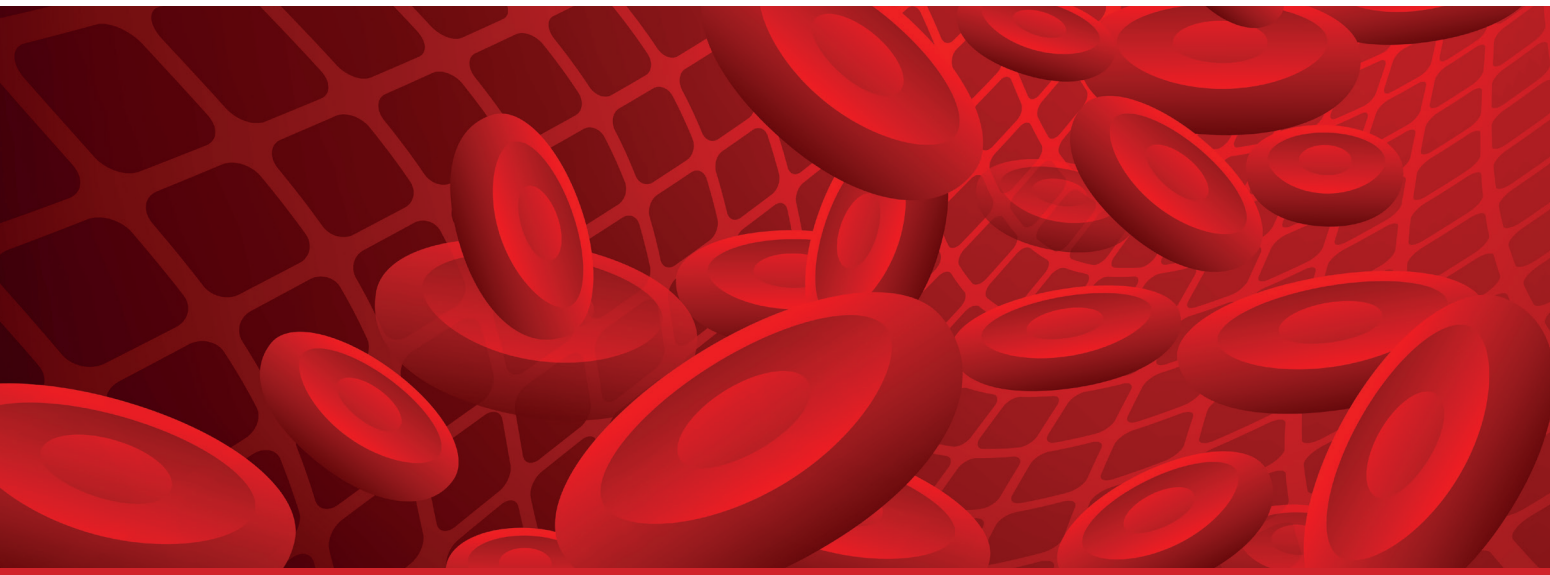
Number 1 ■ Volume 54 ■ January–February 2023 e-ISSN 2300–7117 ISSN 0001–5814



Acta Haematologica Polonica

bimonthly
of the Polish Society of Haematologists and Transfusiologists
and the Institute of Haematology and Transfusion Medicine

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Rating systems: MEiN 100 pts
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Acta Haematologica Polonica is the official peer-reviewed English language journal of the Polish Society of Haematologists and Transfusiologists and the Institute of Haematology and Transfusion Medicine associated with the polish haematology and transfusion since 1970. Journal publishes original research articles, clinical vignettes and reviews. *Acta Haematologica Polonica* covers areas of physiology and pathology in hematology and transfusion medicine, among other leukocytes, erythrocytes, platelets, immune system, mechanisms of hemostasis and clinical aspects of haematological malignancies.

Publication information: *Acta Haematologica Polonica* (ISSN 0001–5814). For 2023, volume 54 (6 issues) is scheduled for publication.

Acta Haematologica Polonica proceeds entirely online at https://journals.viamedica.pl/acta_haematologica_polonica.

The Instructions to Authors can be found on the journal's website https://journals.viamedica.pl/acta_haematologica_polonica/about/submissions/1#authorGuidelines

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Journal abstracted/indexed in: Biological Abstracts, BIOSIS Previews, Baidu Scholar, CNKI Scholar (China National Knowledge Infrastructure), CNPIEC – cnpLINKer, CrossRef, EBSCO, Google Scholar, Index Copernicus, J-Gate, KESLI-NDSL (Korean National Discovery for Science Leaders), Naviga (Softweco), Polish Ministry of Education and Science, Primo Central (ExLibris), ReadCube, Scopus, Summon (Serials Solutions/ProQuest), TDNet, WorldCat.

CME Accreditation: Authors receive 120.32 points according to Index Copernicus (2021), 100 points according to the academic rating system MEiN (2021).

The electronic version of the journal Acta Haematologica Polonica (e-ISSN 2300–7117) is the original (reference) version.

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22-6097.001.001

Acta Haematologica Polonica

The official journal of the Polish Society of Haematologists and Transfusiologists and the Institute of Haematology and Transfusion Medicine

https://journals.viamedica.pl/acta_haematologica_polonica

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EDITORIAL

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DOI: 10.5603/AHP.a2023.0009
ISSN 0001–5814
e-ISSN 2300–7117

Inspiration from American Society of Hematology Annual Meeting

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Each year in early December, all hematology-related specialists look forward to the Annual Meeting of the American Society of Hematology (ASH). The 64th such event was held in New Orleans between 9 and 13 December 2022. The ASH Meeting is a very prestigious scientific meeting. All the most important hematological achievements are presented, and new trends are identified and announced at this gathering. Hematologists used to say that the status of hematology is always located either before or after the ASH Meeting. More than 20,000 attendees participated in the ASH Meeting in December 2022, which included more than 50 general or educational/scientific sessions, more than 50 satellite sessions, and almost 1,000 oral and 4,000 poster presentations selected from submitted abstracts.

The three General Lectures and Prizes were:

- Ham-Wasserman Lecture: Irene Roberts — Leukemogenesis in infants with trisomy 21;
- E. Donnall Thomas Lecture: Bruce R. Blazar — The long and winding road to clinically effective graft-versus-host disease (GvHD) therapeutics;
- Ernest Beutler Lecture: John Atkinson and Peter Hillmen — The complement system and medicine: the good, the bad, the future.

The highest-scoring Top 6 abstracts this year were the following:

1. Dreyling et al. Efficacy and safety of ibrutinib combined with standard first-line treatment or as substitute for autologous stem cell transplantation in younger patients with mantle cell lymphoma: results from the randomized triangle trial by the European MCL Network.
2. Preston et al. An ancient transcriptional hub couples developmentally regulated gene expression with metabolism during erythropoiesis.
3. Broome et al. Efficacy and safety of intravenous efgartigimod in adults with primary immune thrombocytopenia: results of a phase III, multicenter, double-blinded, placebo-controlled, randomized clinical trial (ADVANCE IV).
4. Stelljes et al. In patients with relapsed/refractory AML sequential conditioning and immediate allogeneic stem cell transplantation (allo-HCT) results in similar overall and leukemia-free survival compared to intensive remission induction chemotherapy followed by allo-HCT: results from the randomized phase III ASAP trial.
5. Grover et al. C1 inhibitor deficiency results in increased activation of coagulation and enhanced venous thrombosis.
6. Reis et al. Discovery of INCA033989, a monoclonal antibody that selectively antagonizes mutant calreticulin oncogenic function in myeloproliferative neoplasms (MPNs).

At the 64th ASH Meeting, Polish scientists presented 22 posters, and coauthored 72 other studies, among them 25 oral (including abstracts #1 and #LBA-6) and 47 poster presentations. This is proof of high activity, at both national and international levels, which is continuously evolving [1–5].

Authors' contributions

JS — sole author.

Conflict of interest

The author declares no conflict of interest.

Financial support

None.

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Received: 04.01.2023 Accepted: 04.01.2023

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.

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VIA MEDICA

EXPERT GUIDELINES

Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 3–5
DOI: 10.5603/AHP.a2023.0001
ISSN 0001–5814
e-ISSN 2300–7117

Recommendations on cardiac safety during ibrutinib therapy

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Abstract

In November 2022, an update of the Summary of Product Characteristics for Imbruvica® (ibrutinib) was published, containing new risk minimization measures, including dose modification recommendations, due to the risk of serious cardiac events in patients receiving ibrutinib.

A team of experts composed of developed practical guidelines aimed at increasing cardiac safety and optimizing the care of patients treated with Bruton's tyrosine kinase inhibitors. The document was based on the recommendations of the European Society of Cardiology.

Key words: ibrutinib, cardio-oncology, hypertension, heart failure, atrial fibrillation

Acta Haematologica Polonica 2023; 54, 1: 3–5

Introduction

There are currently insufficient data to create separate cardiac algorithms for ibrutinib and acalabrutinib. Based on current experience and available publications, it seems that the profile and incidence of cardiac complications may be similar for both therapies and are probably related to the class effect of Bruton's tyrosine kinase (BTK) inhibitors.

It should be highlighted that the high effectiveness of therapy with BTK inhibitors significantly outweighs the risk of substantial toxicity. Additionally and importantly, decisions regarding patients with risk factors for cardiac events should always be made on an individual basis, after assessing the risk-benefit ratio, before starting treatment of ibrutinib.

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Received: 23.12.2022 Accepted: 3.01.2023

Recommendations for cardiac initial assessment and monitoring during the use of BTK inhibitors in accordance with the recommendations of the European Society of Cardiology (ESC) from 2022 (prepared in cooperation with European Hematology Association) [1]

General remarks

1. At present, there are insufficient data to create separate cardiac algorithms for ibrutinib and acalabrutinib — the profile and incidence of cardiac complications appear to be similar for both drugs.
2. BTK inhibitors are used for treatment of lymphoid malignancies, which are common in elderly people with underlying cardiovascular disease. While chronological age alone is not a significant predictor of serious cardiac events (including cardiac death), significant coexisting cardiovascular diseases and reduced patient fitness increase the risk, and thus the likelihood of cardiac complications.
3. Patients taking ibrutinib may be at increased risk of developing hypertension, atrial fibrillation, heart failure, ventricular arrhythmias not associated with QTc prolongation.

European recommendations

In a patient treated with a BTK inhibitor:

1) it is recommended to measure blood pressure at each clinical visit (class I recommendation, level B evidence);
2) weekly home blood pressure monitoring during the first 3 months of treatment and monthly thereafter should be considered (class IIa recommendation, level C evidence);
3) baseline cardiac echocardiography is recommended in high-risk patients (class I recommendation, level C evidence);
4) cardiac echocardiography is recommended for all patients who experience atrial fibrillation (class I recommendation, level C evidence);
5) pulse assessment or ECG is recommended at each clinical visit (class I recommendation, level C evidence).

Practical guidelines developed by a Polish experts panel

1. **Cardiac baseline assessment and optimization of cardiac treatment:**
   a) **high-risk** patient — any patient with a history of heart disease — for such a group of patients it is recommended to perform an echocardiography and echocardiogram (ECG), as well as to order a cardiological consultation;
   b) a patient **of at least intermediate risk** — a patient with arterial hypertension or diabetes or cardiac arrhythmias — for such a group of patients it is recommended to perform an ECG. In addition, echocardiography and cardiological consultation should be considered.
2. **Monitoring during treatment with ibrutinib:**
   a) blood pressure measurements at each clinical visit, it is also worth recommending home measurements
      → in the case of elevated blood pressure, modification of antihypertensive treatment is indicated;
   b) assessment of the pulse at each clinical visit and heart rate at least during auscultation, it is optimal to perform an ECG;
   c) informing the patient about the need to report any new symptoms, such as: dyspnea, decrease in exercise tolerance or feeling of irregular heart rhythm
      → in the case of the above symptoms, it is advisable to perform an ECG;
      → if arrhythmias are diagnosed, echocardiography is indicated.
3. **Ibrutinib dosage modifications:**
   a) discontinuation of ibrutinib or dose reduction occurs after the diagnosis of cardiac complications specified in the table I [2]. Consultation with a cardiologist is then recommended. Treatment may be restarted according to the new dose modification recommendations [3];
   b) a cardiologist evaluating each ibrutinib-related cardiac complication should additionally refer his diagnostic decisions to the latest definition of cancer therapy-related cardiovascular toxicity (CTR-CVT) proposed by the International Cardio-Oncology Society [4] and accepted by the European Society of Cardiology. In the aspect of cancer therapy related cardiac dysfunction (CTRCD), it is possible to implement preventive strategies at very early stages of myocardial damage (even asymptomatic ones), which may prevent cardiac events, the occurrence of which necessitates the discontinuation of ibrutinib or reduction of his dose;
   c) the Summary of Product Characteristics (SmPC) of Imbruvica® does not contain contraindications for patients with hypertension or cardiac comorbidities. Ibrutinib has been studied in a broad patient population worldwide, including patients with underlying cardiac comorbidities or cardiac risk factors. There are also available data suggesting that dose reduction will not have a significant impact on the efficacy of ibrutinib [3].

Table I. Diagnostic criteria proposed by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 [3] and proposed rules for dose reduction or discontinuation of ibrutinib for cardiac reasons

Type of complication	Definition of a complication	Recommendations for the use of ibrutinib
Grade 4 heart failure	Life-threatening condition — urgent hospitalization, intravenous administration of drugs, *etc.*	Discontinuation of the drug after the first occurrence
Grade 4 arrhythmia	Life-threatening condition: hemodynamic disorders, thrombus in the heart cavities	
Grade 3 heart failure	Dyspnea at rest or with minimal activity	
Grade 3 arrhythmias	Symptoms of arrhythmia require urgent intervention	• First occurrence → dose reduction by 140 mg • Second occurrence → drug discontinuation
Grade 2 heart failure	Dyspnea occurs with moderate activity	• First and second occurrence → dose reduction by 140 mg • Third occurrence → drug discontinuation

Authors' contributions

SS — preparation of the draft version of the manuscript. IH, KG, KJ, TR — critical, independent evaluation of manuscript. SS, IH, KG, KJ, TR — acceptance of the final version of the manuscript.

Conflict of interest

SS — fees for lectures or Advisory Board or support for attending meetings from companies: Amgen, Angelini, Astellas, AstraZeneca, Bayer, BMS, Gilead, Janssen-Cilag, Pfizer, Teva. IH — fees for lectures and advisory meetings: Janssen, AstraZeneca, Abbvie, Roche. KG — honoraria and research grants from companies Janssen-Cilag, AstraZeneca, Abbvie, BeiGene, Roche, Sandoz. KJ, TR — no conflict of interest reported.

Financial support

Not reported.

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.

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Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 6–10
DOI: 10.5603/AHP.a2022.0002
ISSN 0001–5814
e-ISSN 2300–7117

REVIEW ARTICLE

Hematology on Twitter

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Abstract

Twitter's impact on information dissemination and the possibility of exchanging opinions between people around the world have made this social platform particularly appealing for hematologists. We have evaluated the potential use of Twitter in the field of hematology for both physicians and patients, and sought out direct examples of Twitter's current application in medicine and hematology. With the use of the site https://followerwonk.com we have created a list of the most followed hematologists and hematological organizations and described their activity on Twitter.

Key words: hematology, social media, Twitter

Acta Haematologica Polonica 2023; 54, 1: 6–10

Introduction

The advent of social media enabled people all over the world to communicate and spread information much easier and faster. Between 2005 and 2015, an almost tenfold increase in adult Americans using social networking sites was observed (from 7% in 2005 to 65% in 2015) [1]. Apart from sources of entertainment, news and means of communicating, users of social media use them to obtain information related to health. As a consequence, those related to medicine, alongside medical organizations and journals, tend to post about the latest discoveries, standards of diagnosis and treatment etc. on their profiles. As hematology is one of the branches of medicine present in social media, in this paper we investigate its activity on Twitter.

What is Twitter?

Twitter, which started in July 2006, is a real-time, microblogging site with over 300 million monthly users [2]. To communicate, users of Twitter post short messages (up to 280 signs, including emojis). These are called 'tweets' [3–6]. As the content must be short, they often use acronyms or hashtags which are words or phrases preceded by a hash sign (#), used to identify specific topics. The tweet can also contain a photograph, short video clip, other website link or thumbnail [3, 7]. In order to receive updates of a particular account's tweets, one has to 'follow' it and become its 'follower'. For example, Barack Obama's account has 131 million followers [2]. Users who see a tweet can react by 'favoriting' or 'retweeting' it, which results in their followers seeing it and so the content rolling out to a wider audience.

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Received: 03.12.2022 Accepted: 05.12.2022

Moreover, users can tag others by using the '@' symbol [3, 7]. All these functions make Twitter very useful for those connected to hematology in spreading information, sharing points of view, and discussing medical issues.

Twitter in medicine

Twitter's environment has become one of the favored forums for physicians to discuss healthcare issues. Numerous papers and articles have explored the actual and potential value of social media for both physicians and patients [8]. Not only does it help to disseminate up-to-date information among people in the healthcare system, but also brings opportunities for professional development [3, 5–11]. Nowadays, news on social media spreads more rapidly than in traditional newspapers or radio or television broadcast [8]. Therefore many respected medical journals have their own Twitter accounts where they publish the latest information on a daily basis [3, 7, 11]. Data obtainable from these sites includes the latest articles, guidelines, clinical trials, educational opportunities, information about annual meetings, and more. The ease with which one can 'tag' specialists from around the world, or mention other physicians' tweets, enables discussions on medical issues which would not be possible otherwise. Such exchanges of views can lead to international cooperation [3, 6–9, 11, 12]. Weyand et al. [4] even mention a situation when one tweet lamenting a product label contraindication led to the establishment of an international registry.

On a personal level, Twitter makes it possible to follow experts in a particular medical branch and get their opinions on different issues. It is also a way to stay up-to-date with their latest articles and research. Such a network of virtual mentors is of enormous benefit for beginners in the field who are seeking career guidance [3, 7]. Furthermore, building a strong presence on Twitter can be seen as personal branding. Being active on a professional forum can lead to career opportunities and academic advancement [9]. Twitter can also be perceived as a useful tool to promote publications. Phillips et al. [13] stated that covering publications in the mainstream media had led to more journal citations, going back to 1991. Different studies have shown that sharing and pre-publishing papers on Twitter also results in significantly more citations [4, 6, 13]. The increasing influence of Twitter (and all social media) has resulted in the creation of the Altmetric scoring system, which shows how much attention an article has received across an array of platforms including mainstream and social media. This system, however, does not measure the quality of each work, and thus there have been concerns raised of manipulation attempts such as purchasing mentions [4].

With the swiftly growing and widespread popularity of Twitter, more patients with rare disorders have united together and formed communities. Not only does this strengthen the communication between people suffering from a disease, it also enables engagement from healthcare providers, scientists and advocates forming an international infrastructure. Stakeholders of such communities can express their issues with the use of disease-specific hashtags (e.g. #leusm for leukemia patients, #mmsm for multiple myeloma patients). As a result, physicians can receive direct feedback from their patients and follow their treatment. Moreover, specialists in the field can educate these communities and correct misconceptions. As Twitter enables real time interaction, physicians have an opportunity to learn more about the course of the particular disease as patients are usually open to sharing their experiences [9]. Furthermore, a study of prostate cancer by Huber et al. showed that online communities contribute to the decision making process regarding the choice of treatment [9, 14].

Hematology on Twitter

Being an international social media platform, Twitter is a place where one can gain recognition and build one's reputation. The most common way of measuring an account's popularity is by counting its followers, which tells you how many people (i.e. Twitter accounts) receive your tweets.

We have created a list of the most followed organizations/institutions and people associated with hematology. In order to achieve that, we used the site https://followerwonk.com/ which allows its users to find accounts with particular words in their Twitter profiles. We searched for accounts containing the words 'hematologist', 'hematology', 'hematologic', and 'hematological' and divided them into groups of organizations/institutions and individuals. It is important to remember that one is free to include whatever one wants on one's Twitter profile, regardless of the authenticity of this information. Having ranked our obtained groups in order of declining number of followers, we have created lists of the most popular accounts (Table I).

Among the most popular we find not only organizations or societies with @ASH_hematology (number 1 in the ranking) having the most followers but also @ASCOPost (number 2) and @OncologyTimes (number 3). Each account has its own profile of published posts, and their graphic design varies as well. @ASH_hematology, with almost 60,000 followers, tweets about its annual meetings (dedicated hashtag for the one held in 2022: #ASH22), ethical issues, FDA updates and innovative therapies. Furthermore, some of the posts contain disease-riddles using the association's own image bank. @CancerNetwrk's (#7, c.25,000 followers) tweets reviews of data from trials, announcements of works published in journals, and recent Food and Drug Administration (FDA) approvals. In some of these, podcasts/interviews with authors are attached. Moreover, every week a tweet with the top five articles of this period appears. @CancerNetwrk also retweets content published

Table I. Top 15 hematology societies, organizations or institutions on Twitter

	Society, organization or institution	Followers	Tweets	Account age [years]	Social authority*
1	@ASH_hematology | ASH	59,701	17,278	13.08	57
2	@ASCOPost | The ASCO Post	57,443	30,354	12.93	56
3	@OncologyTimes | Oncology Times	50,478	26,774	13.82	53
4	@BloodJournal | Blood Journal	45,191	6,551	7.29	63
5	@BloodAdvances | Blood Advances	30,432	5,22	6.51	53
6	@CancerNetwrk | CancerNetwork®	25,257	15,741	13.72	55
7	@EHA_Hematology | European Hematology Association	23,516	4,863	11.62	59
8	@OncJournal | The Oncologist	21,172	2,69	12.31	38
9	@ASHClinicalNews | ASH Clinical News	19,362	3,372	8.07	44
10	@VJHemOnc | VJHemOnc	18,224	31,337	7.58	62
11	@TheLancetHaem | The Lancet Haematology	17,54	3,772	8.39	56
12	@ESHaematology | ESH (Haematology)	11,997	1,775	11.74	42
13	@DFBC_PedCare | Dana-Farber/Boston Children's	8,713	6,22	13.38	43
14	@MDedgeHemOnc | MDedge Hematology & Oncology	7,946	11,257	13.42	33
15	@ELShematology | Elsevier Hematology	7,549	2,691	9.13	49

*Social authority is a reliable metric scored out of 100, which is calculated by: The retweet rate of users' last few hundred tweets. How recently they have tweeted. A retweet-based model trained on user profile data.

live by lecturers during conferences (so called 'real time reports'), which increases its prevalence. #8 @EHA_Hematology: beyond purely scientific content and promoting the next annual meeting (#EHA23), this leads weekly quizzes called #thinkingthursdays, #ehacase and #learningMondays, allowing its followers to verify their knowledge. In the top 10 organizations, places 2–5 and 8–10 were taken by journal accounts whose tweets are mainly focused on their recently published articles/retweeting from hematology-related associations. A unique form of tweets is published by @VJHemOnc (#10; The Video Journal of Hematological Oncology) as they contain links to video-interviews and podcasts which are free and possible to see on the journal's website/Youtube. However, these are intended for healthcare personnel (HCP) only.

Unlike the first group, tweets published by individuals (set out in Table II) concern not only medical issues but also matters of everyday life. These people also tend to offer their private opinions on 'hot topics' such as politics or sport. The majority of content is still hematology-related, yet more frequently associated with practical issues for physicians. In order to engage with followers, owners of these accounts publish clinical cases in the form of quizzes or riddles to solve. Twitter enables the creation of questions in the shape of polls displaying the percentage of people who have chosen the correct answer. Making concise summaries of particular hematological issues, e.g. the causes of B12 deficiency, is common as well. Besides, Twitter is a place where physicians promote charity events e.g. healthcare workers against hunger (@acweyand). Given the ability to retweet or reply, owners of these accounts can discuss the latest articles and/or research trials. Furthermore, individual hematologists can engage remotely in hematological annual meetings e.g. ASH 2022 by stating their opinions with occasional hashtags.

Conclusions

Given the rapid growth of Twitter's popularity, it comes as no surprise that hematology has found a way of using it in multiple aspects. The unique method of posting short messages of up to 280 signs rewards concision and flexibility to best convey the essence of information in quickly readable tweets [3–6]. As a result, physicians can stay up to date with the most recent publications, research trials and new drug approvals by simply scrolling through this social platform [3, 9, 11]. It also gives them the opportunity to make a name for themselves and receive recognition internationally [9]. One can also follow leaders of particular areas of medicine in order to obtain knowledge from the best [6, 7, 9, 12, 15].

However, it is imperative to prioritize the welfare of patients by protecting their confidential health information and remaining professional with adherence to general standards while tweeting. In today's world, which is filled with fake information on social media, every physician should be particularly careful when retweeting different materials [3, 9, 11]. Furthermore, as everything posted on Twitter is

Table II. Top 15 hematologists on Twitter

	Hematologist	Followers	Tweets	Account age [years]	Social authority*
1	@AaronGoodman33 | Aaron Goodman — 'Papa Heme'	103,818	10,535	5.59	85
2	@acweyand | Shematologist, MD	63,768	41,581	5.82	81
3	@nihardesai7 | Nihar Desai	33,550	16,644	13.17	78
4	@DoctorYazanA | Yazan Abou-Ismail, MD	20,891	5,565	11.79	63
5	@j_thePA | aj PA-C	20,506	30,636	10.63	60
6	@Alaskar98 | Alaskar	19,661	6,901	10.96	64
7	@DavidSteensma | David Steensma, MD	19,565	6,521	8.28	56
8	@DrFadloKhuri | Dr. Fadlo Khuri	17,268	5,743	8.96	51
9	@Faisal_Alsayegh | Faisal Alsayegh	16,232	28,513	11.79	60
10	@HallekMichael | Michael Hallek	14,318	2,316	3.96	59
11	@Mohty_EBMT | Mohamad Mohty	14,179	34,589	8.42	66
12	@marwanalhajeili | Marwan Al-Hajeili	13,222	6,000	7.94	43
13	@MPaiMD | Menaka Pai, MSc MD FRCPC	12,837	8,96	6.29	61
14	@NicoGagelmann | Nico Gagelmann	12,807	4,493	4.07	69
15	@AMarshallMD | Ariela Marshall MD	12,611	4,749	9.96	54

*Social authority is a reliable metric scored out of 100, which is calculated by: The retweet rate of users' last few hundred tweets. How recently they have tweeted. A retweet-based model trained on user profile data.

considered permanent, the possible dissemination of inappropriate or inaccurate data can have very negative consequences [8, 9].

Authors' contributions

JS — design of study; TS, JS — literature search and analysis of data, writing manuscript. All authors — critical revision and final approval.

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.

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VIA MEDICA

ORIGINAL RESEARCH ARTICLE

Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 11–17
DOI: 10.5603/AHP.a2022.0003
ISSN 0001–5814
e-ISSN 2300–7117

Changing risk factors in childhood acute lymphoblastic leukemia: experience from Kujawsko-Pomorski region 1976–2018

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Risk factors in childhood ALL have changed during recent decades, mostly due to treatment personalization.

The aim of this study was to analyze therapy results and prognostic factors in childhood ALL in the Kujawsko-Pomorski region of Poland between 1976 and 2018.

Material and methods: Data from 495 patients (0–18 years old) diagnosed with ALL from the Kujawsko-Pomorski region between 1976 and 2018 was analyzed. Prognostic factors were analyzed separately in specific therapeutic groups, which were defined by several therapy protocols.

Results: Prognostic factors have changed over the course of consecutive therapeutic periods. Between 1976 and 1988 (the first and second therapeutic protocols), central nervous system involvement was the most important risk factor. During the third therapeutic period, an unsatisfactory treatment response on days 8 and 14 was related to a poor outcome. In 1995–2002, the risk factors were hepatomegaly, splenomegaly, lymph nodes involvement, and unsatisfactory therapy response on days 15 and 33. Between 2002 and 2011, immunophenotype other than 'common' and hemoglobin level at diagnosis were the risk factors, and a lack of BCR-ABL aberration was related to better therapy results. During the final analyzed period (2011–2018), failure to achieve remission on day 33 was a risk factor, and patients classified as non-high risk group and those aged <6 years had better outcomes.

Conclusions: The changing profile of risk factors in ALL has reflected progress in ALL therapy, with the gradual elimination of factors related to poor outcomes, mostly due to modifications in treatment and the development of diagnostic methods as well as therapy monitoring.

Key words: acute lymphoblastic leukemia, prognostic factors, risk factors, children, therapeutic era

Acta Haematologica Polonica 2023; 54, 1: 11–17

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Received: 07.08.2022 Accepted: 27.11.2022

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and represents more than 20% of all malignancies in patients aged 0–18 years. Each year, c.200–220 children are diagnosed with ALL in Poland [1]. Therapy outcomes have improved significantly over recent decades — the probability of five-year overall survival has increased from 31% in 1975 to c.85% with current therapy protocols [2, 3]. The identification of prognostic factors was undoubtedly one of the milestones in ALL therapy: the presence of risk factors enabled risk group stratification and therapy adjustment. Patients with factors related to a poor outcome have received more intensive treatment, whereas in children with more favorable features, treatment has been modified to avoid severe toxicity and short-term as well as long-term side effects [4].

Prognostic factors in ALL can be divided into three groups: factors related to patient characteristics, factors related to disease features, and factors related to treatment response. Age at diagnosis, race and sex are prognostic factors related to patient characteristics. Factors related to disease include leukocytes count at diagnosis, blasts immunophenotyping, chromosomal aberrations in blast cells, and the presence of extramedullary infiltrations. Prognostic factors related to therapy include response to treatment on days 8, 15 and 33 and the presence of minimal residual disease (MRD) at later timepoints [5].

The aim of this study was to analyze therapy results and the significance of prognostic factors in childhood ALL in the Kujawsko-Pomorski region between 1976 and 2018.

Material and methods

Design of study

In this study, data from 495 patients (0–18 years old) diagnosed with ALL from the Kujawsko-Pomorski region of Poland between 1976 and 2018 was analyzed. Children were treated in the Department of Children's Hematology and Oncology of Antoni Jurasz University Hospital in Bydgoszcz. Prognostic factors were analyzed separately in specific therapeutic groups, which were defined by several therapy protocols.

Definitions

Treatment response was assessed on days 8, 14/15 and 28/33. Prednisone good response (PGR) was defined as absolute blast count in peripheral blood <1,000/μL on day 8 of therapy. Prednisone poor response (PPR) was defined as absolute blast count in peripheral blood ≥1,000/μL on day 8. MRD was calculated as blast cells count according to cells immunophenotyping. Patients stratified to the standard risk (SR) group should have MRD <0.1% on day 14/15 to remain in the SR group. In a case of MRD between 0.1% and 10%, they were stratified to the intermediate risk group, and in a case of MRD above 10% they were stratified to the high risk group. Response definition on day 28/33 was divided into three groups, based on blast count in the bone marrow:

- **M1** <5% of blasts in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis;
- **M2** 5 <25% of blasts in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis;
- **M3** ≥25% of blasts in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis.

Hepatomegaly and splenomegaly was defined as enlargement of liver and spleen above the value normal for the patient's age. Central nervous system (CNS) involvement was defined as clinical or imaging findings of CNS disease and the presence of blasts on cytospin preparation in cerebrospinal fluid. Complete remission (CR) was achieved when the following criteria were fulfilled on day 33 of therapy: <5% blast cells (M1) in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis; ≤5 nucleated cells/μL and no evidence of blasts in cytospin and no evidence of leukemic infiltrates as evaluated clinically and by imaging; and a preexisting mediastinal mass must have decreased to at least one third of the initial tumor volume.

Treatment protocols

According to therapy protocols, patients were divided into six groups:

1. 1976–1983 — MEMPHIS V–VII (56 patients) [6];
2. 1983–1988 — BFM-83 (33 patients) [7];
3. 1988–1995 — NOPHO-86 (81 patients) [8];
4. 1995–2002 — BFM-90 (96 patients) [7] and New York I–II (19 patients) [9];
5. 2002–2011 — ALL-IC-2002 (115 patients) [10];
6. 2011–2018 — ALL-IC-2009 (95 patients) [11].

Risk factors

Prognostic factors analyzed in the entire group included age at diagnosis, sex, CNS involvement, lymph nodes involvement, mediastinal mass, splenomegaly >4 cm, hepatomegaly >4 cm, risk group according to the Berlin–Frankfurt–Munster (BFM) protocol, leukocyte count at diagnosis, hemoglobin (Hgb) level at diagnosis, and treatment response (GPR vs. PPR) on day 8 of therapy.

From 1990 onwards, additional prognostic factors were analyzed: blasts morphology according to the French–American–British (FAB) classification; blasts immunophenotyping; and treatment response on days 14/15 and 28/33. From 1996 onwards, chromosomal aberrations BCR-ABL, TEL-AML1, MLL-AF4, and the presence of hypodiploidy or hyperdiploidy were evaluated.

Table I. Prognostic factors analyzed in respective therapeutic groups

Group	Years	Prognostic factors
1	1976–1983	Age at diagnosis, sex, leukocyte count and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass)
2	1983–1988	Age at diagnosis, sex, leukocyte count, hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8
3	1988–1995	Age at diagnosis, sex, leukocyte count and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 14 and 28
4a/4b	1995–2002	Age at diagnosis, sex, leukocyte count and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 15 and 33, blast immunophenotyping, FAB classification, hypodiploidy, BCR-ABL rearrangement
5	2002–2011	Age at diagnosis, sex, leukocyte count, platelets number and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 15 and 33, MRD on day 15, blast immunophenotyping, FAB classification, hypodiploidy, hyperdiploidy, BCR-ABL, TEL-AML1 and MLL-AF4 rearrangement, risk group
6	2011–2018	Age at diagnosis, sex, leukocyte count, platelets number and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 15 and 33, MRD on day 15, blast immunophenotyping, FAB classification, hypodiploidy, hyperdiploidy, BCR-ABL, TEL-AML1 and MLL-AF4 rearrangement, risk group

CNS — central nervous system; FAB — French–American–British; MRD — minimal residual disease

Risk factors analyzed in the respective therapeutic groups are set out in Table I.

Statistical methods

The probability of overall survival (pOS), probability of event-free survival (pEFS), and probability of relapse-free survival (pRFS) were calculated with the Kaplan–Meier method, and compared by log-rank test. An 'event' was defined as relapse, death or secondary malignancy. Cox regression model was used to calculate univariate and multivariate analysis of prognostic factors. Factors with *p*-value <0.1 in univariate analysis were included into the multivariate model. Odds ratio (OR) was calculated with 95% confidence interval.

Results

For each therapeutic group, pOS, pEFS and pRFS were calculated. Risk factors of death, event and relapse were analyzed separately in each group. Results of multivariate analysis are shown in Tables II, III and IV.

Group 1

Group 1 includes patients treated between 1976 and 1983 according to the St. Jude Memphis therapeutic protocol. 5-year pOS was 19.6% (±5.3%). None of the evaluated factors achieved statistical significance in pOS analysis. 5-year pEFS was 7.4% (±3.4%). Event occurred in 92.9% of patients. The only factor with a significant impact on pEFS in univariate analysis was CNS involvement. Relapse occurred in 80.4% of patients and the 5-year pRFS was 11.2% (±4.9%). In both univariate and multivariate analysis, CNS involvement had a significant impact on pRFS and was related to a more than 20-fold increased risk of relapse. Other important adverse prognostic factors included mediastinal mass and Hgb level <8 g/dL at diagnosis.

Group 2

The second group was treated between 1983 and 1988 according to the BFM-83 therapeutic protocol. 5-year pOS was 54.5% (±8.7%) and pEFS was 53.2% (±8.8%). CNS involvement was a risk factor of death and event in univariate and multivariate analysis of both parameters. Additionally, age <1 year and >6 years at diagnosis had a significant impact on pOS; patients of this age had a 3-fold higher risk of death during this therapeutic era. Relapse occurred in 12 patients (36.4%) and 5-year pRFS was 61.0% (±9.2%). None of the analyzed factors achieved statistical significance in either univariate or multivariate analysis of pRFS.

Group 3

Between 1988 and 1995, patients were treated according to the NOPHO-86 protocol. In this group, 5-year pOS was 58.0% (±5.5%) and 37 children died during the observational period, which represented 45.7% of the entire group. The most important prognostic factor on pOS was treatment response on day 8. Patients with PPR at this timepoint had a 3-fold higher risk of death. In univariate analysis also Hgb level <8 g/dL had a significant impact on pOS, although this effect was not shown in multivariate analysis. 5-year pEFS was 51.9% (±5.6%). In univariate analysis, therapy response on days 8 (PPR) and 14 (M3) as well as Hgb level

Table II. Multivariate analysis of prognostic factors for probability of overall survival

Group	Years	Prognostic factors	OR* (95% CI)	*p*
1	1976–1983	No parameter reached statistical significance	–	–
2	1983–1988	CNS involvement	10 (1.7–64)	*p* = 0.010
		Age at diagnosis <1 year or >6 years	3.8 (1.1–13)	*p* = 0.033
3	1988–1995	Treatment response on day 8 (PPR)	3.1 (1.6–6.2)	*p* = 0.001
4a	1995–2002	Risk group — HR	5.6 (2.21–14)	*p* <0.001
		Hepatomegaly	4.6 (1.7–12)	*p* = 0.002
		Treatment response on day 33 (bone marrow morphology — M2)	10 (1.03–96)	*p* = 0.047
4b	1995–2002	No parameter reached statistical significance	–	–
5	2002–2011	Immunophenotype other than 'common ALL'	3.1 (1.2–8.2)	*p* = 0.019
		Lack of BCR-ABL arrangement	0.1 (0.02–0.3)	*p* < 0.001
6	2011–2018	Risk group — non-HR	0.2 (0.1–0.5)	*p* < 0.001

*Odds ratio (OR) >1 means an increased risk of failure; CI — confidence interval; CNS — central nervous system; PPR — prednisone poor response; HR — high risk; ALL — acute lymphoblastic leukemia

Table III. Multivariate analysis of prognostic factors for probability of event-free survival

Group	Years	Prognostic factors	OR* (95% CI)	*p*
1	1976–1983	CNS involvement	8.3 (1.6–43.7)	*p* = 0.012
2	1983–1988	CNS involvement	8.6 (1.5–49)	*p* = 0.015
3	1988–1995	Treatment response on day 14 (M3)	2.6 (1,2–5.9)	*p* = 0.018
4a	1995–2002	Risk group — HR	3.5 (1.5–7.9)	*p* = 0.003
		Splenomegaly	2.9 (1.3–6.3)	*p* = 0.008
4b	1995–2002	Lymph nodes involvement	4.2 (1.3–13)	*p* = 0.011
		Treatment response on day 15 (M2)	23 (1.6–100)	*p* = 0.022
5	2002–2011	Hgb <8 g/dL at diagnosis	2.3 (1.1–4.8)	*p* = 0.028
6	2011–2018	Failure to achieve CR on day 33	10.7 (1.0–114)	*p* = 0.049
		Age <6 at diagnosis	0.2 (0.1–0.9)	*p* = 0.031

*Odds ratio (OR) >1 means an increased risk of failure; CI — confidence interval; CNS — central nervous system; HR — high risk; Hgb — hemoglobin; CR — complete remission

Table IV. Multivariate analysis of prognostic factors for probability of relapse-free-survival

Group	Years	Prognostic factors	OR* (95% CI)	*p*
1	1976–1983	CNS involvement	34 (4.2–270)	*p* = 0.001
		Mediastinal mass	4.9 (1.04–23)	*p* = 0.044
		Hgb <8 g/dL at diagnosis	2.8 (1.1–7)	*p* = 0.029
2	1983–1988	No parameter reached statistical significance	–	–
3	1988–1995	Treatment response on day 8 (PPR)	1.8 (0.8–4.2)	*p* = 0.019
4a	1995–2002	Splenomegaly	5.0 (1.7–14)	*p* = 0.002
		T-cell immunophenotyping	4.3 (1.4–13)	*p* = 0.009
4b	1995–2002	Treatment response on day 15 (M2)	7.7 (1.04–56)	*p* = 0.042
5	2002–2011	Hgb >8 g/dL at diagnosis	3.9 (1.5–10.4)	*p* = 0.007
6	2011–2018	Failure to achieve remission on day 33	24 (1.4–402)	*p* = 0.027
		Age <6 at diagnosis	0.1 (0.01–0.7)	*p* = 0.027

*Odds ratio (OR) >1 means an increased risk of failure; CI — confidence interval; CNS — central nervous system; Hgb — hemoglobin; PPR — prednisone poor response;

lower than 8 g/dL had significant impacts on pEFS, but in multivariate analysis only therapy response on day 14 was related to a worse outcome and doubled the risk of event. 5-year pRFS was 66.2% (±6.9%). The only risk factor related to pRFS was therapy response on day 8.

Group 4

Group 4 was divided into two subgroups due to different therapeutic protocols: the BFM-90 protocol (group 4a) and the NEW YORK I–II protocol (group 4b).

In group 4a, 5-year pOS was 77.9% (±4.3%) and 5-year pEFS was 68.8% (±4.7%). The most important prognostic factor in both pOS and pEFS was treatment response on day 8, which was correlated with a 10-fold increased risk of event and a more than 3-fold higher risk of death in patients with PPR. Other factors that achieved statistical significance in univariate analysis in pOS and pEFS were risk group, hepatomegaly or splenomegaly at diagnosis, leukocyte count at diagnosis >20,000/μL, blasts phenotype, and treatment response on days 15 and 33 (bone marrow classified as M2). Relapse occurred in 16 children (16.7%) and mean time to relapse was 2.5 years. Among factors significant in univariate analysis, only T-cell blasts phenotype and splenomegaly proved significant in multivariate analysis.

In group 4b, 5-year pOS was 73.7% (±10.1%). None of the analyzed factors had an impact on pOS. 5-year pEFS was 68.4% (±10.7%). Involvement of lymph nodes and treatment response on day 15 had significant impacts on pEFS. Relapse was observed in five cases (26.3%) and four patients in this group died. Treatment response on day 15 was the only prognostic factor related to pRFS.

Group 5

Group 5 included 115 patients treated between 2002 and 2009 according to the IC-BFM 2002 protocol. 5-year pOS was 79.1% (±3.8%). Mean OS was 7.4 years [95% confidence interval (CI): 6.8–7.8 years). The most important factor with a significant negative impact on patient pOS was the presence of BCR-ABL fusion gene [as a result of translocation t(9;22)]; children with this mutation had a more than 7-fold lower pOS. In univariate analysis, hepatomegaly and splenomegaly at diagnosis had a significant impact on pOS as well. 5-year pEFS was 71.1% (±4.2%). Relapses occurred in 27 (23.5%) children and 5-year pRFS was 79.3% (±3.9%). Only Hgb <8 g/dL at diagnosis had a significant impact on both pEFS and pRFS, with a 2.3-fold higher risk of event and an almost 4-fold higher risk of relapse in patients with this feature.

Group 6

In group 6, data from children treated according to the ALL IC-BFM2009 protocol was analyzed. 5-year pOS was 90.7% (±3.4%). Mean OS was 4.1 years (95% CI: 2.7–6.5 years). In univariate analysis, only hypodiploidy had a significant impact on pOS. 5-year pEFS was 86.6% (±4.1%). Among prognostic factors related to lower pEFS, only Hgb level at diagnosis <8 g/dL was statistically significant. Relapses occurred in nine patients and 5-year pRFS was 90.1% (±3.6%). In univariate analysis, patients who did not achieve remission on day 33 had a more than 35-fold higher risk of relapse (data not shown). Other factors related to a worse pRFS were hepatomegaly, splenomegaly, and age <10 years at diagnosis.

Discussion

Decades of research into childhood ALL have resulted in the identification of several clinical and laboratory features which have had significant impacts on therapy outcomes. The best-known factors include age, leukocyte count at diagnosis, immunophenotype and chromosomal abnormalities in blasts, and response to initial therapy. The presence of prognostic factors has enabled risk group stratification and led to therapy intensification in patients at risk of treatment failure [4, 12]. The present data reflects improvements in therapy outcomes in childhood ALL as well as developments in diagnostic methods achieved due to international collaboration and great research effort.

During the first two analyzed periods, CNS involvement was one of the most important factors related to a poor outcome. Patients with CNS involvement had a 34-fold higher risk of relapse in the period 1976–1984 ($p = 0.001$) and a 10-fold higher risk of death between 1983 and 1988 ($p = 0.010$). This impact was also observed in international therapy protocols analysis, and resulted in the introduction of CNS prophylaxis and the introduction of the administration of high doses of methotrexate, which improved 5-year pEFS from 9% to 36% [6]. In other research, CNS prophylaxis with intrathecal methotrexate and cranial irradiation reduced the risk of CNS relapse from 32.5% to 1.4% after hematological remission [13]. Further efforts have been made towards limiting the side effects of CNS prophylaxis, and currently only a strictly limited group of patients who are at the highest risk of CNS relapse are treated with cranial irradiation.

Another feature early identified as a risk factor was age at diagnosis. Infants, especially in the first year of life, have significantly worse outcomes compared to children aged between one and six. In our analysis, patients aged <1 year treated between 1983 and 1988 had significantly lower pOS ($p = 0.033$) and pEFS ($p = 0.082$). This effect is caused by the different leukemia biology in this particular group and the high risk of long-term side effects [14]. The answer for issues related to infant ALL was the development of dedicated therapy protocols, conducted by three large collaborative groups — the Children's Oncology Group (COG), the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), and the Interfant Study Group [14].

Infant-dedicated protocols, as well as previous observations, resulted in better understanding of infant ALL genetic background and the identification of risk factors in this group, and provided necessary information about treatment toxicity [14].

The role played by Hgb concentration at diagnosis is unknown, with a significant impact of Hgb <8/dL on EFS and RFS. This phenomenon was also reported by Schrappe et al. [15] in their analysis of BFM-90 protocol results. This is difficult to explain, but hypothetically it might correspond to marrow blasts involvement or cellular sensitivity.

One of the most important prognostic factors in childhood lymphoblastic leukemia is early response to treatment. It has been proved that the hematological response to prednisone on day 8 of therapy, and the bone marrow response at later timepoints, have crucial impacts on long-term outcomes [2, 16, 17]. In our study, this effect was mostly seen in children treated in the period 1988–1995, when PPR was related to a more than 3-fold higher risk of death (p = 0.001) and an almost 2-fold higher risk of relapse (p = 0.019). Due to this observation, patients with PPR were stratified into a high risk group with therapy intensification, which led to an improvement in therapy outcome in this particular group [18]. Furthermore, in our analysis, the response to treatment was one of the most important risk factors during subsequent therapeutic periods [4, 19]. That resulted in the development of diagnostic methods related to therapy response assessment, and the implementation of MRD monitoring. This in turn enabled the early identification of patients at risk of relapse, even at times when the disease seems to be in remission. Moreover, it allows us to reduce therapy in standard-risk patients with a low level of MRD [20].

Genetic aberrations in blast cells proved to be crucial to the proper understanding of ALL biology and therapy response. One of the first genetic aberrations identified as a risk factor was the BCR-ABL mutation, and patients with this feature were thus stratified into a high risk group [21]. In our cohort, genetic diagnostics become available in 1996. In the period 2001–2011, a lack of the BCR-ABL mutation was the most important factor related to a better pOS (p <0.001). Unsatisfactory therapy results in this group resulted in treatment modification, with the introduction of targeted therapy with tyrosine kinase inhibitors (TKI), which have dramatically improved patients' outcomes. The success of TKI drove further research into targeted therapy in childhood ALL [21].

Conclusions

Prognostic factors in ALL have changed during the last few decades, and the development of diagnostic methods have led to a better understanding of the underlying causes of the disease. Medicine has become more aware of ALL's genetic background, and this has triggered further research in the field of genetic diagnostics and contributed to its accessibility. Furthermore, the changing landscape of risk factors in ALL has reflected sustained progress in ALL therapy, with the gradual elimination of features related to poor outcomes, mostly due to modifications in treatment and developments in diagnostic methods as well as therapy monitoring.

The modern era of immunotherapy and treatment focused on molecular pathways facilitates a more targeted approach, with new opportunities regarding the high risk group of patients [22]. Moreover, targeted therapy has had a great impact on treatment toxicity reduction in specific subgroups. New therapy protocols should bring answers regarding the efficiency and side effects of novel therapies in ALL.

Authors' contributions

JS — data collection and interpretation, statistical analysis, description of results. ED, AJG — data collection and interpretation, statistical analysis. NB, AK, SK, KC, MRP, RD, MP, BT, PK, JC, ME, AM, AD, AU, EG, KJ, EW, DK, MŁ, MA, SW, OG, ST, MM, MD, MK, BKR, ED, AM — data collection and interpretation. JS — thesis draft, critical review and important intellectual content, acceptance of final version for publication.

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.

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Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 18–30
DOI: 10.5603/AHP.a2022.0058
ISSN 0001–5814
e-ISSN 2300–7117

ORIGINAL RESEARCH ARTICLE

Comparison of depressive, anxiety, and somatic symptoms in patients with Philadelphia-negative chronic myeloproliferative neoplasms treated with interferon alpha

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Abstract

Introduction: The aim of this study was to analyze the occurrence of depression, anxiety, and somatic symptoms in patients with chronic myeloproliferative neoplasms (essential thrombocythemia, polycythemia vera, and myelofibrosis) and to check whether individual side effects of interferon alpha treatment may contribute to the occurrence of depression, anxiety, and somatic symptoms. In addition, it was decided to check whether there were any relationships between age, gender, duration of treatment, and the intensity of anxiety, divided by the occurrence of individual side effects.

Material and methods: The study involved 84 patients and was conducted at the Hematology Clinic of the University Hospital in Krakow, Poland and the Clinic of Hematology, Blood Cancer and Bone Marrow Transplantation in Wrocław, Poland. The following questionnaires were used: the David Goldberg Questionnaire GHQ-28, and the four-dimensional 4DSQ Questionnaire.

Results: The most frequently reported side effects of treatment were abdominal pain, fatigue, and bone and joint pain. Almost 40% of the respondents obtained a moderately or strongly increased result on the depression scale, less than 50% on the anxiety scale, and over 60% on the somatization scale. Somatic symptoms had the greatest impact on the occurrence of mental disorders, with anxiety symptoms being second in significance. There are differences in the severity of depressive, anxiety, and somatic symptoms depending on the side effects of interferon alpha treatment.

Conclusions: The findings of this study indicate the need for further research into the importance of detecting depressive, anxiety, and somatic disorders, and to addressing concomitant physical symptoms, both in patients with myeloproliferative neoplasms receiving interferon alpha and in those treated with other methods. In patients treated chronically, the occurrence of side effects of high intensity and lasting for a long time should alert medical personnel. The available data on patients with myeloproliferative neoplasms who have suffered from mental and physical symptoms of the disease or its treatment justifies the need for caring psychological, psychiatric, and educational care.

Key words: depresson, anxiety, somatization, myeloproliferative neoplasms, essential thrombocythemia, polycythemia vera, myelofibrosis, interferon alpha

Acta Haematologica Polonica 2023; 54, 1: 18–30

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Received: 29.08.2022 Accepted: 01.11.2022

Introduction

Chronic myeloproliferative neoplasms (MPNs) are a heterogeneous group of disorders characterized by the overproduction of mature cells from one or more myeloid lineages. The most common are polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis (primary; PMF, or post-ET-MF or post-PV-MF), and chronic myeloid leukemia (CML), which is treated separately due to the presence of the Philadelphia chromosome and different treatments [1].

In most patients with myeloproliferative neoplasms without the Philadelphia chromosome, mutations in the *JAK2* [2], *MPL* [3, 4] or *CALR* genes [5] are detected.

In the initial phase of the disease, a significant proportion of patients do not develop any clinical symptoms, and the disease is usually detected via routine blood tests. The exception is myelofibrosis, where, in more than half of cases, symptoms may appear in the form of significant weakness, bone and muscle pains, fever, itching of the skin, night sweats or discomfort in the abdominal cavity. The peripheral blood count of patients with MPN may include leukocytosis, thrombocythemia, or/and an increase in the number of erythrocytes, hemoglobin, and hematocrit. Typically, this type of cancer develops slowly and can affect people of all ages, but the most common age at incidence is between 50 and 70 years. In Poland, the annual incidences are: of polycythemia vera 2.5/100,000 population [men suffer more often than women (1–2:1)]; of essential thrombocythemia 1.5/100,000 of the population; of primary myelofibrosis 0.5–1.5/100,000 population; and of CML 0.7/100,000 population. The treatment used depends on the type of myeloproliferative disorder and on the presence of risk factors [6–10].

In the pharmacological treatment of PV, ET, and MF, interferon alpha (IFNα) [11–13] is often used, mainly in the form of peginterferon alpha-2a (Pegasys®) [14, 15] or ropeginterferon alpha-2b (Besremi®) [16]. Interferon alpha was introduced to the treatment of patients with myeloproliferative neoplasms without the Philadelphia chromosome more than 30 years ago [17]. This medication also has antiviral properties; therefore it is also used in the treatment of viral diseases such as hepatitis B and C and Kaposi's sarcoma [18].

The side effects of interferon alpha in patients suffering from myeloproliferative neoplasms have been widely reported in the literature [19–21]. Apart from hematological, neurological, and rheumatological symptoms, the most common side effects include fatigue, loss of appetite, nausea, diarrhea, muscle pain, skin rash, headaches, and abnormal triglyceride levels [22–27].

Both cancer itself (with its mental and physical comorbidities) [28] and the side effects of treatment can contribute to the development of depression and anxiety symptoms [29]. Many researchers have presented this topic in their work on the occurrence of anxiety and depression among patients with myeloproliferative neoplasms, analyzing the influence of the disease (its symptoms) on the occurrence of depression or anxiety [30–34]. Many studies have also focused on the side effects of treatment with various forms of interferon alpha in MPN [35], and some indicate that depression is one of them [23, 35–37]. Raison et al. [38] indicated that significant depressive symptoms occur in 21–58% of patients receiving non-pegylated IFNα, with symptoms usually appearing within the first few months of treatment, and may be due to high medication dose, female gender, history of depression, and duration of treatment.

It is noteworthy that due to the use of different definitions of depression in research and various diagnostic tools and interviews, the word 'depression' can encompass various psychiatric or neurological symptoms not necessarily related to clinical depression.

The literature does not provide studies that analyze the coexistence of anxiety, depression, somatic symptoms, and side effects of MPN treatment together. Usually, the influence of chronic myeloproliferative neoplasms (including its symptoms) on the occurrence of depression and/or anxiety or the general side effects of the drug (where depression is one of the side effects) have been examined. However, it has not been investigated whether possible side effects of the drug (e.g. fatigue, diarrhea) may contribute to the emergence of anxiety/depression. One of the difficulties may be determining whether a particular disease symptom is a side effect of treatment, or a somatic symptom of the disease. To our best of our knowledge, only a study by Padrnos et al. [34] on symptoms of depression in patients with myeloproliferative neoplasms drew attention to the relationship between depression and other variables. It showed that side effects may influence the development of depressive disorders [34].

The Bioethics Committee at the Jagiellonian University in Krakow approved our study (No. 1072.6120.113.2020). Each participant obtained information about the study and gave their written consent to participate.

The aim of our study was to analyze the occurrence of depression, anxiety, and somatic symptoms in patients with chronic myeloproliferative neoplasms (ET, PV, and PMF) and to check whether individual side effects of interferon alpha treatment may contribute to the occurrence of depression, anxiety, and somatic symptoms. In addition to this, we decided to check for a relationship between the age and the sex of the patient as well as the duration of the treatment and the severity of depressive, anxiety, and somatic symptoms; the data was divided depending on the occurrence of the individual side effect. The aim of the study was not to diagnose depressive or anxiety disorders, but instead to check the possibility of their development during IFNα treatment.

Material and methods

The study was carried out at the Hematology Clinic of the University Hospital in Kraków and the Clinic of Hematology, Blood Cancer and Bone Marrow Transplantation in Wrocław, Poland. The study involved 105 adult patients on interferon alpha treatment for a minimum of three months who gave their written consent. The patients were diagnosed with essential thrombocythemia, or polycythemia vera, or primary myelofibrosis. 21 patients were excluded from the study because they met our exclusion criteria i.e.: psychiatric or psychological (psychotherapeutic) treatment during the study period or the three months before its start, discontinuation of interferon alpha treatment or switching to another drug, initiation of interferon alpha treatment during the study or up to three months before starting treatment, feeling similar symptoms to those mentioned in the questionnaire, and the presence of anemia or disorder of the thyroid gland at least one month before starting treatment with alpha interferon. Ultimately, 84 patients (65 women and 19 men) were enrolled into the study. Data on the prevalence of anemia or hypothyroidism was collected from laboratory test results performed on the day of the questionnaire. The mean age in the research group was 39 [standard deviation (SD) = 10.199] years. Median IFNα dosing was 45 μg/week, with a minimum value of 45 μg/week and a maximum of 180 μg/two weeks. Detailed characteristics of the study group are set out in Table I.

Table I. Description of study group

Variable		Me ± SD	(Min–max)
Age (years)		37.50 ± 10.199	(20–65)
Treatment time (years)		9.50 ± 6.185	(1–23)
Number of side effects		4.00 ± 2.781	(0–11)
Type of MPN		**N**	**[%]**
Essential thrombocythemia		32	38.1
Polycythemia vera		28	33.3
Primary myelofibrosis		24	28.6
Variable		**N**	**[%]**
Sex	Female	65	77.4
	Male	19	22.6
Education	Basic vocational education	1	1.2
	Secondary	36	42.9
	Higher	47	56.0
Place of residence	City	63	25.0
	Village	21	75.0
Residence status	Living alone	5	6.0
	Living with family	79	94.0

Me — median; SD — standard deviation; MPN — myeloproliferative neoplasm; N — number of patients

Research tools

1. Sociodemographic questionnaire, which includes questions about age, sex, place of residence, marital status, education, type of MPN (ET, PV, PMF, and others), duration of the disease, side effects of interferon alpha treatment divided into periods and their duration. The list of side effects of interferon alpha treatment was prepared based on the results of studies on its effects and toxicity [22, 23, 27].
2. Goldberg's General Health Questionnaire 28 (GHQ-28) [39] questionnaire was used to assess mental health in adults. This questionnaire is sometimes used as a screening tool to detect people at risk of developing mental disorders and to analyze four symptoms of mental disorders: depression, anxiety, somatic and social dysfunction. In this study, the general, current mental state of the respondents and three dimensions of mental health: depressive, anxiety, and somatic symptoms, were analyzed. Additionally, the focus was on identifying people who may be at risk of developing mental disorders.
   Two scoring methods were used in the study: 1) the GHQ method, in which a dichotomous scale is used to identify people with a mental disorder, the cut-off point in this method being 6 points; and 2) a modified Likert scale from 0 to 3 points, which is used to check the general mental state of the respondents and to analyze three mental health factors: depressive, anxiety and somatic symptoms. Each scale contains seven questions, and a maximum of 21 points can be obtained. Sten norms were used to assess the results of general mental state.
3. Four-Dimensional Symptom Questionnaire (4DSQ), measuring the severity of current depressive symptoms (six questions), anxiety (12 questions), somatic (16 questions), and distress (16 questions) [40]. This study focused on analyzing three out of four dimensions: depression, anxiety, and somatic symptoms. In the case of depressive symptoms, the maximum number of points that can be obtained is 12, for anxiety symptoms — 24, and for somatic symptoms — 32. The cut-off points for individual scales are presented in Table II.

Table II. Cut-off points for individual scales of the Four-Dimensional Symptom Questionnaire

Factor	Distress	Depression	Anxiety	Somatization
Moderate	>9	>2	>3	>10
High	>20	>5	>9	>20

Table III. Occurrence of side effects with division into time of their appearance and duration

Side effect	PLT N [%]	PLNT N [%]	L3T N [%]	L3NT N [%]	TOTAL TR N [%]	TOTAL W N [%]
Water retention	25 (29.8)	11 (13.1)	8 (9.5)	1 (1.2)	33 (39.3)	45 (53.6)
Frequent infections	15 (17.9)	3 (3.6)	–	–	15 (17.9)	18 (21.4)
Fatigue	45 (53.6)	6 (7.1)	5 (6.0)	–	50 (59.5)	56 (66.7)
Bruising	31 (36.9)	7 (8.3)	–	–	31 (36.9)	38 (45.2)
Diarrhea	9 (10.7)	19 (22.6)	–	5 (6.0)	9 (10.7)	33 (39.3)
Loss of appetite	25 (29.8)	14 (16.7)	–	–	25 (29.8)	39 (46.4)
Bone and joint pain	34 (40.5)	9 (10.7)	6 (7.1)	3 (3.6)	40 (47.6)	52 (61.9)
Nausea, indigestion	27 (32.1)	7 (8.3)	–	8 (9.5)	27 (32.1)	42 (50.0)
Abdominal pain	44 (52.4)	19 (22.6)	6 (7.1)	–	50 (59.5)	69 (82.1)
Cramps, muscle aches	30 (35.7)	8 (9.5)	5 (6.0)	5 (6.0)	35 (41.7)	48 (57.1)
Skin rash, itching	28 (33.3)	20 (23.8)	–	3 (3.6)	48 (57.1)	48 (57.1)
Anemia	18 (21.4)	2 (2.4)	1 (1.2)	1 (1.2)	19 (22.6)	21 (25.0)
Hypothyroidism	13 (15.5)	1 (1.2)	1 (1.2)	1 (1.2)	14 (16.6)	16 (19.0)

PLT — treatment side effects that appeared early in treatment and are still ongoing; PLNT — treatment side effects that started at the onset of treatment but are no longer present; L3T — treatment side effects that started three months after onset of treatment and are still ongoing; L3NT — treatment side effects that started three months after onset of treatment but are no longer present; TOTAL TR — treatment side effects that appeared at the beginning of treatment and are still ongoing (PLT) and treatment side effects that appeared three months after onset of treatment and are still ongoing (L3T); TOTAL W — sum of all side effects of treatment; N — numer of patients

The names of the scales in both questionnaires: depression, anxiety, and somatization should be treated as depressive, anxiety and somatic symptoms, respectively. The above tests are used as screening tests or for identifying people who may be at risk of developing mental disorders, and by themselves do not diagnose disorders. The diagnosis of depressive, anxiety, or somatic disorders requires the fulfillment of specific diagnostic criteria of the International Statistical Classification of Diseases and Related Health Problems 11th revision (ICD-11) or Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) classification. In the presented study, depressive symptoms are not equivalent to the terms "depression" or "depressive disorder".

Statistics

Statistical analyzes were performed using IBM SPSS Statistics version 26. It was used to perform a frequency analysis, basic descriptive statistics analysis, a series of multivariate linear regression analyses, a series of correlation analyses with Spearman's rho coefficient, and a one-way ANOVA with repeated measures along with a post hoc test with Benferroni correction. The normality of the distribution was verified by the Kolmogorov-Smirnov test. The level of significance was $\alpha = 0.05$.

Firstly, the basic descriptive statistics of the variables analyzed later in the work were calculated. For quantitative variables, mean values were presented with standard deviations, and nominal variables — with the frequency of occurrence.

Table IV. Incidence of depressive, anxiety and somatic symptoms measured with the Four-Dimensional Questionnaire (4DSQ)

4DSQ	All patients (n = 84)					
	Depression		Anxiety		Somatization	
	N	[%]	N	[%]	N	[%]
Moderate	24	28.6	31	36.9	43	51.2
High	8	9.5	10	11.9	19	22.6

Results

The most frequently reported side effects of treatment were abdominal pain (82.1%), fatigue (66.7%), and bone and joint pain (61.9%). Detailed data is set out in Table III.

As the next step, the side effects that persisted until the day of the study (TOTAL TR) were analyzed.

The general mental state of the respondents was checked using the GHQ-28 questionnaire and GHQ scoring (0 — no symptom, 1 — symptom occurrence). Thirty patients (35.71%) at risk of developing mental disorders were identified. These people exceeded the threshold of 6 points, which is the cutoff point for identifying people with mental disorders. Tables IV and % present the results of the 4DSQ and GHQ-28 questionnaires.

Analysis of the occurrence of depressive, anxiety and somatic symptoms in patients with chronic myeloproliferative neoplasms showed that almost 40% of the respondents obtained a moderately or strongly increased

Table V. Overall score and score for individual scales of General Health Questionnaire 28 (GHQ-28) and the Four-Dimensional Questionnaire (4DSQ)

Questionnaire	Overall score		Somatization		Anxiety		Depression		F
	M	SD	M	SD	M	SD	M	SD	
GHQ-28	24.48	11.575	6.96[a]	3.338	6.10[b]	4.041	2.93[b]	3.104	70.577*
4DSQ	–	–	11.24[a]	7.996	3.29[b]	4.694	1.74[c]	2.523	138.988*

[a, b, c]Different indices mean statistically significant differences at level of p <0.001; *p <0.001; M — medium; SD — standard deviation; F — F value

Table VI. Depressive, anxiety, and somatic symptoms divided by side effects of interferon alpha treatment

Side effect		Somatization		Anxiety		Depression		F
		M	SD	M	SD	M	SD	
Water retention	GHQ	7.48[a]	3.28	5.88[b]	3.91	3.24[c]	3.55	25.74*
	DSQ	12.00[a]	7.76	3.67[b]	5.10	1.85[c]	2.69	65.31*
Frequent infections	GHQ	10.73[a]	2.87	8.73[a]	3.60	4.53[b]	3.38	22.10*
	DSQ	15.80[a]	8.49	4.47[a]	5.44	2.87[b]	2.97	43.20*
Fatigue	GHQ	8.20[a]	2,85	7.46[a]	4.02	3.62[b]	3.24	42.79*
	DSQ	12.52[a]	7.51	3.42[b]	4.38	1.80[c]	2.30	105.10*
Bruising	GHQ	8.23[a]	3.77	7.10[b]	4.11	3.19[c]	2.99	38.40*
	DSQ	12.39[a]	7.82	3.81[b]	4.59	2.32[b]	2.88	59.10*
Diarrhea	GHQ	9.11[a]	3.14	8.22[b]	3.14	3.67[c]	3.80	70.58*
	DSQ	12.44[a]	8.31	1.78[b]	1,56	1.67[c]	2.00	138.98*
Loss of appetite	GHQ	8.56[a]	3.34	7.84[a]	3.35	5.08[b]	3.14	23.01*
	DSQ	12.36[a]	7.80	3.76[b]	4.48	2.36[b]	3.07	50.84*
Bone and joint pain	GHQ	8.13[a]	3.66	7.05[b]	3.80	3.83[c]	3.47	33.91*
	DSQ	12.85[a]	8.42	3.73[b]	4.41	2.08[c]	2.56	72.17*
Nausea, indigestion	GHQ	7.93[a]	3.03	8.26[a]	3.28	4.41[b]	3.43	28.71*
	DSQ	11.07[a]	6.87	3.67[b]	4.28	1.85[b]	2.69	54.78*
Abdominal pain	GHQ	8.30[a]	2.94	7.58[a]	3.24	4.14[b]	3.39	44.60*
	DSQ	12.34[a]	7.57	3.68[b]	4,18	1.92[c]	2.47	140.88*
Cramps, muscle aches	GHQ	8.86[a]	3.02	8.00[a]	3.33	4.51[b]	3.51	24.90*
	DSQ	13.66[a]	7.62	3.86[b]	4.59	2.34[b]	2.66	85.78*
Skin rash, itching	GHQ	6.69[a]	3.37	5.67[b]	4.39	3.54[c]	3.55	23.36*
	DSQ	12.42[a]	9.10	3.48[b]	5.46	2.04[b]	2.77	72.99*
Anemia	GHQ	6.81[a]	0.90	5.75[b]	1.16	2.25[b]	0.72	13.44*
	DSQ	10.31[a]	1.93	2.44[a]	1.16	1.38[b]	0.65	34.27*
Hypothyroidism	GHQ	8.48[a]	0.61	8.14[b]	0.47	6.43[b]	0.64	8.405*
	DSQ	16.19[a]	1.84	5.24[a]	1.20	2.27[b]	0.74	47.19*

[a, b, c]Different indices mean statistically significant differences at level of p <0.001; *p <0.001; M — medium; SD — standard deviation; F — F value; GHQ — General Health Questionnaire; DSQ — The Four-Dimensional Questionnaire

result on the depression scale, less than 50% on the anxiety scale, and over 60% on the somatic symptoms scale (Table IV).

Using the GHQ-28 questionnaire and the 4DSQ questionnaire, the general mental state of the respondents and the influence of individual disorders on their severity were checked (Table V).

The overall result of the GHQ-28 test showed an average mental condition of the patients. Analysis with the use of a one-way analysis of variance in the intergroup scheme showed that somatic symptoms had the greatest impact on the occurrence of mental disorders, with anxiety symptoms being second in significance. Similar results were observed using the 4DSQ.

Table VII. Spearman's correlation coefficients between anxiety, depressive and somatic symptoms [measured by General Health Questionnaire (GHQ) and Four-Dimensional Questionnaire (4DSQ)] and age and duration of treatment by perceived side effects of interferon alpha treatment

Side effect	Variables	Somatization		Anxiety		Depression	
		GHQ	DSQ	GHQ	DSQ	GHQ	DSQ
Water retention	Age	0.93	0.21	0.08	–0.03	–0.21	–0.02
	Treatment time	0.11	–0.14	–0.25	–0.04	0.02	–0.17
Frequent infections	Age	0.26	–0.04	–0.19	–0.33	–0.18	0.13
	Treatment time	0.13	0.43	0.25	–0.12	0.01	0.03
Fatigue	Age	–0.25	0.21	0,15	0.17	–0.09	0.17
	Treatment time	–0.11	0.08	–0.02	0.08	–0.30*	–0.08
Bruising	Age	0.08	–0.09	0.31	0.29	–0.01	0.24
	Treatment time	0.03	0.08	0.36*	0.40	0.02	–0.02
Diarrhea	Age	–0.21	0.05	–0.03	0.13	–0.18	0.08
	Treatment time	0.04	–0.01	0.16	0.03	0.04	0.02
Loss of appetite	Age	–0.55**	–0.08	–0.09	0.18	–0.23	0.01
	Treatment time	–0.57**	–0.12	–0.45**	–0.22	–0.62**	–0.23
Bone and joint pain	Age	–0.27	0.18	–0.03	–0.05	–0.24	–0.06
	Treatment time	–0.24	–0,08	–0,13	–0,20	–0,37*	–0.27
Nausea, indigestion	Age	–0.34	–0,01	0,04	0,18	–0,08	0.11
	Treatment time	–0.41	–0,08	–0,07	–0,02	–0,45*	–0.10
Abdominal pain	Age	–0.38**	0.04	0.15	0.17	–0.23	0.18
	Treatment time	0.01	0.17	0.09	0.06	–0.07	0.05
Cramps, muscle aches	Age	–0.19	0.25	0.09	–0.17	0.15	–0.01
	Treatment time	–0.08	0.15	0.04	–0.05	–0.35*	–0.14
Skin rash, itching	Age	–0.18	0.03	0.17	0.07	–0.18	–0,07
	Treatment time	0.11	–0.08	–0.10	–0.23	–0.10	–0.37*
Anemia	Age	–0.10	0.37	–0.07	–0.65	–0.27	–0.18
	Treatment time	0.00	0.48*	0.06	0.10	–0.46*	–0.20
Hypothyroidism	Age	–0.13	–0.40	–0.42	–0.17	–0.03	–0.27
	Treatment time	–0.07	–0.38	–0.33	–0.36	–0.17	–0.38

*p <0.05; **p <0.01

As the next step, the severity of depressive, anxiety, and somatic symptoms were checked, and divided into side effects of interferon alpha treatment, using the 4DSQ and GHQ-28 questionnaires (Table VI).

With the use of a one-way analysis of variance in the intergroup scheme, it was shown that there are differences in the severity of depressive, anxiety, and somatic symptoms depending on the side effects of interferon alpha treatment. In the case of the study with the GHQ-28 questionnaire, in most of the experienced side effects of interferon alpha treatment, the greatest influence on the occurrence of psychological disorders were somatic symptoms, followed by anxiety and anxiety-related insomnia. Only in the cases of side effects of nausea and indigestion was anxiety the leading factor in inducing mental disorders.

The side effects with the greatest severity of somatic symptoms were hypothyroidism-related symptoms, frequent infections, diarrhea, muscle cramps, and pain. Similar results were obtained for the deterioration of anxiety symptoms, but additional side effects with high scores were nausea and indigestion. In the case of depressive symptoms, the side effects obtaining the greatest results were: loss of appetite, frequent infections, and muscle pain. The 4DSQ survey showed that all experienced side effects of treatment were associated with increased levels of somatization and anxiety. In the case of depressive symptoms, elevated levels were observed, in order of severity: hypothyroidism-related symptoms, frequent infections, loss of appetite, muscle cramps and pain, bruising, diarrhea, bone, and joint pain, skin rash, and itching.

The next analysis examined whether there was any relationship between age and duration of treatment and the severity of depressive, anxiety, and somatic symptoms, divided by individual side effects (Table VII).

Significant, high or moderate correlations occurred between the occurrence of anxiety (r_s = –0.57), depression (r_s = –0.45) and somatic (r_s = –0.67) symptoms and the time of treatment. In these patients, the longer the treatment duration, the lower the intensity of depression, anxiety, and somatic symptoms. Additionally, in this group of respondents, there was a negative, high correlation (r_s = = –0.55) between the occurrence of anxiety symptoms and age. The older the person was, the lower the level of anxiety. There were also moderate negative correlations between the occurrence of individual symptoms of mental disorders and the age and duration of treatment in patients who experienced the following side effects of interferon treatment: fatigue, bone, and joint pain, nausea and indigestion, muscle cramps and pain, and skin rash and itching and anemia. Two positive correlations occurred between depressive symptoms and the duration of treatment (r_s = 0.36), in people experiencing the side effect of bruising, and between anxiety symptoms and the duration of treatment in patients experiencing anemia (r_s = 0.48).

The results of the analysis of the relationship between the severity of anxiety, depression, and somatic symptoms measured with the GHQ-28 questionnaire and age, gender, place of residence, number of side effects, and duration of treatment are set out in Table VIII.

In the analysis of the impact of the side effects of treatment on the severity of somatic, anxiety, and depression symptoms measured with the GHQ-28 questionnaire, regression models made it possible to explain to explain 45%, 27% and 32% of the variance.

Based on the results presented in Table VIII, we found that the number of side effects was a common predictor of the occurrence of somatic, anxiety, and depressive symptoms. The more the patient experienced them, the greater the severity of all symptoms of mental disorders.

Place of residence also turned out to be an important predictor of somatic symptoms. People living in the city felt more anxious than those living in the countryside. In the case of anxiety symptoms, age was also an important prognostic factor. The older the person was, the lower the intensity of anxiety symptoms. The analysis also showed that the female gender was an unfavorable prognostic factor for the occurrence of depressive symptoms.

In the study of the relationship between the severity of anxiety, depression, and somatic symptoms measured with the 4DSQ questionnaire and age, gender, place of residence, number of side effects and duration of treatment, neither model was statistically significant.

Next, a regression analysis was performed to verify the relationship between the severity of anxiety, depression and somatic symptoms measured by the GHQ-28 questionnaire and the incidence of side effects of interferon alpha treatment (Table IX).

Table VIII. Multidimensional relationships between severity of anxiety, depression, and somatic symptoms and age, gender, place of residence, number of side effects, and duration of treatment

Variables	B*	*p*
Somatization		
Duration of treatment	0.009	0.849
Age	–0.024	0.408
Number of side effects	0.760	<0.001
Sex (male vs. female)	1.222	0.063
Place of residence (village vs. city)	1.899	0.004
Adjusted R^2 = 0.447 (F = 14.438)		
Anxiety		
Duration of treatment	0.049	0.470
Age	–0.082	0.046
Number of side effects	0.749	<0.001
Sex (male vs. female)	0.329	0.718
Place of residence (village vs. city)	1.234	0.177
Adjusted R^2 = 0.262 (F = 6.904)		
Depression		
Duration of treatment	–0.031	0.537
Age	–0.009	0.768
Number of side effects	0.635	<0.001
Sex (male vs. female)	–1.377	0.043
Place of residence (village vs. city)	–0.312	0.640
Adjusted R^2 = 0.323 (F = 8.937)		

*Crude regression coefficients

The analysis showed that the prevalence of somatic symptoms was: frequent infections, fatigue, muscle cramps, and pain, as well as skin rash and itching. All side effects, with the exception of skin rash and itching (B = –1.452, p = 0.017), were positively associated with the response variable. Three side effects were predictors of anxiety symptoms: fatigue (B = 2.036, p = 0.027), nausea and indigestion (B = 2.694, p = 0.013), and skin rash and itching (B = –1.309, p = 0.039). In the case of depressive symptoms: loss of appetite (B = 1.787, p = 0.021), abdominal pain (B = 1.939, $p \leq 0.007$), skin rash and itching (B = 1.173, p = 0.031), and anemia (B = 3.000, $p \leq 0.001$) were significant predictors of the development of depressive disorders. All side effects of treatment were positively associated with the response variable.

In regression analysis between the severity of anxiety, depression, and somatic symptoms — measured with the 4DSQ questionnaire and divided by side effects — neither model was statistically significant.

Table IX. Relationships between severity of anxiety, depression, and somatic symptoms measured with General Health Questionnaire 28 (GHQ-28) and side effects of interferon alpha treatment

Side effect	B*	*p*
Somatization		
Water retention	1.096	0.108
Frequent infections	3.240	<0.001
Fatigue	1.667	0.012
Bruising	0.717	0.296
Diarrhea	0.308	0.767
Loss of appetite	1.361	0.113
Bone and joint pain	–0.779	0.271
Nausea, indigestion	–0.117	0.879
Abdominal pain	0.641	0.417
Cramps, muscle aches	1.670	0.031
Skin rash, itching	–1.452	0.017
Anemia	–1.161	0.835
Hypothyroidism	0.695	0.335
Adjusted R^2 = 0.481 (F = 6.917)		
Anxiety		
Water retention	–0.690	0.462
Frequent infections	2.229	0.068
Fatigue	2.036	0.027
Bruising	–0.066	0.946
Diarrhea	0.467	0.746
Loss of appetite	–0.869	0.463
Bone and joint pain	–0.638	0.515
Nausea, indigestion	2.694	0.013
Abdominal pain	1.056	0.336
Cramps, muscle aches	1.309	0.219
Skin rash, itching	–1.309	0.039
Anemia	1.042	0.335
Hypothyroidism	0.973	0.330
Adjusted R^2 = 0.317 (F = 3.967)		
Depression		
Water retention	0.039	0.948
Frequent infections	0.422	0.588
Fatigue	–0.207	0.724
Bruising	–0.753	0,220
Diarrhea	–1.007	0.281
Loss of appetite	1.787	0.021
Bone and joint pain	–0.530	0.402
Nausea, indigestion	–0.089	0.897
Abdominal pain	1.939	0.007
Cramps, muscle aches	0.743	0.279
Skin rash, itching	1.173	0.031
Anemia	3.000	<0.001
Hypothyroidism	0.262	0.684
Adjusted R^2 = 0.519 (F = 7.877)		

*Crude regression coefficients

Discussion

Many scientific studies have been devoted to side effects occurring during treatment with various types of interferon alpha.

The incidence and type of side effects of interferon alpha treatment reported in the literature and observed in our analyzed group of patients were similar.

Fatigue and flu-like symptoms (headache, muscle pain, back, and joints, fever, chills) were most frequently reported [35, 40, 41]. Skin rash, abdominal pain or hypothyroidism-related symptoms are side effects less common in people with myeloproliferative neoplasms, but they occur in other conditions treated with interferon alpha [42–46]. An analysis of the incidence of side effects of interferon alpha treatment depending on the period of their appearance and persistence showed that the most common side effects occurred at the beginning of treatment and are still ongoing, followed by those that occurred at the beginning of treatment, but do not exist anymore (Table III). The most common side effects in these groups were fatigue, skin rashes, and itching, and abdominal pain. Analysis of the occurrence of depressive, anxiety, and somatic symptoms in patients with chronic myeloproliferative neoplasms showed that, on average, every second person has at least one symptom of a mental disorder in the form of somatic, anxiety or depression symptoms, with the highest indication being of somatic symptoms, followed by anxiety symptoms (Tables IV, V).

These results suggest that these patients may develop a somatic disease, and additionally they may be affected by physiological symptoms of the disease and/or in some people there may be a tendency to somatize the symptoms of the disease. The obtained results do not differ from those presented in the literature; somatic, anxiety, or depressive symptoms are common in cancer patients [30, 31, 47]. Studies by Scherber et al., McFarland et al. and Brochmann et al. have indicated that depression or anxiety symptoms appear in 13–31% of patients with MPN [30, 33, 48].

In our study, somatic symptoms were the most frequent and severe symptoms in the study group. These results may indicate that the side effects of alpha interferon treatment may resemble typical somatic symptoms e.g. nausea, fatigue, abdominal pain, diarrhea, weight loss, and loss of appetite. Some of them could be aggravated by alpha interferon-induced hypothyroidism. In addition, the disease itself may also be characterized by similar symptoms, and the coexistence of anxiety or depressive disorders may indicate somatic symptoms. In a study by Katon et al. [49], in which patients suffered from diabetes, lung disease, heart disease, and arthritis, it was found that the presence of comorbid depression or anxiety disorders is associated with an increased burden of somatic symptoms in patients with chronic disease. On the other hand, the results of Akechi et al. [50] suggest that individual somatic

symptoms in cancer patients differ in nature and that, for example, symptoms related to appetite and reduced thinking ability can be used to diagnose depression, while sleep disturbances and fatigue can not be used.

It is difficult to determine whether the somatic symptoms in patients with myeloproliferative neoplasms are related to the disease itself and the side effects of its treatment or to the accompanying anxiety or depressive symptoms. For this reason, subsequent analyzes attempted to determine to what extent the side effects of treatment may contribute to the development of somatic, anxiety, or depressive disorders.

Our study showed that individual side effects of interferon alpha treatment contribute to the occurrence and development of mental health disorders, and some of them (frequent infections, muscle cramps and pain, fatigue, nausea and indigestion, loss of appetite, abdominal pain, anemia and skin rash and itching) are prognostic factors for the occurrence of somatic, anxiety or depression symptoms (Tables VI and IX). The literature confirms that the numerous and troublesome side effects of interferon alpha treatment can contribute to the deterioration of the quality of life of patients [40, 51, 52] and the emergence of depressive and anxiety symptoms [53].

The study conducted into the relationship between the age of the patient, duration of the treatment, and the severity of depressive, anxiety and somatic symptoms, which was divided by the occurrence of individual symptoms, showed that patients experiencing side effects such as loss of appetite, bone and joint pain, nausea and indigestion, cramps and muscle pain as well as skin rashes and itching of the skin, were more likely to experience less severe mental disorder symptoms the longer the disease persisted.

On the other hand, among patients experiencing side effects such as loss of appetite and abdominal pain, the older the person is, the less frequent the occurrence of anxiety symptoms and the less severe. In patients who develop anemia as a result of interferon alpha treatment, the longer the patients were treated, the higher the occurrence of depressive symptoms (Table VII).

The results show that the group of patients experiencing certain side effects adapts better to the ongoing disease and more easily achieves the appropriate defense strategy. Numerous studies have emphasized that chronic disease and health problems resulting from it are a constant source of stress for patients, and various coping strategies (based on, among others, religion, meditation, trust in medical staff, positive attitude, patient's own resources or social support) may contribute to effective adaptation in chronically ill people [54–59]. In contrast, in a study by Trask et al. [60] on the course of depression, fatigue, and quality of life before and during interferon therapy in patients with melanoma, it was observed that somatic complaints, depression, and fatigue as a side effect of interferon treatment increased significantly during therapy, and that the patient's quality of life decreased in the areas of physical and functional well-being and additional symptoms [60]. These differences may be due to the type of interferon used, the duration of treatment, the dose administered, and/or the nature of the disease.

Our results on the variables that can influence the appearance of anxiety, depression, and somatic symptoms showed that the number of side effects was an important predictor of mental disorders (Table VIII). Similarly, in the study by Trask et al. [60], it was shown that fatigue, which is one of the main and most common side effects of interferon alpha treatment, can contribute to the development of mental health disorders. Another study by Brandberg et al. [61] on health-related quality of life in patients with melanoma taking interferon alpha-2b indicated a deterioration in the quality of life and several side effects associated with this treatment. The cited study did not analyze the relationship between these two variables but only focused on identifying side effects and quality of life during the treatment period [61]. The results of the studies in the analyzed group of patients are not surprising, as the occurrence of side effects of almost any treatment usually affects the quality of life of patients, but their number, type, duration, and coping strategy may significantly affect the presence of mental disorders.

Age was a predictor of anxiety symptoms. The older the person, the lower the intensity of anxiety symptoms. In a study by Brown et al. on the relationship between age and anxiety and depression symptoms in quality of life, 443 adults aged 30–98 years were examined. It showed that there is no difference between the psychological and social quality of life and age, while the environmental quality of life increases and the physical quality decreases with age [62]. Nickel's studies [63] of depression and anxiety in patients with chronic heart disease showed that younger patients (under 65) experienced more anxiety and depression symptoms than patients over 65. Other studies have shown that the ability to adapt to changes increases with age [64, 65], and our own results confirm this.

Another analysis showed that women were more likely to develop depressive disorders; the results are identical to most of the data available in the literature, which indicate that women are more likely to develop anxiety or depressive disorders [47, 63, 66] or are more often diagnosed with depression [67]. However, some studies show no such relationship [33, 68].

The differences may be caused by the influence of additional variables on the obtained results, such as the homogeneity of the studied groups, the type of disease, the age of the patient, the duration of the treatment, taking

antidepressants, quantity, and severity of the experienced side effects and their duration, social situation or the process of adaptation to the disease. There are some studies that suggest that women perceive and construct social reality differently than men; they play a protective role in relationships and are more sensitive, often at the expense of their own emotional stability [69–71].

Study limitations

The conducted research has some limitations. Despite the initial history of the side effects of treatment (whether they occurred before the drug was introduced or arose later), it is difficult to say with 100% certainty whether, for example, fatigue or diarrhea and its relationship with depressive, somatic, or anxiety symptoms are the effects of the disease itself (MPN), a side effect of the drug, or a depressive, anxiety or somatization disorder.

Another limitation of the study was the use of a non-validated symptom burden measurement tool (self-survey). Our rationale was to use the same questionnaire used in several previous studies in a different group of patients, which will be compared with the currently studied. The study was based on the most common side effects in patients with chronic myeloproliferative tumors and lymphoproliferation.

Another limitation was the use of self-description questionnaires, which are not used to diagnose depression or anxiety disorders but are only used to indicate the possibility of certain symptoms of mental disorders. To diagnose these disorders, the diagnostic criteria of ICD 11 or DSM 5 should be used. Therefore, the obtained results are exploratory and require further research.

Clinical implications

A questionnaire-based examination of the mental state of patients, both newly diagnosed with myeloproliferative neoplasms and those already undergoing treatment, may be an option that could be offered to patients; if the results of the questionnaire exhibited depressive, anxiety and/or somatic symptoms, the patient could then be offered psychiatric treatment and/or psychological support.

Another option that could be introduced is having the medical professionals consult with the patients about the possible side effects of the treatment as well as how to deal with them, which could increase the patient's overall understanding of the process and in turn reduce possible depressive, anxiety and somatic symptoms.

Conclusions

Some of the side effects of interferon alpha treatment in patients with chronic myeloproliferative neoplasms influence the occurrence of depression, anxiety, and somatic symptoms and are a clear indicator of their severity. Somatic symptoms had the greatest impact on the occurrence of mental disorders, with anxiety symptoms being second in significance.

In the case of the relationship between the age of the respondents and the duration of treatment, divided by individually occurring side effects, patients experiencing the side effect in the form of loss of appetite, the person was younger and the duration of treatment was shorter, the severity of anxiety symptoms was lower.

In the case of all disorders of the mental sphere, significant predictors were the number of side effects, in addition to somatic symptoms — the place of residence (city), anxiety symptoms — age (younger person), and depressive symptoms — gender (woman).

The findings of our study indicate the need for further research into the importance of detecting depressive, anxiety, and somatic disorders, and addressing concomitant physical symptoms, both in patients with myeloproliferative neoplasms receiving interferon alpha and those treated with other methods.

In patients treated chronically, the occurrence of side effects of high intensity and lasting for a long time should alert medical personnel.

The collected data on patients with myeloproliferative neoplasms who have suffered from mental and physical symptoms of the disease or its treatment justifies the need for caring psychological, psychiatric, and educational care.

Authors' contributions

KG — design of the study, literature search and analysis of data, original draft preparation. TS — design of the study, review and editing, supervision. KC — review and editing, supervision.

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.

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VIA MEDICA

ORIGINAL RESEARCH ARTICLE

Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 31–35
DOI: 10.5603/AHP.a2023.0004
ISSN 0001–5814
e-ISSN 2300–7117

Letermovir use in children after hematopoietic cell transplantation: summary of reported data

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Abstract

Introduction: Letermovir (LMV) is approved for primary prophylaxis of cytomegalovirus infection (CMVi) in CMV-seropositive adult patients undergoing allogeneic hematopoietic stem cell transplantation. However, it is not registered for CMVi pre-emptive treatment, CMVi secondary prophylaxis, or the treatment of CMV disease. There is very limited data regarding LMV's use in pediatric patients, as it has not been approved so far as any kind of treatment in children, with its use remaining off label. The aim of this study was to summarize reported data on the efficacy and safety of LMV in pediatric patients.

Material and methods: Studies and case reports regarding LMV's use in pediatric patients were searched in PubMed.

Results: Overall, nine reports that fulfilled the search criteria, published between 2019 and 2022, were found and analyzed. The total number of cases involved in research was 46 with patient age ranging from 2–19 years; one child was counted twice due to another transplant.

The most common serostatus of donor/recipient was D+/R+ (47%), followed by D–/R+ (42%), then D+/R– (2%), and then unknown (9%). Most patients had received the transplant from a matched unrelated donor (40%). There were 47 incidents of LMV administration as CMV management strategy. The analyzed patients received LMV as primary prophylaxis (74%), secondary prophylaxis (15%), pre-emptive therapy (6%), or treatment of CMV disease (4%). One patient received LMV as a treatment and then as a secondary prophylaxis. In 44/46 (95.6%) cases, no symptomatic CMVi occurred during LMV administration, with only transient CMV DNA-emia present on rare occasions.

Conclusion: The use of LMV is safe in pediatric patients.

Key words: letermovir, children, transplantation, CMV

Acta Haematologica Polonica 2023; 54, 1: 31–35

Introduction

Cytomegalovirus infection (CMVi) is one of the most severe complications for immunosuppressed patients undergoing hematopoietic stem cell transplantation (HSCT). Its harmful effect comprises both direct and indirect toxicity. Direct toxicity is the result of ongoing infection, while indirect toxicity concerns the immunological effects of the virus and the side effects of the used drugs [1, 2]. CMV infection is associated with higher non-relapse mortality (NRM) and all-cause mortality [3]. CMV reactivation happens in up to 70% of CMV-seropositive recipients (R+) [4, 5]. The most

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Received: 27.11.202 Accepted: 11.12.2022

common clinical manifestations of CMVi in HSCT patients include pneumonia, hepatitis, enteritis, retinitis and bone marrow suppression. Moreover, CMVi increases the risk of life-threatening secondary bacterial and fungal infections as well as graft-versus-host disease (GvHD) development and graft failure [2, 6, 7]. Documented high risk factors of CMVi include: CMV-seronegative donor/recipient, CMV positive serostatus (D–/R+) [odds ratio (OR) = 11.0], grade 3–4 of acute GvHD (aGVDH) (OR = 5.4), and unrelated (OR = 6.0) and mismatched donors (OR = 4.2) [8, 9]. Furthermore, older age, male sex and nonwhite/nonblack race are non-modifiable risk factors in pediatric patients [10]. Pharmacological strategies to prevent CMV infections include prophylaxis and preemptive therapy. Prophylaxis is based on the administration of antiviral drugs to prevent infection, whereas preemptive therapy requires repetitive screening assay and treating asymptomatic, infected patients [2].

Before the letermovir (LMV) era, gancyclovir (GCV), valgancyclovir (VGC) and foscarnet (FOS) were used as a preemptive therapy, but not prophylaxis due to their myelo- and nephrotoxicity [2–4, 7, 10, 11]. LMV, which is devoid of these side effects, became a new treatment strategy in adults. LMV inhibits CMV by disrupting the viral terminase. Studies on LMV used as primary prophylaxis proved its high efficacy at reducing the incidence of CMV disease and the number of deaths caused by CMVi [2–7, 11]. In 2017, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved LMV for primary prophylaxis in CMV-seropositive adult patients undergoing allogeneic HSCT (allo-HSCT) [2–8, 10, 11]. However, it was not registered for CMVi preemptive treatment, CMVi secondary prophylaxis, or the treatment of CMV disease [2, 3, 7]. There is very limited data regarding LMV's use in pediatric patients as it has not been approved so far as any kind of treatment in children, with its use remaining off label [1–8, 10–12]. The aim of this study was to summarize reported data on the efficacy and safety of LMV in pediatric patients.

Material and methods

Studies and case reports regarding LMV use in pediatric patients were searched in PubMed. Searched queries included 'letermovir' AND 'child*'; 'letermovir' AND 'pediatr*'. The following data was retrieved from these reports: number of patients treated with LMV, gender, underlying disease, serostatus, type of transplantation, CMV treatment before LMV, type of CMV management, treatment outcome, dosage of LMV, and the initiation and duration of treatment.

Based on published reports, we used the term 'breakthrough symptomatic CMVi' during LMV administration to denote the presence of viral DNAemia in a patient with symptoms in a case of primary/secondary prophylaxis and preemptive therapy. We considered it also as ongoing symptomatic CMVi unsuccessfully treated with LMV.

Results

We found nine reports that fulfilled the search criteria, published between 2019 and 2022 (Table I) [1, 4–8, 10–12]. The total number of cases involved in research was 46, with the patients' ages ranging from 2 to 19 years. Out of 43 children with a known gender, 22 (51%) were male. In the vast majority of patients, the underlying hematological disease was acute lymphoblastic leukemia or acute myeloid leukemia. All but one child had undergone HSCT at some point, with the only exception being the case of a 2-year-old girl suffering from medulloblastoma complicated by refractory CMVi. One patient had had two allo-HSCTs, and thus was considered to be two cases.

The most common serostatus was D+/R+ (21/45; 47%), followed by D–/R+ (19/45; 42%), then D+/R– (1/45; 2%), and four were unknown (9%). Most patients had received the transplant from a matched unrelated donor (MUD; 18/45; 40%).

There were 47 courses of LMV administration as CMV management strategy. Analyzed patients received LMV as primary prophylaxis (35/47; 74%), secondary prophylaxis (7/47; 15%), pre-emptive therapy (3/47; 6%), or CMVi treatment (2/47; 4%). One patient received LMV as a treatment and then as a secondary prophylaxis.

In 8/9 analyzed reports, the same dose of LMV in children >30 kg body weight (b.w.) was provided as in adults i.e. 240 mg/day [intravenous/*per os* (iv/*po*)] with concomitant cyclosporine and 480 mg (iv/*po*) per day without cyclosporine. In all studies with patients <30 kg b.w., the dose of LMV was 120 mg/day with concomitant cyclosporine and 240 mg/day without cyclosporine. This was regardless of the type of CMV management (i.e. primary/secondary prophylaxis or treatment). In a case described by Pérez Marín et al. [11], initially 7 mg/kg b.w. of LMV was administered once a day with an escalation to 24 mg/kg twice a day due to lack of efficacy of the lower dosage. It is however worth noting that when used as CMVi treatment method, LMV was (in both found cases) administered concomitant to foscarnet (FOS). 10/46 (22%) patients received other anti-CMV treatment before switching to LMV.

The use of LMV was safe in pediatric patients. The incidence of adverse effects occurring due to LMV administration in children was inconclusive, so we the authors considered different ones. Most common were nausea, vomiting and transient liver function impairment. The latter, however, cannot be fully associated with LMV toxicity as patients simultaneously took other hepatotoxic drugs (e.g. mycophenolate mofetil). The same applies to the enteritis described by Kilgore et al., being difficult to differentiate between LMV-induced, progressive GvHD or effects of ongoing CMV colitis [7].

Overall, in 44/46 (95.6%) cases, no symptomatic CMVi occurred during LMV administration, with only transient CMV DNA-emia present on rare occasions.

Table I. Summary of reported cases of use of letermovir (LMV) in children

Author	Patients	Sex	Median age; range	CMV management	Serostatus of CMV	HLA match	Breakthrough symptomatic CMVi during LMV administration
Styczyński et al. [1]	5	1 M, 1 F 3 N/A	N/A	2 × PP 3 × SP	2 × (D+/R+) 3 × N/A	1 × MUD 1 × MMRD 3 × N/A	0/5
Cheng et al. [8]	4	3 M, 1 F	16,1 (9.2–17.8)	4 × PP	4 × D–/R+	2 × MRD 1 × MUD 1 × MMUD	0/4
Richert-Przygonska et al. [6]	13	6 M, 7 F	13,2 (7.1–16.9)	12 × PP 1 × SP	8 × (D+/R+) 5 × (D–/R+)	4 × MRD 8 × MUD 1 × haplo	0/13
Strenger et al. [12]	2	2 M, 0 F	8.8 (6–11.5)	2 × PET	2 × (D+/R+)	2 × MRD	0/2
Pérez Marín et al. [11]	1	0 M, 1 F	2	1 × TOC	–	–	1.1
Kuhn et al. [10]	9	4 M, 5 F	14 (4–19)	7 × PP 2 × SP	5 × (D+/R+) 1 × (D+/R–) 2 × (D–/R+) 1 × N/A	1 × MRD 5 × MUD 3 × haplo	0/9[b]
Chiereghin et al. [5]	1	1 M, 0 F	17	1 × PET	1 × (D–/R+)	1 × MMUD	0/1
Kilgore et al. [7]	1	0 M, 1 F	14	1 × TOC/SP	1 × (D–/R+)	1 × DUBT	1/1[c]
Daukshus et al. [4]	10[a]	5 M, 5 F	15.2 (10–17.6)	10 × PP	6 × (D–/R+) 4 × (D+/R+)	2 × MRD 3 × MUD 5 × MMUD	0/10
Total	46	22 M (47.8%) 21 F (45.7%) 3 N/A (6.5%)	Range (2–19)	35 × PP (74.5%) 7 × SP (14.9%) 2 × TOC (4.3%) 3 × PET (6.4%)	21 × (D+/R+) (46.7%) 19 × (D–/R+) (42.2%) 1 × (D+/R–) (2.2%) 4 × N/A (8.9%)	11 × MRD (24.4%) 1 × MMRD (2.2%) 18 × MUD (40.0%) 7 × MMUD (15.6%) 4 × haplo (8.9%) 1 × DUCBT (2.2%) 3 × N/A (6.7%)	2/46 (4.3%)

[a]One patient had two hematopoietic cell transplantatios and is counted as two; [b]one patient had CMV DNA-emia of 467 IU/mL and had LMV discontinued in favor of valgancyclovir; [c]LMV was used concomitant to foscarnet for cytomegalovirus infection (CMVi) treatments, which was successful. Then LMV was used in monotherapy as secondary prophylaxis and patient developed symptomatic cytomegalovirus (CMV) after 2.5 months; HLA — human lymphocyte antigen; M — male; F — female; N/A — not available; PP — primary prophylaxis; SP — secondary prophylaxis; D — donor; + — seropositive of CMV; R — recipient; MUD — matched unrelated donor; MMRD — mismatched related donor; – — seronegative of CMV; MRD — matched related donor; haplo — haploidentical transplant; PET — preemptive therapy; TOC — treatment of CMVi; MMUD — mismatched unrelated donor; DUCBT — double umbilical cord blood transplant

Primary prophylaxis

Primary prophylaxis was the most common use for LMV in CMV management strategy in the analyzed reports (35/47; 74.5%). Out of 29 cases with known LMV initiation time, the median was day +1. In three cases, LMV administration was started prior to allo-HSCT procedure. Two children had switched to LMV for primary prophylaxis because of gancyclovir/valgancyclovir (GCV/VGC) intolerance, thus they only started administration of LMV on days +83 and +84. No patient developed symptomatic CMVi. One child, in the work by Kuhn et al., developed viral load of 467 IU/ /mL which resulted in discontinuation of LMV in favor of VGC [10]. This patient was cured and remained asymptomatic. It remains unknown whether the patient would have developed symptomatic CMVi, had it not been for the switch of treatment.

Secondary prophylaxis

LMV was used as secondary prophylaxis in seven cases (7/47; 14.9%) following successful treatment with GCV/ /VGC. In 6/7 cases (85.7%) no symptomatic CMVi was observed. A girl described in the work by Kilgore et al. [7] received LMV as secondary prophylaxis after successful CMV treatment with a combination of iv FOS and LMV, and 2.5 months after the resolution of her initial CMV-DNAemia, this patient presented with symptomatic CMVi. Further tests revealed *UL56* mutation (R369S) which conferred LMV resistance. Therapy was changed to concomitant GCV and FOS which resulted in a decrease of CMV-DNAemia.

Pre-emptive therapy

There were three cases of LMV use as pre-emptive therapy in our research (3/47; 6.4%). The median initiation time was day +120 (range: +11 to +203) with median treatment duration of 24 days (range 10–57). None of the cases included administration of LMV as first line treatment. Patients had their primary pharmacotherapy switched after intolerance (1/3; 33.3%) or refractory high CMV-DNA-emia (2/3; 66.7%). All children (3/3; 100%) became CMV negative after LMV was initiated in monotherapy (time range: 1 week–42 days).

Treatment of CMV

In 2/47 cases (4.3%), LMV was administered with concomitant FOS as CMVi treatment due to a lack of response to standard therapy. In one case described by Perez Marin et al., therapy was unsuccessful and the patient died due to a massive subdural hemorrhage, although the viral load was reduced from 360,000 copies/mL to 4,300 copies/mL [11]. The same combination of antivirals, as described by Kilgore et al., was successful in overcoming CMVi [7]. FOS was withdrawn and secondary prophylaxis with oral LMV in monotherapy was initiated.

Discussion

The use of LMV in prophylaxis of CMV infection in patients after allo-HSCT has changed the paradigm of prevention of this infection, and will hopefully contribute to decreases in other infections and complications [1–3, 13, 14]. In this paper, we have summarized all publications on LMV use in off-label indications in pediatric populations available on PubMed. Despite increased interest in the use of LMV, there is still limited data regarding this issue. In 44/46 (95.6%) cases, no symptomatic CMVi occurred during LMV administration, with only transient CMV DNA-emia present on rare occasions. One patient with symptomatic CMV received LMV as a treatment option which failed to decrease viral load to undetectable levels. A second one developed symptomatic CMVi during secondary prophylaxis which was preceded by successful treatment with LMV. This patient however developed LMV resistance.

Although a daily dose of LMV in children is not established yet, patients >30 kg b.w. in 8/9 analyzed publications were provided the same treatment as adults (240 mg with/480 mg *po*/iv without cyclosporine per day); for <30 kg b.w., the dosage was halved. This resulted in no severe side effects. Nevertheless, due to the absence of data about pharmacokinetics of LMV in pediatric population, selecting dosage should be done with caution [8].

Only two papers included control groups in the methodology, with Cheng et al. noting a trend towards delay in platelet engraftment in the LMV group ($p = 0.088$) [8]. However, this was not the case for Richert-Przygońska ($p = 0.452$) [6]. It is difficult to draw statistically significant conclusions considering the small sizes of both LMV and control groups in these papers. Nonetheless, they support the promising effect LMV can bring to CMV prophylaxis among pediatric patients.

The presented data suggests high effectiveness and safety regarding the use of LMV for CMVi prophylaxis in immunosuppressed children. There is not enough information regarding its use in pre-emptive therapy, because it was not utilized as the first line treatment in any of the cases. A similar scenario occurred with analysis of treatment of ongoing CMV, where a combination of LMV and FOS was once successful and once was not. However, the complexity of these two cases, and the use of polytherapy prior to LMV administration, makes it difficult to evaluate LMV for this indication.

More data about LMV effectiveness and safety in pediatric populations will be available after the much-anticipated outcome of a currently ongoing study (MK-8228-030) (Clinical-Trials.gov identifier NCT03940586) [4, 10].

Acknowledgements

The authors thank Prof. Jan Styczyński for critical revision of the paper.

Authors' contributions

KC, JS — design of study. All authors — analysis of clinical data. TS, JS — literature search and analysis of data. TS, JS — writing manuscript. All authors — critical revision and final approval.

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.

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Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 36–42
DOI: 10.5603/AHP.a2023.0005
ISSN 0001–5814
e-ISSN 2300–7117

ORIGINAL RESEARCH ARTICLE

Clinicomorphological spectrum of hemophagocytic syndrome in a tertiary care hospital

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Abstract

Introduction: The HLH-2004 trial established the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH), a severe hyperinflammatory condition. It typically develops due to inappropriate macrophage activation.

Our objective was to assess the spectrum of hemophagocytic syndrome presentations by identifying hemophagocytic activity in the bone marrow, and to unravel the etiopathogenesis of this condition.

Material and methods: A retrospective study was carried out in the Department of Pathology in a tertiary care hospital reporting the clinical and laboratory findings of patients who had been previously diagnozed with hemophagocytosis in the bone marrow. The parameters in the diagnostic criteria of HLH of the same patients were documented and analyzed.

Results: The characteristics of the 32 patients who presented with hemophagocytosis in the bone marrow were documented. Persistent fever was the most frequent presentation. Mild to moderate anemia (69%), severe leucopenia (59%), and mild to moderate thrombocytopenia (63%) were other frequent findings. The incidence of primary HLH was found to be only 3%; 87% had hyperferritinemia, 78% had bicytopenia, 59% had hypertriglyceridemia, and 53% had splenomegaly. Infections followed by malignancies were shown to be the most frequent cause of secondary HLH, while the prognosis for malignancy-associated HLH appeared to be poor.

Conclusions: Based on the findings of this study, conclusions about the clinical symptoms and etiologies of HLH may be drawn, which will assist in early identification. Hence, all subjects with a clinical suspicion of HLH should be thoroughly investigated for a possible etiology.

Key words: bone marrow, hemophagocytic lymphohistiocytosis (HLH), hyperferritinemia, primary HLH, secondary HLH

Acta Haematologica Polonica 2023; 54, 1: 36–42

Introduction

Hemophagocytosis is a pathological disease in which activated macrophages phagocytoze bone marrow cellular components (erythrocytes, leukocytes, platelets, and their progenitors) [1, 2]. Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphocytic lymphohistiocytosis (HLH) is a rare, potentially fatal condition of immune dysregulation due to failure in making a timely diagnosis and appropriate treatment [3–6]. It describes a spectrum of enhanced macrophage activity as a result of a cytokine storm and multi-organ failure, as measured by certain laboratory markers (i.e. elevated ferritin, triglycerides, soluble CD25, transaminases, lactate dehydrogenase, and fibrinogen) [3, 5, 7].

Although HLH has been observed in people of all ages, it is most frequent in children and young adults [8]. It is usually split into two categories: primary/familial HLH (fHLH) and acquired/secondary HLH. Primary HLH is a condition that affects children and is caused by a hereditary defect

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Received: 12.09.2022 Accepted: 01.11.2022

in natural killer and T-cell cytotoxic activity [9]. Secondary HLH is most common in adults, with average age at diagnosis being 48 to 50 years. Infection, cancer, immunological insufficiency, and rheumatological diseases are the most common causes of secondary HLH [3–5, 7].

Hyperpyrexia, spleen enlargement, and pancytopenia are clinical features of HLH, whether primary or secondary [4, 6]. Rashes, liver dysfunction, hyperferritinemia, hypertriglyceridemia, coagulation problems, and renal insufficiency are some other clinical manifestations. The pathognomonic hallmark of HLH is the presence of hemophagocytosis in the bone marrow, lymph nodes, spleen, or liver [10]. The liver and spleen are the most commonly affected organs. The lungs, intestines, kidneys, and skin are also organs that are regularly implicated. The prognosis for certain individuals with neurological disorders is exceedingly dismal [11]. In 1994, the Histiocyte Society published therapeutic recommendations for the treatment of HLH, and in 2004 a revised set of diagnostic criteria was released. Diagnostic criteria with their clinical and laboratory features have been previously established in the literature [4].

The objective of this study was to determine the range of hemophagocytic syndrome presentations by identifying hemophagocytic activity in the bone marrow and correlating it with clinical and biochemical parameters found in HLH. Since the patient's overall prognosis is determined by prompt diagnosis and treatment, the current study also aimed to demonstrate the etiopathogenesis of this disorder, which can play a key role in determining the patient's prognosis.

Materials and methods

This retrospective study was conducted in the Department of Pathology in a tertiary care hospital which reports the clinical observations and laboratory findings of individuals who have presented with hemophagocytosis in the bone marrow. Thirty-two individuals who had visited the department in the past, irrespective of age, sex, or health status, were incorporated into the present study.

Patient requisition forms, the hospital information system, and discharge summaries were used to collect clinical and laboratory data for each patient. The patient's age, fever, splenomegaly, peripheral blood counts, triglycerides levels, fibrinogen levels, ferritin levels, bone marrow findings, and examinations pertinent to the underlying pathology of hemophagocytosis were all recorded.

Bone marrow aspiration and trephine biopsy were performed under aseptic conditions and local anesthesia. A smear was prepared using the squash technique and stained with Giemsa stain. The trephine samples of bone marrow were sent to a histopathology facility in 10% neutral buffered formalin. These biopsies were decalcified with pH 7.6 aqueous ethylene diaminetetraacetic acid (EDTA). The blocks were processed, and sections were taken for hematoxylin and eosin (H&E) staining and immunohistochemical marker (IHC) studies. All tests for viral markers [including Epstein-Bárr virus (EBV), and cytomegalovirus [CMV]) were conducted pertaining to the clinical presentation of the patients.

With the Institutional Human Ethics Committee, PSG Institute of Medical Sciences & Research (IMS&R) approval (Project No. 15/394), the present study was conducted and carried out as per the ICH-GCP/ICMR/Schedule Y guidelines. Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software. Results were presented as mean, frequency, and percentages.

Results

The characteristics of 32 subjects who presented with hemophagocytosis in the bone marrow were documented. These included age, fever, splenomegaly, and laboratory parameters such as blood counts, ferritin, triglyceride, and fibrinogen levels.

Out of the total number of patients incorporated in our study, 59% were males and 41% were females; 62% were ≥18 years and 38% were <18 years. The mean age was 30.7 years.

The clinical and laboratory observations of the subjects according to the HLH-2004 criteria were extracted from the medical records and were analyzed (Figure 1). At diagnosis, all patients (100%) had a fever, 87% had hyperferritinemia, 78% had bicytopenia, 59% had hypertriglyceridemia, 53% had splenomegaly, and 31% had hypofibrinogenemia.

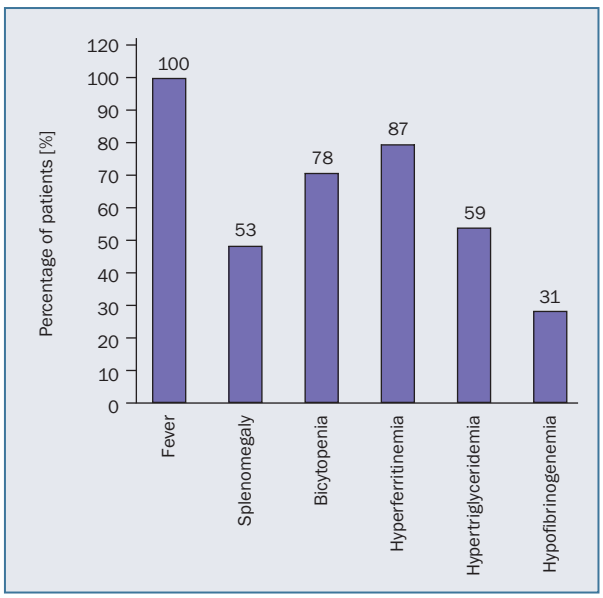

Figure 1. Clinical and laboratory observations of patients according to Hemophagocytic Lymphohistiocytosis-2004 criteria

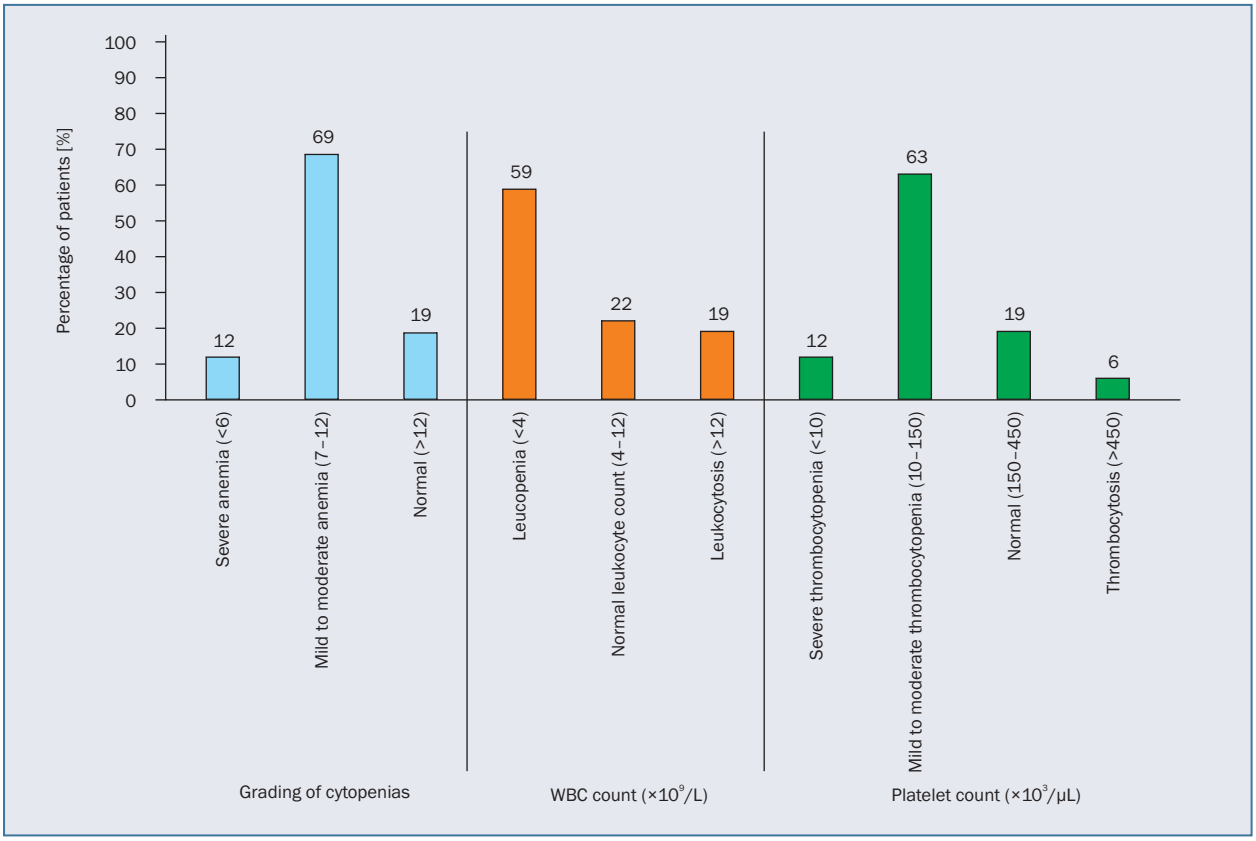

Figure 2. Grading of cytopenias and their percentage of presentation in subjects with hemophagocytic lymphohistiocytosis; WBC — white blood cells

Grading of cytopenias

Figure 1 shows that 78% of subjects presented with bicytopenia. The hematological parameters were again graded according to their severity [12].

Observations of the subjects according to the grade of severity of the hematological parameters are set out in Figure 2.

Bone marrow trephine

About 19% of the participants had hemophagocytosis in both the bone marrow aspirate and the trephine, whereas the remaining 81% had hemophagocytosis solely in the bone marrow aspirate. No patient tested positive for trephine but negative for bone marrow aspirate. IHC marker CD68 was used to indicate hemophagocytic activity in the bone marrow trephine (Figures 3A, B).

Types of HLH

In the present study, 3% of subjects (one case) had primary HLH (associated with Cheidiak Higashi syndrome) and the remaining 97% had secondary HLH. Abnormal granules in leucocytes and hemophagocytosis in the same subject is represented in Figures 4A, B.

Etiology

Infection was the most prevalent cause of HLH in this study, accounting for almost 70% of the participants. Bacterial infections accounted for 55%, viral infections for 28%, parasitic infestations for 9%, and fungal infections for 4%. The causal bacterium could not be isolated in the remaining 4% of cases. Tuberculosis was the most common infection, accounting for 23% of those infected. Disseminated sepsis was the second most prevalent cause, accounting for 19% of cases. Typhoid fever accounted for 15%, dengue fever, also known as scrub typhus, accounted for 9%, and human immunodeficiency virus (HIV) accounted for another 9%. Hepatitis A, nocardiosis, viral pneumonia, and pyrexia of unknown origin (PUO) each accounted for 4% of the total.

Neoplasms associated with HLH

After infections, neoplasm-associated HLH was the most common cause of hemophagocytosis, accounting for 16% of all patients. Lymphomas accounted for 40% of the HLH linked with neoplasms. (Figures 5A, B).

Non-lymphoma Hodgkin patients made up roughly 6% of the total. The remaining 3% of patients had myelofibrosis,

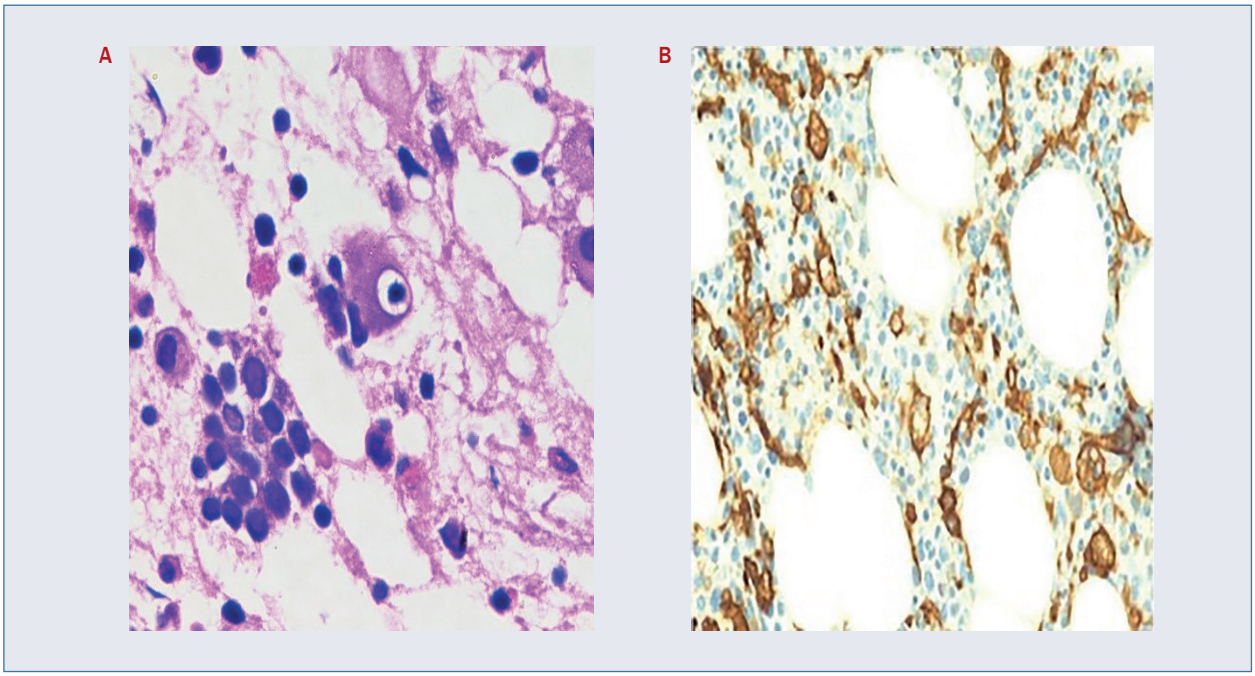

Figure 3. Hemophagocytosis in trephine (**A**) highlighted using immunohistochemical marker CD68 (**B**)

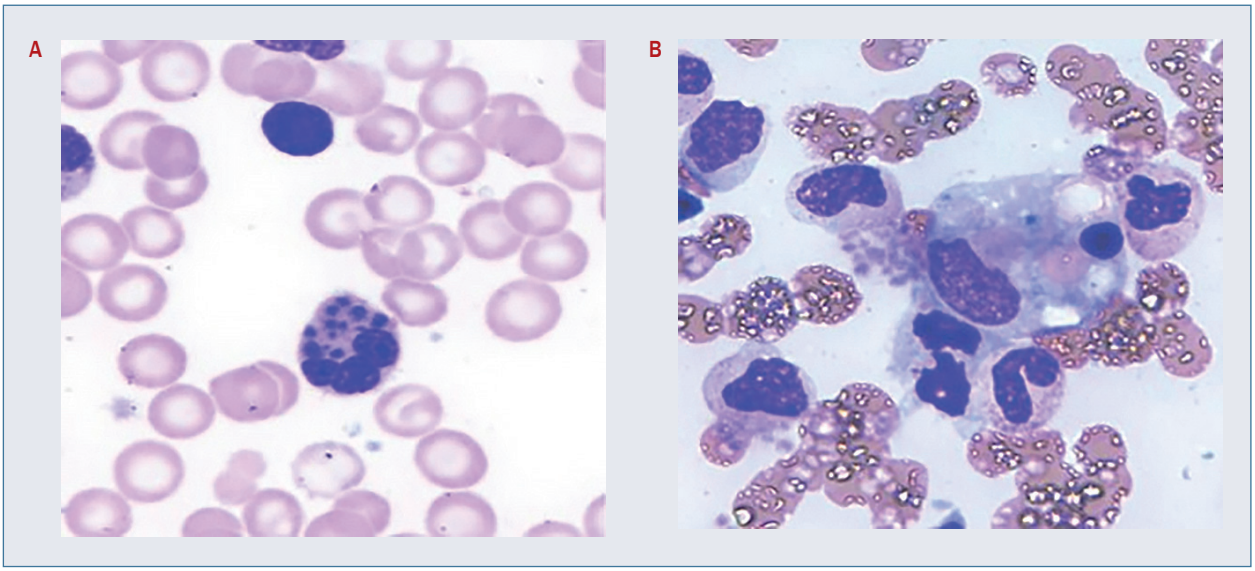

Figure 4. Abnormal granules in cytoplasm of white blood cellss in peripheral smear of individual with Chediak Higashi syndrome: **A.** Within neutrophil; **B.** Hemophagocytosis in one marrow of same individual, in Giemsa 100×

multiple myeloma, myelodysplastic syndrome, aplastic anaemia, Kikuchi Fujimoto Disease, Chediak Higashi Disease, or systemic lupus erythematosus.

Twenty per cent of subjects had a diagnosis of multiple myeloma. Myelodysplastic syndrome and myelofibrosis (Figure 6) each accounted for 20%.

Deaths associated with HLH

Nineteen per cent of the total participants in this study had an extremely unstable clinical course, which culminated in their deaths. Sepsis was responsible for 32% of the fatalities related to HLH. Scrub typhus, hepatitis A, diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM) each accounted for 17%.

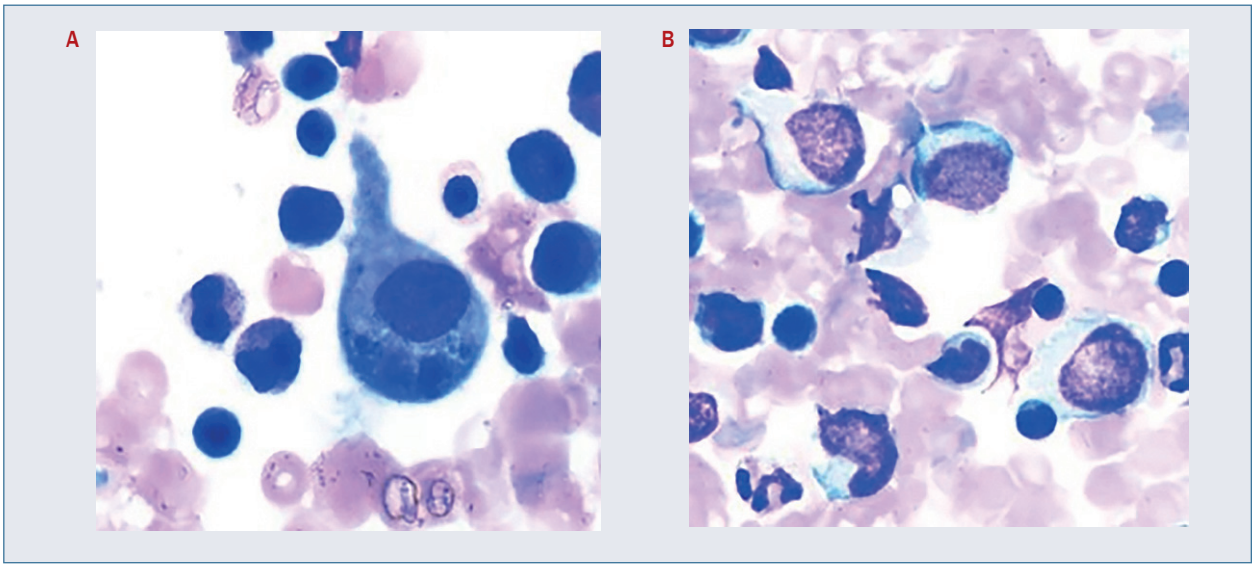

Figure 5. Hemophagocytosis (**A**) in subject with atypical lymphoid cells (**B**) in bone marrow diagnosed to be diffuse large B-cell lymphoma, in Giemsa 100×

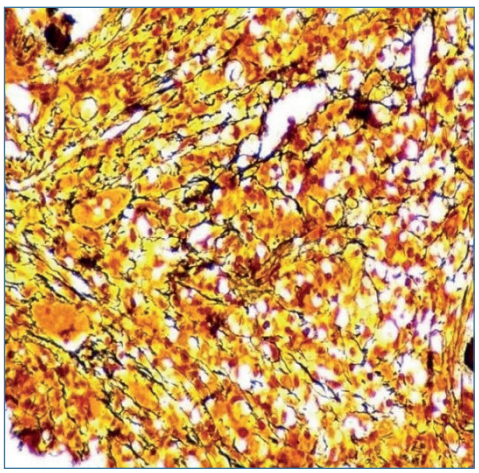

Figure 6. Bone marrow trephine of patient with myelofibrosis in reticulin stain 40×

Discussion

HLH is a syndrome, not a specific disease, that can manifest itself in a variety of circumstances. The incidence of HLH is estimated to be 1 in 100,000 live births [3].

The purpose of this study was to determine the range of hemophagocytic syndrome presentations and to elucidate the varied etiopathogenesis of HLH. Awareness of the various etiologies of this important condition will go a long way toward ensuring prompt diagnosis and treatment.

59% of the total individuals in the study were males, while 41% were females; 62% were adults (18+ years), while 38% were in the paediatric age group (0-17 years). The average age of the participants was 30.7 years. These findings are almost identical to those of Iqbal et al. [12], who found that the average age of HLH presentation was 30.8 years. In our investigation, there was no significant difference between the presentations of males and females, and this again was similar to the findings of Iqbal et al. [12].

In the diagnostic criteria, fever was the common clinical presentation in our study. Fever was the most prevalent clinical manifestation, according to the diagnostic criteria. This was in accordance with George et al. [13] and Otrock et al., [10] who observed that almost 100% of HLH subjects presented with fever. Iqbal et al. [12] stated that 65.2% of patients presented with fever, which was less than in our study. It may be inferred that the most prevalent symptom of HLH is a prolonged and persistent fever that is refractory to treatment.

In this study, splenomegaly was seen in 53% of subjects. This result approximately correlates with Fardet et al. [14], where splenomegaly was seen in 65% of patients, whereas Iqbal et al. [12] observed splenomegaly in 37.2%. In contrast to this, George et al. [13] stated that splenomegaly was present in 100% of individuals with primary HLH and in 80–90% with secondary HLH. Iqbal et al. [12] graded the cytopenias and gave percentages accordingly.

George et al. [13] observed cytopenias in 80%; in line with this, 78% of subjects in our study presented with bicytopenia.

The level of ferritin in macrophages is a good predictor of their phagocytic activity [15]. Hyperferritinemia was discovered in 87% of the individuals in our study, which matches the findings of George et al. [13], who reported hyperferritinemia in 70–90% of patients, whereas Chandra et al. [2] found it in only 40%.

In this study, hypertriglyceridemia was detected in 59% of HLH cases, whereas George et al. [13] found

hypertriglyceridemia in 40% of patients and Chandra et al. [2] found abnormal lipid levels in 45% of cases. In the studies by George et al. [13] and Chandra et al. [2], 40% of participants presented with hypofibrinogenemia. In contrast with this, in our study, fewer (31%) cases presented with low fibrinogen levels.

IHC marker CD68 was utilized by Caleb Ho et al. to identify hemophagocytosis in bone marrow samples. This improved sensitivity allowed the assessment of hemophagocytic activity in trephine biopsies [16]. In contrast to this, using the marker CD68 on trephine biopsies did not improve the sensitivity of identification of aberrant phagocytic activity in our study.

HLH is divided into two groups: primary HLH and secondary HLH. Primary HLH is mostly seen in children of less than one year of age. Primary HLH accounts for 25% of the HLH presenting in the pediatric age range, according to Zhang et al. [17]. HLH was observed in 38% of the pediatric age group in our study. In contrast to this, the percentage of individuals with primary HLH was just 3%. This is due to a lack of equipment for diagnosing genetic alterations, as well as the study population's financial restrictions.

In this study, infection was the common cause of secondary HLH, accounting for 70% of the total cases. George et al. [13] reported a 50% infection-related HLH, while Chandra et al. [2] reported a 13% infection-related HLH. Though the percentage of cases varied, infection-related HLH was the most prevalent cause of secondary HLH in all three studies.

Typhoid, according to Non et al. [18], is an extremely uncommon cause of HLH. In this study, typhoid was found in 15% of the infection-associated HLH patients. In our investigation, dengue and HIV-associated viral infections were found to be more prevalent, accounting for 9% of all instances of hemophagocytosis. Malaria was shown to be the most frequent parasite illness linked with HLH by Chandra et al. [2]. Scrub typhus, on the other hand, was the most frequent parasite infection in the current research (9%).

The second most prevalent etiological factor for secondary HLH, according to George et al. [13], Zhang et al. [17], and Hust et al. [19], is neoplasm-associated HLH (both hematological and non-hematological). Of the malignancies, lymphoma was common in all the studies. In the present study, 16% of cases were due to malignancies (both hematological and non-hematological).

There are a few limitations to our present study. Firstly, this was a retrospective study based on case selection criteria and diagnosis coding in medical records. Since many patients were lost to follow-up, information on therapy response and prognosis of the subjects was not accessible. The procedures for assessing NK cell activity and CD25 levels were not accessible at the research institution, and hence those parameters were not examined. There were also no resources for molecular diagnosis of mutations associated with primary hemophagocytic lymphohistiocytosis, which may have contributed to the lower incidence of primary HLH (3%) in the current research when compared to other investigations [20].

Conclusions

A confirmed diagnosis of HLH is based on a comprehensive examination of patients in a clinical setting. Conclusions on the clinical symptoms and etiologies of HLH may be drawn from this study, which will assist in early diagnosis. As a result, all individuals with a clinical suspicion of HLH should be thoroughly investigated for a probable etiology. For early diagnosis and therapy, a complete and detailed examination of the bone marrow of individuals suspected of having HLH is required. As a result, further research is needed to increase awareness of this condition, and enhance the efficacy of the current treatment regimen.

Authors' contributions

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Conflict of interest

The authors declare no conflict of interest.

Financial support

This study did not receive any form of funding from public, government, or not-for-profit sectors.

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.

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VIA MEDICA

SHORT COMMUNICATION

Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 43–45
DOI: 10.5603/AHP.a2023.0006
ISSN 0001–5814
e-ISSN 2300–7117

Thromboembolic complications associated with COVID-19 infection in children

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Introduction

With increasing knowledge of the course of coronavirus disease 2019 (COVID-19) in children, it is possible to detect complications associated with the disease more frequently, such as thromboembolic complications, with the most frequently observed being venous thromboembolisms, covering the spectrum of deep vein thrombosis and pulmonary embolism [1–3]. The prothrombotic and proinflammatory state accompanying COVID-19 infection can lead to ischemic stroke in children [4]. One parameter that closely correlates with thromboembolic incidents is elevated D-dimer level [5]. Moreover, thrombotic events occur in some patients despite thromboprophylaxis [3].

The objective of the work was to present two cases of pediatric patients who developed thromboembolic complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

We here describe two patients hospitalized in the Department of Pediatrics, Hematology and Oncology (PHO) between December 2021 and March 2022.

Case series

Patient 1

The first presented case associated with thromboembolic complications was a 4-month-old boy admitted to the PHO because of coagulation disorders. The patient was born at 40 weeks' gestation by emergency cesarean section due to maternal COVID-19 infection. He scored 7/10 on the Apgar scale due to respiratory failure and moderate birth asphyxia. On the first day of life, the patient developed convulsive seizures with breathlessness, and these were resistant to treatment with phenobarbital, diazepam, clonazepam and pyridoxine. Hence, he was transferred to the Neonatal Intensive Care Unit. Due to suspected early onset sepsis, combined empiric broad-spectrum antibiotic therapy was applied. On the second day of life, polymerase chain reaction (PCR) test for SARS-CoV-2 was found to be positive. Based on cerebrospinal fluid examination, neuroinfection was excluded. Blood and stool cultures were also negative. On the following days, the neonate's condition deteriorated, including cough, fever, increasing inflammatory markers and coagulation disturbances tending towards hypercoagulopathy (high D-dimers, high fibrinogen, and decreased antithrombin III level). A chest X-ray confirmed pneumonia in the newborn. Improvement occurred after antibacterial treatment. At the first screening of D-dimers, the measured value reached 1,537 ng/mL (norm <500 ng/mL), gradually decreasing over the following days. In the course of further diagnostics, a computed tomography (CT) scan of the head was performed, which described an edematous-ischemic area in the left frontoparietal region 25 × 68 mm in dimension. An initial magnetic resonance imaging (MRI) scan confirmed an ischemic stroke, describing a 55 × 22 × 33 mm ischemic lesion in the left temporal lobe and a 14 × 10 × 6 mm small hemorrhagic area in the left occipital region.

At the age of 4 months, the patient was admitted to the PHO. The only abnormality was slight muscle weakness in the right upper limb. Laboratory results showed normal blood count parameters, as well as slightly elevated

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Received: 12.09.2022 Accepted: 01.11.2022

D-dimers (686 ng/mL) and decreased fibrinogen levels (154 mg/dL; normal 200–393 mg/dL). Moreover, laboratory tests for thrombophilia were performed. Factor VIII and protein S concentrations were normal. Genetic testing excluded factor V Leiden mutation and prothrombin gene mutation. A follow-up MRI scan showed no ischemic changes in the acute phase within the brain, and some changes corresponding to a post-stroke scar.

During the hospitalization, the patient received enoxaparin 1.5 mg/kg 1 × daily subcutaneously, valproic acid 2 × 7.5 mg/kg, as well as iron, cyanocobalamin, folic acid and pyridoxine supplementation. From the overall clinical presentation, and by excluding other possible causes of coagulopathy, it was established that the possible cause of the thromboembolic incident was SARS-CoV-2 infection.

Patient 2

A 13-year-old girl was admitted to hospital because of deep vein thrombosis of the left lower limb. A week before admission, sudden pain in the left lower limb had appeared. The patient denied chronic diseases, trauma, prolonged immobilization, and taking medication, including contraceptives. Two months before hospitalization, she had an upper respiratory infection (no swabbing for SARS-CoV-2). On admission to the PHO, physical examination revealed: forced positioning, edema, redness and positive Homans' sign in the left lower limb. Dyspnea, chest pain and hemoptysis were not observed. Laboratory tests showed elevated D-dimers (6,610 ng/mL), prolonged prothrombin time (15.9 s; normal 10.2–12.9 s), and elevated C-reactive protein (CRP) (50 mg/L; normal <5 mg/L).

Doppler ultrasound showed no flow in the left external iliac and common iliac veins. Also, inferior vena cava with visible thrombus in the central part and marginal flow: the thrombus reached the level of the right renal vein outlet. Enoxaparin 2 × 1 mg/kg was started, with clinical improvement. Lupus anticoagulant, p-cardiolipin antibodies and anti-beta$_2$-glycoprotein antibodies were not found, thus antiphospholipid syndrome was excluded. Congenital thrombophilia was excluded by genetic testing. Positive IgG anti-SARS-CoV-2 antibodies were found in the examined sample.

An angio-CT of the chest described a thrombosed, obstructed superior lobe artery together with segmental arteries to the upper part of the upper lobe of the right lung. In addition, in the right pulmonary artery and segmental arteries there were present small defects in contrasting which could correspond to thrombi. Moreover, a thrombus within the inferior vena cava at the level of the hepatic vein outflow was suspected — the flow at this level was mainly peripheral. Therefore, abdominal angio-CT was performed, which described venous thrombosis of the left iliac axis in the inferior vena cava from the junction of the iliac veins to the segment just below the renal veins. Hepatic vein thrombosis was excluded. The girl was consulted by a cardiologist — cardiac markers were negative, electrocardiogram (ECG) showed sinus rhythm, regular heart rate 80/min, corrected QT interval (QTc) 0.43 s, no ST-T disturbances, and no hypertrophy. In echocardiogram, no abnormalities were found, despite weak low velocity flow in right pulmonary artery.

During hospitalization, pain and swelling of the left lower limb decreased. Based on the whole clinical picture, the thromboembolic changes were most probably due to the COVID-19 infection.

Discussion

In both presented cases, SARS-CoV-2 infection possibly increased the risk of a thromboembolic complication. Recent studies have described a spectrum of thromboembolic incidents in children as a consequence of COVID-19, including acute ischemic stroke involving one or more vessels and deep vein thrombosis with pains in an extremity, edema and pruritus [6, 7].

It has been proven that complications can occur in children of different ages, particularly affecting those over 12 years of age, but cases of thrombotic incidents have also been reported in infants [3]. A feature uniting our patients was elevated D-dimers. The first patient, during COVID-19 infection and after the incident of ischemic stroke, showed increased D-dimers. The result was slightly reduced but was still above the norm even after several months. In the second patient, D-dimers were the highest with accompanying CRP elevation and signs of extensive venous thrombosis. In addition, the laboratory test of both patients indicated hypercoagulopathy. Elevated levels of fibrinogen, ferritin, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), increased platelet count and prolonged prothrombin time (PT) were also observed in pediatric patients after COVID-19 infection in a 2020 US study [8]. Each patient was diagnosed for thrombophilia, protein C and S and coagulation factor VIII levels, as well as genetic tests for factor V Leiden mutation and prothrombin gene mutation. Antiphospholipid syndrome was also excluded. Low-molecular-weight heparin had been used in the treatment of patients.

Current works report a low percentage of possible COVID-19 intrauterine infection. The factor in determining the moment of infection (i.e. *in utero*, intrapartum or postpartum) is the timing of the sample collection and contact with the infected mother [9].

It is difficult to assess the moment of infection in patient 1. The boy remained asymptomatic for the first few days, which supports a possible postnatal exposure. In addition, seizures were the symptom of stroke, but possibly also of SARS-CoV-2 infection, which may suggest that the symptoms of infection appeared as early as day 1 of life and the neonate could have been infected in an intrauterine

manner. Studies are needed to determine which route of infection induces thromboembolic complications most frequently in newborns.

In the 13-year-old girl, the detection of IgG antibodies to SARS-CoV-2 raised the suspicion that the patient could developed pediatric inflammatory multi-organ syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Several research studies have also demonstrated an increased prevalence of coagulopathy in patients with PIMS-TS [5, 10]. The diagnosis of PIMS-TS requires the fulfilment of six criteria, based on definitions according to the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) [11, 12], plus Polish guidelines such as: age (0–18 years); fever >38.0°C for ≥3 days; high inflammatory markers (elevated values of: CRP; procalcytonin; fibrinogen; D-dimers; ferritin); multi-organ damage (symptoms from at least two organs); exclusion of other causes; and COVID-19-association. Our 13-year-old patient did not meet the fever criterion and presented symptoms only from the cardiovascular system. Therefore, her symptoms and disease manifestation were not a manifestation of PIMS-TS and were probably related to recent COVID-19.

To conclude, coronavirus-infected children, as well as adults, can develop thromboembolic complications after SARS-CoV-2 infection. Pediatric patients with COVID-19 present coagulation abnormalities and a predisposition to thrombosis [8, 13, 14], indicated mostly by elevated D-dimers. Further exploration of the mechanisms and predisposition to thromboembolism in children following SARS-CoV-2 infection would be advisable.

Authors' contributions

AJ, MC, NC, KC, MRP — design of the study. MRP — provision of clinical data. AJ, MC, NC, MRP — literature search and analysis of data. AJ, MC, NC, MRP — manuscript writing. AJ, MC, NC, KC, MRP — critical revision and final approval.

Conflicts 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 and uniform requirements for manuscripts submitted to biomedical journals.

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Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 46–47
DOI: 10.5603/AHP.a2023.0007
ISSN 0001–5814
e-ISSN 2300–7117

VIA MEDICA

Systemic mastocytosis associated with hematological neoplasm: a diagnostic challenge

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Case report

A 58-year-old male with a history of alcoholic liver cirrhosis, hypertension and peptic ulcer was admitted to the local hospital in August 2016. He complained of easy fatigue and significant weight loss (>10 kg within the previous six months). On physical examination, hepatosplenomegaly and ascites were observed. Complete blood count (CBC) showed moderate anemia [hemoglobin (Hb) = 10 g/dL] and thrombocytopenia [platelets (PLT) = 46 × 10^9/L]. Leukocyte count was elevated with monocytosis (1.76 × 10^9/L) and eosinophilia (6.5 × 10^9/L). Magnetic resonance imaging (MRI) confirmed the presence of ascites and hepatosplenomegaly (liver 175 mm, spleen 155 mm). The patient was referred to the Hematology Unit. On admission in September 2016, the blood film was in line with the previous findings. Bone marrow aspirate was normal except for eosinophilia. The *BCR-ABL* and *FIP1L1-PDGFRA* gene rearrangements were not detected, and karyotype was diploid on conventional cytogenetics. The patient was diagnosed with idiopathic hypereosinophilic syndrome and prescribed prednisone. As a result, blood eosinophilia normalized and platelet count increased to 140 × 10^9/L, but monocytosis persisted. He remained stable for four years. In April 2021, platelet count dropped to 60 × 10^9/L despite continued steroid treatment. Abdominal ultrasound and computed tomography (CT) scan detected splenomegaly, retroperitoneal lymphadenopathy, and fractures of the thoracic vertebrae. The patient was admitted to our Department in August 2021. He was thrombocytopenic (PLT = 52 × 10^9/L) and blood monocytosis was as high as 1.69 × 10^9/L. Eosinophilia was not present. On biochemistry, bilirubin concentration was slightly increased to 29.1 µmol/L (N: 3.42–20.6), while alkaline phosphatase (AP) was normal. Trephine biopsy showed the presence of spindle-shaped mast cells in 40% with 95% bone marrow cellularity. Flow cytometry on bone marrow aspirate demonstrated 5.1% of abnormal mast cells and 15.5% of monocytes. Serum tryptase level was elevated to 128 µg/L (N: 0–11.4). The *KIT D816V* mutation on bone marrow cells was detected with allelic load of 70%. A next generation sequencing (NGS) study demonstrated the mutations of *RUNX1* and *SRSF2*. The patient was diagnosed with systemic mastocytosis with chronic myelomonocytic leukemia (SM-CMML). Treatment with midostaurin (Rydapt®, Novartis) at 100 mg twice daily was started. Two weeks later he died of infectious complications.

Discussion

Mastocytosis is characterized by an accumulation of abnormal mast cells in various organs. The 2022 World Health Organization classification recognizes three main types of mastocytosis: cutaneous mastocytosis (CM), systemic mastocytosis (SM), and mast cell sarcoma (MCS) (Table I) [1]. Advanced SM (AdvSM) is an umbrella term encompassing the three variants of SM: 1) SM with an associated hematological neoplasm (SM-AHN); 2) aggressive SM (ASM); and 3) mast cell leukemia (MCL) [2]. Recent years have witnessed huge progress in the diagnosis and treatment of systemic mastocytosis. Based on our patient, we would like to draw attention to some important findings regarding patients with SM-AHN.

Firstly, one should keep an eye on blood eosinophilia, which is strongly associated with an unfavorable prognosis. In a study of 2,350 mastocytosis patients, the incidence of eosinophilia was 9.9% and it was mainly present in patients with AdvSM. Of note is that eosinophilia at diagnosis and at follow-up is a strong predictor of inferior progression-free survival (PFS) and overall survival (OS) [3].

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Received: 26.09.2022 Accepted: 04.12.2022

Table I. 2022 World Health Organization classification of mastocytosis [1]

Types of mastocytosis	Subvariants
Cutaneous mastocytosis (CM)	*Urticaria pigmentosa*/maculopapular cutaneous mastocytosis (UP/MCPM): • monomorphic • polymorphic
	Diffuse cutaneous mastocytosis (DCM)
	Cutaneous mastocytoma: • isolated • multilocalized
Systemic mastocytosis (SM)	Bone marrow mastocytosis (BMM)
	Indolent systemic mastocytosis (ISM)
	Smoldering systemic mastocytosis (SSM)
	Aggressive systemic mastocytosis (ASM)
	SM with an Associated Hematological Neoplasm (SM-AHN)
	Mast cell leukemia (MCL)
Mast cell sarcoma (MCS)	

Therefore, we suggest measuring serum tryptase level in those with elevated unexplained blood hypereosinophilia.

CMML remains the most common AHN associated with SM [4]. However, it is important to rule out the most common reactive causes of monocytosis. Of note is that *KIT D816V* can be detected both in mast cells and monocytes of patients with SM-CMML [5].

NGS is used to identify somatic mutations, including those prognostic for systemic mastocytosis (i.e. *SRSF2, ASXL1, RUNX1*). The presence of at least one from these mutations, thrombocytopenia (platelets <100 × 10^9/L), anemia (hemoglobin <10 g/dL), and age ≥60 years have been shown to adversely affect the outcome. Depending on the risk group, median OS was not reached for the low risk category, and was 3.9 years for the intermediate, and 1.9 years for the high risk [6].

Another method which should be used is droplet digital polymerase chain reaction (ddPCR) which serves as a tool for quantification of the *KIT D816V* variant allele fraction (VAF) [7]. It has been proven that in SM patients treated with midostaurin for at least six months, a significant reduction in *KIT D816V* allele burden of ≥25% was the strongest predictor of better survival [8].

In summary, the diagnosis of SM-AHN represents a major challenge for physicians. The physician's vigilance should be heightened already at the stage of blood differential analysis. An unexplained monocytosis and/or eosinophilia should serve as pointers towards mastocytosis. New molecular techniques should be implemented in order to better characterize patients' outcomes.

Authors' contributions

KC — manuscript preparation. KC, KB, MD — data collection. GH — supervision, final approval.

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 and uniform requirements for manuscripts submitted to biomedical journals.

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Acta Haematologica Polonica 2023
Number 1, Volume 54, pages 48–49
DOI: 10.5603/AHP.a2023.0008
ISSN 0001–5814
e-ISSN 2300–7117

VIA MEDICA

Native myocardial T1 mapping in β-thalassemia major patients with and without iron overload

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Three patients with known β-thalassemia major who received multiple blood transfusions were referred for myocardial iron overload by magnetic resonance imaging (MRI). Standard cardiac MRI sequences Cine Steady State Free Precession were acquired in short axis and 4-chamber planes for calculation of ventricular volumes and functions. For clinical quantification of myocardial iron overload, T2* mapping sequence was obtained in short axis.

We present the cases of the three patients: one without, one with mild, and one with severe myocardial iron overload. The T2* values were 29 ms denoting no myocardial overload, and 17 ms and 5.2 ms denoting mild overload and severe myocardial overload respectively (normal >20 ms, mild overload 15–20, moderate 10–15, severe iron overload <10 ms) [1] (see Figure 1).

Additionally, native myocardial T1 mapping sequence was obtained (modified look locker inversion recovery MOLLI--Siemens Healthcare) and revealed T1 values of 944 ms (within the normal reference range), 865 ms (mildly reduced), and 523 ms (severely reduced) respectively. The Z scores were –0.3, –4 and –20 respectively.

Myocardial iron deposition results in local magnetic field inhomogeneities causing reductions in T1, T2 and T2* relaxation times [2]. Currently, T2* mapping is the method

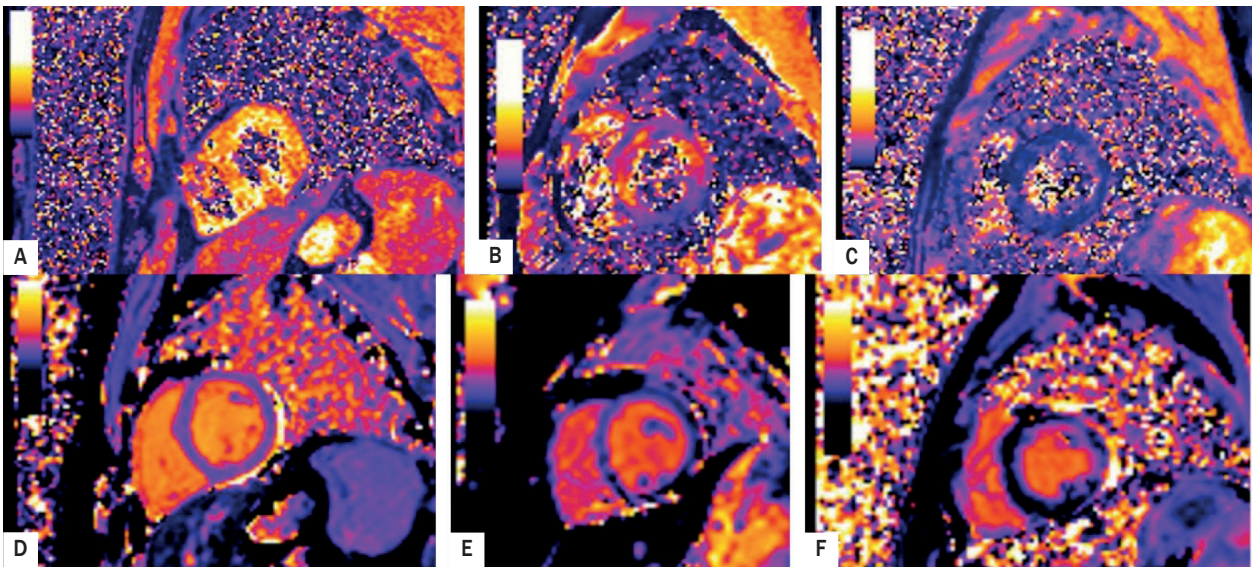

Figure 1. Cardiac magnetic resonance (MR) mid short-axis T2* color maps in β-thalassemia major patients without myocardial iron overload (**A**), with mild myocardial iron overload (**B**), and with severe myocardial iron overload (**C**). Cardiac MR mid short-axis native T1 color maps in β-thalassemia major patients without myocardial iron overload (**D**), with mild myocardial iron overload (**E**), and with severe myocardial iron overload (**F**)

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Received: 10.11.2022 Accepted: 04.12.2022

of choice for cardiac iron quantification and is incorporated into clinical guidelines [3].

Recently, myocardial T1 mapping was proposed as a potential complementary technique for iron overload quantification [4]. A significant correlation was found between native T1 and T2* values in patients with β-thalassemia major [2]. The reported normal reference T1 mean value is 972 ± 43 ms, with upper and lower limits of 885 and 1,059 ms [1]. A cutoff T1 value of 904 ms has been proposed to distinguish between β-thalassemia major and healthy subjects [5]. In patients with myocardial iron overload evident on T2* (<20 ms), the T1 value ranged from 474 to 804 ms, mean 653 ± 133 ms [6].

One advantage of T1 mapping is its better reproducibility compared to T2*, which is important for serial studies monitoring disease progression [5]. In addition, T1 mapping is less vulnerable to magnetic field inhomogeneity compared to T2*, and therefore it may be useful when T2* is borderline reduced to differentiate between local field inhomogeneities and iron content [6].

Authors' contributions

All authors have participated in article preparation and have approved the final article.

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 and uniform requirements for manuscripts submitted to biomedical journals.

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