Cancer is diagnosed in 1.5 million people in the United States each year, and more than 12,000 cancer patients are younger than 21 years.1 Parents sit across the table from the medical team and learn about the side effects of treatment that their child may experience. The child will lose his or her hair, miss school, experience nausea and vomiting, and endure multiple laboratory and diagnostic tests. Families learn that their day-to-day life, once filled with school, work, soccer games, and other family-centered activities, will now consist of hospital admissions, doctor visits, and isolation to abate the possible side effects of treatment. In addition, parents will need to learn how to administer clinical care, such as subcutaneous injections of medications to improve the child’s immune system, at home.

Neutrophils are a critical member of the phagocytic system and provide a first-line defense against bacterial organisms.2 Neutropenia is defined as a reduction in circulating neutrophils to less than 1,500/µL.1 Chemotherapy-induced neutropenia is the primary treatment-related dose-limiting toxicity in children with cancer. Severe neutropenia (neutrophils less than 500/µL) can occur as a result of chemotherapy treatment. Children who receive intensive chemotherapy have a 40% chance of developing febrile neutropenia.3 Chemotherapy-induced neutropenia...
neutropenia increases a child’s risk of infection. Management of chemotherapy-induced neutropenia comes with substantial clinical and financial costs, and imposes a strain on the quality of life for patients and their families.1

**GRANULOCYTE COLONY-STIMULATING FACTOR**

Treatment regimens changed markedly for many children in 1991 when the FDA approved granulocyte colony-stimulating factor (G-CSF) for the management of chemotherapy-induced neutropenia.1 G-CSF is a cytokine produced by monocytes, endothelial cells, and fibroblasts that acts as a physiological regulator of both neutrophil production and function. It is a growth factor frequently used to shorten the duration of neutropenia after chemotherapy treatment. G-CSF not only prevents infections and febrile neutropenia in patients receiving anticancer regimens, but study findings show it leads to a shorter duration of antimicrobial therapy needed and prevents delays in chemotherapy administration.1 G-CSF has also proven useful in facilitating hematopoietic recovery after bone marrow transplant and mobilizing peripheral blood progenitor cells in healthy donors.5 In addition, G-CSF has been associated with a 20% reduction in febrile neutropenia and shorter hospital stays for children admitted for fever and neutropenia.2 Two forms of G-CSF are approved for use in pediatric cancer patients in the United States: filgrastim (Neupogen) and pegfilgrastim (Neulasta).

**Filgrastim** is a recombinant G-CSF. It is administered daily via subcutaneous injection in the evening, beginning 24 hours after chemotherapy is completed and continuing until a target absolute neutrophil count (ANC) is achieved (approximately 5,000/µL). Filgrastim significantly reduced the risk of infection-related mortality from 3.3% to 1.7% (P = .01) and reduced the proportion of cancer patients with febrile neutropenia from 37% to 20% (P = < .001).2 The normal half-life (t½) of neutrophils is very short, approximately 7 to 10 hours; and the response rate to G-CSF is estimated at 60×106 neutrophils/min. Despite obvious benefits, the main drawback to filgrastim therapy is its short t½ of 3 to 4 hours. Patients must endure daily 5-µg/kg injections for up to 10 days during chemotherapy treatment.2 The injections can be painful and inconvenient, which may result in decreased adherence to the therapeutic regimen.

**Pegfilgrastim** was formed by adding a polyethylene glycol molecule to the N-terminal residue of filgrastim to increase its half-life. The molecular weight of the new molecule is too high to be cleared by the kidneys and, therefore, is mostly cleared by a self-regulation mechanism dictated by neutrophil uptake and utilization.6 Pegfilgrastim clearance increases as neutrophil counts increase. Neutrophil-mediated clearance takes longer than renal clearance, thereby increasing the half-life of the drug to approximately 42 hours.7 As a result, only one 100-µg/kg subcutaneous injection is needed per chemotherapy cycle. Children who weigh more than 45 kg can receive one standard 6-mg dose of pegfilgrastim.2

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**COMPARISON STUDIES DEMONSTRATE SIMILAR EFFICACY IN BOTH G-CSFs**

Although studies on the safety and effectiveness of pegfilgrastim in pediatric patients are limited, comparisons of filgrastim with pegfilgrastim have shown similar efficacy. Comparable similarities in incidence and duration of severe febrile neutropenia and need for transfusions have also been found. Prevalence of side effects is similar between the two G-CSFs as well, indicating that pegfilgrastim holds significant promise for pediatric patients.

Wendelin and colleagues found the duration of grade 4 neutropenia after highly myelosuppressive VIDE (vincristine, ifosfamide [Ifex, generics], doxorubicin [Doxil, generics], etoposide) chemotherapy regimen was 6.1 days with pegfilgrastim and 5.9 days with filgrastim.6 However, after the less myelosuppressive VAI (vincristine, actinomycin D, ifosfamide) and VAC (vincristine, actinomycin D, cyclophosphamide [Cytoxan, generics]) chemotherapy cycles, mean neutropenia duration was 0.4 days with pegfilgrastim versus 0.9 days with filgrastim.6 Spunt and colleagues found the duration of grade 4 neutropenia after VIDE chemotherapy was comparable between the two G-CSF agents as well (6.0 days with pegfilgrastim vs 5.0 days with filgrastim).8 The incidence of febrile neutropenia post-VIDE treatment was 78% with pegfilgrastim versus 56% with filgrastim. Incidence of febrile neutropenia was 0% with pegfilgrastim and 5% with filgrastim post-VAI and -VAC treatments.6 Spunt’s group found that 68% of the pediatric patients in the pegfilgrastim group developed febrile neutropenia after chemotherapy, whereas 83% of the filgrastim group developed the condition.8 In the te Poele study, approximately 22% of participants developed
febrile neutropenia after pegfilgrastim administration. However, caution should be used when interpreting these results because the high rates of neutropenia and adverse effects can be attributed to the highly myelosuppressive nature of the chemotherapy alone and are not necessarily related to the G-CSF treatment.

Very few adverse effects have been reported with G-CSF. The most commonly reported effect with either pegfilgrastim or filgrastim treatment was bone pain. In the Spunt study, 11% of participants reported bone pain after pegfilgrastim administration and 17% reported bone pain after filgrastim administration. Milano-Bausset and colleagues had two patients report bone pain, and the Wendelin study reported only one patient experienced bone pain after treatment. In studies by te Peole and colleagues and Cesaro and colleagues, bone pain was not reported after administration of either drug. However, caution should be used when interpreting these results because the high rates of neutropenia and adverse effects can be attributed to the highly myelosuppressive nature of the chemotherapy alone and are not necessarily related to the G-CSF treatment.

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Risk of neutropenia is significantly reduced with G-CSFs, which could mean fewer hospitalizations and less disruption for a child and family.

CONCLUSION

Children maintain a sense of stability when they have a routine in their life. Cancer disrupts that routine in many different ways and can lead to patients and families feeling a lack of control. This feeling is magnified when the child has to be hospitalized due to febrile neutropenia. The child is unable to attend school with friends, practice sports, or even play with siblings. The parent or caregiver often must take a leave of absence from work in order to be with their sick child, leading to increased financial worries. The risk of neutropenia is significantly reduced with G-CSFs, specifically pegfilgrastim, which could mean fewer hospitalizations and less disruption for a child and family who are already facing so much. The child would be able to maintain a sense of normalcy by attending school and interacting with friends, and the parents would retain control of working and being available for all the family members.

Neutropenia negatively affects quality of life by predisposing patients to hospital admissions and isolation. Fever and neutropenia require hospitalization for IV antibiotics and place both an emotional and financial toll on families due to loss of work and disruption of family life. Granulocyte colony-stimulating factors have been proven to decrease the incidence of fever and neutropenia in children with cancer. Studies comparing filgrastim with pegfilgrastim in pediatric oncology patients demonstrate that pegfilgrastim can be used safely and efficacy is similar with both drugs. The need for fewer injections with pegfilgrastim can improve quality of life for pediatric oncology patients and their families.

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REFERENCES


