Allogeneic transplation from HLA-haploidentical donors in KBC Zagreb

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GRADUATE THESIS

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This graduation paper was made at University Clinical Hospital “Rebro” in Zagreb at the Department of Hematology under the supervision of Nadira Duraković, MD, PhD, and was submitted for evaluation in the academic year 2015/2016. Junior staff in the Division of Hematology aided in the collection and analysis of data for the study of this subject.

Mentor: Nadira Duraković

ABBREVIATIONS

List of abbreviations:

BMT- bone marrow transplant

BuCy – conditioning regimen of busulfan & cyclophosphamide

CMV – cytomegalovirus

EBV – Epstein-Barr virus

GVHD – graft-versus-host disease

GVL - graft-versus-leukemia effect

HSCT – hematopoietic stem cell transplant

MMF – mycophenolate mofetil

MUD – matched unrelated donor

NRM – non-relapse mortality

PBSC – peripheral blood stem cells

PTCy – post-transplantation cyclophosphamide

RIC – reduced intensity conditioning

TBI- total body irradiation

TCD- T-cell depletion

UHC – Clinical University Hospital (Hospital “Rebro”, Zagreb; used interchangeably with the Croatian acronym KBC)

Contents:

Title: Allogeneic transplantation from HLA-Haploidentical donors in KBC Zagreb

Author: Brian Jacob Melamed

Summary:

Background: The use of haploidentical stem cell transplantation (HSCT) has recently arisen as an effective treatment for refractory hematological malignancies, and several approaches have been shown to offer similar outcomes to HLA-matched allogeneic HSCT with the benefit of a larger and more accessible donor pool, particularly in smaller countries and ethnic minorities. High-dose post-transplant cyclophosphamide (PTCy) is a simple and well-studied approach being newly utilized at UHC Zagreb.

Objective: We evaluated several key outcomes of patients receiving haploidentical HSCT at UHC Zagreb in order to determine whether they were acceptable in comparison to other centers performing haploidentical HSCT as well as studies of HLA-matched HSCT.

Methods: In a retrospective study, ten patients with various refractory myelogenous and lymphoid malignancies underwent PTCy haploidentical HSCT at UHC Zagreb from 2012-2015. Both myeloablative and RIC conditioning regimens were employed. Data was collected towards the primary endpoints of engraftment, relapse and GVHD rates.

Results: Median times to neutrophil and thrombocyte recovery were 12 and 21 days post-transplant, respectively. Relapse rates were 50%, with a mean relapse time of 5.6 months. Rejection rate was 10%. NRM was 20% with a median time of 15.3 months. Acute and chronic GVHD rates were 10% and 30% respectively, with a mean diagnosis time of 11.2 months for chronic GVHD.

Conclusion: HLA-haploidentical HSCT at UHC Zagreb using PTCy is associated with acceptable rates of engraftment, relapse, and GVHD.

Keywords: stem cell transplantation, haploidentical, graft-versus-host, post-transplantation cyclophosphamide

1. Introduction

The use of hematopoietic stem cell transplantation has been a therapy used alone or in conjunction with chemotherapy and radiation to treat a variety of hematologic malignant and nonmalignant diseases for over 50 years (1), with varying but consistently improving results, so much so that these transplants (previously referred to as bone marrow transplants) are now an expected secondary modality of treatment in patients who have had recurrences after standard chemotherapy regimens (2).

Allogeneic HSCT is the only possible curative therapy for a number of hematological malignancies, as well as a number of non-malignant diseases such as severe combined immunodeficiencies and aplastic anemia. However, only 30% of patients have an available family HLA-identical donor (3). The probability of having a fully-matched sibling is 1-(0.75)□, where N= number of siblings (4). For other patients we have the possibility of finding an unrelated HLA-matched donor, but still for a considerable portion of patients we are unable to identify an MUD, particularly for patients who belong to a certain ethnic group (5). In the case of Croatia, biobanking of bone marrow donors and cord blood donors are recorded through their respective organizations, but are sporadically utilized and limited in scope (6). Haploidentical transplantation is a method that was underused previously due to an increased incidence of graft rejection compared to HLA-matched donors, as well as increased incidence of severe GVHD (7). In recent times, due to the increasing need for non-traditional donor pools in HSCT, researchers have revisited the possibility of using haploidentical donors, and three major approaches have been developed.

T-cell depletion (TCD) is an important component of ensuring low rates of acute and chronic GVHD, and this can be achieved *ex vivo* via immunomagnetic selection of CD34+ before donation, or *in vivo* with infusion of antithymocyte globulin (ATG) in the donor (8). Addition of a megadose infusion of CD34+ into the recipient will result in a niche competition, wherein stem cells have a preferential advantage over any remaining donor T-cells.

Early studies showed development of conditioning-resistant anti-donor T-cells. Therefore, disease-free survival (DFS) is low, and NRM using the TCD approach is high due to the patient's increased susceptibility to infections, especially due to reactivation of viruses such as cytomegalovirus and Epstein-Barr virus (9).

The GIAC strategy, first applied in Peking University and Beijing Air Force University in China, uses *in vivo* modulation of allografts without T-cell eradication. GIAC is an acronym for a protocol that consists of GCSF-stimulation of the donor pre-transplant, intensified immunosuppression, Antithymocyte globulin infusion for the recipient during conditioning, and a combined PBSC and bone marrow grafting. T-cells in the stimulated grafts were less proliferative and were more likely to differentiate to Th2 cells than Th1 (recognized as a greater stimulator of a GVHD response), thought to be caused by an increase in IL-10 secretion and a downregulation of CD86 expression on antigen-presenting cells (4). This technique comes with the caveat of being complex, and faces significant rates of GVHD and an increased risk of infection due to the depression of Th1 differentiation in the donor grafts (10).

At UHC Zagreb, we decided to proceed with haploidentical transplantation using post-transplantation cyclophosphamide application (the "Baltimore" protocol) as our institutional protocol. Since 1963, murine studies demonstrated beneficial host tolerance to skin allografts using post-transplantation cyclophosphamide (4). Mechanisms of cyclophosphamide are direct elimination of host and donor alloreactive T-cells that are proliferative, while sparing quiescent alloreactive T-cells such as those that are virus-specific (11). PTCy also affects intrathymic clonal deletion of alloreactive T-cells, though this effect is less pronounced in adults. Essential to the favorable profile of PTCy is the sparing of host CD4+ regulatory T-cells, which promote tolerance to donor grafts and help prevent GVHD (12). This is due to high secretion by T-reg cells of aldehyde dehydrogenase, an enzyme that degrades cyclophosphamide. Low doses of cyclophosphamide and fludarabine are given pre-transplantation

as part of reduced-intensity conditioning, and TBI of 200cGy is administered on the day before transplantation. PTCy is given on days 3 and 4, and MMF on day 5 until an average of 35 days post-transplantation (13). Tacrolimus is also started on day 5 and terminates variably on presence and presentation of GVHD signs, usually 180 days (Figure 1).

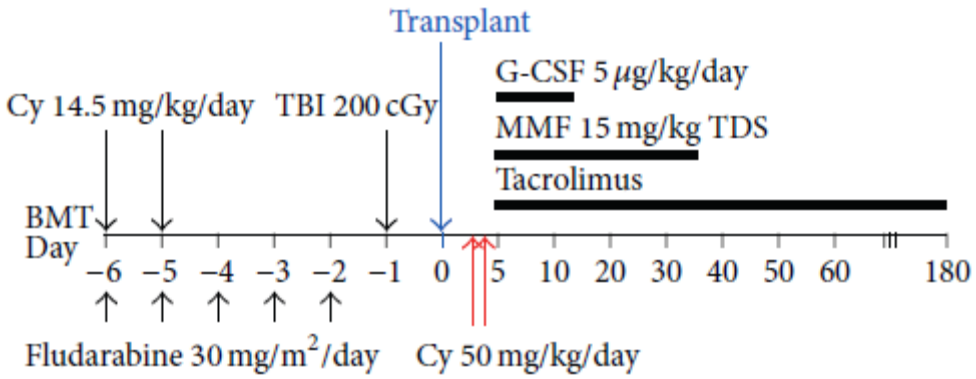

Figure 1. Visual representation of Baltimore RIC and post-transplantation cyclophosphamide regimen. Taken from (13) with permission under Creative Commons license.

A 2002 Johns Hopkins phase I study using a single dose of PTCy on day 3 with T-cell replete haploBMT patients showed an 80% engraftment rate, 60% acute GVHD grade II-IV, and 60% survival after a median follow-up period of 284 days. A subsequent phase II study added a second PTCy dose on day 4 and prolonged tacrolimus treatment resulted in improved engraftment rate, an acute GVHD rate of 34%, and a reduction of extensive chronic GVHD from 25% to 5%. Nonrelapse mortality (NRM) due to infection was limited to two patients who died of fungal infection, and none of the patients had detectable CMV reactivation or EBV-linked lymphoproliferative disease (4). Remarkably, there was no observable effect on the degree of HLA disparity in reference to acute GVHD or progression-free survival. A large number of studies using this protocol points to similar outcomes using PTCy haploBMT with alloBMT using HLA-matched sibling or MUD (14).

Risks of high dosages of cyclophosphamide can include hemorrhagic cystitis, a condition also attributable to reactivation of the BK virus and one which is treatable. A comparison of haplo-HSCT to both matched related donors and MUD by Bashey found equivalent outcomes between all groups when using this approach, with an improvement over the matched groups in disease-free survival (15). Overall, the relative simplicity, familiarity, and favorable outcomes of PTCy make it a desirable option for treatment in centers where matched sibling donors are unavailable and matched unrelated donors are harder to find due to demographic considerations.

2. Hypothesis

The preliminary trials with patients receiving HLA-haploidentical HSCT at UHC Zagreb with a post-transplant cyclophosphamide regimen is feasible and results in acceptable rates of graft rejection as well as GVHD incidence.

3. Objectives

This retrospective study will focus on the primary objective of investigating the rejection rates for haploidentical HSCT and acute and chronic GVHD incidence in patients transplanted at UHC Zagreb. In addition, we will investigate secondary aims of patient outcomes over our observational period. These will include survival without disease progression, overall survival, NRM, and rates of hematopoietic recovery.

4. Methods

4.1 Study population

Ten patients with various hematological malignancies were transplanted with haploidentical HSCT using the post-transplant cyclophosphamide regimen at UHC Zagreb. Transplantations were performed from 24 May 2012 until 15 September 2015, and data was collected on these patients through February 2016.

This is a retrospective study of the outcomes previously listed in the Objectives section. More detailed information can be found below in Table 1.

Table 1. Patient characteristics receiving HSCT at UHC Zagreb.

Pt. #	DOB	Gender	Primary Dg	Date of Dg	Previous lines of therapy	Donor relation	Donor type	Conditio-ning
1	8.9.1964	M	AML arising from JAK2+ myelofib rosis	1.9.2011	DCEx1 (9.2011), HAM (10.2011), 1+5 (11.2011), 6-thioguanine (12.2011)	son	Combin ed bone marrow/ PBSC	Baltimore
2	7.5.1974	M	T-ALL	1.5.2012	GRAALL (5.2012), HyperCVADx7 (11.2012)	mother	Bone marrow	Baltimore
3	5.5.1957	M	AML	25.11.2013	DCEx1 (10.2013), DIA consolidation (10.2013)	daughter	Bone marrow	Baltimore
4	15.6.1973	M	CML (Philadel phia)	2.9.2013	Hydroxyurea (10.2013), nilotinib/dasatinib (5.2014), fludarabine & cyclophosphamide (11.2014)	mother	Bone marrow	Baltimore
5	27.7.1969	F	AML	3.2014	Hydroxyurea & DCEx1 (4.2014), DIA (6.2014), MRC (8.2014), 1+5 (10.2014)	daughter	Bone marrow	Baltimore
6	21.1.1952	M	AML	16.7.2014	3+7 (7.2014), NOVIAx1 consolidation, 2+5 & mitoxantrone	daughter	Bone marrow	Baltimore
7	28.7.1952	F	AML arising from MDS	8.2014 (MDS)	Azacitidine x7 (9.2014), DCE x1 (5.2015), DIA (7.2015)	mother	Bone marrow	Baltimore
8	26.2.1988	M	HL	2012 (primary), 13.4.2014 (relapse)	ABVD x4 & rituximab (2012), HDIM x2/miniBEAM, autotransplant (9.2013), BEAM/eBEACOPP/Br+D HAP x2/brentuximab (8.2014)	father	Bone marrow	Baltimore
9	24.12.1985	F	AML arising from MDS	4.2015 (MDS)	BISHOP/DIA x1 (6.2015)	sister	PBSC	BuCy
10	15.11.1981	F	AML	1.11.2013	ICE/DIA x1/HAM/autologous transplant (11.2013), FLAG-IDA/HAM (4.2015)	brother	Bone marrow	BuCy

4.2 Ethics statement

This study has been approved by the Institutional Review Board at UHC Zagreb and the University of Zagreb Medical School. Retrospective data is used and all patient identifying information is removed in compliance with protection of patient privacy.

4.3 Transplant protocols

Transplantation was carried out at the Department of Hematology at UHC Zagreb. Eight patients received unmanipulated bone marrow transplants, one patient received PBSC only, and one patient received a combination of bone marrow and PBSC.

Conditioning for the recipient followed the RIC Baltimore protocol (fludarabine 30mg/m² IV on days -6 to -2 pre-transplant, cyclophosphamide 14.5mg/kv IV on days -3 and -2, and TBI of 200cGy on day -1) in eight patients. Two patients received a standard myeloablative conditioning regimen of busulfan 3.2mg/kg IV on days -7 to -4 pre-transplant, and cyclophosphamide 60mg/kg IV on days -3 and -2 (16).

4.4 Post-transplant cyclophosphamide and immunosuppression

All patients were administered a post-transplant cyclophosphamide regimen and immunosuppressive therapy as shown in Figure 1. MMF was discontinued on day 35 post-transplant and tacrolimus was administered for an mean of 180 days or by the discretion of the attending physician on follow-up. Mesna is used as a treatment in the event of development of hemorrhagic cystitis.

4.5 Tracking of patient data

All patient data for this study was recorded and updated on BIS, the electronic medical recording system used in medical centers across Croatia.

5. Results

Baseline characteristic

As seen in Table 1, our patients were 60% male and 40% female, ranging in age from 28 to 64 with a mean age of 44.5 years. 70% of our patients were indicated for transplant on the diagnosis of refractory acute myelogenous leukemia, and two of those patients had refractory AML that arose from myelodysplastic syndrome, which increased the likelihood of relapse due to resistance to previous lines of chemotherapy. Previous lines of therapy shown in Table 1 were appropriate to the treatment of the patients' primary diagnoses but were ultimately unsuccessful in preventing relapse.

5.1 Hematopoietic markers of engraftment

Of our ten patients, complete data on recovery of thrombocytes and absolute neutrophil count (ANC) was available for seven. Median thrombocyte recovery time was 12 days and neutrophil recovery at 21 days. Our patients showed a significant positive correlation between the amount of infused donor CD34+ hematopoietic stem cells from the donor and recovery times for neutrophils and thrombocytes. Furthermore, there was an increased incidence of GVHD in those patients with impaired recovery of thrombocytes from 20,000 to 50,000 as seen in the spike at 51 days. The data in Figure 2 shows identical patterns when comparing engraftment markers to the quantity of CD3+ (cytotoxic T-lymphocyte) cells infused.

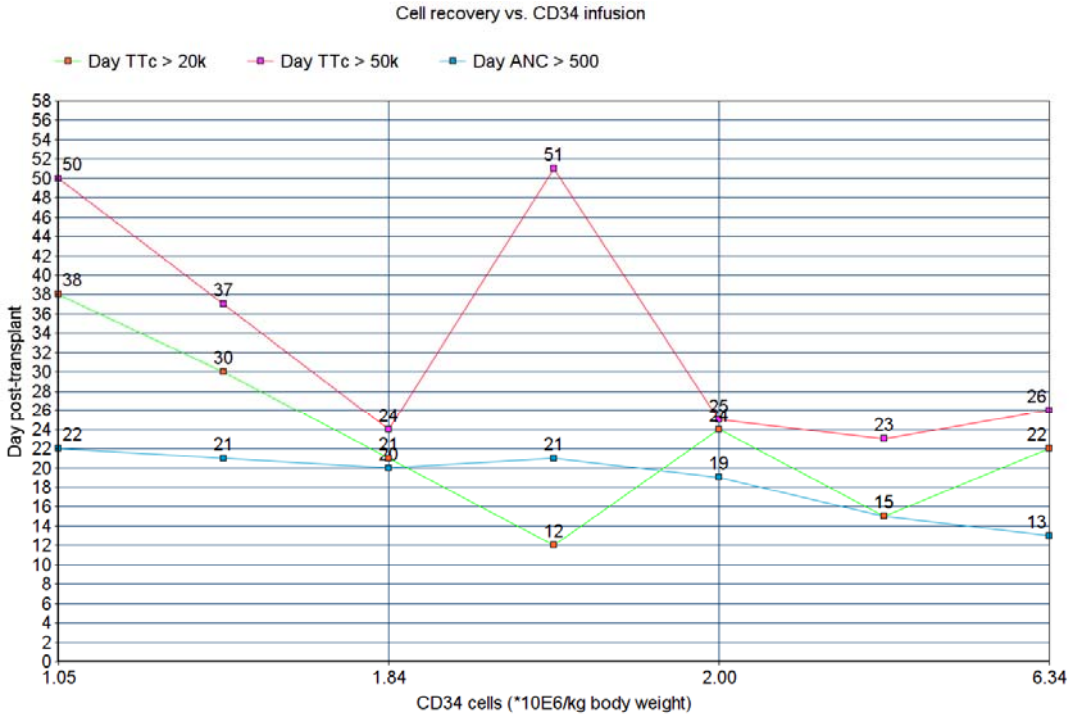

Figure 2. Recovery of hematopoietic markers in transplanted patients.

5.2 Rates of Relapse and Rejection

50% of the patients in our study encountered relapse of their primary disease over the course of our study, with a mean relapse time of 5.6 months post-transplant. Relapse was determined by cytology at UHC Zagreb. Patients who relapsed were majority male, had positive cytogenetic markers for poor prognosis, and all were over 40 years old.

One patient's cytology suggested transplant rejection 17 months post-transplantation. He subsequently received a PBSC infusion from his mother but post-transplant data was not available to include this into the study.

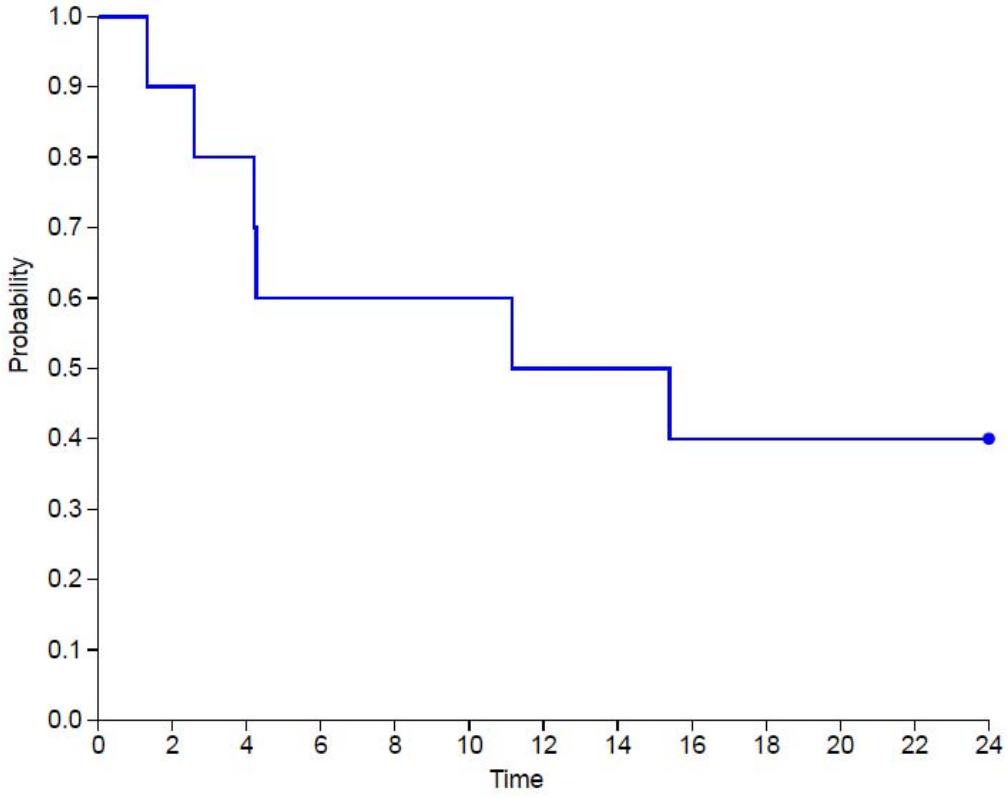

Figure 3. Disease-free survival.

5.3 Nonrelapse mortality

Two patients (20%) died during the period of observation, with a median time of 460 days or 15.3 months. Both patients were male over the age of 40, which indicate a higher risk for complications post-transplant according to the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI).(Sorror) Cause of death in both patients was multisystem organ failure.

5.4 Development of GVHD

Determination of acute and chronic GVHD was made by clinical observation on follow-up and confirmed by biopsy in the Pathology department of UHC Zagreb. Acute GVHD less than 100 days post-transplant was observed in only one patient, who developed a maculopapular rash.

Three patients (30%) developed chronic GVHD, with a mean time to diagnosis of 11.2 months or 336 days. These patients were all over the age of 40. Presentations included ocular irritation and gastrointestinal erosions and bleeding. Two of these patients also had sclerodermatous hyperpigmented patches which were confirmed as grade II-IV on the NIH organ grading table. There was no observable association between delayed recovery of thrombocytes and development of GVHD in these patients.

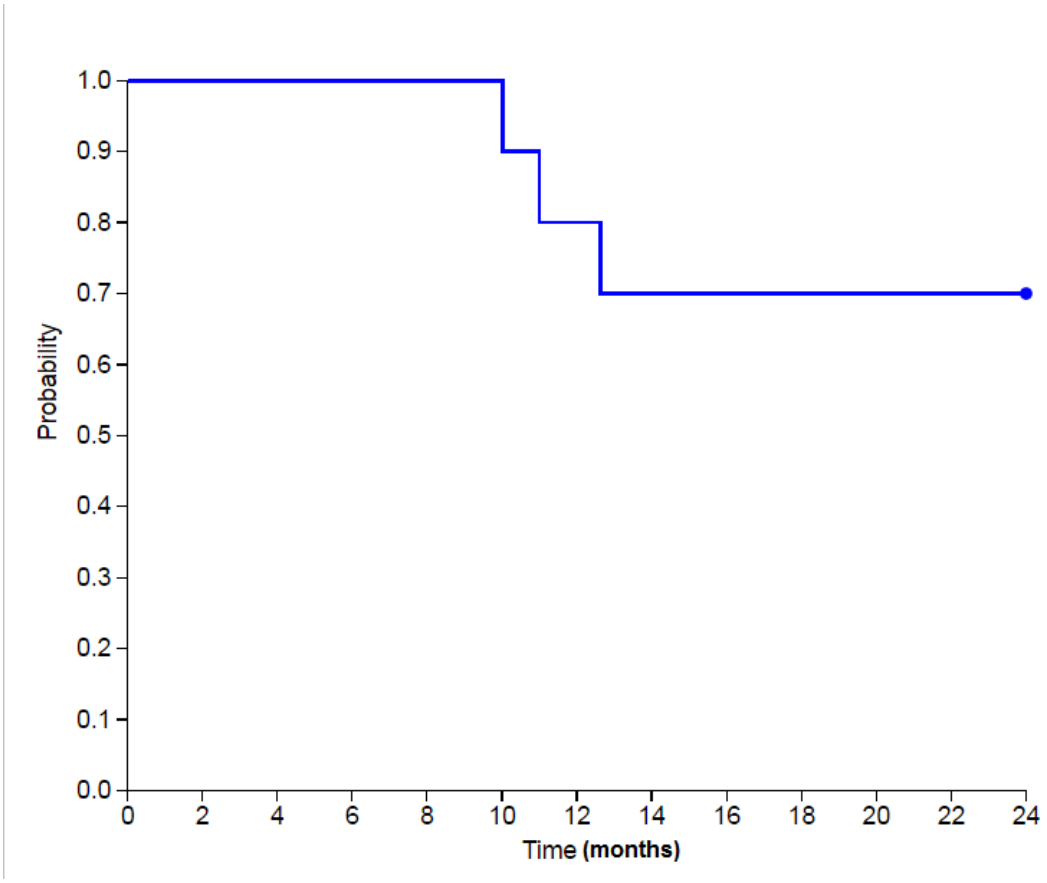

Figure 4. Development of chronic GVHD.

5.5 Development of infection

All donors and recipients were screened for antibodies against CMV before transplant; all participants showed positive immunoglobulin G and negative active infection. One patient showed reactivation of CMV post-transplant as evidenced by presence of CMV DNA.

Two patients (20%) had complications related to the development of bacterial infections. One patient was released on day 43 post-transplant after treatment for vancomycin-resistant enterococcus, *S. epidermidis* dermatitis, and colistin-sensitive *P. aeruginosa*. The other patient, who underwent a splenectomy previous to transplantation, was treated for two episodes of sepsis and intestinal candidiasis.

6. Discussion

6.1 Hematopoietic markers of engraftment

These markers are important as they are a signifier of effective engraftment of donor cells. An ANC above 500 cells/μL is the clinical threshold for neutropenia and marks a clinical milestone in the recipient's ability to ward off bacterial infection. Thrombocyte counts below 20,000/μL is associated with risk of severe bleeding and thrombocyte counts below 50,000/μL that do not improve after further platelet transfusions are a marker of secondary failure of platelet recovery (SFPR), and are associated with higher rates of acute and chronic GVHD in those patients. (10).

Our rates of ANC and thrombocyte recovery are comparable to a study that showed median recovery times of 15 days for neutrophils and 24 days for thrombocytes (4), but in our case the numbers have been flipped. While the association between a larger donor stem cell infusion and reduced time to recovery remains, our small sample size led to an aberration that make a generalization difficult.

Several studies have confirmed the link between amount of CD34+ cell infusion quantity and positive outcomes (17). Stimulation of the donor with granulocyte colony stimulating factor will markedly increase the amount of hematopoietic stem cells and a threshold of 2.5*10^6/kg cells infused will ensure sustained engraftment in most cases of HLA-matched transplants. Recovery of thrombocytes to 20,000/µl by day 14 and neutrophil count to 500/µl should take place by day 12 in these patients. (12). Our results compared similarly with HLA-matched patients in this regard.

The presence of a high number of donor CD3+ T-lymphocytes in the graft is also associated with increased engraftment, lower infection rates, and a graft-vs-leukemia effect in the setting of the recipient's dysfunctional immune system. Donor CD4+ cells aid in the prevention of bacterial infection and CD8+ cells induce a graft-versus-leukemia effect that will continue to foster the conditions for stem cell homing and engraftment (10).

6.2 Rates of Relapse and Rejection

Rates of relapse in several studies (4, 17) show an incidence in one-year relapse of 50%; this was consistent with our findings, although our patients had an earlier mean occurrence of relapse compared with other studies. There was an increased likelihood of relapse in relation to myelogenous malignancies than with lymphoid malignancies. Relapse was the major cause of treatment failure in our sample group.

The effect of GVL in patients treated with a RIC regimen has been shown to lead to lower NRM and treatment-related mortality but a higher relapse rate, leading to similar rates of overall survival for patients compared to myeloablative regimens (18, 16). The two patients with BuCy myeloablative conditioning did not experience relapse in our observation period.

6.3 Nonrelapse mortality

Non-relapse mortality, as shown in other studies, has a tendency to level out between 1 and 2 years post-transplant, at a rate of 15% (4) for haploidentical HSCT, compared with 20% in our group, who died at 405 and 516 days post-transplant, respectively.

These patients were both over the age of 40 (putting them at higher risk of complications according to HCT-CI) and showed previous complications with primary therapies including treatment interruptions and a relapse of myelodysplastic syndrome pre-transplant.

6.4 Development of GVHD

Occurence of GVHD is common to any tissue transplant from an immunocompetent donor into an immunocompromised recipient, and the clinical significance of this phenomenon in the setting of HSCT must be balanced with the effect of donor tissue on GVL, and against the possibility of graft failure (21). This is correlated with the degree of HLA disparity, resulting in greater alloreactivity in a bidirectional manner (17,19).

Our rate of acute GVHD (10%) was lower than that found in other studies (Luznik Odonnell)(Bashey) of 25-34%. This result should not be suggestive of any conclusion other than our small sample size, regardless of the high skill level of physicians and staff at UHC Zagreb.

Surveys of patients with active chronic GVHD show a marked decrease in physical activity and social functioning, as well as an increase in pain and emotional and cognitive functioning (20). Determination and grading of chronic GVHD was made using NIH criteria, but also involve an interdisciplinary team of specialists to determine emergence and development of symptoms that affect multiple organs. Rising rates of chronic GVHD can be attributed to the availability of allogeneic HSCT to older and more high-risk patients, and rates for chronic cGVHD in all allogeneic patients approach 50% (22).

Studies for haploidentical HSCT show a moderate-severe chronic GVHD rate of 13-20% after 1 year (2,13). Our cGVHD incidence of 30% is higher than rates found in other haploidentical studies; however, the small sample size may have been a factor in this result. The continuation of haploidentical HSCT using PTCy at UHC Zagreb will increase the data pool.

6.5 Development of infection

Persistent viruses such as EBV and CMV are normally controlled through CD8+ cytotoxic T-lymphocyte response, and incidence approaches 50% in some studies, but that the CD8+ count during reconstitution may be less important than recovery of CD4+ T-cells and NK cells as immune modulators (11). Furthermore, there is evidence of an association between development of CMV viremia and a reduced incidence of relapse in haploHSCT patients. On the reverse side of this, GVHD rates were higher in CMV-reactivated patients, likely due to a mechanism of greater differentiation toward and activity of cytotoxic T-lymphocytes (23). Our one patient (10%) with CMV reactivation shows an overall lower incidence than other haploHSCT studies. The use of immunosuppression in recipients with tacrolimus, MMF, and corticosteroid therapy has the dual result of preventing GVHD in early stages and resulting in a higher chance for infection.

7. Conclusions

The benefits of haploidentical donors using PTCy-modified HSCT has been shown to confer several benefits over HLA-matched donors. These donors are readily available, highly motivated to donate in order to help cure a family member, and are more often available post-transplant. In the case of Croatia, though we have a source of potentially HLA-matched stem cells in our umbilical cord blood bank (6), a haploidentical HSCT is cheaper to source and perform.

Conclusions from several studies at Johns Hopkins of the success of PTCy have allowed them to achieve similar outcomes as matched sibling HSCT and allowed them to forgo MUD searches except for the 5% of cases where the patient has no haploidentical options.

Our data indicate that, while the sample size was small and the protocols employed new to UHC Zagreb, results of graft rejection and GVHD were acceptable in comparison to HLA-matched patients as well as consistent with other studies of PTCy around the world.

This study is the first set of data of patients receiving haploidentical HSCT in Croatia and the promising findings should point to continuing progress in the standing of UHC Zagreb and its hematologist-oncologists as leaders in the region for treatment of hematologic malignancies.

Competing interests

The authors declare that they have no competing interests.

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Minor, Anthropology, University of Illinois at Urbana-Champaign

2010-2016

M.D., University of Zagreb School of Medicine, Medical Studies in English

-Student demonstrator, Hematology Department, UHC Zagreb

-Student instructor, “Improv for student doctor communication”, Department of Palliative Care and Medical Education (CEPAMET)

2016

Medical clerkships in the United States:

Center for Advanced Heart Failure, Cardiovascular and Transplant Surgery, University of Texas Health Center, Houston

Emergency Medicine Department, Weiss Memorial Hospital, Chicago