Prevention and treatment of febrile neutropenia

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Febrile Neutropenia is a relevant factor for mortality after chemotherapy. Dependent upon factors like duration of neutropenia (≥ 7 d means high-risk situation), patient- and disease specific criteria e.g. defined in the MASCC score (Multinational Association of Supportive Care in Cancer) the individual risk for the patient for the need of being hospitalized can be estimated. Antimicrobial therapy has to be started immediately, to avoid high mortality. Empiric or calculated anti-infective therapy includes broadspectrum-lactam antibiotics in first-line. After 72 to 96 h of treatment, when the patients are still febrile and clinically not improving, an empiric switch of the antibiotic treatment can be considered, e.g. closing the gaps in the gram-positive spectrum. In this situation high risk patients also should receive an antifungal agent with activity against *aspergillus* spp. Strategies to prevent infection in neutropenia are anti-infective prophylaxis or the use of G-CSF (granulocyte-colony stimulating factor). Antibiotic prophylaxis might help to prevent infections and to improve outcome esp. for high risk patients. Antifungal prophylaxis including *Aspergillus* species is recommended in the situation of induction therapy for acute myelogenous leukemia. Patients, expecting a phase of prolonged neutropenia with a history of mold infection should receive a secondary antifungal prophylaxis.

Keywords: Febrile neutropenia, empirical anti-infective treatment, anti-infective prophylaxis, granulocyte-colony stimulating factor.

Introduction

Neutropenia after chemotherapy is one of several important risk factors for infection. The infection risk depends upon the duration of neutropenia and other patient-specific or therapy-specific factors. The most common symptom of infection is fever. Documented evidence of infection is present in only about 40% of patients [1, 2]. Physicians are often confronted with fever of unknown origin, and the therapeutic regimens are empiric or calculated on the basis of therapeutic trials. Because of the risk of rapid deterioration, empiric anti-infective

therapy must be started immediately. Here we discuss recommendations for the diagnosis, therapy and prophylaxis of febrile neutropenia after chemotherapy, excluding the context after allogenic stem-cell transplantation.

Febrile neutropenia

Definitions - risk assessment

Neutropenia is classified in intrinsic defects, like cyclic neutropenia, and acquired causes. In this article, we focus upon chemotherapy-induced neutropenia, the major cause of acquired neutropenia. Clinically significant neutropenia, associated with an increased risk for infection, is defined as a neutrophil count below 500/ μ l, whereas a count below 100/ μ l is considered as severe neutropenia. Patients with an absolute neutrophil count predicted to drop to below 500/ μ l in the next two days are also considered as having significant neutropenia. In terms of chemotherapy-induced neutropenia, the discrimination between a duration of less than or equal 7 days (referred to as a standard risk for infection) and a prolonged duration of over 7 days (referred to as a high risk for infection, i.e. after induction therapy for acute myelogenous leukaemia) [3] is relevant to the management of neutropenia. Patients after autologous stem cell transplantation cannot be explicitly assigned to either of these groups, because the duration of neutropenia is usually between 6 and 10 days. We shall not address the unique situation after allogenic transplantation in this report.

Inclusion of additional parameters predicting the outcome of febrile neutropenia led to a scoring system (Multinational Association for Supportive Care in Cancer = MASCC Score) that may define a carefully selected patient group for outpatient antibiotic treatment (Table 1; a risk score of >2.1 identifies low risk patients) [4, 5].

Fever in neutropenia is defined as an oral temperature of 38.3°C once, or a temperature of 38.0°C twice within 12 h or lasting longer than 1 h. Even if there are other possible reasons for fever-like B-symptoms, reaction against medication or blood products, it must be assumed that the cause of fever in neutropenia is an infection. Fever occurs in 10 to 50% of patients after chemotherapy for solid tumours during neutropenia and in more than 80% after chemotherapy for haematological malignancies [6]. Some patients do not develop

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Tab. 1: MASCC score

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms*	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease†	4
Solid tumour or haematological malignancy with no previous fungal infection‡	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms*	3
Outpatient status	3
Age <60 years	2

NOTE. The maximum value of the score is 26.
 *Burden of febrile neutropenia: Refers to the patient's general clinical status as influenced by the febrile neutropenic episode. It should be evaluated on the following scale: no or mild symptoms (score of 5); moderate symptoms (score of 3); severe symptoms or moribund (score of 0). Scores of 3 and 5 are not cumulative.
 †Chronic obstructive pulmonary disease: Means active chronic bronchitis, emphysema, decrease in forced expiratory volumes, need for oxygen therapy and/or steroids and/or bronchodilators requiring treatment at the presentation of the febrile neutropenic episode.
 ‡Previous fungal infection: Means demonstrated fungal infection or empirically-treated suspected fungal infection.

fever (i.e. under treatment with steroids or pain medication like novaminsulfon), but show signs of infections. These patients should be treated in the same way as with fever in neutropenia.

Diagnostic evaluation

In the presence of fever, in accordance with the aforementioned definition, immediate anti-infective treatment should be started and diagnostics be performed. Diagnostics should include clinical examination (mandatory every day or twice a day), assessing any changes in skin and mucosa, exit sites of central and peripheral venous access, upper and lower respiratory tracts, urogenital tract, abdomen and perianal region, and the monitoring of blood pressure, pulse rate and respiratory frequency.

- At least 2 pairs of blood cultures: two from each lumen of central venous access and at least two from a peripheral vein.
- Complete blood cell count including neutrophil count and platelets
- Serum levels of creatinine, electrolytes, ALAT, ASAT, alkaline phosphatase, gamma-GT, bilirubin, INR, PTT, CRP
- Other cultures from sites of suspected infections
- A chest CT scan (alternatively chest X-ray) in case of pulmonary symptoms

Anti-infective treatment of febrile neutropenia

Fever occurs in 10–50% of patients after chemotherapy for solid tumours during neutropenia and in more than 80% after chemotherapy for haematological malignancies. Despite diagnostic procedures, the source of infection can be identified in only 40% of fever episodes [1, 2] and only 23% of episodes are associated with a positive blood culture [7]. Therefore, the

Tab. 2: Most common pathogens in neutropenic patients

Gram-negative pathogens
<i>Escherichia coli</i> (including ESBL pathogens)
<i>Klebsiella species</i> (including ESBL pathogens)
<i>Enterobacter species</i>
<i>Pseudomonas aeruginosa</i>
<i>Citrobacter species</i>
<i>Acinetobacter species</i>
<i>Stenotrophomonas maltophilia</i>
Gram-positive pathogens
<i>Coagulase-negative staphylococci</i>
<i>Staphylococcus aureus</i> (including MRSA)
<i>Enterococcus species</i> (including VRE)
Other <i>Streptococci</i> (<i>S. viridans</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i>)
<i>Corynebacteria species</i>
Less frequent are anaerobic pathogens
<i>Clostridium species</i>
<i>Bacteroides species</i>
<i>Fusobacterium species</i>
<i>Propionibacterium species</i>

MRSA methicillin resistant staphylococci; VRE vancomycin resistant enterococci; ESBL extended-spectrum β -lactamase.

spectrum of empiric antimicrobial treatment must cover gram-negative aerobic bacteria (enterobacteriaceae and pseudomonas aeruginosa), gram-positive cocci (streptococci, staphylococcus aureus and enterococci), and it should be adapted to the local resistance profile (i.e. MRSA, VRE and ESBL-producing bacteriae). Anaerobic pathogens or fungi do not have to be considered in the first-line empiric anti-infective regimen. The most common pathogens are listed in Table 2 [8]. Without antibiotic prophylaxis, gram-negative cocci are the most often isolated pathogens. When using antibiotic prophylaxis, there is a trend toward gram-positive cocci [9]. The interpretation of microbiological results must consider that positive cultures for coagulase-negative staphylococci or corynebacteriae often resemble contamination. It is therefore recommended that only two positive cultures detecting these pathogens be considered as relevant. Furthermore, results from positive cultures should be used to include these pathogens in the anti-infective regimen, but not to narrow the treatment's spectrum.

Anti-infective therapy must be initiated immediate, because any delay can worsen the prognosis of patients with infection in neutropenia [10]. It is important not to wait for diagnostic findings before starting therapy.

The ideal choice of empiric antibiotics is a broad-spectrum regimen, covering the most common pathogens. Single agent regimens have been proven to be equivalent to combination treatment [11–20]. Thus a first-line treatment with a pseudomonas aeruginosa-covering β -lactam antibiotic is recommended. Specifically, piperacillin/tacobactam, ceftazidime, cefepime, imipenem or meropenem are recommended. Because of the increase in ESBL-producing organisms, the use of cephalosporins is questionable [21], and there is reluctance to use cefepime, because that agent might be associated with an increase in mortality compared to alternative antibiotic regimens [22]. A combination with aminoglycosides is discouraged [23]. The addition of glycopeptides should be restricted to patients with suspected se-

Fig. 1: Algorithm of treatment decision for febrile neutropenia

vere mucositis, skin or soft-tissue infection, or a suspected foreign body (e.g. central venous access)-related infection. Included in empirical first-line treatment, it does not improve outcome [24]. The median time to defervescence in patients with haematological malignancies is about 5 days [25], and in patients with solid tumours and low risk about 2 days [26].

For patients with persistent fever and no clinical improvement after 72 to 96 hours, it is recommended to repeat the aforementioned diagnostic procedures and to switch an empirical anti-infective regimen if there is no detectable infection source. The gaps in the gram-negative spectrum should be closed. Thus after piperacillin/tazobactam or cephalosporine as first-line, imipenem or meropenem is a reasonable choice. After first-line carbapenem, the addition of an aminoglycoside or glycopeptide should be considered. In the high-risk group (expected duration of neutropenia >7 days) the addition of empiric antimycotic treatment should be considered if the infection is not under control after 4 to 7 days of antibiotic treatment. A pre-emptive approach for high-risk patients using information from CT scans and blood tests (such as the serum galactomannan test in combination with clinical evidence) have resulted in reduced antifungal

treatment (7.7% of patients) compared to an empirical strategy (35% qualified for empirical antifungal treatment) without compromising patient outcomes [27]. Liposomal amphotericin-B, caspofungin or voriconazole are reasonable choices for empirical antifungal treatment in high-risk patients showing a risk for aspergillus infection. Clinically unstable patients on antimycotic prophylaxis active against aspergillus should switch to empirical treatment with an antifungal agent of another class. Unless there is a documented or suspected viral infection, no antiviral therapy is indicated.

Only those patients with an expected duration of neutropenia of under 7 days and assignment to the low-risk category according to the MASCC score should be managed in an outpatient setting with oral antibiotics (amoxicillin/clavulanate in combination with ciprofloxacin or levofloxacin) [4, 28]. Fluorochinolones have gaps in the gram-positive spectrum and should not be used as single therapy. Also, there is no indication for fluorochinolones after fluorochinolone prophylaxis. If there is no defervescence and the patients are not clinically stable, they should be hospitalised and intravenous antibiotic treatment must be started empirically, e.g. with piperacillin/tazobactam.

Anti-infective treatment must be continued for two days after defervescence and a neutrophil count $>500/\mu\text{l}$. Documented infections may be handled differently, as pneumonias or soft-tissue infections must be treated for 10 to 14 days, independently from neutrophil recovery.

We do not specifically address herein all situations involving documented infection, but the anti-infective regimen should cover the documented infection and still cover the broad spectrum of empiric treatment.

Role of haematopoietic growth factors

Concerning neutropenic fever, G-CSF (granulocyte-colony-stimulating factor) is the most important haematopoietic growth factor worthy of discussion.

In several studies, the use of G-CSF has been shown to reduce the incidence of neutropenic fever and infection-related mortality. According to a meta-analysis of 17 randomised trials, most demonstrated a benefit of G-CSF independent of the basic risk of febrile neutropenia in the specific trial [29]. Thus it is recommended that G-CSF be used as primary prophylaxis in patients undergoing chemotherapy with a risk of $\geq 20\%$ febrile neutropenia [3], particularly in those with additional risk factors like older age, comorbidities such as liver, kidney, lung or cardiac disease, poor Karnofsky performance status, or an impaired immune system. After an episode of febrile neutropenia, patients should receive G-CSF after the next course of chemotherapy as secondary prophylaxis. There is no indication for prophylactic G-CSF with a risk of febrile neutropenia of $\leq 10\%$. Patients in the risk group between 10 and 20% should be evaluated individually regarding the other risk factors.

In the specific situation after autologous stem cell transplantation, where patients have a risk of neutropenic fever of approximately 60%, G-CSF reduces the risk of fever, infection, reduces the number of days on antibiotic treatment, but has no significant influence on outcome and mortality. Its use is therefore optional.

The interventional approach starting G-CSF in the context of neutropenic fever has not been shown to improve outcome. The results for reducing the days on antibiotics and duration of hospitalisation are inconsistent [30, 31]. None of the guidelines (2010 update of the Guideline by the “Infectious Diseases Society of America” (IDSA) and Guideline of the “Deutsche Gesellschaft fuer Haematologie und Onkologie” (DGHO)) advocate using G-CSF in this situation.

The different active substances (lenograstim, filgrastim, PEG-filgrastim) display equivalent effects [29] and can be used in the situations described above. GM-CSF (granulocyte-macrophage-colony stimulating factor) plays no role in febrile neutropenia.

Prophylaxis with anti-infective agents

There is good evidence of the efficacy of antibiotic anti-infective prophylaxis during neutropenia. We have been aware for many years that febrile episodes and documented infections can be reduced [32]. Fluorochinolones have been well studied. In a randomised trial, prophylaxis with levofloxacin was very effective in reducing episodes of fever, documented infections, especially gram-negative bacterial infections [33].

High-risk patients with profound neutropenia for more than 7 days also show a survival benefit. Despite the potential risk of inducing resistant pathogens [34, 35], antibiotic prophylaxis is recommended in this particular patient group. Patients after autologous stem-cell transplantation also benefit, but a survival advantage has not been observed. Therefore most guidelines do not recommend antibiotic prophylaxis in these patients.

Nor do low-risk patients with solid tumours or lymphoma benefit routinely from a prophylactic approach. Even if there is a reduction in febrile episodes, there is no difference in documented infections compared to the placebo group [36] in that patient population.

The duration of prophylaxis should start before neutropenia, that is after finishing chemotherapy and continued until the neutrophils rise above $500/\mu\text{l}$ or empirical antibiotic therapy is started.

Although the risk for fungal infection is relatively high after allogenic transplantation, we do not address this situation discussed in this paper.

Risk for candida infection is higher when the mucosal barrier has been damaged [37] e.g. induced by intensive chemotherapy. The risk for fungal infections is highest in patients with persistent, [38, 39] profound neutropenia. Patients undergoing intensive induction chemotherapy for acute leukaemia are at risk for candida and aspergillus infections [40]. Prophylactic approaches should cover both groups of fungal pathogens. A randomised study showed posaconazole to be superior to fluconazole or itraconazole [41]. Even if there are problems with absorption and drug interaction (coadministration with chemotherapy should be avoided), in the posaconazole group, the rate of aspergillus infections was reduced to 1%, compared to 7% with the other antifungal agents. Posaconazole prophylaxis is therefore indicated in these patients.

In patients with prior invasive aspergillus infection who are expected to experience a chemotherapy-induced period of neutropenia especially of more than 7 days, a secondary prophylaxis with a mold-active antifungal agent is recommended.

Conclusion

Febrile neutropenia is one of the complications after chemotherapy carrying a relevant risk for death. It is now considered standard therapy in several high-risk patient groups to use anti-infective prophylaxis to prevent infection, and in patients with a risk for febrile neutropenia of $\geq 20\%$, to use G-CSF. Besides the prophylactic approach, it is important to deal with febrile neutropenia by employing adequate diagnostic procedures, but not to delay the appropriate therapy. Empiric antibiotic treatment should start immediately. A change of antimicrobial therapy is mandatory after a sufficient duration of therapy and clinical deterioration or an unstable situation and might be considered in case of persisting fever. Here the coverage of the spectrum of pathogens by the anti-infective treatment has to be adapted to the risk profile of the patient. Knowledge of the local epidemic situation, especially for resistant pathogens is essential for an appropriate choice of calculated or empiric antibiotic therapy. Documented infections must be incorporated in the strategy, but the spectrum of anti-infective treatment should not be narrowed.

Conflict of interest

Florian Weissinger received lecture honoraria from Chugai. Werner Heinz received research support from Astellas, Basilea, Gilead, MSD/Merck (formerly Essex/Schering-Plough) and Pfizer, is member of the scientific advisory board of Merck and Pfizer and received lecture honoraria from Gilead, MSD/Merck (formerly Essex/Schering-Plough) and Pfizer.

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