Open-label pilot study of romiplostim for thrombocytopenia after autologous hematopoietic cell transplantation

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Key Points

- There are no prior prospective studies of thrombopoietin receptor agonists to enhance platelet recovery after auto-HCT.

- As studied, romiplostim did not shorten the duration and depth of the platelet nadir, but it enhanced platelet recovery after day +15.

There are no standard treatments to prevent or hasten the recovery from severe conditioning-regimen–induced thrombocytopenia occurring after autologous hematopoietic cell transplantation (auto-HCT). We conducted an open-label, single-arm pilot study of romiplostim, a thrombopoietin receptor agonist, to enhance platelet recovery in patients with multiple myeloma or lymphoma undergoing auto-HCT. All patients were treated weekly with romiplostim starting day +1 after auto-HCT until the platelet count was >50 × 10^9/L without transfusion. Compared with contemporary retrospective data from romiplostim-naïve patients (N = 853), romiplostim-treated patients (N = 59) had a similar median number of days of grade 4 thrombocytopenia or days requiring transfusions, time to platelet engraftment, and number of platelets transfusions during the auto-HCT. However, romiplostim-treated patients had enhanced platelet recovery to normal values beginning at approximately day +15. In matched cohort multivariable analyses, romiplostim treatment was associated with higher platelet counts by an average of 40 × 10^9/L (95% confidence interval (CI) (14, 67), P = .003) and 118 × 10^9/L (95% CI [84, 152], P<.001) at days +21 and +30, respectively, compared with those of no romiplostim. Only 1 adverse event was deemed possibly attributable to romiplostim: a low-risk pulmonary embolism in a patient with multiple myeloma. In conclusion, romiplostim showed promising activity and safety after auto-HCT, but the improvement in platelet counts occurred later than the goal of shortening the duration and depth of the platelet nadir. This trial was registered at www.clinicaltrials.gov (#NCT04478123).

Introduction

High-dose therapy and autologous hematopoietic cell transplantation (auto-HCT) is routinely used in the treatment of plasma cell neoplasms and lymphomas.[1] Essential to auto-HCT is the use of a dose-intensive, myeloablative conditioning regimen that consists of a single agent or combination chemo-therapies aimed at eliminating residual disease and possible chemoresistance. In doing so, conditioning

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The full-text version of this article contains a data supplement.

regimens result in pancytopenia that require infusion of a patient's autologous hematopoietic stem cells to restore normal bone marrow function.[2] Although pancytopenia is expected before engraftment, severe and sometimes prolonged thrombocytopenia may increase the risk of bleeding complications, use of health care resources, and length of hospital stay.[3,4] Currently, the management of conditioning-regimen–related thrombocytopenia after auto-HCT involves the administration of platelet transfusions given at clinical discretion during the peripheral blood count nadir to prevent bleeding events.[5,6] Platelet units are a limited resource carrying potential short- and long-term complications, including transfusion-related reactions and induction of alloreactive platelet refractoriness, respectively.[7] Moreover, responses to platelet transfusions are variable and often transient in the early post-HCT period because of factors that increase peripheral consumption, such as organ dysfunction, infections, and sepsis.[8,9]

Romiplostim (Nplate) is a thrombopoietin receptor agonist (TPO-RA) that is approved for use in patients with chronic immune thrombocytopenia (ITP).[10] Successful use of romiplostim in ITP led to its study in the setting of chemotherapy-induced thrombocytopenia (CIT).[10-13] In a phase 2 study of patients with advanced stage solid tumor malignancies, weekly romiplostim administered for CIT led to improvement in and maintenance of platelet counts, thereby reducing disruptions in cancer-directed therapy.[14] Importantly, there were no observed adverse effects on bone marrow function and no appreciable increased risk of thrombosis compared with the expected rates in these patients. Given these promising results, we studied the use of romiplostim in the enhancement of thrombopoiesis in patients with hematologic malignancies undergoing auto-HCT. We hypothesized that romiplostim would reduce the severity of thrombocytopenia, decrease the time to platelet engraftment, and limit the use of platelet transfusions.

Methods

We conducted an investigator-initiated, single-center, open-label, single-arm, pilot study of romiplostim in patients ≥18 years old with adequate organ function and performance status undergoing planned auto-HCT for either multiple myeloma (MM), Hodgkin lymphoma (HL), or non-Hodgkin lymphoma (NHL). Eligible conditioning regimens included high-dose melphalan for patients with MM, and carmustine, etoposide, cytarabine, melphalan (BEAM); cyclophosphamide, carmustine, etoposide (CBV); or thiotepa, busulfan, cyclophosphamide (TBC) for patients with lymphoma. Patients were excluded if they had a previous diagnosis of a myeloid malignancy, a history of symptomatic arterial thrombotic event within 6 months of auto-HCT, a previous diagnosis of ITP, or if they previously received romiplostim and/or any other TPO-RA (or any other investigational platelet-producing agent). Patients with a history of a prior symptomatic or incidental venous thromboembolic event within 6 months of auto-HCT were eligible if they were on and tolerating anticoagulation for >6 months if they had completed or remained on anticoagulation.

The Memorial Sloan Kettering Cancer Center (MSKCC) institutional review board approved the study (NCT04478123). The planned target accrual was 60 patients consisting of ≥20 patients with MM, ≥20 patients with lymphoma, and the remaining accrual included patients with either MM or lymphoma as available to reach the final sample size. A total of 62 patients enrolled for the study between July 2020 and July 2021. Two patients voluntarily withdrew after enrollment before treatment initiation and were replaced. One patient with lymphoma was found to be ineligible after enrollment and treatment initiation; therefore, 59 romiplostim-treated patients were evaluable for analyses.

Study treatment

All patients received standard conditioning followed by infusion of peripheral blood–mobilized cryopreserved stem cells on day 0. During and after auto-HCT, all patients received supportive care as per the MSKCC Adult Bone Marrow Transplant Service institutional guidelines, including pegylated granulocyte–colony stimulating factor, blood products, and antimicrobial prophylaxis. Platelet transfusion thresholds of $<20 \times 10^9$/L and $<10 \times 10^9$/L were used for outpatients and inpatients, respectively. The initial dosage of romiplostim was 3.0 µg/kg subcutaneously once weekly beginning on day +1. However, after noting platelet overshoots in a few patients, the dosage schema was amended to reduce the potential for further overshoots. The initial and amended romiplostim treatment schedules are detailed in supplemental Table 1. All patients were treated with subcutaneous romiplostim, beginning day +1 after auto-HCT and weekly until the platelet count was $>50 \times 10^9$/L without platelet transfusion(s) for 2 days. Patients received no more than 6 doses of romiplostim even if platelets had not improved to $>50 \times 10^9$/L by day +42 after auto-HCT. In instances of platelet decline to $<20 \times 10^9$/L after recovery to $>50 \times 10^9$/L, resumption of romiplostim was allowed for medical necessity during the auto-HCT hospitalization at the discretion of the treating physician.

Laboratory assessments, including a complete blood count with differential counts, comprehensive metabolic panel, and immature platelet fraction (IPF) were done daily from the day of auto-HCT (day 0) until day +15, then at least weekly until day +30.[15,16] Weekly laboratory tests were conducted for patients who required ≥3 doses of romiplostim if the platelet count remained ≥25 to 50×10^9/L. For patients who required ≥3 doses of romiplostim and whose platelet counts remained $<25 \times 10^9$/L, lab assessments were drawn every other day until the platelet count was $\geq25 \times 10^9$/L. All patients received laboratory evaluations on days +30, +60, and +100 after auto-HCT.

Biostatistical analyses

The primary endpoint was the number of days requiring platelet transfusions or with grade 4 thrombocytopenia after auto-HCT. Secondary endpoints included the number of platelet transfusions issued during auto-HCT admission, the time to platelet engraftment, the length of auto-HCT stay (inpatient or outpatient), and adverse events (AEs) associated with romiplostim. For all outcomes, the reference date was the date of auto-HCT (day 0), not the date of the first romiplostim dose (day +1). Platelet engraftment was defined as the first of 3 consecutive platelet values $>20 \times 10^9$/L obtained on different days with no platelet transfusions administered for 7 consecutive days. Neutrophil engraftment was defined as the first of 3 consecutive days of absolute neutrophil count $\geq0.5 \times 10^9$/L.[17] We defined high or very high platelet overshoots as platelet count increases to 450 to 550×10^9/L and $>550 \times 10^9$/L, respectively, that occurred after expected nadir and after the second (day +8 after auto-HCT) dose

of romiplostim. AEs were assessed and graded weekly until 7 days after the last dose of romiplostim using the Common Terminology for Adverse Events version 5.0. We analyzed platelet counts by the median with interquartile ranges (IQRs) and means with 95% confidence intervals (CIs) and compared these summary statistics with the retrospective data from a cohort of contemporary consecutively treated patients who underwent auto-HCT at MSKCC between 2017 and 2020 and did not receive romiplostim. Notably, IPF values were available only for romiplostim-treated study patients. Curves to plot values over time were generated using locally weighted regression scatterplot smoothing (lowess) from the ggplot package in Rv4.0.1. Additionally, we performed a 1:2 matched analysis including romiplostim-treated study patients (N = 59) and a subset of the contemporary retrospective patients (N = 108) using the following key variables: age (±10 years), sex, conditioning regimen, and CD34+ stem cell dose (±0.75 × 10^6/kg). Multivariable linear models evaluating platelet values at days +21 and +30 were constructed on the matched cohort to evaluate the difference in platelet values between romiplostim and control patients controlling the matching variables in addition to the number of lines of prior therapy, which was obtained on further retrospective review because it was unavailable for the entire dataset. Days +21 and +30 were selected both because these were study assessment timepoints and generally the times when use of platelet transfusions was less common.

Results

The characteristics of the 59 evaluable study participants and retrospective data are shown in Table 1. A total of 58 patients were undergoing their first auto-HCT, and 1 patient with MM was undergoing a second auto-HCT. All 40 study patients with MM received high-dose melphalan, and the 19 patients with lymphoma received either BEAM (84%) or TBC (16%). Of the 40 patients with MM, 7 (18%) were in complete remission, 19 (48%) were in very good partial remission, 9 (22%) were in partial remission, and

Table 1. Romiplostim study and retrospective patients characteristics

Characteristic	Romiplostim, N (%)	Retrospective, N (%)
Number of patients (total)	59	853
Age, median (range)	63 (24-75)	60 (19-80)
Sex		
Male	34 (58)	503 (59)
Female	25 (42)	350 (41)
Disease		
Multiple myeloma	40 (68)	484 (57)
NHL or HL	19 (32)	369 (43)
Conditioning regimen		
Melphalan	40 (68)	484 (57)
BEAM	16 (27)	296 (35)
TBC	3 (5)	73 (8)
CD34$^+$ cell dose (× 10E6/kg), median (range)	5.2 (2.9-8.7)	5.1 (1.47-16.3)

BEAM, carmustine, etoposide, cytarabine, melphalan; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; TBC, thiotepa, busulfan, cyclophosphamide.

5 (12%) had stable or progressive disease before auto-HCT. All patients with lymphoma were in complete remission before auto-HCT. Fifty-four patients (92%) underwent stem cell mobilization with granulocyte-colony stimulating factor with or without plerixafor, and 5 patients (8%) underwent mobilization with chemotherapy and granulocyte-colony stimulating factor. The median baseline platelet count before conditioning among all patients was 189 × 10^9/L (range, 73-383 × 10^9/L), 192 × 10^9/L (range, 83-369 × 10^9/L) for patients with MM, and 182 × 10^9/L (range, 73-383 × 10^9/L) for patients with lymphoma. Among all patients, the median infused CD34$^+$ stem cell dose was 5.2 × 10^6/kg (range, 2.9-8.2 × 10^6/kg). For patients with MM and lymphoma, the median infused CD34$^+$ stem cell dose was 4.9 × 10^6/kg (range, 2.9-7.9 × 10^6/kg) and 5.7 × 10^6/kg (range, 3.2-8.7 × 10^6/kg), respectively.

Of the 11 patients (19%) who were treated with the initial dosing schedule, we noted platelet overshoots in 2 patients which led to a study amendment of lowering the second dose of romiplostim to 2 μg/kg. The remaining 48 patients (81%) were treated with the amended dosing schedule (supplemental Table 1). The median number of doses of romiplostim administered to achieve a platelet count >50 × 10^9/L without platelet transfusion(s) for 2 days were 3 (range, 2-5) for the whole cohort as well as for patients with MM and lymphoma when analyzed separately. There were no medical circumstances wherein a patient required resumption of romiplostim treatment after the platelet count recovered to >50 × 10^9/L. Auto-HCT was done as inpatient and outpatient in 39 (66%) and 20 (34%) patients, respectively. Of the 39 inpatients, 28 (72%) had MM and 12 (28%) had lymphoma. Of the 20 outpatients, 12 (60%) had MM and 7 (40%) had lymphoma. The median length of auto-HCT inpatient hospital stay was 18 days (range, 14-49 days).

Platelet and hematopoietic recovery and comparison with retrospective data

The median times to neutrophil and platelet engraftments were 10 days (95% CI, 9-10 days) and 19 days (95% CI, 17-20 days), respectively. There were no differences in median times to neutrophil and platelet engraftments when stratified by patients who underwent auto-HCT for MM or lymphoma. There was a relatively similar depth and duration of hemoglobin nadir when comparing the study patients with the retrospective data; however, romiplostim-treated patients had enhanced hemoglobin recovery beginning between days +20 and +25. This trend was similarly seen when evaluating hemoglobin recovery for the patients with MM and lymphoma only but with a more pronounced effect in the MM cohort (supplemental Figures 1 and 2). Among all patients, median platelet count recovery kinetics from day 0 to day +90 after auto-HCT are shown in Figure 1. There was a similar depth and duration of the platelet count nadir on comparing those aspects of study patients with those in the retrospective data. However, romiplostim-treated patients had enhanced platelet recovery beginning between days +15 and +21 after auto-HCT. At day +21, romiplostim-treated patients had a median platelet count of 211 × 10^9/L (IQR, 118-250 × 10^9/L) vs 100 × 10^9/L (IQR, 54-140 × 10^9/L) in the retrospective data. This was similar in romiplostim-treated patients with MM, in which median platelet counts at day +21 were 224 × 10^9/L (IQR, 80-252 × 10^9/L) compared with 102 × 10^9/L (IQR, 52-149 × 10^9/L) for retrospective patients (Figure 2A). In romiplostim-treated patients with

Figure 1. Platelet count recovery for romiplostim-treated vs retrospective data. Solid lines represent the median platelet count ($\times 10^9$/L) with 95% CIs (blue = romiplostim study patients; red = retrospective data).
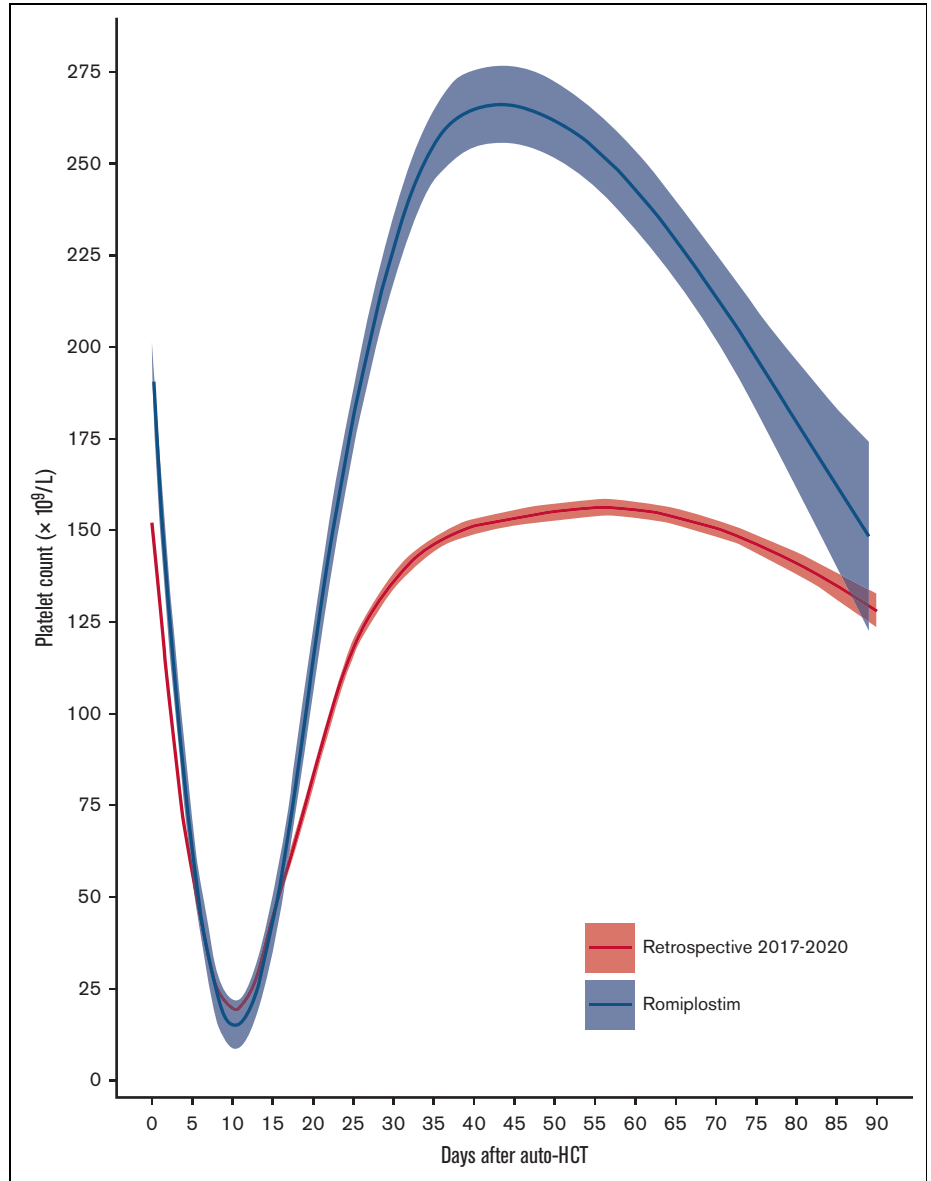

lymphoma, this effect was seen later in which median platelet counts at day +30 were 251×10^9/L (IQR, 129-334 $\times 10^9$/L) compared with 153×10^9/L (IQR, 105-212 $\times 10^9$/L) for retrospective patients (Figure 2B). By day +30, no romiplostim-treated patients vs 18 retrospective patients (2%) had a platelet count $<20 \times 10^9$/L. This trend was similar for patients with MM. However, no romiplostim-treated patients vs 14 retrospective patients with lymphoma (10%) had a platelet count $<20 \times 10^9$/L by day +21 after auto-HCT. Among all patients, IPF values began increasing by day +10 after auto-HCT with a peak value of 8% (range, 4-11 days) at day +16. IPF increase preceded overall platelet recovery, which peaked at day +30 after auto-HCT (Figure 3).

Romiplostim-treated patients with MM had a median number of days of platelet transfusions or grade 4 thrombocytopenia of 6 (range, 0-17), and the median number of platelet transfusions received per patient during the auto-HCT was 2 (range, 0-7). The median number of days of platelet transfusions or grade 4 thrombocytopenia for romiplostim-treated patients with lymphoma was

11 (range, 11-17), and the median number of transfusions issued per patient during the auto-HCT was 5 (range, 2-10). Mean and median values were similar when compared with retrospective data as shown in Table 2. In the 1:2 matched analysis, a multivariable model evaluating platelet recovery at day +21 and day +30 showed that romiplostim-treated patients had a higher platelet count by an average of 40×10^9/L [95% CI (14, 67), $P = .003$] and 118×10^9/L [95% CI (84, 152), $P<.001$], respectively, compared with matched contemporary retrospective patients (supplemental Table 2).

Safety/AEs

All 59 romiplostim-treated patients (100%) experienced $\geq$1 AE during the study period. A total of 544 any grade AEs, including 65 (12%) grade $\geq$3 events, occurred. AEs observed were consistent with those expected in patient population who underwent auto-HCT. We observed a total of 7 patients with high (N = 3) and very high (N = 4) platelet count overshoots. Of the 11 patients
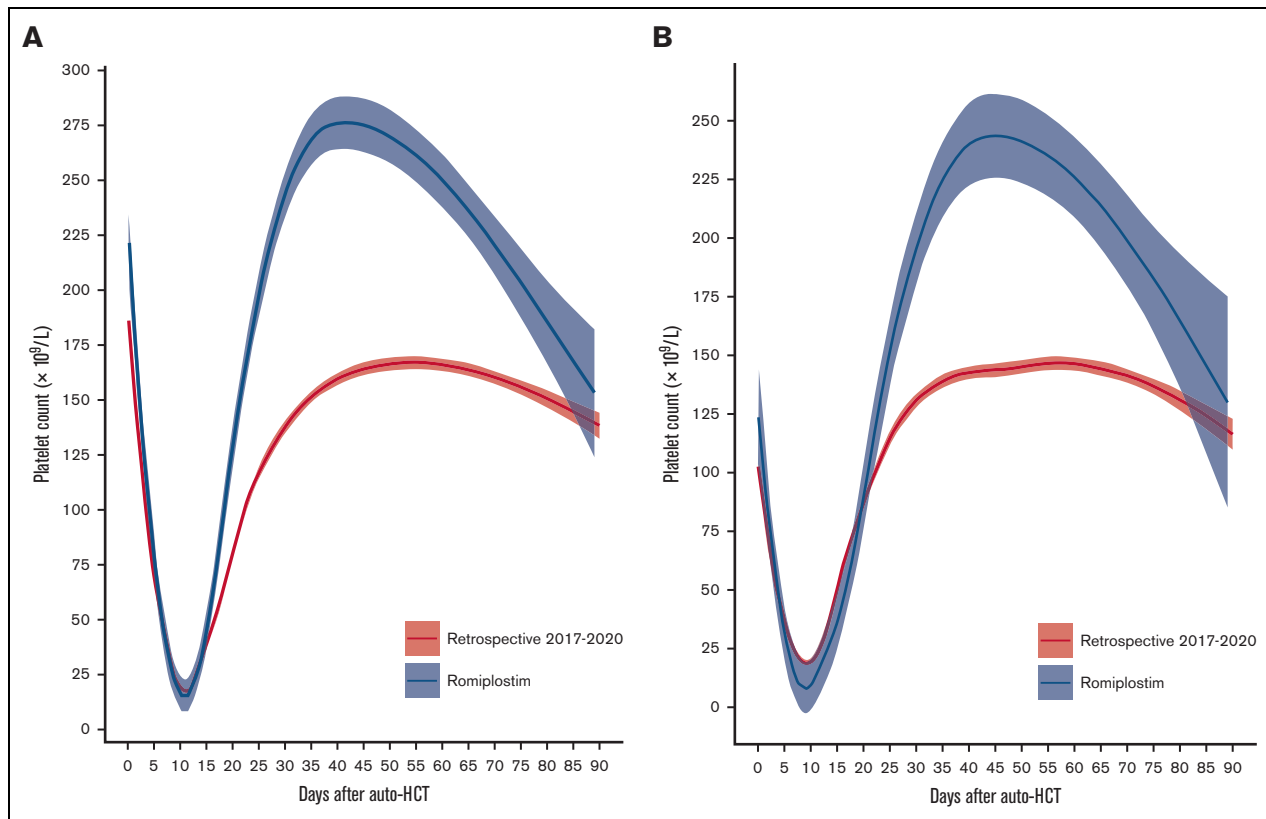
Figure 2. Platelet count recovery stratified by disease [romiplostim-treated MM (A) and lymphoma (B)] vs retrospective data. Solid lines represent the median platelet count ($\times 10^9$/L) with 95% CIs (blue = romiplostim study patients; red = retrospective data).

treated with the initial romiplostim dosing schema, 2 (18%) had very high platelet overshoots at a median of day +27 after auto-HCT and after a median of 3 doses (range, 2-4) of romiplostim. One of these very high platelet overshoots occurred in a patient with MM who developed right posterior pleuritic chest pain and was found to have a low-risk pulmonary embolism on imaging at day +30. During the event, the patient was clinically stable and was managed as an outpatient with therapeutic anticoagulation. There were no other episodes of thrombosis in romiplostim-treated patients and no other AEs attributable to romiplostim on study. Of the 48 patients treated with the amended dosing schema, 3 (6%) had high and 2 (4%) very high asymptomatic platelet overshoots. A detailed summary of all AEs is shown in supplemental Table 2.

Discussion

In this study, we evaluated romiplostim to enhance thrombopoiesis in patients with MM and lymphoma after auto-HCT and found that the number of days of severe thrombocytopenia, time to platelet engraftment, and the use of platelet transfusions were similar in romiplostim-treated patients and those observed in contemporary retrospective collected data. However, romiplostim-treated patients had significantly better platelet counts by day +21 after HCT and overall faster platelet recovery to normal values, indicating clear biological activity of romiplostim at the studied doses. By day +21, no romiplostim-treated patients with lymphoma vs 10% of patients

from our retrospective data with lymphoma had platelet counts $<20 \times 10^9$/L. As the field moves towards the use of more outpatient auto-HCT for patients with lymphoma, in whom transfusion thresholds may have to be set higher (eg, $<20 \times 10^9$/L rather than $<10 \times 10^9$/L), the use of romiplostim may help reduce transfusions in this setting. Moreover, romiplostim treatment in these patients on trial and at the studied doses appeared safe, adding no appreciable increase in toxicities, including venous thromboembolic event, outside of what is typically seen in patients after high-dose therapy and auto-HCT.[18,19] Although we did not have IPF values available from our retrospective patient data for comparison, we observed that IPF is an indicator of imminent platelet recovery that may serve as useful biomarker of romiplostim activity in future studies of TPO-RAs.[15,16,20] We also noted enhanced hemoglobin recovery in romiplostim-treated patients compared with that observed in the retrospective data, highlighting that romiplostim not only stimulates the megakaryocytic lineage but also has effects on hematopoietic stem cells.[10]

Published studies of TPO-RAs for CIT in patients with hematologic malignancies in the non-HCT and HCT settings have had limited sample sizes.[13,21] In patients who have undergone HCT, TPO-RA studies have largely focused on improving platelet counts in those with prolonged thrombocytopenia after allogeneic HCT, whereas we used romiplostim to proactively improve platelet recovery akin to the routine use of granulocyte–colony stimulating factor to reduce the duration of neutropenia.[22] Moreover, prior studies have been limited by heterogeneity in patient and HCT characteristics,
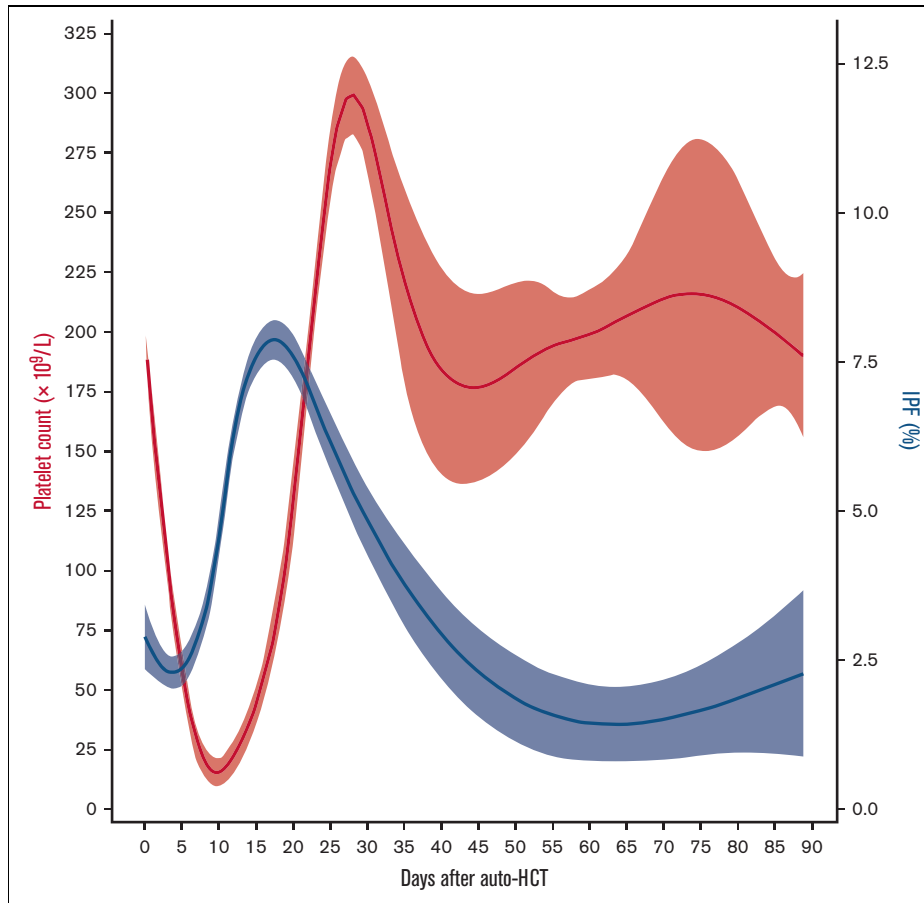
Figure 3. Relationship of IPF and platelet count recovery in romiplostim-treated patients. Solid lines represent the median IPF (%) and median platelet count (× 10^9/L) with 95% CIs (blue = IPF; red = platelet count).

hematopoietic cell sources, graft-versus-host disease prophylaxis, etc.[21,23,24] Our study cohort was relatively homogeneous because all patients received autologous grafts and the same supportive care. We observed that the platelet counts of romiplostim-treated patients undergoing auto-HCT for lymphoma improved to normal values slightly slower than that of patients with MM. This may relate to several factors including differences in the intensity of the conditioning regimens and the number of lines of prior therapy.[25] Interestingly, although total stem cell dose infused is associated

with improved hematopoietic engraftment after auto-HCT, the median infused stem cell dose for patients with lymphoma was slightly higher than that of patients with MM in our study.[26] Apart from the enumeration of total nucleated and CD34$^+$ hematopoietic cell counts, we do not routinely evaluate the cellular composition of autografts. Therefore, it is unknown whether certain autografts inherently have enhanced megakaryocytic proliferative capacity and ability to respond more robustly to romiplostim early after auto-HCT, though this would be of great interest to evaluate in future

Table 2. Comparison of romiplostim-treated patients and retrospective data

		N	Days of plt transfusions or G4 thrombocytopenia median (range)	Days of plt transfusions or G4 thrombocytopenia mean (IQR)	Plt transfusions per patient median (range)	Plt transfusions per patient mean (IQR)
Romiplostim	MM Melphalan	40	6 (0-17)	6.2 (4-8)	2 (0-7)	2.2 (1-3)
	Lymphoma BEAM; TBC	19	11 (4-17)	10.9 (8.5-13.5)	5 (2-10)	5.1 (3-6.5)
Retrospective data	MM Melphalan	485	5 (0-53)	6.8 (3-8)	2 (0-19)	2.7 (1-3)
	Lymphoma BEAM/CBV TBC	296 73	8 (2-68) 10 (5-38)	9.5 (6-10) 12 (8-13)	4 (0-44) 5 (2-32)	5 (3-6) 6.3 (4-7)

BEAM, carmustine, etoposide, cytarabine, melphalan; CBV, cyclophosphamide, carmustine, etoposide; G4, grade 4; plts, platelet(s); TBC, thiotepa, busulfan, cyclophosphamide.

studies.[27,28] Compared with matched retrospective patients, our romiplostim-treated patients had significantly better platelet counts on days +21 and +30 in multivariable models even when adjusting for these key factors associated with hematopoietic engraftment.

We initially chose the starting romiplostim dose of 3.0 μg/kg subcutaneously on day +1 as it approximated the mean effective dose given in our prior study of romiplostim for CIT in patients with advanced solid tumor malignancies and the median dose needed to achieve a response in clinical trials for ITP.[10,14] Interestingly, we noted platelet overshoots in a few patients, which led to a slight change in dosing. With an amended dosing schema (supplemental Table 1) that lowered the second dose of romiplostim, we observed milder and fewer instances of overshoots. Given that we saw a similar depth and timing of platelet count nadir and time to platelet engraftment in our patients compared with those observed in the retrospective data, this suggests that a higher first dose of romiplostim on day +1, rather than higher subsequent doses, may stimulate earlier engraftment after auto-HCT. A strategy of high-dose romiplostim given 1 day after lethal, myeloablative total body irradiation resulted in superior platelet recovery and overall survival in mice and nonhuman primates.[29] Further pharmacokinetic and pharmacodynamic simulations showed the potential survival benefit of a single 10 μg/kg dose in adult and pediatric patients that led to Food and Drug Administration approval of romiplostim for use after an acute radiation event.[30] Whether this approach would be successful in the context of chemotherapy-induced myeloablative injury requires further study.

Our study has several limitations. Although we compared our results with those of a robust, contemporary retrospective dataset, this was a nonrandomized, single-center study. Our treated cohort was relatively large, but there were fewer patients with lymphoma than with MM. A potential confounder in our study was the varying platelet transfusion thresholds of $<20 \times 10^9$/L and $<10 \times 10^9$/L used for outpatients and inpatients, respectively. Also, ideally, platelet count values would be collected every day until the platelet count reached $\geq 50 \times 10^9$/L. However, we felt this practice was impractical and would add an additional burden of outpatient visits during the COVID-19 pandemic. Despite these limitations, to our knowledge, this is the largest prospective clinical trial using romiplostim, or any TPO-RA, to prevent severe CIT in patients with hematologic malignancies, and specifically in patients after HCT.[21] Based on our results, we intend to study a higher first dose of romiplostim early after auto-HCT with the goal of reducing time to platelet engraftment, the depth of platelet nadir, and importantly, the use of platelet transfusions. Moreover, future studies will aim to evaluate the patient and HCT characteristics and the hematopoietic precursors within the infused autografts that are associated with a greater benefit from romiplostim.

Acknowledgments

Authorship

Contribution: M.S. and G.A.S. were responsible for the study conception, design, and writing of the protocol; M.S., L.J.G., G.L.S., C.S.S., D.J.C., H.J.L., O.B.L., R.J.L., P.B.D., M.-A.P., S.A.G., and G.A.S. were responsible for screening and enrolling eligible patients on the study; M.S., L.J.G., D.M.H., J.R.F., S.M.D., L.K.N., J.D.R., and G.A.S. were responsible for data acquisition and data analyses; M.S. and G.A.S. were solely responsible for writing the manuscript and the decision to submit the manuscript for publication; and all authors reviewed the results, provided critical feedback on data interpretation, and approved the final version of the manuscript.

Conflict-of-interest disclosure: M.S. served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation; received research funding from Angiocrine Bioscience, Inc., and Omeros Corporation; served on ad hoc advisory boards for Kite, a Gilead Company; and received honoraria from i3Health and Medscape for CME-related activity. G.L.S. has received research funding to the institution from Janssen, Amgen, and Beyond Spring. C.S.S. has served as a paid consultant on advisory boards for Juno Therapeutics, Sanofi-Genzyme, Spectrum Pharmaceuticals, Novartis, Genmab, Precision Biosciences, Kite, a Gilead Company, Celgene/Bristol Myers Squibb (BMS), Gamida Cell, Karyopharm Therapeutics, and GlaxoSmithKline. He has received research funds for clinical trials from Juno Therapeutics, Celgene/BMS, BMS, Precision Biosciences, Actinium Pharmaceuticals, and Sanofi-Genzyme. D.J.C. receives research funding from Genentech. H.J.L. has served as a paid consultant for Takeda, Genzyme, Janssen, Karyopharm, Pfizer, Celgene, Caelum Biosciences, and has received research support from Takeda. O.B.L. served on advisory boards for MorphoSys, Inc. P.B.D. has served on an advisory board for Kite, a Gilead Company. M.-A.P. reports honoraria from AbbVie, Astellas, BMS, Celgene, Equilium, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Novartis, Nektar Therapeutics, Omeros, OrcaBio, Takeda, and VectivBio AG, Vor Biopharma; serves on the data and safety monitoring board for Cidara Therapeutics, Medigene, Sellas Life Sciences, and Servier, and the scientific advisory board of NexImmune; has ownership interests in NexImmune and Omeros; and received research support for clinical trials from Incyte, Kite/Gilead, Miltenyi Biotec, and Novartis. S.A.G. is a consultant and receives research funding from Amgen, Actinium, Celgene, Johnson & Johnson, and Takeda and is a consultant for Jazz Pharmaceuticals, Novartis, Kite, a Gilead Company, and Spectrum Pharmaceuticals. G.A.S. has served as a paid consultant for Anthos Therapeutics, Jiangsu Hengrui Pharmaceuticals Company Ltd., and Dova/Sobi Pharmaceuticals. The remaining authors declare no competing financial interests.

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