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Haploidentical bone marrow transplants for hematological malignancies using non-myeloablative conditioning therapy and post-transplant immunosuppression with cyclophosphamide: results from a single Australian centre

Ian A. Bilmon, John Kwan, David Gottlieb, Ian Kerridge, Mary McGurgan, Gillian Huang, Biju George, Mark Hertzberg, Kenneth F. Bradstock (2013)

Correspondence: Kenneth F. Bradstock, Blood and Marrow Transplant Service, Westmead Hospital, Darcy Rd, Westmead, NSW, 2145, Australia, Email: ken.bradstock@sydney.edu.au

ABSTRACT

Background: HLA haploidentical bone marrow transplantation is a treatment option in patients with hematological malignancies who have no available HLA matched donor, but is limited by conditioning regimen toxicity, graft failure, relapse and graft versus host disease.

Aims: To demonstrate safety and efficacy of haploidentical bone marrow transplantation with nonmyeloablative conditioning and high-dose post-transplant cyclophosphamide in adult patients with leukaemia or lymphoma.

Methods: 12 patients, median age of 51 years, underwent transplantation with T cell replete bone marrow from a haplotype matched relative. The conditioning regimen consisted of cyclophosphamide, fludarabine, and low-dose TBI. Post-transplant immunosuppression consisted of a single dose of cyclophosphamide 50 mg/kg on day 3, followed by oral tacrolimus and mycophenolate mofetil. Outcomes reported are overall survival, engraftment and chimerism, toxicity, and clinical outcome.

Results: All patients had neutrophil recovery (median 14.5 days), and 11 of 12 had platelet engraftment (median 17 days). Two patients had autologous reconstitution. Seven of 9 assessable patients had complete donor chimerism. Four patients had grade II-III GvHD, and none had grade IV GvHD. Four patientsdeveloped limited stage chronic GvHD. Five patients with AML relapsed. Two patients died of non-relapse causes, both from other malignancies, and 5 patients remain alive and relapse free. Median overall survival was 324 days (range 88-1163).

Conclusion: This regimen is feasible and well-tolerated in older patients with high risk leukemia or lymphoma, with minimal short-term toxicity, and low rates of GVHD. The proportion of disease-free survivors indicates a graft versus malignancy effect is present in survivors.

Keywords: hematological malignancy, bone marrow transplant, haploidentical, post-transplant cyclophosphamide

BACKGROUND

Haploidentical allogeneic hematopoietic cell transplantation (HCT) is currently under investigation as a treatment strategy for high risk hematological malignancies and for those who otherwise lack a suitable donor. The optimum donor for allogeneic HCT is generally regarded as a matched sibling,[1] however approximately 70% of potential HCT recipients have no sibling donor, and the chance of finding an appropriately matched unrelated donor (MUD) from international marrow donor registries is highly dependent on ethnicity.[2] Unrelated umbilical cord blood (UCB) banks have increased the number and speed of donor unit availability with less stringent HLA-matching requirements,[3] but are limited in the adult setting primarily due to inadequate cell dosing, though this may be partly overcome by the use of multiple UCB units.[4] In contrast every patient shares at least one HLA haplotype with each parent and any children, and has a 75% chance of sharing at least one HLA haplotype with each sibling. The use of HLA haploidentical related donors would provide virtually all patients with a potential donor irrespective of ethnicity, thus extending allogeneic HCT to over 90% of those who could potentially benefit.[5] The main challenges involve overcoming the dual problems of graft-versus-host disease (GvHD) and graft rejection due to HLA disparity.

Several broad approaches to haploidentical HCT have been evaluated. Myeloablative conditioning therapy combined with heavily T cell depleted grafts containing 'mega-doses' of $CD34^+$ progenitor cells have proved feasible,[6-8] but with delayed immune reconstitution and increased infection risk. Non-myeloablative (NMA) conditioning approaches for haploidentical transplantation have also been investigated to reduce conditioning regimen toxicity. One such approach has employed the combination of fludarabine, cyclophosphamide, and low dose total body irradiation (TBI) for conditioning therapy, with an unmanipulated T cell-replete bone marrow (BM) graft, and post-transplant immunosuppression with high dose cyclophosphamide.[9, 10] The rationale for high-dose cyclophosphamide early after transplant is the immunological tolerance conferred by the ability of alkylator therapy to preferentially affect proliferating lymphocytes over resting cells, resulting in deletion of alloreactive T cells. This spares the non-proliferating graft T cells which contribute to immune reconstitution and anti-tumour activityin the longer term.[11, 12] Preclinical studies validated the safety of administrating high-dose cyclophosphamide on day 3 post-transplant,[13] and early phase human trials using cyclophosphamide 50 mg/kg on day 3, or both days 3 and 4 have now been published.[10, 14] Using this regimen Luznik and colleagues[10] demonstrated low rates of graft failure (13%), grade III-IV acute GvHD (6%) and chronic GvHD (22%).

We have adapted this protocol and report our experience over 2 years in transplanting 12 patients with poor-risk hematological malignancies who lacked matched related or unrelated donors.

PATIENTS AND METHODS

Patients:

12 consecutive patients with poor-risk hematological malignancies underwent allogeneic HCT from a HLA haploidentical related donor at Westmead Hospital from April 2008 to November 2010. All patients gave informed consent for treatment.Patients were considered eligible for haploidentical HCT if no suitable HLA-matched sibling or unrelated donor was available, where autologous HCT was inappropriate, and had

poorrisk hematologic malignancy. Patient median age was 51 years (range 27-62) (Table 1[1]). Nine patients had acute myeloid leukaemia (AML) with a high risk for relapse on the basis of prior relapse (n=2), secondary or therapy related AML(n=2), persistent cytogenetic abnormality following induction chemotherapy (n=1), or poor risk cytogenetics (n=4). Two patients had follicular lymphoma, one transplanted for progressive disease despite multiple prior lines of treatment, and the other with marrow failure following the most recent line of chemotherapy. One patient had chronic myeloid leukemia (CML) in chronic phase, refractory to tyrosine kinase inhibitor therapy, with a T315I BCR-ABL mutation (Table 1).

Donors were selected after review of HLA typing data for available family members. Criteria for selection of haploidentical relatives included availability, age and fitness for marrow harvest under general anesthesia, CMV serostatus and ABO blood group matching with the patient. Kir typing was not done.

Transplant protocol:

The transplant schedule was adapted from that described by Luznik and colleagues.[10] Conditioning therapy consisted of cyclophosphamide 14.5 mg/kg/day ivi + mesna 14.5mg/kg/day on days -6 and -5, fludarabine 30 mg/m^2/day ivi on days -6 to -2, and total body irradiation with a single fraction of 200cGy on day -1. Donor bone marrow was harvested under general anaesthetic aiming for a minimum total nucleated cell (TNC) count of 2 x 10^8 per kg recipient weight. In major ABO-mismatched transplants the graft was red-cell depleted using a Cobe 2991 cell processor (CaridianBCT, Lakewood, Co, USA). T cell depletion or other manipulation of the marrow was not performed. Monoclonal or polyclonal anti-T cell preparations were not used pre- or post-transplant.

Post-transplant prophylaxis against GvHD consisted of cyclophosphamide 50 mg/kg ivi over 60 minutes on day +3, with mesna 50 mg/kg/day as a 24 hour infusion, followed by tacrolimus 2mg bd po and mycophenolate mofetil (MMF) 15 mg/kg/dose tds po starting on day +4. In the absence of GvHD, MMF was weaned from day +30 and tacrolimus from day +84.

Supportive care:

Granulocyte colony-stimulating factor (G-CSF) 5 µg/kg/day was administered from day +4 until neutrophil recovery > 1.0 x10^9/L. Infection prophylaxis was as standardly used at our institution for related allogeneic transplants, and consisted of ganciclovir 5 mg/kg bd days -8 to -1 in those recipients who were cytomegalovirus seropositive, cotrimoxazole 160/800 mg bd from day -8 to day -1, metronidazole 400 mg po tds, ciprofloxacin 750 mg bd, acyclovir 800 mg bd, and fluconazole 400 mg starting day 0. Penicillin V 250 mg bd and cotrimoxazole 160/800 mg bd twice weekly were commenced on day +28.

Chimerism analysis:

Flow-sorted peripheral blood T cells or peripheral blood mononuclear cells (PBMCs) were analysed for chimerism using polymerase chain reaction (PCR) on highly polymorphic short tandem repeat (STR) markers. Complete engraftment was defined as the lack of recipient specific STR on polyacrylimide gel analysis, with mixed chimerism detectable when greater than 5% recipient STR present. In one patient with a sex-matched graft and without an informative STR marker graft rejection was confirmed by HLA-typing on peripheral blood mononuclear cells.

Statistical methods:

Engraftment and survival were analysed using the method of Kaplan-Meier. Survival outcomes were estimated using a close-out date of 30-6-11.

[1] All tables and figure are located at the end of this document.

RESULTS

Bone marrow grafts:

Details of the HLA-matching, donor source and cell doses are shown in Table 1. Donors were either siblings (n=9) or children (n=3). HLA-matching at HLA-A, -B, and –DRB1 was either 3/6 (n=11), or 4/6 (n=1). The median bone marrow TNC count was 3.05 x 10^8/kg, (range 2.4-5.7), and median $CD34^+$ dose infused was 2.55 x 10^6/kg (range 1.3-4.8).

Engraftment and chimerism:

All 12 patients had sustained neutrophil recovery to > 0.5 x 10^9/L, at a median time of 14.5 days (range 4-55). One patient failed to reach a platelet count >20 x10^9/L prior to death from relapse, the remainder showed platelet recovery at a median of 17 days post transplant (range 1-66). Five patients did not reach nadir platelet counts ≤ 20 x 10^9/L. One patient required no platelet transfusions, and3 others avoided both red cell and platelet transfusions.

Chimerism status was assessable in 9 patients. Two patients had early relapse and no post transplant chimerism testing was performed. One patient had no informative STR marker available, and autologous reconstitution was demonstrated by repeat HLA typing. One patient had 90% donor T cell chimerism at day 31, but subsequent autologous reconstitution was shown on day 73, while another had persistent mixed chimerism to day 123, then relapsed. The remaining 7 patients achieved complete donor T cell chimerism.

Transplant toxicity:

The procedure was well tolerated, with all patients surviving to discharge and no patients requiring ICU admission or parenteral nutrition. No patients experienced hepatic sinusoidal-obstructive syndrome, haemorrhagic cystitis or grade III-IV mucositis. The median length of hospital stay was 25 days (range 11-52). Bacteraemias post transplant were detected in 4 patients (33%), central line-related coagulase negative staphylococcus in 3 cases, and a skin contaminant bacillus species in the other case, but no patients developed septic shock or required inotropic or ventilator support. Only 3 out of 9 at risk patients required pre-emptive CMV therapy, all with a complete response. There were no proven or probable invasive fungal infections, although one patient was treated for aspergillus on the basis of a sputum isolate, in the absence of CT chest signs (Table 2).

Four out of 12 patients developed grade II-III acute GvHD, all responding to corticosteroids and tacrolimus, but no patients experienced grade IV acute GvHD. Limited stage chronic GvHD occurred in 4 out of 11 evaluable patients, with no patient developing extensive cGvHD.

Transplant-related mortality at 1 year was 16%, with both patients dying from secondary malignancy at 220 and 256 days post-transplant respectively.

Relapse:

Overall 5 patients had relapse of their hematologic malignancy, all with AML. Four subsequently died of relapse, while the other died in CR2 from acute GvHD following umbilical cord blood transplantation.

Survival:

With a median follow up of 685 days post transplant (minimum follow up 231 days) the median overall survival for the group is 324 days (range: 88–1163) (Fig. 1). The cumulative incidence of mortality at day 100 is 8%, with one patient succumbing to relapse after 88 days, while the mortality at 1 year is 50% (5 of 10 evaluable patients), with 3 dying of relapse, and 2 of secondary malignancies. Five of 12 patients are alive and relapse-free, with median follow up of 384 days (range 231-1163).

One patient was transplanted for TKI refractory CML in chronic phase with a T315I mutation. Dasatinib was ceased on day -9. Baseline qPCR for BCR-ABL was 11.2%, but by day 31 the level had reduced to 0.0027%, and was undetectable at day 76. She remains in complete molecular response with undetectable BCR-ABL and no GvHD after a follow up 384 days.

DISCUSSION

This report demonstrates the feasibility of the use of unmanipulated T cell replete bone marrow transplantation from HLA-haploidentical related donors following a reduced intensity conditioning regimen in a group of patients with high risk hematological malignancies. The use of a high dose of cyclophosphamide following infusion of the donor bone marrow to deplete alloreactive donor T cells enabled stable engraftment in the majority and prevented serious GVHD - obviating the need for T cell depletion of the graft and reducing the risks of immunosuppression and infection. The regimen was well-tolerated, with minimal mucositis and no serious bacteraemias, enabling its use in older patients who lacked matched related or unrelated donors, and for whom a myeloablative unrelated cord blood transplant was contra-indicated. In addition, since it requires no graft manipulation or *in vivo* T cell depletion, it is simple, less costly, and practical to implement, particularly where cost constraints may apply.

Our results are consistent with the reported experience from the USA using the same regimen. Seventeen percent (2 out of 12) of our patients had graft loss and autologous reconstitution, compared with 20% (2 out of 10 patients) in the original Phase 1 trial reported by O'Donnell and colleagues[14] and 14% (9 out of 66 patients) in the subsequent report by Luznik and colleagues.[10]

The overall cumulative incidence of relapse in our cohort is 42% (5 of 12 patients) and non relapse mortality is 17% (2 of 12 patients), compared to that of Luznik of 51% and 15% respectively at 1 year. The risk of post-transplant relapse is strongly influenced by pre-transplant disease type and status. Two of our patients relapsed early post transplant, both with advanced AML. Given the relatively low intensity of the conditioning regimen, this protocol may not be appropriate for patients at high risk of early relapse. We are implementing a modified protocolusing a more intensive conditioning regimen using fludarabine and intravenous busulfan for such patients.

Two patients died while in remission of their hematological malignancy from other malignancies. One patient had a malignant melanoma resected several years previously with no evidence of recurrence, however presented with an aggressive metastatic melanoma post HCT. The other patient had been a heavy smoker for many years, and succumbed very rapidly with multi-organ failure at approximately 7 months post transplant. Post-mortem examination subsequently revealed widespread adenocarcinoma of probable lung origin. It is highly likely that both malignancies were present prior to transplant and it is possible that their presentation was hastened by the post-transplant immunosuppression.[15]

One of our patients was transplanted for TKI refractory CML with a T315I mutation. Allogeneic transplantation results have been published in this group with long term survivors reported.[16, 17] Our early results with a haploidentical family donor are encouraging, with a complete molecular response from day 71, and no significant GvHD to date. In the absence of an alternate novel agent, clinical trial, or suitable matched donor, this approach may be a viable alternative for this patient group without other options.

The choice of haploidentical donors or unrelated umbilical cord blood (UCB) units for allogeneic transplantation where no HLA-matched donor is available is currently being questioned. Parallel phase 2 studies of haploidentical and double UCB transplantation were recently published.[18] The outcomes of haploidentical transplantation using NMA conditioning and post-transplant cyclophosphamide were equivalent to RIC UCB in terms of survival and GvHD rates, and indeed were comparable to registry outcomes for HLA-matched RIC HCT. The outcomes of unrelated UCB transplantation using myeloablative conditioning at our institution have been published.[19.20] For UCB transplants 5 out of 11 patients died within

2 months post transplant from transplant related complications, largely as a result of prolonged time to neutrophil engraftment, and there did not appear to be a significant improvement in survival using 2 versus 1 UCB units. Our results for haploidentical RIC HCT appear safer, and given the ease and speed of identifying haploidentical relatives, and the contrasting expense and complexity of unrelated cord blood searches and procurement, this approach seems more amenable, particularly to older high risk patients.

In summary we report the outcome for 12 patients with poor-risk haematologic malignancies having haploidentical allogeneic HSCT, demonstrating low rates of transplant morbidity in terms of infections and GvHD, low NRM, and acceptable rates of graft failure and relapse in this high risk cohort. This reduced intensity haploidentical approach appears simple and feasible, and extends the availability of a potentially curable treatment in a patient group with limited therapeutic options. Additional measures, including outpatient conditioning, modification of conditioning regimen dosing, post-transplant donor lymphocyte infusion (DLI) or the use of PBSC rather than BM (which is under investigation in our institution) may be necessary to improve outcomes in patients at high risk of relapse.

REFERENCES

1 Szydlo R, Goldman J, Klein J, Gale R, Ash R, Bach F*, et al.* Results of allogeneic bone marrow transplants for leukemia using donors other than HLA-identical siblings. *Journal of Clinical Oncology*. 1997; **15**: 1767-77.

2 Velickovic ZM, Carter JM. Feasibility of finding an unrelated bone marrow donor on international registries for New Zealand patients. *Bone Marrow Transplant*. 1999; **23**: 291-4.

3 Barker JN, Krepski TP, DeFor TE, Davies SM, Wagner JE, Weisdorf DJ. Searching for unrelated donor hematopoietic stem cells: Availability and speed of umbilical cord blood versus bone marrow. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2002; **8**: 257-60.

4 Schoemans H, Theunissen K, Maertens J, Boogaerts M, Verfaillie C, Wagner J. Adult umbilical cord blood transplantation: a comprehensive review. *Bone Marrow Transplant*. 2006; **38**: 83-93.

5 Henslee-Downey PJ, Abhyankar SH, Parrish RS, Pati AR, Godder KT, Neglia WJ*, et al.* Use of Partially Mismatched Related Donors Extends Access to Allogeneic Marrow Transplant. *Blood*. 1997; **89**: 3864-72.

6 Reisner Y, Bachar-Lustig E, Li HW, Aversa F, Velardi A, Martelli MF. The role of megadose CD34+ progenitor cells in the treatment of leukemia patients without a matched donor and in tolerance induction for organ transplantation. *Ann N Y Acad Sci*. 1999; **872**: 336-48; discussion 48-50.

7 Aversa F, Terenzi A, Tabilio A, Falzetti F, Carotti A, Ballanti S*, et al.* Full Haplotype-Mismatched Hematopoietic Stem-Cell Transplantation: A Phase II Study in Patients With Acute Leukemia at High Risk of Relapse. *J Clin Oncol*. 2005; **23**: 3447-54.

8 Bachar-Lustig E, Rachamim N, Li HW, Lan F, Reisner Y. Megadose of T cell-depleted bone marrow overcomes MHC barriers in sublethally irradiated mice. *Nat Med*. 1995; **1**: 1268-73.

9 Brodsky RA, Luznik L, Bolanos-Meade J, Leffell MS, Jones RJ, Fuchs EJ. Reduced intensity HLA-haploidentical BMT with post transplantation cyclophosphamide in nonmalignant hematologic diseases. *Bone Marrow Transplant*. 2008; **42**: 523-7.

10 Luznik L, O'Donnell PV, Symons HJ, Chen AR, Leffell MS, Zahurak M*, et al.* HLA-Haploidentical Bone Marrow Transplantation for Hematologic Malignancies Using Nonmyeloablative Conditioning and High-Dose, Posttransplantation Cyclophosphamide. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2008; **14**: 641-50.

11 Symons HJ, Fuchs EJ. Hematopoietic SCT from partially HLA-mismatched (HLA-haploidentical) related donors. *Bone Marrow Transplant*. 2008; **42**: 365-77.

12 Luznik L, Fuchs EJ. High-dose, post-transplantation cyclophosphamide to promote graft-host tolerance after allogeneic hematopoietic stem cell transplantation. *Immunol Res*. 2010; **47**: 65-77.

13 Luznik L, Jalla S, Engstrom LW, Iannone R, Fuchs EJ. Durable engraftment of major histocompatibility complex–incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide. *Blood*. 2001; **98**: 3456-64.

14 O'Donnell PV, Luznik L, Jones RJ, Vogelsang GB, Leffell MS, Phelps M*, et al.* Nonmyeloablative bone marrow transplantation from partially HLA-mismatched related donors using posttransplantation cyclophosphamide. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2002; **8**: 377-86.

15 Inamoto Y, Flowers MED, Lee SJ, Carpenter PA, Warren EH, Deeg HJ*, et al.* Influence of immunosuppressive treatment on risk of recurrent malignancy after allogeneic hematopoietic cell transplantation. *Blood*. 2011; **118**: 456-63.

16 Basak G, Torosian T, Snarski E, Niesiobedzka J, Majewski M, Gronkowska A*, et al.* Hematopoietic stem cell transplantation for T315I-mutated chronic myelogenous leukemia. *Ann Transplant*. 2010; **15**: 68-70.

17 Velev N, Cortes J, Champlin R, Jones D, Rondon G, Giralt S*, et al.* Stem cell transplantation for patients with chronic myeloid leukemia resistant to tyrosine kinase inhibitors with BCR-ABL kinase domain mutation T315I. *Cancer*. 2010; **116**: 3631-37.

18 Brunstein CG, Fuchs EJ, Carter SL, Karanes C, Costa LJ, Wu J*, et al.* Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011; **118**: 282-88.

19 Bradstock K, Hertzberg M, Kerridge I, Svennilson J, George B, McGurgan M*, et al.* Single versus double unrelated umbilical cord blood units for allogeneic transplantation in adults with advanced haematological malignancies: a retrospective comparison of outcomes. *Internal Medicine Journal*. 2009; **39**: 744-51.

20 Bradstock KF, Hertzberg MS, Kerridge IH, Svennilson J, McGurgan M, Huang G*, et al.* Unrelated umbilical cord blood transplantation for adults with haematological malignancies: results from a single Australian centre. *Internal Medicine Journal*. 2006; **36**: 355-61.

Table 1: Patient and graft details

BMT number	Gender	Age (years)	Diagnosis	Disease Status (comments)	Donor	HLA Match[†]	CMV Donor/Recipient	Total Nucleated Cell Dose ($x10^8$/kg)	CD34 Dose ($x10^6$/kg)
654	F	50	AML	CR2	Sister	4 of 6	Pos/Pos	2.6	1.9
663	M	53	NHL	PR3 (Multiply relapsed FL, prior autograft 2006)	Brother	3 of 6	Pos/Pos	3.7	1.7
664	M	56	AML	CR1 (Preceding myelodysplasia)	Brother	3 of 6	Pos/Pos	2.6	1.8
687	M	50	AML	CR1 (Chemo/radiotherapy 2007 for throat ca)	Brother	3 of 6	Pos/Pos	5.7	2.9
692	F	56	AML	CR1 (Monosomal karyotype)	Sister	3 of 6	Pos/Pos	3.2	2.6
703	M	59	NHL	CR2 (Marrow failure following chemotherapy)	Brother	3 of 6	Neg/Pos	3	1.3
729	M	48	AML	CR1 (Persistent cytogenetic abnormality post induction)	Son	3 of 6	Pos/Pos	2.9	2.5
739	M	27	AML	CR1 (Complex cytogenetic abnormality)	Brother	3 of 6	Pos/Pos	3.1	3.7
744	M	49	AML	PR1 (Reinduction failure following relapse)	Brother	3 of 6	Pos/Neg	2.9	1.9
761	F	53	CML	Chronic phase (TKI refractory - T315I mutation)	Daughter	3 of 6	Neg/Neg	5.5	4.8
775	F	35	AML	CR1 (Complex cytogenetic abnormality)	Brother	3 of 6	Neg/Neg	4.4	3.7
791	F	62	AML	CR1 (Monosomy 7)	Son	3 of 6	Pos/Pos	2.4	2.6
	Median	51					Median (range)	3.05 (2.4-5.7)	2.55 (1.3-4.8)

[†]Matching at HLA loci A, B, and DRB1.CR: complete remission; PR: partial remission; FL: follicular lymphoma; TKI: tyrosine kinase inhibitor; HLA: human leukocyte antigen

Table 2: Transplant outcomes

BMT, *n*	Infections	Acute GVHD (grade)	Chronic GVHD		Disease status	Patient status	Cause of death	Survival (days)
			Stage	Severity				
654			NE	NE	Relapsed	Deceased	Relapse	88
663	Aspergillus in sputum, no CT changes, treated.	I	Limited	Mild	CR	Alive		1163
664	CMV reactivation	I	Limited	Mild	CR	Alive		1112
687	Nil	Nil	Nil	Nil	Relapsed[1]	Deceased	Relapse	1041
692	Nil	II	Limited	Moderate	Relapsed	Deceased	Relapse	285
703	VZV	II	Nil	Nil	CR	Deceased	Melanoma	256
729	CMV reactivation	I	Nil	Nil	CR	Deceased	Lung adenocarcinoma	220
739	Nil	Nil	Nil	Nil	Relapsed	Deceased	GvHD following UCB HCT[2]	384
744	Nil	Nil	Nil	Nil	Relapsed	Deceased	Relapse	234
761	Nil	Nil	Nil	Nil	CR[3]	Alive		363
775	RSV	II	Nil	Nil	CR	Alive		384
791	CMV reactivation	III	Limited	Mild	CR	Alive		231
							Median	324

[1]Autologous reconstitution, then later relapse day 712. [2]Autologous reconstitution then relapse day 181,received UCB HCT in CR2, then succumbed with GvHD.[3]Baseline BCR-ABL:11.2%, day 30: 0.0027%, and sustained complete molecular response by day 77. NE, not evaluable; CMV, cytomegalovirus; VZV, varicella zoster virus; RSV, respiratory syncitial virus; CR, complete remission

Figure 1: Overall survival curve.