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Pediatric GCSF Choice

Sound of Social Responsibility

Introduction

Infection is a major cause of morbidity and mortality in cancer patients. Fever may be the first manifestation of a life-threatening infection, particularly during periods of neutropenia. Febrile episodes occur in approximately one-third of neutropenic episodes in children with chemotherapy-induced neutropenia or after hematopoietic stem cell transplantation. The approximate rate of occurrence is 0.76 episodes per every 30 days of neutropenia.

The demonstration of markedly reduced infection-related morbidity and mortality with the empiric use of broad-spectrum antibiotics during periods of febrile neutropenia was a major advance in the field of oncology in the 1970s. Subsequent studies identified factors associated with a higher risk of bacterial infection and facilitated a more tailored approach to empiric therapy (1, 2). As Febrile neutropenia (FN) is common in patients with chemotherapy and many studies have reported that G-CSF reduces the incidence of FN; for adults, we suggest the use of both pegylated and non pegylated form, However for pediatric patients. we do not have a specific suggestion because the evidence is nonexistent, so it is necessary to carry out clinical trials to obtain evidence (3, 4).

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. 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. Not only dose G-CSF prevent infections and febrile neutropenia in patients receiving anticancer regimens, but, as shown by study findings, it leads to a shorter duration of antimicrobial therapy needed and prevents delays in chemotherapy administration(5). G-CSF has also been proven to useful in facilitating hematopoietic recovery after bone marrow transplant and mobilizing peripheral blood progenitor cells in healthy donors. 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 (6). Prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) reduces the severity and duration of chemotherapy-induced neutropenia and the consequent risk of FN. Furthermore, it plays an increasingly broad role in supporting the delivery of myelosuppressive chemotherapy(7).

Who should receive G-CSFs?

Official guidelines from Europe and the USA now agree that primary G-CSF prophylaxis should be given when the overall risk of FN due to regimen and patient factors is ≥20%. Prior to 2006, primary G-CSF prophylaxis was recommended for chemotherapy regimens associated with a relatively high FN risk of 40%. However, data showed that clinical benefit was obtained at a much lower risk threshold, and the importance of individual patient risk factors was also recognized. Regimens with an overall risk of FN of ≥20% include anthracycline/taxane regimens that are used for treatment of breast cancer, cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)-like regimens used for non-Hodgkin's lymphoma (NHL) and the docetaxel, cisplatin and 5-fluorouracil (DCF/TPF) regimen used for gastric and head and neck cancer.
For regimens that are associated with a 10–20% risk of FN, individual patient factors must also be considered when determining the need for G-CSF support (Fig. 1).

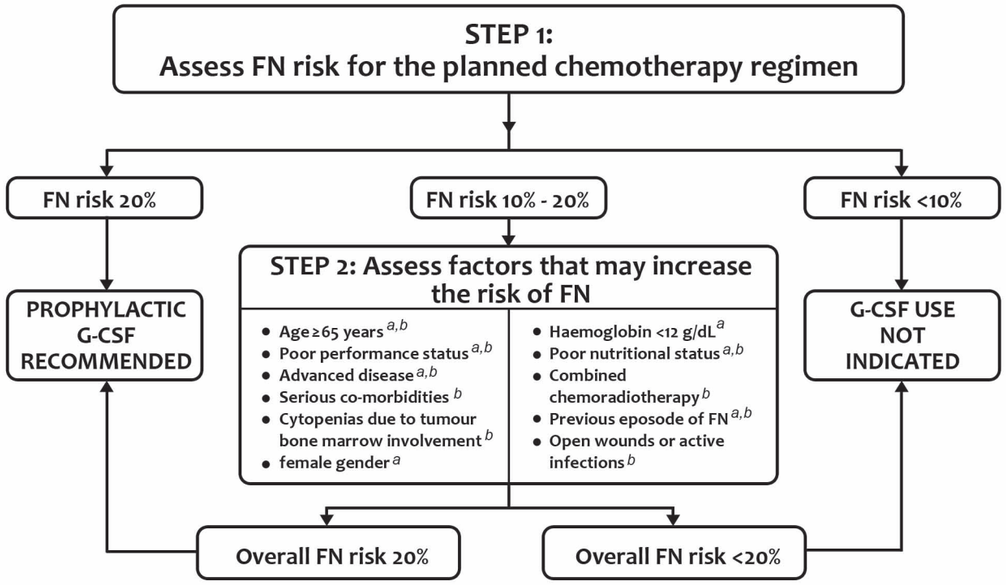

Fig. 1: Algorithm for determining whether granulocyte colony-stimulating factor (G-CSF) prophylaxis is indicated in patients undergoing chemotherapy (represents a combined interpretation of the 2006 G-CSF guidelines of the European Organisation for Research and Treatment of Cancer and the American Society of Clinical Oncology)

Our Choice for Pediatric Use

The non-PEGylated G-CSFs, standard G-CSF (filgrastim). and glycosylated G-CSF (lenograstim) appear to be broadly comparable in efficacy. However, a growing body of evidence suggests that pegfilgrastim a PEGylated formulation of filgrastim with neutrophil-regulated pharmacokinetics that is given as a single dose once per cycle is more effective than filgrastim.
A meta-analysis of five studies in a total of 617 patients treated for breast cancer or lymphoma showed that a single dose of pegfilgrastim was significantly more effective than 10–14 days of filgrastim in reducing FN (RR 0.64, 95% CI 0.43–0.97) .Data from the larger meta-analysis by Kuderer et al. also suggest that pegfilgrastim was more effective than either lenograstim or filgrastim, although it must be noted that the pegfilgrastim data came from a single study. These findings might reflect the sustained stimulation of bone marrow by pegfilgrastim throughout the period of neutropenia (8).

In addition, pegfilgrastim has been allowed to be used in children recently. Before May 2015, FDA had not approved this form of G-CSF in patient under 18 year's old, and Neulasta monograph had no part for pediatric use and was not recommend for children(9, 10), However, FDA has recently approved this form for pediatric use and defined dosing information. (Table 1).

Pegfilgrastim is not designed to allow for direct administration of doses less than 0.6 mL (6 mg). ***The syringe does not bear graduation marks which are necessary to accurately measure doses of Pegfilgrastim less than 0.6 mL (6 mg) for direct administration to patients. Thus, the direct administration to patients requiring dosing of less than 0.6 mL (6 mg) is not recommended due to the potential for dosing errors (11).***

Also in most clinical administrations, PEGylated formulation of filgrastim has more bone pain than non PEGylated form.

Table 1. Dosing of pegfilgrastim for pediatric patients weighing less than 45 kg

Volume to Administer	pegfilgrastim Dose	Body Weight
See below*	See below*	Less than 10 kg*
0.15 mL	1.5 mg	10 -20 kg
0.25 mL	2.5 mg	21 -30 kg
0.40 mL	4 mg	31 -44 kg

*For pediatric patients weighing less than 10 kg, administer 0.1 mg/kg (0.01 mL/kg) of pegfilgrastim.

So it seems that still the best option for GCSF therapy in prophylaxis of chemotherapy induced FN in children is still non pegylated GCSF that is mostly available in many countries as 300 mcg/0.5 ml prefilled syringe.

The recommended initial dose for GCSF is 5mcg/kg which means it`s very likely that we use only half of every prefilled syringe for pediatric daily usage and discard the left over because these single dose prefilled syringes have no preservative and should not be kept for the next dose due to the risk of Contamination.

Arya Tina Gene, as a biopharmaceutical company in Iran Innovated and manufactured GCSF prefilled syringe for pediatric use in dose of 120 mcg per 0.2ml with advantages such as:

- Lower price for patients and other payers like Insurance Companies and the government
- Product waste decrease, which is clearly a national treasure
- A decrease in the risk of incorrect dose injection and dose overestimation
- A decrease in the risk of keeping used syringe, contamination and the high risk of mortality due to injection of contaminated product.

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