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Letter to the editor

CD34+-selected stem cell "Boost" for poor graft function after allogeneic hematopoietic stem cell transplantation

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Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is widely used in the treatment of hematologic diseases whether in remission or in the relapsed/refractory setting [1]. However, this treatment modality is associated with several complications leading to a high risk of morbidity and mortality. Among these complications, poor graft function (PGF) occurs in 5 to 27 % of patients after allo-HSCT [2]. Primary PGF is defined as persistent neutropenia (Absolute Neutrophil Count $\leq 0.5 \times 10^9$ /L), thrombocytopenia (platelets $\leq 20 \times 10^9$/L), and/or anemia (hemoglobin $\leq$70 g /L). PGF can be secondary occurring after prompt neutrophil recovery. Moreover, in patients with PGF, the chimerism is full donor and it should be distinguished from graft failure where the chimerism is mixed.

The pathogenesis of PGF remains unclear. It has been reported by Wang et al suggested, that dysregulated T cell responses might contribute to the pathogenesis of PGF after allo-HSCT. In patients with PGF they find higher proportions of stimulated CD4+ and CD8 + T cells that produce IFN-γ (Th1 and Tc1 respectively) while the proportions of IL-4-producing T cells (Th2 and Tc2 cells) were decreased [3]. In addition to Th1 and Tc1 cells, Th17 cells may also contribute to PGF, given the ratio of Th17 cells to regulatory T cells was dramatically increased in the bone marrow of PGF patients compare to that in patients with good-graft function patients [4].

Nevertheless, treatment strategies are mainly based on the administration of granulocyte colony stimulating factor (G-CSF) which has a short-term effect [5]. Alternatively, second allo-HSCT have been performed but at the cost of an increased toxicity [6]. Alternative and more recent treatment modality is the infusion of CD34+-selected stem cell "Boost" from the same donor without prior conditioning. We, therefore, therefore retrospectively studied the efficacy and safety of CD34+-selected stem cell "Boost" for the treatment of PGF after allo-HSCT.

We included10 patients who received a "Boost" of CD34 +-selected stem cells for poor graft function after allo-HSCT between January 2014 and January 2016. 4 patients were males and 6 were females with a median age of 45 (range, 19-67) years at time of transplant. Underlying hematologic malignancies diagnoses include acute myeloid leukemia in 4 patients, myelofibrosis in 2 patiens, chronic myelomonocytic leukemia in 2 patients, acute lymphoblastic leukemia in 1 patient and diffuse large B-cell lymphoma in 1 patient. Patients, disease and transplant characteristics are summarized in the Table 1.

Diagnosis of PGF was retain after careful exclusion of any other causes of pancytopenia after allo-HSCT, including relapse, infection, drug induced myelotoxicity, graft failure or other causes that could explain cytopenias. In addition all patients must have full donor chimerism. Once the diagnosis of PGF established, patients were allow proceeding to the boost treatment. The same original allo-HSCT donor was used to collect the CD34+ cells after mobilization with G-CSF. Patients did not receive any conditioning therapy prior to CD34+-selected stem cell "Boost" infusion.

Overall 10 patients fulfilled the criteria for PGF and proceed to boost therapy. Eight patients had refractory pancytopenia, while two patients had only refractory thrombocytopenia. Four of them had received allo-HSCT from a matched related donor, 2 from a matched unrelated donor, and 5 from a haploidentical donor with post-transplant cyclophosphamide (PT-Cy). At transplant, 5 were in complete remission, 2 in partial response, 2 had allo-HSCT frontline, and 1 was in relapse. Graft source was peripheral blood stem cells in 8 patients and bone marrow in the remaining 2. Six patients had secondary PGF and 4 patients had primary PGF. Patients received the "Boost" infusion at a median of 120 days (range, 76-352) after allo-HSCT. All patients had full donor chimerism at time of "Boost". The median number of CD34+ cells infused was 4.77×10^6/kg (range, 2.91-7.99 $\times 10^6$/kg). The median number of CD3+ cells was 1.27×10^3/kg (range, 0.34-2.0 $\times 10^3$/kg).

Seven patients had full counts recovery at a median of 19 days (range, 7-30) after "Boost", while 3 had an incomplete response with persistent anemia and/or thrombocytopenia. Of these 3 patients, 1 patient had a full recovery of his leucocyte and platelet counts 7 days after the "Boost", but had persistent anemia because of persistent bleeding from refractory hemorrhagic cystitis. The other 2 patients had a full recovery of their leucocyte counts at 19 and 57 days, respectively, but suffered from persistent thrombocytopenia.

Regarding graft-versus-host disease (GVHD), while four patients developed acute and chronic GVHD after allo-HSCT, we did not observed clinically significant GVHD symptoms increase after the "Boost" with. a median follow-up of 42 months

After a median follow up of 42 months (range, 3-59), 7 patients were alive of whom 1 patient had molecular relapse 1 year after allo-HSCT and 16 days after "Boost". This patient received salvage therapy and he is currently alive and in complete remission. Meanwhile, the 3 patients with incomplete response died due to severe infections 1, 6 and 13 months after the "Boost". These infections were due to herpes simplex virus-related encephalitis, BK virus related hemorrhagic cystitis, and pneumonia due to extended spectrum beta lactamase-producing Klebsiella and multidrug resistant Pseudomonas.

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Table 1
Patients', disease and transplant characteristics.

Pt.	Age at HSCT	Diagnosis	Disease status at HSCT	Type of transplant	Conditioning regimen	HSCT complications and Concomitant infections	Chimerism at CD34+ "Boost"	GVHD after HSCT	Interval from HSCT and "Boost" (days)	Reason for "Boost"	Number of CD34+ cells infused ($x10^6$/Kg)	Interval from "Boost" to recovery (days)	Last FU
1	29	DLBCL	PR	Haplo-identical	TBF-ATG (RIC)	CMV	99.9% donor cells	0	76	Refractory thrombocytopenia	4.29	23	CR
2	53	AML M7	CR 2	Haplo-identical	TBF	EBV, Toxo	100% donor cells	Chronic Oral Lichenoid	129	Refractory pan-cytopenia	5.9	Persistent thrombocytopenia after "Boost", recovery of leucocyte count 20 days after "Boost"	Death
3	44	CML	Cytologic CR, Molecular PR	HLA identical sibling	Bu-Cy	0	99.72% donor cells	Chronic skin	109	Refractory pancytopenia (mainly neutropenia)	2.91	7	CR
4	46	AML M1	CR	Haplo-identical	TBF-ATG (RIC)	CMV	100% donor cells	0	352	Refractory pancytopenia	4.77	13	CR
5	22	AML M5	CR	HLA identical sibling	Clo-Ara C-Cy-Bu-ATG	0	100% donor cells	Acute and chronic skin	456	Refractory thrombocytopenia	4.7	30	CR
6	51	CML	MF	MUD 8/10	TBF-ATG (RIC)	EBV, CMV, HSV1, Toxo	100% donor cells	0	112	Refractory pancytopenia (mainly thrombocytopenia)	Missing	14	CR
7	57	MF	MF	MUD 10/10	TBF-ATG	CMV, Cerebral Toxo	99.9% donor cells	0	76	Refractory pancytopenia	7.99	30	CR
8	32	ALL	Relapse	Haplo-identical	TBF-ATG	CMV, HSV1	100% donor cells	0	62	Refractory pancytopenia	4.98	Recovery of leucocytes and platelets counts 7 days after "Boost", persistent anemia due to hemorrhagic cystitis	Death
9	19	AML M1	CR 3	Haplo-identical	TBF (RIC)-Cy	CMV, EBV	100% donor cells	Chronic skin	214	Refractory pancytopenia	6.12	15	CR
10	67	MF	PR	HLA identical sibling	TBF-ATG	0	99.9% donor cells	0	143	Refractory pancytopenia	4.67	Persistent thrombocytopenia after "Boost" requiring transfusion	Death

F: Female; M: Male; RR: Refractory relapsing; DLBCL: Diffuse large B-cell lymphoma; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; ALL: Acute lymphoid leukemia; MF: Primary myelofibrosis; CR: Complete remission; PR: Partial remission; MUD: Mismatched unrelated donor; T: Thiotepa; B or Bu: Busulfan; F: Fludarabin; ATG: Antithymocyte globulin; RIC: Reduced-intensity conditioning regiment; Cy: Cyclophosphamide; Clo: Clofarabine; ara-C: Cytarabine; CMV: Cytomegalovirus; EBV: Epstein Barr Virus; Toxo: Toxoplasmosis.

Here we report 10 patients treated with CD34+-selected cells "Boost" for PGF after allo-SCT. The complete response rate was 70% and the median time to response was 15 days with all responding patients recovering within the first month after "Boost". Larocca et al compared 3 modalities of treatment approach for PGF: No treatment, infusion of unmanipulated stem cells from the same donor without conditioning or infusion of CD34+-selected cells "Boost" without prior conditioning. The highest rate of recovery was observed in the "Boost" therapy arm with a rate of 75%, similar to our findings [7].

All our patients received and failed previous therapy with growth factor prior to "Boost" infusion. In a study published by Bittencourt et al, G-CSF was used for the treatment of PGF. Sustained response was observed in 77% of the patients and all those patients responded within 3 days of G-CSF infusion [5]. Hence, treatment of PGF could be initiated with growth factor infusion. Afterthought, "Boost" therapy can be offered to non-responders.

Moreover, none of our patients experienced an increased in GVHD after "Boost" infusion. This finding could be explained by the CD34+-selection and the low amount of CD3+ T-cell in the "Boost" that are a well-established mediator of acute GVHD [8].

It is important to mention that the chimerism status is an imperative element to decide on the "Boost" therapy. Patients with mixed donor chimerism and cytopenias are in graft failure and would not benefit from "Boost" therapy but rather they should be treated with a second allogeneic stem cell transplantation. Thus, all our patients had a full donor chimerism prior to "Boost" therpay. In a study published by Mohty et al describing 3 patients with cytopenias after allo-HSCT treated with "Boost" therapy only the 2 patients with full donor chimerism benefited from this technique. The third patient with mixed donor chimerism did not show any sign of improvement [9]. Furthermore, the infusion of the CD34+-selected cells "Boost" without any prior conditioning rise the safety of this technique.

Based on these results, we suggest that post-transplant CD34+ selected "Boost" therapy could be effective in restoring normal graft function in patients with poor graft function with full donor chimerism after allo-HSCT, including in those patients who received haploidentical stem cell transplant, allowing hematopoietic recovery without increase in GVHD. Further larger studies should be implemented to confirm our results in an attempt to avoid aggressive toxic strategies including a second transplant in patients with PGF.

Disclosure of conflict of interest

There is no relationship to disclose.

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