

LETTER TO THE EDITOR

Filgrastim desensitization in a patient with Hodgkin lymphoma

To the Editor:

Filgrastim is a granulocyte-colony stimulating factor (G-CSF) that stimulates production of neutrophils, and it is used to prevent or treat febrile neutropenia in patients undergoing chemotherapy.^{1–6} Hypersensitivity reactions to G-CSF formulations, such as filgrastim, pegfilgrastim, and biosimilars, are rare, and few reports exist regarding desensitization protocols, particularly in the pediatric population.^{7–9} Below, we describe successful desensitization and subsequent use of G-CSF (biosimilar product: Nivestym) in an adolescent with a severe hypersensitivity reaction to pegfilgrastim.

A 14-year-old previously healthy Caucasian female was diagnosed with classical Hodgkin lymphoma (nodular sclerosing subtype, stage IIA with mediastinal bulky disease, intermediate risk) and received treatment per Children's Oncology Group study AHOD0031 (NCT00025259) with doxorubicin, bleomycin, vincristine, etoposide, prednisone, and cyclophosphamide.¹⁰

On day 2 of chemotherapy administration, the patient developed cough, facial swelling, shortness of breath, and diffuse hives near the end of etoposide infusion (despite diphenhydramine premedication and infusion over 2 hours per institutional standards). Due to this reaction, etoposide was substituted with etoposide phosphate for subsequent doses, which the patient tolerated without any further reactions. Additionally, due to a remote history of allergy to sulfa drugs, trimethoprim-sulfamethoxazole was substituted with nebulized pentamidine for *Pneumocystis* prophylaxis. The patient was discharged after completion of planned chemotherapy. Consistent with supportive care recommendations, the patient was prescribed G-CSF for prevention of febrile neutropenia. On day 4, 1 hour after home administration of pegfilgrastim (Neulasta), the patient developed facial edema, cough, difficulty breathing, cyanosis, diffuse hives, and diarrhea. She was immediately transported to an emergency room, where she received intramuscular (IM) epinephrine and intravenous (IV) methylprednisolone, which led to improvement of symptoms. However, 1 hour later, the patient had recurrence of symptoms and was treated with a second dose of IM epinephrine as well as IV diphenhydramine. During transport to our pediatric intensive care unit (PICU), the patient required a third dose of IM epinephrine due to hypoxemia requiring supplemental oxygen. Upon admission, the patient was treated with an epinephrine infusion, which resulted in improvement in her symptoms. An attempt to wean the epinephrine infusion within a few hours of admission resulted in recurrence of symptoms, and therefore, a slow wean was conducted over the next 48 hours. Given the multiple allergic reactions, a pediatric allergy consultation was pursued. A

serum tryptase level and *c-KIT* gene mutation analysis for evaluation of systemic mastocytosis were sent, which were both normal.

Due to high risk of myelosuppression and associated infections with this chemotherapy regimen, the patient and her family elected to proceed with desensitization to allow for subsequent use of G-CSF.¹⁰ Based on hospital product formulary, filgrastim-aafi (Nivestym) was used for this desensitization. Desensitization solutions and protocol followed are described in Tables S1 and S2. For the first desensitization, the patient was monitored in the PICU with close supervision by a pediatric allergist and the nurse. Vital signs were monitored every 15 minutes and medications for emergency use were kept at bedside. Desensitization was completed in approximately 3 hours and 5 minutes. The patient was monitored for any hypersensitivity reactions for 1 hour following the desensitization. After successfully completing the desensitization without adverse events, the patient was able to receive full dose filgrastim-aafi 300 µcg subcutaneously once daily beginning the day after desensitization, which was continued at home through neutrophil nadir and recovery. This protocol was initiated 24 hours after each cycle of chemotherapy, allowing successful use of G-CSF for the remainder of her treatment.

The Food and Drug Administration package insert for pegfilgrastim recommends permanent discontinuation of drug upon occurrence of a serious allergic reaction, including anaphylaxis.¹¹ However, given the dose-intensive treatment, the patient and her family elected to attempt desensitization to mitigate risk of adverse events with neutropenia. Given the long half-life of pegfilgrastim (15–80 h), we avoided desensitization with this formulation in case of recurrence of hypersensitivity reactions and used our available biosimilar product filgrastim-aafi (Nivestym).¹¹ Using the aforementioned approach, we were able to successfully administer subsequent doses of filgrastim-aafi and the patient-tolerated chemotherapy well without unexpected adverse events or delays due to neutropenia. Our patient's history of hypersensitivity reactions to both etoposide and pegfilgrastim (Neulasta) is intriguing. Pegfilgrastim (Neulasta) contains polyethylene glycol, which may have cross reactivity with polysorbate products.¹² Hypersensitivity reactions to etoposide are caused by its carrier polysorbate-80, while the carrier for pegfilgrastim is polysorbate-20, all of which are immunologically cross-reactive.¹² As polysorbate-80 is a carrier across all filgrastim formulations, switching to another short-acting G-CSF product was not considered safe. It is possible that the hypersensitivity reaction to pegfilgrastim may have been exacerbated by resolving hypersensitivity to polysorbate-80 from etoposide. Discontinuation of pegfilgrastim removed the patients' exposure to polysorbate-20

and polyethylene glycol, and desensitization to filgrastim-aafi likely allowed tolerance to polysorbate-80 and subsequent use of the drug. Through this report, we highlight clinicians to the potential of cross-reactivity between chemotherapy and supportive care medications used to treat childhood cancer, and present potential means of safely using these drugs despite a severe hypersensitivity reaction.

CONFLICT OF INTEREST

The authors whose names are listed above certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Supplemental Information

Supplemental Table S1. Concentration of solutions of used for desensitization

	Volume	Solution concentration (mcg/mL)	Total dose in each solution (mcg)
Solution A	20 mLs	0.15	3
Solution B	20 mLs	1.5	30
Solution C	20 mLs	15	300
<i>*Total dose to infuse: 300 mcg</i>			

Supplemental Table S2. Desensitization protocol

Step	Solution	Rate (mL/h)	Time (min)	Administered dose (mcg)	Cumulative dose infused (mcg)
1	A	0.5	15	0.02	0.02
2	A	1	15	0.04	0.06
3	A	2	15	0.08	0.14
4	A	4	15	0.15	0.29
5	B	1	15	0.38	0.67
6	B	2	15	0.75	1.42
7	B	4	15	1.5	2.92
8	B	6	15	2.25	5.17
9	C	1.5	15	5.63	10.8
10	C	3	15	11.25	22.05
11	C	6	15	22.5	44.55
12	C	9	114	256.5	301.05
*Solution A: Infusion started at 0.5 mL/hr for 15 minutes. If no hypersensitivity, then increased to 1 mL/hr for 15 minutes, then 2 mL/hr for 15 minutes, then 4 mL/hr for 15 minutes. If no hypersensitivity after 15 minutes at 4 mL/hr, then start SOLUTION B.					
*Solution B: Infusion started at 1 mL/hr for 15 minutes. If no hypersensitivity, then increased to 2 mL/hr for 15 minutes, then 4 mL/hr for 15 minutes, then 6 mL/hr for 15 minutes. If no hypersensitivity after 15 minutes at 6 mL/hr, then begin SOLUTION C.					
*Solution C: Infusion started at 1.5 mL/hr for 15 minutes. If no hypersensitivity, then increase to 3 mL/hr for 15 minutes, then 6 mL/hr for 15 minutes, then 9 mL/hr for 114 minutes.					