CoV-2, 23% died.

Results/Conclusions: Logistic regression showed a lower risk of death among patients treated with proteasome inhibitor and a higher risk of death for those who had a severe or a very severe course of disease.

Key words: myeloma, COVID-19

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing global health emergency. The case fatality rate (CFR), calculated by the ratio of deaths divided by the number of documented infections in the whole population, varies according to the method of calculation, the time and the country. Reported figures as of 17 September 2020 were: 12.2% in Italy, 4.9% in Spain, 3.0% in Brazil, and 3.0% in the USA. Just two months later on 12 November, 2020, these numbers had converged, with the CFR for each being 4.9%, 2.8%, 2.9%, and 2.3%, respectively [1]. Patients with cancer are purported to have poor COVID-19 outcomes, with a mortality rate approaching 50% [2]. However, the effect of infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on patients with multiple myeloma remains uncertain. Thus, we performed a survey among 23 centers in Poland, USA, Hungary, Czechia, Turkey, Lithuania, and Romania with an estimated population of 5,780 myeloma patients to determine the epidemiology and the risk of severe COVID-19 in patients with multiple myeloma.

Material and methods

This study was a retrospective analysis performed according to the Declaration of Helsinki with the approval of the Ethics Committee at Poznan University of Medical Sciences in Poznan, Poland. Patient data was reported anonymously based on a unified questionnaire. The survey covered the period of the first and second waves of the pandemic between March 2020 and March 2021.

Results

We recorded data on 352 patients with myeloma and SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR). Taking into account the population of myeloma patients in participating centers, the incidence rate was 6.1%. Among all patients (median age 67 years) 36% had newly diagnosed myeloma with the remainder having relapsed or refractory disease. The majority of patients were actively receiving chemotherapy: 20% a proteasome inhibitor (PI), 24% an immunomodulatory drug (IMID), 29% a combination of PI and IMID, 14.5% a chemotherapy containing the monoclonal antibody, and 6% other drugs (stem cell transplantation, selinexor, melflufen, melphalan). Only 6% of patients were not receiving any treatment. 24.4% of patients were in complete response (CR) or stringent complete response (sCR), 19% were in a very good partial response (VGPR), 21% were in a partial response (PR), and 20% had either stable (SD) or progressive disease (PD). The status of the disease was unknown for 14% of the analyzed subjects. A large majority of patients (69%) had at least one comorbidity, and this percentage was higher among the subpopulation of patients who eventually died. A summary of patient characteristics with a description of the subpopulation of patients who died is set out in Table I.

Mild or moderate infection was observed in 58% of cases, and in 18% the disease was considered to be severe or very severe with the necessity of hospitalization in anintensive care unit (ICU). 42 patients were intubated. Among them, only four survived. Four patients hospitalized in the ICU were not intubated but died, leading to a CFR of hospitalized patients in the ICU of 66% and 95% for patients who were ventilated. Out of all 352 analyzed patients with myeloma and SARS-CoV-2 infection, 80 died (CFR 23%).

Linear regression showed that patients with lower disease control (less than CR/sCR or VGPR) had a higher risk of death [hazard ratio (HR) 3.3, 95% CI: 1.7–6.1], while in patients treated with regimens containing a proteasome inhibitor (HR 0.3; 95% CI: 0.09–0.8) the risk of death was lower compared to other treatments. The risk of death was also higher for those who were hospitalized in an ICU (HR 9.3; 95% CI: 4.9–17.6), and those who were on a respirator

Table I. Patient characteristics

Parameter	Whole group (n = 352)	Patients who died (n = 80)
Activity of myeloma		
sCR + CR/VGPR/PR/SD + PD/unknown	25%/19%/21%/21%/14%	12%/ 14%/15%/39%/20%
Status of disease		
NDMM/RRMM	36%/74%	30%/50%
Treatment		
PI/IMMID/PI + IMMID/MoAb/other/no treatment	20%/24%/29%/14.5%/6%/6%	31%/24%/15%/21%/6%/2.5%
Comorbidities		
None/HA or CHD/DM/KF/COPD/more than one	31%/30%/3.5%/8%/5%/18%	11%/17.5%/27.5%/7.5%/24%/12.5%
Age		
<65 years of age/>65 years of age	25%/75%	25%/75%

sCR — stringent complete response; CR — complete response; VGPR — very good partial response; PR — partial response; SD — stable disease; PD — progressive disease; NDMM — newly diagnosed multiple myeloma; RRMM — relapsed and refractory multiple myeloma; PI — proteasome inhibitor; IMMID — immunomodulatory drug; MoAb — monoclonal antibody; HA — hypertension; CHD — coronary heart disease; DM — diabetes mellitus; KF — kidney failure; COPD — chronic obstructive pulmonary disease

or who had a severe course of disease (G3 and G4) (HR 3.2; 95% CI: 1.4–7.0 for G3 and 16.8; 95% CI: 6.2–45.6 for G4). Logistic regression confirmed a lower risk of death among patients treated with PI [odds ratio (OR) 0.12; 95% CI: 0.02–0.70] and a higher risk of death for those who had a severe (OR 10.14, 95% CI: 11.66–62.04) or a very severe course of disease (OR 17.37; 95% CI: 3.61–83.55).

Specific treatments for SARS-CoV-2 were reported for only 42 patients (12%). These treatments consisted of differing combinations of remdesivir, tocilizumab, dexamethasone and convalescent plasma. Only one patient was vaccinated, who was infected and developed mild symptoms of COVID-19 not requiring hospitalization. Out of those who were treated against SARS-CoV-2, there were four deaths. Due to the low number of reported treatments and variabilities, no conclusions on the impact of antiviral therapy in myeloma patients can be made.

Discussion

Although our study was conducted in conditions without the existence of a vaccine against SARS-CoV-2, and although the virulence of the virus is now lower, our observations remain relevant. Similar retrospective analyses have indicated a relatively similar range of mortality rates, varying from 22–55% [3, 4] with, notably, an analysis of 650 patients reported by Chari showing a mortality range of 34% [5].

The risk of death among hospitalized and ventilated patients is also similar, ranging from 60–100% among ventilated patients and patients who were hospitalized (10–53%). The most common reported independent predictors of adverse outcomes with COVID-19 infection are: advanced age, high-risk myeloma, renal disease, and suboptimal myeloma control.

Our survey does not exclude this observation but indicates that PI treatment is correlated with a lower risk of death that has not been previously reported. SARS-CoV-2 infection in myeloma patients is associated with a high risk of a severe course of COVID-19 and a high mortality rate. Since the effects of anti-SARS-CoV-2 treatment remain undetermined, vaccination is highly recommended especially during an outbreak of the pandemic. Any reported correlation with PI treatment must be confirmed in further studies.

Authors' contributions

DD and LG collected and analyzed data and wrote manuscript, the rest authors collected the data and supported the writing of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

References

1. Cavataio J, Schnell S. Interpreting SARS-CoV-2 seroprevalence, deaths, and fatality rate — making a case for standardized reporting to improve communication. Math Biosci. 2021; 333: 108545, doi: 10.1016/j.mbs.2021.108545, indexed in Pubmed: 33460673.
2. Kuderer NM, Choueiri TK, Shah DP, et al. COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet. 2020; 395(10241): 1907–1918, doi: 10.1016/S0140-6736(20)31187-9, indexed in Pubmed: 32473681.
3. Martínez-López J, Mateos MV, Encinas C, et al. Multiple myeloma and SARS-CoV-2 infection: clinical characteristics and prognostic factors of inpatient mortality. Blood Cancer J. 2020; 10(10): 103, doi: 10.1038/s41408-020-00372-5, indexed in Pubmed: 33077708.
4. Terpos E, Engelhardt M, Cook G, et al. Management of patients with multiple myeloma in the era of COVID-19 pandemic: a consensus paper from the European Myeloma Network (EMN). Leukemia. 2020; 34(8): 2000–2011, doi: 10.1038/s41375-020-0876-z, indexed in Pubmed: 32444866.
5. Chari A, Samur MK, Martinez-Lopez J, et al. Clinical features associated with COVID-19 outcome in multiple myeloma: first results from the International Myeloma Society data set. Blood. 2020; 136(26): 3033–3040, doi: 10.1182/blood.2020008150, indexed in Pubmed: 33367546.

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ORIGINAL RESEARCH ARTICLE

Long-term allogeneic hematopoietic cells transplantation survivors' proinflammatory cytokine profiles compared to their respective donors and immunophenotype differences depending on GvHD history and infection status

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Abstract

Introduction: In the course of allogeneic hematopoietic cell transplantation (allo-HCT) the donor's hematopoietic progenitor cells are exposed to immense proliferative stress to reconstitute in the recipient the functional hematopoiesis. Moreover, recipients who develop infections or chronic graft-versus-host disease (GvHD) are subjected to further proliferative stress, especially in the lymphocyte subset. We hypothesized that allo-HCT may induce changes in proinflammatory cytokines profile and immunophenotype in the allo-HCT recipients, especially in patients with a chronic GvHD history.

Material and methods: We compared the cytokine profile [interleukin (IL)-6, IL-10, and tumor necrosis factor α (TNF-α)] between long-term allo-HCT recipients and their respective donors and we analyzed cytokine profiles and the immunophenotype of lymphocytes in long-term recipients grouped according to their infection and GvHD history.

Results: We found no differences in the proinflammatory cytokines between allo-HCT recipients and their respective donors, or between recipients grouped according to their infectious risk status. Immunophenotyping of recipients grouped according to their GvHD status revealed an increased percentage of B-cell presenting programmed death-1 in recipients without a history of GvHD.

Conclusions: A lack of differences in proinflammatory cytokines concentrations between recipients and donors of allo-HCT would suggest that allo-HCT does not induce acceleration of the 'inflammaging'-resembling phenomenon.

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No differences in the cytokine profile and immunophenotype between recipients grouped according to infectious risk status suggest that infectious risk is not reflected by the immunophenotype and cytokine profile. Furthermore, the lack of significant differences in immunophenotype of the recipients grouped according to a history of GvHD may suggest that in long-term survivors the immune system tends to stabilize with time.

Key words: GvHD, cytokines, allo-HCT, immunophenotype

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Introduction

The introduction of allogeneic hematopoietic cell transplantation (allo-HCT) as a standard method of treatment for several malignant and non-malignant hematological diseases has created an excellent platform upon which to study human immunology and cell senescence. Since only a small percentage of the donor stem cells pool is collected and infused into the donor to engraft and reconstitute hematopoiesis, the cells are exposed to immense proliferative stress.

However, successful allo-HCT requires also that two important immunological barriers be overcome: host versus graft and graft versus host. Graft-versus-host reaction results from the exposure of lymphoid donor cells to the recipient antigens which induce donor lymphocyte activation and proliferation. Partially in patients with malignant diseases, this reaction is responsible for HCT's success in eradicating the residual malignant cells (graft-versus-leukemia reaction). However, it may also lead to undesirable complications such as graft-versus-host disease (GvHD) resembling autoimmune diseases affecting several host organs. To prevent and control symptoms of graft versus host reaction, immunosuppressive agents disrupting lymphocyte proliferation (such as methotrexate and calcineurin inhibitors) are routinely administered after transplantation. A key role in GvHD is played by donor T cell lymphocytes but also B-lymphocytes [1, 2]. Involved donor lymphocytes undergo an additional intensive proliferation which may contribute to the accelerated telomere shortening in donor lymphocytes.

All of the above lead to the immense proliferative activity of the cells, including lymphocytes in allo-HCT recipients. We hypothesized that this could lead not only to accelerated telomeric shortening but also to immunophenotypic changes characteristic of natural aging. Healthy human ageing process includes in its characteristics the phenomenon of 'inflammaging'. It may be defined as chronic, low-grade inflammation, without the presence of infection. In biochemical evaluation it presents with increased concentrations of proinflammatory cytokines due to antigenic stimulation over a lifespan of an individual [2].

It is also well known that the concentration of some proinflammatory cytokines [such as tumor necrosis factor α (TNF-α), interleukin (IL)-6] increases, whereas others decrease (such as IL-10) during the course of chronic GvHD [3–5].

We reported recently our observations regarding the changes in immunophenotype and shortened telomeres in CD8+ lymphocyte subpopulation in long-term allo-HCT recipients compared to their respective donors [6]. Here, we present data on the proinflammatory cytokine profile of the same population of patients, i.e. long-term recipients of allo-HCT and their respective donors, to determine whether allo-HCT led to the changes in the proinflammatory cytokines. Moreover, we compared the immunophenotype of the recipients grouped according to their infection and cGvHD status.

Material and methods

The content of the materials and methods section were adapted from Czarnogórski et al. 2022 [6].

Patients

The study consist of 20 allo-HCT recipient-donor pairs. The span from the transplantation was more than 12 years ago. The study was conducted at University Clinical Center, Medical University of Gdansk. From all participants full venous blood sample was collected (50 mL).

GvHD and infectious status assessment

Patients were stratified according to their history of chronic GvHD status (yes vs. no) and infectious complications according to an infection risk status score developed for the purpose of this study [6].

Peripheral blood mononuclear cells and lymphocyte isolation

Perpheral blood mononuclear cells collection was performed from full venous blood with Ficoll-Hypaque centrifugation technique. Following lymphocyte isolation was performed by immunomagnetic separation. The lymphocyte subpopulations were TCD4+, TCD8+, B-lymphocytes and natural killers (NK) cells. The quality of collected material was assessed according to validated protocols [7, 8].

Proinflammatory cytokine concentrations

Proinflammatory cytokines concentrations (IL-1B, IL-2, IL-4, IL-6, IL-10, TNF-α and IL-17F) were assessed with flow cytometry. The results which did not reach the reference were excluded from the study.

Immunophenotyping

Immunophenotyping was performed according to protocol used by Czarnogórski et al. [6].

Statistical analysis

The statistical analysis was performed by STATISTICA 12.0 and with Microsoft Exel, detailed analysis was described according to Czarnogórski et al. [6]. The W Shapiro-Wilk test, and the Leven's (Brown-Forsythe) test were used. The significance of differences between the two groups (independent samples model) was tested by Student's *t*-test or by U Mann-Whitney. The significance of differences between more than two groups was verified using the Kruskal-Wallis test. In the case of receiving statistically significant differences between groups, the Dunn test was performed. A *p* value <0.05 was considered significant.

Results

Patient characteristics

The time from Tx to full venous blood cytometric analysis was at least 12 years with range 12–25 years (median 17.4 years). The population studied consisted of 12 males and 8 females. The prevalence of chronic graft versus host disease among recipients was 40%. Infection risk status was assessed according to Czarnogórski et al. [6]: 12 low risk recipients and 8 high risk recipients.

Proinflammatory cytokine concentrations

Surprisingly, we have found no statistically significant differences in the concentrations of the cytokines: TNF-α, IL-6, IL-10 (Table I). The results of assessment of IL-17F, IL-1β, IL-4, IL-2 concentrations were out of range, therefore they could not be included into analysis.

Neither we have found any differences between recipients when grouped according to infection risk status (Table II).

Immunophenotype of allo-HCT recpients grouped according to chronic GvHD history

The analysis of immunophenotype of the allo-HCT recipients grouped according to cGvHD history showed no significant differences (*see* Supplementary Table 1), with the exception of a few parameters such as Treg Helios-Eomes+, B1 PD1+, B2 PD1+ and C19 PD1+. Lymphocytes B in recipients of allo-HCT who did not develop cGvHD had greater expression of PD-1 (Table III).

Table I. Recipients and donors of hematopoietic cell transplantation — cytokines concentrations

Parameter	R	D	*p* value
IL-6 [ng/L]:	N = 20	N = 20	0.5792*
• avr (standard deviation)	0.99 (1.17)	1.61 (2.37)	
• range	0.38–5.42	0.07–9.53	
• median	0.58	0.72	
• 95% CI	0.44–1.54	0.50–2.72	
IL-10 [ng/L]:	N = 19	N = 18	0.5333*
• avr (standard deviation)	0.58 (0.69)	0.72 (0.71)	
• range	0.01–3.20	0.15–3.04	
• median	0.42	0.52	
• 95% CI	0.25–0.91	0.36–1.07	
TNF-α [ng/L]:	N = 18	N = 19	0.3234*
• avr (standard deviation)	0.77 (1.53)	0.83 (1.91)	
• range	0.01–6.78	0.02–8.51	
• median	0.33	0.22	
• 95% CI	0.01–1.54	–0.09–1.75	

*U Mann-Whitney test; IL — interleukin; CI — confidence interval; TNF-α — tumor necrosis factor α

Table II. Recipients grouped according to infection risk status — cytokines concentrations

Parameter	Low risk	Intermediate/ /high risk	*p* value
IL-6 [ng/L]:	N = 12	N = 8	0.3159*
• avr (standard deviation)	1.19 (1.49)	0.69 (0.20)	
• range	0.38–5.42	0.48–1.10	
• median	0.52	0.61	
• 95% CI	0.24–2.14	0.52–0.86	
IL-10 [ng/L]:	N = 11	N = 8	0.9671*
• avr (standard deviation)	0.68 (0.88)	0.45 (0.27)	
• range	0.01–3.20	0.11–0.87	
• median	0.48	0.39	
• 95% CI	0.09–1.27	0.23–0.67	
TNF-α [ng/L]:	N = 12	N = 6	0.1898*
• avr (standard deviation)	1.02 (1.85)	0.28 (0.20)	
• range	0.09–6.78	0.01–0.62	
• median	0.37	0.28	
• 95% CI	–0.15–2.19	0.07–0.49	

*U Mann-Whitney test; IL — interleukin; CI — confidence interval; TNF-α — tumor necrosis factor α

Table III. Recipients grouped according to chronic graft-versus--host disease (cGvHD) status — immunophenotype

Parameter	cGvHD	Without cGvHD	*p* value
Treg Helios–Eomes:			**0.0227**
• avr (standard deviation)	4.1 (1.3)	8.7 (4.8)	
• range	2.4–5.4	4.2–19.1	
• median	4.6	7.2	
• 95% CI	2.7–5.5	5.2–12.1	
B1 PD1:			**0.0147**
• avr (standard deviation)	4.0 (2.7)	10.4 (5.5)	
• range	0.2–8.7	3.6–18.7	
• median	3.7	9.7	
• 95% CI	1.2–6.9	6.4–14.3	
B2 PD1:			**0.0448**
• avr (standard deviation)	0.7 (0.7)	1.8 (1.8)	
• range	0.1–2.1	0.6–6.2	
• median	0.5	1.1	
CD19 PD1:			**0.0147**
• avr (standard deviation)	1.2 (0.9)	3.3 (2.3)	
• range	0.2–2.9	1.2–8.9	
• median	0.9	3.0	
• 95% CI	0.2–2.2	1.6–4.9	

SD — standard deviation; CI — confidence interval

Discussion

In this study, we tried to answer the question of whether allo-HCT accelerates the aging of the hematopoietic system by determining the differences in cytokine profile between long-term allo-HCT survivors and their respective donors of allo-HCT.

Studying donor-recipient pairs creates a unique model in which donor cells remaining in the donor could be compared to the donor cells infused into respective recipients. We were particularly interested in the features of postulated 'inflammaging'. We also compared the same cytokine profile of the recipients when grouped according to infectious status (low vs intermediate/high) (see Czarnogórski et al. [6]). We hypothesized that allo-HCT recipients should have higher concentrations of proinflammatory cytokines as a robust indicator of aging. We also hypothesized that low-risk recipients according to their infection status would have increased concentrations of the same cytokines as an adaptation for fighting the infections.

Physiologically, the proinflammatory cytokine profile of older people is characterized by increased concentrations of the aforementioned cytokines (IL-1B, IL-2, IL-4, TNF-α, IL-6, IL-10, IL-15, IL-17, IL-18). These concentrations however do not exceed the upper reference range. Hence, inflammaging is defined as the process of chronic, sterile, low-grade inflammation.

There is no data on inflammaging in a population of allo-HCT survivors compared to their respective recipients serving as controls. We did not find any statistically significant differences in IL-6, IL-10 and TNF-α concentrations, either between main groups (recipients vs. donors) nor between recipients grouped according to infection risk status. Our data did not confirm our initial hypothesis that allo-HCT accelerates the inflammaging-resembling process.

We also did not find any differences between low and intermediate/high risk recipients stratified by their infection status, which could imply that infectious risk is not directly connected to the efficacy of one's innate immune response. It would imply that allogeneic hematopoietic cells transplantation by itself does not impact the inflammaging [9]. However, the issue remains controversial since chronic low-grade inflammation (inflammaging) is a well-established risk factor for developing neoplasia [10, 11] which could be debatable in the population of our allo-HCT survivors since they were diagnosed with hematological malignancies in their 20 s and 30 s. On the other hand, there is ample data on the reduction of relapse risk after allo-HCT in patients who developed chronic GvHD that is in fact a chronic inflammation [12]. Moreover, it is difficult to differentiate if heightened concentrations of proinflammatory cytokines after allo-HCT result from chronic GvHD [13] or possibly are an adaptation for fighting the infection. There is some data correlating the occurrence of inflammaging and immune exhaustion in some hematological malignancies, such as plasmocytic myeloma [14]. Thus, it is challenging to determine whether the inflammaging features are due to older age or to the neoplasia itself.

Surprisingly, the incidence of chronic GvHD also did not impact any studied parameters, especially immunophenotype with the exception of B-cells expressing PD-1 which serves as the programmed death ligand-1 (PD-L1) receptor and plays a role in modulating immune response [15]. We also found no differences in T-cells expressing PD-1. An increased percentage of B-cells presenting PD-1 in recipients without chronic GvHD in anamnesis is difficult to interpret. Those differences in receptor expression in antigen-presenting cells (APCs) such as B-cells seem to be insignificant or accidental. The lack of differences in long-term (12 years+ from Tx) recipients of allo-HCT when grouped according to cGvHD history may suggest that the immune system tends to stabilize in the years following Tx. Many factors might explain such notion, that is immune suppression used, history of chronic degenerative diseases, GvHD resolution and small number of participants. Our study has

several limitations. Firstly, it was performed in long-term survivors who were able to fight infections successfully and whose cGvHD status became stable. Secondly, the results are affected by the small population (20 pairs) and unfortunately the results of some cytokines assays were out of range, which might be related to laboratory errors. Unfortunately, we were unable to repeat tests with out-of-range results due to sample destruction during an electricity outage. Nevertheless, our results may suggest that allo-HCT does not accelerate the aging of the hematopoietic system despite a clear reduction of telomere shortening in specific cell populations and some immunophenotypic differences reported by us [6].

Authors' contributions

All authors revised manuscript and read and approved final manuscript. MCC and JMZ wrote manuscript. MCC, PT, JMW, MD, JMZ were responsible for study design. MCC, AP, AS, JMZ, EZ, MB, MD, AH took part in patient recruitment and clinical data acquisition. MCC, IO, JMW, JMZ, MM and KRD performed laboratory and clinical data analysis. MC, JS, MM, MZ, JMW and PT performed laboratory work.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

This study was approved by the Ethics Committee at the Medical University of Gdańsk — NKBBN/394-594/2019 and NKBBN/394-45/2020. Each participant signed an informed consent form.

Supplementary Table 1. Comparative characteristics of allogeneic hematopoietic cell transplantation recipients immunophenotype when grouped according to graft-versus-host disease status

Parameter	*p* value	Parameter	*p* value	Parameter	*p* value
B1	0.1193	NK CD39	0.5508	B1 PD1	0.0147
B2	0.0973	NK CD56 dim	0.2548	B2	0.2123
CD19	0.6511	NK CD56 high	0.2548	B2 Fas	0.9567
CD3	0.9599	NK Eomes	0.9567	B2 PD1	0.0448
DNT	0.4808	NK Perforin	0.7042	CD19	0.9567
NK	0.7595	NKT like	1.00	CD19 Fas	0.9567
NK CD56 dim	0.9512	Q1	0.5508	CD19 PD1	0.0147
NK CD56 high	0.4624	Q1 CD39	0.8708	CD4 CD27+CD28–	0.3290
NKT like	0.0662	Q1 Eomes	0.3566	CD4 CD27+CD28+	0.2123
T CD4	0.7250	Q1 IL10	0.5508	CD4 CD27–CD28–	0.4808
T CD8	0.9567	Q1 Perforin	0.0827	CD4 CD27–CD28+	0.7042
B1	0.0927	Q2	0.9567	CD4 CD28	0.3566
B1 CD39	0.4159	Q2 CD39	0.3028	CD4 CD57	0.3028
B1 Eomes	0.3566	Q2 Eomes	0.7863	CD4 FasL	0.8283
B1 IL10	0.1752	Q2 IL10	0.1585	CD4 PD-1	0.6255
B2	0.0927	Q2 Perforin	0.1752	CD8 CD27+CD28–	0.7683
B2 CD39	0.7449	Q3	0.3290	CD8 CD27+CD28+	0.1949
B2 Eomes	0.0577	Q3 CD39	0.7042	CD8 CD27–CD28–	0.6800
B2 IL10	0.6255	Q3 Eomes	0.2123	CD8 CD27–CD28+	0.5959
CD19	0.4808	Q3 IL10	0.1931	CD8 CD28	0.7683
CD19 CD39	0.4159	Q3 Perforin	0.8708	CD8 CD57	0.6800
CD19 Eomes	0.0448	RTE	0.1158	CD8 PD-1	0.3165
CD19 IL10	0.4477	T CD4	0.7863	DNT	0.3566
CD3	0.6255	T CD8	0.7863	Memory B	0.0735
CD4 CD39	0.4808	Treg FoxP3	0.9567	NK	0.2123
CD4 CM	0.3028	Treg FoxP3 CD39	0.6255	NK CD27	0.7449

→

Supplementary Table 1 (cont.). Comparative characteristics of allogeneic hematopoietic cell transplantation recipients immunophenotype when grouped according to graft-versus-host disease status

Parameter	*p* value	Parameter	*p* value	Parameter	*p* value
CD4 EM	0.7042	Treg FoxP3 Eomes	0.9136	NK CD28	0.8708
CD4 Eomes	1.00	Treg FoxP3 IL10	0.0735	NK CD56 dim	0.2123
CD4 IL10	0.5508	Treg FoxP3 Perforin	0.2548	NK CD56 high	0.5508
CD4 Naive	0.9567	Treg Helios–	0.6255	NK CD57	0.3566
CD4 Perforin	0.0577	Treg Helios– CD39	0.3566	NK PD-1	0.6255
CD4 Temra	0.7863	Treg Helios– Eomes	0.0227	NKT like	0.9567
CD8 CD39	0.8137	Treg Helios– IL10	0.1752	Q1	0.8708
CD8 CM	0.3768	Treg Helios– Perforin	0.2548	Q1 CD27	0.9567
CD8 EM	0.0875	Treg Helios+	0.7042	Q1 CD28	0.1431
CD8 Eomes	0.2159	Treg Helios+ CD39	0.7042	Q1 CD57	0.2123
CD8 Naive	0.2629	Treg Helios+ Eomes	0.0577	Q1 FasL	0.7863
CD8 Perforin	0.3768	Treg Helios+ IL10	0.0927	Q1 PD-1	0.3566
CD8 Temra	0.953	Treg Helios+ Perforin	0.6255	Q2	0.9567
DNT	0.4159	B1	0.2123	Q2 CD27	0.7449
NK	0.2123	B1 Fas	0.8708	Q2 CD28	0.5508
Q2 CD57	0.0735	CD3	0.9567	Treg FoxP3 CXCR5	0.1431
Q2 FasL	0.4159	CD4 CD152	0.6255	Treg FoxP3 TIGIT	0.7863
Q2 PD-1	0.9567	CD4 CXCR4	0.7042	Treg Helios–	0.4808
Q3	0.1158	CD4 CXCR5	0.1431	Treg Helios– CCR5	0.5508
Q3 CD27	0.3566	CD4 TIGIT	0.4477	Treg Helios– CD152	0.7042
Q3 CD28	0.7449	CD8 CXCR4	0.7683	Treg Helios– CXCR4	0.4159
Q3 CD57	0.0057	CD8 CXCR5	0.1116	Treg Helios– CXCR5	0.6255
Q3 FasL	0.1431	CD8 TIGIT	0.5169	Treg Helios– TIGIT	0.7042
Q3 PD-1	0.0577	DNT	0.4159	Treg Helios+	0.5508
T CD4	0.7042	NK	0.2123	Treg Helios+ CCR5	0.8708
T CD8	0.6255	NK CCR5	0.4477	Treg Helios+ CD152	0.7042
Treg FoxP3	0.9567	NK CD56 dim	0.2123	Treg Helios+ CXCR4	0.6255
Treg FoxP3 CD27	0.1037	NK CD56 high	0.4159	Treg Helios+ CXCR5	0.4808
Treg FoxP3 CD28	0.7042	NK CXCR4	0.2548	Treg Helios+ TIGIT	0.8708
Treg FoxP3 CD57	0.0735	NK CXCR5	0.3566		
Treg FoxP3 FasL	0.1931	NK TIGIT	0.4808		
Treg FoxP3 PD-1	0.4808	NKT like	0.9567		
Treg Helios–	0.0735	Q1	0.5508		
Treg Helios– CD27	0.9567	Q1 CCR5	0.4159		
Treg Helios– CD28	0.3028	Q1 CD152	0.5876		
Treg Helios– CD57	0.0577	Q1 CXCR4	0.8708		
Treg Helios– FasL	0.2781	Q1 CXCR5	0.1431		
Treg Helios– PD-1	0.4808	Q1 TIGIT	0.3028		
Treg Helios+	0.7863	Q2	0.8708		
Treg Helios+ CD27	0.1585	Q2 CCR5	0.9567		
Treg Helios+ CD28	0.8708	Q2 CD152	0.3028		
Treg Helios+ CD57	0.0079	Q2 CXCR4	0.4477		

→

Supplementary Table 1 (cont.). Comparative characteristics of allogeneic hematopoietic cell transplantation recipients immunophenotype when grouped according to graft-versus-host disease status

Parameter	*p* value	Parameter	*p* value	Parameter	*p* value
Treg Helios+ FasL	0.3028	Q2 CXCR5	0.9567		
Treg Helios+ PD-1	0.7863	Q2 TIGIT	0.2548		
B1	0.0927	Q3	0.4159		
B1 CCR5	0.3566	Q3 CCR5	0.7863		
B1 CD152	0.0735	Q3 CD152	0.6255		
B1 CXCR5	0.2548	Q3 CXCR4	0.7042		
B2	0.0577	Q3 CXCR5	0.4808		
B2 CCR5	0.7449	Q3 TIGIT	0.6644		
B2 CD152	0.3028	T CD4	0.8708		
B2 CXCR5	0.4477	T CD8	0.8708		
CD19	0.4159	Treg FoxP3	0.9567		
CD19 CCR5	0.4159	Treg FoxP3 CCR5	0.7042		
CD19 CD152	0.1752	Treg FoxP3 CD152	0.7042		
CD19 CXCR5	0.7042	Treg FoxP3 CXCR4	1.00		

*U Mann-Whitney

References

1. Choi SW, Levine JE, Ferrara JLM. Pathogenesis and management of graft-versus-host disease. Immunol Allergy Clin North Am. 2010; 30(1): 75–101, doi: 10.1016/j.iac.2009.10.001, indexed in Pubmed: 20113888.
2. Magenau J, Runaas L, Reddy P. Advances in understanding the pathogenesis of graft-versus-host disease. Br J Haematol. 2016; 173(2): 190–205, doi: 10.1111/bjh.13959, indexed in Pubmed: 27019012.
3. Barak V, Levi-Schaffer F, Nisman B, et al. Cytokine dysregulation in chronic graft versus host disease. Leuk Lymphoma. 1995; 17(1-2): 169–173, doi: 10.3109/10428199509051718, indexed in Pubmed: 7773155.
4. Skert C, Damiani D, Michelutti A, et al. Kinetics of Th1/Th2 cytokines and lymphocyte subsets to predict chronic GVHD after allo-SCT: results of a prospective study. Bone Marrow Transplant. 2009; 44(11): 729–737, doi: 10.1038/bmt.2009.80, indexed in Pubmed: 19398965.
5. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999; 340(6): 448–454, doi: 10.1056/NEJM199902113400607, indexed in Pubmed: 9971870.
6. Czarnogórski MC, Sakowska J, Maziewski M, et al. Ageing-resembling phenotype of long-term allogeneic hematopoietic cells recipients compared to their donors. Immun Ageing. 2022; 19(1): 51, doi: 10.1186/s12979-022-00308-6, indexed in Pubmed: 36324179.
7. Zielinski M, Tarasewicz A, Zielinska H, et al. Impact of donor and recipient human cytomegalovirus status on kidney transplantation. Int Immunol. 2017; 29(12): 541–549, doi: 10.1093/intimm/dxx062, indexed in Pubmed: 29121254.
8. Trzonkowski P, Debska-Slizień A, Jankowska M, et al. Immunosenescence increases the rate of acceptance of kidney allotransplants in elderly recipients through exhaustion of CD4+ T-cells. Mech Ageing Dev. 2010; 131(2): 96–104, doi: 10.1016/j.mad.2009.12.006, indexed in Pubmed: 20060852.
9. Fülöp T, Larbi A, Witkowski JM. Human inflammaging. Gerontology. 2019; 65(5): 495–504, doi: 10.1159/000497375, indexed in Pubmed: 31055573.
10. Aunan JR, Cho WC, Søreide K. The biology of aging and cancer: a brief vverview of shared and divergent molecular hallmarks. Aging Dis. 2017; 8(5): 628–642, doi: 10.14336/AD.2017.0103, indexed in Pubmed: 28966806.
11. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144(5): 646–674, doi: 10.1016/j.cell.2011.02.013, indexed in Pubmed: 21376230.
12. Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. Blood. 2017; 129(1): 22–29, doi: 10.1182/blood-2016-08-686659, indexed in Pubmed: 27821505.
13. MacDonald KPa, Blazar BR, Hill GR. Cytokine mediators of chronic graft-versus-host disease. J Clin Invest. 2017; 127(7): 2452–2463, doi: 10.1172/JCI90593, indexed in Pubmed: 28665299.
14. Zelle-Rieser C, Thangavadivel S, Biedermann R, et al. T cells in multiple myeloma display features of exhaustion and senescence at the tumor site. J Hematol Oncol. 2016; 9(1): 116, doi: 10.1186/s13045-016-0345-3, indexed in Pubmed: 27809856.
15. Cassady K, Martin PJ, Zeng D. Regulation of GVHD and GVL activity via PD-L1 interaction with PD-1 and CD80. Front Immunol. 2018; 9: 3061, doi: 10.3389/fimmu.2018.03061, indexed in Pubmed: 30622541.

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Relation between blood levels of iron, interleukin 6 and infection rates in children: a pilot study

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Abstract

Introduction: Iron deficiency is the most common micronutrient deficiency worldwide. Iron activates the growth and differentiation of immune cells and cytokine actions. Interleukin 6 is a pro-inflammatory cytokine that stimulates the differentiation of B lymphocytes into plasma cells and activates T lymphocytes. Our study aimed to evaluate the correlation between blood levels of iron and interleukin 6 (IL-6) and its impact on infection rates in children.

Materials and methods: The study included 36 children. The serum concentration of IL-6, iron, and morphology parameters from a venous blood sample were assessed. An anonymous survey of children's parents was conducted regarding the frequency of infections before and after the diagnosis of anemia.

Results: In the study group, the levels of IL-6 were higher than in the control group and showed greater variability between individual patients. There was a statistically significant, negative correlation between IL-6 and iron levels within the study group ($p = 0.012$), and a decrease in the number of viral diarrheas after the diagnosis of anemia compared to the state before diagnosis ($p = 0.041$). There was no statistically significant change in the number of colds or the mean duration of infection ($p = 0.144$, $p = 0.498$), nor in the incidence of other infectious diseases and antibiotics intake in the study group before and after iron deficiency anemia diagnosis ($p = 0.500$, $p = 0.219$).

Conclusions: IL-6 might play a role in iron deficiency anemia. Increased levels of IL-6 were shown not to correspond with visible changes in rates and the course of colds, but did result in a reduction in the frequency of viral diarrhea. Further research on a larger group of carefully selected patients is required to determine the effect of anemia on the immune system.

Key words: iron deficiency, anemia, interleukin 6, infections

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Introduction

Iron deficiency (ID) is the most common micronutrient deficiency worldwide. Iron deficiency anemia (IDA) is a serious public health problem that affects mental and physical development, health, and work efficiency. Despite extensive progress in understanding regarding iron metabolism, there are still uncertainties regarding the correct diagnosis and treatment of IDA [1, 2].

Diagnostic biomarkers are required to differentiate the different types of anemia and to treat them appropriately. Some of them are well established (concentrations

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of serum ferritin, serum iron, soluble transferrin receptor (sTfR), and sTfR/log ferritin index). Others, such as serum hepcidin, hold considerable promise, although they are not yet widely used [3, 4]. Iron metabolism is one of the most complex processes involving different tissues. Many pathophysiological disorders are responsible for changes in iron homeostasis. These can ultimately result in iron deficiency or iron excess, both of which have detrimental effects, not only on erythropoiesis but also on the immune system [5]. Ferritin and transferrin are proteins notably influenced by inflammation, which behave as acute-phase reactants and make it difficult to differentiate between IDA, which occurs when iron deficiency is severe enough to limit erythropoiesis, and anemia of chronic disease (ACD) occurring with malignancy or infection. For the detection and differentiation of IDA, the sTfR and the sTfR index appear to be important. Moreover, sTfR may be of greater clinical value as an added value to serum ferritin in the detection of ACD [6].

Anemia of inflammation (AI) is the second most common type of anemia. Inflammation-inducible cytokines and the major regulator of iron homeostasis, hepcidin, block intestinal iron absorption and cause iron retention in the mononuclear phagocyte system (MPS), resulting in iron-restricted erythropoiesis [7]. Due to the toxicity of iron in the human body, there is a complex, precise mechanism that controls its levels inside and outside of cells. Hepcidin is crucial in this mechanism [8]. Interleukin 6 (IL-6) is involved in the regulation of serum iron levels via the control of ferroportin 1 which is an iron transporter. IL-6 induces hepcidin production, which blocks the action of ferroportin 1 on the gut, and thus reduces serum iron levels [9]. This means that the IL-6-hepcidin axis is responsible for hypoferremia and anemia associated with chronic inflammation. These changes in acute phase protein levels and red blood cells are used for the evaluation of inflammatory severity in routine clinical laboratory examinations [10]. Labile iron and inflammatory conditions during infection can generate high levels of toxic free radicals and oxidative stress that can trigger cellular damage and cause diseases in different tissues and organs [5]. Furthermore, inflammatory cytokines shorten the lifespan of erythrocytes, impair the production and function of erythropoietin (EPO), and inhibit the proper proliferation and differentiation of erythroid progenitor cells [11].

Experimental evidence in recent decades has shown that iron is a fundamental element for the normal development of the immune system. Its deficiency affects the capacity to have an adequate immune response. The role of iron for immunity is necessary for immune cell proliferation, particularly lymphocytes, associated with the generation of a specific response to infection [12]. Iron is required for monocyte/macrophage differentiation, while macrophages require iron as a cofactor for the execution of important antimicrobial effector mechanisms. Little is known concerning the effect of clinical iron deficiency on cytokines, although it has been reported that *in vitro* production of cytokines by lymphocytes of iron deficiency patients may be impaired [2].

The aim of this pilot study was to evaluate the relationship between blood levels of iron, IL-6 and infection rates in children with IDA compared to a control group.

Material and methods

The study included 36 patients matched for age and gender (18 in the study group and 18 in the control). The study group included children with iron deficiency anemia diagnosed based on an interview, physical examination (pallor, fatigue, impaired concentration), and laboratory tests (decreased hemoglobin below 2 standard deviations for sex and age, mean corpuscular volume <80 fL, serum ferritin <30 µg/L). Patients from the study group were before or during iron therapy, and were selected from the ambulatory clinic of the Department of Pediatric Hematology, Oncology and Transplantology, Medical University of Lublin, Poland, or from hospitalized patients in the same ward. Patients outside the 1–18 age range, with coexisting autoimmune diseases, cancer, immunodeficiency, protein and energy malnutrition, acute or chronic systemic disease known to affect the immune system, and chronic infections, were excluded from the study. Children taking immunosuppressants and currently or previously treated with chemotherapy or radiotherapy were also ineligible to participate in the study.

The control group consisted of children without iron deficiency anemia who did not meet the exclusion criteria. All patients in the control group had normal hemoglobin levels for their age and sex, with normal red blood cells, serum iron, and ferritin levels and were selected only from the ambulatory clinic. At the time of sampling, individuals from the test and control groups showed no symptoms of infection.

We evaluated several different parameters: red blood cells (RBC), hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), medium cell hemoglobin concentration (MCHC), iron, transferrin, ferritin, white blood cells (WBC), and neutrophils. The serum concentration of IL-6 from a venous blood sample of each patient was assessed using the electrochemiluminescence method on Cobas apparatus (Elecsys IL-6 immunoassay, Roche Diagnostics GmbH, Mannheim, Germany). A sandwich test with the following reagents was used for the assays: streptavidin-coated microspheres, anti-IL-6~biotin antibodies, biotinylated monoclonal anti-IL-6 mouse antibodies, and anti-IL-6 antibodies labeled with a ruthenium complex. The measurement range of the apparatus was 1.5–5,000 pg/mL. The reference range of IL-6 in an external study using the Elecsys IL-6 test was 0.00–7.00 pg/mL. According to the methodology for IL-6 assays, *in vitro* tests were carried out for the 18 most commonly used drugs and 13 drugs used in special cases. No interference was found.

The coefficient of variation (CV) in periodic quality control was 2.08% and 2.62%. All blood samples for IL-6 determination from anemic patients and controls were collected during routine diagnostic tests.

The children's parents were surveyed regarding basic data, nutrition, duration of anemia, other diseases, medications (from both groups), and frequency of infections during the year before the diagnosis of IDA and during the disease (in the study group).

This study was approved by the Bioethics Committee of the Medical University of Lublin, Poland (committee's reference number: KE-0254/52/2021). Written, informed consent to participate from the patients' parents, and cumulative consent from patients above 16 years old and their parents were obtained.

Statistical analysis of the study results was performed using the IBM SPSS Statistics program. Three levels of statistical significance were adopted: $p < 0.001$, $p < 0.01$, and $p < 0.05$, in each of which the difference was defined as statistically significant. The following tests and statistical coefficients were used: Pearson's chi^2 test of independence (to determine whether there was a statistically significant relationship between nominal variables or between nominal and ordinal variables), Shapiro-Wilk test (to determine whether the analyzed variables measured at the ratio level were consistent with or deviated from the normal distribution), Spearman's rho correlation coefficient (to determine whether there were statistically significant linear correlations), Mann-Whitney U test (to determine whether the two groups differed statistically significantly in terms of variables measured at the ordinal level or in terms of variables measured at the ratio level, but whose distribution was statistically significant to deviate from normal distribution), the Wilcoxon rank test (to determine whether there was a significant difference between two measurements (in the same group) of an ordinal variable or between two measurements (in the same group) of a quotient variable whose distribution was statistically significantly different from the normal distribution statistically), and McNemar's test (to determine whether there was a statistically significant difference between two measurements (in the same group) of a nominal variable).

Analysis of the study results began with checking the normality of the distribution of variables measured at the quotient level, in order to select the appropriate tests and coefficients for the main part of the analysis. Distributions of 17 out of 25 variables in the study group and of 10 out of 16 variables in the control group significantly differed from the normal distribution. Only in the cases of RBC, MCH, and MCHC were the distributions in both groups normal, and thus only in their cases would it be acceptable to use parametric tests when comparing groups. Thus, in order to maintain full comparability of the results, a decision was made to use tests and non-parametric coefficients in the entire statistical analysis.

Results

Demographic and medical data regarding the study and control group is set out in Tables I and II.

There was no statistically significant difference between the groups in terms of the frequency of consumption of meat, milk, or dairy products ($p = 0.502$, $p = 0.485$, $p = 0.301$, respectively). Children from the study group had had anemia from one week to 8 years before the IL-6 study, and on average for just under one year (11.79 months). Half had more than and half had less than 1 year and 10 months. The standard deviation of 6.5 months shows that the study group was highly diversified in terms of the duration of anemia (time from diagnosis to the day of the IL-6 test).

There were statistically significant differences between the groups in terms of the following test results: Hb, MCV, MCH, MCHC and iron. In all these parameters, significantly higher results were recorded in the control group than in the study group (Table III). In addition, the difference in the case of ferritin was close to statistical significance ($p = 0.052$). There were much higher results in the control group. However, the test was performed on only two people from this group.

Further, the number of colds, viral diarrheas, the incidence of other serious infectious diseases and the average

Table I. Characteristics of study and control groups

Parameters	Study group N = 18	Control group N = 18	Statistics
Age range	From 1 year 4 months to 17 years	From 3 to 17 years	
Mean age [years]	10.33	Nearly 9.80	$p = 0.837$
Median age [years]	13.13	9.00	
Sex	12 females, 6 males	6 females, 12 males	**$p = 0.046$**
Mean height [cm]	138.1	138.9	$p = 0.962$
Median height [cm]	153.0	138.0	
Mean weight [kg]	37.3	39.2	$p = 0.862$
Median weight [kg]	39.0	32.0	
Mean body mass index [kg/m^2]	17.7	18.3	$p = 0.849$
Median body mass index [kg/m^2]	17.2	18.0	

Table II. Characteristics of comorbidities, medications, diet, and dietary supplements in study and control groups according to survey

Parameter	Study group N = 18	Control group N = 18	Statistics
Comorbidities	13 had none (72.2%) 2 allergy/atopic dermatitis 1 insulin resistance 1 arthrogryposis 1 kidney stones	11 had none (61.1%) 4 hemophilia 2 neutropenia 1 spherocytosis (1 hypothyroidism — not given by answerer)	$p = 0.480$
Permanent medications	12 none (66.7%) 3 iron 1 metformin and isotretinoin 1 desloratadine, dimenhydrinate and mometasone	15 none (83.3%) 1 coagulation factors 1 vitamin B6, folic acid 1 levothyroxine	$p = 0.248$
Diet	16.7% of group on a diet	11.1% of group on a diet	$p = 0.630$
Dietary supplements	Used by 50.0% of group	Used by 61.1% of group	$p = 0.502$

Table III. Comparison of groups in terms of blood test results

Blood test results	Group	Mean	Median	Number of patients	Mann-Whitney U test
Hemoglobin [g/dL]	Study	10.76	10.85	18	**$p = 0.002$**
	Control	12.83	12.35	18	
MCV [fL]	Study	73.56	71.65	18	**$p = 0.044$**
	Control	77.44	79.40	18	
MCH [pg]	Study	23.31	24.30	18	**$p = 0.001$**
	Control	27.93	27.55	18	
MCHC [g/dL]	Study	31.53	32.35	18	**$p < 0.001$**
	Control	34.28	34.30	18	
Ferritin [µg/l]	Study	19.75	16.20	15	$p = 0.052$
	Control	74.15	74.15	2	
Iron [µg/dL]	Study	50.11	27.75	14	**$p = 0.044$**
	Control	151.33	201.00	3	
IL-6 [pg/mL]	Study	4.47	3.74	18	$p = 0.133$
	Control	2.75	2.28	18	

MCV — mean corpuscular volume; MCH — mean corpuscular hemoglobin; MCHC — medium cell hemoglobin concentration; IL-6 — interleukin 6

duration of the infection before the diagnosis of anemia and after the diagnosis were compared in the study group (Table IV). The analysis of IL-6 levels in both groups is presented in Table V. No statistical significance was noted between groups in terms of IL-6 level ($p = 0.133$).

The relationships between the level of IL-6 and the parameters included in the study, measured at the quotient level were examined separately in the study group and the control group [age, height, weight, body mass index (BMI), duration of anemia from diagnosis up to the day of the examination of IL-6, hemoglobin, RBC, MCV, MCH, MCHC, ferritin, transferrin, iron, WBC, neutrophils, the frequency of meat/milk/dairy products consumption per week, number of colds and viral diarrheas before anemia diagnosis, mean duration of illness before anemia diagnosis, number of colds and viral diarrheas after anemia diagnosis, and mean duration of illness after anemia diagnosis].

In the study group, there was a statistically significant, strong, negative correlation between IL-6 and iron levels ($p = 0.012$), which is presented in the diagram below (Figure 1). Several negative trends close to statistical significance were found, according to which the higher the level of IL-6, the lower the results of MCH and ferritin ($p = 0.083$ and $p = 0.061$, respectively). The other parameters did not correlate with IL-6 ($p > 0.05$). In the control group, no statistically significant or close to statistical significance was found between IL-6 and the parameters included in the study, measured at the quotient level ($p > 0.05$ for each parameter).

Table IV. Characteristics of incidence of infections in study groups before and after diagnosis of anemia

Parameter	Study group before diagnosis N = 18	Study group after diagnosis N = 18	Statistics
Mean number of colds	3.28	2.81	$p = 0.144$
Mean number of viral diarrheas	1.17	0.39	**$p = 0.041$**
Mean number of other infectious diseases	0.17	0.28	$p = 0.500$
Mean duration of infection [days]	5.42	6.58	$p = 0.498$
Taking antibiotics	Taken by 58.8% of group	Taken by 41.2% of group	$p = 0.219$

Table V. Analysis of interleukin 6 (IL-6) levels in study and control groups

Parameter of IL-6	Study group N = 18	Control group N = 18
Mean level [pg/mL]	4.47	2.75
Median level [pg/mL]	3.74	2.28
Range of values [pg/mL]	1.5–10.84	1.5–6.86
Standard deviation	3.05	1.62

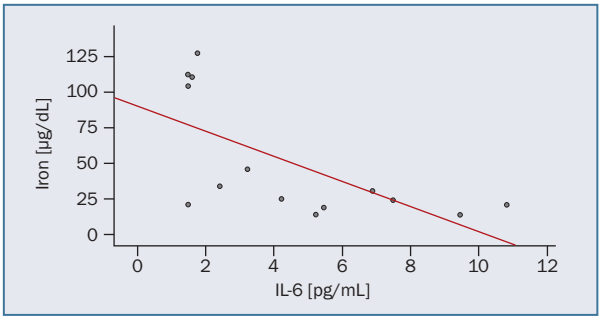

Figure 1. Correlations between interleukin 6 (IL-6) and iron levels in study group

Discussion

Iron is a fundamental element for the normal development of the immune system and is necessary for cell proliferation [2]. In the studies published, a statistically significant correlation has been found between serum iron level and IL-6. Hassan et al. concluded that IL-6 is influenced in patients with iron deficiency anemia [2]. Patients with iron deficiency anemia in this study had significantly lower IgG and serum IL-6 levels than controls. Interestingly, a positive correlation was found between serum iron levels and IL-6.

In the study by Ekiz et al. [13] (32 children with IDA, 29 in the control group) the mean levels of IL-6 were 5.6 ± ± 3.9 pg/mL in children with IDA and 10.3 ± 5.3 pg/mL in the control group (p <0.001). In our study, we observed an opposite correlation; the levels of IL-6 were higher in the study group.

Interestingly, Abdul-Hussein et al. [14] found that patients with sickle cell anemia had significantly higher IL-6 and IL-8 levels than healthy children (p <0.05). This is a similar correlation to our results, but their study concerned another type of anemia.

Consumption of large quantities of non–iron-fortified cow's milk and dairy products favors the occurrence of iron deficiency anemia [15]. However, we did not observe a statistically significant difference in diet between the study and control groups.

Furthermore, anemia is most common in children during late infancy/early childhood because of rapid growth, exhaustion of gestational iron, and low levels of dietary iron. The second period when there is an increased occurrence of anemia is adolescence, due to rapid growth, suboptimal iron intake, and menstrual blood loss in females [15]. Due to the prevalence of anemia in these two age groups, we included in our study patients aged from 1 to 17 years.

The literature concerning the effect of iron deficiency anemia on the development of infections in children is very limited; however, individual studies have supported this association. Children with iron-deficiency anemia have a higher prevalence of episodes of acute otitis media compared to healthy, non-anemic children, and there is a direct relationship between the degree of anemia and the number of episodes [16]. A further study shows that anemia may affect the innate immunity of children and may result in a decreased level of salivary human beta defensin-3 (HβD3), thus increasing vulnerability to decay [17]. In our study, the average number of viral diarrheas decreased significantly after the diagnosis of IDA compared to before the diagnosis. This may be explained by an improvement in the condition of the immune system after starting treatment for IDA, as well as by reduced exposure to viral infections, as patients stayed at home during the coronavirus disease 2019 (COVID-19) pandemic. However, there was no statistically significant change in the number of colds and the mean duration of the infection.

There are several limitations that we can point to after conducting this pilot study. To begin with, the sizes of our study and control groups need to be expanded to determine whether the results are reproducible. Secondly, the survey

for the parents holds a risk of data inaccuracy, as the answers were subjective. This problem was however limited by the fact that each time after completion of a questionnaire, one of our researchers checked it and answered the parent's doubts about the content of the questions. Moreover, our study was performed in a hematology clinic (for organizational reasons), and therefore some patients included in the control group had chronic diseases and took medications. We tried, to the best of our knowledge, to exclude from both study and control groups patients with infections, neoplasms, autoimmune diseases, immunodeficiency, malnutrition, and other diseases that might affect the iron metabolism or influence the immune system [2, 18–20].

In the future, we would be inclined to select the subjects for control from a family doctor's clinic to avoid comorbidities that may affect the results of blood tests. That might comprise children who report for health checks or vaccinations. However, the downside of such a solution would be the need to take a separate blood sample from the patient, because preventive blood tests are rarely performed in healthy children. Our research was based on minimizing suffering during the assays.

Moreover, the time from the diagnosis of IDA in the study group varied from one week to 8 years before the IL-6 study (on average 11.79 months), which shows that the group is highly diversified in terms of the duration of anemia. After analyzing the pilot study, we suggest conducting a further study on a larger group of patients and dividing them into subgroups with different durations of anemia, since our group was too small to be divided into subgroups. A minority of children had levels of blood C-reactive protein (CRP) tested, because the influence of iron on the immune system and infections is not so commonly associated and it is not routine practice to test CRP in all patients with IDA. In addition, our patients did not have an infection during the study, so there was no indication to order a CRP test.

We analyzed a possible effect of chronic diseases on the level of IL-6 according to the literature and our results. Madhok et al. [21] stated that hemophilic patients have increased IL-6 concentrations. However, theirs is a relatively old article, and in our four control patients with hemophilia the mean IL-6 level was 3.125 pg/mL, slightly higher than in the whole control (2.75 pg/mL) but still lower than in the study group (4.47 pg/mL). In our study, there was no statistically significant correlation between levels of neutrophils and IL-6 either in the study or the control group ($p = 0.303$ and $p = 0.266$, respectively) and two patients with neutrophilia might not disturb the results. According to Vinchi et al. [22], hereditary spherocytosis is associated with an increase in IL-6 levels. Our patient with spherocytosis from the control group had IL-6 at the level of 1.5 pg/mL, which is below the mean [22]. Our study did not concern the study of IL-6 levels in various hematological diseases, and the information obtained during the analysis of the results of patients from the control group might be treated as an inspiration for further analyses.

Conclusions

As a result of this pilot study, we suggest that there might be a relation between iron and IL-6. Our findings suggest that IL-6 may play a role in iron deficiency anemia and, together with iron, affect the immune system. Increased levels of IL-6 in the study group did not correspond with visible changes in rates and the course of colds, but resulted in a reduction in the frequency of viral diarrhea. Further research on a larger group of patients more closely matched for the duration of anemia, and without any comorbidities in the control group, is required to determine the effect of IDA on the immune system.

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Author's contributions

AK — study conception and design, data collection, manuscript writing. GR — study conception and design, data collection, manuscript writing. ZR — data collection, manuscript writing. AB — data collection, manuscript writing. MJ — statistical analysis. KD — study conception and design, revision of manuscript, supervision. All authors read and approved manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

This study was approved by the Bioethics Committee of the Medical University of Lublin, Poland (committee's reference number: KE-0254/52/2021). Written, informed consent to participate was obtained from the patients' parents, and cumulative consent from patients above 16 years old and their parents.

References

1. Camaschella C. New insights into iron deficiency and iron deficiency anemia. Blood Rev. 2017; 31(4): 225–233, doi: 10.1016/j.blre.2017.02.004, indexed in Pubmed: 28216263.
2. Hassan TH, Badr MA, Karam NA, et al. Impact of iron deficiency anemia on the function of the immune system in children. Medicine (Baltimore). 2016; 95(47): e5395, doi: 10.1097/MD.0000000000005395, indexed in Pubmed: 27893677.
3. Camaschella C. Iron deficiency. Blood. 2019; 133(1): 30–39, doi: 10.1182/blood-2018-05-815944, indexed in Pubmed: 30401704.
4. Schümann K, Solomons NW. Perspective: what makes it so difficult to mitigate worldwide anemia prevalence? Adv Nutr. 2017; 8(3): 401–408, doi: 10.3945/an.116.013847, indexed in Pubmed: 28507005.
5. Yiannikourides A, Latunde-Dada GO. A short review of iron metabolism and pathophysiology of iron disorders. Medicines (Basel). 2019; 6(3), doi: 10.3390/medicines6030085, indexed in Pubmed: 31387234.
6. Infusino I, Braga F, Dolci A, et al. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia. A meta-analysis. Am J Clin Pathol. 2012; 138(5): 642–649, doi: 10.1309/AJCP16NTXZLZFAIB, indexed in Pubmed: 23086764.
7. Weiss G, Ganz T, Goodnough LT, et al. Anemia of chronic disease. N Engl J Med. 2005; 352(10): 1011–1023, doi: 10.1056/NEJMra041809, indexed in Pubmed: 15758012.
8. Słomka A, Łęcka M, Styczyński J. Hepcidin in children and adults with acute leukemia or undergoing hematopoietic cell transplantation: a systematic review. Cancers (Basel). 2022; 14(19), doi: 10.3390/cancers14194936, indexed in Pubmed: 36230859.
9. Nemeth E, Rivera S, Gabayan V, et al. IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest. 2004; 113(9): 1271–1276, doi: 10.1172/jci200420945.
10. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014; 6(10): a016295, doi: 10.1101/cshperspect.a016295, indexed in Pubmed: 25190079.
11. Chaparro CM, Suchdev PS. Anemia epidemiology, pathophysiology, and etiology in low- and middle-income countries. Ann NY Acad Sci. 2019; 1450(1): 15–31, doi: 10.1111/nyas.14092, indexed in Pubmed: 31008520.
12. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr. 2001; 131(2S-2): 568S–579S; discussion 580S, doi: 10.1093/jn/131.2.568S, indexed in Pubmed: 11160590.
13. Ekiz C, Agaoglu L, Karakas Z, et al. The effect of iron deficiency anemia on the function of the immune system. Hematol J. 2005; 5(7): 579–583, doi: 10.1038/sj.thj.6200574, indexed in Pubmed: 15692603.
14. Abdul-Hussein HK, Al-Mammori HS, Hassan MK. Evaluation of the expression of red blood cell CD36, interleukin-6 and interleukin-8 in sickle cell anemia pediatric patients. Cytokine. 2021; 143: 155534.
15. Matysiak M. Anemia in children: a pediatrician's view. Acta Haematol Pol. 2021; 52(4): 402–405, doi: 10.5603/AHP.2021.0075.
16. Golz A, Netzer A, Goldenberg D, et al. The association between iron-deficiency anemia and recurrent acute otitis media. Am J Otolaryngol. 2001; 22(6): 391–394, doi: 10.1053/ajot.2001.28075, indexed in Pubmed: 11713723.
17. Faheem S, Maqsood S, Hasan A, et al. Associations of early childhood caries with salivary beta defensin-3 and childhood anemia: a case-control study. BMC Oral Health. 2021; 21(1): 445, doi: 10.1186/s12903-021-01810-x, indexed in Pubmed: 34521396.
18. Rose-John S. Blocking only the bad side of IL-6 in inflammation and cancer. Cytokine. 2021; 148: 155690, doi: 10.1016/j.cyto.2021.155690, indexed in Pubmed: 34474215.
19. Tanaka T, Narazaki M, Kishimoto T. Interleukin (IL-6) immunotherapy. Cold Spring Harb Perspect Biol. 2018; 10(8), doi: 10.1101/cshperspect.a028456, indexed in Pubmed: 28778870.
20. Uciechowski P, Dempke WCM. Interleukin-6: a masterplayer in the cytokine network. Oncology. 2020; 98(3): 131–137, doi: 10.1159/000505099, indexed in Pubmed: 31958792.
21. Madhok R, Cruickshank A, Gracie AJ, et al. Increased interleukin 6 concentrations in the absence and presence of HIV-1 infection in haemophilia. J Clin Pathol. 1992; 45(9): 766–769, doi: 10.1136/jcp.45.9.766, indexed in Pubmed: 1401204.
22. Vinchi F, Sparla R, Passos ST, et al. Vasculo-toxic and pro-inflammatory action of unbound haemoglobin, haem and iron in transfusion-dependent patients with haemolytic anaemias. Br J Haematol. 2021; 193(3): 637–658, doi: 10.1111/bjh.17361, indexed in Pubmed: 33723861.

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VIA MEDICA

Tisagenlecleucel CAR-T for relapsed/refractory diffuse large B-cell lymphoma; one therapy, two clinical presentations: urgent need to design adverse event predictors

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Chimeric antigen receptor (CAR) T-cell therapy for diffuse large B-cell lymphoma (DLBCL) has revolutionized treatment outcomes yet it poses new challenges to clinicians. In parallel with its success, CAR-T will inevitably reach clinical units inexperienced in the use of this treatment type.

That was the case in Poland, where the Ministry of Health launched a reimbursement of tisagenlecleucel for adult patients with CD19-positive lymphoid malignancies only in 2022 [1]. In this article, we aim to compare the first two cases of patients treated with tisagenlecleucel at the Department of Hematology, Transplantation and Internal Medicine in the Medical University of Warsaw, Poland. The two patients developed highly contrasting clinical presentations after CAR-T infusion. The different clinical courses between these subjects constitute a valuable example of the highly variable systemic responses to tisagenlecleucel. In addition, we briefly discuss an adverse event (AE) prediction concept developed by research teams worldwide.

Initially, both patients were diagnosed with DLBCL not otherwise specified (NOS) and were subsequently treated in units not certified for CAR-T. A summary of the patients' treatment before CAR-T is set out in Table I. Initially, Patient#1 had a stage IV DLBCL compared to a stage II E diagnosed in Patient#2 [2]. Both patients were females with no comorbidities except for obesity in Patient#1. Moreover, both had no bone marrow or central nervous system (CNS) involvement at the time of diagnosis. Their detailed characteristics are given in Table I. Notably, at the time of diagnosis, Patient#2 was in the 24th week of pregnancy.

Following the diagnosis, Patient#1 received six cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone) chemoimmunotherapy with subsequent irradiation of the involved areas (IF-RT). Due to progressive disease, the patient received R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin) salvage therapy. Additionally, MTX/DEX (methotrexate, dexamethasone) was administered intrathecally for CNS prophylaxis. After one cycle of R-DHAP, the treatment was continued with R-ICE (rituximab, ifosfamide, carboplatin, etoposide) due to a lack of response to the former (disease progression, macroscopic assessment). Subsequently, the patient was qualified for CAR-T and continued R-ICE as a bridging therapy, resulting in remission prior to CAR-T treatment.

On the other hand, Patient#2 received pre-phase treatment with cyclophosphamide and glucocorticoids followed by four cycles of CHOP, four cycles of R-CHOP, and IF-RT. Subsequently, four cycles of R-ICE were administered, resulting in progressive disease and Patient#2 was qualified for CAR-T therapy. Later, due to the large tumor burden, the intention-to-treat was to administer Pola-BR (polatuzumab vedotin, bendamustine, rituximab) as bridging therapy before CAR-T. However, because of progression the patient subsequently received one cycle of R-DHAP, with macroscopic progression during the cycle, and one cycle of GemOX (gemcitabine and oxaliplatin), administered because of a coronavirus disease 2019 (COVID-19) diagnosis at the planned time of the initiation of lymphodepleting chemotherapy. R-DHAP was complicated by sepsis caused by *Klebsiella pneumoniae*. Moreover, thrombosis of the

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Table I. Clinical course of patients — general characteristics

	Patient#1		Patient#2	
		Date*		Date*
Sex, age	Female, 45	N/A	Female, 38	N/A
Diagnosis (IHC confirmed)	DLBCL, NOS, non-GCB, MYC-positive, BCL2-positive Ki-67 95%	Apr 2021	DLBCL, NOS, GCB, MYC-negative BCL2-negative Ki-6 100% mut*TP53*-positive	Jun 2021
Disease stage at diagnosis (Lugano classification)	IV	Apr 2021	II E	Jun 2021
Prephase treatment	–	–	CTX + GCs	Jun 2021
First-line therapy	R-CHOP (6 cycles)	2021	CHOP (4 cycles) R-CHOP (4 cycles)	Jul–Nov 2021
	IF-RT	2021	–	-----
Salvage therapy	R-DHAP (1 cycle)	May 2022	IF-RT (50 Gy – 2 Gy × 25 fractions)	Dec 2021–Jan 2022
Second-line salvage therapy	R-ICE (1 cycle)	Jun 2022	R-ICE (4 cycles)	May–Aug 2022
Bridging therapy	R-ICE (2 cycles)	Jul–Aug 2022	P + BR R-DHAP (1 cycle) GemOX (1 cycle)	Sep 2022 Oct 2022 Nov 2022
Other therapeutic regimens	Intrathecal MTX/DEX	May 2022	mPRED 96mg/day	Aug 2022
Disease status at lymphodepletion	CR		PD	
Lymphodepletion	Flu/CTX	Sep 2022	Flu/CTX	Nov 2022
CAR-T infusion	Completed	Sep 2022	Completed	Nov 2022
Treatment result	CR	Dec 2022	PD	Dec 2022
CRS	No	–	Grade 3	Nov 2022
CRS characteristics	N/A	N/A	Fever >40°C BP 90/60, peripheral hypoperfusion, HR 150, facial and neck edema, elevated CRP and IL-6 ICU admission: oxygen delivery 25 l/min, vasopressor, tocilizumab administration	N/A
ICANS	No	–	Grade 1	Nov–Dec 2022
ICANS characteristics	N/A	N/A	ICE score 8, confusional state, mental status changes	N/A
EASIX score before lymphodepletion	0.88	Sep 2022	1.50	Nov 2022
EASIX score on infusion day	0.95	Sep 2022	1.08	Nov 2022
EASIX-F score before lymphodepletion	183.54	Sep 2022	682.52	Nov 2022
EASIX-F score on infusion day	149.72	Sep 2022	887.37	Nov 2022

*Date of observation/procedure/treatment duration; ABC — activated B-cell; BCL2 — B-cell lymphoma 2 protein; BP — blood pressure; CAR-T — chimeric antigen receptor T-cells; CR — complete remission; CRP — C-reactive protein; CRS — cytokine release syndrome; CTX — cyclophosphamide; DLBCL — diffuse large B-cell lymphoma; EASIX — Endothelial Activation and Stress Index, defined as [lactate dehydrogenase (LDH); U/L] × creatinine [mg/dL])/platelets [PLTs; × 10^9/L]; EASIX-F — defined as EASIX × ferritin [ng/mL]; Flu/CTX — fludarabine + cyclophosphamide; GCs — glucocorticoids; GCB — germinal B-center; GemOX — gemcitabine + oxaliplatin; Gy — gray; HR — heart rate; ICANS — immune effector cell-associated neurotoxicity syndrome; ICE — immune effector cell encephalopathy; ICU — intensive care unit; IF-RT — involved-field radiation therapy; IHC — immunohistochemistry; IL-6 — interleukin 6; Ki-67 — nuclear protein Ki-67; mPRED — methylprednisolone; MTX/DEX — methotrexate + dexamethasone; MYC — MYC proto-oncogene bHLH transcription factor; N/A — not applicable; NOS — not otherwise specified; P+BR — polatuzumab, vedotin + bendamustine, rituximab; PD — progressive disease; R-CHOP — rituximab + cyclophosphamide, adriamycin, vincristine, prednisone; R-DHAP — rituximab + dexamethasone, cytarabine, platinum agent; R-ICE — rituximab + ifosfamide, carboplatin, etoposide; TP53 — tumor protein P53

right iliac vein was diagnosed one day before the lymphodepletion, as well as acute pancreatitis in the course of lymphoma, infiltrating the pancreas.

In both cases, tisagenlecleucel was administered as initially planned. Following the infusion, Patient#1 experienced no AEs, whereas Patient#2 developed grade 3 cytokine release syndrome (CRS) and grade 1 neurotoxicity [immune effector cell-associated neurotoxicity syndrome (ICANS)] [3]. The onset of CRS was on day +1 post-infusion and manifested initially with increasing fever and facial edema. The patient's condition deteriorated, resulting in a transfer to the intensive care unit (ICU). The patient developed tachycardia, hypotension, fever, head and neck edema, and required oxygen therapy (details in Table I). Tocilizumab and vasopressors were administered, resulting in CRS subsiding on day +5 and a return from ICU. On day +6, the patient developed mild neurotoxicity symptoms (grade 1).

These two cases show very different clinical presentations following treatment, which could not be determined in advance. The current guidelines state that CRS prediction is not yet possible, indicating factors such as high tumor burden associated with a higher risk of CRS [3]. Recently, CRS and ICANS have been linked to endothelial dysfunction [4], and various endothelial activation markers have been proposed as AE predictors [5, 6]. The simplest measure of endothelial activation is the Endothelial Activation and Stress Index (EASIX), defined as [lactate dehydrogenase (LDH); U/L] × creatinine [mg/dL])/platelets [PLTs; × 10^9/L] and its derivatives, for instance: EASIX × ferritin [4, 5]. The EASIX scores for Patients#1 and 2 are provided at the bottom of Table I, and have been calculated for day –7 (i.e. before lymphodepletion) and day 0 (day of CAR-T infusion). Unfortunately, EASIX scores are bias-susceptible. For instance, renal insufficiency or tumor lysis syndrome will lead to changes in creatinine and LDH concentrations, respectively, impacting EASIX.

Nevertheless, Penack et al. [4] have shown that a baseline EASIX of 4.67 could be used as a cutoff for severe CRS prediction (grade ≥3). And according to Pennisi et al. [7], EASIX scores before lymphodepletion are associated with CRS occurrence. The median value was 1.88 in Pennisi et al.'s 'CRS group' [7] compared to 1.06 in their 'no CRS group'.

Even so, EASIX scores are not validated predictors of CRS occurrence, and we cannot draw conclusions from the calculated values. However, as the endothelium can be damaged by factors such as chemotherapy, cytokines, or sepsis [8], it appears reasonable to deduce that Patient#2 developed AEs due to having been previously exposed to infection and more chemotherapy regimens. In addition, other factors predicting CRS are currently under investigation. When endothelial activation occurs, cytokines, adhesion molecules, and other markers such as angiopoietins, are released, and their serum concentrations are being evaluated as potentially more accurate predictors [6, 9].

To sum up, treating DLBCL with tisagenlecleucel may be associated with very different clinical scenarios that pose significant challenges for clinical teams. Therefore, accurate predictors of adverse events would be extremely beneficial, and endothelial activation is emerging as a potential candidate.

Authors' contributions

All authors contributed equally to manuscript preparation. All authors read and agreed to published version of manuscript.

Conflict of interest

The authors declare no conflict of interest.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

References

1. Obwieszczenie Ministra Zdrowia z dnia 20 kwietnia 2022 r. w sprawie wykazu refundowanych leków, środków spożywczych specjalnego przeznaczenia żywieniowego oraz wyrobów medycznych. Dz. Urz. Min. Zdr. 2022.41. https://dziennikmz.mz.gov.pl/legalact/2022/41/ (April, 20, 2022).
2. Cheson BD, Fisher RI, Barrington SF, et al. Alliance, Australasian Leukaemia and Lymphoma Group, Eastern Cooperative Oncology Group, European Mantle Cell Lymphoma Consortium, Italian Lymphoma Foundation, European Organisation for Research, Treatment of Cancer/Dutch Hemato-Oncology Group, Grupo Español de Médula Ósea, German High-Grade Lymphoma Study Group, German Hodgkin's Study Group, Japanese Lymphorra Study Group, Lymphoma Study Association, NCIC Clinical Trials Group, Nordic Lymphoma Study Group, Southwest Oncology Group, United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32(27): 3059–3068, doi: 10.1200/JCO.2013.54.8800, indexed in Pubmed: 25113753.
3. Kröger DN, Gribben DJ, Chabannon C, Yakoub-Agha I, Einsele H. ed. The EBMT/EHA CAR-T cell handbook. Springer, Cham 2022.
4. Korell F, Penack O, Mattie M, et al. EASIX and severe endothelial complications after CD19-directed CAR-T cell therapy — a cohort study. Front Immunol. 2022; 13: 877477, doi: 10.3389/fimmu.2022.877477, indexed in Pubmed: 35464403.

5. Greenbaum U, Strati P, Saliba RM, et al. CRP and ferritin in addition to the EASIX score predict CAR-T-related toxicity. Blood Adv. 2021; 5(14): 2799–2806, doi: 10.1182/bloodadvances.2021004575, indexed in Pubmed: 34264268.
6. Hong F, Shi M, Cao J, et al. Predictive role of endothelial cell activation in cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukaemia. J Cell Mol Med. 2021; 25(24): 11063–11074, doi: 10.1111/jcmm.17029, indexed in Pubmed: 34734474.
7. Pennisi M, Sanchez-Escamilla M, Flynn JR, et al. Modified EASIX predicts severe cytokine release syndrome and neurotoxicity after chimeric antigen receptor T cells. Blood Adv. 2021; 5(17): 3397–3406, doi: 10.1182/bloodadvances.2020003885, indexed in Pubmed: 34432870.
8. Palomo M, Diaz-Ricart M, Carbo C, et al. The release of soluble factors contributing to endothelial activation and damage after hematopoietic stem cell transplantation is not limited to the allogeneic setting and involves several pathogenic mechanisms. Biol Blood Marrow Transplant. 2009; 15(5): 537–546, doi: 10.1016/j.bbmt.2009.01.013, indexed in Pubmed: 19361745.
9. Wei Z, Cheng Qi, Xu N, et al. Investigation of CRS-associated cytokines in CAR-T therapy with meta-GNN and pathway crosstalk. BMC Bioinformatics. 2022; 23(1): 373, doi: 10.1186/s12859-022-04917-2, indexed in Pubmed: 36100873.

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Cell based-therapies in patient with relapsing diffuse large B-cell lymphoma

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Relapse of diffuse large B-cell lymphoma (DLBCL) after autologous hematopoietic cell transplantation (auto-HCT) confers a poor prognosis. Many different regimens with a high-dose methotrexate (HD-MTX) backbone have demonstrated efficacy in relapsed or refractory cases, but the choice regarding subsequent lines remains a challenge [1–3]. It has been shown that chemotherapy alone is not sufficient for a cure. A cell-based consolidation with innovative chimeric antigen receptor (CAR) T-cells, or more standard allogenic hematopoetic cells, should be used to achieve long-term remission [4, 5].

Here, we present cell-based treatments in a patient with extranodal relapsing lymphoma after auto-HCT.

A 48-year-old male was diagnosed with a DLBCL (with unknown cell of origin subtype) in December 2009 with clinical stage (CS) IV. He was refractory to two cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and received auto-HCT as a consolidation, partially responding to second-line R-ESHAP (rituximab, etoposide, methylprednisolone, high-dose cytarabine, cisplatin).

Eight years later, he relapsed with extranodal disease infiltrating the chest (with histopathological confirmation of primary diagnosis, non germinal center B-cell (GCB) subtype, no molecular test was done, immunohistochemistry: BCL2–/+; BCL6+/–, c-myc–). He received six more cycles of R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone), achieving complete metabolic remission that was consolidated with a second auto-HCT in January 2019. In March 2020, he relapsed with extensive central nervous system (CNS) involvement. He recieved treatment specific for CNS lymphomas: high doses of R-MIV (methotrexate, rituximab, ifosfamide, and vincristine) [6]. After the third cycle, he achieved complete metabolic remission. He received three more R-MIV cycles with allogeneic cell consolidation from a matched unrelated donor after reduced-intensity conditioning comprising T-FluBu2 (thiotepa, fludarabine and busulfan) combined with anti-thymocyte globulin (ATG; 5 mg/kg) and standard cyclosporine and methotrexate immunosuppression. The post-transplant course was complicated only by neutropenic fever and urinary tract infection. He was engrafted in November 2020. He developed acute, and later chronic, graft-versus-host disease limited to the skin and was treated only with topical steroids.

In June 2022, the patient reported difficulties in concentrating and memory loss. Positron emission tomography–computed tomography (PET-CT) and brain magnetic resonance did not show any abnormality; the donor chimerism was 100%-donor. In August 2022, the patient's mental status began to worsen. In both magnetic resonance imaging (MRI) and PET-CT, infiltration of the ocular muscle was described with SUV_{max} 20.1 (Figure 1). In addition, infiltration of the sacral bone was also noticed (SUV_{max} 10.2) (Figure 2). Only those two regions were affected by lymphoma in PET-CT. Biopsy of the involved muscle suggested DLBCL relapse, but no CNS involvement by flow-cytometry was detected. The patient was qualified for CAR T-cell therapy (tisagenlecleucel) with polatuzumab vedotin (PV) bridging. Lymphocyte apheresis was done in September 2022, and two subsequent cycles of PV were given over the following two months. A clinical response was observed, but no control imaging was done. Infusion of CAR T-cells was carried out in November 2022 after limphodepletion therapy with fludarabine and cyclophosphamide with no severe early toxicity. An initial disease assessment was carried out in January 2023 with PET-CT, with no lymphoma presence (LPS 2).

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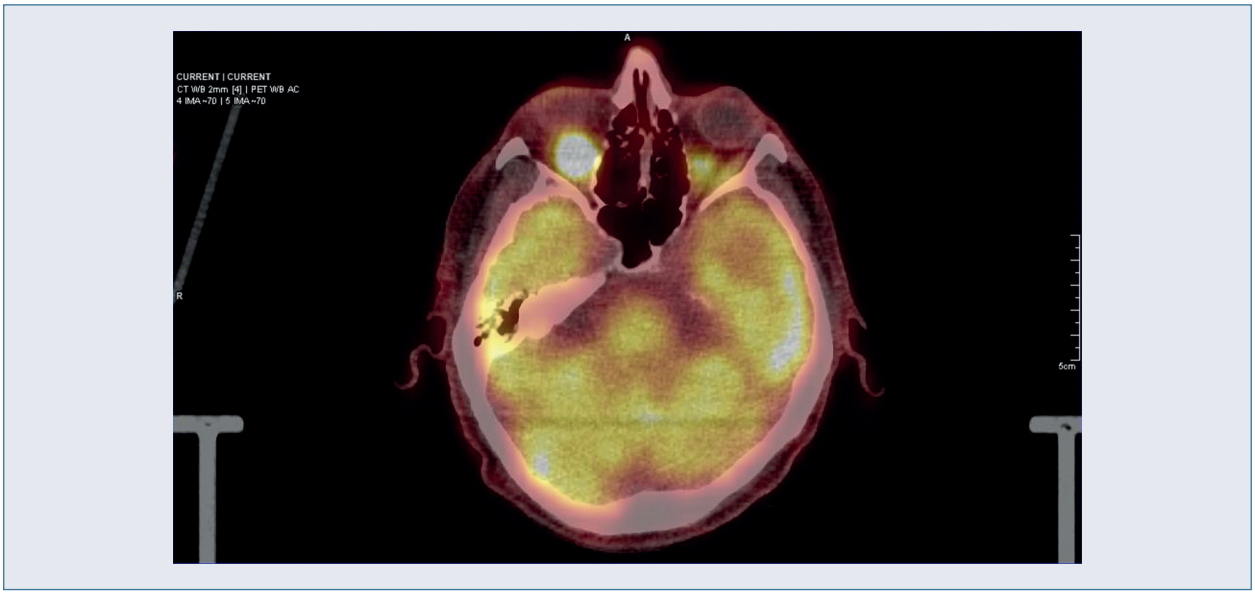

Figure 1. Positron emission tomography–computed tomography scan of head

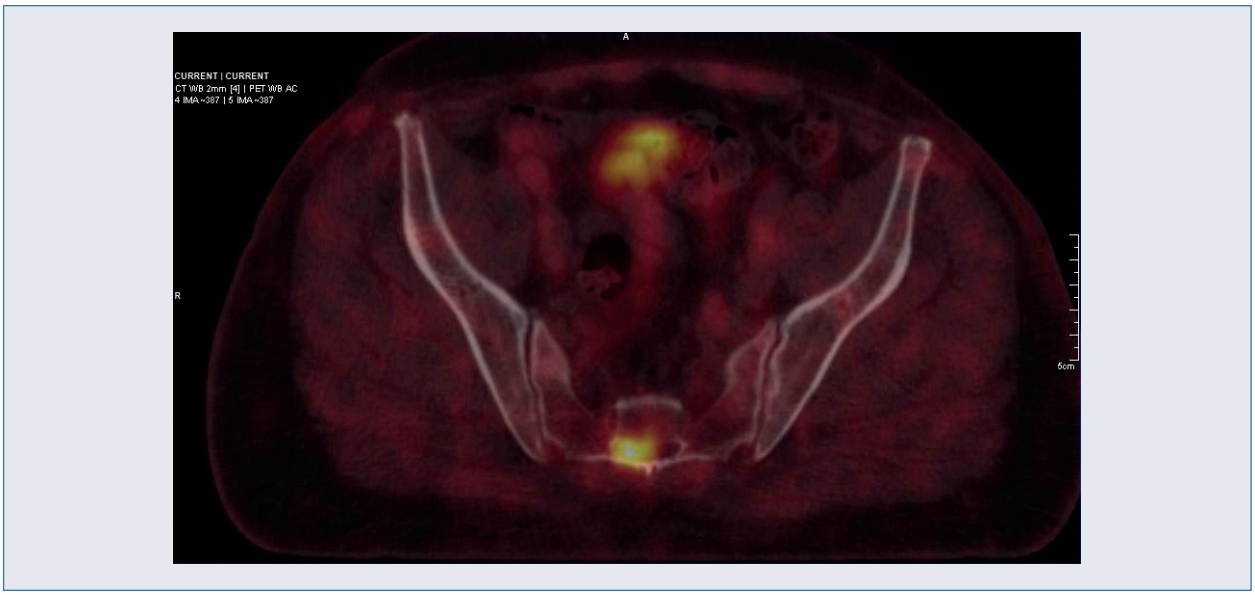

Figure 2. Positron emission tomography–computed tomography scan of pelvis

We conclude that cell-based therapies offer a unique opportunity to achieve remission in chemotherapy-resistant DLBCL. The optimal usage of CAR-T and allogeneic cells should be individualized.

Authors' contributions

AS wrote the manuscript with support from JMZ. MD and MT planned the treatment. All authors provided critical feedback and helped shape the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References

1. Nabors LB, Portnow J, Baehring J, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Central Nervous System Cancers. https://static1.squarespace.com/static/5c0062f3e17ba398a2a5aaf4/t/63868a55df9a7151186345ad/1669761628408/cns.pdf (September 29, 2022).
2. Holdhoff M, Mrugala MM, Grommes C, et al. Challenges in the treatment of newly diagnosed and recurrent primary central nervous system lymphoma. J Natl Compr Canc Netw. 2020; 18(11): 1571–1578, doi: 10.6004/jnccn.2020.7667, indexed in Pubmed: 33152700.
3. Ferreri AJM, Holdhoff M, Nayak L, et al. Evolving treatments for primary central nervous system lymphoma. Am Soc Clin Oncol Educ Book. 2019; 39: 454–466, doi: 10.1200/EDBK_242547, indexed in Pubmed: 31099614.
4. Karschnia P, Blobner J, Teske N, et al. CAR T-cells for CNS lymphoma: driving into new terrain? Cancers (Basel). 2021; 13(10), doi: 10.3390/cancers13102503, indexed in Pubmed: 34065471.
5. Siddiqi T, Wang X, Blanchard MS, et al. CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma. Blood Adv. 2021; 5(20): 4059–4063, doi: 10.1182/bloodadvances.2020004106, indexed in Pubmed: 34492703.
6. Ostrowska B. Primary central nervous system lymphoma: how to treat younger patients? Acta Haematol Pol. 2021; 52(4): 340–344, doi: 10.5603/AHP.2021.0065.

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Pneumatosis intestinalis after allogeneic hematopoietic cell transplantation

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Pneumatosis intestinalis (PI) is a radiographic sign showing the presence of gas in the subserosal and submucosal layers of the bowel wall [1, 2]. PI is not a disease itself, but rather a radiographic finding resulting from an underlying pathology [1, 2]. PI can occur as a complication following allogeneic hematopoietic cell transplantation (allo-HCT) in children. The risk factors include: conditioning chemotherapy or irradiation, antibiotic exposure, gastrointestinal (GI) infections with *Clostridioides difficile* or *Escherichia coli*, GI graft-versus-host disease (GvHD), and prolonged immune suppression [1–3].

PI presents as two different conditions: life-threatening PI and benign PI [1, 2]. Additionally, another entity, pneumatosis cystoides intestinalis (PCI), is a rare phenomenon belonging to the spectrum of benign PI, and is characterized by the presence of gas-filled cysts in the subserosa and submucosa [4, 5].

Pathogenetically, PI occurs as primary (idiopathic) (in 15% of cases) or secondary (in 85% of cases) [1, 4]. Clinical symptoms include diarrhea, vomiting, pain, tenderness, and flatulence [1, 2]. The diagnosis is usually made by computed tomography (CT), but sometimes it is identified by abdominal X-ray. PI is managed conservatively, and surgery is optional in cases of subsequent complications [1–4].

We present the case of a pediatric patient with secondary severe bone marrow aplasia who developed PI following a second allo-HCT.

A 5-year-old boy underwent allo-HCT for acute myeloid leukemia from a matched unrelated donor. Due to late secondary marrow aplasia, he had a second allo-HCT from another donor five years later, after conditioning with fludarabine, cyclophosphamide and thymoglobulin. GvHD prophylaxis included cyclosporin and methotrexate. His complications were cytomegalovirus infection, hypogammaglobulinemia, acute skin GvHD, and acute followed by chronic GI GvHD. He was treated with high-dose steroids, mycophenolate mofetil, anti-tumor necrosis factor (TNF) agent (etanercept), and extracorporeal photopheresis (ECP). 12 months after the second allo-HCT, he developed a mediastinal pneumothorax and the presence of free air nuclei in the subphrenic area was detected. In a CT scan, gas was found in the expanded intestinal wall of the transverse colon, the sigmoid colon and the descending colon, as well as in the peritoneal cavity (Figure 1). He was treated with antibiotics, total parenteral nutrition, immunoglobulins and blood products. No surgery was necessary. Two months later, all CT symptoms from the GI tract had resolved.

The probable mechanism of developing PI after allo-HCT is chemotherapy and immunosuppression, which can induce atrophy of the Peyer's patches [2, 4]. This can lead to the loss of integrity and focal damage of the bowel mucosa [4]. Subsequently, gas migration occurs into the submucosal and subserosal regions [4]. On the other hand,

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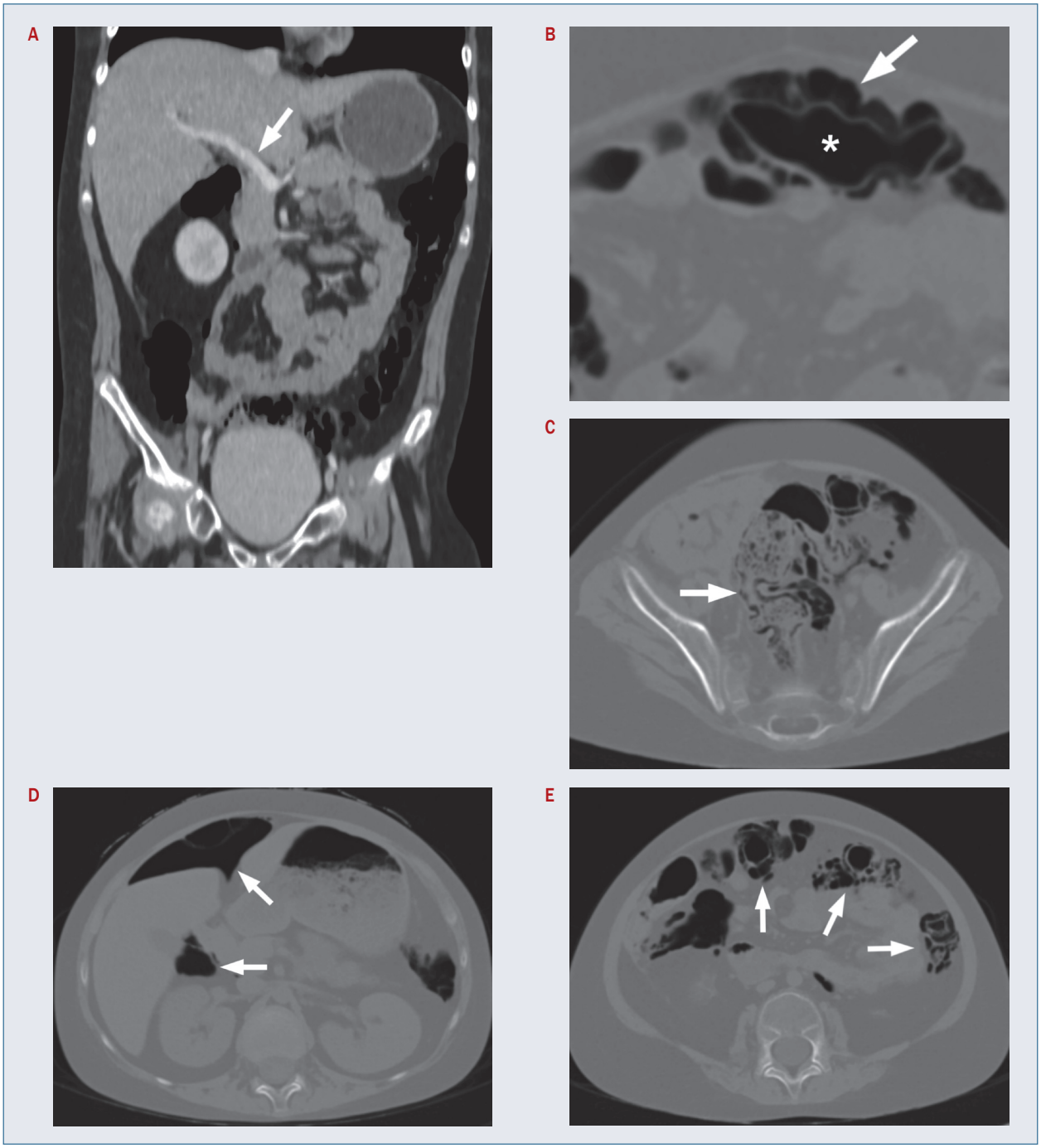

Figure 1. Pneumatosis intestinalis in computed tomography imaging: **A.** Contrast-enhanced computed tomography (CT). No evidence of gas in portal vein (arrow); **B.** Non-contrast-enhanced CT. Zoomed image of transverse colon. Gas in lumen of intestine (asterisk) and gas in expanded intestinal wall (arrow); **C.** Non-contrast-enhanced CT. Pneumatosis of sigmoid colon (arrow); **D.** Non-contrast-enhanced CT. Gas in peritoneal cavity (arrows); **E.** Non-contrast-enhanced CT. Pneumatosis of transverse colon and descending colon (arrows)

gas-forming bacteria or other immunosuppressive drugs such as steroids can contribute to PI development [1, 2]. PI shows no typical clinical presentation, and a definitive diagnosis is usually made by a CT scan [1–4]. There is no standard treatment for PI [1, 2]. In most cases, patients with PI are managed conservatively with wide-spectrum antibiotics, bowel rest and total parenteral nutrition [1–5]. Surgical therapy is considered as a second-line therapy which can be chosen in patients with other severe complications [1–5].

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Authors' contributions
KC, TS — design of study. RD, MRP, KC — provision of clinical data. ZS — imaging. All authors — analysis of clinical data. TS, JS — literature search, analysis of data, writing of manuscript. All authors — critical revision and final approval.

Conflict of interest
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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

References
1. Frolova Gregory P, Angus J, Brothers AW, et al. Risk factors for development of pneumatosis intestinalis after pediatric hematopoietic stem cell transplantation: a single-center case-control study. Transplant Cell Ther. 2022; 28(11): 785.e1–785.e7, doi: 10.1016/j.jtct.2022.08.023, indexed in Pubmed: 36038104.
2. Wallace G, Rosen N, Towbin AJ, et al. Pneumatosis intestinalis after hematopoietic stem cell transplantation: when not doing anything is good enough. J Pediatr Surg. 2021; 56(11): 2073–2077, doi: 10.1016/j.jpedsurg.2020.12.020, indexed in Pubmed: 33455803.
3. Korhonen K, Lovvorn HN, Koyama T, et al. Incidence, risk factors, and outcome of pneumatosis intestinalis in pediatric stem cell transplant recipients. Pediatr Blood Cancer. 2012; 58(4): 616–620, doi: 10.1002/pbc.23242, indexed in Pubmed: 21721114.
4. Baldari D, Pizzicato P, Tambaro FP, et al. Pneumatosis cystoides intestinalis, a rare case in a pediatric patient following allogeneic hematopoietic stem cell transplantation: CT findings and literature review. Radiol Case Rep. 2021; 16(10): 3120–3124, doi: 10.1016/j.radcr.2021.07.053, indexed in Pubmed: 34457100.
5. Shulman SC, Chiang F, Haight AE, et al. Pneumatosis intestinalis in pediatric hematopoietic stem cell transplantation patients: an uncommon complication. Fetal Pediatr Pathol. 2012; 31(5): 309–314, doi: 10.3109/15513815.2012.659389, indexed in Pubmed: 22432915.

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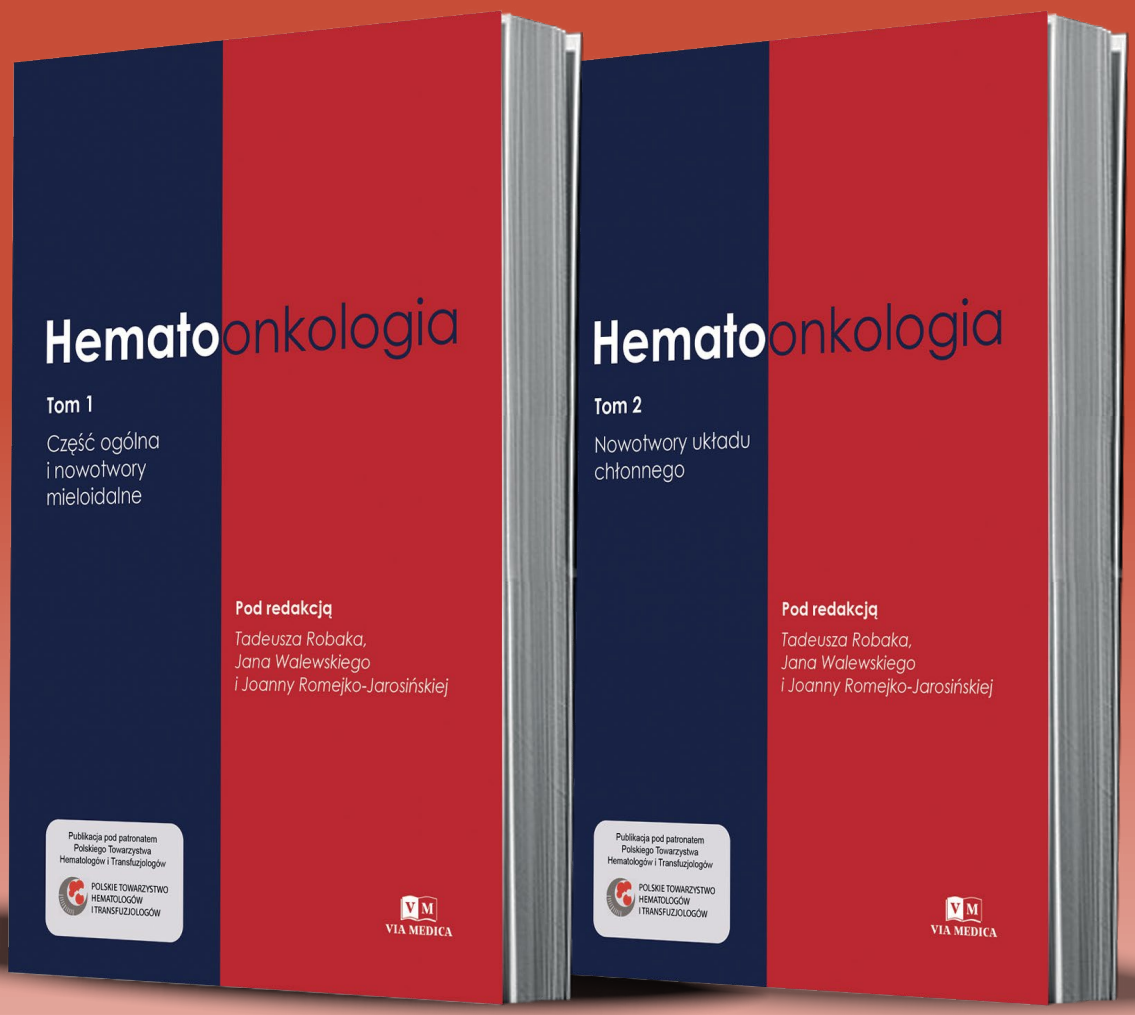

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