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First Analysis of Same-day Pegfilgrastim Use with Concurrent Capecitabine-based Regimens in Patients with Gastrointestinal Malignancies

Muhammad Wasif Saif*, Nausheen Hakim, Jeffrey Chi, Hasan Rehman, Shreya Prasad Goyal, Coral Olazagasti, Patnita Forde Sheperd and Jyothi Jose

Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra, Feinstein Institute for Medical Research, Lake Success, NY

Correspondence should be addressed to Muhammad Wasif Saif, wsaif@northwell.edu

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ABSTRACT

BACKGROUND: Pegfilgrastim is administered 24 hours. after chemotherapy to reduce risks of myelosuppression. This requires an additional clinic visit, which can be difficult for some patients (pts) due to work and transportation issues. In GI malignancies, patients receiving capecitabine-based regimens also require pegfilgrastim to reduce myelotoxicity. We present here the first study to analyze safety and efficacy of administering pegfilgrastim on the same day as capecitabine-based regimens in patients with GI malignancies.

METHODS: We evaluated 157 patients with GI malignancies who received a capecitabine-based chemotherapy regimen, including XELOX, EOX, ECX, XELIRI, MIXE, gemcitabine-capecitabine and same-day pegfilgrastim (6 mg) within 1 hr of completion of systemic agents. As per institutional guidelines, patients were counseled on risks of same-day pegfilgrastim prior to its administration. Patients were followed to determine the degree of neutropenia and toxicity.

RESULTS: A total of 914 chemotherapy cycles in 157 patients were analyzed. Median ANC nadir for all cycles was 5634/uL (range: 450 - 23800). Grade 1 and 2 neutropenia developed in 11 of 914 cycles. Bone pain reported in 9 pts. There was 1 episode of grade >3 neutropenia resulting in infection and antibiotic use. No other patient required dose reductions, chemotherapy delays, or hospitalizations. No increased toxicity of capecitabine was noticed.

CONCLUSIONS: We believe our study is the first in GI malignancies to report that same-day pegfilgrastim administration with capecitabine-based regimens may be as effective and safe as next-day administration. Additionally, given the absence of CD in human bone marrow, it appears capecitabine can be used concurrently with pegfilgrastim. Prospective studies should be done to further investigate, as this practice can benefit patients clinically, decrease office visits, increase patient's satisfaction and reduce healthcare costs.

KEYWORDS

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

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INTRODUCTION

Neutropenia is a serious adverse complication following myelosuppressive chemotherapy that enhances the risk of hospitalization, life-threatening infection, and delays in treatment which may impact outcome in certain cases. This is related to increased health-care costs [1]. Use of granulocyte stimulating factors has been mitigated the risk of chemotherapy induced neutropenia. Currently two forms are used in clinical practice: A short-acting filgrastim and pegfilgrastim, Pegylated filgrastim [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 often requiring patients to make additional office visits, which can be cumbersome for some patients due to work and transportation issues.

In GI malignancies, patients receiving capecitabine-based regimens also require pegfilgastrim to reduce myelotoxicity, though often related to other agents such as oxaliplatin, docetaxel, etc. [4-11]. Capecitabine is an oral fluoropyrimidine that mimics continuous infusion 5-FU and generates 5-FU intratumorally. Capecitabine was rationally designed and following absorption through the gastrointestinal tract, capecitabine is first metabolized to 5′-deoxy-5-fluorocytidine (5′-DFCR) by carboxylesterase in the liver. 5′-DFCR is then converted to 5′-deoxy-5-fluorouridine (5′-DFUR) by cytidine deaminase (CDA) in the liver and tumor tissue (Figure 1) [12]. Finally, 5′-DFUR is converted to 5-FU by thymidine phosphorylase (TP), is significantly more active in tumor tissue than in healthy tissue, thereby, results in high intratumoral concentrations of 5-FU while minimizing plasma concentrations of 5-FU [13]. It has been fully acknowledged that dihydropyrimidine dehydrogenase (DPD) enzyme deficiency can lead to enhanced toxicity following capecitabine [14]. As mentioned previously, capecitabine activation also involves CDA, a ubiquitous enzyme found in the liver and in tumors but its role is not fully defined at present [15].

Recently we published the first study of safety and efficacy of same-day administration of pegfilgrastim in patients receiving chemotherapy for gastrointestinal malignancies [16]. In the current study, we present here the first study to analyze safety and efficacy of administering pegfilgrastim on the same day as capecitabine-based regimens in patients with GI malignancies.

METHODS

A retrospective study was performed of patients with GI malignancies who received pegfilgrastim concurrently with a capecitabine-based chemotherapy regimen, including XELOX, EOX, ECX, XELIRI, MIXE, gemcitabine-capecitabine (Gem-Cap). Patients were treated from January 2014 through January 2020 and received pegfilgrastim within 1 hour of completion of chemotherapy. The decision to administer pegfilgrastim was based on ASCO or NCCN guidelines [17,18]. Patients had an average of 4 risk factors for febrile neutropenia: advanced disease, age >65, 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 to determine the degree of neutropenia and toxicity. Data collected included patient demographics, pathology reports, blood counts (drawn on days 8, 15 or 21 days according to the chemotherapy regimen), incidence of neutropenia, febrile neutropenia, hospitalization, use of antibiotics, bone pain,

toxicity, chemotherapy regimen, chemotherapy dose, and day of pegfilgrastim administration.

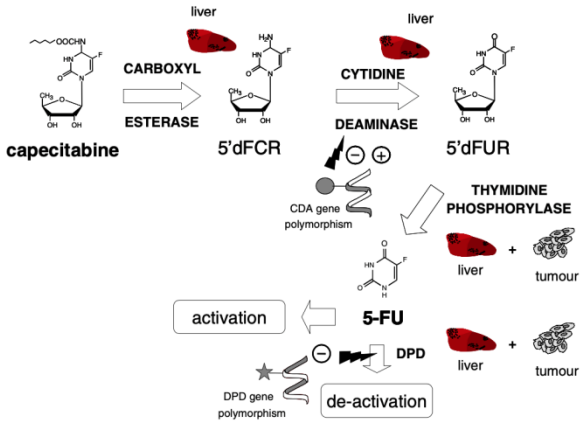

Figure 1: Metabolic pathway of capecitabine [15].

RESULTS

Patient Demographics

A total of 914 chemotherapy cycles in 157 unique patients who received same-day pegfilgrastim with concurrent capecitabine-based chemotherapy were analyzed. Median patient age was 64 years (range 53-91) and 70% of patients were over 65. Included patients had an average of four risk factors for febrile neutropenia including advanced disease, gender, age over 65 and chemotherapy regimen.

The most common sites of GI malignancies included colorectal (35%), pancreas (25%), gastric (20%), cholangiocarcinoma (10%), anal (5%) and others (5%).

Patients received a variety of different chemotherapies including XELOX (40%), EOX (20%), ECX (5%), XELIRI (5%), MIXE (10%), Gem-Cap (10%), and others (10%).

Efficacy

Median ANC nadir for all cycles was 5634/uL (range: 450-23800). Grade 1 and 2 neutropenia developed in 11 of 914 cycles. There was only one episode of grade >3 neutropenia resulting in infection and antibiotic use. No other patient required dose reductions, chemotherapy delays, or hospitalizations.

Toxicity

Bone pain reported in 9 patients. No increased toxicity of capecitabine was noticed.

DISCUSSION

To the best of our knowledge, we believe our study is the first in GI malignancies to report that same-day pegfilgrastim administration with capecitabine-based regimens may be as effective and safe as next-day administration. Non-inferiority of same day dosing has been documented in several different malignancies and chemotherapy regimens, including NHL, NSCL, breast, gynecological cancers, showing no statistical difference observed G3-4 neutropenia, febrile neutropenia, treatment delays or dose modifications between same and next-day dosing [19-22]. Contrary to these studies, others noticed that increased risk for febrile neutropenia in patients receiving same day versus next day pegfilgrastim administration [23]. Hence, this issue of pegfilgrastim dosing schedule of remains conflicting and controversial.

Additionally, given the absence of CD in human bone marrow, it appears capecitabine can be used concurrently with pegfilgrastim [16,24]. Prospective studies should be done to further investigate, as this practice can benefit patients clinically, decrease office visits, increase patient's satisfaction and reduce healthcare costs.

Capecitabine was rationally designed to provide an oral therapy that generates 5-FU preferentially in tumor tissue [12,13,25]. An additional aim was to mimic continuous infusion 5-FU. Oral administration enables convenient, patient-oriented, home-based therapy, which most patients prefer to intra- venous treatment administered in the clinic [6,26,27]. In addition, oral therapy avoids the

problems and inconvenience associated with venous access [28,29].

Capecitabine is generally well tolerated, with a safety profile similar to infusional 5-FU. The most common toxicities secondary to capecitabine include hand-foot syndrome (HFS), diarrhea, mucositis, and nausea [4-11,26,27]. Grade 4 toxicities as well as alopecia and bone marrow suppression were relatively rare with capecitabine either due to tumor localization of 5-FU due to TP or related to CD enzyme in human beings [13,15]. Studies in breast and CRC have also suggested that dose reduction for toxicities did not have a negative impact on the efficacy of capecitabine [30].

Onpro® kit was approved by the FDA in 2017, which includes a specially designed, single-use prefilled syringe co-packaged with an on-body injector for pegfilgrastim [31]. Though this is an attractive device which can be adhered to the skin on the day of chemotherapy administration and auto-injects the recipient on the following day, we recently published our experience [31] in which some patients declined to accept its administration due to bulky attachment to skin, fear of an unwitnessed administration, fear of a reaction or lack of confirmation of proper dose administration [32].

We know that our study has limitations, including small sample size, retrospective nature of data and two-institutional analysis of a diverse patient population. However, this offers acknowledgment of the fact that with many regimens that incorporated capecitabine for GI and breast cancer, administration of pegfilgrastim did not impact the toxicity and efficacy of these regimens, including XELOX, XELIRI, ECX, EOX, Gem-CAP, CAOP-TEM, CAP-XRT, MIXE, DCX, DX, etc.

In summary, we believe that our study is the first- in GI malignancies to report on the administration of pegfilgrastim concomitantly with capecitabine-based chemotherapy. Administering pegfilgrastim on concurrently with capecitabine appears to be safe, effective, and convenient in selected patients receiving myelosuppressive chemotherapy for GI malignancies. Possibly the tumor localization of TP and relatively less common polymorphism of CD in humans make it a good pair. Additionally, no effect was seen on efficacy and safety of other agents in the regimens as mentioned above, including oxaliplatin, gemcitabine, irinotecan, etc. While we would still recommend the approved next-day administration schedule for pegfilgrastim, 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 averse to the OnPro delivery kit.

Prospective studies should be done to further investigate, as this practice can benefit patients clinically, decrease office visits, increase patient's satisfaction and reduce healthcare costs.

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