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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Comprehensive evaluation of risk factors for the development and complications of chemotherapy-induced febrile neutropenia

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SUMMARY
Febrile neutropenia is a serious adverse effect of chemotherapy. It can lead to complications and death, as well as delays in treatment, chemotherapy dose reductions, compromised treatment efficacy, and reduced survival. The assessment of the patient-related risk factors plays a significant role in the prevention of febrile neutropenia and its complications. In the case of intermediate-risk chemotherapy, the patient-related factors contribute to the estimation of an overall febrile neutropenia risk as well as to timely planning of primary prophylaxis using growth factors. Patients presenting with febrile neutropenia undergo a detailed initial risk assessment for serious complications so that an appropriate treatment can be selected. Recommendations given by the guidelines outline the classification of and risk factors for febrile neutropenia complications. The use of patient-related factors and validated tools for the risk assessment of complications makes it possible to optimize the treatment for each patient and to reduce the risk of morbidity and mortality due to febrile neutropenia.
Keywords: febrile neutropenia; patient-related risk factors; risk assessment

INTRODUCTION

Febrile neutropenia (FN) is an oncology emergency and one of the most frequent and most serious complications of chemotherapy treatment [1]. It is a significant cause of morbidity, mortality, and burden to healthcare services [2]. The incidence of FN in patients receiving chemotherapy for solid tumors is 10–50%, while for hematological malignancies it is up to 80% [1, 3]. Around 20–30% of patients with FN will present with complications requiring hospitalization with an overall mortality of 10% [1].

FN is defined as a fever (oral temperature of > 38.3°C or two consecutive readings of > 38°C, one hour apart) in patients with severe neutropenia (absolute neutrophil count of $< 0.5 \times 10^9$/l, or expected to fall below 0.5×10^9/l)[1, 3, 4]. In the majority of patients with FN, symptoms and signs of infection are absent. Bacteriaemia is documented in 20% of FN patients [1]. In the past, there used to be a prevalence of Gram- (G) negative bacteriemia among patients with FN, but in the last few decades the shift has occurred towards G-positive bacteriemia and at the present time the ratio between G-positive and G-negative bacteria is 60:40 [5]. Patients with FN and proven bacteriemia have poorer prognosis, with a mortality rate of 18% (G-negative) and 5% (G-positive) [1]. The most common isolated G-positive bacteria are *Staphylococcus spp.,* enterococci, and viridans streptococci, while among G-negative bacteria the most common are *Escherichia coli, Klebsiella spp.*, and *Pseudomonas aeuruginosa* [5]. Fungal and viral infections in patients with FN are rarely an initial type of infection and are related to prolonged severe neutropenia induced with high-dose chemotherapy regimens such as in hematological malignancies.

RISK FACTORS FOR THE DEVELOPMENT OF FEBRILE NEUTROPENIA

There is a clear relationship between the severity of neutropenia and the dose-intensity of chemotherapy [1]. According to the risk to induce FN, all chemotherapy regimens are classified as high risk (incidence of FN > 20%), intermediate risk (incidence of FN of 10–20%), or low risk ones (incidence of FN < 10%). The majority of high-risk regimens are high-dose chemotherapy regimens for the treatment of lymphomas, leukemias, osteo- and soft tissue sarcomas, and certain regimens for the treatment of colorectal, pancreatic, and breast cancer [6].

It has been shown that several factors, other than chemotherapy itself, are responsible for increasing the risk of FN and its complications, which is of special importance in the case of intermediate-risk chemotherapy regimens. These patient-related factors augment the risk produced by chemotherapy and create an overall risk for developing FN. The overall FN risk is high if one or more patient-related factors

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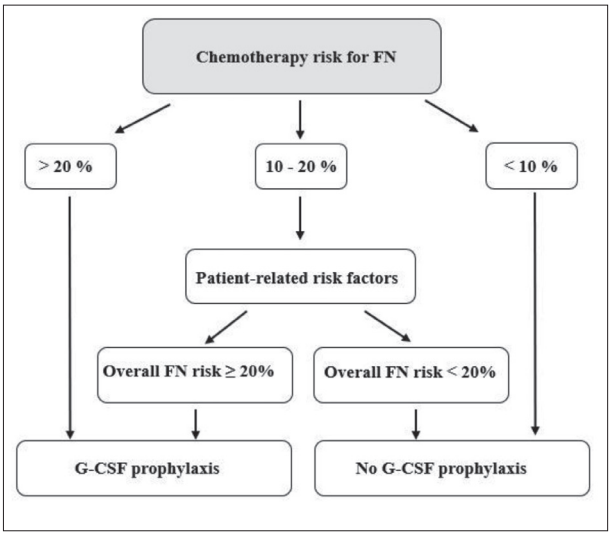


Figure 1. Decision making algorithm regarding the use of the granulocyte colony-stimulating factor (G-CSF) in primary prophylaxis of febrile neutropenia (FN)

are present. In everyday clinical practice, the majority of standard-dose chemotherapy protocols with the intermediate risk for FN are used for the treatment of various types of solid tumors [6]. Assessment of patient-related factors is of importance in order to prevent occurrence of FN and, consequently, morbidity, mortality, and burden to health care services. On the other hand, assessment of patient-related factors in order to prevent FN results in better prevention of chemotherapy dose delays and dose reductions that may affect overall survival.

Several meta-analyses have shown that primary prophylaxis with the granulocyte colony-stimulating factor (G-CSF) reduces the risk of FN by at least 50% in patients with solid tumors and lymphomas as well as early mortality during chemotherapy and infection-induced mortality. [7, 8, 9]. Most guidelines recommend the use of the G-CSF prophylactically if the risk of FN is > 20% for all planned cycles of treatment [1, 3, 6]. For patients with an intermediate risk, it is important to consider patient-related factors, as already mentioned (Figure 1) [1, 3, 6]. With most chemotherapy used for the treatment of common malignancies, the risk of FN is maximal during the first course of chemotherapy [4]. Thus, for patients at risk, primary prophylaxis of FN is recommended from the first cycle of therapy.

Data from the guidelines regarding patient-related risk factors are heterogenous (Table 1) [1, 3, 6].

Patient age is one of the most important patient-related risk factors for FN and the only one that all the guidelines agree upon. Advanced disease, comorbidities, poor performance status, as well as nutritional status, are equally important. The presence of malnutrition increases treatment-related toxicities in cancer patients receiving chemotherapy [10]. It is estimated that in 10–20% of patients, death is caused by malnutrition-related adverse events and not by the tumor itself; therefore, early assessment for malnutrition and adequate nutritional interventions before the start of the treatment are recommended [10]. Before the diagnosis of malnutrition is considered, it is mandatory to assess patients for being "at risk" of malnutrition by any validated risk screening tool (e.g. Malnutrition Universal Screening Tool, MUST) [11].There are several criteria that should be addressed in order to diagnose malnutrition: weight loss, anorexia, body composition (e.g. fat-free mass index, FFMI), anthropometry (e.g. body-mass index, BMI), and biochemical markers (albumin levels, C-reactive protein levels). The proposed criteria for the diagnosis of malnutrition are as follows: unintentional weight loss > 10% indefinite of time, or > 5% over the last three months combined with either BMI < 20 kg/m^2 (< 70 years), or < 22 kg/m^2 (≥ 70 years), or FFMI < 15 and 17 kg/m^2 in women and men, respectively [11].

In general, careful assessment of patient-related risk factors in patients scheduled to receive chemotherapy of intermediate risk for FN enables adequate estimation of an overall FN risk and, consequently, timely planning of primary prophylaxis with the G-CSF in order to prevent FN and its complications.

RISK FACTORS FOR THE COMPLICATIONS OF FEBRILE NEUTROPENIA

As mentioned before, FN is one of the most serious complications of chemotherapy treatment. However, not all the patients with FN will have complications or require hospitalizations. For example, a worse prognosis is expected in high-risk FN with the case of proven bacteriemia or the presence of a focal site of presumed infection (e.g. pneumonia, cellulitis) [1].

Multiple randomized control trials have demonstrated that outpatient treatment is safe and feasible in patients with low-risk FN, with associated savings in resources and improved patient's quality of life [12].

Table 1. Patient-related factors considered by the guidelines as risk factors for febrile neutropenia

NCCN	ASCO	ESMO
Prior ChT or RT	Age > 65 years	Age
Persistent neutropenia	ECOG performance status	Advanced disease
Bone marrow involvement by tumor	Nutritional status	History of prior FN
Recent surgery and/or open wounds	Comorbidities	No antibiotic prophylaxis or G-CSF use
Liver disfunction (bilirubin > 2)	History of prior FN	Mucositis
Renal disfunction (creatinine clearance < 50)		Poor performance status
Age > 65 years receiving full dose chemotherapy		Cardiovascular disease

NCCN – National Comprehensive Cancer Network; ASCO – American Society of Clinical Oncology; ESMO – European Society for Medical Oncology; ChT – chemotherapy; RT – radiotherapy; ECOG – Eastern Cooperative Oncology Group; G-CSF – granulocyte colony-stimulating factor; FN – febrile neutropenia

Table 2. Multinational Association for Supportive Care in Cancer tool for risk stratification in febrile neutropenia

Burden of illness	Severe symptoms Moderate symptoms No or mild symptoms	0 3 5
No hypotension (systolic blood pressure > 90 mmHg)		5
No chronic obstructive pulmonary disease		4
Solid tumor or hematological malignancy with no previous fungal infection		4
No dehydration requiring parenteral fluids		3
Outpatient at presentation		3
Age < 60 years		2

Table 3. Clinical Index of Stable Febrile Neutropenia score for risk stratification in febrile neutropenia

ECOG performance status ≥ 2	2
Stress-induced hyperglycemia ≥ 6.7 mmol/L or ≥ 13.9 mmol/L in diabetics or if on steroids	2
Chronic obstructive pulmonary disease	1
Cardiovascular disease	1
NCI mucositis ≥ 2	1
Monocytes < 200/μl	1

ECOG – Eastern Cooperative Oncology Group; NCI – National Cancer Institute

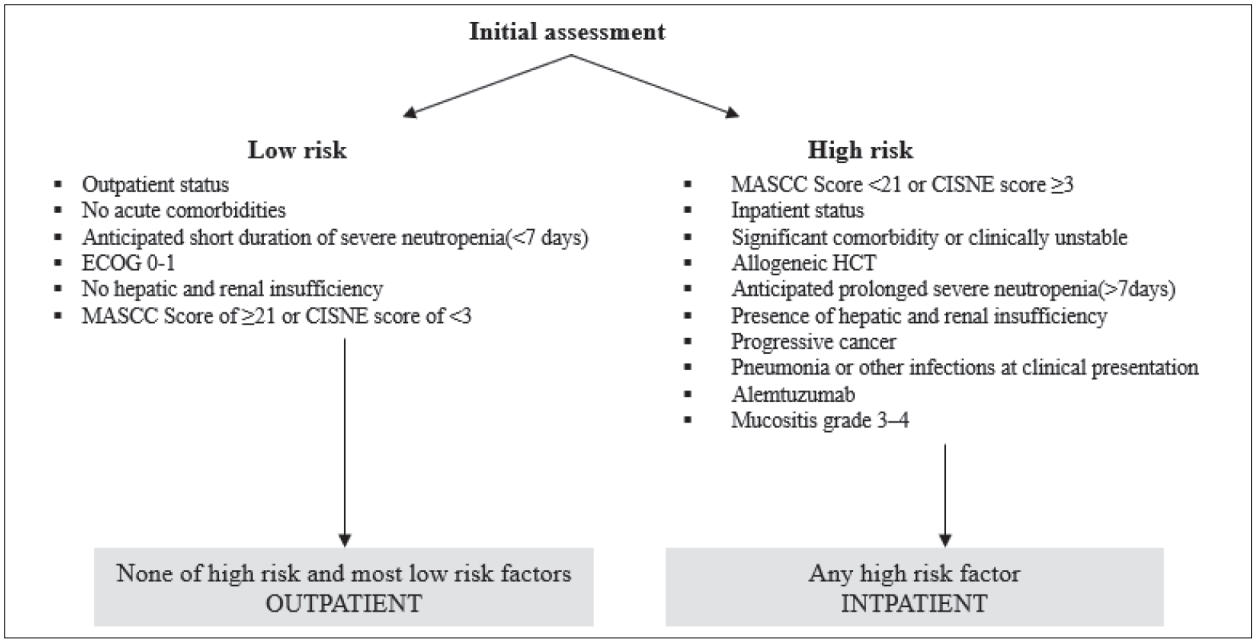


Figure 2. National Comprehensive Cancer Network; (NCCN) initial risk assessment algorithm for FN patients;
ECOG – Eastern Cooperative Oncology Group; MASCC – Multinational Association for Supportive Care in Cancer; CISNE – Clinical Index of Stable Febrile Neutropenia

Considering that the rate of complications from FN is still high, it is crucial to accurately stratify patients who can safely be treated on an outpatient basis. Several tools have been proposed in order to recognize patients with high-risk FN. One of the most common used tools for risk stratification is the Multinational Association for Supportive Care in Cancer (MASCC) tool (Table 2) [13].

An MASCC score of 21 or more identifies low-risk patients eligible for outpatient care with a positive predictive value of 91%, a specificity of 68%, and a sensitivity of 71% [12]. Another commonly used risk stratification tool is the Clinical Index of Stable Febrile Neutropenia (CISNE) score (Table 3) [13].

It was validated to predict major complications in FN patients who are assigned a score ≥ 3 (high risk). Due to the validation study design, the CISNE can only be applied to patients with solid tumors treated with standard-dose chemotherapy) [13].

Although these scores are validated and no-time consuming tools for the prediction of complications in FN patients, it is not clear whether they could be applied to all FN patients. In a recent paper published in the Journal of Oncology Practice, the authors deem that one tool cannot fit all the patients with FN [14]. In this paper, it is stated that the treatment of FN should be personalized and that several patient-related, treatment-related, and logistic factors should be taken into account in order to decide whether to treat the FN patient as an inpatient or as an outpatient. It is discussed that an ideal tool to help decision-making in this regard probably should be a system that accommodates all components of patient care and patient-related factors: type of cancer, expected prognosis, intent of cancer treatment and type of chemotherapy regimen, expected severity and duration of neutropenia, patient's comorbidities, patient's performance status, hemodynamic stability, adherence to oral antibiotics, patient's compliance to close monitoring, and availability of emergency health care services. Once again, the focus is on the patient-related factors.

The current American Society of Clinical Oncology (ASCO)/Infectious Diseases Society of America (IDSA) guideline recommends the use of MASCC score and clinical criteria to identify patients with high-risk FN [3]. In the ASCO guideline, Taplitz et al. [3] based clinical criteria

on various patient-specific and organ-specific symptoms, signs, and conditions. Patients with an MASCC score < 21 and the presence of clinical criteria are candidates for inpatient treatment. In the case of an MASCC score ≥ 21 and the absence of clinical criteria, patients with FN should be treated as outpatients. This guideline also recommends the use of the CISNE score in the case of clinically stable low-risk FN patients with solid tumors treated with mild-to-moderate intensity chemotherapy, as already mentioned [3]. The current ESMO guideline recommends the use of the MASCC score to identify low-risk and high-risk FN patients [1]. The current National Comprehensive Cancer Network guideline recommends the use of these tools (MASCC or CISNE) together with several additional patient-related factors (Figure 2) [4].

CONCLUSION

Chemotherapy-induced FN may lead to serious complications and represents a burden to healthcare services. A careful and comprehensive assessment of risks for FN development and its complications plays a key role in determining whether the G-CSF should be initiated for primary prophylaxis or not. In the case of developed FN, it is crucial to perform a careful risk assessment for complications with validated tools to determine whether the FN management should be inpatient or outpatient. Besides the validated tools, the guidelines suggest the use of clinical criteria in order to make a treatment of FN more personalized and to reduce the incidence of its complications including death.

Conflict of interest: None declared.

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Свеобухватна процена фактора ризика за развој и компликације фебрилне неутропеније изазване хемиотерапијом

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САЖЕТАК

Фебрилна неутропенија је озбиљно нежељено дејство хемиотерапије. Може довести до појаве компликација и смрти, као и до кашњења у примени хемиотерапије, до смањења доза антинеопластичних лекова, што може утицати на ефикасност онколошког лечења и скраћење преживљавања. Процена фактора ризика порекла болесника игра значајну улогу у превенцији фебрилне неутропеније и њених компликација. У случају хемиотерапије умерене мијелосупресивности, фактори порекла болесника морају да се узму у обзир јер повећавају укупан ризик за фебрилну неутропенију. Адекватна процена укупног ризика за фебрилну неутропенију омогућава правовремено планирање примарне профилаксе применом фактора раста. Код болесника који развију фебрилну неутропенију детаљно се процењује ризик од озбиљних компликација, укључујући ту и смртни исход, како би се одредио одговарајући приступ у лечењу. У водичима су дате препоруке за процену ризика за компликације на терену фебрилне неутропеније. Коришћењем валидираних помагала за процену компликација и адекватном проценом фактора ризика порекла болесника могуће је прилагодити лечење фебрилне неутропеније сваком болеснику и смањити ризик од компликација и смрти.

Кључне речи: фебрилна неутропенија; фактори ризика порекла болесника; процена ризика