Bone Marrow Transplantation (2021) 56:4–6
https://doi.org/10.1038/s41409-020-0975-5

EDITORIAL

Therapy of posttransplant poor graft function with eltrombopag

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Received: 9 April 2020 / Revised: 28 May 2020 / Accepted: 9 June 2020 / Published online: 22 June 2020

Poor graft function is a serious complication of allogeneic hematopoietic cell transplantation. The diagnosis is based on presence of ≥2 of the following: (1) haemoglobin concentration < 100 g/L; (2) neutrophils < 1.0 × 10E + 9/L; and (3) platelets < 30 × 10E + 9/L) on day ≥ 30 post transplant [1]. Other criteria include receiving RBC and platelet requiring transfusions, decreased bone marrow cellularity, complete donor chimerism and no graft-versus-host disease (GvHD) or relapse. Late failure of platelet recovery is defined as a decrease of platelet to <20 × 10E + 9/L for 7 consecutive days or receiving platelet transfusions after achieving sustained platelets ≥ 50 × 10E + 9/L without platelet transfusions for 7 consecutive days post transplant. Poor graft function is reported in 5–25% of allotransplant recipients and is associated with increased morbidity and mortality [1]. Current therapies including RBC and platelet transfusions, intravenous immunoglobulin, molecularly cloned hematopoietic growth factors such as granulocyte- and granulocyte/macrophage colony-stimulating factors (G- and G/M-CSF), additional donor blood or bone marrow (termed a boost) or mesenchymal cells and/or a second transplant from the same or a different donor. These interventions are only partially effective [2, 3]. Eltrombopag, an oral thrombopoietin receptor agonist, is reported effective in severe aplasia anaemia, idiopathic thrombocytopenic purpura and in thrombocytopenia from hepatitis-C infection [4–7]. There are six reports of eltrombopag given to improve posttransplant graft function with encouraging results [8–12].

Between January 2013 and February 2019, 37 of 765 consecutive allotransplant recipients at our centre (5%) developed poor graft function post transplant. Ten received a second transplant, all were aplastic anaemia and thalassaemia, and fourteen received eltrombopag. Seven of the fourteen eltrombopag recipients were male. Median age was 44 years (range, 8–61 years). Four previously received conventional pretransplant conditioning and ten received reduced-intensity conditioning. Eight donors were HLA-identical siblings and six were HLA-haplotype-matched relatives. Median CD34-positive cell dose was 5.38 × 10E + 6/kg (range, 2.63–9.48 × 10E + 6/kg). Median interval between transplant and diagnosis of poor graft function was 81 days (range, 24–300 days) and median interval to starting eltrombopag was 103 days (range, 24–300 days). Median weekly eltrombopag dose was 525 mg/week (range, 350–700 mg/week) and median treatment duration was 2.4 months (range, 0.4–12 months). Detailed data are displayed in the Table 1.

Six subjects had primary and eight had late poor graft function, six of whom had only thrombocytopenia. Eltrombopag was started at a dose of 50 mg/day and increased by 25 mg increments every 2 weeks if no response. Median haemoglobin concentration before eltrombopag was 86 g/L (range, 60–140 g/L), median neutrophils 2.3 × 10E + 9/L (range, 2.0–8.5 × 10E + 9/L) and platelets 21 × 10E + 9/L (range, 6–50 × 10E + 9/L). Seven subjects had platelets < 20 × 10E + 9/L and eight had decreased or absent bone marrow megakaryocytes.

Eight subjects responded to eltrombopag with haemoglobin concentration > 100 g/L, neutrophils > 1.0 × 10E + 9 and platelets > 50 × 10E + 9/L without blood product transfusions or G- or G/M-CSF for ≥7 consecutive days and with continued response after stopping the drug. Median interval to response was 30 days (range, 6–43 days). Median (range) platelets and WBC response dynamics are illustrated in Fig. 1. Median follow-up for responders was

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Table. 1 Subject-, disease- and transplant-related variables.

Number	Age	Sex	Underlying disease	Conditioning	GvHD prevention	Graft source	CD34 × 10E + 6/kg	D–R ABO mismatch	Prior therapy	Dose/ w (mg)	Best response	Disease state	Survivals
1	60	M	MDS	Flu /TBI	CSA/MMF	PBSC	4.4	No	SDP, IGIV, G-CSF	350	NoR	CR	Dead
2	34	M	AA	CY/ATG	CSA/MTX	PBSC	2.75	No	SDP, IGIV, G-CSF	350	CR	CR	Alive
3	47	M	MDS	Bu/CY/ATG	TAC/MMF	PBSC	6	No	SDP, IGIV, G-CSF	700	NoR	CR	Alive
4	48	F	AML	Flu/CY/TBI	CSA/MMF/ PTCY	PBSC	4.2	No	SDP,IVIG, G-CSF	700	NoR	CR	Dead
5	43	F	HL	Flu/Bu	CSA/MMF	PBSC	4.76	Yes	SDP, IGIV	525	CR	CR	Dead
6	8	M	AA	Flu/CY/TBI/ATG/ PTCY	TAC/MMF/ PTCY	BM	9.19	Yes	SDP, IGIV, G-CSF	700	NoR	CR	Alive
7	47	F	AML	Flu/CY/TBI/PTCY	CSA/MMF	PBSC	6.56	No	SDP, G-CSF	350	NoR	CR	Dead
8	49	F	ALL	BuCY/TBI/PTCY	TAC/MMF/ PTCY	BM	4.32	Yes	SDP	700	CR	CR	Alive
9	28	M	HL	Flu/CY/TBI	CSA/MMF	PBSC	6.2	No	SDP	350	CR	NCR	Dead
10	45	F	AML	Bu/CY	CSA/MTX	PBSC	6.45	Yes	SDP, IGIV, G-CSF	450	CR	CR	Alive
11	61	F	PMF	TBF	TAC/MTX	PBSC	8.88	Yes	SDP, IGIV, G-CSF	525	CR	CR	Alive
12	26	M	DC	Flu/CY/TBI/ATG	TAC/MMF	BM	4.58	Yes	SDP, IGIV	350	CR	CR	Alive
13	26	F	FA/MDS	Flu/CY/TBI/ATG	TAC/MMF	BM	2.63	No	SDP, IGIV	625	CR	CR	Alive
14	37	M	HL	Flu/CY/TBI/PTCY	CSA/MMF/ PTCY	PBSC	9.48	No	IGIV	700	NoR	CR	Alive

PGF poor graft function, *MDS* myelodysplastic syndrome, *AA* aplastic anaemia, *AML* acute myeloid leukemia, *HL* Hodgkin lymphoma, *ALL* acute lymphoblastic leukemia, *PMF* primary myelofibrosis, *FA* Fanconi anaemia, *DC* Deskeratosis congenita, *Flu* fludarabine, *TB* total body irradiation, *CY* cyclophosphamide, *ATG* anti-thymocyte globulin, *BU* busulfan, *PTCY* posttransplant cyclophosphamide, *T* thiotepa, *CSA* cyclosporine, *MM* mycophenolate mofetil, *BCT* blood cells transplant, *BM* bone marrow, *BMT* bone marrow transplant, *D–R ABO mismatch* donor–recipient ABO mismatch, *SDP* single-donor platelet, *IVIG* intravenous immunoglobulin, *G-CSF* granulocyte colony-stimulating factor, *CR* complete response, *NR* no response.

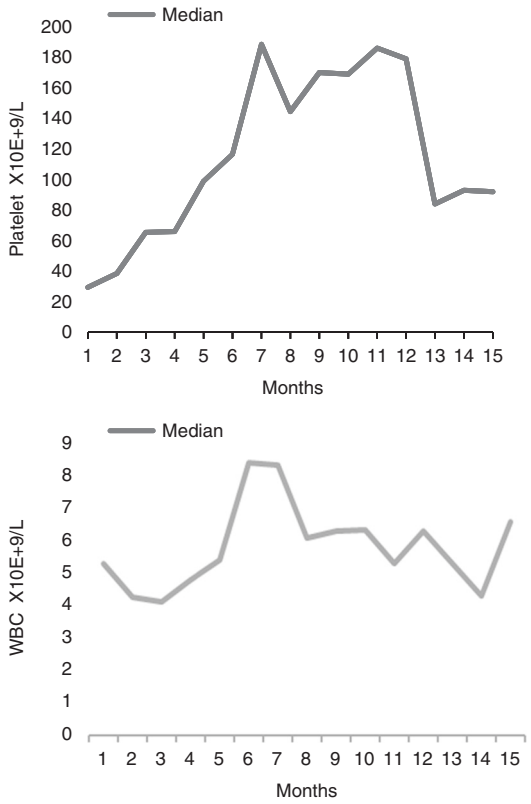

Fig. 1 Platelets and WBC response to eltrombopag. (**a**) Median (range) platelets (**b**) Median (range) WBC.

13 months (range, 6–43 months). The six subjects with adequate bone marrow responded. Only five of six subjects with late thrombocytopenia responded. The six of responders are alive at a median follow up of 14 months (range, 10–41 months) with normal blood cell concentrations. Two non-responders relapsed and died and two had ongoing infections and two had ongoing GvHD. There was no treatment-related morbidity or mortality including no cataracts or thrombosis.

In summary, 8 of 14 subjects with poor graft function failing prior therapies responded to eltrombopag. There were no major adverse events. All subjects with adequate bone marrow megakaryocytes responded. Eltrombopag is a safe and effective therapy of poor graft function post allotransplant.

Funding RPG acknowledges support from the National Institute of Health Research Biomedical Research Centre funding scheme.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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