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ORIGINAL ARTICLE

A single-arm, retrospective analysis of the incidence of febrile neutropenia using same-day versus next-day pegfilgrastim in patients with gastrointestinal cancers treated with FOLFOX or FOLFIRI

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Abstract

Background Practice patterns of same-day versus next-day pegfilgrastim vary in numerous practice settings across the country. Current utilization with same-day pegfilgrastim reduced overall visits and reduced treatment time for chemotherapy administration.

Objective To assess the efficacy and safety of same-day versus next-day pegfilgrastim in patients with colorectal cancer.

Methods Patient data was extracted through electronic health records (EHR) search of ICD-9 codes that matched patients with CRC and treated with FOLFOX or FOLFIRI from November 2013 to January 2016. The incidence rates of primary and secondary endpoints were estimated for patients who received either FOLFOX or FOLFIRI and same-day pegfilgrastim with 2-sided 95% confidence intervals. Fisher's exact test for 2×2 contingency tables was used to compare the incidence of primary and secondary endpoints between the two study groups performed at the $\alpha = 0.05$ significance level. A study by Hecht et al. served as a historical control for next-day pegfilgrastim.

Results A total of 109 out of an initial 330 patients with appropriate ICD-9 criteria were eligible for study inclusion. The primary endpoint of incidence of FN recorded over 4 chemotherapy cycles with either FOLFOX6 or FOLFIRI occurred in 3.7% of patients (95% CI, 1.1–9.4%). Secondary endpoints also occurred with a relatively low incidence: 13 patients developed grades 3/4 neutropenia (11.9%; 95% CI, 7.0–19.5%); 11 patients required dose reductions because of neutropenia or FN (10.1%; 95% CI, 5.6–17.3%); and 5 patients were hospitalized due to neutropenia or FN (4.6%; 1.7–10.6%). There were 4 reported events of FN (3.2%; 95% CI, 1.0–8.3%) for those who received next-day pegfilgrastim compared to 11 events in the placebo group (9.4%; 95% CI, 5.1–16.4%). The incidence of dose delays or dose reductions due to neutropenia or FN were 5 (4.1%, 95% CI, 1.5–9.4%) in the next-day pegfilgrastim group versus 26 (22.1%, 95% CI, 15.5–30.4%) in the placebo group.

Limitations The study was retrospective in design and utilized a historical control for the comparator.

Conclusions Our study results suggest that same-day pegfilgrastim administration may be a safe and effective alternative to 24-h post-chemotherapy administration in patients with esophageal, gastric, appendiceal, or colorectal cancer undergoing treatment with FOLFOX or FOLFIRI.

Keywords Gastrointestinal cancers · FOLFOX · FOLFIRI · Same-day pegfilgrastim · Febrile neutropenia

Background

Gastrointestinal cancers include colorectal, esophageal, gastric, and appendiceal cancers. Of these, colorectal cancer (CRC) represents the third most common cancer in the world and the fourth most common cause of cancer-related deaths [1]. Unfortunately, almost half of all CRC patients will develop metastatic disease [2]. Common treatment options for metastatic colorectal cancer (mCRC) are 5-fluorouracil (5-FU)/leucovorin (LV) plus oxaliplatin or irinotecan [3–5]. The

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FOLFOX treatment regimen consists of 5-fluorouracil (5-FU)/leucovorin (LV) plus oxaliplatin while the FOLFIRI treatment regimen is the same but it exchanges irinotecan for oxaliplatin (see Appendix Table 5 for further detail). One of the predominant adverse events associated with these regimens is neutropenia [3–5]. The incidence of grade 3 or 4 neutropenia in patients receiving FOLFOX or FOLFIRI has been reported to be as high as 42% and 46%, respectively [6].

Severe neutropenia and febrile neutropenia are important dose-limiting toxicities, which can lead to delays in chemotherapy or dose reductions of chemotherapy. Delays in therapy or dose reductions may then lead to tumor progression and decreased overall survival [7]. Studies have shown that using prophylactic granulocyte colony-stimulating factors (G-CSFs) reduce the incidence of neutropenia in patients with non-myeloid malignancies, which prevents delays in chemotherapy and increased relative dose intensity (RDI) compared to patients who did not have G-CSF supportive care [6–11].

Filgrastim is a G-CSF that works by stimulating production and maturation of neutrophils in the bone marrow thereby reducing the incidence of neutropenia [12, 13]. Filgrastim (Neupogen®) requires once daily dosing owing to a short half-life of only 3–4 h [13]. To prolong the duration of action of filgrastim, a pegylated formulation, pegfilgrastim (Neulasta®), was developed to increase its half-life to 42–46 h [13]. Pegfilgrastim has garnered much interest with clinicians because it allows for once per cycle dosing compared to daily dosing with filgrastim [12–14]. According to manufacturer labeling information, pegfilgrastim should not be administered in the period between 14 days before and 24 h after chemotherapy administration [14]. These restrictions can present logistical challenges when providing care for patients on an outpatient basis.

Over the last several years, researchers have begun evaluating same-day versus next-day pegfilgrastim in a wide array of cancer types with various chemotherapy regimens [15, 16]. Despite numerous studies, there is no widespread agreement regarding same-day versus next-day pegfilgrastim. In a randomized prospective study, Burris and colleagues examined same-day versus next-day pegfilgrastim in patients with non-Hodgkin's lymphoma (NHL), breast cancer, non-small cell lung cancer (NSCLC), and ovarian cancer [15]. The authors concluded that pegfilgrastim should be administered 24 h post-chemotherapy despite a lack of statistical significance of their primary end-point, duration of neutropenia between the two groups [15]. In contrast, a study by Whitworth et al. investigated same-day versus next-day pegfilgrastim in patients with gynecologic malignancies and found that pegfilgrastim administered on day 1 of chemotherapy was as safe and effective and more convenient than 24-h post-chemotherapy pegfilgrastim administration [16]. In accordance with mounting evidence of safe use of same-day pegfilgrastim, The National Comprehensive Cancer Network (NCCN) myeloid growth factor guidelines have been updated to include same-day pegfilgrastim (although no formal recommendations exist regarding cancer types and treatment regimens) [17]. To our knowledge, this is the first published study investigating same-day versus next-day pegfilgrastim in patients undergoing FOLFOX of FOLFIRI treatment for CRC.

Objective

This retrospective study examined the incidence of febrile neutropenia (FN, ANC $\leq$ 1000 cells/mm^3 and temperature $\geq$ 38.0 °C or a diagnosis of "neutropenic fever" on chart review) in patients with esophageal, gastric, appendiceal, or colorectal cancer undergoing treatment with either FOLFOX or FOLFIRI. Patients must have been receiving same-day pegfilgrastim, defined as patients who received pegfilgrastim on the day of disconnect from the 5-fluorouracil (5-FU) pump. Secondary endpoints included incidence of grades 3/4 neutropenia (grade 3, $\leq$1000 cells/mm^3 and grade 4, $\leq$1000 cells/mm^3), dose delays and/or reductions because of FN or neutropenia, and hospitalizations due to FN.

Methods

Patient data was extracted through electronic health records (EHR) search of ICD-9 codes that matched patients with CRC and treated with FOLFOX or FOLFIRI from November 2013 to January 2016. Criteria for patient eligibility included $\geq$ 18 years of age, biopsy confirmed diagnosis of esophageal, gastric, appendiceal, or colorectal cancer and a history of treatment with FOLFOX or FOLFIRI. Patients were excluded from study if there was a diagnosis of biliary or pancreatic cancer or received any chemotherapy agents in addition to FOLFOX or FOLFIRI, including biologic agents such as bevacizumab or cetuximab.

A study by Hecht et al. had two treatment arms, placebo, and next-day pegfilgrastim [6]. The arm utilizing next-day pegfilgrastim served as a historical control to compare the incidence of primary and secondary endpoints. The primary endpoint of same-day pegfilgrastim was febrile neutropenia defined as ANC $\leq$ 1000 cells/mm^3 and temperature $\geq$ 38.0 °C or a diagnosis of "neutropenic fever" on the patient's chart review. Secondary endpoints of this study included incidence of grades 3/4 neutropenia (ANC, $\leq$1000 cells/mm^3), dose delays/reductions because of FN or neutropenia, and hospitalizations due to FN. Study endpoints were recorded over 4 chemotherapy cycles.

The incidence rates of primary and secondary endpoints were estimated for patients who received either FOLFOX or

FOLFIRI and same-day pegfilgrastim with 2-sided 95% confidence intervals. Fisher's exact test for 2 × 2 contingency tables was used to compare the incidence of primary and secondary endpoints between the two study groups performed at the $\alpha = 0.05$ significance level.

Results

A total of 109 out of an initial 330 patients with appropriate ICD-9 criteria were eligible for study inclusion. Most of the 221 patients who did not meet criteria were excluded due to history of receiving combination therapy with either bevacizumab or cetuximab. Most patients who received same-day pegfilgrastim ($N = 25$) were male (60%), had metastatic disease (64%), had received previous chemotherapy (76%), completed 4 cycles of chemotherapy (56%), and received same-day pegfilgrastim as secondary prophylaxis (76%) (Table 1).

The primary endpoint of incidence of FN recorded over 4 chemotherapy cycles with either FOLFOX6 or FOLFIRI occurred in 4 patients (3.7%; 95% CI, 1.1–9.4%) (refer Appendix Table 5 for treatment regimens). Secondary endpoints also occurred with a relatively low incidence: 13 patients developed grades 3/4 neutropenia (11.9%; 95% CI, 7.0–19.5%); 11 patients required dose reductions because of neutropenia or FN (10.1%; 95% CI, 5.6–17.3%); and 5 patients were hospitalized due to neutropenia or FN (4.6%; 95% CI, 1.7–10.6%). It should be noted that further characterization of hospital events could not be compiled due to a loss of data from changing electronic health records. Refer to Table 2 for results of same-day pegfilgrastim.

Hecht et al. recorded all grades of febrile neutropenia as number of events [6]. There were 4 reported events (3.2%; 95% CI, 1.0–8.3%) for those who received pegfilgrastim compared to 11 events in the placebo group (9.4%, 95% CI, 5.1–16.4%) [6]. Grades 3/4 neutropenia (ANC < 1.0×10^9/L) occurred with a high incidence of 104 reported events in the placebo group (87.9%; 95% CI, 81.0–92.9%) compared to 27 patients in the next-day pegfilgrastimg group (22.2%; 95% CI, 15.5–30.1%) [6]. The incidence of dose delays or dose reductions due to neutropenia or FN were 5 (4.1%, 95% CI 1.5–9.4%) in the pegfilgrastim group versus 26 (22.1%, 95% CI 15.5–30.4%) in the placebo group (Table 3) [6].

Discussion

The continued discussion over same-day pegfilgrastim and next-day pegfilgrastim continues to drive a further discussion on efficacy and safety of the growth factor for supportive care in the prevention of FN. Labelling for pegfilgrastim states that the drug should not be administered in the period between 14 days before and 24 h after chemotherapy administration [14]. However, we continue to see further data and practices utilize current treatment with same-day pegfilgrastim in a number of different disease states [15, 18, 19].

Hecht et al. conducted a 1:1 randomized, double-blind, placebo-controlled study with patients receiving 6 mg of

Table 1 Patient demographics of those who received same-day pegfilgrastim

Number of patients, *N* (%)	Received same-day pegfilgrastim	*N* = 25 (22.5%)
	Total patients	*N* = 109
Age, years	Mean	65
	Range	34 to 86
Sex, *N* (%)	Male	*N* = 15 (60%)
	Female	*N* = 10 (40%)
Primary diagnosis, *N* (%)	Colorectal	*N* = 14 (56%)
	Esophageal	*N* = 5 (20%)
	Gastric*	*N* = 4 (16%)
	Adenocarcinoma of the appendix	*N* = 2 (8%)
Staging, *N* (%)	Stage 3	*N* = 9 (36%)
	Stage 4	*N* = 16 (64%)
Received previous chemotherapy, *N* (%)	Yes	*N* = 19 (76%)
	No	*N* = 6 (24%)
Completed 4 cycles of chemotherapy, *N* (%)	Yes	N = 14 (56%)
	No	*N* = 11 (44%)
Received pegfilgrastim as primary prophylaxis, *N* (%)	Yes	*N* = 6 (24%)
	No	*N* = 19 (76%)

*One patient who is listed as gastric cancer had GE junctional cancer

Table 2 Incidence of neutropenia, FN, dose modifications, and hospitalizations in patients receiving same-day pegfilgrastim

Incident	Regimen	Incidence, N (%) ($N = 109$)
Grades 3/4 neutropenia	FOLFOX6/FOLFIRI	$N = 13$ (11.9%) [95% CI, 7.0–19.5%]
Febrile neutropenia (FN)	FOLFOX6/FOLFIRI	$N = 4$ (3.7%) [95% CI, 1.1–9.4%]
Dose delays or dose reductions because of neutropenia or FN	FOLFOX6/FOLFIRI	$N = 11$ (10.1%) [95% CI, 5.6–17.3%]
Hospitalization as a result of neutropenia or FN	FOLFOX6/FOLFIRI	$N = 5$ (4.6%) [95% CI, 1.7–10.6%]

pegfilgrastim vs placebo for each of three different treatment regimens [6]. The three every 2-week chemotherapy regimens used in the study were FOLFOX4, FOLFIRI, and FOIL [6]. Pegfilgrastim injection was given subcutaneously 24 h at the end of the 5-FU infusion for each chemotherapy cycle as primary prophylaxis against neutropenia/FN. Our study suggests that same-day pegfilgrastim administration on the day of the 5-FU pump disconnect may be as safe as 24-h post-treatment pegfilgrastim administration. The incidence of febrile neutropenia, grade 3 or 4 neutropenia, dose delays/reductions, and hospitalizations were all similar between same-day and post-treatment pegfilgrastim administration.

One could expect a higher incidence of FN and neutropenia in our study population because the majority of patients who received same-day pegfilgrastim received it as secondary prophylaxis (76%) while in the study by Hecht et al. all patients received pegfilgrastim as primary prophylaxis [6]. Patients receiving pegfilgrastim as secondary prophylaxis more closely follows NCCN recommendations that place the FOLFOX/FOLFIRI regimens in the intermediate risk group of developing FN (risk > 10%) [17]. Thus, only select patients are likely to receive same-day pegfilgrastim as primary prophylaxis based on patient-specific risk factors. The primary endpoint was the incidence of grades 3/4 neutropenia (ANC $< 1.0 \times 10^9$ L) [6]. The study listed the incidence of FN for each treatment group for both placebo and pegfilgrastim [6]. The reported incidence in the pegfilgrastim arm for FOLFOX4 and FOLFIRI were 6.6 and 15.6% respectively [6]. These percentages were combined in as an incidence of (22.2%; 95% CI 15.5–30.1%) composite endpoint for each chemotherapy regimen to reflect composite endpoints in our study between the two treatment regimens of FOLFOX or FOLFIRI (Table 3).

The incidence of FN (3.7 vs 3.2%, $p = 0.709$) was comparable between same-day and next-day pegfilgrastim. Table 4 directly compares primary and secondary endpoints between our study and the one conducted by Hecht et al. The incidence of dose delays/reductions were also similar between the two study groups (4.6% vs 4.1%, $p = 0.117$). The principle difference between the two studies was the incidence of grades 3/4 neutropenia (11.9% vs 22.2%, $p = 0.055$), which could owe to differences between FOLFOX6/FOLFOX4 and FOLFIRI based regimens (refer to Table 5 included in the appendix for a list of treatment regimens).

Several limitations were noted in this study; primarily, the study is retrospective in nature and could be prone to selection bias. Primary and secondary endpoints between our study population and the historical control cannot be directly

Table 3 Incidence of neutropenia with next-day pegfilgrastim (Hecht et al.) [6]

Incident	Regimen	Incidence	
		Placebo ($N = 118$)	Pegfilgrastim ($N = 123$)
Grades 3/4 neutropenia	FOLFOX4/FOLFIRI	$N = 104$ (87.9%) [95% CI, 81.0–92.9%]	$N = 27$ (22.2%) [95% CI, 15.5–30.1%]
Febrile neutropenia (FN)	FOLFOX4/FOLFIRI/FOIL	$N = 11$ (9.4%) [95% CI, 5.1–16.4%]	$N = 4$ (3.2%) [95% CI, 1.0–8.3%]
Dose delays or dose reductions because of neutropenia or FN	FOLFOX4/FOLFIRI/FOIL	$N = 26$ (22.1%) [95% CI, 15.5–30.4%]	$N = 5$ (4.1%) [95% CI, 1.5–9.4%]

Table 4 Comparison of study results

	Hecht et al. ($N = 123$)	Eckstrom et al ($N = 109$)	P value
Grades 3/4 neutropenia	27	13	0.055
Febrile neutropenia	4	4	0.709
Dose delays or dose reductions because of neutropenia or FN	5	11	0.117

compared owing to slight differences in treatment regimens, receiving pegfilgrastim as primary vs secondary prophylaxis, and how febrile neutropenia was defined in each study population. Patients in our study were considered to have developed febrile neutropenia if the ANC was ≤ 1000 and the temperature was ≥ 38.0 °C or there was a diagnosis of "febrile neutropenia" upon chart review. Thus, all patients seen in clinic or admitted to the hospital with a chief complaint of febrile neutropenia were included. Lastly, a larger study population would increase the power to detect statistically significant differences between study groups.

Conclusion

The results from our study suggest that same-day pegfilgrastim administration may be a safe and effective alternative to 24-h post-chemotherapy administration in patients with esophageal, gastric, appendiceal, or colorectal cancer undergoing treatment with FOLFOX or FOLFIRI. These effects may be consistent whether using pegfilgrastim as primary or secondary prophylaxis. These results warrant further investigation of same-day versus 24-h post-chemotherapy pegfilgrastim administration in patients undergoing chemotherapy treatment for esophageal, gastric, appendiceal, and colorectal cancer.

Appendix

Table 5 Treatment regimens based on study group

Chemotherapy abbreviation	Regimen
FOLFOX6 (UACC)	Oxaliplatin 85 mg/m^2 on day 1; Leucovorin 200 mg/m^2 on day 1; 5-Fluorouracil 400 mg/m^2 IV on day 1, then 2400 mg/m^2 IV administered over 46 h
FOLFOX4 (Hecht et al)	Oxaliplatin 85 mg/m^2 IV on day 1; Leucovorin 200 mg/m^2 IV on days 1 and 2; 5-Fluorouracil 400 mg/m^2 IV bolus, then 600 mg/m^2 IV administered over 22 h on days 1 and 2
FOLFIRI (UACC)	Irinotecan 180 mg/m^2 IV on day 1; Leucovorin 350 mg/m^2 IV on day 1; 5-Fluorouracil 400 IV mg/m^2 bolus, then 2400 mg/m^2 IV administered over 46 h
FOLFIRI (Hecht et al.)	Irinotecan 180 mg/m^2 IV on day 1; Leucovorin 200 mg/m^2 IV on days 1 and 2; 5-Fluorouracil 400 mg/m^2 IV bolus, then 600 mg/m^2 IV administered over 22 h on days 1 and 2
FOIL	Irinotecan 175 mg/m^2 IV on day 1; Oxaliplatin 100 mg/m^2 IV on day 1; Leucovorin 200 mg/m^2 IV on day 1; 5-Fluorouracil 3000 mg/m^2 IV administered over 48 h starting on day 1

UACC: The University of Arizona Cancer Center

Hecht al: Treatment regimen used in the study by Hecht et al. (Hecht et al., Clinical Colorectal Cancer 2010) [6]

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