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HCT for Non Malignant Disorders

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HCT for Non Malignant Disorders

Wednesday February 13, 2013  10:30-12:00

Salt Palace Convention Center

Chair: R. Saccardi, MD

2. Mary Eapen: Choice of Alternative Donors for Aplastic Anemia
3. Riccardo Saccardi: HCT for severe Multiple Sclerosis
ALLOGENEIC HCT IN SICKLE CELLS DISEASES: WHEN AND HOW

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The first successful HSC transplant in a patient with SCD was reported in 1984 in a pediatric patient with co-existing AML\(^1\) and established the curative potential of this approach. Myeloablative conditioning with busulfan and cyclophosphamide followed by HLA-matched marrow infusion was later successfully employed in Europe\(^2,3\) and the United States\(^4\) as primary treatment for severe SCD in children without an underlying malignancy. Antithymocyte globulin was subsequently added to decrease the risk of graft rejection in this frequently alloimmunized population\(^4\). While indications for transplant have remained controversial in the pediatric setting, in one series, patients were divided into 2 groups to reflect their access to care, those in Europe with access to care in whom severity criteria were used and those in Africa where access to such care is limited. In the second group, the only indication was SCD, and disease severity criteria were not employed. While overall results were favorable, the best results were seen in the second group, suggesting that transplantation before complications are observed results in better outcomes\(^5\). The most recent results reported in 2007 demonstrate that with the addition of ATG, rejection rates decreased from 22.6% to 3% and event-free survival rates rose to 95.3% among those transplanted after January 2000. These results establish HLA-matched transplants using myeloablative conditioning as the standard of care for eligible pediatric patients with SCD. Now, hundreds of affected pediatric subjects have undergone fully myeloablative allogeneic HSCT with favorable results.

Though these results in children are encouraging, procedural toxicities that increase with advancing age have limited this approach to pediatric patients. The ability to achieve engraftment of allogeneic HSCs without myeloablative conditioning prompted many to consider this strategy in nonmalignant disorders as increased safety was assumed, potentially allowing application to older patients and patients co-morbidities. In many such studies, prompt myeloid engraftment was observed in all, yet appeared to result from a donor T cell mediated alloimmune response that was associated with significant rates of graft versus host disease (GVHD) driving both morbidity and
mortality\textsuperscript{6}. Furthermore, early studies attempting nonmyeloablative transplantation in SCD proved unsuccessful\textsuperscript{7}. Others began to explore reduced intensity conditioning (RIC), which often contained agents that are ablative at near ablative doses, with improved success\textsuperscript{8}. Based upon rapamycin’s ability to promote T cell tolerance even when T cells are stimulated in the presence of costimulation\textsuperscript{9} both in vitro and in vivo\textsuperscript{10}, a clinical trial testing this approach was initiated in severely affected adults. The primary endpoint of the study was the proportion of patients with stable engraftment, with the incidence of GvHD as a secondary endpoint. HLA identical relatives underwent G-CSF mobilization and these unmanipulated hematopoietic stem cells (HSCs) were infused after conditioning with alemtuzumab 1mg/kg total, given over 5 days, a single dose of 300 cGy total body irradiation and oral sirolimus (rapamycin) initiated on day -1. Stable mixed chimerism and disease reversion was observed in 9 of the first 10 patients treated\textsuperscript{11}. Additionally, no GvHD was observed among engrafted patients. Expansion of the cohort to now 25 patients has resulted in similar rates of engraftment, with 22 of 25 patients disease free again in the absence of GvHD. These data support mixed chimerism as a suitable goal for HSC transplantation in SCD.

The success of this regimen provides indirect evidence for graft specific tolerance, opening the possibility of expanding to alternative donor sources. Indeed, the main limitation has been a lack of HLA-matched sibling donors in the majority of patients with SCD. To determine availability of alternative donor sources, ten patients who met all study criteria on full screening for sibling matched HSCT but who did not have a suitable donor were selected for alternative donor searching in the National Marrow Donor Program (NMDP) and Bone Marrow Donors Worldwide (BMDW). Though 7 of 10 had a potential 6/6 matched unrelated donor, only 1 of 7 had a greater than 1% probability of having a 6/6 HLA match according to Haplogic. When cord blood units were searched, 9 of 10 had at least one 4/6 cord blood match identified ($\geq 1.5 \times 10^7$ total nucleated cells per kilogram body weight and ABO-matched). When higher degrees of matching (5/6) and higher cell doses were queried ($2.5 \times 10^7$ total nucleated cells per kilogram body weight and ABO-matched) only 2 patients had a suitable cord product (Hsieh, personal communication).
Thus nonmyeloablative haplo-identical HSC transplantation strategies are currently being explored as they appear the only current reliably obtainable stem cell source. Though extension of the low dose TBI/Campath/Rapamycin approach may be feasible in the haplo-identical setting, additional methods aimed at reducing the risk of both rejection and GVHD will likely be required. Cyclophosphamide given from two to three days after bone marrow transplantation has been shown to facilitate engraftment and prevent the development of GVHD by targeting activated lymphocytes. Recently, 14 individuals with sickle cell disease who received nonmyeloablative haploidentical bone marrow transplantation employing post-graft cyclophosphamide were reported, with engraftment in just over half of the subjects. Though higher rates of engraftment would be desirable, these results are encouraging as they were achieved in the absence of significant GvHD and no mortality was seen. Additionally, a haplo-identical protocol employing TBI/Campath/Rapamycin has also recently opened to accrual at the National Institutes of Health. The study is designed as a dose escalation study testing post graft cyclophosphamide and accrual is ongoing.

In summary, HSCT for patients with SCD is highly effective, reversing the phenotype even when low levels of donor engraftment are achieved with newer, less toxic regimens. Results in children with myeloablative conditioning in the current era suggest that this therapy is underutilized. Future well designed studies testing nonmyeloablative conditioning regimens and alternative donor sources are poised to expand the application of the approach and lead the field in immune tolerance. Continued efforts to develop allogeneic transplantation for SCD with the goal of maximizing engraftment rates while minimizing morbidity and mortality are indeed justified.
References


CHOICE OF ALTERNATIVE DONORS FOR APLASTIC ANEMIA

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Treatments for aplastic anemia include immune suppressive therapy (IST) with anti-thymocyte globulin (ATG), which lyses lymphocytes, and cyclosporine, which blocks T lymphocyte function, and hematopoietic stem cell transplantation (HCT), which replaces all hematopoietic progenitor cells, including lymphopoietic cells. There is general agreement that, when a human leukocyte antigen (HLA) matched sibling is available, HCT is first-line treatment for most patients with severe aplastic anemia (SAA). On the other hand, IST is used as first-line therapy is employed for patients who do not have an HLA-matched sibling and must seek an alternative donor. Whether alternative donor HCT should be done after the failing one or more than one course of IST is uncertain and depends, in part, on patient factors predicting the likelihood of further response to IST and the likelihood of good outcome with HCT, as well as timely availability of a suitable donor.

**Unrelated adult donor transplantation**

Unrelated donor transplantation is an effective therapy for SAA but is limited by the availability of a suitably matched unrelated donor and is associated with higher risks of graft failure, GVHD and mortality than HLA-matched sibling transplantation. Selecting an appropriately matched donor for HCT is an important component of success. Several groups have attempted to compare outcomes of transplantation for aplastic anemia using 8/8 HLA matched versus HLA-mismatched grafts. Among 118 children and adolescents with aplastic anemia transplanted between 1989 and 2003 with unrelated adult donor bone marrow (BM) grafts, mortality risks were lower after HLA-matched versus mismatched transplants. Ten-year probabilities of overall survival were 57% after 8/8 HLA- matched transplants compared to 39% after ≤7/8 HLA matched transplants. In a more recent report, survival probabilities after 8/8 HLA-matched unrelated donor bone marrow transplantation was higher at 75%. In that report, lower survival rates were 61% after peripheral blood stem cell transplantation. These observations support bone marrow is the preferred graft when considering unrelated donor transplantation. Importantly, advances in transplantation
strategies including selection of better-matched donors have resulted in substantial improvements in survival after unrelated donor transplantation (32% before 1998; 61% before 2005 and now 75%).

In the absence of a suitably matched adult unrelated donor, umbilical cord blood (UCB) has been used as an alternative graft. Data from Eurocord and the Japan Cord Blood Bank Network suggest survival probabilities of about 40%. In addition to HLA disparity and the less than optimal cell dose in UCB grafts it is likely that in some cases the reason for inferior survival is the fact that these transplantations are often done for patients who have failed multiple courses of IST. To-date there are no direct comparisons of outcomes after a second (or third) course of IST and unrelated donor transplantations.

**Transplantation strategies – conditioning regimen**

Alternative donor transplants have higher rates of graft failure, regimen-related toxicity and GVHD than HLA matched sibling transplants, even when the donor and recipient are 8/8 HLA matched. Unrelated donor transplantations performed in the eighties and nineties incorporated high doses of total body irradiation (TBI) to prevent graft failure. However, high dose TBI containing regimens are associated with severe acute toxicity and secondary malignancies. Therefore, to lower early toxicity and secondary malignancy, recent transplant conditioning regimens have used lower doses of TBI in combination with cyclophosphamide and ATG. Deeg and colleagues identified 200 cGy of TBI administered as a single dose together with cyclophosphamide (200 mg/kg) and equine ATG (90 mg/kg) as the optimal regimen in a radiation dose de-escalation study; graft failure occurred in 5% of patients and 5-year survival was 55%. Regimen-related toxicity (grade 3 or higher) and death decreased with de-escalation of the TBI dose. Age was an important predictor of survival; the 5-year probability of overall survival in younger patients (≤20 years) was 73% compared to 46% in older patients (p=0.05). Lowering the dose of TBI had no impact on graft failure. Further attempts at deescalating the dose of cyclophosphamide had yielded mixed results. A recent report from on on-going clinical trial in the United States showed excess mortality in the
TBI (200cGy), cyclophosphamide 150 mg/kg, fludarabine 120 mg/m², ATG 9 mg/kg or ATGAM 90 mg/kg and excess graft failure when cyclophosphamide was eliminated from the regimen.\textsuperscript{6} Accrual to the cyclophosphamide 100 mg/kg and 50 mg/kg continue and the trial is expected to complete accrual early 2013.

**Conclusion**

The selection of more closely HLA-matched unrelated donors and lowering the intensity of transplant conditioning regimens, have had a significant impact on survival after transplantation for SAA. Bone marrow is the preferred graft source. The role of UCB transplantation in patients without an HLA-matched adult donor needs further exploration.
References


HCT FOR SEVERE MULTIPLE SCLEROSIS

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Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease believed to be mediated by autoreactive lymphocytes that invade the Central Nervous System (CNS) and cause oligodendrocyte, axonal and neuronal damage as well as glial scarring, resulting in demyelination, neuronal death and brain atrophy. In the majority of patients the onset of the disease is characterized by recurrent attacks, with or without incomplete recovery, resulting in an accumulation of disability, intermediated by clinical remissions (Relapsing-Remitting phase, RR). This phase is pathologically characterized by focal perivenular infiltrates dominated by T- and monocytoid cells. After years to decades, the inflammatory component gradually becomes more diffuse, the attacks become less apparent and more often disappear whilst the disability tends to slowly progress (Secondary-Progressive phase, SP). During this phase the continuous clinical deterioration is mainly sustained by degenerative changes including axonal and neuronal loss and a more diffuse microglial infiltration.

Neurological monitoring is carried out through both clinical and MRI parameters. A number of indexes have been developed to assess the clinical disability according to different performance scores; the most popular is the Kurtzke Expanded Disability Status Scale (EDSS), ranging from 0 (normal neurological examination) to 10 (MS-related death). Progression of the disability is defined as an increase of the EDSS score, confirmed after 3-6 months. Magnetic resonance imaging (MRI) has become the most important diagnostic tool in MS and as of a number of years, the diagnosis of MS is largely based on MRI alterations that show brain lesions disseminated in space. Conventional MRI metrics include Gadolinium-enhancing lesions (Gd+), a measure of blood-brain barrier disruption associated with acute inflammatory lesions and T2 lesions, a sensitive measure of demyelinating lesions. Loss of brain tissue or atrophy is determined by measuring decreased brain volume.

Available treatments for MS include high-dose steroids for the treatment of acute phases and immunomodulatory/immunosuppressive drugs chronically administered to reduce the number of
relapses, decrease their severity and slow down the progression of disability. However, no disease modifying agent has been shown to modify long-term outcome; moreover a subset of patients shows an aggressive clinical pattern at the onset associated with a poor response to the conventional treatments. It is particularly this group of patients, i.e. those failing multiple treatments and accumulating clinical disability rapidly, for which treatment alternatives are needed.

Autologous Hematopoietic Stem Cell Transplantation (HSCT) has been experimented with over the last fifteen years in the treatment of severe autoimmune diseases (AD), that progress despite the administration of standard treatments. The rationale is derived both from experimental models and from the observations of positive effects of transplants for conventional indications and a coincidental AD. Autologous HSCT for MS has been employed since 1997 and currently approximately 1,000 patients have been treated worldwide, who are either in the Registry of the European Group for Blood and Marrow Transplantation (EBMT, www.ebmt.org) or in that of the Center for International Blood & Marrow Transplant Research (CIBMTR, www.cibmtr.org). This HSCT procedure results in a profound renewal of the immune system and in a drop of inflammatory activity, as assessed by MRI. Most patients were included in small, either single-center or multi-centre, phase 1–2 trials and no data are currently available from prospective comparative trials. A major clinical response was reported in most of the published studies, the neurological outcome being particularly favorable in patients transplanted in the RR phase and/or showing an inflammatory pattern at MRI during the pre-transplant screening. Case series, and reports about the excellent outcome in particularly aggressive forms of MS, support the efficacy of HSCT in MS patients with prominent inflammatory activity. In particular, a sustained EDSS improvement was reported more frequently in RR patients over SP patients.

PBSC are usually well mobilized in MS patients; mobilization with the administration of G-CSF and without chemotherapy (i.e. Cyclophosphamide) results in a high incidence of disease
recurrences and must be prevented by the administration of steroids. High intensity conditioning regimens, including either Busulphan or TBI, were not shown to result in a more efficient control of the disease\[^7\]. Reduced-intensity regimens (Cyclophosphamide and ATG) showed a low transplant-related toxicity but a higher incidence of relapses\[^8\]. BEAM plus ATG is the most frequent regimen reported to the EBMT Registry, showing a satisfactory equipoise of toxicity and efficacy\[^9\]. Transplant-related mortality dropped from 7.3% in the years 1995-2000 to 1.3% in the years 2001-2007\[^2\], probably due to a better patient selection and the use of less intense conditioning regimens.

Indications for HSCT in MS have been recently reviewed by the EBMT\[^9\] in light of the clinical outcomes reported in the literature. The ideal target patient for autologous HSCT is one who is in the RR phase, shows high inflammatory activity, both clinically and with an MRI. SP patients should only be considered when some inflammatory activity is still present, either clinically (evidence of relapses in the previous year) or by MRI (accumulation of lesion in T2 scans in the previous year), therefore representing the transition phase between the RR and the SP, respectively. Data reported in prospective phase 1-2 studies show that an 80-90% progression-free survival (PFS) at 3 years from HSCT is expected in RR patients, whilst it drops to 50% in SP forms. An EBMT retrospective analysis on 143 MS patients showed that 63% of patients, mostly transplanted in the SP phase, were stable or improved at a median of 41.7 months after HSCT\[^10\]. However, MS is a chronic, progressive disease and assessment of long-term outcome is needed to provide a realistic evidence of efficacy of any treatment. A joint EBMT/CIBMTR retrospective study, collecting data from patients with a follow-up ranging between 4 and 12 years, is currently ongoing. A prospective, comparative trial is also in preparation\[^11\].
References


