

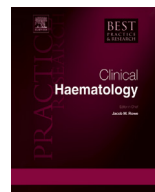


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Recent developments in HLA-haploidentical transplantations



Margaret Showel, Ephraim J. Fuchs*

Division of Hematologic Malignancies, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 289 Cancer Research Building, 1650 Orleans Street, Baltimore, MD 21287, USA

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ABSTRACT

While allogeneic hematopoietic stem cell transplantations have a curative potential, several patients with hematologic malignancies cannot avail themselves of this therapeutic option due to lack of matched donor availability. Although HLA-haploidentical transplantations were previously associated with poor outcomes, recent evidence with use of post transplantation cyclophosphamide indicate improved safety and efficacy. The following paper discusses the most recent developments in this area.

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Introduction

Allogeneic hematopoietic stem cell transplantation is a curative option for some hematologic malignancies including leukemia. However, many patients are unable to find an HLA-matched sibling or an unrelated donor and donor availability remains an important problem. To address this issue, other options such as HLA-haploidentical transplantation, partially mismatched related or unrelated donor transplantation, or cord blood transplantation have been explored. HLA-haploidentical, or partially HLA-mismatched related donor stem cell transplantations provide the benefit of more potential donors per patient, faster graft acquisition time and improved treatability of post-transplantation relapse, over HLA-

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BMT, bone marrow transplantation; CAR T cell, chimeric antigen receptor T cell; Cy, cyclophosphamide; DRI, disease risk index; GVHD, graft versus host disease; haplo-BMT, HLA-haploidentical BMT; MRD, minimal residual disease; NHL, non-Hodgkin's lymphoma; PRAME, preferentially expressed antigen in melanoma; PTCy, post transplantation cyclophosphamide; RIC, reduced intensity conditioning.

* Corresponding author. Tel.: +1 410 955 8143; fax: +1 410 502 8651.

E-mail address: fuchsep@jhmi.edu (E.J. Fuchs).

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matched transplantations. Despite these advantages, historical outcomes have been poor with HLA-haploidentical transplantations (almost 10% survival at 5 or more years) [1]. This has been attributed to bidirectional alloreactivity which causes severe graft versus host disease (GVHD), delayed engraftment and graft failure [1–3]. Although depletion of T cells from the donor graft has been associated with a reduction in graft-versus-host disease, this approach can result in poor immune reconstitution, and high mortality from infections [4]. Therefore there has been a need to address alloreactivity in a selective manner in HLA-haploidentical transplantation. The following discussion provides a brief summary of the most recent progress in improved HLA-haploidentical transplantation protocols.

Selective allo-depletion with high-dose PTCy

Cyclophosphamide (Cy) is an alkylating agent that targets actively proliferating cells and has been previously used to induce immunological tolerance. The high dose post-transplantation cyclophosphamide (PTCy) protocol involves administration of a high dose of Cy (50 mg/kg/day) on days 3 and 4 after transplantation, which results in selective elimination of proliferating alloreactive T cells from the donor and the host. On the other hand, quiescent non-alloreactive T cells, including T cells against pathogens such as cytomegalovirus and herpes simplex virus from the host and the donor are resistant to Cy. This ensures selective mitigation of alloreactivity without complete immunosuppression [5,6].

RIC haplo-BMT with PTCy

The protocol of reduced intensity conditioning and HLA-haploidentical bone marrow transplantation (RIC haplo-BMT) with high-dose PTCy has incorporated this principle and was used for the treatment of 374 patients with hematologic malignancies (120 patients with myeloid disease and 249 with lymphoid disease). The median age of the patients was 55 years (18–75 years), median HLA mismatch was 4/10 (0–5 on the HLA-A, -B, -C, -DRB1 and -DQB1) and the disease risk index (DRI) included low- (19%), intermediate- (65%), and high-risk (16%) patients. Outcomes data on these patients have shown that the incidence of grade II–IV GVHD was 32% and grade III–IV GVHD was 3.3% at 200 days post-transplantation. Similarly, the cumulative incidence of chronic GVHD was reported as 11% at 300 days post transplantation. Notably the incidences of relapse and non-relapse mortality 4000 days after transplantation were 51% and 17% respectively. The overall survival after 5 years was 40% and progression-free survival was 31% (Fig. 1) [7]. Analysis of disease-specific outcomes for RIC haplo-BMT with PT-Cy demonstrate that the overall 5-year survival for AML, ALL, B-cell NHL and Hodgkin lymphoma was 43%, 32%, 49%, and 52%, respectively (Fig. 2) [7]. More specifically, overall survival and progression-free survival 10 years after transplantation among AML patients were 42% and 35%, respectively (Fig. 2). Patients with minimal residual disease (MRD) detectable by flow cytometry had significantly worse outcomes than patients with no evidence of MRD, with long-term survival of >50% in those without MRD versus 10% in those with MRD (unpublished results). Interestingly, older patients, including patients aged 60–75 years, seem to tolerate RIC haplo-BMT with PTCy (Fig. 3) [8]. Although older patients (age 70–75 years) were associated with higher GVHD (~50%) as compared to patients 60–69 years (~30%) and 50–59 years (~20%), they were associated with a lower rate of relapse and lower non-relapse mortality. This is evident from the fact that overall survival and progression-free survival rates were comparable among all patient age groups (Fig. 3). Altogether, these data are encouraging, since the median age at diagnosis of AML is around 66 years and thus this transplantation platform represents a viable option for AML patients.

Comparison with HLA-matched BMT

The disease risk index (DRI) can be used to predict outcomes of BMT among heterogeneous patients based on diagnosis and disease status. DRI can be used as a prognostication tool irrespective of conditioning intensity or graft source [9,10]. Fig. 4 shows that DRI (low, intermediate or high risk) consistently prognosticates outcomes among patients undergoing RIC haplo-BMT with PT-Cy and the differences in the risk categories can be attributed to differences in the corresponding relapse rates (Fig. 5). The non-relapse mortality however, is not significantly different between the low-,

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