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Non-myeloablative Allogeneic Hematopoietic Stem Cell Transplant Using Mismatched / Haploidentical Donors: A review

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Abstract

Haploidentical hematopoietic stem cell transplantation (HSCT) provides an opportunity for patients to benefit from HCT when a human leukocyte antigen (HLA) genotypically matched sibling is not available. Initial results with the use of mismatched allograft has been disappointing, due to the high incidence of graft-versus-host disease (GVHD), and infectious complications resulting in an unacceptable treatment-related morbidity and mortality. Recent advances with effective T-cell depletion, the use of ‘megadose’ of stem cells and reduced intensity conditioning has significantly decreased the early transplant related mortality and GvHD, while enabling robust and prompt engraftment, and hence enhancing the therapeutic benefits of haploidentical transplantation. However, the cardinal problems related to delayed immune reconstitution causing post-transplant infectious complications and relapse remain, limiting the efficacy of haploidentical transplant. Preliminary data has demonstrated the great potential in the use of adoptive cellular immunity and selective allodepletion in rapidly reconstituting immunity without GvHD. The encouraging reports from haploidentical transplant using noninherited maternal antigen (NIMA)-mismatched donors or natural killer alloreactive donors may greatly increase the donor availability and open a way to more appropriate donor selection in HLA-haploidentical HSCT. Future challenges remain in determining the safest approach for haploidentical transplant to be performed with minimal risk of GvHD, while preserving effective graft-versus-leukemia activity and promoting prompt immune reconstitution.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) has been successfully used to treat many high risk hematological malignancies and marrow failure syndromes. The best results with allogeneic HSCT have been obtained in patients receiving allograft from HLA-matched siblings. As the chance of finding a human leukocyte antigen (HLA) genotypically identical sibling donor is only 25%, much attention has been focused on the use of alternative donors, either from the matched unrelated volunteer adult donors, umbilical cord blood or partially matched related donors. Despite the expansion of worldwide unrelated donor registries that have markedly improved the chances of finding a donor for many patients,¹ the application of transplantation using unrelated adult volunteer donors has been limited by some major obstacles, which include (i) the wide range of chance of finding a phenotypically matched

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unrelated donor, from 60–70% for Caucasians to under 10% for ethnic minorities.^{2, 3} (ii) the cumbersome process of identifying, typing, and harvesting an unrelated donor, with the median time interval between initiation of a search and the donation of marrow of about 4 months,⁴ rendering this option less viable for patients who urgently need transplantation, such as those with acute leukemia. This is because many such patients do not survive the long waiting period until a suitable donor can be found. Moreover, allogeneic transplant using the matched unrelated donor is associated with a high transplant-related mortality (30–40%) and high long-term morbidity.^{5, 6, 7, 8, 9} Umbilical cord blood, on the other hand, may overcome some of these limitations due to easy procurement, the absence of risk for donors, potential reduced risk of GVHD,¹⁰ and less stringent criteria for HLA matching for donor-recipient selection. However, engraftment remains a major concern due to the low number of progenitor cells contained in an umbilical cord blood unit. Moreover, delayed neutrophil recovery and transplant-related mortality (TRM) remain the main obstacles for successful UCB transplantation, particularly in adult patients receiving myeloablative preparative regimens.^{11, 12}

The use of hematopoietic stem cells from relatives who are partially matched for HLA provides some advantages for patients lacking HLA-matched sibling donors or fully matched unrelated donors. Virtually all patients have at least one HLA-partially matched family member, parent, sibling or child, who is immediately available to serve as a donor. Also, the immediate availability of mismatched family member as a donor has important financial implication as the considerable expenditure of additional typing and procurement of unrelated donor graft can be avoided.

Non myeloablative transplant – Crossing HLA barrier without using ‘megadose’ approach

While the approach adopted by Aversa et al, using the highly immunosuppressive and myeloablative conditioning regimen and a ‘megadose’ of extensively T cell-depleted GCSF mobilized PBSC cells, has demonstrated encouraging survival results, it is not without limitations. Firstly, the procedure is associated with significant regimen-related toxicity from the intensely myeloablative conditioning, and high treatment-related mortality (in the range between 35–40%)^{Error! Bookmark not defined., Error! Bookmark not defined.} due to delayed immune recovery and infections. Secondly, a megadose of purified CD34+ cells is crucial in overcoming the barrier of residual anti-donor cytotoxic T-lymphocyte precursors in T-depleted mismatched transplant. There is continuing concern with regard to the slow engraftment, namely of platelets or graft failure, in patients receiving graft with lower cell dose. Previous studies from Tuebingen have shown delayed engraftment at CD34 doses less than 8×10^6 /kg body weight.¹³ As such, most physicians would usually target for ‘megadose’ of stem cell ($> 10 \times 10^6$ CD34+ cells/kg body weight) from the donor while planning for haploidentical transplants, and this can place considerable demand on both the donors and the pheresis service for the following reasons: (i) The high graft contents is easily achieved in children but can be a major obstacles in adults. (ii) The immobility from long hours of pheresis can be exhausting for the donors and the procedure is often associated with significant pheresis-related adverse effects. (iii) For the pheresis and stem cell processing laboratory staff, the procedures involved can be time-consuming and labor-intensive. Also, the remarkable results achieved by the Perugia group using the haploidentical “megadose” PBSC approach did not seem to be reproducible by other investigators in United States. Graft failure in the range of 5–14% has been reported by other studies.^{14, 15, 16} Communication from investigators and reports given at conferences on haploidentical transplantation have indicated that both graft failure and GvHD remained a problem and there were few survivors, leading to closure of many of these trials in United States.¹⁷ Developing new strategies of T-depletion or graft manipulation

aiming at improved engraftment without the need for megadose CD34⁺ cells, and a better tolerated, less toxic dose-reduced conditioning regimen, has become an important area of research.

Although the number of mismatched allogeneic transplant has increased steadily over the past few decades, this high risk procedure can only be offered only to minority of patients, since most subjects are the beyond the age where this approach involving the use of myeloablative preparative regimens can be performed within a reasonable degree of safety. GvHD, TRM and other toxicities remain significant and have limited their use in otherwise healthy, relatively young patients. To extend allogeneic transplant to older and those with comorbidities, reduced-intensity or nonmyeloablative conditioning lacking such toxicities have been developed.

Results from Duke University

Rizzieri et al¹⁸ from Duke University recently reported one of the largest series of patients with nonmyeloablative transplant using 3-5/6 HLA-matched family donors. Forty-nine patients with hematological malignancies or marrow failure were accrued. The patients in this group were, in average, older (median age of 48) than most other reported series haploidentical transplantation. Using a non-myeloablative preparative regimen consisting of fludarabine and cyclophosphamide in combination with alemtuzumab for in vivo and in vitro T cell depletion on, the group reported successful engraftment in 94% of patients, low treatment related mortality rates of 10.2% and severe GVHD of 8%. With more than half of patients not in first CR at transplantation, the high CR rate of 75% was encouraging. With 4.25 years of median follow up, 1 year overall survival in this high risk group was 31%. Subgroup analysis of 19 standard risk patients showed 63% 1 year overall survival and 3 year median survival, which compared favorably to reports using alternative matched unrelated donors or cord blood. Despite the use of T-cell depleting regimen, immune reconstitution analysis demonstrated encouraging evidence of quantitative lymphocyte recovery through expansion of transplanted T cells by 3 to 6 months.

Results from Tuebingen/ Dresden

Based on the promising experiences gained at St Jude's Children Research Hospital (SJCRH), Memphis, in the pediatric population,^{19,20} investigators from Tuebingen explored a new T-cell depletion strategy in adult patients following dose-reduced conditioning.²¹ Using this new approach, T-and B-cells (CD3/CD19) are negatively depleted from PBSC with 3.5 – 4 log T-depletion using anti-CD3- and anti-CD19-coated microbeads on a CliniMACS device. In contrast to the CD34⁺ selection strategy pioneered by the Perugia group, CD3/CD19-depleted grafts harvested using this strategy not only contain CD34⁺ stem cells but also CD34⁺ progenitors and natural killer, dendritic, and graft-facilitating cells. Dose-reduced conditioning consisting of fludarabine (150–200 mg/m²), thiotepea (10 mg/kg), melphalan (120 mg/m²), and OKT-3 (5 mg/day, day –5 to +14) was used. Ten adult patients with a median age of 43, and advanced hematological malignancies received mismatched transplant using this approach. Rapid engraftment with full donor chimerism was seen after 2 weeks in all patients. Six patients developed grade II GVHD and 1 developed lethal grade IV GVHD. Treatment-related mortality was 30% and overall survival was 50% with 4 patients in complete remission and median follow of > 1 year. The fast engraftment seen in this CD3/CD19 group with CD34 doses as low as 5.2×10^6 CD34⁺ cells/kg demonstrates that successful haploidentical transplant may be feasible even without megadoses of CD34⁺ stem cells. Importantly, the favorable immune reconstitution with fast reconstitution of NK cells was noted with this approach, resulting in fewer infectious complications in this group of patients.

In another recent study from Tuebingen,²² Handgretinger et al reported the outcome of 38 pediatric patients with high risk hematological malignancies and severe aplastic anemia

receiving haploidentical transplant using this approach. The dose-reduced conditioning was modified with fludarabine dose reduced (to reduce neurotoxicity) and OKT3 been omitted. Primary sustained engraftment occurred in 83% of patients and final engraftment was 98% when the remaining patients with graft failure had repeat transplant. Grade II–IV acute GvHD occurred in only 27% of patients. Overall TRM was low at 2.6%. The favorable event free survival of 70% seen only in patients with nonmalignant disease and those in remission at time of transplant, suggests that disease relapse is a major obstacle among patients with refractory malignancies undergoing haploidentical transplant. Additional post-transplant cellular or humoral strategies for relapse prevention need to be evaluated.

Results from Massachussettes General Hospital

Based on murine models established by Sykes and colleagues,²³ a series of haploidentical stem cell transplantation have been conducted at Massachusetts General Hospital. To address the problems of graft failure and GvHD, the initial regimen has been modified to its current form which includes cyclophosphamide, fludarabine, MEDI-507 (a monoclonal anti-CD2 antibody) and thymic irradiation. Mixed ‘split lineage’ lymphohaematopoietic chimaerism has been achieved in most cases with this strategy, with a predominance of donor myeloid chimaerism and a much lower percentage of donor T-cell chimaerism. In addition, mixed chimaerism, including the low percentage of donor T-cell chimaerism, can be successfully converted to full or nearly full donor chimaerism with either no GVHD or manageable, primarily cutaneous GVHD. Recurrent malignancy and late infections have been the chief reasons for treatment failure with this approach. Efforts are underway to optimize the ex vivo T-cell depletion of the product and to explore different doses of delayed DLI.^{24, 25, 26}

Results from John Hopkins University

O'Donnell et al from John Hopkins University have performed nonmyeloablative haploidentical transplant using low-dose TBI 200 2Gy/fludarabine (with or without cyclophosphamide) on 13 patients with hematologic malignancy with high-dose posttransplant cyclophosphamide, 50 mg/kg on day 3, was added onto tacrolimus/mycophenolate mofetil to improve GVHD prophylaxis.²⁷ Acute GVHD developed in 6 of the 13 patients. Six of the 13 patients were alive, 5 of whom were in a complete remission at a median of 191 days post-transplant, including 2 patients with graft rejection. The results suggest possible benefits of pre and posttransplantation Cyclophosphamide in promoting engraftment and prevention of GVHD.

Results from Osaka University, Japan

Ogawa et al²⁸ from Osaka University Hospital in Japan investigated the use of ATG-based nonmyeloablative conditioning regimen as previously reported by Slavin et al,²⁹ in the haploidentical transplant of 26 patients who had hematologic malignancies in an advanced stage or with a poor prognosis. Using a conditioning consisting of fludarabine, busulfan, and anti-T-lymphocyte globulin and GVHD prophylaxis consisting of tacrolimus and methylprednisolone (1 mg/kg/day), 26 patients underwent transplantation using peripheral blood stem cells from an 2-3 antigen HLA mismatched donors without T-cell depletion. All patients except for 1 achieved donor-type engraftment. Full donor was chimerism achieved by day 14. Only 5 (25%) out of 20 evaluable patients developed grade II GVHD. Sixteen of the 26 patients are alive in complete remission. Four died of transplantation-related causes, and 6 died of progressive disease. The event-free survival at 3 years was 55%.

Results from Tokyo University, Japan

Kanda et al³⁰ evaluated the feasibility of haploidentical unmanipulated peripheral blood stem cell transplantation from 2 or 3 loci-mismatched family member using in vivo alemtuzumab in

12 patients (median age 49.5 years) with high-risk hematological malignancies. Six patients received a TBI-based myeloablative regimen, whereas the remaining 6 patients older than 50 years received less intensive or nonmyeloablative fludarabine-based conditioning. Alemtuzumab was added on days –8 to –3 and CsP+MTX were used as GvHD prophylaxis. There was no graft rejection, and the incidence of grade III–IV acute GvHD was only 9%. The non-relapse mortality was observed in only 2/12 patients. None of the patients died of infectious causes despite impaired T cells immune reconstitution during the first 2 months after transplantation.

Conclusions

Haploidentical HSCT provides an opportunity for patients to benefit from HCT when an HLA genotypically matched sibling is not available. It presents a better logistic and practical alternative to matched unrelated donor transplantations. This may be especially important when dealing with a patient suffering from a disease with a rapid tempo where the urgency of transplant does not allow transplant from an unrelated donor to be organized; and also for non-Caucasian patients, in whom the chances of finding an unrelated match are still low, making the option of haploidentical transplant a more realistic prospect. Recent advances with effective T-cell depletion and reduced intensity conditioning has significantly decreased the early transplant related mortality and GvHD, while enabling robust and prompt engraftment, and hence enhancing the therapeutic benefits of haploidentical transplantation. However, post-transplant infectious complications and relapse remain the most important barriers yet to overcome, and new directions in the use of adoptive cellular immunity appear to be promising. Preliminary data has demonstrated the great potential of selective allodepletion in rapidly reconstituting immunity without GvHD. It appears that in some T cell-depleted haploidentical transplants, the given benefits of NK alloreactivity is expected to encourage the greater use of haploidentical transplants for a larger number of leukemia patients without matched donors. In addition, there are emerging data to suggest the use of NIMA-mismatched donors in providing an especially attractive strategy for patients who would not tolerate GVHD and prolonged immunosuppression. There are many issues that remain unresolved, including the role and timing of haploidentical SCT. The relative merits of a haploidentical family donor *versus* mismatched unrelated or umbilical cord blood donor remain to be defined, and it is hoped that guideline will emerge from large registry study. Current challenges are to improve our ability to identify those patients most likely to benefit from haploidentical transplantation, to better select donors, to develop transplant conditioning regimens that are safer and more effective and to develop strategies that effectively eliminate GvHD while preserving anti-tumor and anti-microbial immunocompetence. In the meantime, ongoing translational research is very likely to improve this modality of treatment further.

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