

## Safety and Efficacy of Same-Day Administration of Pegfilgrastim in Patients Receiving Chemotherapy for Gastrointestinal Malignancies

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### **ABSTRACT**

#### **BACKGROUND**

Pegfilgrastim is typically administered 24 hours after chemotherapy per package insert; however some patients are unable or unwilling to return for this additional visit due to work or transportation especially with regimens consisting of infusional 5-FU. Same-day dosing eliminates need for this additional visit. Results from prior studies in other tumor types are inconclusive as few support same-day dosing whereas others show inferiority. Purpose of our study was to determine safety and efficacy of administering pegfilgrastim on same day as chemotherapy in patients with gastrointestinal (GI) malignancies.

#### **METHOD**

A single-institution retrospective review was conducted of 69 patients with GI malignancies who received chemotherapy and same-day pegfilgrastim (6 mg) within 1 hour of completion of chemotherapy from Jan 2014 through Jan 2017. As per institutional guidelines, patients were counseled on risks of same-day pegfilgrastim prior to its administration. These patients were compared with a set of 70 patients who received pegfilgrastim 24-hours after completing the chemotherapy for GI cancers.

#### **RESULT**

A total of 536 chemotherapy cycles in 69 patients were analyzed. Median absolute neutrophil count nadir for all cycles was 4538/uL (Range: 1160 - 25168). Grade 1 and 2 neutropenia developed in 6 of 536 (1%) cycles. Bone pain reported in 3 patients (4%). There were no episodes of grade 3 or 4 neutropenia or febrile neutropenia. None had dose reductions, chemotherapy delays, hospitalizations, or antibiotic use due to neutropenia.

#### **CONCLUSION**

We believe our study is the first in GI malignancies to report that same-day pegfilgrastim administration may be as effective and safe as next-day administration, benefiting patients and might reduce costs.

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## KEYWORDS

Chemotherapy; Pegfilgrastim; Neutropenia; Leukopenia; Fever; Side effects

### 1. INTRODUCTION

Neutropenia is a serious adverse complication of myelosuppressive chemotherapy that predisposes patients to life-threatening infection, hospitalization and delays in treatment. This is associated with significant mortality as well as increased health-care associated costs [1]. Chemotherapy induced neutropenia has been mitigated by advent of granulocyte stimulating factors. The first of this class of drug to be widely used was filgrastim, a recombinant version of endogenous growth factor that stimulated the proliferation and differentiation of neutrophils. Due to its small size, filgrastim is rapidly cleared by the kidneys and requires daily dosing. Pegfilgrastim, a filgrastim molecule linked to a large polyethylene glycol molecule, is a popular alternative as the large pegylated moiety slows renal clearance and requires dosing only once during a chemotherapy cycle [2]. Per the dosing administration instructions, pegfilgrastim should not be given 14 days before or 24 hours after administration of cytotoxic chemotherapy. This is largely based on a theoretical risk of paradoxically increasing hematologic toxicity as GSF is thought to increase the population of chemotherapy-susceptible granulocyte precursors [3]. This dosing regimen is cumbersome, often requiring patients to make additional office visits. In light of this, some patients opt to receive pegfilgrastim on the same day as chemotherapy despite the potential risks. Studies estimate an average of 13% of cancer patients receiving prophylactic GSF receives same-day dosing [4]. In this study, colorectal cancer patients were the most likely to opt for same-day dosing with 19% of these patients receiving pegfilgrastim within 24-hours of cytotoxic chemotherapy. Studies looking at the safety and efficacy of same day dosing compared to traditional next day

administration have been conflicting. Some have cited increased incidence of FN and duration of severe neutropenia associated with same-day dosing of pegfilgrastim in various solid tumors and NHL [5-7] while others found non-inferiority [8-10]. In June 2018, the U.S. Food and Drug Administration today approved fulphila (pegfilgrastim-jmdb) as the first biosimilar to pegfilgrastim [11].

Investigators have looked into the safety and efficacy of same day pegfilgrastim dosing in many tumor types, however, data remains conflicting. Such studies mostly included patients with non-gastrointestinal (GI) cancers such as lung and hematological malignancies. GI malignancies combines together constitute the most common cancer world-wide and hence data is necessary to address this issue in this patient population.

To answer this question, we examined the safety and efficacy of same-day dosing of pegfilgrastim in patients with GI malignancies. In this single center, retrospective study we attempted to characterize the complications of same day dosing including incidence of neutropenia, febrile neutropenia and GCSF-related bone pain in patients treated for GI malignancy.

### 2. METHOD

A single center, retrospective study was performed of patients with GI malignancies who received pegfilgrastim as an adjunct to cytotoxic chemotherapy. Patients were treated at the Tufts University Cancer Center from January 2014 through January 2017 and received pegfilgrastim with-in 1 hour of completion of chemotherapy. The decision to administer pegfilgrastim was based on ASCO or NCCN guidelines [12,13]. Patients had an average of 4 risk factors for febrile

neutropenia: Advanced disease, age >65 years, and gender, and chemotherapy regimen.

As per institutional guidelines, patients were counseled on risks of same-day pegfilgrastim prior to its administration. Information was obtained exclusively through review of individual electronic medical records. Data collected included patient demographics, pathology reports, blood counts (drawn on days 8, 15 days or 21 days according to the chemotherapy regimen), incidence of neutropenia, febrile neutropenia, and hospitalization, use of antibiotics, bone pain, toxicity, chemotherapy regimen, chemotherapy dose, and day of pegfilgrastim administration.

### 3. RESULT

#### *Patient demographics*

A total of 536 chemotherapy cycles in 69 unique patients who received same-day pegfilgrastim were analyzed. Median patient age was 61 years (range 32 - 87) and 58% of patients were over 65.

	n	% of points
<b>Patients</b>	69	
Median Age (years)	61	
Age range (years)	32 - 87	
Male	39	57%
Over 65 years	40	58%
Multiple regimens	16	23%
<b>Location of Disease</b>		
Colorectal	30	43%
Pancreas	12	17%
Stomach	12	17%
Cholangiocarcinoma	7	10%
Appendix	3	4%
Esophagus	3	4%
Unknown primary	2	3%
<b>Regimen Backbone</b>		
FOLFOX	29	42%
FOLFIRINOX	16	23%
FOLFIRI	8	12%
EOX	6	9%
<b>Total Cycles of Treatment</b>	536	

**Table 1:** Patient demographics.

Included patients had an average of four risk factors for febrile neutropenia including advanced disease, gender, age over 65 and chemotherapy regimen. Patients were stratified based on the location of GI malignancy. The most common malignancies included colorectal (48%), pancreas (17%) and gastric (17%). Patients received a variety of different chemotherapies.

The most common regimens included mFOLFOX6 (42%), FOLFIRINOX (23%) and FOLFIRI (12%) (Table 1).

#### *Efficacy*

Grade 1 and 2 neutropenia (defined as ANC 2000/ $\mu$ L - 1500/ $\mu$ L and 1500/ $\mu$ L - 1000/ $\mu$ L, respectively) was observed in 6 of 536 (1%) cycles (Table 2). There were no episodes of grade 3 or 4 neutropenia or febrile neutropenia. The median absolute neutrophil count (ANC) was calculated for each chemotherapy cycle for each patient using available blood count data. Median ANC nadir per chemotherapy cycle across all regimens was 4538/ $\mu$ L (range: 1160 - 25168).

None had dose reductions, chemotherapy delays, hospitalizations, or antibiotic use due to neutropenia.

	1/ $\mu$ L
<b>Median</b>	4538
<b>Range</b>	1160 - 25168

**Table 2:** ANC Nadir.

#### *Toxicity*

Bone pain reasonably attributed to pegfilgrastim administration was reported in 3 patients (4%). These included patients who had a strong temporal relationship between the onset of bone and pegfilgrastim dosing (Table 3).

		n	% of points
<b>Neutropenia</b>			
	G1-2	6	9%
	G3-4	0	0%
<b>Febrile Neutropenia</b>		0	0%
<b>Bone Pain</b>		3	4%

**Table 3:** Treatment complications.

#### 4. DISCUSSION

To the best of our knowledge, this is the first study to examine the efficacy of same day pegfilgrastim dosing in patients with GI malignancies. Based on our data it appears same day administration of pegfilgrastim is effective in prevention of neutropenia in patients with GI malignancies and should at least be considered a reasonable option for patients especially inconvenienced by traditional next-day dosing (Figure 1).

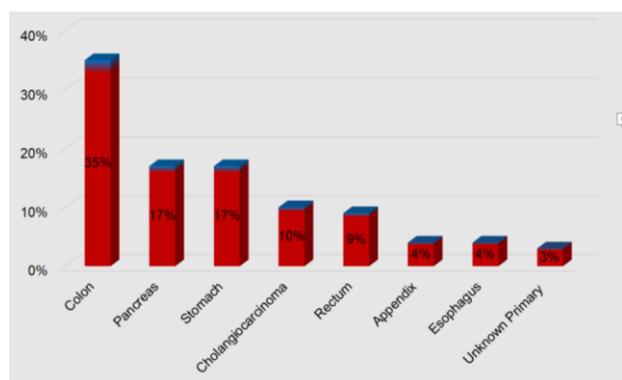


Figure 1: Types of GI malignancies.

Non-inferiority of same day dosing has been documented in several different malignancies and chemotherapy regimens. In a study of 113 patients receiving Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) for NHL there was no difference in rates of FN between same-day and next-day G-CSF (either filgrastim or pegfilgrastim) dosing (25.8% same day vs. 25.6% next-day, p = 0.91) [9]. Additionally, there were no significant differences in relapse free or overall survival. In a retrospective analysis of 230 patients with gynecological malignancy there was no statistical difference observed G3-4 neutropenia, febrile

neutropenia, treatment delays or dose modifications between same and next-day dosing. The majority of these patients had advanced disease and was treated with carboplatin in combination with either docetaxel or paclitaxel [10].

A randomized phase II trial found no difference in neutropenia between same day-day vs. next-day pegfilgrastim dosing in lung cancer patients receiving carboplatin and docetaxel [13]. Furthermore, a retrospective analysis of 159 patients with over 15 tumor types and multiple chemotherapy regimens found there was no statistical difference in the rate of ANC recovery between same day vs. next day dosing of pegfilgrastim. The authors went on to suggest that same day administration may be a safe and convenient alternative to traditional next-day dosing [8].

While there are several studies showing non-inferiority, data surrounding the efficacy of same day pegfilgrastim dosing remains conflicting and controversial. There have been several recent studies that point to a potential harm of same day dosing. The largest of these is a retrospective analysis of greater than 45,000 patients undergoing treatment for a variety of solid tumors or for NHL. The authors found a significantly increased OR for febrile neutropenia in patients receiving same day vs. next day pegfilgrastim administration (OR = 1.6, 95 % CI = 1.3 - 1.9, p<0.001) [14].

A study combining four Amgen sponsored trials found that next-day administration reduced the degree and duration of ANC suppression in patients undergoing treatment for NHL, breast cancer, relapsed or refractory ovarian cancer or advanced or metastatic NSCLC compared to same-day dosing [15]. Notably there was no difference in rates of FN.

Additionally, a small retrospective study of NHL patients treated with CHOP +/- Rituximab did demonstrate a

difference in incidence of FN among all cycles (9.4 vs. 5.1% in the same-day versus the next-day group ( $p = 0.03$ )) though incidence of FN following the first cycle, when rates are highest showed no difference (19.4 vs. 11.1% for the next-day group ( $p = 0.27$ )) [6].

Many oncologists believe that the conversation surrounding efficacy of dosing pegfilgrastim dosing has been made moot through the introduction of the OnPro Delivery Kit [16]. This is a device that can be adhered to the skin on the day of chemotherapy administration and auto-injects the recipient on the following day, thus eliminating the need for a return office visit. While this is an attractive alternative, about 20% of our patient population who would be qualify for this device decline its application. Anecdotally, patients often site not liking a bulky attachment to their skin and having trepidation over an unwitnessed administration of pegfilgrastim both for fear of reaction and/or lack of confirmation of proper dose administration [17].

Our study had several limitations. Most notably, the small sample size did not allow for adequate capture of the most clinically significant endpoints. We did not observe any episodes of G3-4 neutropenia or febrile

neutropenia. There were also not enough intra-cycle blood draws to allow for reliable trending of the ANC nadir and recovery time. Additionally, this was a single institution retrospective analysis which may limit the extrapolation of results to a more diverse patient population.

## **5. CONCLUSION**

We believe our study is the first in GI malignancies to report on the administration of pegfilgrastim on same day as chemotherapy. Administering pegfilgrastim on same day appears to be safe, effective, and convenient in selected patients receiving myelosuppressive chemotherapy for GI malignancies. Safety, efficacy and cost analysis is warranted in future studies, especially given that patients with certain GI malignancies are living longer and receiving many lines of therapy as well as the increase in geriatric population in USA predisposed to malignancies. While we would still recommend the approved next-day administration schedule, our data suggests that say same-day dosing may be a safe and reasonable alternative for those with significant barriers to the required return visit or those who are adverse to the OnPro delivery kit.

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