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Editorial Address

Klinika Nowotworów Płuca i Klatki Piersiowej
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa, Poland
Phone: (+48 22) 546 21 69
e-mail: sekretariat4@pib-nio.pl

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Supportive care Neutropenia

Editors:
Piotr Potemski, Maciej Krzakowski

Authors:
Piotr Potemski[1, 2], Rafał Czyżykowski[2, 1]

[1]Chemotherapy Clinic, Medical University of Lodz, Poland
[2]Chemotherapy Clinic, Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz, Poland

Key words: neutropenia, fever, antibiotic therapy, granulocyte-colony stimulating factors, prophylaxis

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According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-ran-domized cohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

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Definitions

Neutropenia

Neutropenia is a reduction in absolute neutrophil count below the lower limit of normal. Clinically important is the reduction in neutrophil count below 1000/μL, which corresponds to at least grade 3 intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) classification. The term "agranulocytosis" is usually used when the neutrophil count is less than 100/μL, which is associated with a significantly higher risk of infection.

Febrile neutropenia

According to CTCAE version 5.0 [1], febrile neutropenia (FN) is defined as:

— a reduction in neutrophils count below 1000/μL and
— a fever (body temperature > 38.3°C in single measurement or at least 38°C lasting for at least 1 hour).

Febrile neutropenia is an adverse reaction of at least grade 3. In a life-threatening situation and the necessity of urgent medical intervention, FN is assigned grade 4.

FN definition of the European Society of Medical Oncology (ESMO) is the most commonly used in clinical practice. In comparison with the CTCAE criteria, ESMO definition [2] includes body temperature measured in the mouth > 38.3°C or > 38°C reported twice during 2 hours with accompanying decrease in the absolute number of neutrophils below 500/μL or predicted reduction below 500/μL. The IDSA (Infectious Diseases Society of America) and NCCN (National Comprehensive Cancer Network) definitions are similar [3, 4].

Incidence

Almost all patients receiving cytotoxic therapy develop neutropenia of different intensity (most often without associated symptoms and the need for treatment). Of clinical importance, especially in a context of prophylaxis, is an expected risk of FN. The risk depends primarily on chemotherapy regimen (Table 1). In addition to the type and dose of medications, other important factors include the line of ChT, advanced age, poor performance status, comorbidities (especially of cardiovascular system), previous exposure to bone marrow damaging factors (including radiation therapy), higher stage of cancer and occurrence of FN in the past.

Combinations of CDK4/6 inhibitors with hormone therapy are associated with a small (< 10%) risk of FN despite neutropenia grade 3/4 even in 50–60% of patients. In the majority of clinical studies the addition of anti-VEGF (vascular endothelial growth factor) drugs, anti-EGFR (epidermal growth factor receptor) antibodies as well as anti-PD1 (programmed death receptor 1) or anti-PD-L1 (programmed death-ligand 1) drugs to chemotherapy was not associated with a significant increase in the incidence of FN.

Pathogenesis

The most common cause of neutropenia in cancer patients is the disturbed production of neutrophils in the bone marrow due to dose-dependent myelotoxic effects of cytotoxic drugs. The period with the greatest reduction in the number of granulocytes is called nadir — it usually occurs 7–14 days after ChT administration, but with some drugs (nitrosourea) it can take even several weeks.

Drug-induced, dose-independent neutropenia (e.g. after phenylbutazone as one of the symptoms of bone marrow aplasia), neutropenia due to the formation of autoantibodies, as well as, vitamin B12 or folic acid deficiency is rarely seen.

Consequences

Neutropenia is one of the most important factors predisposing for infections, which occur in about half of patients with FN (approximately 10–25% of patients has bacteremia and 20–30% of patients clinically overt infection). The likelihood of infectious complications depends primarily on the duration and severity of neutropenia. The most important sign of neutropenia is a fever. Due to immunosuppresion other symptoms and signs often are less pronunced or atypical.

The consequence of asymptomatic neutropenia may be a decrease in treatment intensity following a delay in the administration of the next cycle of ChT and/or a reduction in the dose of drugs. It has been shown that in some patients this situation may lead to reduced treatment effectiveness (see — prophylaxis of neutropenia).

Etiology of infection during febrile neutropenia

The infection has been microbiologically documented in 21% of 750 patients with FN of low complications risk (risk assessment is discussed later in this chapter). Bacteremia was found in 58% of cases (12% of all FN patients) and urinary tract infections in 25% (5% of all patients). In 49% of patients the infection was induced by Gram-positive bacteria (most frequently staphylococcal species — coagulase-negative staphylococci [CNS]

Table 1. Probability of febrile neutropenia (FN) associated with selected chemotherapy (ChT) regimens [5, 13]

Incidence GN	Diagnosis	ChT regimens
> 20%	Breast cancer	TAC (docetaxel, doxorubicin, cyclophosphamide), AT (doxorubicin, docetaxel)
	Gastric cancer	DCF (docetaxel, cisplatin, fluorouracil)
	Lymphomas	BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), DHAP (dexamethasone, cytarabine, cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), ICE (ifosfamide, cisplatin, etoposide)
	Germ-cell tumors	VeIP (vinblastine, ifosfamide, cisplatin), TIP (paclitaxel, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin)
	Small cell lung cancer	Topotecan
	Soft tissue sarcomas	MAID (doxorubicin, ifosfamide, dacarbazine)
10–20%	Breast cancer	AC → T (100 mg/m^2) (doxorubicin, cyclophosphamide → docetaxel), CEF (cyclophosphamide, epirubicin, fluorouracil)
	Gastric cancer	ECF (epirubicin, cisplatin, fluorouracil), ECX (epirubicin, cisplatin, capecitabine)
	Lymphomas	R-CHOP-21 (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)
	Germ-cell tumors	BEP (bleomycin, etoposide, cisplatin)
	Small cell lung cancer	PE (cisplatin, etoposide), CAV (cyclophosphamide, doxorubicin, vincristine)
	Non-small cell lung cancer	Docetaxel, PE (cisplatin, etoposide)
	Ovarian cancer	Topotecan
	Bladder cancer	M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin)
	Head and neck cancer	TPF (docetaxel, cisplatin, fluorouracil)*
	Soft tissue sarcomas	Ifosfamide (9 g/m^2)
< 10%	Breast cancer	CMF (cyclophosphamide, methotrexate, fluorouracil), AC (doxorubicin, cyclophosphamide), docetaxel (75 mg/m^2), FAC (fluorouracil, doxorubicin, cyclophosphamide) TC** (docetaxel, cyclophosphamide) TCH*** (docetaxel, carboplatin, trastuzumab)
	Gastric cancer	EOX (epirubicin, oxaliplatin, capecitabine), trastuzumab + PF (cisplatyna, fluorouracyl), docetaksel
	Pancreatic cancer	FOLFIRINOX*** (calcium folinate, fluorouracil, irinotecan, oxaliplatin); gemcitabine + nab-paclitaxel; OFF (oxaliplatin, calcium folinate, fluorouracil)
	Colon cancer	FOLFIRI (calcium folinate, fluorouracil, irinotecan), FOLFOX (calcium folinate, fluorouracil, oxaliplatin), CAPOX (capecitabine, oxaliplatin), FOLFOXIRI (calcium folinate, fluorouracil, oxaliplatin, irinotecan), capecitabine, LVFU2 (calcium folinate, fluorouracil)
	Non-small cell lung cancer	PN (cisplatin, vinorelbine), PG (cisplatin, gemcitabine), cisplatin with pemetrexed, pemetrexed
	Ovarian cancer	Carboplatin with paclitaxel
	Germ-cell tumors	GP (gemcitabine, paclitaxel), GO (gemcitabine, oxaliplatin)
	Prostate cancer	Docetaxel with prednisone
	Bladder cancer	PG (cisplatin, gemcitabine)
	Head and neck cancer	PF (cisplatin, fluorouracil)
	Soft tissue sarcomas	Doxorubicin (75 mg/m^2)

*Depending on the drug dosing regimen in the TPF protocol, the risk of FN was 5% and 12% in 2 phase III studies; in both studies, ciprofloxacin was used prophylactically on days 5–15 of the cycle

**In the pivotal study fluoroquinolone prophylaxis was recommended; in the meta-analysis of mostly retrospective studies FN risk > 20%

***In clinical trials the primary prophylaxis with G-CSF was allowed; in some retrospective analyzes the risk of FN > 20%

and *Staphylococcus aureus*, as well as streptococci and enterococci), in 36% of patients Gram-negative bacilli (most often *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*) were isolated, and in 15% of patients, the etiology of infection was mixed [6]. In the group of almost 2,150 unselected patients with FN (including 17% undergoing intensive ChT due to acute leukemia) bacteremia was found twice as often (23% of patients), and the cause in most patients was also Gram-positive bacteria (usually coagulase-negative staphylococci) [7]. The most common etiology of bacteremia in patients with FN are presented in Table 2. Fungal infection is rarely the main cause of fever in patients with neutropenia, however, the risk of infection with fungi (especially *Candida sp.* and *Aspergillus sp.*) is increased with longer duration (> 7 days) of neutropenia.

Assessment of risk associated with febrile neutropenia

The risk of serious FN complications (e.g. renal failure, respiratory failure, hypotension, heart failure, disseminated intravascular coagulation, consciousness disorders) is about 13% (risk of death — about 5%). Patients with some hematopoietic malignancies (e.g. acute leukemia) are at least 2 times more likely to die.

The probability of FN complications occurrence depends on many factors, among which the most important are the following:

— type and stage of cancer and cancer control;
— method of cancer treatment;
— FN occurrence during hospitalization;
— duration and intensity of neutropenia;
— presence of an organ infection;
— comorbidities;
— other organs injuries (including mucous membranes);
— age and performance status.

Based on the analysis of FN course in a group of more than 1,000 patients with various cancers, the Multinational Association for Supportive Care in Cancer (MASCC) [8] proposed a practical risk index score for assessing the risk associated with this complication (Table 3). In patients with low MASCC risk (≥ 21 points), the incidence of serious neutropenia complications is 6% (risk of death — 1%). If the number of points is less than 21, then the risk of serious complications is as much as 39% (risk of death — 14%). The MASCC score due to its simplicity and ease of use is routinely used in clinical practice to assess the risk related to FN.

The occurrence of bacteremia worsens the prognosis. Serious complications affect 10% of patients with sterile blood cultures (death — 3%), while in patients with bacteremia, the complications risk is 21% (death — 10%). Mortality in the course of FN with bacteremia depends on the type of pathogen. Mortality associated with bacteremia caused by Gram-positive and Gram-negative microorganisms is about 5% and about 20%, respectively [9]. Bacteremia etiology adds additional prognostic value to the MASCC score, especially in patients at high risk of complications (Table 4).

Table 2. The most common etiology of bacteremia in patients with febrile neutropenia [7]

Cause	Type of staining	Bacteria	Incidence (%)
Infections with one microorganism			90
	Gram-positive		57
		Staphylococcus (coagulase-negative)	28
		Streptococcus	15
		Staphylococcus (coagulase-positive)	5
	Gram-negative		34
		Escherichia coli	14
		Pseudomonas aeruginosa	8
		Klebsiella pneumoniae	4
Mixed infections			10
	At least one Gram-negative		6
	Gram-positive only		4

Table 3. MASCC risk index score for febrile neutropenia complications [8]

Characteristics	Points
Clinical symptoms	
— absent or minor	5
— moderate	3
Systolic blood pressure > 90 mm Hg	5
Absence of chronic obstructive pulmonary disease	4
Non-hematological or hematological cancer if there was no previous fungal infection	4
Absence of dehydration	3
Occurrence of symptoms outside the hospital	3
Age < 60 years	2

The points assigned to individual characteristic are added. If the clinical symptoms are significant, no points are assigned. The maximum and possible number of points is 26. A low risk of complications is considered when the number of points is ≥ 21

Table 4. Mortality in patients with febrile neutropenia and bacteremia depending on the type of pathogen and risk according to the MASCC index score [7]

Number of MASCC points	Mortality (%)	
	Gram-positive	Gram-negative
≥ 21	2	6
15–20	6	23
< 15	28	43

Febrile neutropenia — diagnostic procedures

Medical history

The medical history should provide information regarding: cancer type and stage, date of administration of last ChT cycle and doses of the drugs, recent surgical procedures and other methods of anticancer treatment, comorbidities, previous episodes of fever or infection, exposure to infectious agents, additionally used medicines (including antibiotics and glucocorticosteroids), results of microbiological tests, accompanying symptoms that may indicate the location of the infection (e.g. cough, abnormal urination, diarrhea, sore throat), drug allergies.

Physical examination

The physical examination provides an assessment of patient's general condition, hydration status, and potential sites of infection (skin, anal area, respiratory system, oral cavity, site of venous catheter insertion). Blood pressure measurement is necessary. Due to neutropenia, symptoms of infection can be very weakly expressed or even latent; and the clinical manifestation of infection may be distorted during glucocorticoids use or in the elderly.

Some patients with infectious complications of neutropenia do not have a fever, and body temperature may be even lower than normal. Situations in which neutropenia is accompanied by symptoms suggesting an inflammatory process (e.g. abdominal pain, focal lesions on the skin or erosions of mucous membranes) should be considered as an active infection (IV, B). Concomitant significant weakness, hypotonia, and decrease in body temperature in individual with neutropenia can suggest the possibility of sepsis (especially caused by Gram-negative bacteria).

Additional evaluations

In all cases the following tests must be performed (IV, A):

— complete blood counts (CBC) with leukocyte smear and platelet count;
— serum concentration of urea, creatinine, sodium, potassium and bilirubin;
— serum level of asparagine (AST) and alanine aminotransferase (ALT);
— blood cultures taken from 2 sites, but in case of a central venous catheter or chemotherapy port implanted it is strongly recommended to collect blood from a peripheral vein puncture as well as the second from a catheter/port); the sample should be taken before antibiotic administration.

It is also recommended to perform chest X-ray (IV, C) in all patients with FN (in patients with symptoms suggestive of pulmonary infection it is absolutely necessary and computed tomography (CT) of the chest should be also considered).

Optionally other tests could be performed, depending on the clinical situation: cultures from other places, X-ray of paranasal sinuses, ultrasound (US) of the abdominal cavity, CT — depending on the clinical indications — of the chest, abdomen and pelvis or central nervous system (CNS) (in case of suspected inflammation, it is also necessary to perform lumbar puncture to collect cerebrospinal fluid for testing), urinalysis and urine culture, examination of stool for anaerobic bacteria (primarily *Clostridium difficile* toxins A and B) and other pathogens, blood gas test, C-reactive protein (CRP), procalcitonin, coagulogram and other (IV, C).

In every patient with suspected infection, a diagnosis of sepsis should be carried out (IV, A). As part of the current consensus (Sepsis-3) [10], the initial qSOFA test (blood pressure ≤ 100 mm Hg, respiratory rate ≥ 22/min, disorders of consciousness) allows estimating the risk of sepsis (greater when at least 2 factors are present). To diagnose sepsis, it is necessary to document organ failure based on the SOFA score (sudden change of ≥ 2 points) taking into account oxygenation index, platelet count, bilirubin and creatinine concentration, mean arterial pressure, and level of consciousness according to Glasgow Coma Scale (GCS).

Treatment

The management depends on the risks associated with FN. There are several possibilities: hospital treatment, short-term hospitalization with the continuation of therapy in outpatient settings or completely outpatient treatment.

According to the NCCN recommendations [4], hospitalization is necessary (high-risk FN), among others, in the following situations:

— the number of points in the MASCC scale is less than 21 or
— at least one of the following characteristics occurs:
  • FN occurred during hospitalization,
  • significant diseases co-occur or the clinical condition is unstable,

- the expected duration of agranulocytosis (neutrophil count < 100/μL) is at least 7 days,
- symptoms of hepatic insufficiency occur (ALT or AST level 5 times above the upper limit of normal),
- symptoms of renal insufficiency occur (creatinine clearance < 30 mL/min),
- disease progression or no complete remission in patient with acute leukemia,
- pneumonia or any other clinically significant infection occurs,
- alemtuzumab treatment is used,
- grade 3 or 4 mucositis is found.

Remaining patients (from the so-called low-risk FN group) may be treated in outpatient or hospital settings. The decision on a completely outpatient treatment is also significantly influenced by organizational, social and psychological conditions (constant home care, time of arrival from the patient's place of residence to the hospital ≤ 1 hour, easy telephone contact with the oncological center, good compliance with medical recommendations, etc.) (IV, C).

The most important treatment component in patients with FN is empirical broad-spectrum antibiotic therapy, which should cover potentially the most important pathogens (Table 5) (I, A), as well as take into account the epidemiological situation in healthcare unit (including the incidence of infections with individual pathogens and their antibiotic sensitivity) and data regarding carrier state (e.g. MRSA, Methicillin-resistant *Staphylococcus aureus*) (IV, A).

It is recommended to initiate antibiotic therapy as soon as possible after a diagnosis of FN, preferably within 1 hour (III, B).

After pathogen identification and determining its sensitivity to antibiotics, empirical treatment should be replaced with antimicrobial therapy according to culture results (I, A).

Treatment of low-risk FN patients [2, 4]:

— empirical oral antibiotic therapy with ciprofloxacin and amoxicillin with clavulanic acid (I, A) [or moxifloxacin alone (I, A) or levofloxacin (II, B)] or intravenous antibiotic therapy (in hospitalized patients). Quinolones should not be used in patients who have received ciprofloxacin as prophylaxis of FN (IV, A);
— it is recommended to administer the first dose of antibiotics in the hospital and observe the patient's clinical condition and tolerance of the treatment for at least 4 hours before discharge (in patients not requiring hospitalization) (IV, B);
— patients who required hospitalization and the use of intravenous antibiotics may continue oral treatment in outpatient settings in case of stable general condition, clinical improvement and fever resolution after 48 hours of in-hospital stay (IV, C).

Treatment of high-risk FN patients [2, 4]:

— intravenous broad-spectrum antibiotic therapy in hospital settings (I, A).

As part of the initial treatment, antibiotics can be used as monotherapy (the risk of nephrotoxicity is smaller) or in combination, depending on the clinical situation. In patients with a higher risk of long-term neutropenia, with bacteremia, complicated FN or resistance to treatment, the combination of a beta-lactam antibiotic with activity against *Pseudomonas spp*. in combination with aminoglycoside (I, C) or sometimes with vancomycin should be considered (I, C).

In some clinical situations, the recommendations are modified as follows [2, 4]:

— sepsis — aminoglycoside and vancomycin should be added (I, A) to broad-spectrum beta-lactam antibiotic (cefepime, meropenem, imipenem/cilastatin, piperacillin/tazobactam), empirical antifungal therapy should be considered (IV, B);
— septic shock — also fluid therapy, oxygen therapy, vasopressors and possibly corticosteroids — e.g. hydrocortisone 50 mg *i.v.* every 6 hours (IV, A);

Table 5. Most commonly used antibacterial drugs in empirical therapy in patients with febrile neutropenia [2, 4]

Way of treatment	Drugs
Intravenous antibiotic therapy	
— combined	— aminoglycoside + piperacillin with tazobactam
	— aminoglycoside + ceftazidime
	— ciprofloxacin + piperacillin with tazobactam
	— aztreonam + vancomycin (in case of penicillin allergy) (IV, B)
— monotherapy	— imipenem/cilastatin
	— meropenem
	— ceftazidime
	— piperacillin/tazobactam
	— cefepime
Oral antibiotic therapy	— ciprofloxacin + amoxicillin with clavulanic acid
	— ciprofloxacin + clindamycin (in case of penicillin allergy) (IV, B)

— pneumonia — the combination is expanded to include an active drug against *Mycoplasma* (macrolide) (IV, B), and if *Pneumocystis* etiology is suspected, cotrimoxazole is the drug of choice (IV, A);
— diagnosis of Gram-positive bacteremia prior to the final identification of the pathogen — vancomycin adding is advisable (IV, A);
— diarrhea — metronidazole or vancomycin (oral) should be added to the combination and a fecal test for e.g. *Clostridium difficile* toxins should be performed (IV, B);
— suspected bacteremia associated with the presence of a venous catheter — including a glycopeptide (e.g. vancomycin) is recommended to consider (II, A). It is absolutely necessary to obtain the microbiological diagnosis as soon as possible. A useful and simple (although requiring an automatic device for detection of bacterial growth) method of recognizing bacteremia associated with the presence of a vascular catheter is to perform two cultures of blood samples taken simultaneously from the catheter and the peripheral vein and note the time to obtain a positive result [11]. If the time to bacterial growth for a catheter sample is shorter by at least 2 hours compared to a peripheral vein sample, this is likely to indicate an infection associated with the presence of a vascular catheter (I, A) that in some situations should be removed [especially in case of infection of implanted vascular port (II, B), prolonged fever and bacteremia despite antibiotic therapy, in case of *Candida*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* infection or venous thrombosis];
— intra-abdominal or pelvic infections — metronidazole is included in the combination (unless patient receives carbapenem or piperacillin/tazobactam) (IV, B);
— skin and subcutaneous tissue infections — it is recommended to consider adding a glycopeptide (IV, C);
— suspected viral infection: HSV or VZV (mucosal vesicles, herpes zoster) — acyclovir (I, A) is included in the combination, in case of suspected influenza virus infection — zanamivir or oseltamiwir (IV, C);
— suspected fungal infection (necrotizing ulceration of oral mucosa, symptoms of oral candidiasis, painful swallowing) — microbiological diagnostics for mycosis should be implemented and an antifungal drug should be added to the combination (if the clinical symptoms suggest candidiasis — fluconazole) (I, A);
— infections in patients during intensive ChT with massive mucosal damage (higher risk of penicillin-resistant streptococcal infection) — vancomycin should be considered as part of the initial treatment, especially when ceftazidime was previously initiated (IV, B);
— infections preceded by quinolones prophylaxis — vancomycin should be considered as part of the initial treatment (IV, B).

During the empirical treatment, the patient's clinical condition should be monitored daily and additional tests (CBC, serum creatinine and other, depending on the clinical situation) should be repeated until the fever has resolved and the stable increase in neutrophil count to at least 500/μL is observed (IV, A). If the patient's condition is stable, assessment of treatment response is made after 48 hours. Further management depends on the clinical situation and should be as follows (Fig. 1):

1. Resolution of fever + no signs of infection + sterile blood culture + neutrophil count at least 500/μL:
   a) low risk — continuation of oral antibiotic therapy (possibly in outpatient settings) (II, A);
   b) high risk — the continuation of intravenous antibiotic therapy (possible discontinuation of aminoglycoside) (IV, B);
   c) if fever does not occur for another 24–48 hours — discontinuation of antibiotic therapy (IV, A);
   d) antibiotic therapy can also be discontinued if the neutrophil count is less than 500/μL and the fever has not been present for at least 5–7 days.
2. Persistence of fever + patient's stable condition + absence of infection symptoms + sterile blood culture — continuation of current treatment to meet the conditions as above. If the fever lasts 3–5 days, despite empirical antibiotic therapy, and the bacterial pathogen has not been isolated from repeated blood cultures, the implementation of microbiological diagnostics for fungal infection should be considered and intravenous empirical antifungal therapy with fluconazole (in case of low risk of aspergillosis) or amphotericin B in various forms, itraconazole (injectable preparations are not available in Poland), echinocandin (e.g. caspofungin) or optionally voriconazole should be initiated (I, A). CT scan of chest with liver and spleen is also recommended. In case of probable or confirmed fungal infection targeted treatment should be implemented, depending on the clinical situation and the results of the microbiological test (I, A).
3. Microbiological identification of the pathogen — treatment in accordance with the antibiogram (treatment duration depends on the clinical situation, usually at least 10–14 days, and in case of confirmed fungal infection — several weeks) (I, A).
4. Persistence of fever + unstable patient's condition + no pathogen identification — repeating of additional tests (including diagnostics for non-infectious cause, non-bacterial or bacterial infection with drug-resistant pathogens) and change of current antibiotic therapy (adding an antifungal drug

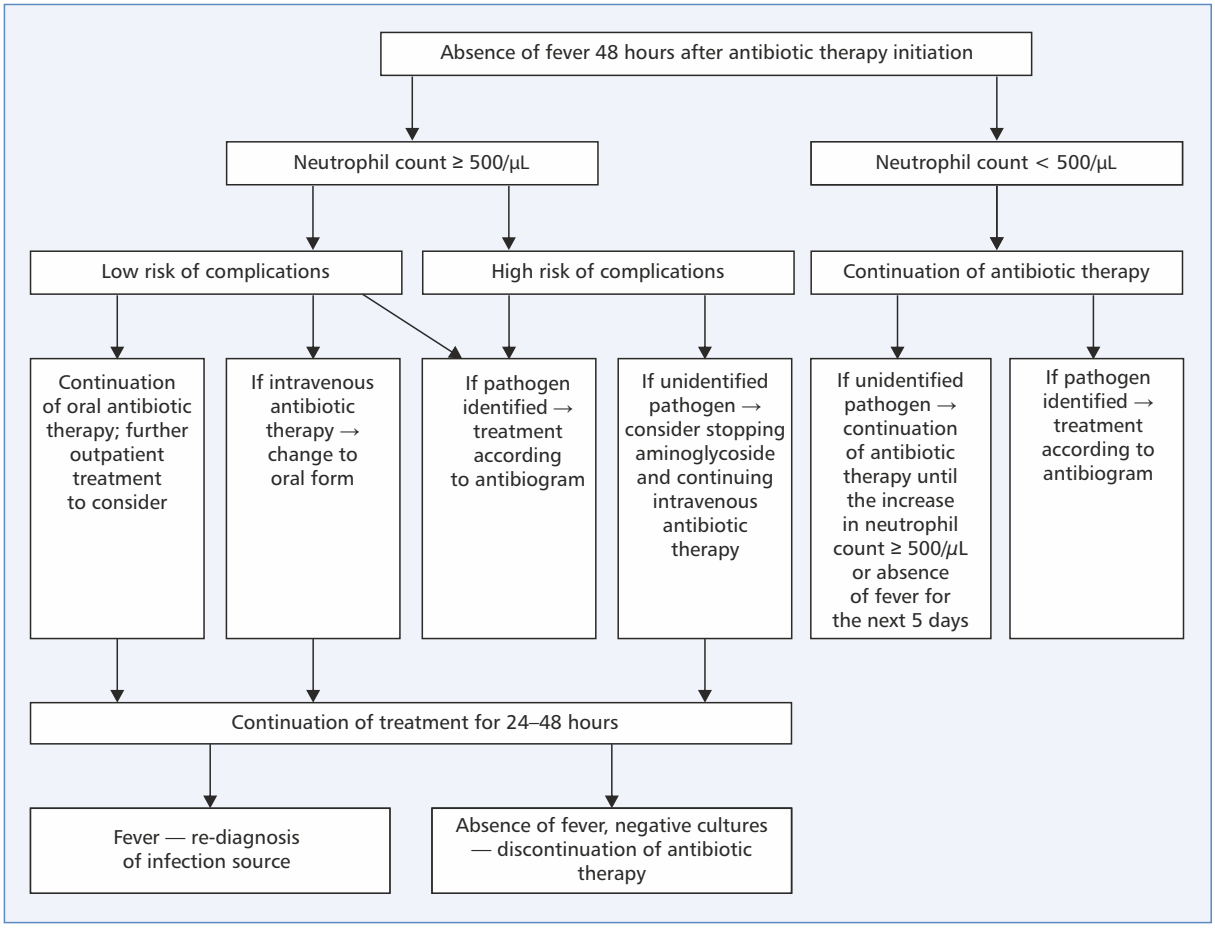

Figure 1. Treatment algorithm for patients without fever after 48 hours of antibiotic therapy

in accordance with the above recommendations, adding a glycopeptide, possible use of carbapenem, if not previously used) and consultation of a hospital microbiologist (IV, A).

Routine use of G-CSF is definitely not recommended for the treatment of all patients with FN. In a meta-analysis of 14 randomized clinical trials in which the use of granulocyte or granulocyte-macrophage colony-stimulating factors was compared to placebo in a group of approximately 1,500 patients, there was no improvement in overall mortality and infection-related mortality by the use of G-CSF (a shorter hospitalization time and time to increase neutrophil count were showed) [12] (I, A). However, adding G-CSF to antibiotic therapy should be considered in the following situations [13] (IV, A):

— there is no response to antibiotic therapy;
— severe and life-threatening infection or complications (sepsis, septic shock);
— FN is diagnosed, despite the prophylactic use of non-PEGylated growth factors;
— other factors increasing the risk of complications co-occur (age > 65 years, neutropenia < 100/μL or lasting > 10 days, fungal infections, the occurrence of FN during hospitalization, previous FN episodes).

There is no evidence that patients with FN may benefit from granulocyte transfusion.

Prophylaxis of neutropenia

Secondary prophylaxis

In case of post-ChT occurrence of FN, the use of secondary prophylaxis with G-CSF from the next cycle should be considered [13]. An alternative approach, preferred in most clinical situations, is to reduce the dose of drugs or to use a less myelotoxic ChT regimen. The decision depends largely on treatment intention. In selected cases, the indication for secondary prophylaxis may be not only FN but also asymptomatic neutropenia which is the reason for delaying of subsequent ChT cy-

cles. This relates to some cases with radical treatment where, reduction of dose intensity may adversely affect the prognosis (e.g. in adjuvant breast cancer therapy, treatment of some types of lymphoma and testicular cancer). Prophylactic use of G-CSF is not sufficient management in the presence of other significant adverse effects (e.g. thrombocytopenia or organ toxicity) as it does not reduce the risk of their occurrence. In the prophylaxis of FN, two groups of G-CSF preparations can be used — PEGylated (e.g. pegfilgrastim and lipegfilgrastim) or non-PEGylated (e.g. filgrastim) forms. Pegylated forms are used as a single injection (6 mg) after ChT (approximately 24 hours). PEGylated forms should not be used when the frequency of ChT cycles is less than 14 days. Prophylaxis with non-PEGylated G-CSF (e.g. filgrastim) is started between 24 and 72 hours after ChT (5 μg/kg with dose rounded to full ampoule) subcutaneously, daily, until the expected nadir disappears (usually ≥ 5–7 days) and obtaining a normal or slightly reduced but stable neutrophil count. There are no data indicating differences in the effectiveness of G-CSF preparations, including PEGylated and non-PEGylated [14].

Primary prophylaxis

The primary prophylaxis consists of G-CSF use from the first ChT cycle. The results of meta-analysis of controlled clinical trials show that primary prophylaxis reduces the incidence and the duration of FN, antibiotic therapy and hospitalization, and also reduces the risk of infections [15]. These benefits are evident when frequency of FN is higher than 20%. However, there was no effect of primary prophylaxis on reduction of the risk of death, which is independent of ChT myelotoxicity grade. Admittedly, meta-analyzes assessing the impact of primary prophylaxis on, among others, the survival of patients undergoing ChT, indicated a slight decrease in the mortality (despite the higher incidence of acute leukemia or myelodysplastic syndromes [16]), but this effect most likely depends on the assumed higher intensity of treatment in these groups of patients (among others, meta-analysis included studies on chemotherapy with G-CSF support in breast cancer patients). Analysis limited to studies comparing identical treatment regimens revealed only a statistically insignificant trend to prolong survival [17].

Primary prophylaxis is the subject of controversy, and due to the lack of impact on mortality, the pharmacoeconomic analyzes play an important role in determining indications to this procedure.

A widely accepted indication is the need to use ChT with an expected risk of FN greater than 20%, and this indication is independent of other factors (Table 1) [13] (I, A). If the ChT is associated with a 10–20% risk of FN, the indication for primary prophylaxis may be the presence of additional risk factors for FN and its complications (e.g. age > 65 years, the occurrence of FN during previous ChT, advanced stage of cancer, metastases in the bone marrow, radiotherapy covering an area of the skeletal system containing a significant part of the bone marrow, poor performance status, malnutrition, female gender, anemia, impaired renal and liver function and others) (IV, C). The use of primary prophylaxis may be justified in the presence of several of these factors, especially in case of radical treatment. Primary prophylaxis of neutropenia is also an mandatory component of chemotherapy regimens given at shorter than standard intervals (so-called regimens with higher dose-density) (I, A). However, the possibility of replacing the ChT regimen with less myelotoxic one, delaying the start of treatment until normalisation of neutrophiles count or reduction of medications doses should always be considered. Treatment intention is of great importance during qualifying the patients for primary prophylaxis (as far as palliative chemotherapy is concerned, primary prophylaxis is less frequently used) [2, 14, 18].

The pattern of G-CSF administration is analogous to that used for secondary prophylaxis.

Primary prophylaxis is not justified in case of ChT regimens with low risk of FN.

Despite the fluoroquinolone activity demonstrated in FN prophylaxis in clinical studies, their standard use in patients with solid tumors is not recommended due to the increased risk of inducing the development of quinolone-resistant bacterial strains [3]. However, in the high-risk group of patients who are expected to develop long-term (over 7 days) and deep (100/μL) neutropenia, prophylaxis with ciprofloxacin or levofloxacin should be considered (IV, B).

Conflicts of interest

The authors declare to have no conflict of interest.

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Supportive care
Prophylaxis and treatment of infections

Editors:
Piotr Potemski, Maciej Krzakowski

Authors:
Rafał Czyżykowski[1, 2], Adam Płużański[3]

[1]Chemotherapy Clinic. Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz, Poland
[2]Chemotherapy Clinic, Oncology Department, Medical University of Lodz, Poland
[3]Department of Lung Cancer and Chest Tumours, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Key words: infections, prophylaxis, neutropenia

Table of contents

According to the authors and editors, this report contains the most justified principles of diagnostic and therapeutic procedures prepared considering the scientific value of evidence and category of recommendations. These principles should always be interpreted in the context of an individual clinical situation. The recommendations do not always correspond to the current reimbursement rules in Poland. In case of doubt, the current possibilities of reimbursement of individual procedures should be established.

1. *The quality of scientific evidence*
   I — Scientific evidence obtained from well-designed and conducted randomized clinical trials or meta-analyses of randomized clinical trials
   II — Scientific evidence obtained from well-designed and conducted prospective observational studies (non-ran-domized cohort studies)
   III — Scientific evidence obtained from retrospective observational studies or case-control studies
   IV — Scientific evidence obtained from clinical experiences and/or experts, opinions
2. *Category of recommendations*
   A — Indications confirmed unambiguously and absolutely useful in clinical practice
   B — Indications probable and potentially useful indications in clinical practice
   C — Indications determined individually

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Introduction

Patients treated for malignant tumours are at increased risk of infections. Immunosuppression associated with cancer treatment and the malignancy itself affects the intensity of infections and the risk of complications. The clinical course of infections in this group of patients can be unpredictable and limits the possibility of effective oncological treatment, leading to serious complications or death in extreme cases. Rational prevention, diagnosis, and treatment of infections can significantly improve the prognosis in patients with malignant tumours.

Infections risk assessment

The following factors should be taken into account when assessing the overall risk of infection in a patient diagnosed with cancer (Table 1):
— cancer type and stage;
— type of antineoplastic treatment;
— status of the underlying disease (e.g. remission phase, active disease, progression);
— previous chemotherapy or radiotherapy;
— use of immunosuppressive treatment;
— individual state of the immune system (e.g. impairment of non-specific immunity resulting from damage of the natural barriers of the immune system).

Prevention of bacterial infections

Indications for the prophylaxis of bacterial infections depend on the infection risk assessment. In the majority of patients with solid tumours receiving chemotherapy there are no indications for routine antibacterial prophylaxis (I, A).

During asymptomatic neutropenia resulting from anti-cancer therapy, antimicrobial prophylaxis may be considered in the following patients (IV, A):
— undergoing haematopoietic stem cell transplantation;
— receiving alemtuzumab;
— receiving purine analogues;
— diagnosed with acute lymphoblastic leukaemia;
— with at least grade 3 neutropenia according to CTCAE scale lasting > 7 days;
— treated for lymphoma, multiple myeloma, or chronic lymphocytic leukaemia (indications should be considered on an individual basis due to the heterogeneous clinical course of the disease) (IV, C).

Fluoroquinolones (preferably levofloxacin) are recommended for patients qualified for the prophylaxis of bacterial infections (I, B). In the case of contraindications or poor tolerance of fluoroquinolones, trimethoprim/sulfamethoxazole or oral III generation cephalosporin may be used.

In patients undergoing allogeneic haematopoietic stem cell transplantation (allo-HSCT) and receiving chronically high doses of glucocorticosteroids (> 20 mg of prednisone per day) due to graft versus host disease (GVHD) more potent antibacterial prophylaxis can be used with a combination of several antibiotics (e.g. penicillin combined with trimethoprim/sulfamethoxazole) (IV, B).

Prevention of pneumonia caused by *Pneumocystis jirovecii* [1]

Trimethoprim/sulfamethoxazole is a drug of choice for therapy and prophylaxis of infections caused by *Pneumocystis jirovecii*. Preventive treatment is indicated for patients:

Table 1. Infection risk classification in patients with cancer [1]

General risk of infection in cancer patient	Examples of risk factors
Low	— Standard chemotherapy for most solid tumours — Expected duration of neutropenia less than 7 days
Moderate	— Auto HSCT — Treatment with purine analogues — Diagnosis of lymphoma, multiple myeloma, chronic lymphocytic leukaemia* — Expected duration of neutropenia 7–10 days
High	— Allo-HSCT — Acute myeloid and lymphoblastic leukaemia during treatment — Alemtuzumab treatment — Graft versus host disease (GVHD) treated with high doses of glucocorticosteroids (> 20 mg of prednisone daily) — Expected duration of neutropenia of over 10 days

*The type of treatment and clinical disease stage affect the individual risk assessment
Auto-HSCT — autologous haematopoietic stem cell transplantation; allo-HSCT — allogeneic haematopoietic stem cell transplantation

— undergoing allo-HSCT (I, A);
— receiving alemtuzumab (IV, A);
— diagnosed with acute lymphoblastic leukaemia undergoing anticancer treatment (I, A).

In addition, it should be considered in patients (IV, B):
— receiving purine analogues;
— undergoing autologous haematopoietic stem cell transplantation (auto-HSCT);
— receiving intensive corticosteroid therapy due to cancer;
— receiving temozolomide combined with radiation therapy.

Antifungal prophylaxis [1]

Antifungal prophylaxis should not be the standard of care (SOC) in all patients with neutropenia (IV, C).

This should be considered in patients:
— with prolonged neutropenia (e.g. in the course of aplastic anaemia) (IV, C);
— undergoing chemotherapy for acute myeloid leukaemia or myelodysplastic syndromes (I, A);
— after haematopoietic stem cell transplantation (especially after allo-HSCT) (I, A);
— undergoing immunosuppressive therapy due to GVHD (I, A).

Secondary prophylaxis is indicated in patients with a history of invasive mycosis undergoing treatment with a risk of long-term neutropenia (III, B).

Antiviral prophylaxis [1]

Prevention of reactivation of HSV, VZV, and CMV infections

Patients undergoing HSCT, receiving chemotherapy for acute leukaemia, and treated with alemtuzumab, high-dose corticosteroids, or purine analogues due to impairment of cellular immunity are at increased risk of reactivation of latent viral infections. Antiviral prophylaxis is indicated in seropositive patients receiving the aforementioned therapies (IV, B).

Prevention of reactivation of HBV infection

In accordance with the American Society of Clinical Oncology (ASCO) recommendations, screening for the detection of chronic HBV infection (HBs antigen, anti-HBc antibodies) is indicated in cancer patients qualified for chemotherapy with significant immunosuppressive potential or patients with a history of hepatitis B because of more frequent reactivation of the infection (I, A) [2]. If a chronic infection is detected, prophylactic treatment should be initiated after evaluation of viraemia (in Poland a lamivudine drug program in lymphoma patients with planned rituximab treatment) (I, A).

Diagnostics for the detection of clinically silent HCV and HIV infection is indicated in patients planned for treatment with significant immunosuppressive potential (e.g. high-dose chemotherapy, rituximab, alemtuzumab) (III, B). In other cancer patients the advisability of virological diagnostics (HBs-Ag, anti-HBc, anti-HCV, anti-HIV) should be assessed individually (IV, C), although according to the National Cancer Comprehensive Network (NCCN) recommendations all patients for whom chemotherapy or immunosuppressive treatment is planned should be screened [1].

Protective vaccinations [1, 3]

Vaccination with live attenuated viral vaccines is contraindicated in patients with impaired immunity, due to the significantly higher risk of inducing infection as compared to healthy individuals (IV, B). Vaccines with inactivated pathogens do not have such potential and can be safely used in immunocompromised patients.

Yearly influenza vaccination is recommended for:
— patients with either haematopoietic or lymphoid malignancies or solid tumours (IV, B) — inactivated vaccines;
— immediate family members, caregivers, and healthcare professionals (IV, B) — also attenuated vaccines (attenuated vaccines are contraindicated only in persons in the immediate vicinity of patients with a significant reduction in immunity).

In cancer patients (mainly with haematopoietic or lymphoid malignancies) at various stages of the therapeutic procedures, depending on the planned treatment and estimated risk of infection or pathogen invasion, vaccination against HBV (IV, B) as well as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b (IV, C) should also be considered. Revaccination against hepatitis B should be considered in cancer patients undergoing immunosuppressive therapy, depending on anti-HB antibody levels (IV, C).

Respiratory tract infections

The signs and symptoms of respiratory tract infections are not characteristic and include, among others: cough, shortness of breath, fever above 38°C, and chest pain. Differential diagnostics in patients undergoing anticancer treatment with respiratory symptoms and radiological abnormalities in the lungs is difficult and requires consideration of the possibility of cancer progression, cardiovascular disease, adverse drug reactions, and exacerbation of concomitant respiratory diseases.

The laboratory tests helpful in differential diagnosis include:
— complete blood count (CBC) with smear;

— microbiological examination of blood and sputum (before starting antibiotic therapy);
— computed tomography (CT) of the chest;
— in the case of diagnostic difficulties, bronchofiberoscopy with microbiological examination of bronchial lavage for bacterial, viral, fungal, and atypical infections (especially in cases of resistance to previous empirical therapy).

Pneumonia is suspected when auscultatory changes during examination are accompanied with one of the following symptoms: tachycardia > 100 beats/minute, tachypnea > 24 breaths/minute, or fever > 38°C. In such situation chest X-ray is mandatory (II, A).

Pneumonia in patients without neutropenia

If pneumonia is suspected in a patient undergoing systemic anticancer treatment without neutropenia, it is necessary to carefully collect the medical history, taking into account the time of symptoms onset and exposure to environmental infectious agents (infections in people around the patient, contact with animals, travels, air-conditioning system-connected infections, etc.).

Community acquired pneumonia

In the vast majority of cases community acquired pneumonia (CAP) in adults is caused by bacteria (Table 2). Routine bacteriological testing is not necessary in all patients with CAP without indications for hospitalisation (IV, B). Microbiological examination, in particular sputum culture, should be considered when risk factors for infection with a multidrug-resistant (MDR) microorganism are found, or when signs and symptoms of infection suggest a different etiology.

In patients requiring hospitalisation, coughing up purulent sputum, and with moderate or severe symptoms, it is necessary to perform a microbiological examination of sputum and two blood cultures before starting antibiotic therapy. In the case of severe pneumonia not responding to beta-lactam antibiotic therapy, determination of antigens of *Streptococcus pneumoniae* and *Legionella pneumophila* in urine is recommended.

Antibiotic therapy for community-acquired pneumonia should include an antibiotic effective against *Streptococcus pneumoniae* (e.g. oral amoxicillin 3 × 1 g) (I, A). In patients with mild community-acquired pneumonia it is possible to use macrolide in the first line (I, B). In moderate community-acquired pneumonia, amoxicillin/clavulanic acid 3 × 1.2 g intravenously or oral amoxicillin/clavulanic acid with sustained release (SR) at a dose of 2000/125 mg every 12 hours could be used (IV, B). In patients with severe pneumonia, the use of ceftriaxone or cefotaxime in combination with macrolide is recommended (II, B). The recommended duration of treatment of uncomplicated community-acquired mild-to-moderate pneumonia is app. seven days or app. three days after clinical stabilisation.

Hospital-acquired (nosocomial) pneumonia

Hospital-acquired pneumonia is an infection that occurs at least 48 hours after admission and was not during incubation at the time of admission [5].

The etiology of nosocomial pneumonia varies and depends on the epidemiological situation in the hospital. Prior to antibiotic administration, microbiological tests are recommended in all patients — blood and sputum culture or bronchoalveolar lavage.

Treatment should depend on the results of microbiological tests and the risk assessment of infection with a multidrug-resistant bacterial strain. The risk of infection with MDR strain increases with the duration of hospitalisation (> 4 days), in patients who previously received antibiotics or were previously hospitalised (up to 90 days before admission).

Gastrointestinal infections

Bacterial, viral, or fungal gastrointestinal (GI) infections in the course of neutropenia may have similar clinical characteristics, and only microbiological ex-

Table 2. Microorganisms most commonly causing hospital-acquired (nosocomial) and community-acquired pneumonia [4]

Hospital-acquired pneumonia	Community-acquired pneumonia
Klebsiella pneumoniae	*Streptococcus pneumoniae* (30–42%)
Pseudomonas aeruginosa	*Klebsiella pneumoniae* (20%)
Staphylococcus aureus	*Mycoplasma pneumoniae* (10–15%)
Escherichia coli	*Chlamydophila pneumoniae* (3–40%)
Streptococcus pneumoniae	*Haemophilus influenzae* (8–10%)
Legionella pneumophila	Viruses — respiratory syncytial virus (RSV), rhinoviruses (8–10%)
Mycobacterium sp.	*Staphylococcus aureus* (4–5%)
Viruses	*Legionella pneumophila* (3–18%)
	Unidentified (30%)

amination of the material sampled from the infection site makes diagnosis possible. The planned therapy should take into account the probability of various pathogens co-occurrence, therefore, apart from the use of broad-spectrum antibiotic therapy, simultaneous antiviral and/or antifungal therapy may be indicated in clinically justified situations (IV, C).

Esophagitis [6]

The main cause of esophagitis is yeast infection or reactivation of HSV infection. The presence of thrush in the mouth is more indicative of candidiasis, but their absence does not preclude fungal infection. An unambiguous diagnosis can be made after endoscopic examination with sampling material for microbiological examination; however, it is a procedure with a risk of complications, especially in patients with neutropenia or thrombocytopenia. If candidiasis is suspected, empirical treatment with fluconazole should be initiated (I, A). However, in the case of clinical signs and symptoms of esophagitis in patients with neutropenia or undergoing immunosuppressive therapy, the use of fluconazole and acyclovir should be considered (IV, B).

Diarrhoea

The etiology of GI infections in cancer patients may be typical (e.g. *Salmonella*, *Shigella*, *Yersinia*, rotaviruses, adenoviruses, and noroviruses). Anticancer treatment may result in pathological proliferation of bacteria (*Klebsiella, Proteus, Enterococcus sp.*) and fungi (most often *Candida*). Therefore, quite often, endogenous flora is the cause of the infections. Moreover, drug-induced damage of mucous membranes significantly increases the risk of invasion of endogenous pathogens into blood and peritoneum.

Pseudomembranous colitis (*Clostridium difficile* infection) is most often a consequence of antibiotic therapy or hospitalisation itself, but it can also occur in the course of neutropenia [7]. The clinical picture covers a wide range of symptoms ranging from mild diarrhoea to megacolon toxicum. Diarrhoea is most often accompanied by painful abdominal cramps, fever, and leukocytosis. In each case of diarrhoea with a potentially infectious etiology in a patient receiving myelosuppressive therapy or antibiotic therapy, stool (two samples) should be examined, including multi-stage algorithms with the assessment of the presence of toxins or toxins genes A and/or B and glutamate dehydrogenase (GDH) (methods allowing a quick positive result) (IV, C). Stool culture is the most sensitive method but is impractical because of the duration of the culture.

Management of pseudomembranous colitis includes:
- isolation of the patient (IV, B);
- discontinuation of the antibiotic that is causing the infection (may be sufficient for patients with a mild form) (II, A);
- the use of oral vancomycin (I, A) or fidaxomicin (I, A); in the case of mild disease and limited access to these drugs, oral metronidazole (IV, C) may be used; in very severe forms, co-administration of intravenous metronidazole and oral vancomycin should be considered (III, A);
- surgical treatment: megacolon toxicum, perforations, symptoms of toxaemia not responding to conservative treatment (II, B).

Neutropenic enterocolitis is a life-threatening disease with a mortality rate of around 50% [8]. The most commonly identified pathogens are Gram-negative bacteria (less often Gram-positive), and in about 5% of cases fungal infections are the cause (*Candida albicans*). The main symptoms include: nausea, vomiting, flatulence and abdominal pain, fever, and diarrhoea, sometimes bloody. CT scans or ultrasound examination reveal colon wall thickening (> 4 mm). Stool and blood culture and differentiation with *Clostridium difficile* infection is required. Final diagnosis is possible based on histopathological examination; however, due to the significant risk of complications, endoscopic diagnostics is not indicated (IV, C).

Management of neutropenic enterocolitis includes:
- strict diet (except for the mild form) and hydration (IV, A) and possible parenteral nutrition (IV, B);
- the use of broad-spectrum antibiotic therapy covering *Clostridium difficile*, aerobic and anaerobic bacteria; most authors recommend monotherapy with carbapenem, piperacillin with tazobactam or a combination of III or IV generation cephalosporins with metronidazole (IV, A);
- considering the use of G-CSF (I, B);
- surgical treatment in the case of complications (IV, C);
- antifungal therapy if there is no response to antibiotic therapy (IV, B).

Infections of the skin, subcutaneous tissue, and soft tissues

In cancer patients, especially those undergoing immunosuppressive treatment or with deep neutropenia, the clinical features of skin and soft tissue infections often take on a less severe form and look different from those seen in individuals without cancer. Usually, the initial manifestations include delicate erythematous lesions, macular or maculopapular eruptions, nodules or signs of subcutaneous tissue inflammation. Infection

may primarily develop within these tissues or manifest as a generalised infection. The etiological factors include bacteria, viruses, fungi, as well as parasites.

Before starting treatment, it is advisable to collect material for histopathological and microbiological examination (IV, C), and in some patients imaging tests to assess the severity of inflammatory lesions (IV, C). Antibiotic therapy should cover Gram-positive bacteria (the most common etiology) (IV, A). In patients with febrile neutropenia and symptoms suggestive of skin, subcutaneous, or soft tissue inflammation, the use of vancomycin should be considered as standard antibiotic therapy (until cultures are obtained) (I, A), and in patients with long-term neutropenia, the addition of an antifungal drug should be also considered (IV, C).

Infections of the skin and soft tissues of the perineum are most often associated with Gram-negative or anaerobic bacteria. The spectrum of antibiotic therapy should include these groups of pathogens (IV, A).

Catheter-associated infections (connected with the intravascular line) may occur as local infections, catheter tunnel infections, phlebitis, or bloodstream infections. The etiological factors of most infections are Gram-positive bacteria (most often coagulase-negative *Staphylococci*) [9]. In the case of suspected catheter infection, cultures of blood drawn from the catheter and peripheral vein should be performed, time to positive culture should be determined (interpretation in the "Neutropenia" chapter), and vancomycin antibiotic therapy should be initiated (I, A). In patients diagnosed with febrile neutropenia, the suspicion of catheter-associated infection is an indication to add vancomycin to standard empirical antibiotic therapy until bacteriological confirmation (IV, A). Catheter removal is not absolutely necessary if the patient's state is stable and the microbial causative agent is not identified. The likelihood of successful treatment without removing the catheter depends on the clinical judgment and the type of pathogen responsible for the infection. Infection limited to the site usually (except in severe cases) does not require catheter removal; however, as well as from blood cultures, a swab should be taken from the suspected site, followed by antibiotic therapy covering the spectrum of the recognised pathogen.

Indications for catheter removal are as follows (IV, A):
— sepsis, unstable general state in patients with suspected catheter-associated infection;
— severe, clinically apparent infection of catheter tunnel or implantable port for chemotherapy;
— septic thrombophlebitis;
— persistent bacteremia despite antibiotic therapy;
— infection with atypical mycobacteria;
— candidemia;
— catheter removal should also be considered in case of infections: *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter, Bacillus*.

The most common causes of viral skin infections in cancer patients include reactivation of latent herpes simplex virus (HSV) or varicella zoster virus (VZV) [10]. They occur mainly as a vesicular rash; however, in patients with reduced immunity, they take on an atypical (e.g. VZV infection in the form of single or multiple lesions with an accidental location) or generalised form more often than in individuals with normal immunity. Diagnostic procedures involve the collection of a follicle (scraping) or fluid from inside for cytological examination, direct fluorescence examination or culture. Acyclovir treatment should be oral or intravenous depending on the severity of the symptoms (I, A).

Gangrenous ecthyma is a cutaneous manifestation of a generalised infection (most often *Pseudomonas aeruginosa*) [10]. It occurs in the form of rapidly progressing (within 24 hours) skin lesions eventually taking on the form of single or multiple ulcers. Treatment includes antibiotic therapy with high activity against this pathogen (I, A); surgical intervention is sometimes indicated (III, C). Similar skin lesions may accompany generalised infections of *Staphylococcus aureus*, *Streptococcus pyogenes*, Gram-negative bacilli, some fungi, and even HSV.

Necrotising fasciitis (NF) (sometimes with concomitant myositis) is an acute, rapid, subcutaneous tissue infection with common concomitant becteremia [10]. In cancer patients it is more often associated with Gram-negative bacteria or mixed flora infections than in individuals with normal immune function. For an accurate assessment of the inflammatory process severity magnetic resonance imaging is recommended (IV, A). Management of patients with neutropenia includes surgical treatment (in more advanced cases) (IV, A) and broad-spectrum antibiotic therapy (I, A); in some patients the inclusion of G-CSF should be considered (IV, C).

Urinary tract infections

In patients treated for cancer, the risk of developing a urinary tract infection may be affected by the following: urinary tract obstruction, urinary catheter insertion, damage of the urinary tract epithelium as a result of surgery and chemotherapy or radiotherapy, concomitant diseases, as well as kidney function impairment.

Symptoms of lower urinary tract infection (cystitis) include dysuria, polyuria, nocturia, and urinary

incontinence (UI) (involuntary urination). In addition, general symptoms (fever, chills, lumbar pain, nausea, and vomiting) and a positive Goldflam symptom are observed in inflammation of the kidneys (nephritis).

The most common etiological factors of urinary tract infections are *Escherichia coli* followed by *Pseudomonas* sp., *Klebsiella* sp., and *Enterobacter* sp. In hospitalised patients with risk factors (diabetes, immunosuppression, chronic catheterisation) fungal infections can also occur.

The key to determining antibiotic therapy is urine culture, but in cases not responding to treatment and in patients with complicated pyelonephritis (e.g. nephrolithiasis, other urological diseases, recurrent urinary tract infection), CT of the abdomen and pelvis is recommended (IV, A).

The choice of antibiotic in empirical therapy depends on infection severity, kidney function, and the risk of drug resistance. If local resistance to particular groups of drugs is below 20%, fluoroquinolone (ciprofloxacin, levofloxacin), cephalosporin (III–IV generation), aminopenicillin with beta-lactamase inhibitor, and aminoglycoside are most commonly used (II, A). In the case of treatment failure or severe clinical status, the use of piperacillin/tazobactam, carbapenem, or ceftazidime is justified (II, A). Duration of treatment should be 7–14 days, and if there is no improvement within 48–72 hours, it should be modified according to the result of the antibiogram [11].

There are no indications for control urinalysis when clinical effectiveness of the treatment is confirmed.

Conflicts of interest

The authors declare to have no conflict of interest.

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VIA MEDICA

ORIGINAL ARTICLE

Seyed-Mehdi Hashemi[1], Mohammadreza Hormozi[2], Abolghasem Allahyari[3], Ali Arash Anoushirvani[4], Zahra Ameri[5], Samaneh Ghasemipour[5]

[1]Clinical Immunology Research Centre, Department of Internal Medicine, Haematology and Medical Oncology Ward, Ali-Ebne-Abitalelb Hospital, Zahedan University of Medical Science, Zahedan, Iran
[2]Department of Psychiatry, Zahedan University of Medical Science, Zahedan, Iran
[3]Department of Haematology and Medical Oncology, Mashhad University of Medical Sciences, Mashhad, IR Iran
[4]Department of Haematology and Medical Oncology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran
[5]Zahedan University of Medical Sciences, Zahedan, Iran

The prevalence of depression, anxiety, and stress in patients with breast cancer in Southeast Iran in 2019: a cross-sectional study

Address for correspondence:
Seyed-Mehdi Hashemi
Mashahir Sq, Zahedan University of Medical Sciences, Zahedan, Iran
Phone: +98 54 3329 5765
e-mail:
hashemimahdi@zaums.ac.ir

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ABSTRACT

Introduction. Today, breast cancer patients suffer from various psychological symptoms that impose irreversible effects on their quality of life. The aim of the present study was to determine the prevalence of depression, anxiety, and stress in patients with breast cancer.

Material and methods. This descriptive study was performed on 190 women with breast cancer from January 1, 2019 to July 30, 2019. Data collection was carried out using a convenience sampling method. The Standard Depression, Anxiety, and Stress Scale (DASS-21) was used to assess depression, anxiety, and stress.

Results. The mean age of the patients was 46.3 years. Results showed the prevalence of depression, anxiety, and stress to be 28.4%, 43.2%, and 14.7%, respectively.

Conclusion. The results indicate that it is vital to measure the level of depression and anxiety in women with breast cancer, which are two common mental disorders in breast cancer.

Key words: breast cancer, depression, anxiety, stress

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Introduction

Breast cancer is considered one of the most important and most common cancers in women today. Breast cancer caused more than 375,900 deaths in 2017 [1]. Breast cancer also imposes costs of $88 billion a year to patients with breast cancer [2]. Breast cancer diagnosis is one of the most stressful medical situations in a person's life [3]. Breast cancer can have a profound effect on the patient's physical, mental, and social status and overall well-being [4]. Psychosocial interventions can improve the quality of life (symptoms of depression and anxiety) in both groups of women with breast cancer [5]. Depression and anxiety have negative effects on the quality of life of cancer patients, and in this regard, the Hospital Anxiety and Depression Scale (HADS) is currently a useful method to screen for these problems [6, 7]. Studies show that 10–50% of cancer patients suffer from psychosocial disorder (depression, anxiety, despair, social isolation, and work and financial problems), and the above figure increases in last stages of cancer [8, 9]. A recent meta-analysis shows that the global prevalence of depression among breast cancer patients is 32.2% [10]. Depression is a very common disorder in all ages and races, as well as in men and women worldwide [11]. Depression has a negative effect on quality of life, length of stay, and treatment outcome of cancer patients [12]. Another common disorder among cancer

patients is anxiety, the prevalence of anxiety is 41.9% [13]. Anxiety is associated with cancer, and these psychological symptoms are the most common psychological symptoms found in cancer patients. Patients with ineffective coping strategies exhibit higher levels of anxiety and depression, and social support led to a significant decrease in the level of anxiety and depression [14, 15]. Stress or perceived stress was also expressed as another psychological factor in cancer patients and was strongly related with depression [16]. Determining the exact level of depression and anxiety can help policymakers and healthcare providers plan for better control of these diseases. The aim of the present study was to determine the prevalence of depression, anxiety, and stress among patients with breast cancer.

Methods

Design

This cross-sectional study was performed on 190 women with breast cancer stages 3–4 referred to oncology wards of three educational hospitals in three Iranian cities (Zahedan, Arak, and Mashhad) from 1 January 2019 to 30 July 2019. Patients were selected through convenience sampling. Inclusion criteria included patients aged above 18 years, with no systemic disease.

Instruments

The standard depression, anxiety, and stress scale — 21 items (DASS-21) was used to assess depression, anxiety, and stress in patients [17]. This instrument consisted of 21 items, with seven items for each subscale. The instrument was scored based on a four-point Likert scale ranging from of 0 to 3 (never, rarely, sometimes, and always). Depression levels were categorised into four categories, which indicated normal (score: 0–9), low (score: 10–13), moderate (score: 14–20), and severe (28 and above) level of depression. Normal, low, moderate, severe, and very severe anxiety were also indicated by scores of 0–7, 8–9, 10–14, 15–19, and 20 and above, respectively. The validity and reliability of this instrument has been confirmed in various Iranian [18, 19] and international (non-Iranian) [20, 21] populations. The demographic characteristics studied included age, city of residence, level of education, and marital status.

Data collection

Data collection was carried out after making coordination with the hospital cancer department and explaining the study objectives to the patients in simple language. Questionnaires were then distributed among the qualified patients who expressed their consent to participate in the study. Patients were given 15 minutes to complete the questionnaires. Questionnaires were completed by the researcher in the case of illiterate participants.

Ethical considerations

The present study was approved by the Ethics Committee of Zahedan University of Medical Sciences (Ethic code: IR.ZAUMS.REC.1392.5962). Written and oral consent was obtained from all participants, and they were assured that their information would be kept confidential. The STROBE checklist was also used to report the study [22].

Statistical analysis

Descriptive statistical tests (mean, standard deviation, frequency, and percentage) were used to describe demographic characteristics of the participants and analytical tests (chi-square) were also used to examine the relationship between demographic characteristics with stress, anxiety, and depression. SPSS Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to analyse the data. Confidence interval of 95% and a significance level of $P < 0.05$ was considered significant.

Results

All 190 patients with breast cancer were evaluated (response rate = 100%). The mean age of patients was 46.3 years (range: 19–76 years). The majority of the participants lived in Zahedan (77.9%), had high school education (25.3%), and were married (84.2%) (Table 1).

The prevalence of mild, moderate, and severe depression was 18.4%, 9.5%, and 0.5%, respectively. The prevalence of anxiety was 43.2%. The average prevalence of stress was 14.7%, with 12.6%, 1.6%, and 0.5%, for mild, moderate, and severe stress, respectively (Table 2).

Discussion

The present study investigated the prevalence of psychological factors (depression, anxiety, and stress) in breast cancer patients and revealed that 28.4%, 43.2%, and 14.7% of patients suffered from depression, anxiety, and stress, respectively.

Approximately one-third (28.4%) of patients suffered from depression, which is similar to the global prevalence of depression (32.2%) and to results from studies car-

ried out by Montazeri et al. (29.4%) [23], Taghavi et al. (34.2%) [24], and Nikbakhsh et al. (27.5%) [25] in different parts of Iran. The above figure was, however, lower than the rate reported in studies by Ramezani et al. [26] and Mashhadi et al. [27]. This difference could be due to differences in participants' place of residence, demographic characteristics of participants, methodological differences of the studies, and sample size.

High levels of mental distress for sustained periods of time in cancer patients may lead to anxiety, depression, or both [28]. The mortality rate is higher in depressed cancer patients than non-depressed patients [6]. Depression is very common in breast cancer patients; the prevalence of depression is 47.4% [10, 29], which can significantly affect the quality of life of patients [30]. According to various studies, the prevalence of depression in cancer patients ranges from 16–67% [31–33].

The prevalence of anxiety in the present study was 43.2%, which was close to the global prevalence of anxiety (41.9%) [13] and lower than the figure reported in the study by Ashbury (77%) [13]. Anxiety had a significant effect on the feeling of breast cancer patients and their coping mechanisms [34]. Results of a study showed that 16% of women with breast cancer were diagnosed as depressed until 6 to 13 years after treatment [35]. Other studies have shown that the prevalence of depression in cancer patients is estimated to be 15–30% or higher [(36–38], and although anxiety and depression are commonly seen in breast cancer patients, exacerbate the symptoms of the disease, and lead to no response to treatment, these mental disorders are ignored and left untreated [39]. Achieving understanding of these common mental disorders and related psychosocial factors can help plan treatment and may lead to more successful treatment [40]. Lueboonthavatchai concluded that the prevalence of anxiety disorder and anxiety symptoms was 16% and 19%, respectively [41].

Theoretically, stress is defined as the body's response to environmental or mental conflicts, or as the internal response that depends on their ability to cope with environmental stress [42]. In a meta-analysis, researchers concluded that stressful events are not associated with the risk of breast cancer in women [43]; however, high-intensity stress may be a potential risk factor for breast cancer. A study by Nikbakhsh et al. on 150 cancer patients in Iran showed that 44 participants (29.3%) had mild anxiety and 25 (16.7%) had symptomatic anxiety and mild depression, which is inconsistent with the present study, which showed lower stress rates [25]. This difference could be due to the type of cancer being studied and methodological differences. The main strength

Table 1. Participants demographic characteristics of breast cancer patients (n = 190)

Variables	N (%) Mean ± SD
Age (years)	46.3 ± 12.2
City of residence	
Zahedan	148 (77.9)
Mashhad	23 (12.1)
Arak	19 (10)
Education level	
Illiterate	39 (20.5)
Elementary	45 (23.7)
Secondary	23 (12.1)
High school	48 (25.3)
University graduate	35 (18.4)
Marital status	
Single	16 (8.4)
Married	160 (84.2)
Widow	14 (7.4)

Table 2. Prevalence of depression, anxiety, and stress among breast cancer patients

Variables	N (%)	Mean ± SD	Range
Depression		6.7 ± 4.9	0–21
Normal	136 (71.6)		
Low	35 (18.4)		
Moderate	18 (9.5)		
Severe	1 (0.5)		
Anxiety		6.7 ± 4.3	0–18
Normal	108 (56.8)		
Low	26 (13.7)		
Moderate	50 (26.3)		
Severe	6 (3.2)		
Stress		8.9 ± 5.1	37–160
Normal	162 (85.3)		
Low	24 (12.6)		
Moderate	3 (1.6)		
Severe	1 (0.5)		

of the present study was the investigation of depression, anxiety, and stress concurrently. Another strength of the present study was that participants from different cities with different cultures were included, especially from areas where fewer studies had previously been carried out. The main limitations of the present study were as follows: 1. The sample size was low, which could limit the generalisation of results. 2. This is a descriptive study that should consider the specific limitations of these studies when interpreting the study results. 3. Variables were evaluated using self-report measures instead of non-clinical evaluation, which should thus be taken into consideration.

Conclusions

Results showed that approximately one-third of patients suffer from depression and about half of them from anxiety. The high prevalence of depression and anxiety indicates the importance of timely and periodic evaluation of psychological symptoms in patients with breast cancer.

Conflicts of interest

The authors declare to have no conflict of interest.

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ORIGINAL ARTICLE

Katarzyna Kozak, Tomasz Świtaj, Hanna Koseła-Paterczyk, Paulina Jagodzińska-Mucha, Paweł Rogala, Paweł Teterycz, Piotr Rutkowski

Department of Soft Tissue/Bone, Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Summary of experience of melanoma patients treated with BRAF/MEK inhibitors according to Polish National Drug Reimbursement Program Guidelines

Address for correspondence:
Lek. Katarzyna Kozak
Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków
Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie — Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa
Phone: 22 546 20 31
e-mail: wiater.katarzyna@gmail.com

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ABSTRACT

Introduction. Combined inhibition of BRAF and MEK improved progression-free survival and overall survival in patients with *BRAFV600*-mutation-positive metastatic melanoma. We conducted a retrospective study on real-life patients with BRAF-mutant melanoma treated with BRAF/MEK inhibitors.

Patients and methods. Patients with untreated, unresectable stage IIIC/IV melanoma positive for the *BRAFV600* mutation were treated with dabrafenib/trametinib or vemurafenib/cobimetinib. All patients received BRAF/MEK inhibitors as first-line therapy according to Polish National Drug Reimbursement Program Guidelines. Median follow-up time was 41 months. For the survival analysis, the Kaplan-Meier estimator was used with log-rank tests for univariate comparisons.

Results. A total of 95 patients were included (48 women and 47 men; median age: 55 years). 80 patients received dabrafenib/trametinib and 15 received vemurafenib/cobimetinib. Overall, 12 patients continued therapy after the cutoff date. The objective response rate was 71%, including six patients (6%) with a complete response and 62 patients (65%) with a partial response. Median progression-free survival was 10 months and median overall survival was 15 months. High LDH level, ECOG > 0, stage M1c–M1d and three or more metastatic organ sites negatively impacted PFS and OS. Higher adverse event rate was reported in patients receiving vemurafenib/cobimetinib (87%) as compared to patients treated with dabrafenib/trametinib (64%). Overall, grade 3–4 toxicity was reported in 20% of patients. The most frequent adverse events in the dabrafenib/trametinib group were pyrexia, fatigue, nausea and arthralgia. In the vemurafenib/cobimetinib group, the most frequent adverse events were skin toxicity (rash, photosensitivity), arthralgia, myalgia and diarrhea.

Conclusions. Despite the high response rate to BRAF and MEK inhibitor therapy, the overall survival is lower in clinical practice than observed in clinical trials. This difference may be explained by a more heterogeneous patient population seen in routine clinical practice, with more advanced disease and comorbidities.

Key words: *BRAF* mutation, metastatic melanoma, targeted therapy

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Introduction

Standard treatment in patients with metastatic melanoma with the *BRAF V600* mutation is BRAF/MEK inhibitors or immunotherapy based on anti-PD1 antibodies. The *BRAF* V600 mutation (v-raf murine sarcoma viral oncogene homolog B1) is present in about 50% of melanoma patients. Currently, three combinations of BRAF/MEK inhibitors are registered in Europe (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib). The first two combinations are available in Poland within the Drug Reimbursement Program of the Ministry of Health and can be applied in any line of treatment in patients with advanced mela-

noma who have a *BRAF V600* mutation. A second treatment option independent of the *BRAF* mutation status are anti-PD1 antibodies as monotherapy or in combination with an anti-CTLA4 antibody. Currently, in Poland, these antibodies can be used exclusively in monotherapy. Nivolumab and pembrolizumab are available as 1st or 2nd line treatment whereas ipilimumab in the 2nd line of treatment. As both molecularly targeted drugs and immunotherapy prolong the time of progression-free and overall survival it has not been established which treatment should be used in the 1st line, moreover in the light of retrospective analyses both groups of drugs have higher effectiveness when they are used as 1st line treatments. Currently, randomized clinical trials aimed at establishing the optimal mode of treatment are ongoing. Both combined treatment (BRAF/MEK inhibitors plus immunotherapy), as well as different options of sequential treatment, are being investigated. The aim of the present work is the evaluation of the results of treatment with BRAF/MEK inhibitors of patients with advanced melanoma in the scope of everyday clinical practice. Responses to anti-PD1 therapy used in the second line of treatment after failure of treatment with BRAF/MEK inhibitors are also evaluated.

Material and methods

95 patients were included who were on the drug program with BRAF/MEK inhibitors between October 2014 and May 2017. In 27 patients the MEK was added during treatment with a BRAF inhibitor. At that time the drug program allowed targeted treatment of patients with nonresectable or metastatic melanoma positive for the *BRAF* mutation with a good performance status according to the Eastern Cooperative Oncology Group (ECOG 0 or 1). Patients with metastases to the brain could be included in the drug program if the metastases were asymptomatic. The patients were treated to disease progression or unacceptable toxicity. According to the program of evaluation of the response to treatment, this was determined based on the results of imaging tests performed every 8–10 weeks according to Response Evaluation Criteria In Solid Tumours (RECIST 1.1). Data concerning tolerance of treatment were presented according to the fourth version of the scale of treatment toxicity — CTCAE (Common Terminology Criteria for Adverse Events). Overall survival (OS) was calculated from the date of starting targeted treatment to the date of death or the date of the last observation in surviving patients (censored observations). The date for calculating progression-free survival (PFS) was determined similarly. The final date (complete observations) for PFS was the date of disease progression. In patients in whom disease progression had not occurred so far the final date was taken to be the date of the last observation of the patient (censored observations). The Kaplan-Meier method was used to analyze survival. The comparisons of curves in individual patient subgroups (monofactorial analysis) were performed using the log-rank test. Statistical analysis was performed using MedCalc Software (version 19.1.3). The median follow-up time was 41 months (range 2–50).

Results

Most patients (84%) received dabrafenib at a dose of 300 mg/day with trametinib at a dose of 2 mg/day. The remaining patients were treated with vemurafenib (1920 mg/day) in combination with cobimetinib (60 mg/day). All patients received BRAF/MEK inhibitors in 1st line treatment. The median age at the start of targeted therapy was 55 years (range 25–84). The distribution of sex in the investigated group was uniform: 48 women and 47 men. Most patients had an ECOG performance status of 1 (68%). Lactate dehydrogenase (LDH) levels were higher than normal in 41% of patients. Metastases to the central nervous system (CNS) before initiating targeted therapy were present in 37%, and metastases to > 2 organs were found in 43% of patients. The characteristics of patients are presented in Table 1.

The percentage of responses to treatment was 71%. A complete response to treatment was observed in 6% patients, and a partial one in 65% of patients. Median progression-free survival was 10 months, and median overall survival was 15 months (Tab. 2). No differences in median PFS and OS were observed between patients receiving two different combinations. Univariate analyses indicated that factors associated with poorer progression-free survival were ECOG 1, high LDH level and metastases localized in > 2 organs (Tab. 3). Figure 1 and 2 present curves of PFS and OS as a function of LDH concentration and M1. Median PFS in the group of patients with low progression of the disease (number of metastatic organ sites ≤ 2) was 17 months, whereas in the group of patients with the number of metastatic organ sites > 2 it was only 6 months. Median OS for both groups were 29 and 8 months, respectively. The best survival was observed in patients with LDH level within the normal range and ≤ 2 metastatic organ sites. Median PFS and OS in this group of patients were 20 and 34 months, respectively. The shortest survivals were observed in patients with metastases to multiple organs (> 2) and LDH levels > upper limit of normal (ULN). Median PFS and OS in this group of patients were only 5 and 6 months, respectively (Figure 3).

At the time of data analysis, 69 (73%) patients had died due to melanoma progression. Treatment with

Table 1. Patient characteristics

	Number of patients N = 95	
	n	%
Age (median)	55	
Sex		
Women	48	50.5
Men	47	49.5
Performance status according to ECOG		
0	30	31.6
1	65	68.4
Degree of progression at the start of targeted therapy		
M1a	14	14.7
M1b	8	8.4
M1c	38	40
M1d	35	36.8
Lactate dehydrogenase (LDH) level		
≤ ULN	56	58.9
> 1 – ≤ 2 × ULN	29	30.5
> 2 × ULN	10	10.5
Metastases to the central nervous system (CNS)	35	36.8
Number of metastatic organ sites		
≤ 2	54	56.8
> 2	41	43.2
2nd line treatment	41	43.2
Anti-PD1	38	40
Anti-CTLA4	1	1.1
Clinical trial	2	2.1

ULN — the upper limit of normal

Table 2. Results of treatment of patients with a positive *BRAF* mutation with nonresectable/metastatic melanoma with BRAF and MEK inhibitors

	BRAFi + MEKi N = 95
The best response to treatment	
Complete response (CR)	6 (6%)
Partial response (PR)	62 (65%)
Stable disease (SD)	21 (22%)
Progressive disease (PD)	6 (6%)
Objective response to treatment	
Complete response + partial response (CR + PR)	70 (74%)
Progression-free survival (PFS)	
Median (months)	10
Overall survival (OS)	
Median (months)	15

BRAF/MEK inhibitors was continued in 12 patients, 6 patients were receiving anti-PD1 therapy. The remaining patients were receiving subsequent lines of treatment (chemotherapy, repeated treatment with BRAF/MEKi). In total after finishing treatment with BRAF/MEK inhibitors, 38 patients (40%) had received anti-PD1 therapy. The percentage of responses to treatment in this group of patients was 21%. In most patients, disease progression was observed during the first evaluation of response to the treatment.

Adverse events during therapy with BRAF/MEK inhibitors were observed in most patients. They occurred more frequently in patients treated with vemurafenib and cobimetinib (87% patients) than with dabrafenib and trametinib (64% patients). Adverse events at level 3–4 were observed in 20% patients. Dose reduction was necessary in 16% of patients treated with dabrafenib and trametinib and 20% of patients treated with vemurafenib and cobimetinib. Treatment was stopped in two patients because of toxicity (general fatigue, nephrotoxicity). Among the most common adverse effects observed in the group of patients treated with dabrafenib and trametinib were: pyrexia/chills, fatigue, nausea and arthrhalgia. In the case of vemurafenib and cobimetinib skin complications predominated (rash and photosensitivity), myalgia, arthralgia and diarrhea.

Discussion

The use of BRAF/MEK inhibitors in patients with metastatic melanoma and positive for the *BRAF* mutations yields a high percentage of positive responses to treatment also in everyday clinical practice. The objective responses to treatment observed here (71% of patients) are in agreement with the results of large randomized, Phase III clinical trials for both combinations. In the COMBI-d (NCT01584648) and COMBI-v (NCT01597908) trials objective responses to treatment with dabrafenib and trametinib were observed in 68% [1] and 64% [2] patients, respectively, and in the coBRIM (NCT01689519) trial the percentage of responses to treatment with vemurafenib and cobimetinib was 68% [3]. Median PFS and OS in the above-mentioned clinical trials were 11–13 months and 22–26 months, respectively. Despite, the high percentage of responses to therapy observed in patients subjected to the present analysis, median PFS and OS were, however, shorter than those observed in the above-mentioned phase III clinical trials. Median PFS was 10 months, whereas the median OS was 15 months. This is related to the specific effectiveness of BRAF/MEK inhibitors, which allow a high percentage of treatment responses regardless of the stage of the disease, this also is true

Table 3. Results of treatment of patients with nonresectable/metastatic melanoma with BRAF and MEK inhibitors depending on clinical factors

Clinical factor	Number of patients N = 95	Progression-free survival (PFS) Median (months)		Overall survival (OS) Median (months)	
Performance status according to ECOG					
0	30	16	p = 0.0235	32	p = 0.0076
1	65	9		13	
Degree of progression at the start of targeted therapy					
M1a	14	30	p = 0.0668	Not attained	p = 0.0078
M1b	8	7		20	
M1c	38	8		13	
M1d	35	8		13	
Lactate dehydrogenase concentration (LDH)					
≤ ULN	56	14	p = 0.0109	24	p = 0.0009
> 1 – ≤ 2 × ULN	29	6		10	
> 2 × ULN	10	5		6	
Metastases to the central nervous system (CNS)					
Yes	35	8	p = 0.0846	13	p = 0.0298
No	60	11		20	
Number of metastatic organ sites					
≤ 2	54	17	p < 0.0001	29	p < 0.0001
> 2	41	6		8	
Number of metastatic organ sites and lactate dehydrogenase level (LDH)					
≤ 2 and ≤ ULN	57	20	p < 0.0001	34	p < 0.0001
> 2 and > ULN	20	5		6	

ULN — the upper limit of normal

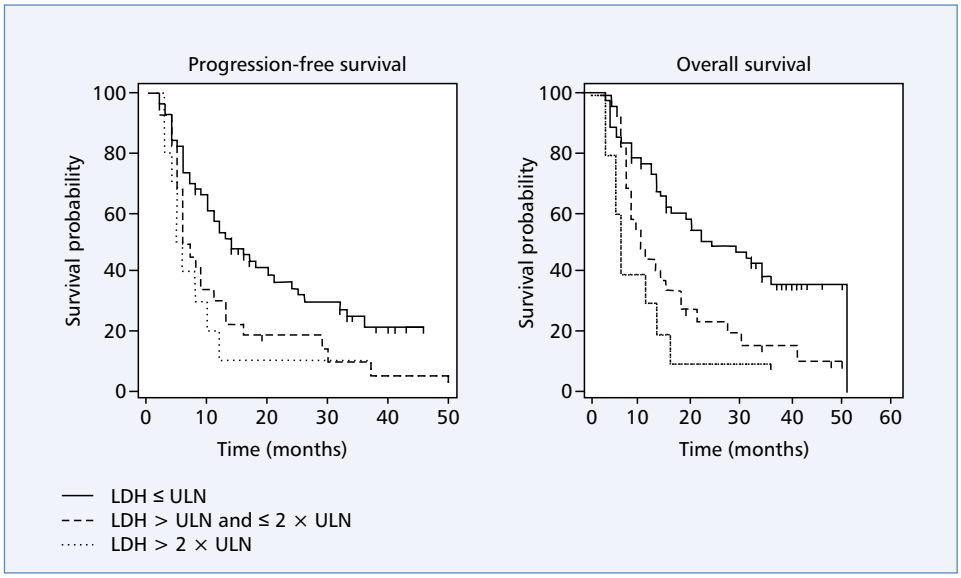

Figure 1. Progression-free survival and overall survival as a function of lactate dehydrogenase (LDH) activity. ULN — upper limit of norma

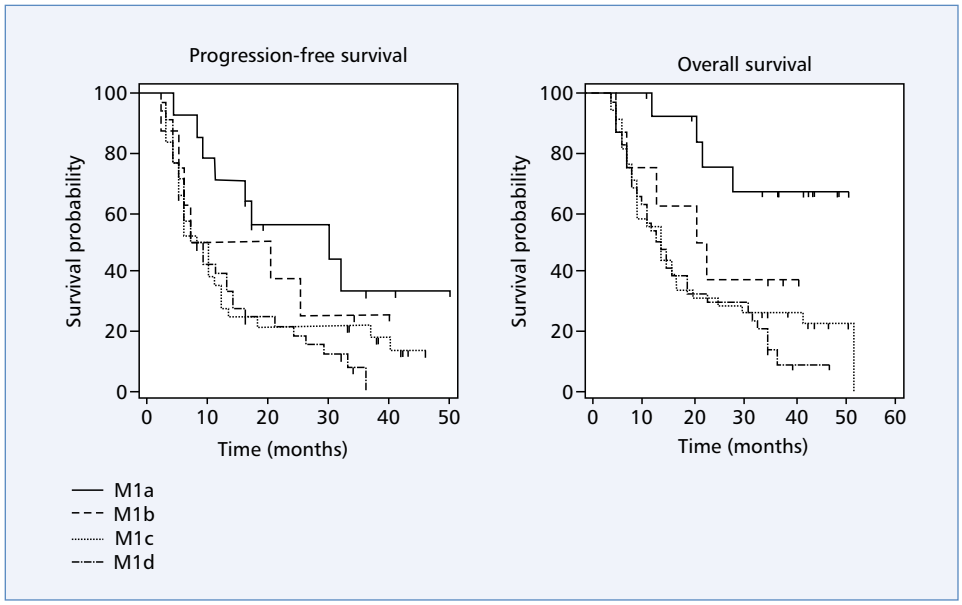

Figure 2. Progression-free survival and overall survival as a function of M1

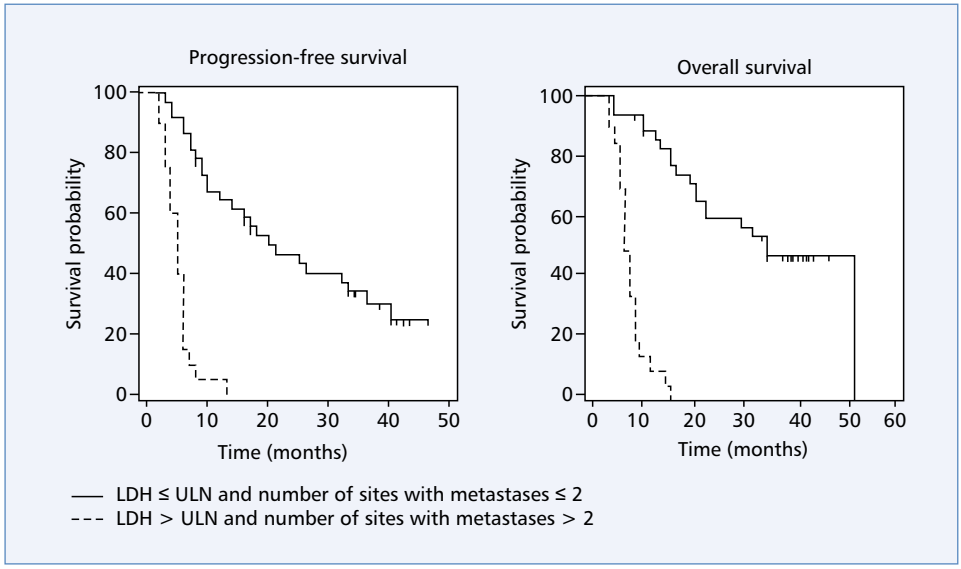

Figure 3. Progression-free survival and overall survival as a function of lactate dehydrogenase (LDH) level and the number of metastatic organ sites. ULN — upper limit of normal

for patients with multiple metastases within the central nervous system (CNS) and multiple metastatic organ sites. The problem in targeted therapy is still the resistance to the applied treatment. How fast it develops depends on how advanced the disease is before initiating BRAF/MEK inhibitor therapy. In everyday clinical practice, which is reflected very well in the analyzed patient population, much more commonly than in clinical trials this group encompasses patients with many metastases to the brain, a high LDH level (especially > 2 × ULN) or metastases to multiple organs. In the analyzed patient population the shortest medians of overall survival were observed in patients with brain metastases (13 months), LDH levels > 2 × ULN (6 months) and in patients with metastases to multiple organs (8 months). An especially short survival was observed in patients with elevated LDH accompanied by metastases to multiple organs. Median PFS and OS in this group of patients were just 5 and 6 months, respectively. It is worth pointing out that the presented patient population was treated with inhibitors as 1st line treatment. This was initially due to the lack of access to immunotherapy based on

anti-PD1 antibodies and a different initial program of drugs with anti-PD1. Due to the present access to immunotherapy based on anti-PD-1 antibodies currently in most patients treated in the Department of Soft Tissue/Bone, Sarcoma and Melanoma immunotherapy is used as 1st line treatment which is in agreement with the tendency worldwide. This is related to the possibility of obtaining responses lasting several years which are maintained even if immunomodulatory therapy is stopped. Therefore in asymptomatic patients with good performance status and not very rapid disease dynamics treatment is more commonly started as immunotherapy. It should, however, be stated that this group also has long-term responses during therapy with BRAF/MEK inhibitors. An analysis summing up the long term effects of treating patients with dabrafenib and trametinib in the scope of COMBi-d and Combi-v trials indicates a high percentage of overall survival in patients with advantageous prognostic factors. The percentages of 5-year progression-free survival and overall survival in patients with normal LDH levels were 25% and 43%, respectively. In the group of patients with normal LDH levels and fewer than 3 metastatic organ sites, the percentage of 5-year overall survivals was as high as 55% [4]. The results of treatment with dabrafenib and trametinib in patients with particularly unfavourable prognostic factors, that is LDH levels two times higher than the upper limit of normal are quite different. Schadendorf et al. in an earlier analysis of the results of the COMBI-d and COMBI-v trials noted in this group of patients median PFS of only 5.5 months and percentages of progression-free 2 and 3-year survivals of 2% and 0, respectively [5]. Based on the results of the CheckMate 067 trial, it seems that the best option in this group of patients is a combination of nivolumab with ipilimumab, which yielded a percentage of overall 3-year survivals of 28% [6].

In this analysis, the response to treatment with anti-PD1 antibodies as 2nd line treatment after unsuccessful therapy with BRAF/MEKi was also evaluated. The percentage of responses to anti-PD1 therapy was 21%, which is confirmed by numerous retrospective analyses published so far [7–9]. Unfortunately in some patients treated with BRAF/MEK inhibitors rapid progression of the disease is observed after the drugs are discontinued. In most patients subjected to this analysis, immunotherapy was stopped already during the first 3 months of treatment because of the progression of the disease. One of the basic reasons for the progression of the disease during targeted treatment is metastasis of the disease to the CNS or progression of already existing metastases to the brain. This localization of metastases is associated with a lower percentage of responses to anti-PD1 antibodies. Taking the results of phase II of the ABC (Anti-PD1 Brain Collaboration) and CheckMate 204 trials the only effective option for immunotherapy in patients with metastases to the brain is a combination of anti-CTLA4 and anti-PD1 antibodies. Intracranial responses to treatment with nivolumab and ipilimumab in the scope of the above-mentioned clinical trials were observed in 46–52% patients [10, 11]. Such treatment is not, however, included in current drug programs for patients with advanced melanoma.

The availability of BRAF/MEK inhibitors in the scope of treatment programs since several years has made their safety profile familiar to oncologists. In patients undergoing the present analysis, the percentage of complications was lower than that reported in clinical trials, which is probably due to the retrospective character of this work. In COMBI-d and COMBI-v trials during treatment with dabrafenib and trametinib, the most common were pyrexia (51–53%), nausea (30–35%), diarrhea (24–32%) and chills (30–31%) [1, 2]. In the coBRIM trial, the most common adverse effects of vemurafenib and cobimetinib were: diarrhea (56%), nausea (40%), skin rashes (32%) and arthralgia (32%) [3]. No strong irreversible complications were observed in the population subjected to the present analysis. In the case of the combination of vemurafenib with cobimetinib the basic adverse effect was skin toxicity, which is relatively easy to avoid by modifying the dose. It should be kept in mind that patients have to be properly educated in order to avoid burning of the skin due to vemurafenib phototoxicity. Protection against UVA light should be constant, regardless of the time of the day or season. During the whole period of treatment, the patients should use broad-spectrum UVA + UVB filters. For the dabrafenib and trametinib combination, the basic problem is pyrexia which occurs in even one half of the patients. In 2015 Menzies et al. published a detailed analysis of the course of pyrexia in patients during treatment with dabrafenib and trametinib. The median time to appearance of the first episode was 19 days, the median time of its duration was 9 days. Successive episodes appeared after 3–4 weeks after the previous one but were shorter (median 4–5 days) [12]. Dose modification in the case of this adverse effect often does not bring the expected result. The only effective measures are interruptions of treatment and proper education of the patients. Interrupting treatment with dabrafenib already upon the appearance of prodromal symptoms makes the pyrexia episodes shorter and less intense. In the case of persistent recurring pyrexia making it difficult to maintain continuous treatment oral prednisone at a dose of 10–25 mg/day should be considered [13].

This analysis confirms the efficacy of BRAF/MEK inhibitors used in everyday clinical practice. BRAF/MEK inhibitors yield responses even in patients with a high degree of disease progression which has a significant impact on improving their quality of life. However,

because of resistance which appears especially early in symptomatic patients further research in overcoming the resistance in order to sustain the initial response to treatment are necessary. The improvement in treatment may be caused by new combinations of drugs with immunomodulating activity and targeted to particular molecules or more intensive immunotherapy.

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VIA MEDICA

REVIEW ARTICLE

Aleksandra Sobiborowicz[1, 2], Anna M. Czarnecka[1, 3], Anna Szumera-Ciećkiewicz[4, 5], Piotr Rutkowski[1], Tomasz Świtaj[1]

[1]Department of Soft Tissue/Bone, Sarcoma and Melanoma, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[2]Medical Faculty, Medical University of Warsaw, Warsaw, Poland
[3]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences Warsaw, Poland
[4]Department of Pathology and Laboratory Diagnostics, Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland
[5]Department of Diagnostic Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland

Diagnosis and treatment of angiomyolipoma (AML) tumours

Address for correspondence:
Dr n. med. Tomasz Świtaj
Narodowy Instytut Onkologii
im. Marii Skłodowskiej-Curie
— Państwowy Instytut Badawczy
ul. Roentgena 5, 02–781 Warszawa
Phone: 22 546 20 31; fax: 22 643 93 75
e-mail: tomasz.switaj@coi.pl

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ABSTRACT

Angiomyolipoma (AML) is the most commonly occurring tumour from the PEComa family (PEC tumours; perivascular epithelioid cell tumours), a rare group of neoplasms of mesenchymal origin. AML may occur sporadically or in the course of tuberous sclerosis and lymphangioleiomyomatosis. The sporadic type form is the most common subtype of benign kidney tumours and is four times more frequent in women. Kid ney tumours of the angiomyolipoma type are most commonly detected by chance during an abdominal cavity ultrasound scan, during which they are visible as hyperechogenic tumours, and in most cases they are not a diagnostic problem. AML growth is slow, and complications are rare. The main AML complication can be bleeding to the retroperitoneal space or to the pelvicalyceal system. The typical method of AML care is active surveillance (AS). Asymptomatic tumours with a diameter under 4 cm require control by ultrasound examination every 12 months whereas tumours with a diameter of less than 2 cm are considered not to require control ultrasounds. AML with a diameter of over 4 cm require more frequent ultrasound scans — every six months. The size of the tumour, the presence of symptoms (e.g. pain in a tumour projection, haematuria), planned pregnancy, or suspicion of a malignant tumour are critical in therapeutic decisions. Active treatment options include: embolisation, ablation techniques, nephron-sparing surgery (NSS), and radical nephrectomy. In adult patients with tuberous sclerosis, who require treatment but do not require rapid surgical treatment, everolimus is used. In the case of AML, initially doses of 1 × 10 mg per day should be used (an appropriate dose decrease is required in the case of liver insufficiency), and subsequently treatment may be individualised after determining the lowest effective dose with acceptable adverse effects. A rare epithelioid variety of AML (EAML) shows the potential for a malignant course. The basis of EAML treatment is radical resection, ensuring a high percentage of cures. For non-resectable EAML, chemotherapy, mTOR inhibitors, and VEGFR inhibitors (pazopanib, apatinib) are used, but objective responses have been described only in a very small percentage of patients.

Key words: AML, angiomyolipoma, everolimus

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Introduction

Angiomyolipoma (AML) is the most commonly occurring tumour from the PEComa family (PEC tumours; perivascular epithelioid cell tumours), a rare group of tumours of mesenchymal origin, composed of perivascular epithelioid cells (PEC) [1] (Figure 1). The following are also included in the PEComa group: clear-cell sugar tumour (CCST) — the pulmonary form and the primary extrapulmonary sugar tumour (PEST), lymphangioleiomyomatosis (LAM), clear-cell myomelanocytic tumour (CCMMT), primary cutaneous PEComa, cutaneous clear cell myomelanocytic tumour (CCCMT), and PEComa NOS (not otherwise specified) — a group description of tumours not classified into any of the categories mentioned earlier. Angiomyoli-

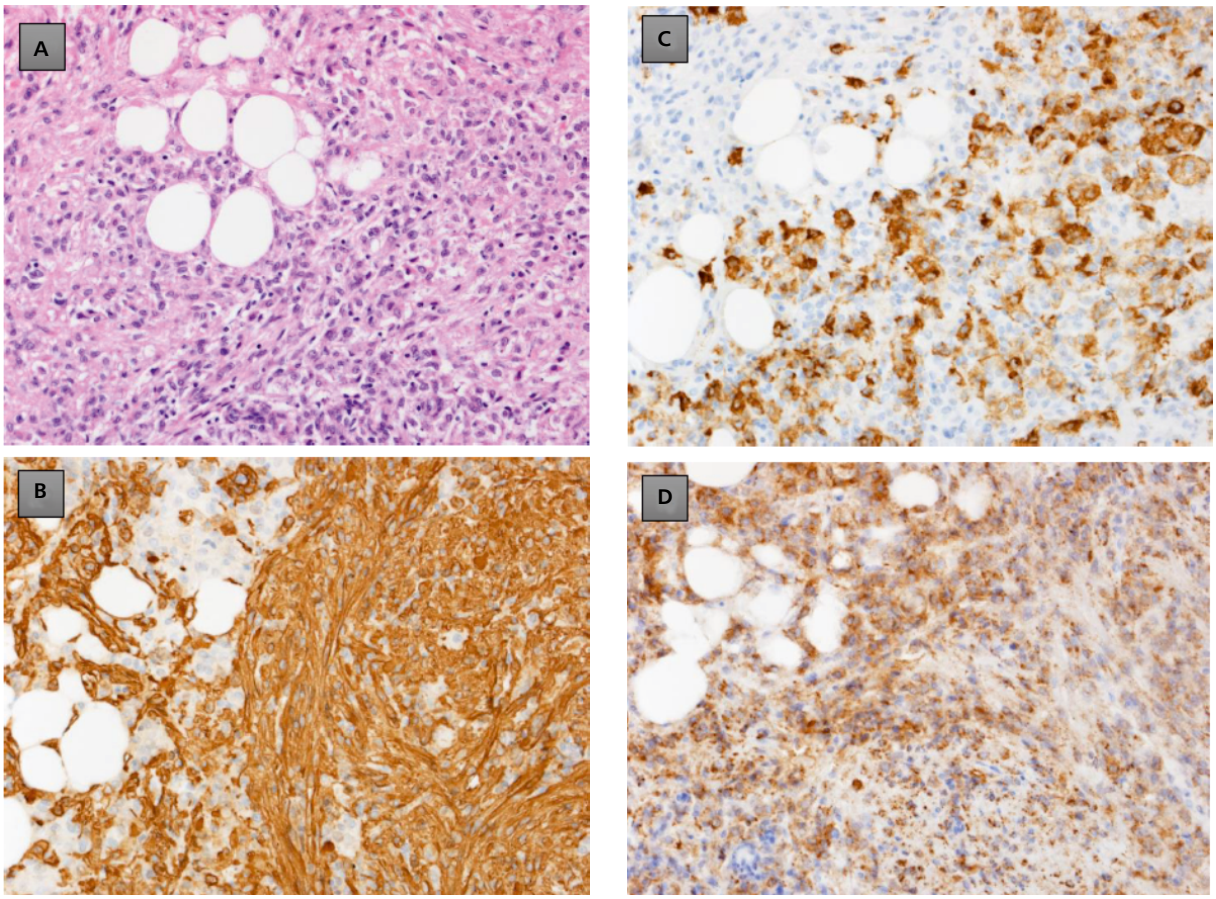

Figure 1. AML containing smooth muscle, fat tissue and blood vessels **A–D** — in order staining HE, SMA, HMB-45, and Cathepsin K [200×]

pomas are most commonly found in the form of a small asymptomatic kidney tumour usually containing a lot of lipid tissue, in a patient without known predisposing factors; this is described as the sporadic form of AML [2]. AML occurrence is also linked to the genetic syndrome caused by germline mutations inactivating the *TSC1* and *TSC2* genes — tuberous sclerosis complex (TSC, Bourneville-Pringle disease), which is characterised by numerous tumours of the hamartoma type, perturbations of the nervous system, including epilepsy, autism, and intellectual disability of various degrees [3]. In this form, AML occurs as large and multiple tumours with a tendency for bleeding, and their presence leads to progressive renal insufficiency [4]. AML is also observed in female patients with lymphangioleiomyomatosis, constituting one of the diagnostic criteria of this disease [5]. In about 8% of AML cases, more commonly in the forms associated with tuberous sclerosis, a predominance of epithelial cells is seen in the tumour, and they may show nuclear atypia [6]. Such tumours are described as the epithelioid subtype of AML (EAML, epithelioid angiomyolipoma), and a small percentage show a tendency to a malignant course, which is atypical for this group [7] (Figure 2).

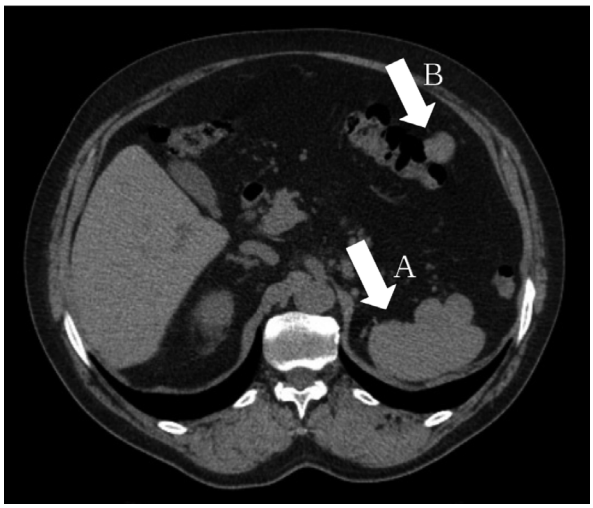

Figure 2. Recurrent (**A**) and disseminated (**B**) EAML after left nephrectomy

Epidemiology

The sporadic form of AML is the most common benign kidney tumour; in a retrospective analysis of 61,389 patients subjected to abdominal cavity ultrasound, this form was found to occur in 0.44% of the general population [2]. In respect to sex, AML occurs 2–4 times more frequently in women [6]. Sporadic forms of AML are observed most frequently in older patients; the average age at diagnosis is about 60 years in both sexes [2]. Sporadic AML in patients younger than 20 years constitutes only about 3.5% of all cases [2]. The AML form associated with tuberous sclerosis occurs very commonly in this group of patients, and its presence is a major criterium for diagnosis of TSC [8, 9]. In the TOSCA trial (TuberOus SClerosis registry to increase disease Awareness), including clinical data from 2216 patients with tuberous sclerosis, AML were present in 51.8%, and among these 88.4% were multiple, and the median age at diagnosis was 12 years [9]. AML associated with tuberous sclerosis are larger than sporadic forms and more often show a tendency to grow [6]. The epithelioid AML subtype (EAML) is characterised by a lower age at diagnosis than the sporadic form, namely approx. 38–41 years [6, 7]. In contrast to the classical AML form, more frequent occurrence in women is not the rule [7]. EAML with atypical epithelioid cells is considered to have a poorer prognosis because of its potential for an unfavourable clinical course [7, 10, 11]. Local recurrences after resection or distant metastases are observed in 18.5–30% of cases [7, 12]. Characteristics indicating a high risk of recurrence or distant metastases have not been unequivocally determined so far because of differing research results and the rarity of this disease entity. The papers available in the literature concerning clinical and pathomorphological characteristics of EAML and factors correlating with a malignant course have been summarised in Table 1.

Anatomic location

Sporadic AML is most commonly localised in the kidney, constituting 0.3–3% of kidney tumours, and is at the same time the most common benign tumour in this anatomical location [18]. AML in general occurs in the form of single sharply delimited asymptomatic tumours, less commonly (5.2%) in multiple forms, and approximately 1.5% occur bilaterally [2, 19]. AML occurs with equal frequency in both kidneys, generally localising in the kidney cortex or in a subcapsular location, and in about 25% of the cases within the kidney capsule and the perirenal fat tissue [2, 20]. In patients with tuberous sclerosis AML localised within kidneys often occur in multiple forms — in one of the analyses, in 76% of patients more than 20 changes were present simultaneously [8]. In such patients they significantly more often show a tendency for growth and in a higher percentage result in complications in the form of intratumoral bleeding, haematuria, or pain [21]. AML, similarly as other tumours of renal origin, can penetrate into the renal veins and the inferior vena cava — a case has even been described of an AML reaching the right atrium of the heart [22]. Fragments of the AML tumour may thus form embolisms [23]. Sporadic extrarenal AML are most commonly localised in the liver [24]. AML localised in the liver also occur in approx. 15% of patients with tuberous sclerosis, with a predominance of the female sex, in the form of asymptomatic tumours several millimetres in size [25]. Single cases of sporadic AML have been described in such locations as: the retroperitoneal space [26], spleen [27], duodenum [28], stomach [29], vagina [30, 31], vulva [32], ovary [33], uterus [34], spermatic cord [35], scrotum [36], palate [37], nasal cavity [38], maxillary sinus [39], cheek mucous membrane [40], auricle [41], parotid salivary gland [42], anterior mediastinum [43, 44], adrenal glands [45], skin [46], tibia [47], or rib [48]. Epithelial AML subtypes, similarly to the classical form, are most commonly localised in the kidney, giving rise to diagnostic difficulties in distinguishing this entity from a poorly differentiated renal cell carcinoma [13]. EAML cases with a malignant course outside the kidney have also been described in the liver [49] and in the retroperitoneal space [50]. There is a description in the literature of an EAML developing inside a classical AML [51].

Diagnosis

Angiomyolipoma most commonly occurs in the form of a small (3–38 mm) asymptomatic tumour with an abundant fat tissue content detected during imaging tests performed for other indications [2]. AML occur with equal frequency in both kidneys localising in general within the kidney capsule or in a subcapsular location [2]. In symptomatic cases the following are most commonly observed: pain (6.1%), hypertension (5.7%), bleeding (5.0%), and renal insufficiency (3.9%) [9, 20]. The imaging technique of choice for AML is computed tomography [52]. Angiomyolipoma detected during abdominal cavity computed tomography is visible as a well-delimited tumour localised in the renal parenchymatous layer, most commonly with a low value of the signal, below –30 Hounsfield units (HU), due to the high fat tissue content [53]. Depending on the fat tissue content AML are divided into three main subtypes differing in values on the Hounsfield scale: fat-rich AML (≤ –10 HU), fat-poor

Table 1. Summary of papers concerning clinical and pathomorphological properties of EAML

Author	Number of cases	F:M	Average age (years)	% TSC	Tumour size, [cm]	% epithelioid cells	% necrosis	Malignant cases	Death due to EAML	Characteristics associated with risk of a malignant course
Aydin et al. [6]	15	6.5:1	38.6	26.7%	8 (1–30)	51% (10–100)	27%	1 — metastasis to LN 2 — infiltration kidney vein	0	–
Faraji et al. [13]	69 (6 own, 63 from the literature)	3:1	44 ± 16	26%	10 ± 6	–	67% (for 6 cases)	6 — LR/metastasis to LN 10 — DM	9	Pronounced cellular atypia, extensive necrosis present, male sex
Brimo et al. [12]	40	1.6:1	50.5 (17–81)	–	7.2 (1.0–17.7)	58% (6–100)	37.5%	9	4	≥ 70% atypical epithelioid cells ≥ 2 fp/ /10 HPF, atypical cell division, extensive necrosis present
Nese et al. [14]	41	1:1	40.7 (14–68)	22%	11.9 (2–37)	100%	73%	6 — LR 16 — DM	11	TSC, AML recurrence, extensive necrosis present, tumour diameter > 7 cm, infiltration of surrounding tissues, tumour growth imitating cancer
Yang et al. [15]	27	1:2.4	42	–	9	–	14.8%	1 — DM	0	–
He et al. [16]	20	1.2:1	49.4 (30–80)	–	8.7 (1–25)	At least 80% in each case	50%	1 — DM	0	–
Lei et al. [17]	52	1:1.4	38.4 (24–76)	–	≤ 4 cm: n = 29; 4–10 cm: n = 11; > 10 cm: n = 3	43.8 ± 22.2	82.7%	3 — infiltration renal vein/inferior vena cava 2 — metastases to LN 2 — DM	2	Large tumour size, high epithelioid cell content, pronounced cellular atypia
Delhorme et al. [10]	5	4:1	54 (45–67)	0%	9 (6.3–21)	–	–	1 — LR 3 — DM	3	–
Tsai et al. [67]	23	2.3:1	42.8	0%	9.5 (1.3–18)	–	57%	4 — infiltration renal vein/inferior vena cava 2 — DM	0	Pronounced nuclear atypia, extensive necrosis present

F:M — ratio of cases in women to men; DM — distant metastases; LN — lymph node; LR — local recurrence; % TSC — frequency of patients with coexisting tuberous sclerosis; necrosis — average necrosis content, % of epithelioid cells — average content of epithelioid cells

Table 2. Diagnostic criteria for tuberous sclerosis, on the basis of [64]

Major symptoms	Minor symptoms
Facial angiofibroma or flat forehead fibromas	Multiple enamel losses
Atraumatic nail fibromas	Anal polyps
> 3 colourless naevi	Bone cysts
Shagreen patches	White brain matter migration foci
Multiple retinal hamartomas	Gum fibromas
Cortical cerebral tumours	Hamartoma with non-kidney localisation
Periventricular subependymal cerebral tumours	Changes in eye retina
Giant cell astrocytoma	Skin changes of the confetti type
Heart rhabdomyoma	Multiple kidney cysts
Pulomonary lymhangioleiomyomatosis	
Renal angiomyolipoma	

Certain diagnosis: occurrence of 2 major symptoms or 1 major and 2 minor
Probable diagnosis: occurrence of 1 major and 1 minor symptom
Possible diagnosis: occurrence of 1 major symptom or ≥ 2 minor symptoms

AML (> –10 HU; tumour:spleen coefficient < 0.71; signal intensity index > 16.5%), and AML with no fat content (fat-invisible) (> –10 HU; tumour:spleen coefficient > 0.71; signal intensity index < 16.5%) [54]. The low-fat form may pose diagnostic difficulties because the low fat tissue content makes it difficult to distinguish from renal cell carcinoma [55]. In one of the analyses, in 4.8% patients who had undergone partial nephrectomy because of a kidney tumour with a diameter of ≤ 4 cm and had a suspicion of renal cell carcinoma, a final diagnosis of low-fat AML was made [56]. Similarly, epithelioid AML subtypes localised in the liver, constituting for approx. 4% of liver AML [57], pose diagnostic difficulties in distinguishing them from hepatocellular carcinoma because both disease entities during analysis using contrast are enhanced in the arterial phase [57, 58]. Currently, many models are being elaborated to distinguish these different entities; for example, the BEARS scale (BEnign Angiomyolipoma Renal Susceptibility), in which female sex, age < 56 years, and tumour diameter < 2 cm suggest a low-fat AML [56] as well as informatic models [59, 60]. In patients with renal insufficiency, magnetic resonance not requiring contrast is to be applied in AML diagnosis where hyperintense foci in T1-dependent images are characteristic without fat tissue suppression and hypointensive with fat tissue suppression [61]. In spite of several reports about the potential utility of the chemical shift in magnetic resonance analysis, this was not confirmed in a meta-analysis encompassing 11 papers concerning this problem [62].

In patients with tuberous sclerosis, because of the common occurrence of low-fat angiomyolipoma, the lack of fat in the tumour mass is not considered as a sufficient factor for performing a biopsy, which should be considered in the case of the presence of calcification, central necrosis, rapid growth, or the presence of a single lesion with a low fat tissue content [63]. Multiple kidney angiomyolipomas are an important element of the clinical picture of patients with tuberous sclerosis (TSC diagnostic criteria are presented in Table 2). In spite of the frequent presence of multiple AML, in over 80% of cases such patients remain asymptomatic [9]. However, because of the increased risk of progression and development of renal insufficiency, their long-term monitoring is necessary. In asymptomatic patients with at least one AML > 4 cm, measurement of creatinine concentrations and TK/MRI are recommended every two years [63]. It is evaluated that in asymptomatic patients without kidney anomalies or AML < 4 cm, monitoring (TK/MRI) and kidney function evaluation may be gradually reduced if the results are stable [63]. The appearance of symptoms indicating kidney complications (pain, feeling of heaviness in the abdominal cavity, haematuria, shock) require immediate TK/MRI imaging [63].

Pathomorphology

A classical angiomyolipoma is a mesenchymal tumour with a non-infiltrating type of growth [1]. It is composed in various proportions of three components: dysmorphic sinuous blood vessels, elongated cells resembling smooth myocytes, and extended epithelioid perivascular cells with abundant lipids, with fat tissue morphology [65]. Depending on the content of lipid-rich cells, an AML fat-poor form is distinguished in which these cells constitute less than 25% of the visual field, and the smooth muscle cell component is dominant [66]. AML localised in the liver are characterised by

the content of a component resembling smooth muscle, which is higher than in classical AML [24]; necrosis and an infiltrating type of growth are more commonly observed [49].

Epithelioid AML (EAML) is characterised by the presence of epithelioid cells with various degrees of nuclear atypia [67]. Giant epithelioid cells, present as groups, may attain a diameter as large as 1 mm, and these are cells with numerous hyperchromatic nuclei with distinct nucleoli [13]. Epithelioid cells are frequently accompanied by the presence of necrosis and the mitotic index of these tumours is generally low — from one to three division figures per 10 large visual fields [13]. Very rarely (approximately 20 known cases) AML with the presence of multiple cysts is observed (angiomyolipoma with epithelial cysts; AMLEC), which indicates a benign course [68] with a cystic morphology [69]. In single cases an extensive infiltration of AML by immune system cells is observed, distinguishing an inflammatory AML subtype (inflammatory angiomyolipoma) [70]. Exceptionally, cases have been described of the occurrence inside AML of other neoplasms: angiosarcoma [71] and renal cell carcinoma (RCC) in a patient with tuberous sclerosis [72].

In immunohistochemical analysis the classical AML subtype shows a strong expression of melanocyte markers: HMB-45 and Melan A in all three tumour components: blood vessels, fat tissue, and smooth muscle, in which at least one of the above-mentioned markers is present in each case [73]. Moreover, frequent expression is observed of NK1-C3 (approx. 2/3 of cases), tyrosinase (in approx. one-half of cases), and KIT (CD117) (from one-half to all cases, depending on the reference) [73, 74]. In the case of epithelioid AML, epithelioid cells typically show co-expression of melanocyte: HMB-45 and Melan A and muscle: SMA and calponin [6] markers. Another melanocyte marker, S-100, characteristic for melanoma cells, most frequently is not expressed in epithelioid cells, but in about 1/3 of cases a cytoplasmic reaction is observed [6]. Moreover, a diffuse expression is observed for: cathepsin K, D2-40 (podoplanin) and progesterone and oestrogen receptors and vimentin [13]. A strong expression of the CD68 marker has also been observed (among others also a macrophage marker), which, because of the lack of its expression in renal cell carcinoma, can be useful in distinguishing these two entities [75]. Cytoplasmic expression of E-cadherin is present both in classical and in epithelioid AML, and in the latter is localised both in the membrane and in the cytoplasm [76]. Stronger diffuse expression of p53 and weaker membrane expression of E-cadherin have been described as characterising cases of malignant EAML, in comparison with other EAML with a benign course [77].

Classical AML with a typical structure composed of muscle tissue, fat tissue, and blood vessels is easy to distinguish from other entities (Figures 1, 3), but its epithelioid subtype may pose diagnostic difficulties (Figure 2).

Differential diagnosis of EAML encompasses poorly differentiated tumours with a frequent localisation within the kidneys or the liver, such as: malignant melanoma metastases, gastrointestinal stromal tumours (GIST), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), adrenocortical carcinoma (ACC), and kidney oncocytoma [78]. Microscopic and immunohistochemical characteristics distinguishing these entities are summarised in Table 3.

Genetics

AML typically occurs in patients with tuberous sclerosis, a genetic syndrome caused by inactivating germline mutations within the *TSC2* gene at locus 16p13.3 or less frequently *TSC1* at locus 9q34 [81]. These genes encode tuberin and hamartin, respectively, which are proteins forming a complex with GTPase activity, with an inhibitory action on the signalling mTORC1 complex [82]. The lack of suppressor activity caused by their mutations causes excessive activity of the mTOR pathway, stimulating proliferation and in effect neoplasm formation. In the TOSCA trial a difference in AML occurrence was found depending on the mutated gene; AML occurs in 33.3% of patients with the *TSC1* mutation and in 59.2% with the *TSC2* mutation [9]. Correlation between the mutation of a distinct gene and the clinical course is not clear [83]. Somatic deletions in the *TSC2* locus are observed in sporadic cases of angiomyolipomas [84], leading to, similarly as in tuberous sclerosis, an increased activity of the mTORC1 complex [85]. Moreover, 0.3% of patients with AML, lymphangioma, and tuberous sclerosis were found to have a codon 72 (R73) polymorphism of the *TP53* gene, and the presence of this polymorphism was linked to an increased risk of AML development [86]. Moreover, a case has been described of a generally healthy woman with bilateral classical AML and multiple uterine fibroids with a balanced 46,XX,t(11; 12)(p15.4;q15) translocation, whose effect could have been the separation of the promoter and the transcription initiation site from the rest of the *NUP98* gene, which had not earlier been associated with the PEComa family, but its fusions are frequently present in haematological neoplasms [87]. In the case of malignant epithelioid AML, other genetic perturbations are also noted, e.g. in two patients with advanced EAML in metastatic tumours a strong expression of MDM2, a ubiquitin ligase participating in the degradation of p53 suppressor protein, has been described, as

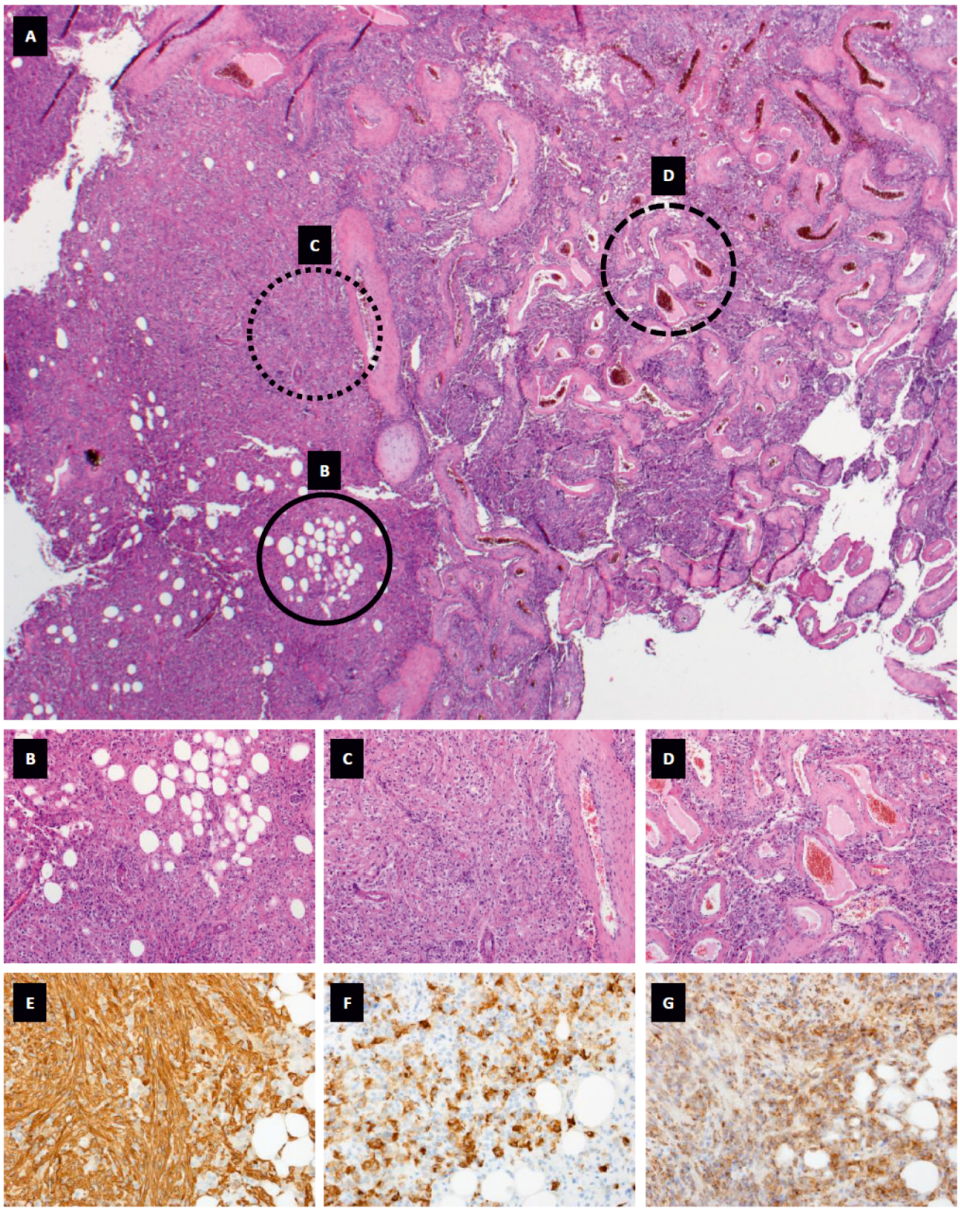

Figure 3. Kidney angiomyolipoma. **A.** According to its name, the tumour contains vessels, smooth muscle, and fat cells [HE, 20×]; **B.** Visible texture of mature fat tissue without atypia characteristics [HE, 200×]; **C.** Solid fragments of the tumour with smooth muscle texture [HE, 200×]; **D.** Sinuous, thick-walled, and partly hyalinised blood vessels [HE, 200×]; **E. F. G.** Panel of characteristic immunochemical staining for angiomyolipomas: successively SMA, HMB-45, and Cathepsin K [HE, 200×]

well as its absence in primary tumours [88, 89]. Further analysis using the FISH method indicated amplification of the *MDM2* gene in part of the cells derived from metastatic tumours, indicating the potential role of *MDM2* in the acquisition of a malignant phenotype by EAML cells. A case of a malignant EAML has been noted with an amplification of the *TFE3* gene, encoding a transcription factor regulated among others by the mTOR kinase, whose fusions and amplifications are frequently observed in malignant PEComa [62].

Classical AML — treatment and prognosis

The majority of sporadic AML are benign and are detected accidentally during imaging tests performed for other indications, remaining asymptomatic and not showing growth [2], thus the treatment of choice is conservative [90]. However, because these tumours can reach large sizes and have a rich blood supply, they may give rise to many complications, the most common being

Table 3. Differential diagnosis of EAML (based on [78–80])

Unit	Microscopic	Immunohistochemical markers						
		HMB-45	Melan-A	S-100	CD-117	Keratins	SMA	Other
EAML	Areas with classical AML morphology, tumour with high cellularity with cells of the histiocyte type; considerable cellular atypia; few divisions. Large nuclei with distinct nucleolus	+	+	±	+	±	±	CD68
ACC	Cells from well differentiated to anaplastic with hyperchromatic, atypical nuclei; considerable mitotic activity with atypical divisions	–	+	±	±	±	–	Inhibin A, calretinin, synaptophysin, SF1, bcl2, p53
RO	Round or polyhedric cells with acidophilic granular cytoplasm. Centrally located nucleus with evenly distributed chromatin	–	–	+	+	+	–	CK8/18, CK14
GIST	Epithelioid and fusiform cells with light, acidophilic cytoplasm without granulosities	–	–	±	+	±	±	DOG1
HCC	Barrel-like distribution of cells with abundant, acidophilic, granular cytoplasm, presence of SINUS vessels	–	–	–	±	+	–	HepPar1, CEA, AFP
RCC	Heterogeneous cell population with differentiated levels of atypia, presence of small cytoplasmic vacuoles; hemosiderin deposits	–	–	±	+	+	–	PAX8, PAX2, CD10, CAIX, RCC, CD63; TF-EB in RCC t(6;11); TFE3 in RCC (X;1p11)/TFE3
M	Cells with many shapes Distinct nucleoli absent	+	+	+	+	±	±	SOX10, BRAF

ACC — adrenocortical carcinoma; HCC — hepatocellular carcinoma; GIST — gastrointestinal stromal tumour; M — melanoma; RCC — renal cell carcinoma; RO — renal oncocytoma

bleeding. Kidney AML are the most common cause of bleeding into the retroperitoneal space not linked to injury [11]. A large size of the tumour (diameter over 3.5–4 cm) is believed to be the main predisposing factor for this complication, significantly increasing the need for invasive procedures [91]. Correlation between the tumour size and the probability of bleeding has, however, been described as unclear in a current, large, systematic review [92]. Other risk factors for bleeding include: the presence of an aneurysm within the tumour, pregnancy, anticoagulation therapy, or injury, even of a low intensity [93]. In sporadic cases independent predictors of tumour growth were shown to be blood group 0 ($p = 0.038$) and De Ritis index (AspAT/AlAT) ≥ 1.24 ($p = 0.047$) [94]. In patients with tuberous sclerosis, the presence of numerous AML taking up most of the parenchyma of both kidneys leads to gradual increase in kidney insufficiency to end-stage insufficiency in as many as 7% of patients [95]. AML progression during successive control visits occurs in about 20% of patients with tuberous sclerosis, and in patients older than 40 years almost one-half require a medical intervention for this reason [9]. This is linked to the need for frequent hospitalisations, in effect lowering the quality of life of these patients [96].

AML — surgical treatment

The most appropriate management method for AML is active surveillance (AS) [97]. Sporadic, asymptomatic tumours with a diameter under 4 cm require an ultrasound control every 12 months (for 2–5 successive years), which in the case of a lack of tumour progression can be limited, whereas tumours with a diameter of under 2 cm are considered in the literature as not requiring controls because of a minimal risk of complications [98]. Asymptomatic sporadic AML with a diameter over 4 cm require more frequent ultrasound controls — every 6 months, because of an increased risk of tumour bleeding and growth [99]. Progression or spontaneous bleeding into the retroperitoneal space is, however, observed only in a small percentage of cases, respectively: 11% and 2% [92]. Of decisive importance for therapeutic decisions

is the tumour size, presence of symptoms (e.g. pain in the tumour projection, haematuria), and a suspicion of malignancy, which correlate with a risk of occurrence of bleeding into the retroperitoneal space [92]. Prophylactic treatment should also be applied in women who are planning a pregnancy, and with AML with a diameter > 4 cm [93]. At the same time, a large tumour size, traditionally taken as a diameter > 4 cm, without other risk factors for bleeding should not determine the need for undertaking prophylactic actions in the form of embolisation or resection [92], because only 1/3 of patients with tumours > 4 cm in diameter will require active therapy [99]. If spontaneous bleeding into the retroperitoneal space or haematuria occur, the presence of a large tumour or clinical symptoms (most commonly pain in the tumour projection) or radiological metastatic characteristics, various therapeutic approaches can be applied: embolisation, ablative techniques, nephron-sparing surgery (NSS), and in selected cases radical nephrectomy is required [90, 92]. If active surveillance has to be interrupted, the treatment of choice is selective arterial embolisation (SAE) [97], as a minimally invasive procedure with optimal maintenance of the function of the affected kidney [100]. Moreover, embolisation, in comparison to resection, is linked to less frequent complications and a reduction in tumour size in most cases, even though in approx. 40–50% of patients the intervention may need to be repeated because of recanalisation or development of new blood vessels [100, 101]. Further AML growth is rarely observed after embolisation; it is linked to the growth of the vascular component of the tumour — these cases require a confirmation of the AML diagnosis [100]. A surgical procedure should only be used in cases where embolisation is not attainable or is technically/anatomically impossible, and it should be as sparing as possible [97]. The use of surgical techniques is linked with frequent occurrence of complications but also with a lower risk of local recurrence [100]. Moreover, partial nephrectomy is considered as a preferred solution in the case of AML of considerable size (> 8 cm diameter) because of their rich vasculature, making embolisation of large tumours complicated and less effective [101], as well as in women with an advanced pregnancy [93].

AML associated with tuberous sclerosis require different procedures because of the frequent tendency of the tumours to grow, spontaneous bleeding into the retroperitoneal space, and the potential development of renal insufficiency. In adult asymptomatic patients with large AML (> 4 cm) it is recommended that the creatinine level be analysed and a control TK/MRI be performed every 1–2 years, whereas asymptomatic patients with smaller tumours can be checked less frequently if their results are stable [63, 102, 103]. The appearance of symptoms indicating kidney complications (pain, feeling of heaviness in the abdominal cavity, haematuria, shock) require immediate imaging diagnosis [63]. Preventive procedures in patients with tuberous sclerosis are recommended in asymptomatic AML with many risk factors for bleeding: size > 8 cm, dominant vascular component, and presence of microaneurysms, and they may be considered in patients with AML > 4 cm when other risk factors are present, e.g. risk of injury in the pelvic area, planned pregnancy, or taking anticoagulants [63]. With increasing frequency for AML associated with tuberous sclerosis, in the scope of bleeding prophylaxis, the use of mTOR inhibitors is recommended as first-line treatment instead of embolisation [104].

AML — systemic treatment

Because of the increased activity of the mTORC1 complex observed in angiomyolipomas, both in cases associated with tuberous sclerosis and with lymphangioleiomyomatosis, over a dozen clinical trials have been performed on the use of mTOR inhibitors in these patients, which have yielded positive results. This led to confirmation by the European Medicines Agency (EMA) in 2011 and the Food and Drug Administration (FDA) in 2012 of everolimus to treat kidney AML in adult patients with tuberous sclerosis, who do not require urgent surgical treatment but are at risk of complications evaluated on the basis of tumour size, the presence of multiple or bilateral tumours, and aneurysms within the tumours. The principles for everolimus use in adult patients with AML in the course of tuberous sclerosis are summarised in Table 4. In the case of impossibility to use a registered drug or the need for therapy of paediatric patients, the use of sirolimus can be considered [63], due to literature references showing its efficacy [105, 106].

One of the first trials of the use of everolimus in patients with tuberous sclerosis was a phase 3 randomised clinical trial EXIST-1 (EXamining everolimus In a Study of Tuberous sclerosis complex 1), encompassing 117 patients with tuberous sclerosis and simultaneous presence of a subependymal giant cell astrocytoma (SEGA) [107]. A decrease in AML volume occurred in 53.3% of patients treated with everolimus, in comparison to 0% of responses in the placebo group. For the largest of the performed trials — a randomised double-blind phase 3 trial EXIST-2 (EXamining everolimus In a Study of Tuberous sclerosis complex 2) — 118 patients with AML with a diameter ≥ 3 cm and tuberous sclerosis or accompanying lymphangioleiomyomatosis were recruited [108]. Seventy-nine patients received everolimus at a dose of 10 mg *p.o.* (median observation time 38 weeks), and treatment response (defined as decrease in tumour mass by at least 50% in relation to the initial size) was observed in 42% of patients receiving everolimus and in none of the patients receiving placebo. Median time until

Table 4. Principles of everolimus therapy in AML in adult patients with tuberous sclerosis (on the basis of [63])

Standard dose		1 × 10 mg/day
With liver insufficiency	A according to Child and Pugh scale	1 × 7.5 mg/day
	B according to Child and Pugh scale	1 × 5 mg/day
	C according to Child and Pugh scale	Max 1 × 2.5 mg/day

- Everolimus is a substrate for the CYP3A4 isoenzyme and glycoprotein P. Inhibitors of CYP3A4 and glycoprotein P may increase its concentration in blood, and inductors may decrease it
- The lowest effective dose should be used with acceptable adverse effects
- Treatment should be continued as long as clinical benefits are observed or until unacceptable toxicity occurs
- Live vaccine use should be avoided
- In the case of simultaneous use of an inhibitor of angiotensin convertase (ACE) — increased risk of angioedema

response to treatment was 2.9 months. After finishing the EXIST-2 trial, on the basis of its promising results, observation of successive patients recruited to the everolimus arm was continued [102]. A decrease in tumour diameter by over a half was observed in 58% of patients, and in 95% some decrease in tumour diameter was seen. Disease progression was observed in 16 patients, among whom in 13 taking of the drug was perturbed because of the occurrence of adverse effects or noncompliance. Retrospective analysis of data from the EXIST-1 and EXIST-2 trials also showed a long-term stabilisation of the glomerular filtration rate during everolimus therapy [109]. In 43.8% of patients who finished treatment after the EXIST-2 trial, AML progression was observed in the form of tumour growth or haemorrhage, but without evidence for increased growth after drug withdrawal [110]. Responses to everolimus treatment, in the form of a decrease in AML size, were also observed in a retrospective analysis of data from the EXIST-1 trial in 33 paediatric patients [111]. In 75.8% (CI: 57.7–88.9%) of patients an objective response was found in the form of a decrease in tumour volume, which was maintained during almost four years of observation. Moreover, in 80% of them the decrease in tumour volume was over 50%. A subsequent nonrandomised, open clinical trial, including 18 patients with TSC, indicated a decrease in AML volume by one-half in 66.67% of cases after a year of receiving everolimus [112]. Similarly as in the EXIST-2 trial, after withdrawal of the drug, a small increase in tumour size was observed — to the value before the beginning of the trial (average tumour volume 12 months after drug withdrawal 77.62 ± 16.66% of the initial value). In a retrospective analysis comparing clinical data of 72 patients with tuberous sclerosis and kidney AML, a significant reduction in size of kidney tumour (85.2% *vs.* 37.9%; p = 0.0003) and a tendency to a lower decrease of the eGFR value were observed (44.4% *vs.* 66.7% of the initial value, p = 0.0840) in 33 patients receiving everolimus in relation to patients only undergoing observation [113]. For better control of adverse effects, due to the need for chronic drug intake, a trial was performed evaluating use of everolimus in an intermittent fashion, in which patients with TSC interrupted the taking of the drug in cases of maintained partial response, and went back on the drug when the size of the tumour reached 70% of the initial value [114]. The average decrease in tumour volume in response to renewal of the treatment was 61% and did not differ significantly from the primary response. There are also reports on long-term, four-year responses to everolimus in a lower dose (2.5–5 mg/d *p.o.*) than is commonly used [115]. The effectiveness of everolimus use was also observed in the case of very large tumours (the largest size over 20 cm in two cases and over 12 cm in a third case) associated with TSC [116]. Moreover, everolimus turned out to be effective as a second-line treatment in the case of AML progression after arterial vessel embolisation [117]. Reduction of tumour volume by over 50% was obtained in 57% of the 14 investigated cases, and the average volume decrease was 53%. It was observed that the rate of reduction of tumour size in response to everolimus depends on its tissue composition — tumours with a rich vasculature and developed smooth muscle shrink over two times faster than tumours composed mainly of fat tissue [118]. This effect is reflected in the change in AML composition during everolimus therapy: the rich vasculature disappears and the relative fat content increases, causing a decrease in the CNR value (contrast to noise ratio) of the tumour image in magnetic resonance [119]. Some nonrandomised open clinical trials have also been conducted on the use of sirolimus in patients with kidney AML and TSC or lymphangioma. In a systematic review including four of these trials [120–123] response to treatment according to RECIST was found in 45.7% patients during one year of therapy and 43.5% in the second year [105]. Among patients who no longer received the drug during the second year of observation, objective response was maintained only in 5%. Excessive activation of the mTORC1 complex, associated, among other things, with somatic mutations inactivating the *TSC2* gene, were also found in sporadic AML, and single reports indicate similar benefits of

using mTOR inhibitors in these patients [85]. However, clinical trials concerning systemic treatment of sporadic AML cases have not been performed.

EAML — treatment and prognosis

The epithelioid AML subtype (EAML) is associated with an uncertain prognosis and the possibility of a malignant clinical course. In rare cases EAML show a tendency for local recurrence or distant metastases, even 12 years after primary tumour resection [124] (Figure 2). In an investigation comparing the clinical course of classical AML and EAML, among 27 patients with EAML, distant metastases occurred in five, and three of them died during the observation. At the same time among 204 patients with classical AML no distant metastases or death due to the disease took place [7]. In another analysis an unfavourable course of the disease (defined as death because of the disease, distant metastases or metastases to local lymph nodes, infiltration of the kidney vein, or local recurrence) was observed in 40% patients with EAML [13]. However, the exact percentage of EAML with a malignant course remains difficult to evaluate, due to the few groups of patients in accessible trials and papers indicating a much smaller scale of the problem, e.g. lack of local recurrence or distant metastases in all analysed EAML cases [6] or the occurrence of distant metastases in only one among 20 patients with EAML [16]. In a systematic review concerning the clinical course of liver EAML, local recurrence after resection was found in 2.4% of cases (6/247), and death due to the disease in 0.8% of cases (2/247) [125]. Factors increasing the probability of finding AML with an epithelioid morphology include a younger age of the patient [6, 7], male sex (OR = 3.33 [7]) and tumour diameter > 4 cm ([OR = 3.8 [7]). EAML diagnosis has been linked with a significantly shorter three-year overall survival (OS) and three-year disease-free survival (DFS) — 50% and 0%, respectively, in comparison to classical AML — OS 100% and DFS 100% [10]. In the same analysis negative prognostic factors for OS were as follows: the EAML subtype, low fat tissue content in the tumour, a broadening of the kidney vein, and insufficient tumour resection. Selection of patients at risk of a malignant course of EAML requires appropriate use of radical surgical treatment and consideration of systemic therapy. However, knowledge concerning the prognosis of a potentially unfavourable disease course is limited. In an investigation including 40 cases of EAML with characteristics of nuclear atypia, it was evaluated that if it fulfils three of four criteria (70% or more atypical epithelial cells, two or more cell divisions in 10 HPF, atypical cell divisions, presence of necrosis), this significantly increases the risk of a malignant course [12]. Another analysis, in which a review of the literature was made (17 EAML cases) and two of the authors' own cases were included, indicated that a significantly increased risk of a malignant character of the tumour is indicated by finding at least five of the following characteristics: diameter ≥ 5 cm, presence of metastases, infiltrating type of growth, the presence of necrosis, at least 50% atypical epithelioid cells, cellular atypia, atypical mitoses, and invasion of vessels [126]. In an analysis of 53 EAML cases, in which in three patients distant metastases occurred, tumours with progression differed from those with a benign course in size — respectively, 10 *vs*. 3.3 cm ($p < 0.001$), epithelioid cell content 83.3 *vs.* 40.9% ($p = 0.001$), and cells with atypia 76.7 *vs*. 24.8 % ($p < 0.001$) [17]. Correlation between tumour size and the number of cell division figures and the ability of EAML to form metastases was, however, not confirmed in another analysis encompassing 23 cases, in which an unfavourable course of the disease was only associated with nuclear atypia and the presence of necrosis [67]. An attempt to classify kidney EAML was made in a trial encompassing 41 patients, dividing tumours into three risk categories on the basis of five characteristics: concomitant tuberous sclerosis, presence of necrosis, renal vein infiltration, infiltrating tumour growth, and tumour diameter > 7 cm [14]. Tumours with more than two characteristics are considered low risk (15% of patients underwent progression), tumours with 2–3 characteristics are considered average risk (64% progression), whereas tumours with four or more characteristics underwent progression in all cases.

EAML treatment

The basis of EAML treatment is radical resection; complete removal of the tumour, even a malignant one, ensures a high percentage of cured cases: from 74% [12] to 100% [6]. In the case of hepatic EAML the most common treatment modality is open surgery [125], although there are reports in the literature of complete removal of hepatic EAML using laparoscopic techniques [57, 127]. Cases of local non-resectable recurrences and distant metastases indicate the need for long-term observation of patients with EAML with malignant properties and of establishing standards of systemic treatment in non-resectable cases. EAML most commonly are resistant to standard chemotherapy with a few exceptions described in the literature, e.g. a stabilisation of the disease lasting several months in response to six cycles of dacarbazine with cisplatin [128]. Similarly as other tumours from this group, epithelioid AML subtypes show an increased activity of the mTORC1 complex and mutations that inactivate *TSC2* [129]. So far, no clinical trials have been performed on the use of mTOR inhibitors in EAML. Over a dozen cases are available in the literature (summarised in Table 5)

Table 5. Cases from the literature of mTOR inhibitor use in systemic therapy

Author	Sex	Age (years)	Localization	Size [cm]	TSC/ /LAM	Somatic mutation	Local recurrence (LR)/ /metastasis (Met)	Radical treatment	Drug	Dose	Best response	Time to progression (months)	Follow-up (months)	Effect
Higa et al. [130]	F	26	Liver	–	LAM	NA	Met: lungs	R	Sirolimus	2 mg/d *p.o.*	PD	4	10	DOD
Wolff et al. [131]	M	24	Kidney	24	TSC	NA	LR	RN	Sirolimus	6 mg/d *p.o.*	PR	NO	12	AWD
	M	72	Kidney	14	–	NA	LR; Met: liver	RN, M	Temsirolimus	–	PR	NO	11	AWD
Shitara et al. [132]	M	52	Kidney	–	TSC	NA	Multiple Met to abdominal cavity	RN	Everolimus	10 mg/d *p.o.*	PR	NO	7	AWD
Kohno et al. [133]	F	50	Kidney	–	–	NA	Met: lungs, liver, pelvis	RN, M	Everolimus	10 mg/d *p.o.*	PR	NO;	6	AWD
											PD	4	4	
									Temsirolimus	–	PR	NO	1	
Faria et al. [134]	M	58	Kidney	5	–	NA	LR	RN	Everolimus	–	PR	NO	4	DOT
Wyluda et al. [135]	F	31	Kidney	–	–	NA	Met: mediastinum	RN	Temsirolimus	–	–	12	17	DOD
Hong et al. [136]	M	58	Kidney	–	–	non. *SMARCB1*	LR; Met: liver, multiple to abdominal cavity	RN, M + RTH	Temsirolimus	25 mg *i.v.* on day 1 and 8/m	PR	8	8	AWD
									Everolimus	7.5 mg *p.o.* for 3 weeks/m	PR	NO	2	
Binyamin et al. [137]	M	56	Kidney	11	–	NA	LR; Met to post-surgery scar, bones	PN	Everolimus	–	PD	2	2	AWD
									Pazopanib	–	SD	6	–	
Anwar et al. [138]	F	27	Adrenal	9	–	NA	–	–	Everolimus	2.5 mg/d	PR	NO	1	AWD
Espinosa et al. [129]	M	34	Kidney	12	–	dup. *TSC2*	Met: liver, lumbar vertebrae	RN, M	Sirolimus	6 mg/d *p.o.*	CR	NO	36	NOD
Hulova et al. [139]	F	28	Kidney	15	–	NA	LR; Met: liver, greater omentum	RN, M	Sunitinib	50 mg/d *p.o.* (1 m + 2 week break)	PD	6	6	DOD
									Everolimus	–	SD	60	76	
Lattanzi et al. [140]	M	38	Kidney	6	–	non.*TP53* and *APC*, frameshift *ATRX*, del. *TSC2*	LR; multiple Met to abdominal cavity	R	Everolimus	–	PR	8	8	AWD
									Nivolumab	3 mg/kg *i.v.* every 2 week	PR	NO	24	
Tayal et al. [141]	F	63	Kidney	–	–	Missense in *KIT, FLT 3, KDR, MET*	Met: lungs, liver, bones, abdominal cavity	R	Imatinib	–	PD	4	4	AWD
									Crizotinib	200 mg/d	PD	4	4	
									Everolimus	5 mg/d *p.o.*	PR	NO	17	

Radical treatment (M — metastasectomy, PN — partial nephrectomy, RN — radical nephrectomy, R — resection, RTH — radiotherapy); NA — not analysed; NO — not reached; somatic mutation (del. — deletion, dup. — duplication, non. — nonsense); CR — complete response; PD — progressive disease; PR — partial response; SD — stable disease; effect: AWD — alive with the disease, DOD — dead due to the disease, DOT — dead from other causes, NOD — no evidence of the disease

of using mTOR inhibitors in systemic therapy of patients with EAML, who had multiple non-resectable recurrences of the disease or developed metastases, sometimes showing long-term partial responses. In some cases, the tumours underwent swift progression in spite of the applied treatment, which indicates that other therapeutic targets must be found. Several cases have been described of responses to treatment with tyrosine kinase inhibitors: a six-month stabilisation of the disease after pazopanib [137] and decrease in the size of EAML metastases to the liver, maintained for over seven months after using apatinib [142]. In the literature there is also a report about a persistent, almost complete response in a patient with recurring and disseminated epithelioid AML after two years of treatment with nivolumab in the second line after therapy with everolimus [140]. Staining of tissues derived from the primary tumour showed a strong expression of PD-L1 (over 50% cells) and the presence of infiltrating T CD8(+) lymphocytes.

Summary

Angiomyolipoma (AML) is a benign mesenchymal tumour, which may occur sporadically or in the frame of tuberous sclerosis and lymphangioleiomyomatosis. The sporadic form is the most common form of benign kidney tumour and occurs four times more frequently in women. Renal tumours of the AML type are most commonly detected during abdominal ultrasound scans, computed tomography, or magnetic resonance. In abdominal cavity ultrasound scans they are visible as hyperechogenic tumours and in most cases do not pose a diagnostic problem. The most important diagnostic method in the case of AML is computed tomography, which is performed in patients with the suspicion of a tumour on the basis of an abdominal cavity ultrasound scan. AML growth is slow and complications are rare. The main AML complication may be bleeding to the retroperitoneal space or the pelvicalyceal system. Only the epithelioid AML variant has a malignant potential. The most appropriate management method of AML is active surveillance (AS). Asymptomatic tumours with a diameter below 4 cm require an ultrasound control every 12 months, whereas tumours with a diameter of under 2 cm are considered in the literature as not requiring controls. Asymptomatic sporadic AML with a diameter over 4 cm require more frequent ultrasound controls — every six months. Of decisive importance for therapeutic decisions is the tumour size, the presence of symptoms (e.g. pain in the tumour projection, haematuria), planned pregnancy, and a suspicion of malignancy. Options for active treatment include: embolisation, ablation techniques, nephron-sparing surgery (NSS), and radical nephrectomy. In adult patients with tuberous sclerosis, who require treatment but do not require rapid surgical treatment, everolimus is used. In the case of AML, initially doses of 1 × 10 mg per day should be used (an appropriate dose decrease is required in the case of liver insufficiency). The treatment should be individualised by determining the lowest effective dose with acceptable adverse effects. In the case of AML subtypes with a malignant course attempts are made to use classical chemotherapy, mTOR inhibitors, or VEGFR inhibitors (pazopanib, apatinib), obtaining objective responses only in some of the patients.

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VIA MEDICA

REVIEW ARTICLE

Kazimierz Drosik

Randomized clinical studies — science, belief or advertisement only

Address for correspondence:
Dr n. med. Kazimierz Drosik
ul. 28 Lawendowa, 45–470 Opole
Phone: +48 506 197 837
e-mail: drosik@go2.pl

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ABSTRACT

The results of randomized clinical studies are important in evaluation of drugs' or medical procedures' efficacy. Statistical analyses are meaningful in publications and conference presentations. This paper discusses the role and value of selected statistical methods. It is clear that in clinical studies patients and time to event (recognized as end study point) are essential. According to that the question arises — do all these statistical analyses are important or do they play only a role in drug promotion.

Key words: clinical studies, statistical analyses

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Introduction

Randomized clinical trials (RCTs) play the most important role in evaluating new drugs and new treatment methods, as well as in establishing the standards of care. The results of these studies are widely accepted; however, their interpretation may raise some doubts. The main problem is connected with the statistical methods used, which are often poorly understood by the average reader or reluctantly scrutinised due to the unlimited reliance on the authors' interpretation.

The value of new anti-cancer drugs and other treatment methods is assessed in the development process, including different phases of studies having varied aims. The study could be aimed at determining the maximum tolerated dose (MTD), determining drug activity, or evaluating its efficacy in terms of the effect on patient survival.

Cancers constitute serious clinical and social problems because they frequently shorten life expectancy. Therefore, determining the effect of a drug or treatment method on extending overall survival is of key importance. Clinical trials with survival as the study endpoint are therefore the most important, and they generally summarise the results of the earliest phase studies. An alternative to overall survival as an endpoint is time to relapse or time to disease progression. Although there is ongoing discussion about the superiority of one endpoint over another, this is not relevant for the purposes of this publication. It is important that in both cases the time is measured from the patient's entry into the study (in a randomised study it should be the date of randomisation) until the event, which may be relapse, progression, or death. The research methodology is the same at least from a statistical point of view. The differences are only associated with the ability to determine the time of the event — the time of death is a single point in time independent of study assumptions. Recurrence or progression of the disease is also a one-off event in the timeline; however, they are most often diagnosed during pre-planned periods in which subsequent control examinations are performed. If, then, the results of the study are presented in the form of a graph, the curve presenting the time to progression or relapse will have a stepped shape, while the overall survival curve will be continuous. For the above reason, it will be easier to discuss the problem of interpretation of study results based on a model with relapse or disease progression as a study endpoint.

Randomised clinical trials

Stratification and randomisation

The greatest difficulty in planning and conducting a clinical trial with "time-to-event" as a study endpoint

is that it is not possible to determine in advance at which time point the event can or should occur. If it was known how long the untreated patient would survive until the event occurred, it would be easy to show how much longer the survival time would be after using the study drug or other treatment. Each patient participating in the study would be his/her own control. Unfortunately, this is not the case, and therefore the clinical trial is based on a comparison of the results in an "experimental" group of patients with the results in the control group. The basic condition is that the patient groups are so similar that the only difference between the studied and control arm is the drug (combination of drugs) or treatment method used.

It would be best to carry out the study on identical twins, but even in this case it would be doubtful whether all events would be the same and occur at the same time. The questions even arise when the study is conducted with unrelated patients. In order to enrol maximally comparable patients into study arms, the principle of stratification and random assignment of patients to particular study groups (randomisation) was introduced. The purpose of stratification is to evenly separate patients in terms of prognostic factors with a known impact on the occurrence of the endpoint event. Obviously, there are an increasing number of factors that should be included in the stratification, which results from the in-depth knowledge about the biology of a given disease. The goal of randomisation is equal distribution of unknown prognostic factors. It is assumed that due to the random distribution of patients, these factors with an unknown effect on the event will be distributed equally in both arms. By definition, these factors are unknown, which makes it impossible to determine them at a given time and to obtain real comparability of patient characteristics in both study arms. One can only believe that it is so. Instead of proof, there is only the belief that we have proof. It is important at this point to pay attention to the correct qualification of patients for the study. Qualifying patients who do not fully meet the inclusion criteria (not entirely eligible) to enable participation "at all costs" can clearly affect the outcome. There should also be no individualisation of decisions to include patients into the study — the rule is that in the participating site, every patient who meets the inclusion criteria should be qualified if he/she agrees. However, any patient who meets the criteria but is not included in the study, for whatever reason, can affect the final result and the quality of the study. Obviously, it is unacceptable to conduct two or more trials with identical selection criteria. The assignment of patients to different concurrently conducted studies based on the doctor's decision completely distorts the sense of randomisation. This important error is unfortunately difficult to detect; one can only appeal to the ethics of investigators.

Course of the study

The patient enrolled into the study, assigned based on stratification and randomisation to the examined or control arm, receives appropriate treatment — it is a new drug (or combination) or a new method of treatment, and in the control group, for example, this is a standard of care. In the case of a study with relapse or disease progression as an endpoint, follow-up examinations are carried out at regular and predetermined intervals. If the assessed event is found, the patient discontinues the study but continues the toxicity (safety) follow-up period. In the present study this aspect is completely omitted because the methods of toxicity assessment are simple and do not require any special knowledge. Interpretation of effectiveness analyses is a real problem.

In the study assessing the effectiveness there are only two elements: the patient and the time to event. All patients had to meet the inclusion criteria and are therefore similar in each arm. However, it should be remembered that within the same arm the patient population is diversified even in terms of stratifying factors.

As a result of subsequent follow-ups, patients with endpoint events are excluded from further evaluation. It is best to examine this on a simple chart in which the number of patients is on the ordinate axis and the time (time intervals in which follow-ups take place) on the abscissa axis. This would be the simplest and most realistic way to present the study results. There is no need to recover an exemplary clinical trial at this time because it is possible to create many models of such a trial and to make charts based on the above principle. If the charts of some real study would be taken as the basis, a model of this study could be also developed. Although there are no absolute numbers in the presentation of the actual study result, only probability curves, at this moment only the shape of the curve is of special interest. This problem will be explained in a later part of this publication. If instead of the probability the actual number of patients were inserted, then it could be revealed that in both arms the number of patients still living event-free decreases; however, in a positive study the number of patients without an event decreases faster in the control arm. In many studies, however, these differences are not large. Many models could be created and then compared to actually published studies. An example would be a study with an equal number of patients in both arms at baseline. If, for example, during the first two assessments the number of events is equal in both arms, both curves on the graph would overlap. Now it could be supposed that in the third assessment the number of events is higher in the control arm. The curves on the chart will spread apart (so-called curve separation) by a size that is the difference in the number of patients with a given event in the examined and control arms. If in subsequent assessments the number of patients without an event decreases in

both arms by the same amount, then the curves will run in parallel and will be further "separated". This gives the impression that there are still differences between the arms, although in reality there is no difference, because the number of events in both arms is the same. There are only fewer patients without an event in the control arm as much as there were more events in this arm at the third assessment. This is presented in Table 1 and Figure 1. In this model, the difference between events in the A and B arms at the third assessment is 10 patients. When an event in the control arm occurs in the middle patient, the curve for that arm will cut a line from the middle of the ordinates. The curve for the studied arm will cross this line with a delay. It could be concluded that the median time-to-event increased for experimental arm.

Let us perform the next experiment and increase the number of patients in the control arm who had an event at the third assessment. The curves will even more separated, and at the same time the difference between the medians will increase, as shown in Table 2 and Figure 2. It follows that increasing or decreasing the difference between medians depends primarily on the difference in the number of events in both arms. If the time point of assessment in which differences were found were changed (not the third one, but any subsequent one), it will transpire that this does not affect the difference between the medians. Still, this difference will depend only on the differences in the number of events, which is presented in Table 3 and Figure 3. Obviously, it is important that these differences occur in the first half of the total number of patients participating in the study. These differences could be identified during each subsequent assessment, and then the sum of them would affect the median.

So, you can see here that the median is more a measure of the number of events, but not the time at which these events occur.

In the created model there are still two separated curves that run parallel to each other. It is assumed that the curves separated because patients in the experimental arm received more effective treatment. What happens, however, when effective treatment is

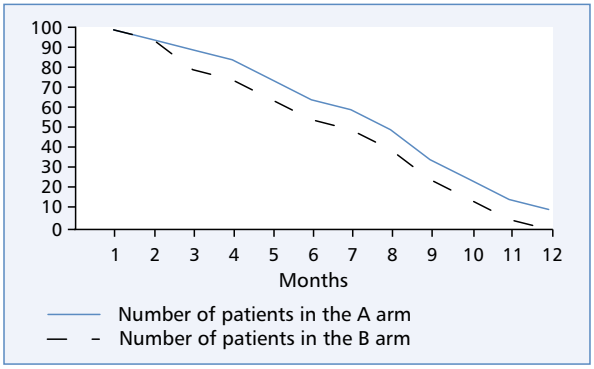

Figure 1. The data are presented in Table 1

Table 1. Columns A1 and B1 present the number of patients starting a given observation period, columns A2 and B2 the number of patients with an event in a given period, and columns A3 and B3 the number of patients without an event at the end of the evaluated period

Months	Number of patients					
	The A arm			The B arm		
	1	2	3	1	2	3
1	100	0	100	100	0	100
2	100	5	95	100	5	95
3	95	5	90	95	15	80
4	90	5	85	80	5	75
5	85	10	75	75	10	65
6	75	10	65	65	10	55
7	65	5	60	55	5	50
8	60	10	50	50	10	40
9	50	15	35	40	15	25
10	35	10	25	25	10	15
11	25	10	15	15	10	5
12	15	5	10	5	5	0

only applied to patients in the control group, who have caused a difference in the number of events in the third assessment (first example) or in the subsequent assessment (second example)? If this treatment is more effective then there should be no events in these patients, and the curve in the control arm will not move down (both curves will still overlap). The above situation confirms the statement that a small number of patients may decide on the final study result. If the final result of the study were presented in absolute numbers, as in the proposed models, there would be clarity as to the actual effectiveness of the new drug, combination of drugs, or another new treatment method. The result would be visible on these simple charts without using any statistics.

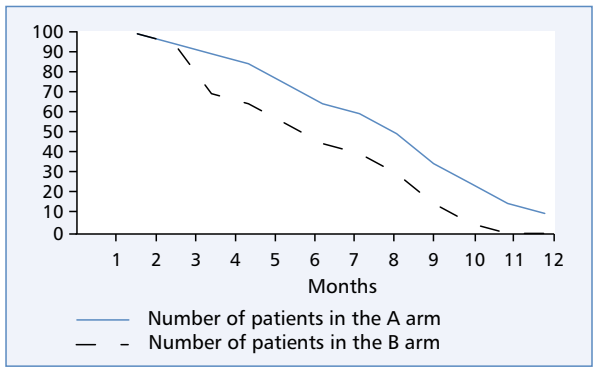

Figure 2. The data are presented in Table 2

Finally, it is worth checking on the models the number of possibilities for running of event curves for the same median difference. In each case it could be found that it always depends on the number of events (not always the time point at which these events occurred).

In publications presenting the result of a clinical trial in the form of graphs of overall survival or time to another endpoint the probability curves are shown instead of absolute numbers.

Kaplan-Meier estimator

The result of the study presented as absolute numbers can easily be understood. However, the main disadvantage of such a solution is that such an analysis would be possible only after completion of the study by all patients (after occurrence of an end point event in all patients). Such a study would last for a very long time, which would particularly apply to adjuvant treatment. For this reason, Kaplan-Meier estimator, i.e. calculation for incomplete observations, is used to analyse the study [1, 2].

Consecutive patients are included in the clinical study, and the time to event is assessed. The difference between the arms is of great interest, so it is prospectively determined. Based on the current data on the number and duration of events in patients treated by the method that will be used in the control arm, the number of patients (sample size) needed to prove the thesis that

Table 2. Columns A1 and B1 present the number of patients starting a given observation period, columns A2 and B2 the number of patients with an event in a given period, and columns A3 and B3 the number of patients without an event at the end of the evaluated period

Months	Number of patients					
	The A arm			The B arm		
	1	2	3	1	2	3
1	100	0	100	100	0	100
2	100	5	95	100	5	95
3	95	5	90	95	25	70
4	90	5	85	70	5	65
5	85	10	75	65	10	55
6	75	10	65	55	10	45
7	65	5	60	45	5	40
8	60	10	50	40	10	30
9	50	15	35	30	15	15
10	35	10	25	15	10	5
11	25	10	15	5	5	0
12	15	5	10	0	0	0

the difference in events will reach the assumed level and will be statistically significant is determined. Please note that it is assumed that the events will occur in both arms, but in a pre-planned period there will be fewer events in the examined arm. The study will not be conducted until all participants experience the end point event (death, relapse, or disease progression) but until the assumed number of events is achieved. Obviously, patients participating in the study, in whom end point event will not occur, will continue the treatment; however, it will no longer be a subject for fundamental analysis.

At the time when the assumed number of events is recorded, i.e. the study as such is completed, patients included in the study will have different follow-up periods, i.e. patients enrolled at the beginning have the longest ones, while patients included shortly before study completion have the shortest ones. Due to the different time of participation in the study, an assessment based on absolute numbers would not be possible. Therefore, estimation using the Kaplan-Meier method is used, i.e. the probability of surviving a specific event-free time is determined and absolute numbers are replaced by the probability. Let us assume that 100 patients were included in each arm. Each month of participation in the study is followed by an evaluation. If all patients survived the first and second month without an event, then after two months there will still be 100 patients in each arm. The probability of event-free survival will be calculated by dividing the number of patients who survived a given period without an event by the number of patients who started that period. In this case it will be 100 : 100 = 1 for the first and second month. However, if during the third assessment (after three months) end point event was detected in five patients in the examined arm, i.e. 95 patients survived without the event, the probability of surviving the given event-free period would be 95 : 100 = 0.95. At the same time, 15 events were found in the control arm, i.e. the probability of event-free survival without an event in the control arm will be 85 : 100 = 0.85. The probability of event-free survival is calculated for each period separately. Thus, 95 patients in the examined arm and 85 patients in the control arm will enter the next assessment period. For example, if during the next assessment an event is found in four patients in

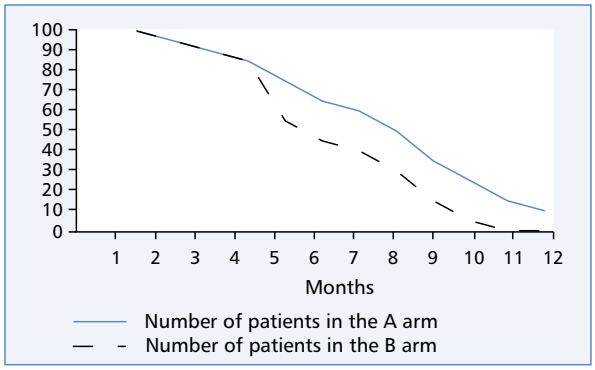

Figure 3. The data are presented in Table 3

Table 3. Columns A1 and B1 present the number of patients starting a given observation period, columns A2 and B2 the number of patients with an event in a given period, and columns A3 and B3 the number of patients without an event at the end of the evaluated period

Months	Number of patients					
	The A arm			The B arm		
	1	2	3	1	2	3
1	100	0	100	100	0	100
2	100	5	95	100	5	95
3	95	5	90	95	5	90
4	90	5	85	90	5	85
5	85	10	75	85	30	55
6	75	10	65	55	10	45
7	65	5	60	45	5	40
8	60	10	50	40	10	30
9	50	15	35	30	15	15
10	35	10	25	15	10	5
11	25	10	15	5	5	0
12	15	5	10	0	0	0

the examined arm, the probability of event-free survival in this period will be 91 : 95 = 0.96. However, to survive these four consecutive months, the patient had to survive the first three months. Because of this, the probability of surviving the following months is multiplied. Therefore, the probability of survival for four months will be $1 \times 1 \times 0.95 \times 0.96 = 0.91$. On the other hand, if in the control arm in the fourth month, for example, six events are found, then the probability of surviving the fourth month will be 79:85 = 0.93, and the probability of surviving four months will be $1 \times 1 \times 0.85 \times 0.93 = 0.79$. In this way, by multiplying the probability of survival of consecutive periods, the probability of survival for the entire follow-up period could be obtained. However, please note that at the completion of some real study the number of patients assessed in particular periods will decrease not only because of diminishing of patients due to end point event occurrence, but also because the patients later included into the study have insufficient follow-up period. For example, patients who have only been participating in the study for six months cannot be taken into account in calculating the likelihood of survival of eight months and longer. This is the advantage of the Kaplan-Meier estimator over the analysis based on absolute numbers. On the graph, the curves presenting the results of the study in absolute numbers are replaced with survival probability curves. If the study was to be completed only after the event occurred in the last patient and presented in the form of curves based on absolute numbers, these curves should coincide with the probability curves obtained earlier. In the publications of randomised clinical trials the graphs of survival probability curves are frequently, albeit not always, presented together with a table showing the absolute numbers of patients who were the basis for calculating the probability of survival for a given period. According to this, it can be seen that although the curve shows that 20% of patients would probably survive, in some cases it was calculated based on survival of only one or two patients. The course of the curves could allow, however, to read out the same thing that would be on the graphs of absolute numbers, i.e. it is possible to calculate the differences in terms of events in individual periods between the arms. The difference between the medians can be seen at the moment when the probability of survival in each arm accounts for 0.5. It does not change the fact that this difference will still depend primarily on the difference in the number of events between the arms. For this reason, the common claim that the "new" treatment increases the survival time by the difference between the medians is not justified. Perhaps, some patients have actually increased their survival to event, but it certainly does not apply to all patients. To be able to state that the new treatment method prolongs the survival time of all patients by the median noted in the study, patients from both arms would not have an event for some time, then at the same time all patients from the control arm would have to have an event, and none from experimental arm, and after some time, corresponding to the median difference, all patients from the experimental arm would have an event at the same time. The reality of such a situation is difficult to imagine.

In the majority of even "positive" trials, most patients have the same survival time in both arms at each assessment period. The final difference found in the study is the sum of the differences in subsequent assessments. The supposition that all patients in the experimental arm benefited is not substantiated. These kinds of statements, which we often find in presentations, however, are merely advertising the medicine or method.

Statistical significance in clinical trials

In order to authenticate study results, statistical significance tests are used. Even if the difference is statistically significant, it does not mean that it is clinically significant. This is observed when the real difference is small.

If there were 10 patients in each of the two arms of the study, and as a result of using the new drug in the examined arm only one patient had an event against nine in the control arm, the difference would be visible with the naked eye and statistical tests would be unnecessary. However, if there were five events in one arm and six in the other, there would be doubts as to whether this difference was not accidental. In this case, statistical tests are necessary as well as increasing the number of patients needed to prove the difference. This is already taken into account at the study planning level. Assuming the size of the clinically significant difference, the number of patients needed to prove the difference in statistical significance tests is calculated. However, an important fact is noteworthy — two arms are compared on the assumption that the only element determining the existence of the difference is the drug or method of treatment used. Unfortunately, it is not possible to prove that, except for the drug or method, the patients in both arms are identical. Only faith remains that thanks to stratification and randomisation this is indeed the case. In this way, however, the value of scientific mathematical proof depends on what we believe. Any misconduct during the study, at any of its stages, may undermine the value of the result obtained. So, science or just faith?

To validate the results, further statistical tests are used. One of them is the so-called hazard ratio (HR). It is calculated in such a way that the risk of an event in one arm (the number of patients with an event divided by the sum of patients with an event and without an event in a given arm) is divided by the equally calculated risk in the other arm. This can be applied to the total number of patients or to individual cohorts created, for example, by age, disease stage, or other criterion [3].

On this basis, it is concluded to what extent the new drug or method reduces the risk of the event. However, it is not about the risk of an individual patient, but the risk of an event in a group of patients from a given arm. Hence, this is the same as can be seen on the charts, but differently presented. Please note that the clinical value of HR will depend not only on the number of events, but also on the number of patients in the study arms or individual cohorts. For example, if there are three events in 10 patients in the A arm and six events in 10 patients in the B arm, the HR will be 0.3 : 0.6 = 0.5. If in another study in the A arm there are three events per 100 patients and in the B arm six events also per 100 patients, the HR will be 0.03 : 0.06 = 0.5. The same result will be obtained with, respectively, three and six events per 1000 patients, 10,000 or more in each of the arms. In all of the examples above the risk reduction was 50%; however, the same magnitude of this reduction will have a completely different clinical significance.

Another statistical analysis is the so-called "forest plot", which shows the results in individual cohorts of patients (by age, disease stage, and other parameters). If the analysis shows differences in the result between patients from different arms, it is most often concluded that all patients benefit from using a new drug or method. This is clearly an erroneous conclusion. The result of this analysis only indicates that patients who have benefited from treatment with the new drug or treatment method belong to all or almost all cohorts. In each cohort, therefore, there are both patients who have benefited and those who have not. This, unfortunately, makes it difficult to detect patients who can actually benefit from treatment with a new drug or method, making it possible to conclude that it is necessary to treat all patients meeting the study eligibility criteria. This is to be proved by statistical tests, which, however, regardless of their number, can show nothing more than the fact that the events are presented in both arms but that only in the experimental arm there are fewer ones (usually by just a small margin). Multiplication of statistical tests that show this in various ways resembles drug advertising more than scientific evidence.

What is missing in the presentation of the result?

The study compares the frequency of events between the arms. However, during each assessment, there are patients in each arm, who have or do not have an event at that time. Of note, the course of the curves indicates that in each arm there are patients in whom the assessed event is found already at the first examination, as well as patients who do not have events until the end of the study. We do not know the decisive differences in terms of patient characteristics because they all meet the same eligibility criteria. It could be assumed that this is due to enrolment in the study of patients with various known risk factors for the event (stratification), but this is not subjected to any analysis. It could be also expected that the end point event will firstly occur in patients with the highest risk of this event at the enrolment, e.g. due to disease stage. This group will be in the first half of patients with assessed events, so they will decide about the median. It is not known whether this is the case. However, if this were true, the outcomes of each study would result from results in patients at the highest risk of the event, and the others would be only a kind of "supplement" justifying the use of a new drug or method in all patients meeting the inclusion criteria, although for many of them it may not matter which arm they are in. It is also not clear why, when assessed at a given time point, events manifest themselves in both arms (although there are fewer in the experimental group). What common features do these patients have in both arms? If they have something in common, what causes the difference in the number of events between the arms? Such questions can be multiplied, but the answers to these questions are sought very rarely. There is no doubt, however, that this is the only way to find patients who should be treated with a new medicine or a new method of treatment, because only those will benefit from such treatment.

Summary

It seems that more weight is attached to convincing everyone that all patients who meet the eligibility criteria should be treated, although only a few will actually benefit. For most patients participating in the study, the time to event is similar in both arms.

In this way, the clinical trial becomes, first of all, a method of promoting the drug or method, for which the statistical analyses used are to make credible.

Conflict of interest

None declared.

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VIA MEDICA

CASE REPORT

Monika Misztal[1], Magdalena Krakowska[1], Mariusz Śliwa[1], Piotr Potemski[1, 2]

[1]Copernicus Memorial Multidisciplinary Centre for Oncology and Traumatology, Lodz, Poland
[2]Chemotherapy Clinic, Oncology Department, Medical University of Lodz, Poland

Transformation of lung adenocarcinoma treated with afatinib into small-cell carcinoma — a case report

Address for correspondence:
Lek. Monika Misztal
Wojewódzkie Wielospecjalistyczne
Centrum Onkologii i Traumatologii
im. M. Kopernika w Łodzi
e-mail: misztalmon@gmail.com

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ABSTRACT

In patients with advanced lung adenocarcinoma harbouring *EGFR* mutations, the use of molecularly targeted therapy has significantly increased progression-free survival (PFS) and in some studies also overall survival (OS). Unfortunately, during therapy all patients develop resistance. In about half of the cases the cause of progression is the appearance of the T790M mutation of the *EGFR* gene. Other described resistance mechanisms are as follows: transformation into small-cell carcinoma (14%), *MET* amplification (5%), and *PIK3CA* mutations (5%). Herein we report the case of patient with disseminated lung adenocarcinoma treated with a tyrosine kinase inhibitor (afatinib), whose disease progressed after 13 months of treatment as a result of transformation into small-cell carcinoma. Despite palliative chemotherapy with cisplatin and etoposide, the patient died six months later.

Key words: lung cancer, EGFR inhibitors

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Introduction

Lung cancer is the most common cancer in the world and the main cause of cancer-related deaths [1]. The distinction between non-small-cell (NSCLC) and small-cell lung cancer (SCLC) is of fundamental clinical importance. NSCLC is diagnosed in 85% of patients, which can be divided into adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma, and other histological types. In patients with advanced lung adenocarcinoma, the presence of epidermal growth factor receptor (*EGFR*) gene mutations and *ALK* and *ROS1* gene rearrangements should be assessed. These molecular disorders are the gripping point for molecularly targeted drugs. The use of tyrosine kinase inhibitors (erlotinib, gefitinib, afatinib or osimertinib) in patients with an activating *EGFR* gene mutation has doubled the median progression-free survival (PFS) and has probably extended overall survival (OS). In phase III clinical studies in patients treated with afatinib, the median PFS reached 11 months and median OS 28 months [2]. Unfortunately, molecularly targeted treatment induces resistance, the mechanism of which in some patients remains unexplained. Only patients with acquired T790M *EGFR* gene mutation may be treated with another targeted drug (osimertinib). Other patients in further treatment lines receive chemotherapy because immunotherapy seems to be ineffective.

Chemotherapy sometimes combined with immunotherapy (atezolizumab) is the main method of metastatic SCLC. Patients with objective benefit from systemic treatment should be offered elective radiation therapy to the central nervous system, and sometimes carefully selected patients also receive radiation therapy to the chest area, although the value of the latter procedure raises serious doubts [3].

A case report

In May 2017, a woman aged 63 years was admitted to the Chemotherapy Department with the diagnosis of left lung adenocarcinoma with liver metastasis. The patient was in a very good condition and did not report

concomitant diseases, she was non-smoker, and the family history of cancer was negative. Molecular studies showed the presence of deletions in the 19th exon of the *EGFR* gene. In June 2017, the patient began treatment with afatinib within the Ministry of Health's drug program. Computed tomography performed after three months of treatment revealed partial remission of the disease according to the RECIST 1.1 criteria. Treatment with afatinib was continued, and a sustained response was observed in the subsequent imaging studies. The tolerance of EGFR inhibitor therapy was quite good and the side effects — acne-like rash, nail shaft inflammation and diarrhoea (all CTCAE grade 1) — resolved after supportive care. In July 2018, after 13 months of afatinib therapy, computed tomography revealed progressive disease in the chest and hepatic lesions as well as the appearance of bone metastases. The anti-EGFR treatment was discontinued.

It was proposed that the patient undergo a liquid biopsy or collect histopathological material from the metastatic liver tumour in order to determine the T790M mutation. The patient chose a coarse needle liver biopsy. Small-cell lung carcinoma was found in the liver specimen. Genetic testing confirmed the presence of deletions in the 19th exon of the *EGFR* gene, and T790M mutation was excluded. Therefore, chemotherapy with cisplatin with etoposide was initiated (first cycle in August 2018). Computed tomography after three cycles of chemotherapy showed partial remission according to RECIST 1.1 criteria and features of asymptomatic pulmonary embolism. Treatment with therapeutic dose of low-molecular weight heparin was initiated, and chemotherapy was postponed for a month. Then another two cycles of systemic treatment were given, during which deterioration of performance status and worsening of tolerability of therapy were observed. After the fifth cycle, the patient was diagnosed with neutropenic fever. Due to the appearance of pain, skeletal scintigraphy was performed, which revealed the progression of bone metastases. Palliative chemotherapy was discontinued. The patient underwent palliative radiotherapy of the right hip and pubic area to alleviate pain. Computed tomography performed in January 2019 revealed multiple metastatic changes in the brain, lungs, and liver. Due to deterioration of the patient's general condition, palliative radiotherapy to the central nervous system was abandoned. Symptomatic treatment was applied. The patient died in January 2019.

Discussion

Patients receiving EGFR inhibitors (reimbursed in Poland in the first line of treatment — erlotinib, gefitinib, afatinib) develop resistance over time. In about half of the patients (49–54%), the cause of disease progression is the appearance of a secondary T790M mutation [4, 5]. In these patients, the use of osimertinib, a third-generation EGFR inhibitor, significantly improves the prognosis compared to chemotherapy. Further resistance mechanisms described comprise: transformation into small-cell carcinoma (14%), *MET* amplification (5%), and *PIK3CA* mutation (5%) [4]. According to the literature, the frequency of transformation in SCLC ranges from 3% to 14% [4, 6]. The described phenomenon can be explained by the formation of secondary mutations leading to a change in the phenotype of the tumour or the primary coexistence of small- and non-small-cell carcinoma cells in the tumour, followed by the selection of SCLC cells during molecularly targeted treatment. In most cases, after transformation in SCLC, the same *EGFR* mutation is still found, suggesting a direct evolution from NSCLC into SCLC, rather than an independent SCLC component [7]. The predisposing factor for the transformation of the lung adenocarcinoma into SCLC is probably the inactivation of the *RB1* and *TP53* genes [8].

In 2018, Marcoux et al. published a retrospective analysis of 67 patients with SCLC with *EGFR* mutation [9]. Eighty-seven per cent of patients were diagnosed with NSCLC and then transformed into SCLC during treatment (93% during *EGFR* inhibitor therapy). Other patients were originally diagnosed with SCLC and underwent *EGFR* mutation. In the NSCLC group, the median time from the initiation of molecularly targeted therapy to transformation into SCLC was 15.8 months, and the median time from the diagnosis of advanced NSCLC to the diagnosis of SCLC was 17.8 months. In this population, the median OS from the first diagnosis of malignancy and survival time from the transformation to SCLC were 31.5 and 10.9 months, respectively. After diagnosis of SCLC, chemotherapy with cisplatin and etoposide was most commonly used, with clinical response in 54% of patients. CNS metastases often appeared in the analysed group.

Ferrer et al. analysed survival parameters in 61 patients previously diagnosed with NSCLC, who were diagnosed with SCLC during treatment [10]. In the group of patients with the *EGFR* mutation (48 patients), the median time to transformation in SCLC was 16 months. Median OS and survival after diagnosis of SCLC were also similar to those obtained by Marcoux, and were 28 and 10 months, respectively. In 45% of patients with SCLC, partial response to cisplatin-etoposide chemotherapy was achieved. Data obtained by Ferrer et al. show that primary SCLC and SCLC induced by molecularly targeted treatment have similar clinical features.

Our patient had slightly worse survival parameters than those presented in the above-mentioned papers. Survival time from the initiation of afatinib

treatment to diagnosis of SCLC was 13.9 months. The patient lived 20.4 months from the diagnosis of NSCLC and 6.1 months after the diagnosis of SCLC.

Conclusion

Transformation of lung adenocarcinoma treated with afatinib into SCLC is an example of a rare, but described in the literature, mechanism of resistance to treatment with EGFR inhibitors. In the presented patient, the collection of tissue material to determine the T790M mutation, followed by repeated histopathological examination, enabled the diagnosis of SCLC and administration of appropriate systemic treatment. The liquid biopsy, because it has a lower sensitivity in detecting the T790M mutation than a tissue biopsy, would not allow the transformation into another histological type to be found.

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