

### The use of romiplostim in treating chemotherapy-induced thrombocytopenia in patients with solid tumors

Thrombocytopenia is common in cancer patients; it may be secondary to the malignancy itself, its treatment, or other etiologies, such as liver disease or infection. In the absence of any currently effective therapy to prevent thrombocytopenia, the usual clinical response is to decrease the dose and/or frequency of chemotherapy, change to less toxic regimens, or stop therapy altogether.<sup>1</sup> Unfortunately, these reactions to thrombocytopenia may reduce therapeutic benefit (and possibly survival) due to inadequate dose intensity or inferior regimens.<sup>2</sup>

While platelet transfusion is the customary treatment for severe chemotherapy-induced thrombocytopenia, only oprelvekin has received regulatory approval for prevention<sup>3</sup> but has adverse effects severely limiting its use. With the discovery of thrombopoietin, two recombinant thrombopoietins [recombinant human thrombopoietin (rhTPO) and pegylated recombinant megakaryocyte growth and development factor (PEG-rhMGDF)] underwent extensive study in patients receiving chemotherapy and were found to decrease the need for platelet transfusions,<sup>4</sup> increase nadir platelet counts, and improve dose intensity.<sup>5</sup> Unfortunately, antibody formation to PEG-rhMGDF ended these developments<sup>6</sup> except in China where rhTPO (TPIAO™) is widely used to treat chemotherapy-induced thrombocytopenia.

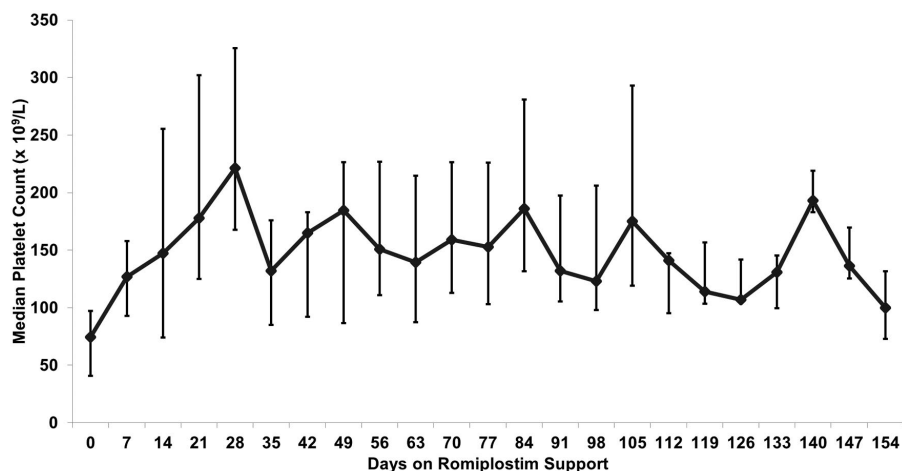
The development of the thrombopoietin receptor agonists romiplostim and eltrombopag has rekindled interest in treating chemotherapy-induced thrombocytopenia.<sup>7</sup> Over the past 8 years romiplostim has been used increasingly at our institution to treat chemotherapy-induced thrombocytopenia, despite this being an off-label use. This is a retrospective analysis of the patients thus treated, assessing the effects of romiplostim on platelet count, time to platelet count  $>100 \times 10^9/L$ , chemotherapy dose reductions and delay, and romiplostim-related complications. This study was approved by the Institutional Review Board (approval 2015P000152/PHS) of Massachusetts General Hospital.

Between January 1, 2010 and April 17, 2017, all patients aged  $\geq 18$  years who received romiplostim were identified from the records at Massachusetts General Hospital and those who receiving romiplostim concurrently with cancer

chemotherapy for a solid tumor were selected for analysis. Moribund patients and those who received fewer than two doses of romiplostim were excluded. The data collected included the patients' age, gender, malignancy type and stage, chemotherapy agents with doses and number of cycles, cause(s) of thrombocytopenia, platelet counts, dates and doses of romiplostim, red blood cell and platelet transfusions, bleeding and thrombotic events.

Of 42 cancer patients treated with chemotherapy and romiplostim, 14 had hematologic malignancies (and were therefore excluded) and 28 had solid tumors; of these 28, 22 met the inclusion criteria. Of the six patients with solid tumors who were excluded, one died of malignancy complications before receiving chemotherapy, two received only one dose of romiplostim, and data were incomplete for three. The median age of the patients was 67 years (range, 21-85), 41% were female. They had a variety of different types of tumor and received a range of treatments. Nineteen patients received cytotoxic chemotherapy, two targeted oral therapy, and one a combination of cytotoxic chemotherapy and targeted oral therapy (Table 1). Most patients had a gastrointestinal malignancy, and the most common chemotherapy regimen was oxaliplatin, 5-fluorouracil and leucovorin. In the 30-day period before romiplostim treatment, the patients' median nadir platelet count was  $58 \times 10^9/L$ ; all patients who had received chemotherapy within 30 days before romiplostim treatment had had a platelet count nadir  $<100 \times 10^9/L$ . On the first day of romiplostim treatment, the median platelet count was  $74 \times 10^9/L$  (range, 21- $145 \times 10^9/L$ ); 50% of patients had platelet counts  $<75 \times 10^9/L$  and 77% had counts  $<100 \times 10^9/L$ . Eighteen patients received romiplostim for chemotherapy-associated thrombocytopenia. Four patients with pre-existing thrombocytopenic conditions, three with chronic immune thrombocytopenia (pre-treatment platelet counts  $95 \times 10^9/L$ ,  $145 \times 10^9/L$ , and  $79 \times 10^9/L$ ) and one with liver cirrhosis (pre-treatment platelet count  $73 \times 10^9/L$ ), had not received prior chemotherapy and were given romiplostim in anticipation of chemotherapy-induced thrombocytopenia.

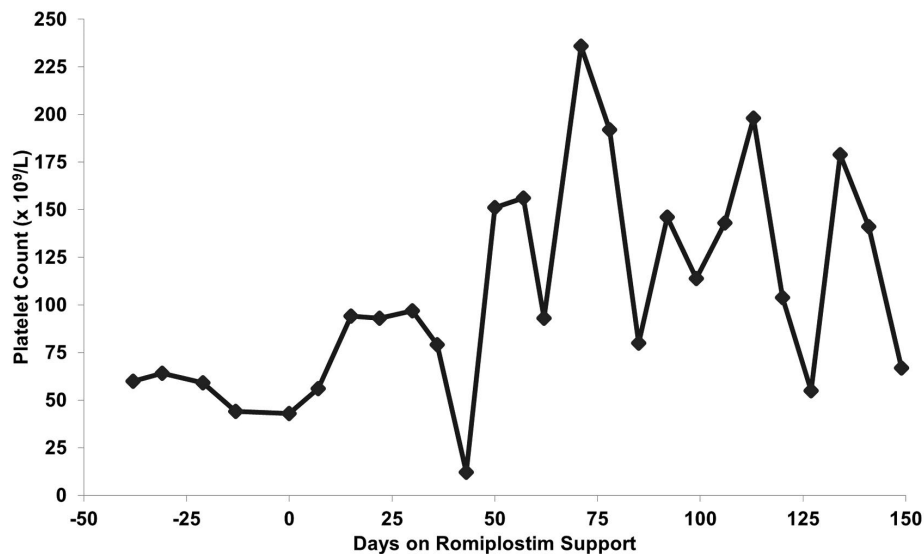
Romiplostim was given weekly, usually on the same day as chemotherapy, and continued until the completion of chemotherapy. The most common (and median) starting dose was  $3 \mu\text{g}/\text{kg}$  (range, 1- $10 \mu\text{g}/\text{kg}$ ). Platelet counts were measured weekly with romiplostim administration; the dose of romiplostim was changed one or more times in 14 patients. For patients with baseline platelet counts



**Figure 1. Median weekly platelet counts.** Median weekly platelet counts (interquartile ranges) over time for the entire cohort while on romiplostim support.

Table 1. Baseline characteristics.

Age (years)	Gender	Malignancy & stage	Contributor(s) to thrombocytopenia	Chemotherapy regimen(s) during romiplostim treatment
85	M	Pancreatic adenocarcinoma (early/localized)	Prior cytotoxic chemotherapy Chronic immune thrombocytopenia	Gemcitabine, 6 cycles
83	F	Lung adenocarcinoma (advanced/metastatic)	Prior cytotoxic chemotherapy	Erlotinib, 3 cycles Rociletinib, 2 cycles Gemcitabine and erlotinib, 4 cycles
26	M	Mediastinal lymphoepithelioma (advanced/metastatic)	Prior cytotoxic chemotherapy	Carboplatin and gemcitabine, 3 cycles
69	F	Esophageal adenocarcinoma (early/localized)	Chronic immune thrombocytopenia	Carboplatin and paclitaxel (weekly), 6 cycles, with concurrent radiation therapy
73	F	Lung adenocarcinoma (advanced/metastatic)	Prior cytotoxic chemotherapy	Rociletinib, 18 cycles
63	M	Gastric adenocarcinoma (early/localized)	Prior cytotoxic chemotherapy Chronic immune thrombocytopenia	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 8 cycles
48	F	Infiltrating ductal carcinoma of the breasts (advanced/metastatic)	Prior cytotoxic chemotherapy	Cisplatin, 8 cycles
39	M	Colorectal adenocarcinoma (advanced/metastatic)	Prior cytotoxic chemotherapy	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 4 cycles
61	M	Esophageal adenocarcinoma (advanced/metastatic)	Chronic liver disease	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 10 cycles
71	M	Colorectal adenocarcinoma (advanced/metastatic)	Prior cytotoxic chemotherapy	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX) with bevacizumab, 17 cycles
64	M	Colorectal adenocarcinoma (advanced/metastatic)	Prior cytotoxic chemotherapy Chronic immune thrombocytopenia	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 2 cycles
58	M	Pancreatic adenocarcinoma (advanced/metastatic)	Prior cytotoxic chemotherapy	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 2 cycles
62	F	Infiltrating ductal carcinoma of the breasts (advanced/metastatic)	Prior cytotoxic chemotherapy Biopsy-proven bone marrow replacement by carcinoma	Doxorubicin (weekly), 2 weeks Eribulin (weekly), 2 weeks Paclitaxel (weekly), 18 weeks
21	F	Small cell endocrine carcinoma of the cervix (early/localized)	Prior cytotoxic chemotherapy Prior pelvic radiation therapy	Etoposide, carboplatin, and paclitaxel, 4 cycles
44	F	Colorectal adenocarcinoma (early/localized)	Chronic liver disease	5-Fluorouracil, 5 cycles
25	M	Medulloblastoma	Chronic immune thrombocytopenia	Vincristine (weekly), 5 cycles, with concurrent radiation therapy. Cisplatin, vincristine, and cyclophosphamide, 4 cycles
77	M	Gastric cancers (advanced/metastatic)	Prior cytotoxic chemotherapy	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 2 cycles
70	M	Glioblastoma	Prior cytotoxic chemotherapy	Ponatinib, 2 cycles
70	M	Gastric cancer (advanced/metastatic)	Prior cytotoxic chemotherapy	Oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX), 5 cycles
74	F	Adenoid cystic carcinoma of the parotid glands (advanced/metastatic)	Prior cytotoxic chemotherapy Biopsy-proven bone marrow replacement by carcinoma	Doxorubicin and cyclophosphamide (AC), 3 cycles
77	F	Cholangiocarcinomas (advanced/metastatic)	Prior cytotoxic chemotherapy	Gemcitabine, cisplatin, and DKN-01, 4 cycles
69	M	Gastric cancers (advanced/metastatic)	Prior cytotoxic chemotherapy Malignant infiltration of hepatic parenchyma	5-Fluorouracil, 4 cycles Paclitaxel, 2 cycles



**Figure 2.** Representative platelet counts obtained on dates of romiplostim administration for an 85-year old man with localized pancreatic adenocarcinoma who received adjuvant gemcitabine with romiplostim support. The dose was 3 µg/kg weekly at initiation on day 0, increased to 6 µg/kg weekly on day 43, decreased to 5 µg/kg weekly on day 57, and was discontinued on day 149 at completion of chemotherapy.

<75x10<sup>9</sup>/L, a median duration of 7 days of romiplostim therapy (a single dose) was required to achieve a platelet count ≥75x10<sup>9</sup>/L. Similarly, a median of only 7 days of therapy was needed to bring those patients with baseline platelets <100x10<sup>9</sup>/L to above the 100x10<sup>9</sup>/L threshold. Ten of 17 (59%) patients with baseline platelet counts <100x10<sup>9</sup>/L achieved counts ≥100x10<sup>9</sup>/L 1 week after a single dose of romiplostim; three additional patients (18%) achieved platelet counts ≥100x10<sup>9</sup>/L after two or three weekly doses; the remaining three patients required seven to 12 weekly doses to reach this threshold. An illustrative trend in platelet counts in one patient is shown in Figure 2. One patient with known bone marrow infiltration by breast carcinoma never achieved a platelet count ≥100x10<sup>9</sup>/L. During romiplostim treatment, 83% and 71% of all platelet counts were ≥75x10<sup>9</sup>/L and ≥100x10<sup>9</sup>/L, respectively.

All 22 patients received two or more cycles of chemotherapy (range, 2-18) while on romiplostim. Four required chemotherapy dose-reductions despite romiplostim; all others proceeded with chemotherapy at, or above, the dose intensity of the cycle immediately before starting romiplostim treatment. Of the 18 patients who received chemotherapy prior to romiplostim, 17 (94%) had chemotherapy delays attributed to thrombocytopenia, with a median per-patient cumulative delay time of 4 weeks (range, 1-11). Eight of all 22 (36%) patients concurrently treated with romiplostim and chemotherapy had such delays ( $P=0.0002$ , Pearson  $\chi^2$  test, compared with pre-treatment), with a median per-patient cumulative delay dropping to 1 week (range, 1-4).

Of the 18 patients who received chemotherapy prior to romiplostim, 14 (78%) had required at least one chemotherapy dose reduction attributed to thrombocytopenia; four of all 22 (18%) patients required at least one such dose reduction on romiplostim ( $P=0.0002$ , Pearson chi-squared test, compared with pre-treatment).

No patient had a thrombotic event while receiving romiplostim.

Three patients (14%) suffered bleeding [1 grade 1 mucosal bleed (platelet count 19x10<sup>9</sup>/L) and 2 grade 3 gastrointestinal bleeds (platelet counts 80x10<sup>9</sup>/L and 239x10<sup>9</sup>/L)] but did not require platelet transfusions. Four patients (18%) received platelet transfusions (2 in preparation for paracentesis; 1 for a patient who was anemic and thrombocytopenic but not bleeding, 1 to boost the platelet count

while receiving chemotherapy). Ten patients (46%) were given red blood cell transfusions while receiving romiplostim, eight of whom for chemotherapy-associated anemia or fatigue.

Few studies have explored use of thrombopoietin receptor agonists in the treatment of chemotherapy-induced thrombocytopenia in cancer patients. In one retrospective analysis,<sup>8</sup> romiplostim was used to treat 20 solid tumor patients with at least 6 weeks of chemotherapy-induced thrombocytopenia (platelet counts <100x10<sup>9</sup>/L). As in our study, this report described that one or two weekly doses of romiplostim raised platelet counts ≥100x10<sup>9</sup>/L and allowed further chemotherapy in most patients, but it did not examine other chemotherapy-related outcomes (e.g., chemotherapy delays). Our study demonstrated that romiplostim statistically significantly reduced chemotherapy delays and dose-reductions due to thrombocytopenia. In addition, romiplostim successfully raised platelet counts in patients with pre-existing thrombocytopenic conditions (e.g., immune thrombocytopenia and cirrhosis) who required chemotherapy.

There were no apparent adverse effects of romiplostim administration in our study. Six patients had platelet counts ≥400x10<sup>9</sup>/L on at least one measurement, prompting dose reductions. Of note, three of these patients had not received prior chemotherapy but had immune thrombocytopenia or liver disease and were given romiplostim to prevent the development of chemotherapy-induced thrombocytopenia; all developed platelet counts ≥400x10<sup>9</sup>/L after the first two doses of romiplostim and subsequently had lower platelet counts following romiplostim dose reductions. There were no cases of venous or arterial thrombosis in our study, but three cases of deep vein thrombosis occurred in the aforementioned published study of 20 patients.<sup>8</sup> Bleeding occurred in three patients but was related to thrombocytopenia in only one. While four patients required platelet transfusions, two were transfused in preparation for a procedure based solely on the physicians' preferences, and only one to enable chemotherapy to be continued.

The flaws of this retrospective study are apparent. This was a non-blinded, non-randomized study of patients with a variety of solid tumors receiving many different chemotherapy regimens. Initial romiplostim dosing was reasonably uniform, but there was no standard for changing or withholding doses. Some patients had doses with-

held because of concern of impending thrombocytosis; patients whose romiplostim doses were withheld more frequently subsequently developed platelet counts  $<100 \times 10^9/L$ . In general, chemotherapy was resumed once the counts were  $\geq 100 \times 10^9/L$ . Nonetheless, our data show that romiplostim treatment increased the platelet count to  $\geq 100 \times 10^9/L$  in 94% of patients who started with counts below this threshold, the majority achieving this goal after one dose. The only exception was one patient who never achieved this goal, possibly because of biopsy-proven infiltration of the bone marrow by malignancy.

This study also illustrates three major flaws inherent in all studies of chemotherapy-induced thrombocytopenia: (i) there is no uniform standard in oncology practice as to when chemotherapy dosage should be adjusted or withheld to avoid thrombocytopenia and bleeding; (ii) there is no consensus as to what constitutes a “safe” platelet count during chemotherapy; and (iii) there is little evidence that raising the platelet count affects survival. While raising the platelet count clearly reduces platelet transfusions<sup>4</sup> and allows chemotherapy to be given on time,<sup>5</sup> only one small study with PEG-rhMGDF suggested improved survival of patients undergoing treatment for non-Hodgkin lymphoma.<sup>9</sup>

This study provides evidence that, in patients with solid tumors and chemotherapy-associated thrombocytopenia or co-existing thrombocytopenic disorders, romiplostim is safe and rapidly increases the platelet count in most such patients, thereby allowing subsequent chemotherapy to be given at full dose and on schedule. Although romiplostim is a widely-used supportive care modality at our institution, the magnitude of its benefit and ultimate effect on patients' survival can only be assessed in properly controlled, prospective studies.

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## References

1. Kuter DJ. General aspects of thrombocytopenia, platelet transfusions, and thrombopoietic growth factors. In: Kitchens C KC, Konkle B, ed. Consultative Hemostasis and Thrombosis. Philadelphia: Elsevier Saunders, 2013:103-116.
2. Denduluri N, Patt DA, Wang Y, et al. Dose delays, dose reductions, and relative dose intensity in patients with cancer who received adjuvant or neoadjuvant chemotherapy in community oncology practices. *J Natl Compr Cancer Netw*. 2015;13(11):1383-1393.
3. Tepler I, Elias L, Smith JW 2<sup>nd</sup>, et al. A randomized placebo-controlled trial of recombinant human interleukin-11 in cancer patients with severe thrombocytopenia due to chemotherapy. *Blood*. 1996; 87(9):3607-3614.
4. Vadhan-Raj S, Verschraegen CF, Bueso-Ramos C, et al. Recombinant human thrombopoietin attenuates carboplatin-induced severe thrombocytopenia and the need for platelet transfusions in patients with gynecologic cancer. *Ann Intern Med*. 2000;132(5):364-368.
5. Fanucchi M, Glaspy J, Crawford J, et al. Effects of polyethylene glycol-conjugated recombinant human megakaryocyte growth and development factor on platelet counts after chemotherapy for lung cancer. *N Engl J Med*. 1997;336(6):404-409.
6. Li J, Xia Y, Bertino A, Coburn J, Kuter DJ. Characterization of an anti-thrombopoietin antibody that developed in a cancer patient following the injection of PEG-rHuMGDF. *Blood*. 1999;94:51a.
7. Kuter DJ. The biology of thrombopoietin and thrombopoietin receptor agonists. *Int J Hematol*. 2013;98(1):10-23.
8. Parameswaran R, Lunning M, Mantha S, et al. Romiplostim for management of chemotherapy-induced thrombocytopenia. *Support Care Cancer*. 2014;22(5):1217-1222.
9. Moskowitz CH, Hamlin PA, Gabrilove J, et al. Maintaining the dose intensity of ICE chemotherapy with a thrombopoietic agent, PEG-rHuMGDF, may confer a survival advantage in relapsed and refractory aggressive non-Hodgkin lymphoma. *Ann Oncol*. 2007; 18(11):1842-1850.