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MINI REVIEW

PROPHYLAXIS AND MANAGEMENT OF CHEMOTHERAPY-INDUCED FEBRILE NEUTROPENIA: THE ROLE OF MYELOID GROWTH FACTORS

PREVENCIJA I LEČENJE FEBRILNE NEUTROPENIJE IZAZVANE HEMIOTERAPIJOM: ULOGA MIJELOIDNIH FAKTORA RASTA

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Abstract

Febrile neutropenia is a serious chemotherapy-related adverse event that can lead to complications and death and it could be a significant burden on the organization of the health care system. The risk for febrile neutropenia is determined by chemotherapy-induced myelosuppression and the presence of patient-related risk factors. In the literature, various patient-related risk factors are taken into consideration. It was suggested that the patient age is the one of the most important ones. If the estimated risk for the febrile neutropenia is high, prophylactic use of myeloid growth factors (granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) is recommended. In patients with solid tumors and lymphomas it was shown that the prophylactic use of myeloid growth factors significantly reduces the incidence of febrile neutropenia, early mortality during chemotherapy and infection-induced mortality. In patients who develop febrile neutropenia, there is less evidence for the therapeutic use of myeloid growth factors compared to prophylactic use, although there is a clear benefit in reducing the time to neutrophil count recovery. There is a clear benefit for hospitalized patients, also, in reducing duration of hospitalization. In patients with febrile neutropenia who have not been previously treated with prophylactic myeloid factors, assessment of risk factors for the complications is advised. In patients with high-risk febrile neutropenia therapeutic use of growth should be considered.

Keywords:
febrile neutropenia, colony-stimulating factors, prophylactic use, therapeutic use

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Sažetak

Febrilna neutropenija je ozbiljno neželjeno dejstvo hemioterapije koje je povezano sa komplikacijama i smrću i predstavlja značajan faktor opterećenja zdravstvenog sistema. Rizik za pojavu febrilne neutropenije zavisi od mijelosupresivnog potencijala hemioterapijskog protokola i faktora rizika poreklom od pacijenta, među kojima su jedan od najvažnijih godine starosti. Ukoliko je procenjeni rizik za febrilnu neutropeniju visok, preporučuje se profilaktička primena mijeloidnih faktora rasta (faktor stimulacije granulocitnih kolonija i faktor stimulacije granulocitno makrofagnih kolonija). Dokazano je da profilaktička primena mijeloidnih faktora rasta značajno smanjuje incidenciju febrilne neutropenije, ranu smrtnost tokom primene hemioterapije i smrtnost izazvanu infektivnim komplikacijama kod pacijenata sa solidnim tumorima i limfomima. Iako postoji jasna klinička korist za terapijsku primenu mijeloidnih faktora rasta kod pacijenata kod kojih dođe do razvoja febrilne neutropenije (skraćenje vremena do oporavka broja granulocita i kraće trajanje hospitalizacije kod hospitalizovanih pacijenata), dokazi nisu tako jaki kao u slučajevima kada se faktori rasta primenjuju profilaktički. Kod pacijenata kod kojih dođe do razvoja febrilne neutropenije, a koji nisu prethodno primali faktore rasta u profilaksi, preporučuje se procena faktora rizika za nepovoljni tok febrilne neutropenije. Ukoliko rizik za razvoj komplikacija na terenu febrilne neutropenije postoji, trebalo bi razmotriti terapijsku primenu faktora rasta.

Ključne reči:
febrilna neutropenija,
faktori stimulacije kolonija,
profilaktička primena,
terapijska primena

Introduction

Febrile neutropenia (FN) is one of the most serious chemotherapy-induced adverse events. In the majority of cases the first and sometimes the only sign, of an infection in a patient with severe neutropenia (absolute neutrophil count (ANC) < 500 per microliter) is usually fever (oral temperature of > 38.3°C or two consecutive readings of > 38.0°C, at least 1 h apart) (1). The overall mortality of FN is around 10%, while in 20-30% of patients FN will cause serious complications requiring inpatient management (1). The risk of FN and FN-related complications correlates with the severity and duration of the neutropenia (2).

Fever in neutropenia is always regarded as a life-threatening infection, which is treated immediately with empirical antibiotics, according to the guidelines (1, 3-5). The increased burdens to the health care services, impairment of quality of life, chemotherapy dose delays, and dose reductions that may affect overall survival are further negative consequences of neutropenia complications. For numerous chemotherapy protocols, required dose-intensity can only be achieved if neutropenia and FN can be avoided or kept within a clinically tolerable range.

Over the past several decades significant progress has been made in the field of research and understanding the role of myeloid growth factors in proliferation, differentiation and activation of white blood cells progenitors of myeloid lineage (2). Among them granulocyte colony-stimulating factor (G-CSF), filgrastim, and the granulocyte-macrophage colony-stimulating factor (GM-CSF), sargramostim were investigated in cancer patients receiving myelosuppressive chemotherapy. Filgrastim is a recombinant human G-CSF which mimics mechanism of action of endogenous CSFs in the stimulation of neutrophil progenitor cell proliferation and differentiation and stimulates final-stage of neutrophil maturation. Sargramostim is another recombinant CSF with the ability to stimulate a partially committed progenitor cell proliferation and differentiation into granulocyte-macrophage pathways (neutrophils, monocytes/macrophages and myeloid-derived dendritic cells). Sargramostim, also, stimulates the activity of mature monocytes/macrophages. It was showed in phase III trials that the use of filgrastim reduced the risk of FN by 50% in patients treated with chemotherapy associated with clinically significant incidence of FN, which led to approval of filgrastim and sargramostim by the Food and Drug Agency (FDA) in United States (US) at the beginning of 1990s (6,7). Since then, several meta-analyses have shown clear benefits with the use of the granulocyte colony-stimulating factor (G-CSF) in primary prophylaxis reducing 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 (8–10). In 2002, first long-acting G-CSF, pegfilgrastim was approved for the use in patients receiving myelosuppressive chemotherapy. Several short-acting and long-acting G-CSF biosimilars were also approved. All the CSFs have been widely used in everyday oncology practice for the approved indications among which the most important is the reduction of severe neutropenia and neutropenic complications, primarily FN, in non-myeloid cancer patients treated with chemotherapy, associated with high incidence of febrile neutropenia. Short-acting CSFs are also used in patients undergoing consolidation therapy for myeloid leukemia in order to reduce the time to neutrophil count recovery and duration of fever, in patients undergoing bone marrow transplantation or peripheral blood progenitor cell collection, as well as in patients with severe chronic neutropenia.

Table 1. Chemotherapy protocols according to the risk to induce FN (14)

High-risk chemotherapy protocols	Intermediate-risk chemotherapy protocols	Low-risk chemotherapy protocols
Bladder cancer • Dose-dense M-VAC (methotrexate, vinblastine, doxorubicin, cisplatin) **Bone cancer** • VAI (vincrtistine, doxoribicin/dactonomycin, ifosfamide) • ciplatin-doxorubicin • VIDE (vincristine, ifosfamide, doxorubicin, etoposide) **Breast cancer** • TAC (docetaxel, doxorubicin, cyclophosphamide) **Head and neck squamous cell cancer** • TPF (docetaxel, cisplatin, 5fluorouracil) **Lymphomas** • Escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) • ESHAP (etoposide, methylpredisolone, cisplatin, cytarabine) • DHAP (dexamethasone, ciplatin, cytarabine) **Testicular cancer** • VeIP (vinblastine, ifosfamide, cisplatin)	**Breast cancer** • Docetaxel • AC (doxorubicin, cisplatin) **Cervical cancer** • Paclitaxel/cisplatin **Colorectal cancer** • FOLFOX (5fluorouracil, oxaliplatin, leucovorin) **Lymhomas** • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) **Non-small cell lung cancer** • Cipslatin/vinorelbine • Carbolpatin/ paclitaxel • Cisplatin/etoposide • Docetaxel **Prosate cancer** • Cabazitaxel **Small cell lung cancer** • Etoposide/carboplatin **Testicular cancer** • PEB (cisplatin, etoposide, bleomycin)	**Breast cancer** • Weekly paclitaxel • CMF (cyclophosphamide, methotrexate, 5fluorouracil) **Colorectal cancer** • Irinotecan • Capecitabine **Lymphomas** • ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)

Short-acting G-CSFs have a half-life of 3.5-4 hours and are eliminated primarily through the kidneys. Due to short half-life multiple daily doses are needed, resulting in prolonged patient's contact with health care services and diminished compliance. On the other hand, pegylated form of filgrastim has a different method of clearance, primarily by the neutrophils, resulting in decreased systemic clearance of pegfilgrastim. Therefore, compared to filgrastim, one single dose of pegfilgrastim is needed per cycle of chemotherapy. Several meta-analyses have shown no obvious advantage of long-acting G-CSFs compared to the short-acting G-CSFs when short-acting G-CSF is administered according to the guidelines (11-13). However, the use of pegfilgrastim impacts the patient's quality of life by decreasing the number of injections, reduces the number of hospital visits and improves compliance.

The role of the G-CSFs in the prophylaxis of FN

Majority of studies have been investigated the use of CSFs in the primary and secondary prophylaxis. Primary prophylaxis refers to G-CSFs administration from the first and subsequent cycles of chemotherapy associated with high incidence of FN. Secondary prophylaxis meaning the use of G-CSF in response to FN in a prior cycle.

There is a clear relationship between the dose intensity of chemotherapy and the severity of neutropenia (1). Due to the risk to induce FN, all chemotherapy regimens are classified into three groups: high risk (incidence of FN >20%), intermediate-risk (incidence of FN 10%–20%), and low risk (incidence of FN <10%). In patients treated with intermediate-risk chemotherapy regimens, patient-related factors can amplify the chemotherapy-related risk, and thus increase the overall risk of FN development. The overall FN risk is high if one or more patient-related factors are present.

All the guidelines generally recommend the use of G-CSFs for primary prophylaxis when the high-risk chemotherapy regimens are administered (incidence of FN >20%) (1, 3-5, 14). For the intermediate-risk chemotherapy regimens (incidence of FN 10%-20%), patient-related factors should be considered: patient age (≥ 65 years), poor performance status, liver, and renal dysfunction, presence of mucositis, prior episodes of FN, advanced disease, co morbidities, poor nutritional status, etc. In the case of intermediate-risk chemotherapy in patients with one or more patient-related factors present, primary prophylaxis with the G-CSFs is recommended (1, 3-5, 14). Examples of high, intermediated and low-risk chemotherapy protocols are presented in **Table 1**.

If FN was detected, the use of G-CSFs for the secondary prophylaxis, in all the subsequent cycles of chemotherapy is recommended (1, 3-5, 14). Secondary prophylaxis has a significant role in the maintenance

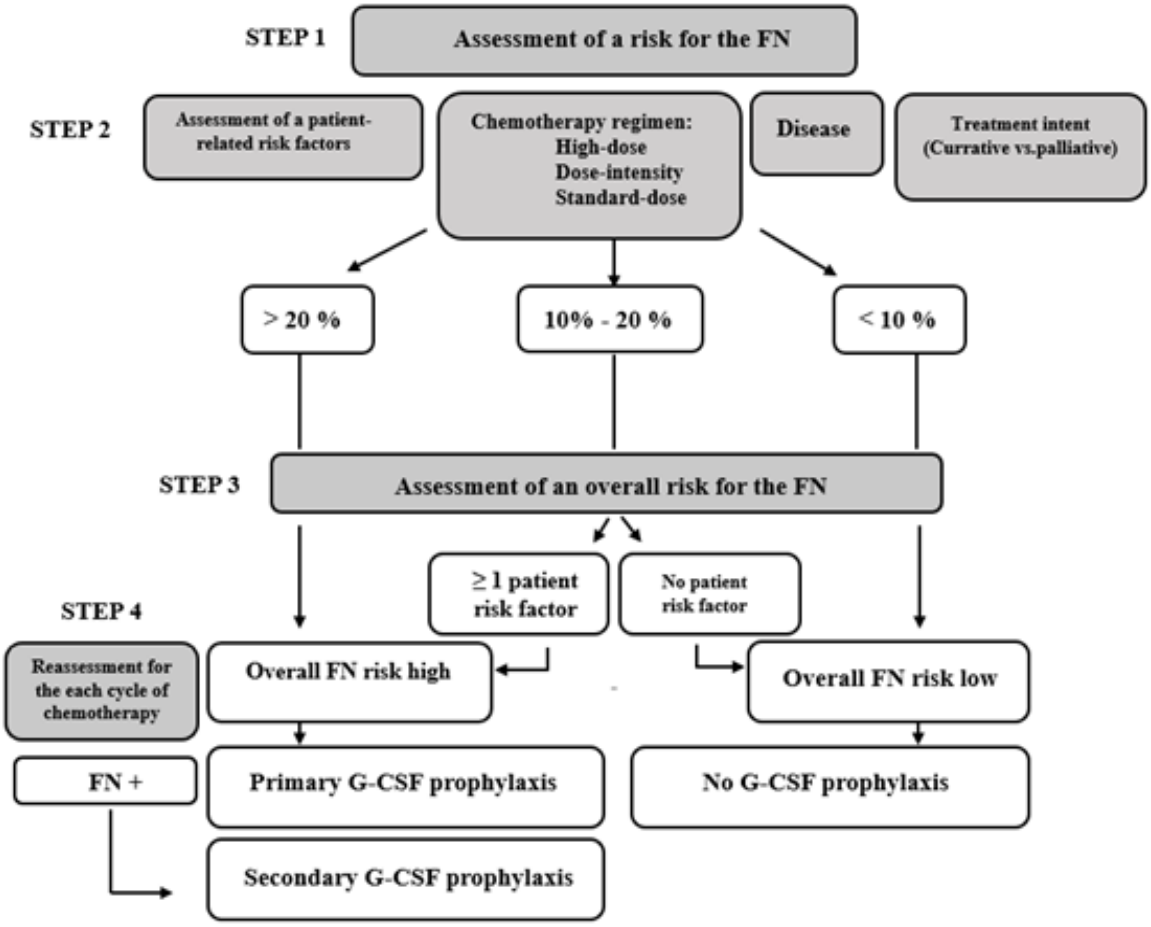

Figure 1. The use of G-CSFs in the primary and secondary prophylaxis of FN (1, 3-5, 14)

of chemotherapy dose-intensity (i.e., neoadjuvant chemotherapy).

Decision-making algorithm regarding the use of G-CSFs for the prophylaxis of FN is presented in **Figure 1**.

The role of the CSFs in the management of FN

The evidence supporting the use of G-CSFs in the management of FN is not so convincing compared to prophylactic use. Although, there is a clear clinical benefit when G-CSF is used in the management of FN (such as shorter length of hospitalization and time to neutrophil recovery), it is still unclear whether these benefits impact survival (6, 15, 16).

According to the guidelines, the therapeutic use of short-acting G-CSFs in patients with FN who received prophylactic short-acting G-CSFs is recommended (1,3-5, 14). There are no data that address the therapeutic use of short-acting G-CSFs in patients with FN who have received prophylactic pegfilgrastim, therefore the use of filgrastim in this setting is not recommended (14). If G-CSFs were not administered as a prophylaxis, in all the patients presenting with FN, assessment of risk factors for the FN-related complications is recommended. Risk factors such as prolonged severe neutropenia (ANC ≤ 100 per microliter; ≥ 7 days), poor performance status at the

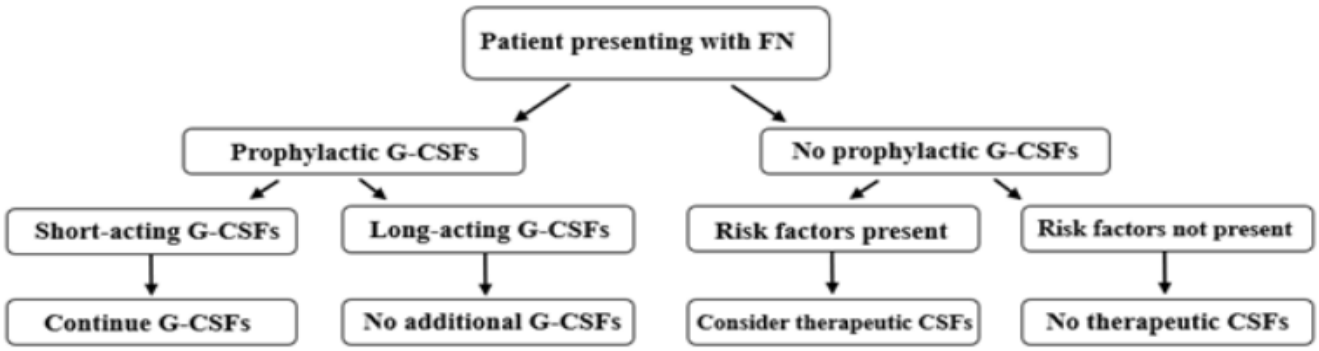

Figure 2. Therapeutic use of CSFs in patients presenting with FN (1, 3-5, 14)

time of fever, clinically significant co morbidities, renal and hepatic insufficiency, advanced cancer, documented infections, high-grade mucositis should be evaluated. The therapeutic use of G-CSF should be considered, if at least one risk factor is present (1, 3-5, 14). A decision-making algorithm regarding the use of G-CSFs for the management of FN is presented in **Figure 2**.

Dosage and administration

The prophylactic use of filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars is recommended in patients receiving chemotherapy associated with high incidence of FN, while sargramostim is not recommended in this setting. First doses of short-acting G-CSFs should be administered 24 - 72h, after the myelosuppressive chemotherapy in the daily dose of 5 mcg/kg subcutaneously until post-nadir ANC recovery to normal or near-normal levels (≥ 2 to 3 x 10^9/L) (17). Pegfilgrastim should be administered as a single 6 mg dose subcutaneously 24-72h after the myelosuppressive chemotherapy. Only short-acting CSFs (filgrastim, tbo-filgrastim and biosimilars, sargramostim) are recommended for the therapeutic use in patients presenting with high-risk FN who have not received prophylactic G-CCSF. The daily dose of filgrastim, tbo-filgrastim, and biosimilars is 5 mcg/kg, while for sargramostim is 250 mcg/m^2. Administration of CSFs should be continued through the neutrophil count recovery to the normal or near normal levels.

Most commonly reported adverse effect associated with CSFs is mild to moderate bone pain and local injection site reactions (18). Other common adverse effects include muscle pain, arthralgia, fever and fatigue which are usually mild to moderate. More severe and life-threatening adverse effects such as pulmonary toxicity, splenomegaly/spleen rupture, and severe allergic reactions are rare.

Conclusion

Febrile neutropenia is a serious chemotherapy-induced complication with a significant burden to the patient and to the healthcare services. The use of CSFs in the prophylaxis, improves patient's quality of life by reducing the incidence of FN and its complications including death. It also impacts the duration of hospitalization, the use of antibiotic therapy and improves cost-effectiveness. In patients presenting with high-risk FN, there is, also, a clinical benefit in the therapeutic use of CSFs.

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