

CASE STUDY

Rash associated with the use of pegylated filgrastim in a patient with advanced pancreatic cancer

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Abstract

Filgrastim and pegfilgrastim are granulocyte colony-stimulating factor (G-CSF) products, which have been part of the supportive treatment of cancer patients for years to increase the white blood cell count and absolute neutrophil count with the primary objective of preventing the appearance of neutropenic fever in patients at risk because of the very toxic chemotherapy. Pegfilgrastim is a glycosylated form of filgrastim with a prolonged duration of effect, a reduced renal clearance, and relatively fewer side effects. Rash in particular has been described rarely (less than 3.7% of cases). Various dermatologic complications have been associated with G-CSF therapy, with filgrastim more than pegfilgrastim. These complications include local skin reactions, folliculitis, vasculitis, and pyoderma gangrenosum as well as the more classic generalized allergic rash associated both with and without anaphylaxis. We present a patient with pancreatic cancer who developed facial rash related to the use of pegfilgrastim that led to discontinuation of the agent and we review the literature on this topic.

Keywords: Pegylated filgrastim; pegfilgrastim; pancreatic cancer; rash

Introduction

Pancreatic cancer is currently the fourth leading cause of cancer-related death in the United States, with a survival rate at five years after diagnosis of less than 5% and overall poor quality of life in advanced cases [1]. Chemotherapy is, for most patients, the only available treatment to palliate symptoms and prolong survival. Gemcitabine has been the drug of choice since 1997 after it showed superiority over 5-fluorouracil (5-FU) [2]. In the pivotal trials, myelosuppression is the major dose-limiting factor associated with gemcitabine therapy. Hematologic side effects including anemia (68%), leukopenia (62%), neutropenia (63%), thrombocytopenia (24%), petechiae (16%), thrombotic thrombocytopenic purpura (0.015% to 1.4%), and sepsis (less than 1%) have been reported. Red blood cell transfusions were required by 19% of patients. Rash was generally a macular or finely granular maculopapular pruritic eruption, mild to moderate in severity, involving the trunk and extremities. Alopecia is usually minimal.

Dermatologic side effects including rash (30%), alopecia (15%), pruritus (13%), and radiation recall have been reported. Cellulitis, pseudocellulitis and severe skin reactions including desquamation and bullous skin eruptions have been reported rarely. A case of linear immunoglobulin A bullous dermatosis has been reported [3].

In studies with gemcitabine plus oxaliplatin for pancreatic cancer, severe grade 4 hematologic toxicities occurred in 13% of patients [4]. In the pivotal trial by Moore et al., grade 3/4 neutropenia and thrombocytopenia were seen in 24% and 10% of patients receiving erlotinib and gemcitabine and 27% and 11% of patients receiving placebo and gemcitabine, respectively [5].

Therefore, granulocyte colony-stimulating factors (G-CSFs) are used in many of these patients to increase the absolute neutrophil count (ANC) and to stimulate the neutrophils' maturation and activation as well as their migratory and cytotoxic capacity. The goal is to prevent the development of severe infections, sepsis, and infection-related deaths. Safety profiles and side

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(Received 28 April 2009; revised 03 July 2009; accepted 11 July 2009)

ISSN 1556-9527 print/ISSN 1556-9535 online © 2009 Informa UK Ltd
DOI: 10.3109/15569520903178208

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effects of these agents, although described, are not that well studied.

Literature from the last several years describes few cases of skin eruptions in patients receiving G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) [6–8]. We present another case of rash related to the use of pegfilgrastim (Neulasta; pegylated filgrastim) in a patient being treated for pancreatic cancer and receiving various chemotherapy regimens.

Case Report

A 71-year-old woman underwent endoscopic retrograde cholangiopancreatography (ERCP) for new-onset jaundice and was found to have a mass in the head of the pancreas histologically confirmed as adenocarcinoma. Upon surgical exploration, she was found to have liver metastases and surgery was aborted. In December 2007, she was started on a gemcitabine plus oxaliplatin (GemOx) chemotherapy regimen. After receiving nearly 15 cycles of the combination chemotherapy, her white blood cell (WBC) count started dropping to $2.1 \times 1,000/\mu\text{L}$ with an ANC of $0.8 \times 1,000/\mu\text{L}$. She was started on pegfilgrastim 6 mg subcutaneously after 24 hours of receiving the chemotherapy. She came back to the clinic within a day after starting pegfilgrastim therapy because of the development of a marked facial rash, which was not present at the time of the start of this cycle. The rash was maculopapular, involving the face, especially in the malar regions, and the posterior aspect of the neck, where it appeared as an eczema type of reaction (distant to the injection sites) (Figures 1 and 2). It was pruriginous but not painful, with slightly

raised borders and no significant scaling. No episodes of fever were documented. The patient was given diphenhydramine (Benadryl) 25 mg intravenously (IV) plus dexamethasone 20 mg IV infusion prior to the next dose of Neulasta, but the rash, although mildly improved, persisted. The patient was actually sent home after this with oral Benadryl, and on the third dose she again received steroid plus antihistamines, with no significant improvement. Because of this persistent rash the patient was sent for a consultation with a dermatologist, who concurred with our findings, and the pegfilgrastim injections were withheld indefinitely. The patient's rash subsided with no other intervention and her WBC count and ANC improved after dropping the use of oxaliplatin and continuing gemcitabine therapy alone.

Discussion

Among the different malignancies, pancreatic cancer stands out as one of the more aggressive ones. Inflammation, particularly in the form of chronic pancreatitis, has been elucidated as another major risk for developing this condition [9]. Even more enlightening has been the description by many documents of pancreatic cancer as an inflammatory condition [10–12]. The production of numerous cytokines as well as an imbalance between stimulatory and inhibitory factors has been described. Peritumoral inflammatory cells as well



Figure 1. The maculopapular rash in the malar eminences of the patient's face.



Figure 2. The raised eczema-like lesions in the posterior aspect of the patient's neck.

as malignant pancreatic cells can produce cytokines like epidermal growth factor, insulin growth factor, interleukin (IL)-1-alpha, IL-8, many other proinflammatory substances exerting autocrine action to promote cancer growth as well as immunomodulatory and angiogenic activity, and products with the ability to interact with extracellular matrix and facilitate metastatic spread [12] (Table 1).

This better understanding of advanced pancreatic cancer opens many doors for future target therapies, but for now serves more to further understand the major impact of this condition in patients' health and function. Hematopoietic cytokines can affect the growth and spread of cancer, and, among these, G-CSF and macrophage-colony stimulating factor (M-CSF) have been studied and found to be secreted in considerable amounts by pancreatic cancer cells, so much so that their measurement has been proposed as a means to assess tumor burden and response to therapy (tumor marker) [13,14]. None of these uses, however, are in practice yet.

Filgrastim and pegfilgrastim are G-CSF products. They have been part of the supportive treatment of cancer patients for years. Their main use is to increase the WBC count and ANC with the primary objective of preventing the appearance of neutropenic fever in patients at risk because of the very toxic chemotherapy regimen or secondary to individual-related risk factors (age, medical history, or malignancy type) [15]. In a 2005 study comparing the use of gemcitabine plus docetaxel with the use of docetaxel plus cisplatin for advanced cancer of the pancreas, NF occurred in 9% and 16% of patients in these groups, respectively [16]. These patients have several risk factors that place them among the intermediate- to high-risk group for developing FN such as age greater than 65 years, poor performance status, liver dysfunction (metastases), hypoalbuminemia, diabetes, and

the need for dose-dense chemotherapy [17]. Therefore, it is common practice to give these agents as primary prophylaxis for patient support.

Pegfilgrastim is a glycosylated form of filgrastim with a prolonged duration of effect (half-life of 15–80 hours vs. 1.8–3.5 hours, respectively), a reduced renal clearance, and relatively fewer side effects described in only 4.5% of patients. Rash, in particular, has been described rarely and, in a series of 54 patients with congenital neutropenia, the use of this agent was complicated by dermatologic manifestations in less than 3.7% of patients. Various skin conditions have been described to be associated with G-CSF therapy, with filgrastim more than pegfilgrastim. These include local skin reactions with eosinophilic infiltration, folliculitis, vasculitis, and pyoderma gangrenosum in addition to the more classic generalized allergic rash associated both with and without anaphylaxis [18]. The development of more cases of rash with regular filgrastim as opposed to pegfilgrastim seems to be mediated by antibodies created to the naked “nonglycosylated” backbone of the former. In other conditions, such as Behçet disease, G-CSF has been linked to rash by antiapoptosis of pathogenic neutrophils infiltrating the skin structures, perpetuating a previous pathogenic process [19]. The presence of large histiocytes on the dermis between collagen bundles has been proposed as a characteristic histopathologic finding in cutaneous eruptions secondary to hematopoietic growth factors [20].

It is unclear at this point whether there is an absolute risk that warrants the universal administration of G-CSF to all patients in chemotherapy for advanced pancreatic cancer. Current practices are based more on generalized acceptance that these patients are at intermediate risk and the use of these stimulating factors is safe and effective. However, there are a couple of questions to be answered. Is it really safe? Multiple articles are arising showing pancreatic cancer as an inflammatory condition with localized (tumor and peritumoral) and generalized production of cytokines, which not promotes only cell growth, but also invasion and distant spread. By administering these growth factors, are we promoting this aggressive tumoral behavior? Is it helping the tumor get resistant to our own cytotoxic treatments? And, assuming that it is in fact not helping this malignancy, at least do we feel completely comfortable with its side effects?

Here we present a case of G-CSF-related rash that merits the discontinuation of the drug. We cannot explain the exact mechanism by which this reaction was produced, but a possible explanation could be a cross-reaction between the exogenous G-CSF and antibodies produced against the native overproduction of this compound by the tumor cells. It could also be an antiapoptotic effect of neutrophils already infiltrating the skin of

Table 1. Cytokines produced in pancreatic cancer [8].

Pathologic step in pancreatic cancer	Cytokines involved
Autocrine	EGF, TNF alpha, IGF-I, TGF-beta1, PDGF, RANTES, MCP-1, GM-CSF, IL-1, IL-8.
Growth	EGF, TNF alpha, IGF-I, TGF-beta1, IL-8, IL-1
Angiogenesis	BFGF, VEGF, EGF, TNF alpha, IGF-I, TGF-beta1, PDGF, IL-8, IL-1
Metastasis	IL-2, IL-4, IL-8, IL-10, RANTES, MCP-1, GM-CSF

BFGF= basic fibroblast growth factor; EGF= epidermal growth factor; GM-CSF= granulocyte-macrophage colony stimulating factor; IGF-I= insulin-like growth factor I; IL= interleukin; MCP-1= monocyte chemo-attractant protein-1; PDGF= platelet-derived growth factor; RANTES= regulated on activation, normal T cell expressed; TGF-beta1= transforming growth factor beta 1; TNF alpha= tumor necrosis factor alpha; VEGF= vascular endothelial growth.

this patient or just an idiosyncratic reaction to the drug, as seen with many other commonly used medications.

Acknowledgements

Declaration of interest: No potential conflict of interest relevant to this article were encountered.

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