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Pure Red Cell Aplasia in Major ABO Mismatched Allogeneic Hematopoietic Stem Cell Transplantation is Associated with Severe Pancytopenia

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Abstract

In Major ABO mismatched allogeneic stem cell transplantation (SCT) persistence of anti-donor isohemagglutinins leads to pure red cell aplasia (PRCA). To investigate severe pancytopenia noted in a previous study of PRCA,[1] we analyzed all major ABO-mismatched HCT between January 2003 and December 2012.Of 83 PRCA patients, 13 (16%) PRCA patients had severe pancytopenia.Severe pancytopenia was defined as Absolute Neutrophil Count (ANC) < 1.5 K/UL or requiring G-CSF, Platelets < 50 K/UL or transfusion dependent, and PRCA with red cell transfusion dependence at post-transplant day 90. In 6 (46%) patients severe pancytopenia resolved after PRCA resolution.2 (15%) patients received a second transplant due to persistent pancytopenia/secondary graft failure. 1 (8%) died from secondary graft failure despite a stem cell boost. 1 (8%) patient did not recover his platelet counts despite red cell/ANC recovery and 3 (23%) patients died from disease relapse.We found that severe pancytopenia is frequently associated with PRCA in 16% of major ABO incompatible HCT with a higher incidence in males and pancytopenia resolved with resolution of PRCA in 46 % of patients..

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Authorship Contribution

F.M.A. collected the data. F.M.A. and U.D. designed the study, analyzed and interpreted the data and wrote the paper. G.R. gave the data. C.C.Y. reviewed and took the photomicrographs of the BM biopsy slides. A.A., S.A., P.A., B.J., B.S.A., Q.B., S.O.C., C.H., R.J., P.K., Y.N., B.O., A.O., S.P., M.Q., N.S., I.K., E.J.S. and R.E.C. treated, monitored the patients and reviewed the manuscript.

Conflict-of-interest disclosure:

The authors declare no relevant financial conflict of interests.

Keywords

Pure red cell aplasia; Hematopoietic Stem cell Transplant; Pancytopenia

Introduction

The persistence of anti-donor isohemagglutinins in Major ABO mismatched allogeneic stem cell transplantation (HCT) leads to pure red cell aplasia (PRCA) in a small proportion of patients.[1,2] In a previous review of 596 major ABO mismatched HSCT patients, PRCA occurred in 7.5% of Major ABO mismatched HCTs and pancytopenia was observed in one patient which resolved upon resolution of PRCA.[3] To further investigate this observation, we retrospectively analyzed a larger cohort of major ABO mismatched allogeneic SCT patients to determine the frequency of pancytopenia in PRCA and the resolution of pancytopenia in patients with PRCA after major ABO incompatible HCT.

Patients, material and methods

This retrospective study was approved by the institutional review board of MD Anderson Cancer Center.

Patients

The study group consisted of 707 patients who received a major ABO-mismatched allogeneic stem cell transplant between January 2003 and December 2012.The patients were identified from the Stem Cell Transplantation and Cellular Therapy database and transplant and transfusion data was collected from the Patients' electronic medical record and Blood Bank data base.

Definition of Pure Red Cell Aplasia

Pure red cell aplasia was determined to be present when the bone marrow biopsy on post-transplant day 30 demonstrated adequate myeloid, lymphoid and megakaryocyte populations in the setting of severe erythroid hypoplasia defined by <5% precursors in bone marrow biopsies with absence of donor red cells on forward red cell typing of the recipient and the recipient being red cell transfusion dependent.

ABO Incompatibility

A major ABO incompatibility existed when the recipient had naturally occurring isohemagglutinins against the red cell antigen(s) present on the surface of the donor's red cells. This occurred between ABO blood groups, A, B or AB donors and group O recipients (A→O, B→O, AB→O) and between group AB donors and group A or B recipients (AB→B, AB→A). Patients with bidirectional mismatches(A→B and B→A) were also included with the major ABO incompatible group.

Blood Group Serology

ABO forward and reverse typing was determined serologically using both the solid-phase and tube methods.(Immuncor, Norcross, GA, USA)

Engraftment

White cell and Platelet Engraftment—The day of neutrophil engraftment was defined as the first of 3 consecutive days on which the patient's absolute neutrophil count was > 500 k/uL. The day of platelet engraftment was defined as the first of 7 consecutive days on which the patient's platelet count was > 20,000 k/uL without platelet transfusion.

Red Cell Engraftment

The day of red cell engraftment was defined as 30 days after SCT for patients who did not require red cell transfusions. For patients who were red cell transfusion-dependent, the day on which the donor red cells appeared on forward red cell typing was taken as the day of red cell engraftment. For patients who did not have ABO typing performed, the day of red cell engraftment was the last day of red cell transfusion. Red cell type and screens were performed every third day for those inpatients who required red cell transfusions.

Severe Pancytopenia

Severe pancytopenia was defined as ANC < 1.5 k/uL or requiring G-CSF, Platelets < 50,000 k/uL and PRCA with red cell transfusion dependent at 90 days post allogeneic SCT.

Results

Of a total of 707 (428 [71%] males: 279 [39%] females) major ABO mismatched HCTs, there were 83 (11.7%) PRCA patients (29 [35%] males: 54 [65%] females, median age 50 [range 15–69 years]).Severe pancytopenia was noted in 13 (16%) PRCA patients (10[77%] males: 3 [23%] females, median age 53 [range 27–66 years]) at 90 days after transplant. 7 (53%) received allogeneic hematopoietic peripheral stem cells. 6 out the 7 donors (2 related vs. 5 unrelated donors) were HLA matched. Of the 6 (46%) patients who received allogeneic hematopoietic bone marrow cells, all of the donors were unrelated with 5 donors being a 7/8 HLA match. Bone marrow cellularity was a median of 5% (range 5–90%) at post-transplant day median 91 (range 52–128). There was a female preponderance of PRCA patients; however a male predominance (10M/3F) was noted in PRCA patients with severe pancytopenia and this was found to be statistically significant (odds ratio 8.9,p=0.001 Fisher's exact test).All patients were red cell and platelet transfusion dependent and all patients received intermittent G-CSF. (Table-1) None of the patients had any other apparent reason for persistent pancytopenia such as CMV or other viral infection or use of drugs like ganciclovir or disease recurrence.

Severe Pancytopenia resolved after the resolution of PRCA in 6 (46%) patients, all of whom are alive at last follow up at a median of 1283 days post-transplant (range 870–4064). One patient received weekly Procrit on D+89 thru 106 and the second patient received Procrit on D+138 and D+145. No other specific measures were instituted and the patients were observed and supported with transfusions. None of the patients underwent therapeutic plasma exchanges or were treated with IVIG. 2 (15%) patients received a second transplant due to persistent pancytopenia/secondary graft failure (115 and 267 days after transplant) and of the two patients, one is alive. 1 (8%) patient died from secondary graft failure despite a stem cell boost on 2611 days after transplant. 1 (8%) patient did not recover his platelet

count despite red cell recovery and died of a myocardial infarct on post-transplant day 303. 3 (23%) patients died from disease relapse which occurred on 205/500/1455 days after transplant. Table-2 Of the 13 patients with severe pancytopenia, red cell recovery in 10 (77%) patients was a median of 160 (95–587) days from transplant, ANC recovery >1.5 K/uL in 7 (54%) patients was a median of 296 (145–777) days from transplant and platelet recovery > 50 K/uL in 6(46%) patients was median of 1283 (870–3334) days from transplant.(Graph 1; Table 2; Figures 1–2).It was noted that patients with PRCA with severe pancytopenia had platelet and white cell recovery after resolution of their PRCA.

Discussion

The occurrence of PRCA due to the persistence of donor isohemagglutinins has been well described by many authors.[1, 2, 3] The immunodominant structure of A and B antigens also called histo-blood group antigens are present as portions of glycoproteins and glycolipids as well as free oligosaccharides. In addition, the expression of these antigens occurs not only in RBCs but also in other types of cells (mostly epithelial and endothelial cells).[4] The naturally occurring anti-A and anti-B antibodies are predominantly IgM, although variable amounts of IgG may also be present. Certain individuals possess higher titers of ABO hemagglutinins, stimulated by pregnancy, immunizations or the ingestion of bacteria in the form of probiotics.[7] Individuals with blood group O are most likely to produce high titers of anti-A IgG, anti-B IgG and anti-A,B IgG, and in this setting host-versus-graft (HvG) reactions may occur leading to delayed RBC and neutrophil engraftment.[5, 6]Interestingly all of our patients were of the blood group O.ABO titers were not performed in any of the patients pre- or post-transplant.

Platelets are known to express ABH antigens on their surface and also adsorbed soluble A and B antigens from plasma.A and H antigen expression on platelets vary according to genotype and several studies have demonstrated that individual platelets express variable levels of A and B antigens in the same person. The blood group ABO antigens are expressed by several platelet Glycoproteins (GPIb, GPIIb, GPIIIa and platelet endothelial cell adhesion molecule [PECAM]). These glycoproteins are also constitutively expressed in tissues other than megakaryocytes and platelets and may play a role in major ABO incompatible HSCT. Family studies have determined that the expression of ABH antigens on platelets to be genetically determined. Elevated levels of A and/or B antigens are expressed in 4–7% of individuals and a subset of this group termed “type II high expressers” has more than 20 times the normal levels of A and B antigens. ABO antibodies reacting with high expresser platelets have been implicated in conditions such as multitransfusion platelet refractoriness..[7–12] Thus pancytopenia is likely in the presence of high titers of ABO antibodies and/or high expression of A or H antigen on blood cells in Major ABO mismatched SCTs with PRCA and pancytopenia. Although unlikely, donor isohemagglutinins from apheresis or pooled platelet products the patients received could have contributed to the pancytopenia and cannot be completely excluded.

Seebach et al.[7, 8] proposed that the delay in neutrophil engraftment to be a direct effect of recipient isoagglutinins possibly by adsorption onto the cell surface on donor granulopoiesis or the presence of neutrophil antibodies. The presence of generation of anti-donor A and

anti-B antibodies by persisting B cells were due to incomplete eradication during conditioning.There is however, a lack of consensus in the literature concerning the occurrence of major ABH antigens on leukocytes,[13–15]which has a proposed mechanism similar to platelets that are known to express and adsorb ABH antigens on their surface.

Rowley et al.[16] described that classification of patients by ABO phenotype ignoring the allelic differences of these antigens may obscure the effect of red cell incompatible transplantation on transplant outcomes. However, this finding has yet to be confirmed, and we do not know whether the differences in other clinically significant red cell antigens between donor and recipient may play a role in PRCA in major ABO incompatible SCTs.

Graft failure developing in two of our patients' raises the questions as to whether anti-A or anti-B isohemagglutinins caused graft failure or was it related to total nucleated cell (TNC) dose received or other factors. One patient received a bone marrow graft, TNC dose 1.36 ×10e8/kg (CD34 dose 1.13×10e6/kg) from a 57 year old male donor with a single allele mismatch in HLA-DP with Busulfan/Clofarabine/ATG conditioning and the second patient was below the age of 30, received peripheral stem cells, TNC dose 1.01×10e8/kg (CD34 dose 4.88×10e6/kg) from a fully HLA matched (HLA-A/B/C/DRB1/DQB1/DPB1) 23 year old male donor with Busulfan/Clofarabine conditioning. Both grafts were previously cryopreserved and major ABO incompatible. HLA mediated graft failure has been described in patients receiving Haploidentical transplantation,[17] but published studies[18–21] are small and do not have the power to detect the difference in a rare event like graft failure. However, a most recent study of a large retrospective analysis by Olsson et al. 27 reported that major ABO incompatibility was associated with the increased risk of primary graft failure.

We do not believe that mixed chimerism played a major role in pancytopenia as there were only two patients with mixed chimerism. One patient died from disease recurrence and the second patient had graft failure. Our analysis revealed that pancytopenia resolved when red cell recovery occurred. Thus, one therapeutic option is to continue supportive care awaiting spontaneous resolution of PRCA or resolution of PRCA after tapering of tacrolimus or cyclosporine. We believe that the comprehensive supportive care provided to the patients has kept the death rate lower. If treatment is felt to be necessary, it should be directed against antibody producing cells to reduce donor specific ABO isoagglutinins. Although our numbers are small we believe that this is a significant finding in PRCA patients who have persistent pancytopenia on post-transplant day 90. In summary, severe pancytopenia is seen in 16% of patients with pure red cell aplasia due to major ABO incompatible hematopoietic cell transplantation, and it resolves in approximately half of the patients after resolution of PRCA.

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Key Points

The majority of PRCA patients with persistent severe pancytopenia after major ABO mismatched SCT resolve after resolution of PRCA.

HIghlights for Review

The majority of PRCA patients with persistent severe pancytopenia after major ABO mismatched SCT resolve after resolution of PRCA.

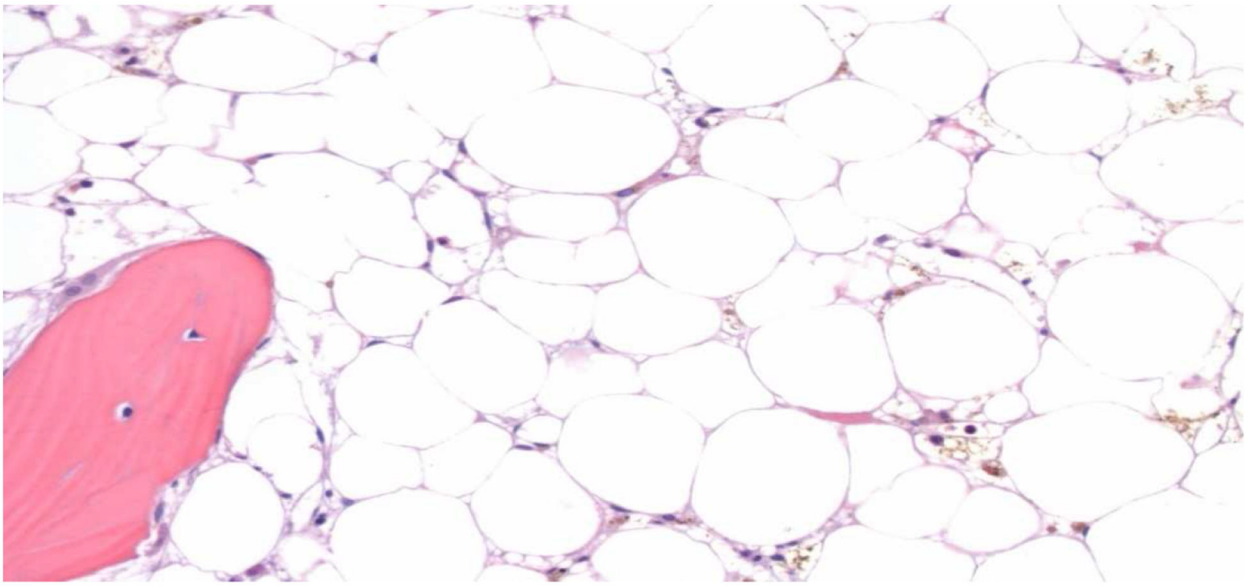


Figure 1: PRCA (Hypocellular) Bone Marrow

The core biopsy shows a markedly hypocellular (<5%) bone marrow with trilineage hypoplasia (H&E, 200x)

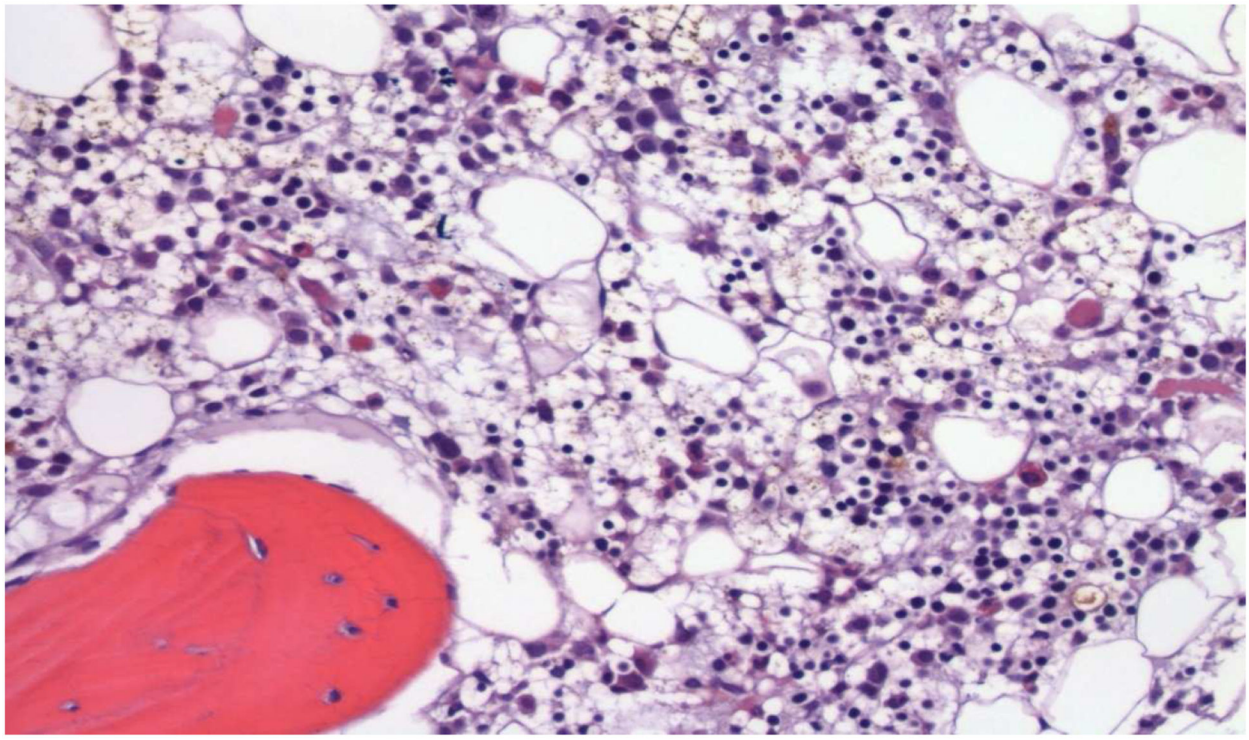
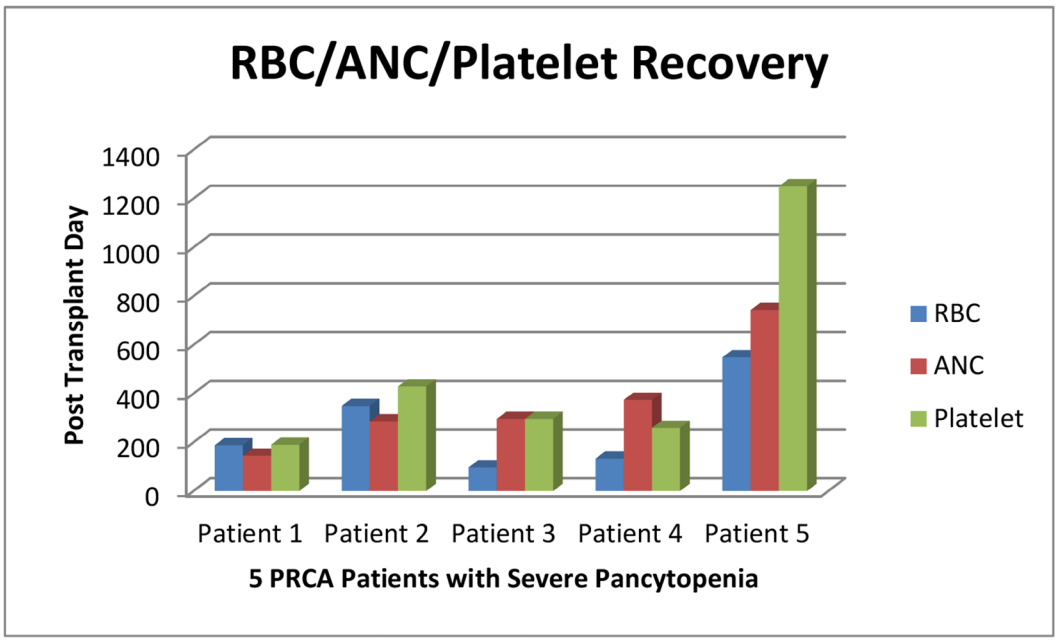


Figure 2: Bone Marrow after PRCA Recovery

The core biopsy shows a cellular (20–30%) bone marrow with trilineage hematopoiesis (H&E, 200x)



Graph 1.
RBC/ANC/Platelet Recovery of 5 PRCA Patients with Severe Pancytopenia

Table 1.

Patient Characteristics

#	Age Patient/ Donor	Gender Patient/ Donor	ABO Patient/ Donor	Diagnosis	Conditioning regimen	Donor*	Graft Source*	GVHD Prophylaxis	CD34 dose x10e6/ kg	TNC dose x10e8/ kg	MC^
1	59/36	M/F	O/A	Lymphoma	Flu/Mel/ Thio/ Rituximab	7/8 ** Matched Unrelated	Bone Marrow	T a cro/ Cytoxa n/MMF	0.703	0.39	No
2	38/39	M/M	O/A	AA/HIV	Flu/Mel/ATG	8/8 Matched Unrelated	Peripheral Blood	Tacro/MTX	7.799	14.18	No
3	56/61	M/F	O/A	CML	Flu/Mel/ Rituximab	8/8 Matched Unrelated	Peripheral Blood	Tacro/MTX	3.95	8.94	No
4	53/30	M/F	O/A	MDS	Flu/Bu/ATG	7/8 *** Matched Unrelated	Bone Marrow	Tacro/MTX	2.281	0.56	No
5	27/45	F/F	O/AB	MDS	Flu/Bu	8/8 Matched Unrelated	Peripheral Blood	Tacro/MTX	3.73	4.28	No
6	66/67	M/M	O/AB	AML	Flu/Bu	8/8 Matched Unrelated	Peripheral Blood	Tacro/MTX	4.51	16.11	No
7	50/38	M/M	O/A	ALL	Bu/Clo/ATG	7/8 **** Matched Unrelated	Bone Marrow	Tacro/MTX	0.941	0.75	No
8	56/55	M/F	O/A	AML	Fu/Mel/Thio/ Post Cy	8/8 Matched Unrelated	Bone Marrow	T a cro/ Cytoxa n/MMF	1.89	0.53	No
9	62/19	M/F	B/O	AML	Flu/Bu/ATG	8/8 Matched Unrelated	Bone Marrow	Tacro/MTX	0.178	0.21	Yes
10	35/35	M/F	A.AB	AML	Flu/Bu/ATG	8/8 Matched Unrelated	Peripheral Blood	Tacro/MTX	3.18	7.57	No
11	56/65	F/F	O/AB	CLL	Flu/Cy/ Rituximab	8/8 Matched Related	Peripheral Blood	Tacro/MTX	8.22	17.27	No
12	42/23	M/M	O/A	MDS	Flu/Bu/ATG	8/8 Matched Unrelated	Peripheral Blood	Tacro/MTX	1.88	1.01	Yes
13	27	57	F/M	ALL	Bu/Clo/ATG	8/8 Matched Unrelated	Bone Marrow	Tacro/MTX	1.13	1.36	No

*Donor HLA Matching: HLA-A/-B/-C/-DRB1

**1 HLA-DRB1 allele level mismatch

***1 HLA-A mismatch

****1 HLA-C mismatch

G-CSF= Granulocyte Stimulating Factor; RBC=Red Blood Cell; ANC=Absolute Neutrophil Count; AML+ Acute Myeloid Leukemia; AA= Aplastic; MDS=Myelodysplastic Syndrome; CLL=Chronic Lymphocytic Leukemia; ALL=Acute Lymphoblastic Leukemia

^MC= Mixed Chimerism

Table 2.

Patient Outcomes

#	Require G-CSF at Day 90	Day 90 - ANC K/uL	Day 90 - Platelet count K/uL	Platelet Transfusion Dependent	RBC Recovery- (Days from transplant)	ANC Recovery 1.5K/uL- (Days from transplant)	Platelet Count >50K/uL without transfusion, (Days from Transplant)	Platelet Recovery >50K/uL- (Days from Transplant)	Alive/Died (Days from Transplant)
1	Yes	2.8	14	Yes	188	145	190	Yes	Alive (978)
2	Yes	1.5	21	Yes	349	286	429	Yes	Alive (870)
3	Yes	1.29	25	Yes	97	296	296	Yes	Alive (3614)
4	Yes	0.43	10	Yes	133	374	259	Yes	Alive (1305)
5	Yes	0.46	6	Yes	549	743	1250	Yes	Alive (1262)
6	Yes	0.97	13	Yes	95	777	3334 **	Yes	Alive (4064)
7	Yes	0.88	17	Yes	211	179	Did not recover	Did not recover	Died - MI (303)
8	Yes	0.32	11	Yes	587	Disease relapse (1098)	Did not recover	Did not recover	Died-Recurrence (1455)
9	Yes	1.04	10	Yes	120	Disease relapse (313)	Disease relapse	Disease relapse	Died - Recurrence (500)
10	Yes	0.93	10	Yes	122	Disease relapse (143)	Disease relapse	Disease relapse	Died - Recurrence (205)
11	Yes	1.7	32	Yes	Secondary Graft Failure (Stem cell Boost)	Secondary Graft Failure (2611)	Secondary Graft Failure	Secondary Graft Failure	Died-Unknown (3112)
12	Yes	0.72	8	Yes	Secondary Graft Failure	Secondary Graft Failure (115) Second transplant	Secondary Graft Failure	Secondary Graft Failure	Died-Infection after second transplant
13	Yes	1.3	14	Yes	Secondary Graft Failure	Secondary Graft Failure (267)Second transplant	Secondary Graft Failure	Secondary Graft Failure	Alive after second transplant

** Lost to follow-up for 3.5 years