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Review Article

Advances in Haploidentical Hematopoetic Stem Cell Transplantation

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INTRODUCTION

Allogeneic Hematopoetic Stem Cell Transplantation (HSCT) is the only curative option for many malignant and inherited hematologic and non-hematologic disorders. The number of allogeneic HSCT performed has been steadily increasing worldwide. This growth can be mainly attributed to the increase in the number of eligible patients as the new less toxic non-myeloablative and reduced intensity conditioning (RIC) regimens have allowed the transplantation of patients over the age of 50. In addition advances in graft versus host disease and infectious disease prophylaxis and treatment have continued to improve the outcomes.

Patient eligibility is mainly limited by donor availability. Ideally patients receive stem cells from a matched related (sibling) donor. But as there is only a 25% chance for a sibling to be HLA matched, there are only about 30% of patients who have a sibling matched donor. This number is expected to continue to drop as the average family size keeps going down. An alternative donor source is an unrelated HLA matched donor that can be identified through the National Marrow Donor Program. But even as the donor pool in the NMDP steadily expands and there are currently more than nine million donors in the registry, only a 60% of Caucasians and even as low as 10% of non-Northern Europeans (especially African American and other minorities) are able to find a Matched Unrelated Donor [1]. This discrepancy is due to more HLA variation in non-Europeans and to underrepresentation of ethnic minorities in the registry. The result is that approximately 5000 patients per year are in need for an alternative donor.

An alternative approach for patients without HLA-matched donors is the use of a mismatched/haploidentical donor. Haploidentical donors have one haplotype in common with the recipient, so they match in at least five out of ten HLA loci. These are most commonly relatives, such as parents, children or siblings. The advantages of this approach besides the possibility to identify a donor for almost all patients also include the avoidance of treatment delay and the higher motivation of the relative donor that facilitates research protocols [2].

The very first trials of haploidentical stem cell transplantation reported a very high incidence of graft rejection, Graft versus Host Disease (GVHD) and nonrelapse mortality (NRM) [3,4]. In order to improve these dismal outcomes strategies with both T cell depleted and T cell replete grafts have been employed [5-7]. As there is no single universally accepted way for performing a haploidentical transplantation, in the following paragraphs we will review the different strategies with a focus on the most recent advances.

Transplantation of a "mega-dose" T cell depleted Haploidentical Stem Cells

Transplantation of an ex vivo T cell depleted graft successfully avoided severe GVHD but was complicated by very high incidences of graft failure and relapse [8-10]. The Perugia group overcame the problem of graft failure by transplanting a "mega-dose" of T cell depleted stem cells after a conditioning regimen of enhanced myeloablation and immunosuppression [11,12] but without post-transplantation GVHD prophylaxis. This approach was based on experimental data that large dose of stem cells can overcomes MHC barriers in mice [13]. The leukemia free survival was acceptable especially for patients transplanted in remission and most importantly long term survivors had a high quality of life without GVHD and without the need for immunosuppression. A high incidence of infectious complications was observed attributed to delayed immune reconstitution after a T cell depleted graft.

The Acute Leukemia Working Party (ALWP) of the European Blood and Marrow Transplant (EBMT) Group analyzed 173 adults with acute myeloid leukemia (AML) and 93 with acute lymphoblastic leukemia (ALL) who received a "mega-dose" T cell–depleted peripheral blood cell haploidentical HSCT [14] and reached the conclusion that haploidentical HSCT using this approach "can be an alternative option for the treatment of high-risk acute leukemia patients in remission, lacking a human leukocyte antigen-matched donor". Similarly to the previously published studies by the Perugia group the "mega-dose" of T cell depleted stem cells was associated with a high engraftment rate and minimal GVHD but the transplantation related mortality was high (36-66% at two years depending on disease status) and mainly due to infections and interstitial pneumonitis. Similar results have been published by other groups [15] and in pediatric patients [16-18].

CD3/CD19 depleted stem cells

Based on the rationale that avoidance of Anti Thymocyte Globulin (ATG) and Total Body Irradiation (TBI) will reduce NRM and that CD3/CD19 depletion of stem cells will leave tumor reactive natural killer and dendritic cells intact and facilitate the Graft versus Leukemia (GVL) effect, several groups in the US and Europe have conducted clinical trials with a RIC regimen followed by transplantation of a haploidentical CD3/C19 depleted graft [19-21]. The results appear to be very promising (especially in patients transplanted in remission) with reduced infectious complications and a higher GVL effect compared to the myeloablative T cell depleted regimen.

Post-transplant T cell infusion

Adoptive immunotherapy with post-transplant infusion of pathogen specific T cells has been attempted as a way to reduce the infectious complications associated with haploidentical HSCT. Several groups have created T cell populations in vitro with specificity against adenovirus [22], EBV [23] (or both [24]), CMV [25] and Aspergillus [26]. Infusion of these cells has been shown to be safe, effective and not cause GVHD [27] but as this technique has not found wider application yet as it is time consuming, expensive and requires expert skills and specialized facilities [28].

Another promising technique is the infusion of donor T cells that have been genetically modified in order to express a suicide gene. The suicide gene can be turned on by the administration of a medication in case the patient develops GVHD. In clinical trials infusion of these cells accelerated immune reconstitution both directly and indirectly by driving the recovery of thymic activity and the few cases of GVHD were very rapidly and effectively controlled by turning on the suicide gene [29-31]. As with the previous technique, technical limitations make a wider application difficult.

Depletion of donor alloreactive T cells

Donor anti-host alloreactive T cells can be activated in vitro in a mixed lymphocyte reaction with donor-derived PBMCs and then depleted with the use an antibody targeting activated T cells such as an immunotoxin that reacts with CD25. The allodepleted T cell product can be safely infused to the donor and may improve T cell recovery as was demonstrated in two trials from Europe [32,33]. Photodepletion of host-reactive T cells is another selective method of allodepletion currently under study [34,35].

Unmanipulated T cell replete haploidentical transplants

A group from China has published on performing unmanipulated haploidentidentical HSCT with the use of intense GVHD prophylaxis and a graft that was composed of GSCF primed harvested marrow and collected peripheral stem cells. In their experience the outcomes with this procedure were comparable to HLA-identical sibling transplantation [36,37]. The same group published the results of a prospective trial in patients with intermediate or high risk Acute Myeloid Leukemia (AML) in first complete remission (CR1) that showed a clear superiority in terms of Overall and Disease Free Survival of the unmanipulated haploidentical HSCT over chemotherapy [38]. A group from Europe also showed that transplantation of unmanipulated GCSF primed bone marrow following either a myeloablative or even a RIC conditioning regimen is feasible with vigorous pre- and post-transplant GVHD prophylaxis [39].

Another group from China has reported on the infusion of haploidentical GCSF mobilized peripheral blood stem cells following not a preparative regimen but conventional chemotherapy [40,41]. Their patients had an impressively high leukemia free and overall survival at six years (84.4% and 89.5% respectively for patients with low or intermediated risk AML in CR1), no patient developed GVHD and nobody engrafted [40]. For elderly patients with AML they showed in a prospective randomized study that their approach was superior to conventional chemotherapy [41]. Presumably the resulting transient microchimerism was just enough for a GVL effect but not sufficient to induce GVHD, although there are still many unanswered questions [42].

T cell replete haploidentical HSCT with Post transplantantion High Dose Cyclophosphamide

Donor and host alloreactive T cells can be depleted in vivo with the post transplantation administration of high dose cyclophopshamide (PTCy) [43]. PTCy needs to be administered within a very short window after the stem cell infusion. Hematoopetic stem cells are relatively spared by the toxic effects of high dose cyclophosphamide thanks to the high expression of aldehyde dehydrogenase [44]. The Hopkins and the Seattle groups have pioneered the use of high dose Cyclophosphamide (50 mg/kg on days +3 and +4) following a reduced intensity regimen (Cyclophosphamide 14.5 mg/kg/day i.v. on days −6 and −5, fludarabine 30 mg/m^2/day i.v. on days −6 to −2, and 200 cGy of TBI on day −1) and haploidentical donor marrow infusion [45]. Among 210 patients treated at Hopkins 87% had sustained engraftment and the cumulative incidences of grades II-IV acute GVHD and chronic GVHD were 27% and 13%, respectively. Five-year cumulative incidence of non-relapse mortality was 18%, relapse 55%, and overall survival 35% [46]. The relatively low observed infectious mortality suggests that memory T cells are spared by PTCy [6].

As this approach is technically simple and cost-effective, it has been adopted by many other centers. A group from Atlanta compared their center's outcomes of haploidentical HSCT using PTCy with those of conventional HLA-matched sibling donor (MRD) or HLA-matched unrelated donor (MUD) HSCT and reported that they were not inferior [47]. The same group has also showed that using a myeloablative preparative regimen and peripheral blood stem cells (PBSCs) as the graft source in conjunction with haploidentical HSCT and PCTy is safe and feasible [48].

The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) recently published the results of 2 parallel multicenter phase 2 trials (BMT-CTN 0603 and 0604) for patients with hematologic malignancies and no suitable related donor [49]. Reduced intensity conditioning (RIC) was used with either unrelated double umbilical cord blood (dUCB) or haploidentical HSCT with PTCY. The outcomes in terms of engraftment, GVHD,

NRM and RFS at one year were similar and comparable to those reported after matched unrelated donor transplantation. These results set the stage for BMT-CTN 1101, a multicenter randomized phase 3 trial of dUCB vs haplo.

Tolerance induction

The achievement of specific tolerance to host but not tumor or infectious alloantigens by selectively inactivating the indicated subsets of alloantigen-specific T-lymphocytes has been the goal of transplant immunology [50]. Our currently expanding understanding of the biochemical and molecular basis of T-cell tolerance provides great promise towards reaching this goal.

The two signal model of T cell activation dictates that for T cell activation to proceed two signals are required: one through the antigen specific T cell receptor (TCR) and the second though the non-antigen specific engagement of a costimulatory molecule by its counterpart on an antigen presenting cell [51]. Engagement of the TCR in the absence of costimulation leads to T cell anergy and to peripheral tolerance formation [52]. Regulatory T cells are believed to abrogate GVHD and enhance immune reconstitution without blocking the GVL effect [53,54].

A group from Harvard conducted a clinical trial where a haploidentical marrow was infused after in vitro co-culture with recipient cells in the presence of CTLA4Ig, which is an antibody that blocks the second costimulatory signal rendering the alloreactive T cells in the culture anergic [55]. 95% of the treated patients engrafted, the GVHD rate was low and the immune reconstitution was rapid resulting in very few viral infections [56]. After the in vitro treatment the frequency of helper T cells that were reactive against the recipient fell by one to four orders of magnitude, whereas third party alloreactivity remained unaffected.

The Perugia group studied the infusion of haploidentical donor derived regulatory T cells (Tregs) followed by CD34+ cells and donor mature T cells in the setting of T cell depleted haploidentical HSCT [57]. Almost all patients engrafted, acute GVHD rate was low, there was no chronic GVHD, immune recovery was rapid and the GVL effect appeared preserved [58].

Rapamycin is an immunosuppressive medication that exerts its action through mTOR inhibition. mTOR inhibitors unlike calcineurin inhibitors (CNI) facilitate immunologic tolerance by inducing T cell anergy, promoting the expansion of regulatory T cells and inhibiting the maturation of dendritic cells [59,60]. In addition rapamycin has a direct antineoplastic effect that might be of clinical significance in the setting of HSCT [61]. The Milan group developed a CNI-free T cell replete haploidentical protocol with GVHD prophylaxis based on rapamycin, mycophenolate mofetil (MMF), ATG and rituximab [62]. Their purpose was to promote a rapid immune recovery with preferential accumulation of regulatory T cells. Their preliminary results look promising with most patients engrafting and acceptable rates of GVHD, NRM and relapse [63]. Furthermore they were able to demonstrate an early T-cell immune reconstitution characterized by the in-vivo expansion of Tregs.

CONCLUSION

Haploidentical HSCT has evolved from a desperate "Hail Mary" attempt for patients with no other options to a reliable procedure with results comparable to those of HSCT with the use of a matched related or unrelated donor. Furthermore it is now in the forefront of exciting research in immunology with the promise to abrogate GVHD while strengthening GVL.

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