Pediatric hematopoietic cell transplantation

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Abstract. Hematopoietic cell transplantation is a potentially curative therapeutic modality for a wide range of pediatric malignant and nonmalignant diseases. Hematopoietic cell transplantation has evolved over time to include more indications for transplantation and broad-spectrum treatment and supportive care strategies. This review will address the process of transplantation, donor and stem cell sources, complications, and transplantable diseases.

Keywords: Hematopoietic cell transplantation, stem cell transplantation, hematopoietic stem cell transplantation, bone marrow transplant, children, pediatrics

1. Introduction

Hematopoietic cell transplantation (HCT) is the process of the infusion of cells capable of restoring hematopoiesis typically following therapy with chemotherapy, radiation, and/or biologic agents. The origins of HCT are in studies of tissue and organ transplantation in the early twentieth century [1]. Modern clinical HCT grew in response to the development of atomic weapons in the Second World War [1, 2]. Since that time, HCT has matured from an experimental therapy to the standard of care for children with certain high-risk cancers and nonmalignant disorders. The use of HCT in children has steadily increased over time and approximately 3000 pediatric transplants are reported annually to the Center for International Blood and Marrow Transplantation [3]. The growth of HCT as a treatment modality is due to expansion of the indications for transplant, scientific progress in donor source and human leukocyte antigen (HLA) technology, and advances in supportive care. This article will review the current status of pediatric HCT.

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2. Type of transplants, donor type, and stem cell source

Autologous HCT involves the infusion of the patient's own hematopoietic cells following conditioning with chemotherapy with or without radiation. The autologous cells are collected by aphaeresis or marrow collection prior to the start of conditioning. Autologous transplant has traditionally been performed for children with high risk or relapsed solid tumors and lymphoma. The purpose of transplant in this setting is to rescue the myeloablation caused by high-dose chemotherapy and/or radiation directed at the tumor. In recent years, autologous HCT has also been incorporated into gene therapy research protocols.

Allogeneic HCT involves the infusion of stem cells collected from the bone marrow, peripheral blood, and/or umbilical cord blood of a related donor (RD) or unrelated donor (URD). Allogeneic transplant offers the advantages of being free of contaminating malignant cells in the setting of cancer and of providing the missing or dysfunctional hematopoietic elements in children with immunodeficiencies, nonmalignant hematologic diseases, and disorders of metabolism. Additionally, allogeneic transplant provides an antileukemic effect, graft-versus-leukemia,

which is an important consideration in certain hematologic malignancies. Disadvantages of allogeneic transplantation are higher risks of transplant related morbidity and mortality compared to autologous HCT, graft failure and the potential for graft-versus-host disease (GVHD).

A primary decision in allogeneic HCT is the selection of a donor. The preferred donor, in most cases, is an HLA-matched RD who does not have the disease for which the recipient is being transplanted. RD transplants have lower risks of GVHD and transplant related mortality compared to URD HCTs. There are additional practical advantages including greater ease of scheduling and donor availability for subsequent transplants, if needed.

Approximately 15% to 40% of children needing an allogeneic HCT will have an HLA-matched RD [4, 5]. Alternative sources of hematopoietic cells are required for those without an HLA-matched sibling. International URD and cord blood registries have been established to find donors for those patients [6–16]. As of May 2014, there were over 23 million URDs and greater than 600,000 cord blood units from 52 countries in international registries [17]. Unfortunately, not all patients in need of URD HCT are able to identify a registry donor. As a result of multiple factors, non-Caucasian recipients have a far more difficult time finding an URD. It is estimated that Caucasian patients have an 80% chance of identifying an URD in contrast to 30% for African-Americans [18].

Hematopoietic cells can be collected from bone marrow, peripheral blood, and umbilical cord blood units. There are advantages and disadvantages to each of these sources. Bone marrow was the first stem cell source for transplantation and is the standard to which other sources are compared. The collection of bone marrow is performed in the operating room, and therefore, carries the associated risks of anesthesia to the donor. The amount of marrow collected depends on the size of the recipient and typically is not a limiting factor for pediatric transplantation. Peripheral blood stem cells (PBSCs) are collected via apheresis, generally after the administration of granulocyte-colony stimulating factor. PBSCs are associated with more rapid immune reconstitution, shorter time to neutrophil recovery, and enhanced graft-versus-leukemia effect compared to bone marrow. However, PBSC transplants have a greater risk of GVHD, and in pediatric studies, this has resulted in greater overall mortality [19–22]. PBSCs are not a preferred stem cell source in pediatrics

as a result of this increased mortality risk. Umbilical cord blood is rich in stem cells, is readily available in cry preserved units stored in public banks, and has a lower risk of GVHD compared to equally HLA-matched marrow [23, 24]. Disadvantages of umbilical cord blood units are that the stem cell yield is limited to that collected at delivery, immune reconstitution is slower than following PBSC or marrow transplantation, and the full medical history of the donor child is unknown.

3. Conditioning

Conditioning is therapy given prior to the infusion of autologous or allogeneic hematopoietic cells. The objectives of the conditioning regimens are to reduce the disease burden in malignant conditions and to induce recipient immunosuppression to facilitate hematopoietic cell engraftment [25, 26]. There are three broad categories of conditioning regimens: myeloablative, reduced intensity conditioning, and nonmyeloablative. Myeloablative conditioning refers to regimens composed of irradiation and/or alkylating chemotherapy, which result in profound pancytopenia that would be unexpected to result in autologous hematopoietic recovery [26]. The definition of a regimen as myeloablative is based on the dose of radiation and alkylating chemotherapy provided. Myeloablative regimens are needed to ensure engraftment and optimal disease control in some diseases, yet are associated with increased transplant related morbidity and mortality compared to less intense regimens [25–28]. Additionally, children are expected to have infertility following most myeloablative therapy.

Nonmyeloablative are designed to open transplant therapy to older adult patients and those with comorbidities that prohibit the use of ablative regimens [26]. Nonmyeloablative regimens may contain lower doses of the same agents used in myeloblative preparations or different medications, and result in immunoablation with minimal cytopenia [26]. Large numbers of donor lymphocytes and stem cells are needed to allow engraftment following nonmyeloablative conditioning [29]. The advantages of nonmyeloablative conditioning are decreased acute transplant related morbidity and mortality as well as less late adverse effects [30, 31]. However, these benefits must be balanced against the risk of decreased disease control and increased graft failure.

Reduced intensity conditioning regimens are those that do not fall into the categories of either ablative or

nonmyeloablative. The dose of alkylating chemotherapy and/or radiation is at least 30% lower than that used in myeloablative regimens [26]. These regimens induce cytopenia and require stem cell support, although it is likely that autologous recovery would occur after a prolonged period of time without such support [26, 32].

4. Acute post-conditioning period

The period between stem cell infusion and neutrophil engraftment is characterized by pancytopenia necessitating blood product transfusion. Toxicity during this time is attributed to the effects of high-dose therapy and pancytopenia. Common acute toxicities include mucositis of the gastrointestinal and urinary tracts necessitating narcotic pain relief and nutritional support, fever with or without a source, nausea, vomiting, electrolyte abnormalities, pancytopenia requiring blood products, and organ dysfunction. Most organ dysfunction is reversible, but can be life-threatening and irreversible. This is a period of profound immunosuppression and heightened risk of infection. Less common complications during the pre-engraftment period that may result in the need for intensive care support are non-infectious lung disease, sepsis, and organ failure.

5. GVHD

GVHD is the most common complication of allogeneic HCT and is the result of immunocompetent cells from the donor graft reacting to antigens on the recipient's (the host's) organs and tissues [33]. GVHD is classified as acute (aGVHD) or chronic (cGVHD).

In aGVHD, the alloreactivity of the donor T cells is triggered which propagates a cycle of inflammation, cytokine release, and recipient tissue damage from these donor T cells and the resulting inflammation [34]. The skin, liver, and gastrointestinal tract are the most commonly involved organ systems of aGVHD and are used to stage and grade disease involvement. Staging is based on the individual organ system involvement. Grading is a composite score of the individual organ staging (Table 1) [35]. Other commonly involved systems are the oral cavity, eyes, and marrow.

The pathogenesis of cGVHD is not completely understood and is thought to involve donor T cells identifying donor antigens as foreign and/or loss of peripheral T cell tolerance. This leads to symptoms less characterized by inflammation, and more by scarring and features similar to those of autoimmune diseases, particularly scleroderma [33]. Almost every organ system can be affected by cGVHD. Frequently involved systems are the skin, liver, eyes, oral cavity, and marrow. The gastrointestinal tract is less frequently involved in cGVHD than in acute disease. The lungs are infrequently involved, but when affected can have life-threatening consequences.

The clinical classification of acute and chronic GVHD were historically based on the time of presentation less than or greater than 100 days post-HCT. These definitions were made based on careful clinical observations made by transplant physicians over many years. However, these definitions were problematic as they did not take into account the biologic mechanisms underlying the symptoms and how different stem cell sources and conditioning regimens impact the development of GVHD. In 2005, the National Institutes of Health convened a consensus conference to address these issues [36]. The currently accepted definitions are based on the diagnostic features. A complete list

Table 1
Acute graft-versus-host disease staging [35]

Stages	Cutaneous	Liver	Gastrointestinal age ≥ 18 yr	Gastrointestinal age <18 yr
1	Maculopapular rash $<25\%$ Body surface area	2-3 mg/dL	500-999 mL/day	10-19.9 mL/kg/day
2	Maculopapular rash 25-50% Body surface area	3.1-6 mg/dL	1000-1500 mL/day	20-30 mL/kg/day
3	Maculopapular rash $>50\%$ Body surface area	6.1-15 mg/dL	>1500 mL/day	>30 mL/kg/day
4	Generalized erythroderma plus bullous formation	>15 mg/dL	Severe abdominal pain with or without ileus	
Grades				
I	Stages 1-2	None	None	
II	Stage 3 or	Stage 1 or	Stage 1	
III	—	Stage 2-3 or	Stage 2-4	
IV	Stage 4 or	Stage 4	—	

of the clinical features of acute and chronic GVHD is beyond the scope of this manuscript.

All patients undergoing allogeneic HCT, with the exception of those with a syngeneic twin donor, require GVHD prophylaxis. This may come in the form of graft manipulation by removing the donor T cells from the stem cell product. This is referred to as T cell depletion. The more standard practice, however, is to provide immunosuppression with combination therapy of medications. Commonly used medications include cyclosporine, tacrolimus, sirolimus, methotrexate, mycophenolate mofetil, and corticosteroids. The regimen used depends on the characteristics of the patient, donor, stem cell source, and transplant center. The first line therapy for GVHD treatment is corticosteroids. There are multiple second and third line agents and modalities for the treatment of steroid dependent and refractory GVHD, but there is no universally accepted standard of care.

6. Engraftment and immune reconstitution

The process of engraftment following the infusion of allogeneic or autologous HCT includes homing of stem cells to the marrow space, cellular expansion, and the eventual production of mature hematopoietic cells. The traditional definition of neutrophil engraftment is an absolute neutrophil count greater than 500 cells/mm³ on 3 consecutive days. The time to neutrophil engraftment depends on the conditioning regimen, GVHD prophylaxis, pre-infusion cell manipulation, donor type, and stem cell source. In general, neutrophil recovery is achieved within 2 to 4 wk. Engraftment occurs most rapidly following autologous and PBSC transplantation due to the higher CD34+ cell counts in these sources [37]. Engraftment occurs most slowly following umbilical cord blood transplantation [38–42].

Although engraftment and the production of hematopoietic cells can occur within weeks of HCT, full immune reconstitution takes many months and patients are at increased risk for infection during this time. Similar to the time to achieve engraftment, the period to full immune reconstitution depends on donor and treatment factors. During the immediate post-transplant period, functional T, B and natural killer cells provide temporary partial immunity. Full immunity requires complete recovery of the marrow and takes 6–12 mo following allogeneic transplant [43].

The immune function of the patient is also impacted by immunosuppressive medications provided to prevent and/or treat GVHD. Children who remain on immunosuppressive medications should be considered immune compromised even in the setting of a normal absolute neutrophil count.

7. Transplantable diseases

7.1. Malignant diseases

Acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) are the most common indications for HCT in childhood [3]. Clinical trials over the last four decades have established the role of post-remission therapy in the treatment of childhood AML. However, it remains unclear whether allogeneic HCT or intensive chemotherapy without transplantation is the best post-remission therapy. Allogeneic HSCT offers the advantages of a higher intensity of the conditioning regimen and the graft-versus-leukemia effect. However, HCT has increased acute and long-term toxicities compared to chemotherapy alone. Additionally, not all patients with high-risk leukemia have an appropriate stem cell donor. Successive trials have attempted to stratify children with AML by risk to identify patients who would benefit most from transplant. Studies have demonstrated that allogeneic transplant in the first clinical remission can improve the outcome for children with high-risk features [44]. Risk stratification is based on the cytogenetic features of the leukemic cells. For patients who are identified as having high-risk disease, the increased risks associated with transplant are off set by the reduced risk of leukemia relapse. Additionally, the clinical response to therapy influences the decision to proceed to transplant. Allogeneic transplant is the standard of care for patients who do not obtain a remission after initial induction therapy or have disease relapse. The presence of minimal residual disease as assessed by polymerase chain reaction or flow cytometry at different points in therapy is increasingly recognized as an important prognostic tool [45–48]. Multiple studies have indicated that the presence of high minimal residual disease at any point prior to HCT leads to an increased relapse rate [45, 46, 48–50]. Standard features of risk stratification are outlined in Table 2.

The survival rates for children with ALL have steadily improved over time and approximately 85% of

Table 2
Clinical and cytogenetic risk features in patients with acute myelogenous leukemia

Low risk	Intermediate risk	High risk
Hematopoietic cell transplantation not recommended as standard of care	Hematopoietic cell transplantation not recommended with unrelated donor; consider with related donor	Hematopoietic cell transplantation recommended with best available donor*
t(15;17), Inv (16)/t(16;16), t(8;21), Down syndrome	Absence of low and high risk features	Monosomy 7, monosomy 5, -5q, induction failure, relapse, Fms-like tyrosine kinase-3 internal tandem duplication, persistent disease/high minimal residual disease, t(6;9), t(8;16), t(16;21), FAB M0 or M6; FAB M7 without t(1;22) or trisomy 21, treatment-related (secondary) acute myelogenous leukemia, refractory anemia with excess blasts-2 or acute myelogenous leukemia arising from prior myelodysplastic syndrome

*Not all features listed are considered high risk in all studies. FAB = French American and British.

children are now cured by risk-stratified regimens containing chemotherapy with or without radiation [51, 52]. However, a subset of children with ALL cannot be cured with standard regimens. HCT remains the standard of care for these children. There are commonly identified features, including the white blood cell count at presentation, age, extramedullary disease involvement, and cytogenetic characteristics used to stratify children into risk categories at diagnosis. The features that identifiable, which children would benefit from upfront HCT are not clearly established. In the past, children with translocations of chromosomes 9 and 22, Philadelphia chromosome positive ALL, were commonly referred for transplant in first clinical remission. However, the role of transplant for these children has evolved in the era of tyrosine kinase inhibitors, and few children with Philadelphia positive ALL are currently referred for HCT in first clinical remission [53, 54]. The role of transplant in first clinical remission is debated for other cytogenetic abnormalities. HCT is considered for children with hypodiploid ALL and other high risk cytogenetics [55–57]. More straight forward indications for HCT in children with ALL are the persistence of disease after initial induction therapy (induction failure) and those with early relapse [58–60]. Early relapse is not consistently defined across studies. A commonly used definition is a non-medullary relapse occurring less than 18 mo from remission and less than 36 mo from remission for bone marrow relapse.

Other childhood leukemias treated with allogeneic HCT are chronic myelogenous leukemia (CML) and juvenile myelomonocytic leukemia (JMML). CML is a stem cell disorder arising from a translocation between

chromosomes 9 and 22 that rarely presents in childhood. HCT was once the standard of care for children. This has changed with the development of tyrosine kinase inhibitor therapy. The role of transplant for children with CML is now debated [61–64]. JMML is an uncommon leukemia of infants and young children that arises from stem cells and falls on the spectrum of myelodysplastic syndromes. HCT is the only curative therapy for children with JMML and proceeding directly to transplant is generally recommended [65, 66].

HCT is not used as part of upfront therapy for children with Hodgkin disease, non-Hodgkin lymphoma, and Burkitt lymphoma. Autologous HCT is recommended for those with refractory or recurrent lymphoma following standard chemotherapy with or without radiation. Both radiations based and chemotherapy-only approaches have been used with similar outcomes. Autologous PBSC is preferred to allogeneic HCT due to lower toxicity and earlier engraftment with comparable relapse rates and potential for cure [67, 68].

There is extensive experience providing high-dose chemotherapy followed by autologous stem cell rescue in children with solid tumors. The principles underlying autologous transplant for solid tumors are that the tumor must be responsive to chemotherapy and that the dose-limiting toxicity for the effective chemotherapy must be hematologic. The greatest experience is in high-risk neuroblastoma and certain brain tumors [69–74]. Other tumors that have been treated with autologous transplant include retinoblastoma, some sarcomas, and Wilms tumor [75–79].

7.2. Nonmalignant diseases

Transplant is being performed for a growing number of nonmalignant diseases including bone marrow failure, hemoglobinopathies, immunodeficiencies, metabolic storage diseases, and autoimmune disorders (Table 3). With the exception of autoimmune disorders and transplants performed as part of gene therapy protocols, transplants for nonmalignant disorders are all allogeneic.

Bone marrow failure syndromes include idiopathic severe aplastic anemia (SAA) and a wide range of inherited disorders. SAA is characterized by pancytopenia and bone marrow hypoplasia. Untreated SAA has a mortality rate approximating 50% [80]. Allogeneic HCT is first line therapy for children with SAA who have an HLA-matched sibling donor. Those without a matched sibling donor typically receive immunosuppressive therapy and proceed to URD transplant in the setting of failed immunosuppression [81–83]. Prior to proceeding to allogeneic transplant,

all children with aplastic anemia must undergo a work-up for inherited bone marrow failure syndromes. This is essential due to the potential for increased sensitivity to conditioning, associated underlying conditions and organ dysfunction, need to screen matched sibling donors for the same condition, and the imperative for disease specific long-term follow-up.

Allogeneic transplantation is a potentially curative option for patients with sickle cell disease, thalassemia, and other hemoglobinopathies [84–86]. Frequent challenges to the transplantation of children with hemoglobinopathies include the availability of unaffected related and URD, pre-transplant comorbidities associated with chronic transfusion and underlying disease, and increased risk of graft rejection [85]. Emphasis in recent years has been on expanding URD options and reducing the intensity of the conditioning regimens for children with hemoglobinopathies [16, 87–90].

Allogeneic HCT is a curative therapy for children with a range of immunodeficiency disorders. The most frequently transplanted immunodeficiency is severe combined immunodeficiency disease (SCID). SCID is a syndrome arising from a variety of genetic defects that result in deficiencies in T cell function [91]. Multiple types of SCID are reported with the common feature being deficient T cell development or function. B cells and natural killer cells are variably involved in the different types of SCID [92, 93]. Allogeneic transplant is the only non-experimental cure for patients with SCID, although gene therapy studies are ongoing [94–97]. Patients with SCID may not require any or full conditioning due to the lack of functional T cells to reject the graft [98]. Other commonly transplanted immunodeficiencies include Wiskott-Aldrich syndrome, chronic granulomatous disease, Omenn syndrome and X-linked hyper-immunoglobulin M syndrome [99, 100]. Transplant outcomes for children with immunodeficiencies have improved over time with advances in supportive care, early diagnosis, and donor selection. Factors that positively influence the outcome of allogeneic transplant include younger age and the lack of pre-transplant exposures to viruses and other pathogens [99]. Gene therapy trials and newborn screening are recent advances in the care of children with certain immunodeficiencies. The impact of these changes on the practice of HCT is not yet known.

Allogeneic transplantation is a curative option for children with select inherited lysosomal and

Table 3
Nonmalignant indications for hematopoietic cell transplant

<i>Marrow failure syndromes</i>
Idiopathic aplastic anemia
Fanconi anemia
Diamond-Blackfan anemia
Fyskeratosis congenita
Congenital amegakaryocytic thrombocytopenia
Severe congenital neutropenia
Shwachman-Diamond disease
GATA2 deficiency
<i>Immunodeficiency/Immune dysfunction syndromes</i>
Severe combined immunodeficiency
Wiskott-Aldrich syndrome
Hemophagocytic lymphohistiocytosis
Chronic granulomatous disease
Omenn syndrome
X-linked syndrome
<i>Hemoglobinopathies</i>
Sickle cell disease
Thalassemia major
<i>Diseases of metabolism</i>
Hurler syndrome and other mucopolysaccharidoses
Krabbe disease
Adrenoleukodystrophy
Metachromatic leukodystrophy
Osteopetrosis

paroxysmal disorders [101]. In considering HCT for children with these rare diseases, it is important to recognize that, in most cases, neurologic and visceral function lost prior to HCT cannot be restored and children with advanced disease do not benefit from transplant. Mucopolysaccharidoses are caused by gene defects that result in the deficiency of lysosomal enzymes needed to degrade glycosaminoglycans resulting in the accumulation of glycosaminoglycans and end organ tissue damage [102, 103]. The success of transplantation for mucopolysaccharidoses is based on correction of the enzyme deficiency mediated by donor leukocytes, enzyme cross correction, and the ability of hematopoietic cells to engraft and distribute macrophage derived tissue cells [103–106]. The pattern of neurologic and other organ damage is unique to each disorder in this class. Transplant is not effective for all diseases in this class and is best established for Hurler syndrome [101, 103–105].

Sphingolipidoses are a group of lipid storage disorders including Tay-Sachs, Niemann-Pick, Fabry, Gaucher and Krabbe diseases and metachromatic leukodystrophy [104]. Transplant is available to children with sphingolipidoses for whom enzyme replacement therapy is not available or tolerated and with limited symptoms of disease. Krabbe disease and metachromatic leukodystrophy are the most frequently transplanted sphingolipidoses [107–109]. Adrenoleukodystrophy (ALD) is an X-linked paroxysmal disorder characterized by adrenal gland dysfunction, progressive debilitating central nervous system demyelination, and degeneration of the spinal cord [110, 111]. Boys with progressive ALD have neurologic deterioration resulting in death within 2–5 yr after the onset of progression [110, 112]. Boys with progressive ALD can be cured with allogeneic transplant if performed shortly after the onset of MRI and/or symptom progression [113, 114].

8. Future directions

Pediatric HCT is an ever-evolving field. There is ongoing emphasis on the development of transplant strategies with less acute and chronic toxicities without sacrificing disease control. Another developing area of study is the incorporation of targeted leukemia-directed therapies prior to and following transplants. A third focus of research is the use of gene therapy for nonmalignant disorders. While the exact future of

pediatric HCT is yet to be determined, it has promise for improved safety allowing it to be used for more diseases and with improved survival.

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