T-cell replete haploidentical bone marrow transplantation and post-transplant cyclophosphamide for patients with inborn errors

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Supplemental materials:

Patients and methods

Patients

Between 2013 and 2018 all patients with inborn errors of hematopoiesis, who lacked a suitable matched related or 10/10 HLA allele matched unrelated donor or had failed a previous matched HSCT were treated according to this institutional protocol. Only patients with a first haploidentical HSCT and who had a follow-up of at least 6 months were included in this chart-based retrospective analysis. All patients or their respective caregivers had given written informed consent to the treatment and to data storage and analysis via the German Pediatric Registry for Stem cell Transplantation (PRST). Patients #7 and #10 are identical twins. Three patients (#3, 6, 7) have previously been published (5). All patients were screened weekly for adenovirus (ADV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV) viremia via PCR until at least day +100.

Graft and donors

The graft was unmanipulated (except for plasma or red blood cell removal if indicated) bone marrow from familial HLA-haploidentical donors with a target dose of 5x10^8 total nucleated cells/kg recipient bodyweight. If both parents were equally fit to donate from a medical perspective, the younger parent was chosen as the donor. If a haploidentical non-carrier donor or a haploidentical sibling of legal age was available, he or she was preferred as was the case in patients #2, 4 and 9. Four patients received ABO mismatched grafts, nine received ABO matched grafts. Red cell lineage chimerism was measured by using differences in minor blood group antigens.

Conditioning regimen

Myeloablative conditioning consisted of alemtuzumab 2x0.2mg/kg/d (day-9 to -8), fludarabine 5x30mg/m^2/d (days -7 to -3), treosulfan 3x14g/m^2/d (days -7 to -5), thiotepa 2x5mg/kg (day-4) and cyclophosphamide 2x14.5mg/kg/d (days -3 to -2) in all patients except patient #5 who received

submyeloablative busulfan (total AUC 55.000ngxh/ml) instead of treosulfan/thiotepa with the intention to enable CNS engraftment of donor derived microglial cells. A single dose of rituximab 375mg/m² was added in patients who had either undergone a previous allogeneic HSCT, had anti-donor HLA antibodies, or had a history of >20 red blood cell (RBC) or platelet transfusions. Patients with anti-donor HLA antibodies were also eligible for five to six cycles of plasmapheresis immediately preceding the conditioning. One such patient declined this treatment.

GVHD prophylaxis

GVHD prophylaxis consisted of cyclophosphamide 50mg/kg/d on days +3 and +4, followed by mycophenolate mofetil (days +5 to +35) and tacrolimus (days +5 to +100 with consecutive tapering) aiming at plasma trough levels of 5-15ng/ml (figure 1).

Statistical analysis and outcome definitions

Data was analyzed retrospectively and statistical analysis was performed with Prism version 5.01 (GraphPad, La Jolla, Ca). Staging of acute GVHD was performed according to modified Glucksberg criteria and chronic GVHD was staged according to NIH consensus standards. Veno-occlusive disease (VOD) was graded according to the new EBMT criteria (7). Neutrophil and platelet engraftment were defined as the first of three consecutive days with >0.5G/l neutrophils and the first of seven consecutive days with >50G/l platelets in peripheral blood respectively.

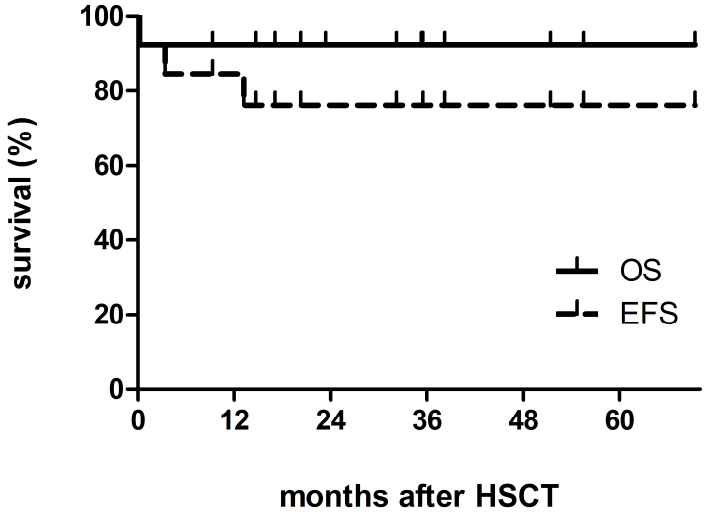
Supplemental table:

patient	antigen specificities	maximum MFI pre-plasmapheresis	maximum MFI post-plasmapheresis
#7	B 44	18.000	4.000
#9	A 26	1.700	negative
#10	B 44	12.000	5.000
#11	A 02, B 35, DRB1 04,	7.000	nd

Supplemental table: Donor-specific anti-HLA antibodies.

Specificity and maximum mean fluorescence intensity (MFI) of donor-specific anti-HLA antibodies before and after plasmapheresis. Patient #11 declined plasmapheresis. All other patients had no detectable anti-HLA antibodies. nd: not done.

Supplemental figure:



Supplemental figure: Overall survival (OS) and event free survival (EFS).

Event defined as disease recurrence or death. |: censored event.