Feasibility and Efficacy of Romiplostim for the Treatment of Persistent Thrombocytopenia after Allogeneic Stem Cell Transplantation. A Single Centre Experience.

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Background

Persistent thrombocytopenia (PT) is a common complication after allogeneic stem cell transplantation (alloSCT) and can lead to higher mortality due to haemorrhagic events and transfusion dependence. Causing factors are several and include viral infections, graft-versus-host disease (GvHD), drug toxicity, thrombotic microangiopathy (TMA) and immune thrombocytopenia (ITP). We also evaluated the influence of cryopreservation of the graft, which was increasingly used during the COVID-19 pandemic. The use of thrombopoietin receptor agonists (TPO-RA) is gaining a fundamental role in the post-transplant setting. To date, the use in PT after transplant has only been investigated in small studies or case reports.

Patients and Methods

We conducted a retrospective study on 119 consecutive patients undergoing alloSCT and receiving Romiplostim for the treatment of PT. Patient characteristics are shown in Table 1.

PT was defined as

- a platelet count <20 Giga/l for 7 consecutive days after engraftment,
- the need for continuous transfusion during the post-transplant follow up or
- a not rapidly reversible decrease of >50% of the platelet count not due to relapse of the underlying haematological disease.

Response to treatment was defined as a platelet count >50 Giga/l for at least 7 consecutive days without transfusion.

Table 1: Patient characteristics.

Characteristic	Value
Number of patients, n	119
Age at time of alloSCT (years), median (range)	57 (18 .- 73)
Sex; male/female, n (%)	73 (61,3) / 46 (38,7)
Disease, n (%)	
AML	52 (43,7)
ALL	13 (10,9)
CMML	4 (3,7)
MDS	16 (13,4)
NHL	7 (5,9)
OMF	21 (17,6)
Other	6 (5)
Type of donor, n (%)	
HLA-identical, related	16 (13,4)
HLA-identical, unrelated	81 (68,1)
HLA-different, unrelated	18 (15,1)
Haploidentical	4 (3,4)

Characteristic	Value
Type of transplant manipulation, n (%)	
Unmanipulated	113 (95)
Campath in the bag	6 (5)
CD34 cell count (x10^6), median (range)	6,71 (1,4-17,9)
Source of stem cells, n (%)	
peripheral blood	116 (97,5)
bone marrow	3 (2,5)
Cryopreservation, n (%)	
Yes	53 (44,5)
No	66 (55,5)
Incidence of concomitant causes (before initiating Romiplostim), n (%)	
TMA	13 (10,9)
Active GvHD (including steroidrefractory forms)	38 (31,9)
Viral infections	21 (17,6)

Results

Out of 255 patients, which underwent alloSCT between 01/2019 and 12/2021, we identified 119 (46,7%) patients with PT receiving Romiplostim as part of their treatment. Median platelet count before initiating Romiplostim was 32 Giga/l (range = 0 - 88). Starting dose was 250µg per week, in 55 patients (46,2%) the dose had to be escalated to 500µg per week during treatment.
Treatment response characteristics are shown in Table 2. Side effects were observed in 10/119 (8,4%) patients (dizziness, deep vein thrombosis, pulmonary embolism, pain syndrome).

Table 2: Treatment response.

Result	Value
Response rate, n (%)	87 (73,1)
Time until response (days), median (range)	40 (7 – 565)
Platelet count after response (Giga/l), median (range)	91 (53 – 212)

In univariate analysis, the only statistically significant factor associated with poor response to Romiplostim was the presence of a viral infection requiring systemic antiviral treatment (see Figure B). The presence of active GvHD (also in case of steroid-refractory (SR) forms), the presence of TMA, the number of CD34-positive stem cells in the transplanted graft and cryopreservation of the graft didn't have a statistically significant impact in determining the efficacy of romiplostim (see Figures A and C – F).

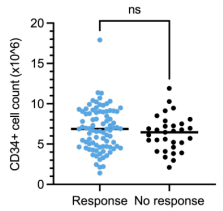

Figure A: CD34⁺ cell count in patients with response and without response.
Median CD34⁺ cell count in patients with response was 6,875 x10^6 (range = 1,4 – 17,9 X10^6), in patients without response 6,45 x10^6 (range = 2,1 – 11,9 x10^6). There was no significant difference (p = 0.3225, Mann-Whitney-test).

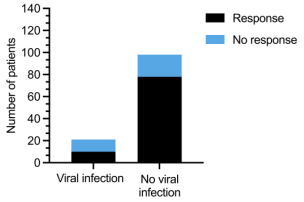

Figure B: Response in patients with and without viral infections.
21/119 (17,6%) patients had at least one viral infection (CMV, EBV, HSV1, BKV) requiring systemic antiviral treatment before initiating treatment with Romiplostim. There was a significant difference in the response rate of patients with viral infection versus patients without (47,6% and 79,6%, respectively; **p = 0,005**, Fishers exact test).

Results

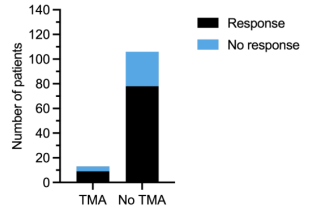

Figure C: Response in patients with and without TMA (p = 0,7459; Fishers exact test).

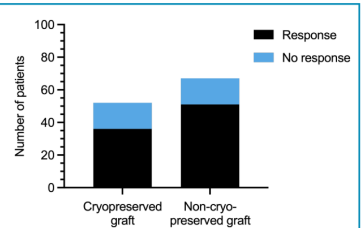

Figure D: Response in patients receiving a cryopreserved vs. non-cryopreserved graft (p = 0.4133; Fishers exact test).

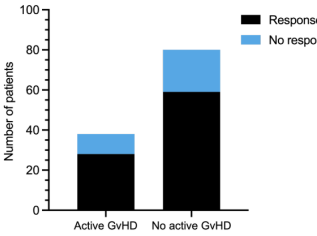

Figure E: Response in patients with and without active GvHD (p = >0.999; Fishers exact test).

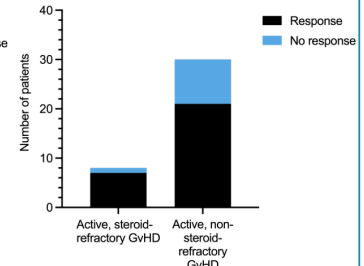

Figure F: Response in patients with and without active and steroid-refractory GvHD (p = 0.6533; Fishers exact test).

Conclusions

- Our results indicate that Romiplostim is overall well tolerated and represents a reasonable and effective treatment for PT after alloSCT.
- Viral infections requiring systemic antiviral treatment could represent a predictor of worse response, this could potentially be explained by the myelotoxicity induced not only by the virus itself but also as a consequence of antiviral substances.
- Active GvHD (including SR) or presence of TMA before initiating therapy with Romiplostim, CD34-positive cell count and cryopreservation of the graft didn't seem to majorly influence the efficacy of Romiplostim.

References

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- Bosch-Vilaseca A, García-Cadenas I, Roldán E, Novelli S, Barba P, Esquirol A, et al. Usefulness of thrombopoietin receptor agonists for persistent clinically relevant thrombocytopenia after allogeneic stem cell transplantation. European Journal of Haematology. 2018;101(3):407–14.

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