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Haploidentical Bone Marrow Transplantation Methodology with Post-Transplantation

Liang Desheng*

Department of Hematology, Paris Val de Marne University, France

Abstract

It has been extremely difficult to find a curative therapy for those with severe sickle cell disease (SCD) who doesn't have an HLA-identical sibling donor. A multi-institutional learning collaborative was created as part of a Phase II clinical trial of nonmyeloablative, related HLA-haploidentical (haplo) bone marrow transplantation (BMT) with post-transplantation cyclophosphamide in order to enhance engraftment while reducing transplantation-related morbidity. All eligible subjects had haemoglobin SS, and 16 out of 18 had a donor who could be identified in 89 percent of cases. Overt stroke was the most frequent reason for transplantation, with a median patient age of 20.9 years. Antithymocyte globulin, fludarabine, cyclophosphamide, and low-dose total body irradiation made up the first 3 patients' conditioning regimen. Following transplantation, cyclophosphamide, mycophenolate mofetil, and sirolimus were used as graft-versus-host disease (GVHD) prevention. Initial graft two of the three patients (or 67%) had rejection, which led to the study-stopping rule being activated.

Keywords: Bone marrow transplant; Haploidentical; Post-transplant cyclophosphamide; Second-degree relatives

Introduction

Thiotepa was added to the conditioning regimen to lower the likelihood of graft rejection, and 15 patients underwent haplo-BMT using this thiotepa-augmented conditioning regimen. With a 100% overall survival rate at a median follow-up of 13.3 months (interquartile range [IQR], 3.8 to 23.1 months), 93 percent (14 of 15) had >95% stable donor engraftment at 6 months. The median time to engraftment for platelets and neutrophils (>500) was 28 days and 22 days, respectively (IQR, 27 days to not reached). One patient had moderate chronic GVHD, two patients had grade III-IV acute GVHD, and six out of seven patients had stopped receiving immunosuppressive medication by the year after transplantation [1]. Our data indicate. Our findings indicate that haplo-BMT combined with post-transplantation cyclophosphamide and thiotepa enhances donor engraftment without noticeably raising morbidity or mortality and could greatly increase the range of curative choices for people with SCD.

Childhood clinical outcomes and survival have improved thanks to supportive care, the use of hydroxyurea therapy, and routine blood transfusion therapy for primary and secondary stroke prevention. Sickle cell disease has changed from a life-threatening condition in early childhood to a chronic disease in adults. The anticipated life expectancy for all infants born with SCD is 99 percent [2]. Stroke is the most dreaded consequence for kids with SCD. Regrettably, regular blood transfusion therapy is palliative for secondary stroke prevention. Within roughly 5 years, 45 percent of children who have had a stroke and are getting frequent blood transfusions will experience an overt or quiet stroke recurrence. Age-dependent chronic organ dysfunction that can accumulate in adults with SCD affects their quality of life and hastens their death. Children with symptomatic SCD can be treated successfully with myeloablative, HLA-identical sibling donor hematopoietic stem cell transplantation (HSCT). The hazards of short- and long-term consequences, such as a transplantation-related mortality rate of 5%, a rate of acute graft-versus-host disease (GVHD) of 10% to 20%, and a 5-year likelihood of chronic GVHD of 14% to 22%, are too great for adults to use this myeloablative method. Adult CD34+-mobilized peripheral blood stem cell transplantation utilising nonmyeloablative HLA-identical sibling donors seems promising, but its applicability is limited, mostly due to the dearth of HLA-matched sibling donors for qualified recipients (approximately 10 percent to 15 percent). Additionally, it is difficult to find unrelated HLA-matched donors for people with SCD, and the outcomes obtained with this method have not been encouraging [3].

Methodology

Nonmyeloablative approaches for related haploidentical HLA-matched donors have been taken into consideration to overcome both the constraints in donor availability and the unacceptable toxicity of myeloablative conditioning regimens in adults with SCD. Initial initiatives to increase the donor pool included the use of T cell-depleted (CD34+-selected) related haploidentical peripheral blood stem cells in recipients with SCD. These efforts resulted in a transplantation-related mortality of 25%, an event-free survival (EFS) rate of 38%, and a disease recurrence of 38%. At a median follow-up of 26 months, the use of CD3/CD19-depleted haploidentical peripheral blood stem cell grafts in patients with severe SCD revealed stable engraftment, a 22% incidence of notable neurologic events, a 4% transplantation-related mortality, and a 56% cumulative incidence of grade I-II acute GVHD. Three individuals those are stable In line-specific chimerism assays of red cell precursors (CD235a, glycophorin A) in the bone marrow, mixed chimerism in the peripheral blood demonstrated full engraftment without SCD-related complications. Similarly, in children with non-malignant disorders [4-6], ex vivo depletion of T cells and B cells from haploidentical peripheral blood stem cell grafts (lymphocyte subset responsible for GVHD occurrence) revealed an EFS of 91 percent, a graft rejection rate of 17 percent, a 13 percent incidence of acute

***Corresponding author:** Liang Desheng, Department of Medicine, Department of Hematology, Paris Val de Marne University, France; E-mail:- Desheng.lia@gmail.com

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GVHD, and 9.3 percent transplantation-related mortality.

Statistical Methods

Haplo-BMT, which combines post-transplantation cyclophosphamide with nonmyeloablative, T cell-replete, related haploidentical bone marrow transplantation (related haplo-BMT), has shown promise in addressing the two main challenges to the use of HSCT as a curative modality for SCD: the lack of adequate donors and regimen-related toxicity. Although there was no transplant-related death in the initial feasibility trial utilising this technique, it was linked to an unacceptable graft rejection rate of 43%. We established a three-site worldwide, multi-institutional learning partnership in 2013 to reduce graft rejection in recipients of haplo-BMT without raising transplantation-related mortality [7]. This three-site joint effort's main goal was to, if possible, offer enough proof for a conclusive multi-institutional Phase II research of haplo-BMT with PTCy in children and adults with We applied an approach for enhancing the quality of healthcare created by the Institute for Healthcare Improvement [35]. This system of short-term learning brings together groups of people from clinics or hospitals to address a clinical issue. In other therapeutic domains, team collaboration employing the learning collaborative approach has shown positive results. A multidisciplinary haplo-BMT consortium for SCD was established by us, with the participation of 3 clinical sites in France, the UK, and the US. An adult and paediatric transplant doctor, a paediatric hematologists, and a statistician made up the Data Safety Monitoring Committee for the learning collaboration. An advisory board examined the project's management twice throughout the first year. Participants were enrolled at the three sites, and the learning collaborative used the following approach [8]:

- Usage of the adoption of uniform eligibility standards,
- Regular phone conferences,
- The gathering of precise and limited data,
- Uniform goals and termination guidelines, and
- A cooperative mindset. Using nonmyeloablative haplo-BMT as a curative method for children and adults with severe SCD, the main goal was to lower the graft rejection rate. If the first five participants had a death rate of more than 20%, graft rejection, or severe chronic GVHD, the study had to be stopped and the protocol had to be modified in accordance with the study-stopping regulations, which were overseen by the Data Safety Monitoring Committee [9].

Result

Participants with severe SCD, such as those with haemoglobin (Hb)SS, HbSb0 and HbSb+ thalassemia, HbSC, HbSE, HbSD, HbSO-Arab, and HbS-HPFH, as well as those with good baseline performance status and ages 1 to 70 who had a qualified and available first-degree haploidentical donor, were eligible [10]. Those who had previously undergone haplo-BMT with graft rejection were qualified. In accordance with the Declaration of Helsinki, parents or participants older than 16 years old provided informed consent, and individuals younger than 16 years old provided assent before to registration. Independent haematologists referred participants for transplantation, and they were fully informed of all possible SCD-related treatment choices. Each participant and his or her caretakers had a lengthy conversation about the advantages and hazards of haplo-BMT. prior to executing informed consent Based on the existence of at least 1 of the following, disease severity was assessed:

Discussion

stroke or cerebrovascular event lasting more than 24 hours; evidence of cerebrovascular disease, confirmed by magnetic resonance angiography despite receiving regular transfusion therapy for at least 12 months; and silent cerebral infarct, defined as an abnormal magnetic resonance imaging (MRI) of the brain (signal abnormality of at least 3 mm in 1 dimension and visible in 2 planes on T2-weighted or fluid-attenuated inversion recovery images), with accompanying evidence of vasculopathol Stage I or II chronic lung disease , recurring vaso-occlusive pain episodes more than two per year for the past two years, and recurrent acute chest syndrome despite hydroxyurea treatment are also present [11]. Despite receiving frequent blood transfusions or hydroxyurea treatment, as well as other problems that have been included as transplant criteria in SCD. It was necessary to have adequate pretransplant organ function, including no liver cirrhosis and a left ventricular shortening fraction of at least 26% [12].

Conclusion

Johns Hopkins haplo-BMT platform was utilised by all 3 sites. Iron chelation and hydroxy-urea therapy were stopped at least 24 hours before the start of conditioning, and the HbS level was kept at 35 percent for at least 7 days prior to the commencement of conditioning. The conditioning protocol included cyclophosphamide, total body irradiation on day 1, thymoglobulin (0.5 mg/kg on day -9, 2 mg/kg on days -8 and -7; total dose, 4.5 mg/kg), and fludarabine (30 mg/m2 on days -6 to -2; total dose, 150 mg/m2) [13]. Cy 50 mg/kg on days +3 and +4, mycophenolate mofetil on days +5 to +35, and sirolimus at a target of 5 to 15 ng/mL for a year were used as GVHD prevention measures. The collaborative learning environment has regarding the best conditioning programme to handle the initial high graft rejection rate, there were conflicting views. First-degree relatives, who gave their agreement, had at least one HLA haplotype in common with the patient, were healthy, and did not have SCD or another hemoglobinopathy had their bone marrow stem cells taken. At the HLA-A, -B, -C, and -DRB1 loci, prospective donors were originally typed at an intermediate- or high-resolution level. High resolution HLA-DRB1 and -DQB1 allele typing was done. When possible, haplotypes were discovered using family research. For five straight days, filgrastim (GCSF) 10 mg/kg/day was administered to all donors as a prime. The target total nucleated cell (TNC) dose was 8 to 16 $ 108 cells/kg of the recipient's ideal body weight, with the volume not to exceed 20 mL/kg of the donor weight once the lowest target dose was attained. The TNCs were infused on day 0 with the target dose falling between those ranges.

Conflict of Interest

None

Acknowledgement

None

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