SUPPLEMENTARY APPENDIX

A multicenter study of romiplostim for chemotherapy-induced thrombocytopenia in solid tumors and hematologic malignancies

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Patient Data Collected. Patient data collected included age, gender, malignancy type and stage, chemotherapy regimens, liver or bone marrow tumor involvement, prior pelvic irradiation, other documented known causes of thrombocytopenia, platelet counts, dates and dosing of romiplostim, chemotherapy dose delays or dose reductions due to thrombocytopenia before and after romiplostim treatment, platelet transfusions, bleeding and thromboembolic events, and total duration of follow-up.

Romiplostim Initiation and Titration (See Also Figure 1 in Main Manuscript). Romiplostim was started at 2-4 μg/kg/week at the discretion of the treating physician with possible dose titration up or down by 1-2 μg/kg weekly to maintain a goal on-chemotherapy platelet count of 100-200×10^9/L while avoiding thrombocytosis (>400×10^9/L). Treating physicians were able to deviate from these pathway guidelines as was clinically indicated.

Predictors of Romiplostim Non-Response Multivariable Model. Multivariable logistic regression modeling with romiplostim response as the dependent variable and age, gender, liver tumor involvement, bone marrow tumor involvement, prior pelvic irradiation, and prior receipt of various chemotherapeutics as the independent variables was used to identify predictors of romiplostim non-response in patients with solid tumors. Exposure to a specific myelosuppressive agent was included in the model if (1) the agent had previously been reported to precipitate chemotherapy-induced thrombocytopenia in ≥10% of recipients in prior clinical studies (either alone or as part of a multi-agent regimen)[1,2] and ≥10 patients received the agent prior to CIT development in the present study. Predictors of non-response found to

be statistically significant in this model were reported and included in multivariable negative binomial regression models comparing weekly vs. intracycle romiplostim dosing to appropriately control for these variables.

Negative Binomial Regression Models Comparing Weekly vs. Intracycle Dosing Outcomes. Rates of thrombosis, bleeding, chemotherapy delay/dose reduction, and platelet transfusion were compared in the two groups using a negative binomial regression model controlling for age, sex, and predictors of romiplostim non-response with duration of treatment designated as the exposure variable. Rates of platelet counts $<50\times10^9$/L, $<75\times10^9$/L, $<100\times10^9$/L, and $>400\times10^9$/L were compared in the two groups using a negative binomial regression model controlling for age and predictors of romiplostim non-response with number of platelet count measurements designated as the exposure variable.

Statistical Software. Statistical analysis was performed and graphs for figures were prepared using Stata version 14.2 (StataCorp LLC, College Station, TX), GraphPad Prism 7 (GraphPad, Inc., San Diego, CA), and Microsoft Excel 360 (Microsoft Corp., Seattle, WA).

Supplemental Table 1. Chemotherapy regimens being administered when CIT developed (and/or contributors to pre-existing thrombocytopenia) and chemotherapy regimens supported with romiplostim. 125 patients received support for a single regimen, 35 patients received support for 2 unique regimens, and 8 patients received support for 3 unique regimens on romiplostim. FOLFIRI, fluorouracil, irinotecan, folinic acid; FOLFIRINOX or FOLFOXIRI, fluorouracil, oxaliplatin, irinotecan, folinic acid; FOLFOX, fluorouracil, oxaliplatin, folinic acid.

Chemotherapy regimen	Being administered when CIT developed, N (%)	Supported with romiplostim, N (%)
Alkylating agent-based regimen[a]	10 (6%)	13 (8%)
Antifolate (methotrexate or pemetrexed single agent)	2 (1%)	4 (2%)
Immunomodulatory (iMID) (e.g. lenalidomide)	6 (3%)	4 (2%)
FOLFIRI	8 (5%)	14 (8%)
FOLFIRINOX or FOLFOXIRI	13 (8%)	11 (6%)
FOLFOX and other platinum/5-FU doublets	33 (19%)	38 (22%)
Fluoropyrimidine (single agent)[b]	9 (5%)	20 (12%)
Gemcitabine (single agent)	5 (3%)	7 (4%)
Gemcitabine plus taxane	4 (2%)	10 (6%)
Platinum plus gemcitabine	9 (5%)	11 (6%)
Platinum plus taxane	9 (5%)	10 (6%)
Platinum plus anthracycline, etoposide, or pemetrexed	8 (5%)	9 (5%)
Single-agent platinum, anthracycline, or vinca alkaloid	3 (2%)	8 (5%)
Taxane or taxane-like[c] (single agent)	10 (6%)	16 (9%)
Temozolomide	13 (8%)	8 (5%)
Targeted therapy[d] (e.g. tyrosine kinase inhibitor)	17 (10%)	20 (12%)
Other[e]	14 (8%)	10 (6%)

[a]Includes cyclophosphamide or bendamustine-based multi-agent chemotherapy regimens.

[b]Includes fluorouracil/leucovorin, capecitabine, or trifluridine/tipiracil.

[c]Includes paclitaxel, docetaxel, cabazitaxel, or eribulin.

[d]Includes LY2606368, palbociclib, idelalisib, ibrutinib, sorafenib, rociletinib, bortezomib, osimertinib, dabrafenib/trametinib, niraparib, entinostat, erlotinib, everolimus, or RO6870810.

[e]Includes immunotherapy (PD-1 or PD-L1 inhibitors) and/or contribution of prior pelvic irradiation, chronic liver disease, or immune thrombocytopenia.

Supplemental Table 2. Time from romiplostim initiation to platelet count ≥100×10^9/L. The three patients who did not go on to receive chemotherapy are included in these analyses. PNR, predictors of non-response (bone marrow invasion by tumor, prior pelvic irradiation, prior temozolomide exposure); Plt, platelet count.

Outcome	All Patients (N=173)	All Solid Tumor Patients (N=153)	Solid Tumor Patients, No PNR (N=122)	Solid Tumor Patients with PNR (N=31)	Solid Tumor Patients, Weekly Dosing, No PNR (N=65)	Solid Tumor Patients, Intracycle Dosing, No PNR (N=57)	Hematologic Malignancy Patients (N=20)
Achieved Plt ≥100×10^9/L ever (%)	137 (79%)	130 (85%)	116 (95%)	14 (45%)	61 (94%)	53 (93%)	7 (35%)
Median Duration to Plt ≥100×10^9/L, Days (IQR)	10 (7-16)	9 (7-15)	9 (7-14)	17 (8-24)	8 (7-14)	9 (7-14)	24 (19-36)
Achieved Plt ≥100×10^9/L within 7 days (%)	47 (27%)	47 (31%)	45 (37%)	2 (6%)	25 (39%)	20 (35%)	0 (0%)
Achieved Plt ≥100×10^9/L within 14 days (%)	96 (55%)	96 (63%)	89 (73%)	7 (23%)	49 (75%)	40 (70%)	0 (0%)
Achieved Plt ≥100×10^9/L within 21 days (%)	118 (68%)	116 (76%)	106 (87%)	10 (32%)	57 (88%)	49 (86%)	2 (10%)

REFERENCES

1. Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park).* 2015;29(4):282-294.
2. Wu Y, Aravind S, Ranganathan G, Martin A, Nalysnyk L. Anemia and thrombocytopenia in patients undergoing chemotherapy for solid tumors: a descriptive study of a large outpatient oncology practice database, 2000-2007. *Clin Ther.* 2009;31 Pt 2:2416-2432.