How to Manage Neutropenia in Multiple Myeloma

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Abstract

Neutropenia is a hematologic adverse event characterized by an absolute neutrophil count (ANC) lower than 1500 cells/mL. This reduction may be due to decreased neutrophil production, accelerated use, a shift in compartments of neutrophils, or a combination of these factors. Neutropenia is often associated with infections, which are major causes of morbidity and mortality in patients with cancer. In patients with multiple myeloma, the novel agents thalidomide, lenalidomide, and bortezomib have improved outcome, but chemotherapy-related neutropenia should be carefully considered. Chemotherapy-related high-risk factors for severe neutropenia include regimens with an expected neutropenia rate of > 50%, such as the 3-drug combinations including lenalidomide plus alkylating agents or doxorubicin, whereas low-risk regimens include combinations of the novel agents with dexamethasone alone. Patient characteristics, disease stage, type of current and previous treatment, and ANC < 1000 cells/mL at baseline are additional factors that define the risk of severe neutropenia.

Granulocyte-colony stimulating factor (G-CSF) should be used to manage chemotherapy-related neutropenia so that patients may stay on treatment for a longer time and benefit from it. Primary G-CSF prophylaxis should be used when high-risk regimens are administered or when low/intermediate-risk regimens are used and additional risk factors are present. Reactive G-CSF treatment is indicated when patients undergoing low-risk chemotherapy experience grade 3/4 neutropenia. If ANC restores to > 1000 cells/mL, therapy can be resumed with no dose modifications. In case of persistence of severe neutropenia, treatment should be delayed until ANC reaches > 1000 cells/mL, and dose reductions are necessary.

Keywords: Absolute neutrophil count, Granulocyte colony-stimulating factor, Multiple myeloma, Myelosuppression, Neutropenia

Definition and Classification of Neutropenia

Neutropenia is a blood disorder related to neutrophilic white cells, which are essential to prevent bacterial and fungal infections. Neutrophils originate from pluripotential stem cells in the bone marrow.1 Two hematopoietic growth factors, namely granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor, regulate the production and deployment of neutrophils.2 Healthy adults have an absolute neutrophil count (ANC) of about 1500-7000 cells/mL (1.5-7.0 × 10^9/L). According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V3.0, it is classified as mild (ANC
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Table 1 Neutropenia Severity According to the National Cancer Institute Common Toxicity Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>ANC (cells/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Within normal limits</td>
</tr>
<tr>
<td>1</td>
<td>$\geq 1500$ to $&lt; 2000$</td>
</tr>
<tr>
<td>2</td>
<td>$\geq 1000$ to $&lt; 1500$</td>
</tr>
<tr>
<td>3</td>
<td>$\geq 500$ to $&lt; 1000$</td>
</tr>
<tr>
<td>4</td>
<td>$&lt; 500$</td>
</tr>
</tbody>
</table>

Abbreviation: ANC = absolute neutrophil count.

1000-1500 cells/mm$^3$, moderate (ANC 500-1000 cells/mm$^3$), and severe (ANC < 500 cells/mm$^3$) (Table 1).

Febrile neutropenia is classified as an ANC lower than 1000 cells/mm$^3$ ($< 1.0 \times 10^9$/L) and with fever higher than 38.3°C (101°F) or a sustained temperature of $\geq 38°C$ (100.4°F) for more than 1 hour (NCI CTCAE V4.0).

Severe neutropenia can lead to serious problems and requires immediate and careful care because the patient could potentially acquire a bacterial, fungal, or mixed infections at any time. Symptoms depend on the level and grade of neutropenia. The lower the neutrophil count, the greater the grade of neutropenia (Table 1) and consequently the higher the risk of infection. This risk normally increases if the neutrophil count remains less than the normal level for more than 3 days. Types of infection include otitis media, tonsillitis, sore throat, mouth ulcers, gum infection, and skin abscesses. Any fever (body temperature $> 38.5°C$ or 101.3°F) must be taken very seriously into account and the physician should be informed. Signs of infection, such as swelling and warmth, are not usually present in neutropenia-associated infections.

Neutropenia in Multiple Myeloma

Multiple myeloma is the second most common hematologic malignancy. It accounts for 1% of all cancers and 13% of hematologic neoplasms; it is typically seen in the elderly, and the median age at diagnosis is 70 years. Although the disease remains incurable, the introduction of novel agents such as the immunomodulatory drugs thalidomide and lenalidomide and the proteasome inhibitor bortezomib, has markedly changed the treatment paradigm of myeloma and considerably improved outcomes. The efficacy of these drugs should always be balanced against their toxicity profile. Therapy-related toxicities may in fact negatively affect outcome and lead to early treatment discontinuation. Neutropenia is a hematologic side effect commonly associated with chemotherapy.

In myeloma patients receiving new drugs, constant monitoring may predict occurrence of neutropenia. Neutropenia can also be managed with appropriate supportive case management, dose adjustment, and growth factor support. In the era of novel agents, neutropenia is less common, especially with thalidomide and bortezomib, unless they are combined with conventional agents, such as alkylating agents. By contrast, lenalidomide-induced neutropenia should always be considered because neutropenia is one of the most frequent side effects of lenalidomide. The reported incidence of grade 3/4 neutropenia with lenalidomide is approximately 35%, and it is about 11% and 1% with bortezomib and thalidomide, respectively. These drugs, particularly when used in association with standard chemotherapy in elderly and transplant-ineligible patients, may cause severe myelosuppression. Since severe neutropenia is a relevant side effect of lenalidomide, a group of experts has provided some clinical guidance for the management of cytopenia. In general, the blood count should be monitored on a biweekly basis during lenalidomide treatment, but weekly monitoring is recommended in patients with cytopenia at baseline. In case of cytopenia, G-CSF or erythropoietin stimulating agents may be necessary, and in some cases dose reductions or interruptions may be needed. Routine antibiotic use is recommended for all patients on initiation of lenalidomide treatment.

This article focuses on neutropenia in multiple myeloma and aims to provide clinicians with a simple algorithm to deal with this side effect. This article is based on the consensus achieved among the authors. Amgen has provided support to write the guidelines but did not provide any comment on the content, data analysis, or interpretation.

Risk Factor Assessment

Low ANC before starting treatment is the primary risk factor for the development of severe neutropenia and neutropenic complications after chemotherapy. Additional risk factors can be identified. They can be classified as patient-specific, cancer-specific, or treatment-specific (Table 2). Patient-specific risk factors are female sex, a small body surface area (BSA) ($< 2 \text{ m}^2$) and age $> 65$ years. These factors represent a major risk for chemotherapy-related toxicity in oncology and are associated with severe myelosuppression because of high systemic absorption of drugs resulting in increased toxicity. Comorbidities such as diabetes mellitus and cardiovascular disease as well as the presence of open wounds and altered hepatic or renal function, which are typical of the elderly, poor nutritional status with low serum albumin levels, and low performance status highly increase the risk of neutropenic complications.

Cancer-specific risk factors for neutropenia include type and status of cancer. The more the abnormal process of growth involves the bone marrow, the higher the severity and grade of cytopenia in peripheral blood, and the slower the recovery after chemotherapy. Patients who have already received chemotherapy and have aggressive or relapsed/refractory disease are at higher risk for the development of grade 3/4 neutropenia. Treatment-specific risk factors include previous exposure to chemotherapy or radiation therapy, which contributes to cytopenia and neutropenia. Of note, all patients who are treated with chemotherapy are at risk for neutropenic complications. The type of chemotherapeutic regimen is one of the primary determinants of the risk of neutropenia in multiple myeloma. Some chemotherapeutic regimens are more myelotoxic than others. High-dose alkylating agents and novel agent–containing therapies for multiple myeloma can cause myelosuppression, especially when used in combination.

Based on the risk of chemotherapy-induced neutropenia in patients with multiple myeloma, 4 categories of risk regimens can be identified: low, low/intermediate, intermediate, and high (Table 3). Overall, in patients who receive chemotherapy for the first time and have no other risk factors, low-risk regimens include novel agents in association with dexamethasone, such as lenalidomide in association...
with dexamethasone (RD), bortezomib plus dexamethasone (VD), and thalidomide plus dexamethasone (TD).24,25 Low/intermediate-risk regimens include thalidomide plus melphalan and prednisone (MPT),26 cyclophosphamide and dexamethasone (CTD), Intermediate-risk regimens include bortezomib–doxorubicin–dexamethasone (PAD),28 cyclophosphamide–bortezomib–dexamethasone (CVD), bortezomib–melphalan–prednisone (VMP),29 and the combinations of bortezomib with dexamethasone plus either thalidomide (VTD)30 or lenalidomide (VRD). High-risk regimens include the 3-drug combinations containing lenalidomide plus doxorubicin–dexamethasone (RAD),31 melphalan–prednisone (MPR), cyclophosphamide–dexamethasone (CRD), or melphalan–prednisone (MPR),22 in which the expected incidence of neutropenia is higher than 50%.

Besides the neutropenia risk associated with the specific regimen, patient and disease characteristics remain fundamental to assess the final risk category. In particular, patients with preexisting cytopenia and high tumor burden in the bone marrow are at higher risk of severe neutropenia.14,33

### Febrile Neutropenia

Febrile neutropenia is defined as a single oral temperature reading higher than 38.3°C (101°F) or a sustained (more than 1 hour) temperature of ≥ 38°C (100.4°F) in a patient with an ANC lower than 1000 cells/mm³ (< 1.0 × 10⁹/L) (NCI CTCAE V4.0). In the past few years, the mortality rate due to febrile neutropenia has decreased steadily, but it remains significant. In some hematologic malignancies, overall mortality from febrile neutropenia reaches 14%, whereas for multiple myeloma it is around 8%.34 Neutropenia alters the host’s inflammatory response, making it difficult to detect the usual signs and symptoms of infection. A careful history and a detailed and repeated physical examination are thus necessary. In patients with central venous catheters, at least 2 sets of blood cultures from the catheters and from a peripheral site, as well as cultures from other sites (eg, urine, stool, throat), should be obtained before starting empirical antibiotic therapy. Cultures should be repeated daily while patients remain febrile. Chest radiography followed by imaging techniques such as high-resolution computed tomography (CT) is essential to detect pulmonary lesions. CT, magnetic resonance imaging, ultrasonography, and radionuclide imaging of any potential site of infection must be performed. Invasive procedures such as bronchoscopic examination and lung, liver, or skin biopsy are also useful to detect infections.

It is hard to predict the risk of complications related to febrile neutropenia. Differentiating between high- and low-risk patients has a significant impact on the patients’ quality of life and outcome, as well as on medical costs for hospitalization.6,35 The degree of neutropenia and its duration are important aspects to consider. Patients who are expected to recover their granulocyte counts in < 1 week are generally considered at low risk of complications after onset of fever. High-risk patients experience prolonged neutropenia lasting > 7 days.36

An internationally validated scoring system to classify patients with cancer according to the risk of febrile neutropenia has been developed by the Multinational Association of Supportive Care in Cancer (MASCC) and is shown in Table 4. This numerical risk score takes into account different features that are likely to contribute to a favorable outcome. A high global score indicates a high probability of fever resolution with no serious complications. A MASCC risk score ≥ 21 identifies low-risk patients with a positive predictive value of 91%, a specificity of 68%, and a sensitivity of 71%.37

Based on this score index, high-risk patients have a global risk score < 21. G-CSF is not routinely indicated as an adjunct to antibiotic therapy in uncomplicated fever and neutropenia. However the use of G-CSF should be considered in patients at high risk for complications, or when prognostic factors are predictive of poor clinical outcome, including expected prolonged (> 10 days) and profound (ANC < 1000 cells/mL) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction.

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**Table 2** Risk Factors for Neutropenia

<table>
<thead>
<tr>
<th>Patient-Related</th>
<th>Cancer-Related</th>
<th>Treatment-Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>Heavy marrow infiltration</td>
<td>History of severe neutropenia with previous chemotherapy</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female Sex</td>
<td>Advanced/uncontrolled disease</td>
<td>High-risk chemotherapy</td>
</tr>
<tr>
<td>Poor Nutritional Status (low albumin)</td>
<td>Relapsed/refractory disease</td>
<td>Extensive previous chemotherapy</td>
</tr>
<tr>
<td>Decreased Immune Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small Body Surface Area &lt; 2 m²</td>
<td>Preexisting neutropenia</td>
<td>Concurrent or previous radiation therapy</td>
</tr>
</tbody>
</table>

**Table 3** Neutropenia Risk Associated with Each Regimen

<table>
<thead>
<tr>
<th>Grade 3/4 &lt; 50%</th>
<th>Grade 3/4 &gt; 50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Intermediate Risk</td>
</tr>
<tr>
<td>RD</td>
<td>MPT</td>
</tr>
<tr>
<td>VD</td>
<td>CTD</td>
</tr>
<tr>
<td>TD</td>
<td>MPV</td>
</tr>
<tr>
<td></td>
<td>VTD</td>
</tr>
</tbody>
</table>

therapy-related Neutropenia in Multiple Myeloma

In patients with multiple myeloma who are treated with novel agent–containing chemotherapy, the risk of severe neutropenia and neutropenic complications should be carefully taken into account. Particular attention should be paid to febrile neutropenia, since it requires hospitalization, involves substantial costs, and has mortality rates that are not negligible.

To limit and manage neutropenia and the related complications, simple guidelines for physicians to appropriately use G-CSF are needed. G-CSF is a glycoprotein that stimulates survival, proliferation, differentiation, and function of neutrophil granulocyte progenitor cells and mature neutrophils. The two forms of recombinant human G-CSF in clinical use (filgrastim and lenograstim) are potent stimulants of neutrophil granulopoiesis and have demonstrated efficacy in preventing infectious complications of some neutropenic states.

Two major strategies for the use of G-CSF are recommended, as either primary or reactive prophylaxis. Primary G-CSF prophylaxis is recommended when using chemotherapy regimens associated with a high risk of the development of grade 3/4 neutropenia, when the expected neutropenia rate is > 50%. Thus G-CSF prophylaxis is recommended with 3-drug regimens containing lenalidomide, such as MPR, CRD, and RAD. In addition, primary G-CSF prophylaxis should be used with low/intermediate-risk regimens with an expected severe neutropenia incidence < 50%, such as the 2-drug regimens RD, VD, and TD and the 3-drug combinations MPT, CTD, PAD, MPT, VMP, VTD, and VRD, only if 1 or more patient- or cancer-related risk factors are also present and ANC is < 1000 cells/mL at the start of chemotherapy (Table 3). Moreover it is strongly recommended that the dose be adjusted correctly based on BSA when using chemotherapy regimens with a high risk for the development of grade 3/4 neutropenia.

Clinical data support the use of primary G-CSF prophylaxis in patients receiving chemotherapy regimens with an expected febrile neutropenia rate higher than 20%, as well as in those with a febrile neutropenia rate of 10%-20% when at least 1 patient-related risk factor for febrile neutropenia is present.

A different approach is recommended when severe neutropenia occurs in a patient with multiple myeloma who has been treated with chemotherapy with a low or low/intermediate risk of severe neutropenia and who does not present with any other risk factors. In these patients, reactive G-CSF prophylaxis should be used, that is to say prophylaxis is administered only after the occurrence of the adverse event. If neutropenia resolves and ANC restores to > 1000 cells/mL after G-CSF administration, therapy can be resumed and no dose modifications are needed (Figure 1). On the contrary, if ANC remains lower than 1000 cells/mL, treatment should be delayed until ANC recovers to > 1000 cells/mL, and dose reductions are necessary (Table 5). If the patient experiences another severe neutropenic event after the first dose reduction, treatment should be suspended again. It can be resumed when the ANC rises to > 1000 cells/mL and treatment can be resumed with further dose reductions (Table 5). Finally, in patients with high tumor burden in the bone marrow, full-dose chemotherapy is recommended; consequent myelosuppression is not to be treated with G-CSF administration, but monitoring until recovery is suggested, unless complications occur (fever, infection).

### Dose and Timing of G-CSF

Since the kinetics and recovery of bone marrow function vary between cytotoxic agents and regimens, it is difficult to provide general recommendations on dose and timing.

G-CSF is contraindicated within 24 hours of chemotherapy, when stimulation of progenitor cells in the presence of cytotoxic agents may worsen the myelotoxicity of the regimen. For cytotoxic drugs with a long half-life, a longer interval may be required to avoid increased myelotoxicity.

Subcutaneous and intravenous G-CSF have equivalent potency, but subcutaneous injection is generally recommended, as it is suitable for outpatients.

Lenograstim 150 µg/m² once daily by subcutaneous injection (vial/syringe size 105 µg and 263 µg) is commonly used in practice in a daily dose of 263 µg (patients with BSA > 1.8 m² may be given an additional 105 µg daily, either initially or if they have an inadequate response to the standard daily dose).

Filgrastim 5 µg/kg is used once daily by subcutaneous injection (vial/syringe size 300 µg and 480 µg). It is common practice for a daily dose of 300 µg to be given; however patients who weigh > 90 kg may be given the 480-µg syringe either initially or if they have inadequate response to the standard dose.

Lenograstim and filgrastim should be started not before 24 hours and not later than 72 hours after cytotoxic treatment is completed. In this way the stimulus provided by G-CSF will be present at a time when the bone marrow is regenerative and able to respond. G-CSF injections should continue until ANC has recovered to at least 1000 cells/mL on 2 consecutive days.

Filgrastim is recommended to manage febrile neutropenia. It should be administered at the standard dose of 5 µg/kg daily, starting the day

### Table 4: Multinational Association of Supportive Care in Cancer Index

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burden of Illness</td>
<td></td>
</tr>
<tr>
<td>No or mild symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>3</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>0</td>
</tr>
<tr>
<td>No Hypotension (Systolic blood pressure &gt; 90 mm Hg)</td>
<td>5</td>
</tr>
<tr>
<td>No Chronic Obstructive Pulmonary Disease</td>
<td>4</td>
</tr>
<tr>
<td>Solid Tumor/Lymphoma With No Previous Fungal Infection</td>
<td>4</td>
</tr>
<tr>
<td>No Dehydration</td>
<td>3</td>
</tr>
<tr>
<td>Outpatient Status (at Onset of Fever)</td>
<td>3</td>
</tr>
<tr>
<td>Age &lt; 60 Years</td>
<td>2</td>
</tr>
</tbody>
</table>

A global score ≥ 21 denotes low risk of complications. Points attributed to the variable “burden of illness” are not cumulative. The maximum theoretical score is therefore 26.
after chemotherapy and finishing after 10-14 days, when the postnadir neutrophil level has recovered to 1000 cells/mL. G-CSF is repeated with each cycle of chemotherapy.47

In patients receiving autologous bone marrow transplantation, the starting dose of G-CSF is 5 μg/kg daily, starting within 24-120 hours after administration of high-dose therapy and tapering the dose according to neutrophil levels during the postnadir neutrophil recovery.

The recommended dose of G-CSF for peripheral blood stem cell mobilization is 10 μg/kg daily subcutaneously starting 4 days before the first leukopheresis and ending after the last one.

Pegylated G-CSF (pegfilgrastim/pegGf) has recently been introduced. It is a novel G-CSF with double molecular weight and an attenuated systemic clearance. It can be used to obtain sustainable G-CSF levels in particularly myelotoxic regimens at the dose of 6 mg once in each chemotherapy cycle, in unique administration, 24 hours after completion of chemotherapy (Table 6).20,39,40–42,47

Conclusion

The combination of novel agents with conventional chemotherapy or dexamethasone has substantially changed the treatment paradigm of patients with multiple myeloma, prolonging disease-free and overall survival. Treatment-related toxicities remain a main concern in the era of new drugs as well. Neutropenia is a main concern with lenalidomide, and caution is suggested when thalidomide and bortezomib are used for the treatment of frail patients.14

A simple algorithm to manage neutropenia associated with novel therapies for multiple myeloma may help physicians to deal with this adverse event appropriately. G-CSF prophylaxis is an optimal strat-
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**Table 6: Recommendations for G-CSF Use**

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Setting</th>
<th>Start</th>
<th>Duration</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF (filgrastim)</td>
<td>Myelotoxic chemotherapy</td>
<td>24-72 hours after administration of chemotherapy</td>
<td>Until ANC ≥ 1000/mL</td>
<td>5 μg/kg/day subcutaneously</td>
</tr>
<tr>
<td></td>
<td>High-dose therapy and ASCT rescue</td>
<td>24-120 hours after administration of high-dose therapy</td>
<td>Dose tapering according to neutrophil levels during the post nadir neutrophil recovery</td>
<td>5 μg/kg/day subcutaneously</td>
</tr>
<tr>
<td></td>
<td>PBSC mobilization</td>
<td>≥ 4 days before first leukopheresis</td>
<td>Continue until last leukopheresis</td>
<td>10 μg/kg/day subcutaneously</td>
</tr>
<tr>
<td>Pegylated G-CSF (pegfilgrastim)</td>
<td>Myelotoxic chemotherapy</td>
<td>24 hours after end of chemotherapy</td>
<td>Once per each chemotherapy cycle</td>
<td>6 mg</td>
</tr>
</tbody>
</table>

Abbreviations: ANC = absolute neutrophil count; ASCT = autologous stem cell transplantation; G-CSF = granulocyte-colony stimulating factor; PBSC = peripheral blood stem cell.

eg to maintain chemotherapy at the desired dose intensity and minimize delays. G-CSF prophylaxis is suggested with chemotherapy regimens with a high risk of neutropenia.

G-CSF should be used as a reactive treatment if severe neutropenia occurs after chemotherapy in order to reduce the duration of neutropenia and related complications. If neutropenia does not resolve despite the use of G-CSF, treatment should be delayed until ANC restores to > 1000 cells/mL. Treatment can then be resumed with appropriate dose reductions. This approach may reduce the risk of early treatment discontinuation for severe neutropenia, thus enabling patients to derive the highest benefit from the therapy.

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