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The Use of Colony-Stimulating Factors with Myelosuppressive Chemotherapy

by Karissa Kusick, PharmD

Introduction: The most common dose-limiting toxicity of cancer chemotherapy is myelosuppression and subsequent infectious complications.[1] Febrile neutropenia (FN) occurs frequently with common chemotherapy regimens, ranging from 25-40% for treatment naïve patients.[2] Neutropenia is defined as an absolute neutrophil count (ANC) <500 neutrophils/mcL or an ANC <1,000/mcL with an expected decline to 500/mcL or less in 48 hours. Fever is defined as a single temperature ≥38.3° C or temperature ≥38.0° C sustained for 1 hour without an obvious cause.[1] Febrile neutropenia is a serious medical problem for patients; despite improvements in clinical treatments, it is associated with high morbidity, mortality, and cost.[3] When patients develop FN, they are normally admitted to the hospital for initiation of appropriate antibiotics. The patients may have delays or dose reductions in chemotherapy treatment which have the potential to impact the patients' quality of life (QOL), as well as their survival. The introduction of colony-stimulating factors has helped prevent the development of FN.[2] There are two granulocyte colony-stimulating factors (G-CSF) currently available, filgrastim (Neupogen®) and pegfilgrastim (Neulasta®). Sargramostim (Leukine®) is a granulocyte-macrophage colony stimulating factor (GM-CSF) that is FDA-approved for use in bone marrow transplant and acute myeloid leukemia patients.[4]

Granulocyte colony-stimulating factors are glycoproteins that act on hematopoietic stem cells to stimulate proliferation, differentiation, and activation of the targeted (granulocyte) cell lines. Endogenous G-CSF is produced by monocytes, fibroblasts and endothelial cells to regulate neutrophil production in the bone marrow. The neutrophils produced are involved in the following physiologic processes: 1) phagocytosis, 2) respiratory burst, 3) antibody-dependent killing, and 4) increased expression of surface antigens. When patients develop an infection, the immune system responds by releasing G-CSF into the bloodstream. A variety of cells act to circulate endogenous G-CSF at the site of infection. The bone marrow responds by stimulating the growth and maturation of stem cells into neutrophils that enhance the immune system and increase phagocytosis of infectious bacteria.[5] See Figure 1 for Blood Cell Development.

Evaluating Patients – Who Should Receive G-CSF? The National Comprehensive Cancer Network (NCCN) has recommended guidelines for the use of myeloid growth factors in adult patients with solid tumors and non-myeloid malignancies. In addition, the American Society of Clinical Oncology (ASCO) published an update to evidence-based recommendations in 2006.[2,7]

The previous edition of ASCO Guidelines only recommended use of prophylactic G-CSF for patients with a 40% risk of developing FN. The updated ASCO and NCCN Guidelines incorporated several large randomized trials designed to reduce the risk of FN in patients with a 20% risk of developing FN. The studies showed a significant reduction in the risk of developing FN in patients receiving primary prophylaxis who originally had at least a 20% risk. One large study by Vogel and colleagues investigated the use of pegfilgrastim in various chemotherapy cycles of breast cancer patients. The study was designed to determine if the use of pegfilgrastim in a myelosuppressive chemotherapy regimen associated with a risk of FN between 10 and 20% provided a reduction in the incidence of FN.[8] Patients in the study received docetaxel 100 mg/m^2 every 3 weeks and a subcutaneous dose of either pegfilgrastim (Neulasta®) or placebo once per cycle on the day after chemotherapy administration. The primary efficacy endpoint was the percentage of patients that developed FN (defined as temperature ≥38.2° C and neutrophils <500/mcL). Overall, the incidence of FN for all chemotherapy cycles was significantly lower in the pegfilgrastim group (1%) compared to placebo (17%; p<0.001). Patients in the treatment group also had a lower incidence of hospitalizations due to FN (14%) compared to the placebo group (1%; p<0.001). This led to less use of intravenous (IV) antibiotics in the pegfilgrastim group (2%) versus placebo (10%; p<0.001). According to the authors of this study, the incidence of FN can be reduced over 90% with the use of pegfilgrastim in first-cycle chemotherapy which prevents hospitalization and the subsequent need for treatment with IV antibiotics.[8]

Data from this trial and others have led to a change in the recommended practice guidelines.[8-10] Currently, if patients have >20% risk of developing FN, they are considered high-risk and should receive primary prophylaxis with G-CSF regardless of the treatment intent. Intermediate-risk is categorized as a 10-20% chance of developing FN. Physicians should evaluate each patient for the risk factors of developing FN and consider prophylactic treatment with G-CSF (Note: All patients should be evaluated regardless of treatment intent). If the intent of chemotherapy is to prolong patient survival, prophylaxis with G-CSF is recommended only if the patient is at significant risk for severe consequences of FN. Patients who have <10% chance of developing FN are at low-risk and do not require any prophylaxis with a G-CSF.[1]

The drugs and doses of each chemotherapy regimen have a large impact on the risk of FN. Examples of chemotherapy regimens with high (>20%) and intermediate (10-20%) risks of FN are located in Table 1.[1] Additional factors should be considered along with the patient specific chemotherapy regimen when evaluating risk for FN. Patients receiving an intermediate-risk chemotherapy regimen that have risk factors for developing FN may warrant primary prophylaxis with G-CSF. Table 2 lists various patient risk factors for developing FN.

Table 1: Example Chemotherapy Regimens[1]

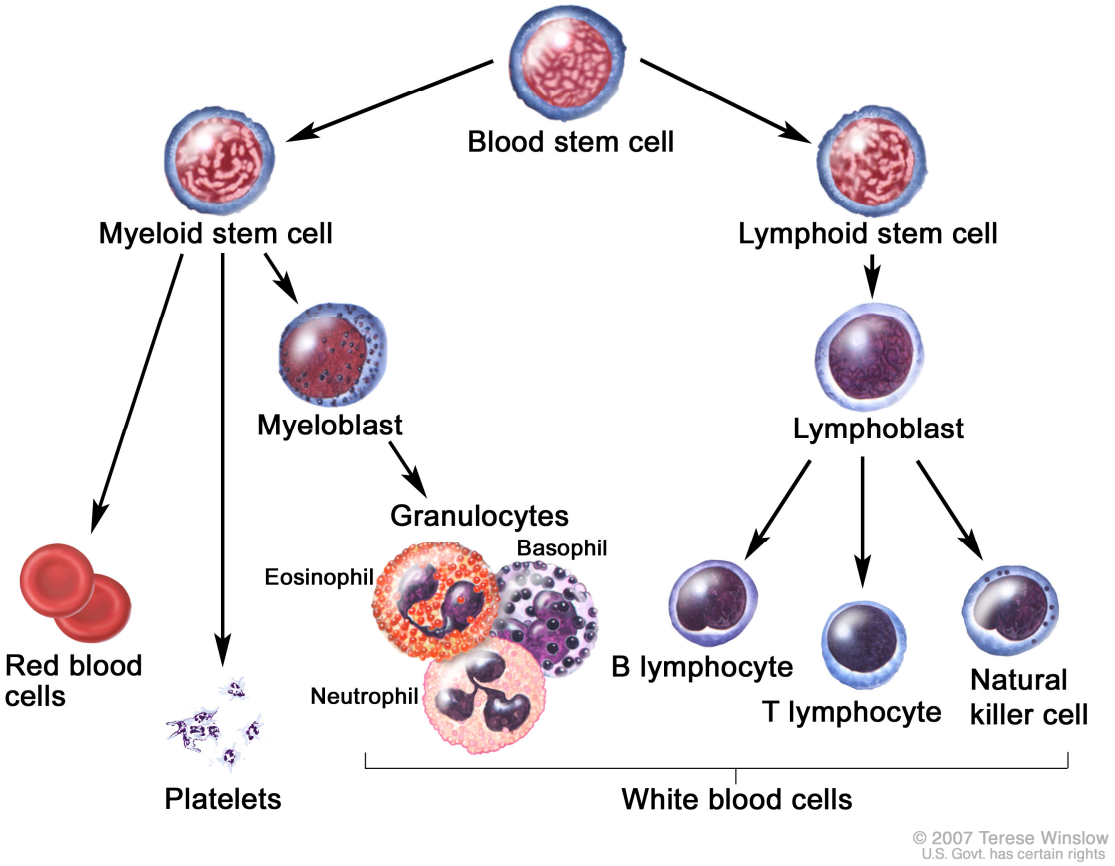
High-Risk (>20%)	Intermediate-Risk (10-20%)
MVAC: Methotrexate, Vinblastine, Doxorubicin, Cisplatin	FOLFOX: Fluorouracil, Leucovorin, Oxaliplatin
ICE: Ifosfamide, Carboplatin, Etoposide	R-CHOP: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
TAC: Docetaxel, Doxorubicin, Cyclophosphamide	ABVD: Doxorubicin, Bleomycin, Vinblastine, Dacarbazine

Table 2: Patient Risk Factors for Developing FN[1]

<table>
<tr><th>Less Risk</th><th>Intermediate Risk</th><th>Greatest Risk</th></tr>
<tr><td>Diabetes</td><td>Type of Cancer:
SCLC, lymphoma, breast</td><td>Chemotherapy: Anthracyclines, Topotecan, Mitomycin, Docetaxel, Etoposide, Gemcitabine, Cisplatin, Carboplatin, Cyclophosphamide, Ifosfamide, Vinorelbine</td></tr>
<tr><td>History of
recent surgery</td><td>Poor renal function:
GFR <30 mL/min/1.73m^2,
age >65 years, elevated SCr</td><td>>2 myelosuppressive agents</td></tr>
<tr><td rowspan="3">Medications:
phenothiazines,
diuretics,
immunosuppressive agents</td><td>Liver dysfunction: elevated bilirubin or alkaline phosphatase</td><td>Dose intensity >85% of standard*</td></tr>
<tr><td>History of previous chemotherapy or radiation therapy</td><td rowspan="3">No planned use of G-CSF</td></tr>
<tr><td>Neutropenia</td></tr>
<tr><td>Infection or open wounds</td></tr>
</table>

*Dose intensity – total dose of chemotherapy delivered over time; SCLC = small cell lung cancer, GFR = glomerular filtration rate; SCr = serum creatinine

Figure 1. **Blood Cell Development**[6]



Recommendations for Primary Prophylaxis (First and Subsequent-Cycle Use): Patients at high-risk for FN based on the previously discussed risk factors should receive primary prophylaxis, defined as a G-CSF after the first cycle of chemotherapy in the attempt to prevent an episode of FN. Chemotherapy regimens that consist of high doses or "dose-dense regimens" require G-CSF prophylaxis (dose-dense chemotherapy is designed to maximize tumor kill by increasing the rate of chemotherapy delivery). Oncology clinicians should also consider special circumstances for each individual patient. Patients with an intermediate-risk of developing FN may benefit from primary prophylaxis if they have other risk factors for FN. All patients should be evaluated for the use of primary prophylaxis with G-CSF, since there are certain clinical risk factors that predispose patients to multiple complications from prolonged neutropenia (See Table 3).[1,7]

Secondary Prophylaxis: When patients experience a neutropenic episode from a previous cycle of chemotherapy and primary prophylaxis was not received, secondary prophylaxis with a G-CSF is recommended if dose reduction of chemotherapy is not an option. In many clinical scenarios, physicians may successfully reduce the dose of chemotherapy or delay treatment until neutropenia resolves. However, for some patients this may compromise disease-free and overall survival and instead of reducing or delaying chemotherapy, they should receive G-CSF for secondary prophylaxis.[1,7] One prospective clinical trial of breast cancer patients who developed neutropenia in the first cycle of chemotherapy were treated with filgrastim 5 mcg/kg/day for the subsequent cycles of chemotherapy. Historical control patients were matched to patients in the treatment arm, resulting in 358 matched pairs. The historical control patients were 2.6 times more likely to receive ≤85% of the planned treatment dose compared to patients receiving filgrastim.

Table 3: Clinical Factors that Increase Patient Risk for Complications[1]

Age >65 years Previous episode of FN Combined treatment with chemotherapy and radiotherapy Poor nutritional status Advanced cancer	Poor performance status Extensive prior treatment Bone marrow involvement of tumor Infection or open wound Co-morbidities

Secondary Prophylaxis (continued): There was a slight increase in the number of FN episodes in the treatment group compared to the historical control group (10.9% versus 9.4%, respectively; odds ratio = 0.9; p = 0.5). Despite the increase in episodes of FN, there were actually fewer hospitalizations due to FN in the treatment group compared to the control group (4.2% versus 4.7%, respectively; odds ratio = 1.1; p = 0.7).[9]

Therapeutic Use of G-CSF: Neutropenic patients need to be admitted to the hospital if they develop a fever. The effectiveness of G-CSF for the treatment of FN remains controversial. A meta-analysis by Berghmans and colleagues reviewed 11 trials to evaluate the therapeutic use of granulocyte- and granulocyte-macrophage colony-stimulating factors in FN cancer patients. The primary outcome was the effect of colony-stimulating factors (CSF) on mortality which was evaluated in 962 episodes of FN. There was no mortality benefit in patients with established FN who received a CSF (relative risk = 0.71; 95% CI = 0.44-1.15). No other outcomes were discussed due to the lack of adequate data in the published studies; however, there was no consistent beneficial effect of CSF in the individual studies reviewed.[11] Based on the available literature, the use of G-CSF should only be considered in patients who are febrile, neutropenic, at high-risk for infection, and acutely ill (See Table 4 for high-risk factors for infection). Neutropenic patients who are afebrile should not routinely receive treatment with G-CSF.[7]

CSF Products: Filgrastim, Pegfilgrastim, and Sargramostim: Filgrastim and pegfilgrastim are the recommended G-CSF used for solid tumors (category 1 recommendation).[1] In addition, the safety data appear to be very similar between these two agents.[12,13] Table 5 demonstrates important information about each drug. Sargramostim is a recombinant granulocyte macrophage colony-stimulating factor that has been studied in patients receiving induction treatment for acute myeloid leukemia (AML) and in various types of stem cell transplant settings (category 2B recommendation).[1] The FDA-approved dose of sargramostim in leukemia patients who have completed induction phase chemotherapy or patients who underwent an autologous/allogeneic stem cell transplant is 250 mcg/m^2/day given IV or SC.[4] Sargramostim is on the Cleveland Clinic Formulary and costs approximately $350 for a 500 mcg vial.[15]

Summary: Granulocyte colony-stimulating factors have helped to reduce the duration of neutropenia and the incidence of FN episodes in patients receiving myelosuppressive chemotherapy. The ASCO and NCCN Guidelines both recommend the use of G-CSF if patients have a 20% risk of developing FN from chemotherapy. Providers may consider primary prophylaxis with G-CSF in patients with intermediate-risk (10-20%) for FN, especially in patients with additional risk factors. The use of G-CSF is not recommended for patients at low-risk (<10%) for FN. Secondary prophylaxis is recommended when patients experience an episode of FN after a previous chemotherapy cycle and did not receive primary prophylaxis. Colony-stimulating factors have demonstrated efficacy by decreasing episodes of FN, however the high cost of these medications require implementation of the most recent guidelines to ensure the appropriate clinical use.

Table 4: High-Risk Factors for Infection in Neutropenic Patients[7]

- Expected prolonged neutropenia (>10 days)
- Profound neutropenia (<100/mcL)
- Age >65 years
- Uncontrolled primary disease
- Pneumonia
- Hypotension
- Multiorgan dysfunction (sepsis syndrome)
- Invasive fungal infection
- Hospitalized at time of fever development

Table 5: Filgrastim and Pegfilgrastim[12-14]

	Filgrastim	Pegfilgrastim
FDA Indication(s)	CIN (nonmyeloid malignancies, AML, and bone marrow transplant); SCN; patients undergoing PBPC	CIN - nonmyeloid malignancies
Dose	CIN: 5 mcg/kg/day	6 mg once per chemotherapy cycle; do not administer in the period between 14 days before and 24 hours after administration of cytotoxic chemotherapy
	Round dose to nearest vial size: 300 mcg or 480 mcg	
Route of administration	SC* or IV	SC
Discontinue	After 10-14 days of therapy or the patient is no longer neutropenic (Note: after discontinuation of filgrastim the ANC may drop by about 50%)	
Primary elimination	Renal	Neutrophil-mediated
Common AE	Neuromuscular/skeletal bone and joint pain, fever, rash, splenomegaly, increased alkaline phosphatase	Neuromuscular/skeletal bone and joint pain, peripheral edema, headache, nausea, vomiting, constipation
Formulary	Yes	Yes
Formulary Restricted	No	Yes – outpatient use only
Cost (AWP)[15]	$250 per 300 mcg	$3,000 per 6 mg

* = preferred method of administration
AE = adverse events, CIN = chemotherapy-induced neutropenia, AML = acute myeloid leukemia, SCN = severe chronic neutropenia, PBPC = peripheral blood progenitor cell collection, AWP = average wholesale price

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Did You Know….

Dexlansoprazole (Kapidex®)
by Kathryn Heimann, Pharm.D. Candidate

Dexlansoprazole (Kadipex®;Takeda Pharmaceuticals) is the newest addition to the proton pump inhibitor (PPI) medication class. Dexlansoprazole works by inhibiting H+/K+ -ATPase enzyme system in order to decrease acid secretion in gastric parietal cells. This drug is the R-enantiomer of lansoprazole (Prevacid®) and is marketed a "dual delayed release capsule." The modified release formulation of dexlansoprazole has been designed in attempt to prolong its concentration-time profile and ultimately increase the duration of acid suppression by releasing the drug in two phases. Inside each capsule are granules with two types of enteric coatings that release medication and peak at separate times; phase one peaks approximately 1 to 2 hours after administration followed by phase two which peaks within 4 to 5 hours after administration.

Dexlansoprazole is indicated in adults for use in the treatment of heartburn associated with non-erosive gastroesophageal reflux disease (GERD) for 4 weeks, treatment of erosive esophagitis for 8 weeks, and maintenance of erosive esophagitis for up to 6 months. This medication is metabolized hepatically through cytochrome P450 (CYP) 2C19 and 3A4 primarily. The majority of drug-drug interactions occur as a result of its effects on the CYP450 enzyme system. Dexlansoprazole is excreted in the urine (~51%) and feces (~48%) as metabolites. Dexlansoprazole is contraindicated in patients that have hypersensitivity to any component in its formulation. Adverse effects most commonly seen with this medication consist of diarrhea (5%), flatulence (1-3%), nausea (3%; same as placebo), abdominal pain (4%; same as placebo), vomiting (1-2%), and upper respiratory tract infection (2-3%).

Symptoms from non-erosive GERD and maintenance of erosive esophagitis require a dose of 30 mg once daily administered orally, while treatment of erosive esophagitis requires 60 mg once daily administered orally. No dosage adjustment is necessary for those with renal impairment. However, the maximum dose for moderate hepatic impairment (Child-Pugh class B) is 30 mg once daily, and it has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Dexlansoprazole may be administered without regard to meals; bioavailability may increase when given with food. Capsules should either be swallowed whole unless the patient is unable; alternatively, the contents of the capsule may be sprinkled over one tablespoon of applesauce and immediately administered. This medication is available in 30- and 60-mg capsules. The cost of dexlansoprazole 30 mg capsules is approximately $150 per month compared to $21.32 per month of omeprazole 20 mg capsules.

In comparing other PPIs with dexlansoprazole, there are no significant differences noted. As previously mentioned, this drug may be taken without regards to meals, with the same being true for both pantoprazole (Protonix®) and rabeprazole (Aciphex®). Dexlansoprazole and rabeprazole are the only two PPIs that cannot be administered through a nasogastric (NG) tube; orally disintegrating lansoprazole (Prevacid® SoluTab™), omeprazole (Prilosec®) suspension and pantoprazole suspension may be given through the NG tube. Dexlansoprazole capsules may be opened and the contents sprinkled onto applesauce as an administration method; pantoprazole and rabeprazole come in tablet formulations and cannot be given via this method. All PPIs are metabolized by CYP2C19 and CYP3A4 to some degree. Currently, dexlansoprazole and its dual delayed release mechanism, has not been proven to possess any clinically superior advantages over other PPIs.

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