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Current Results and Future Research Priorities in Late Effects after Hematopoietic Stem Cell Transplantation for Children with Sickle Cell Disease and Thalassemia: A Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric Hematopoietic Stem Cell Transplantation

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A B S T R A C T

Sustained donor engraftment after allogeneic hematopoietic cell transplantation (HCT) converts to healthy donor hemoglobin synthesis and halts disease symptoms in patients with sickle cell disease and thalassemia major. A disease-free survival probability that exceeds 90% has been reported when HCT using an HLA-matched sibling donor is performed in young patients with low-risk disease or treatment-related risk factors. Alternate donor HCT and HCT in adults is performed infrequently because of a higher risk profile. Transplant-specific risks include conditioning regimen-related toxicity, graft-versus-host disease, graft rejection with marrow aplasia or disease recurrence, and infections associated with immunosuppression and delayed immune reconstitution. The magnitude of risk depends on patient age, clinical status of the underlying disease (eg, organ injury from vasculopathy and iron overload), donor source, and intensity of the conditioning regimen. These risks are commonly monitored and reported in the short term. Documenting very late outcomes is important, but these data are rarely reported because of challenges imposed by patient drop-out and insufficient resources. This report summarizes long-term follow-up results after HCT for hemoglobin disorders, identifies gaps in knowledge, and discusses opportunities for future investigations. This consensus summary will be followed by a second article detailing comprehensive long-term follow-up recommendations to aid in maintaining health in these individuals and identifying late complication risks that could facilitate interventions to improve outcomes.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) for genetic hemoglobin disorders such as sickle cell disease (SCD) and thalassemia has curative potential. This is evidenced by

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a cessation of the acute signs and symptoms of the underlying disorder after stable engraftment of donor cells. The assumption that a successful transplant will extend lifespan and stop disease-related complications is central to decision-making about HCT. The goal of this summary article is to define and address current gaps in knowledge to create a roadmap of clinical investigation in this field. In a subsequent article we will suggest comprehensive monitoring guidelines to inform clinical decision-making that might facilitate health maintenance after HCT for these disorders. These efforts follow an international working group that convened at the Second Pediatric Blood and Marrow Transplant International Consensus Conference on Late Effects after HCT in Minneapolis, Minnesota, USA in May 2016.

CURRENT RESULTS OF HCT FOR HEMOGLOBIN DISORDERS

Thalassemia

More than 4000 individuals with thalassemia major have received HCT, with most reports focused on results in children and young adults. Risk category assignments have been developed in several transplant series, determined by recipient age, liver size, liver histology, and whether or not there is compliance with iron chelation therapy [1-4]. Outcomes are best in young patients who lack risk factors and receive HLA-identical sibling HCT. Among 1493 consecutive transplant registry cases reported to the European Group for Blood and Marrow Transplantation hemoglobinopathy database, the 2-year overall survival (OS) and event-free survival (EFS) rates were 88% and 81%, respectively. However, among children < 2 years of age who received an HLA-identical sibling allograft, the OS and EFS rates at 2 years were 95% and 93%, respectively. Conversely, recipients > 18 years of age had OS and EFS rates of of 80% and 76%, respectively [5]. Results after HLA-identical sibling umbilical cord blood transplantation are very similar, with lower rates of acute and chronic graft-versus-host disease (GVHD) after umbilical cord blood compared with bone marrow transplantation [6]. Thus, most clinicians agree that HCT for thalassemia should be considered in young patients with favorable risk profiles who have an HLA-identical sibling donor [7].

Sickle Cell Disease

Like thalassemia, HCT for SCD is curative in most individuals who receive this treatment, but, unlike thalassemia, HCT is a treatment option that very few families and patients pursue in the United States [8-11]. The principal reason for the lower number of SCD transplants is the lack of a suitable donor. However, concerns about the toxicity of HCT also limit its broader application. Among those who have an HLA-identical sibling donor, results are excellent, and a compilation of several series showed OS and EFS rates of 95% and 92%, respectively [12-14]. In addition, reduced-intensity and nonmyeloablative regimens have been explored as a method to reduce long-term side effects and mitigate the impact of vaso-occlusion–induced organ damage on transplant-related toxicity, particularly in adolescent and adult recipients [15,16]. Results observed after a melphalan/alemtuzumab-based reduced-intensity conditioning (RIC) regimen applied in children and a nonmyeloblative alemtuzumab-based regimen in adults were similar to results after myeloablative conditioning, and EFS rates of 90.7% and 87%, respectively, were observed. The largest registry series reported to date included 1000 recipients with a median age of 9 years treated between 1986 and 2013 [17]. EFS was lower with increasing age at transplant (hazard ratio, 1.08; $P = .002$) and higher if treated after 2006 (hazard ratio, .94, $P = .02$). Of interest, 7 of 70 deaths occurred 5 years or longer after HCT, which highlights the need for long-term follow-up.

Alternate Donor Transplantation for Hemoglobin Disorders

Early reports of unrelated donor HCT for thalassemia were characterized by high rates of graft rejection and transplant-related mortality, in part related to the older age of recipients, advanced disease, and unrefined donor selection methods [5]. T cell–depleted haploidentical transplants for thalassemia had a disease-free survival (DFS) rate of 70% [18]. Registry results after unrelated umbilical cord blood transplantation for thalassemia and SCD were poor, with a DFS rate of 21% in thalassemia and 50% in SCD recipients [19]. Recent modifications in donor selection and transplant conditioning have improved thalassemia-free survival rates during early follow-up. The addition of hydroxyurea/azathioprine before conditioning in mismatched and matched related HCT (94% and 82%, respectively); dexamethasone/fludarabine in advance of conditioning in haploidentical donor HCT (94%); fludarabine, thiotepa, and treosulfan in unrelated donor HCT (82%); and a RIC combination of hydroxyurea, alemtuzumab, fludarabine, melphalan, and thiotepa (79% and 80% after unrelated donor cord and bone marrow, respectively) together have improved outcomes [20-24]. Long-term follow-up after these varied HCT modalities is essential to judge the merits of alternate donor HCT.

Alternate donor HCT in SCD is less well developed compared with thalassemia. The largest pediatric study in severe SCD showed 1- and 2-year EFS rates of 76% and 69%, respectively [25]. Complications related to chronic GVHD that occurred in 38% of recipients, all in the adolescent age group, resulted in late toxicity after this alemtuzumab/melphalan-based RIC regimen. In addition, the application of a reduced-intensity HLA-haploidentical bone marrow transplant in children with severe SCD demonstrated safety with 97% OS but 57% DFS due to graft rejection [26]. Clinical trials are underway that aim to reduce HCT-related complications and increase DFS in both disorders. Again, it is imperative to pair these short-term aims with long-term healthcare goals as listed below.

Research Priorities

1. Develop improved alternative donor HCT approaches for patients who fail standard supportive care (hydroxyurea, RBC transfusions, iron chelation therapy).
2. Optimize conditioning regimens for alternate donor HCT that minimize GVHD risk and reduce long-term consequences of alternate donor HCT.
3. Define the optimal timing and indications for HCT, particularly with respect to survival outcomes and late effects; develop HCT pathways for adult patients who are eligible after optimum supportive care.

ENGRAFTMENT AND CHIMERISM

Thalassemia

Conventional myeloablative conditioning HCT with busulfan and cyclophosphamide in thalassemia showed a 30% incidence of mixed hematopoietic chimerism early after HCT, and those with >25% recipient cells within 2 months were prone to graft rejection [27]. When reduced-toxicity or RIC regimens were used, there was an increased incidence of