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Abatacept acute graft-versus-host disease prophylaxis is feasible and safe when combined with post-transplant cyclophosphamide in the mobilised peripheral blood haploidentical donor setting

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INTRODUCTION

Haploidentical haematopoietic stem cell transplantation (haplo-HSCT) is emerging as a preferred alternative donor source globally, utilising with post-transplant cyclophosphamide (PTCy). PTCy is typically combined with a calcineurin inhibitor and mycophenolate mofetil, which reduces severe chronic graft-versus-host disease (GvHD). However, breakthrough acute GVHD persists as a significant cause of non-relapse mortality (NRM) post-transplant.

CD28-CD80/CD86 axis T-cell co-stimulation blockade with CTLA4-Ig using abatacept (AB) is an emerging acute GvHD prophylaxis strategy, with US Food and Drug Administration (FDA) breakthrough designation. Our centre has successfully combined three doses of abatacept with PTCy in the matched related and unrelated donor myeloablative conditioning (MAC) settings to eliminate severe acute GvHD. In the unrelated donor miss-matched donor setting, four doses of abatacept combined with conventional methotrexate and a calcineurin inhibitor is being investigated (NCT01743131), mostly in children. The feasibility and safety of combining three doses of abatacept with PTCy in the related mismatched (haploidentical) MAC transplant setting is unknown.

AIM

We investigate the feasibility and safety of combining 3 doses of Abatacept with PTCy in the related mismatched (haploidentical) MAC setting.

METHOD

We report our single centre observational experience of seven patients with significant co-morbidities who received a haploidentical donor allogeneic stem cell transplant, with MAC: IV fludarabine 150 mg/m2, IV treosulfan 42 mg/m2 and 2 Gy total body irradiation (TBI). Post mobilised peripheral blood stem cell infusion, IV PTCy 50 mg/kg was administered on d+3 and +4, followed by IV tacrolimus 0.03 mg/kg/day infusion from d+5, and IV mycophenolate mofetil 15 mg/kg TDS. Four, of seven patients received additional aGvHD prophylaxis utilising three doses of IV abatacept 10 mg/kg on d+5, +14 and +28.

RESULTS

The median patient age was 44 years, with median Karnofsky score of 80% and median HCT-CI of 6. Transplant indications included blood cancers (71%) and non-malignant (29%) bone marrow failure indications. Median time to engraftment of white cells was 17 days, neutrophils 18 days, platelets 25 days and 26 days for a target of $20x10^9$/L and $50x10^9$/L respectively. Median time to 100% donor chimerism (CD3+, whole blood or myeloid cells) was d+36 post-HSCT, except for one patient who experienced primary graft failure and required stem cell top-up d+56 post-HSCT without conditioning but with repeated PTCy GVHD prophylaxis. This patient did not receive abatacept prophylaxis and did not experience acute GVHD. No patients required donor lymphocyte infusions (DLIs) for mixed chimerism or relapse. Seventy-one per cent of patients experienced steroid responsive acute GVHD with overall grades of 2–3, with median time to aGVHD onset of 94 days. Of these patients, those receiving abatacept had only gut GVHD whilst patients not receiving abatacept had both gut and skin involvement. No patients relapsed by 180 days and no patients died, with a median follow-up of 399 days.

Table: Haploidentical Allogeneic Stem Cell Transplant

	No Abatacept	Abatacept
Patients	3	4
Age, years (Median)	52	38.5
Females (%)	100.0	0
Karnofsky Score (Median)	70.0	80.0
HCT-CI (Median)	5.0	6.0
MDS (%)	33.3	0.0
AML (%)	33.3	50.0
AA (%)	0	50.0
Myeloma (%)	33.3	0
Engraftment		
Time to white cell engraftment (>0.5 x 10^9/L)(Median, days)	13.0	19.5
Time to neutrophil engraftment (>0.5 x 10^9/L)(Median, days)	13.0	20.5
Time to platelet engraftment (>20 x 10^9/L)(Median, days)	18.0	33.0
Time to platelet engraftment (>50 x 10^9/L)(Median, days)	26.0	37.0
Graft Failure Rate (%)	33.3	0
CMV reactivation requiring treatment		
Rate of CMV reactivation at 100 days (%)	66.7	50.0
Total acute GVHD		
Total 100 day post-HSCT aGVHD rate (%)	33.3	50.0
Total 180 day post-HSCT aGVHD rate (%)	33.3	50.0
Time post-HSCT to aGVHD (Median, days)	89.5	98.0
DLI requirement		
DLI Rate Pre-180 days post-HSCT (%)	0	0
DLI Rate Post-180 days post-HSCT (%)	0	0
Time to DLI post-HSCT (Median, days)	0	0
Mixed Chimerism requiring DLI (%)	0	0
Acute GVHD post-HSCT in the absence of DLI		
Number of patients developing aGvHD (n)	1	2
Time post-HSCT to aGVHD (Median, days)	89.5	98
100 day post-HSCT aGVHD Grade 2-4 (%)	100.0	100.0
100 day post-HSCT aGVHD Grade 1 (%)	0	0
Overall GVHD score, grade 3 (%)	50.0	50.0
Overall GVHD score, grade 2 (%)	50.0	50.0
Overall GVHD score, grade 1 (%)	0	0
Gut involvement (%)	100.0	100.0
Liver involvement (%)	0	0
Skin involvement (%)	100.0	0
Gut involvement Only (%)	0	100.0
Gut and second organ involvement (%)	100.0	0
Skin involvement only (%)	0	0
Relapse rate		
Relapse rate at 100 days (%)	0	0
Mortality		
100 day mortality (%)	0	0

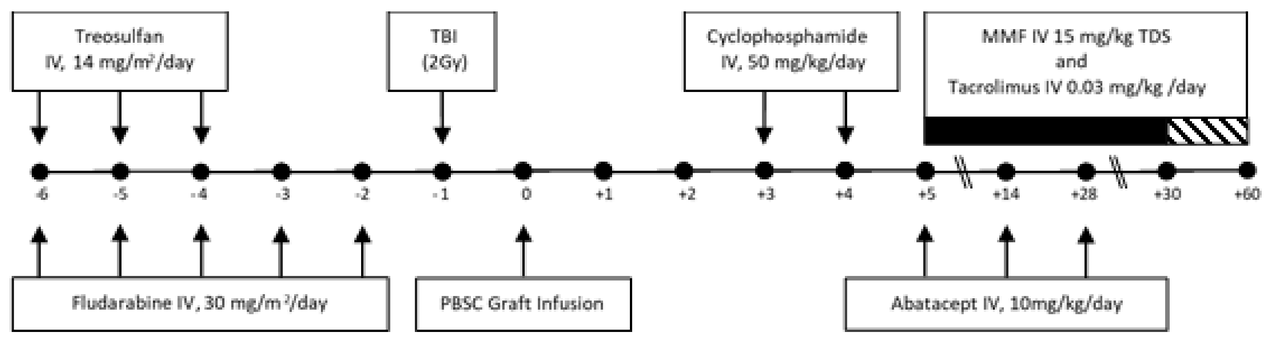

Figure: MAC conditioning regimen, inclusive of Abatacept.

CONCLUSIONS

Three doses of abatacept appears to be feasible and safe in the myeloablative mobilised peripheral blood haploidentical donor setting when combined with PTCy after MAC. A prospective clinical trial is planned.

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