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Making strides and meeting challenges in pediatric allogeneic hematopoietic cell transplantation clinical trials in the United States: Past, present and future☆

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ABSTRACT

Over the past 20 years, the field of pediatric allogeneic hematopoietic cell transplantation has made groundbreaking strides in the successful treatment of patients with both malignant and non-malignant diseases. As the field advances, so does the need for high-quality studies including randomized controlled trials, aimed at answering clinically important questions about optimizing care and outcomes of children undergoing alloHCT. In an effort to actively address emerging clinical questions, three main cooperative groups in the U.S. have joined forces to develop and implement multiple clinical trials for pediatric alloHCT patients. These groups include the Blood and Marrow Transplant Clinical Trials Network, the Children's Oncology Group and the Pediatric Blood and Marrow Transplant Consortium. Though the field of stem cell transplantation continues to advance, conducting clinical trials in the pediatric population is a unique challenge and as a result, optimal outcomes have yet to be reached in this population. Because of the limited number of pediatric transplant patients at each institution in the U.S., trials aimed at answering important clinical questions still struggle to accrue acceptable numbers of patients in an appropriate amount of time and thus gathering statistically useful data has posed a challenge for the field. In an effort to mitigate some of the challenges associated with obtaining statistically and clinically meaningful information about pediatric alloHCT, the implementation of new cooperative group trials is active and ongoing.

1. Introduction

Allogeneic hematopoietic cell transplantation involves the infusion of donor hematopoietic progenitor cells, or "stem" cells, into a recipient individual for the treatment of either a malignant or non-malignant disease. These donor stem cells function to create a new immune-hematopoietic system in the recipient with the aim of either eradicating malignant disease, reconstituting bone marrow in cases of bone marrow failure, introducing missing components of a non-functioning immune system or providing absent enzymes to the recipient in need [1–3].

Advances in the field of pediatric oncology over the last quarter-century are among the most dramatic and successful in modern medicine. Pediatric cancer is a relatively rare entity that encompasses innumerable types of diagnoses, many of which are clinically distinct from one another [4]. Despite this, leaders in the field have been able to optimize outcomes and continuously improve treatment success rates, largely due to national and international collaborative clinical investigation efforts. Today in the United States, more than 95% of pediatric cancer patients under the age of 15 are treated at Children's Oncology Group (COG) institutions and approximately 50–60% of them are entered on clinical trials [5,6]. In pediatric oncology, the focused implementation of large cooperative group trials has enabled collection of statistically meaningful data that continues to improve patient survival and outcomes every day.

Over the course of the last two decades, similar success has been demonstrated in the field of pediatric bone marrow transplantation. The indications for alloHCT in both children and adults have continued to expand as have the modes by which the transplants themselves are performed. Pre-transplant conditioning regimens which once relied almost solely on myeloablative techniques, now include reduced intensity and reduced toxicity regimens with or without total body irradiation. Stem cell donors, who were once required to be human leucocyte antigen (HLA)-matched relatives, now include related and unrelated as well as matched or mismatched donor-options. As the long-term survival of pediatric transplant patients continues to improve, the approach to post-transplant supportive care and graft-versus-host disease (GVHD) management continues to evolve as well. Finally, survivorship, once an almost negligible concept for children undergoing stem cell transplant, is quickly becoming one of the most important fields in pediatric alloHCT. As the field of pediatric alloHCT continues to expand in terms of

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indications, conditioning regimens, donor options and post-transplant supportive care, the development of trials aimed at organizing and optimizing our approach to alloHCT is becoming increasingly essential.

2. National cooperative groups

In the pediatric and adolescent population, accepted indications for stem cell transplantation include at least nine different malignant diseases and upwards of 20 non-malignant diseases. The indications for alloHCT in non-malignant disorders include (but are not limited to) hemoglobinopathies (i.e. sickle cell disease and thalassemia), immunedeficiencies and dysregulation, metabolic diseases and rare leukodystrophies [7,8]. In malignant diseases, indications for transplant include acute leukemias and lymphomas as well as certain solid tumors such as high risk or relapsed neuroblastoma. Despite the many disease indications for transplant in pediatric patients, even the largest transplant centers currently only perform between 50 and 100 transplants per year. Three main cooperative groups in the U.S. and abroad have joined forces in an effort to develop larger and by extension, more impactful clinical trials for pediatric alloHCT patients. These groups include the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), the COG and the Pediatric Blood and Marrow Transplant Consortium (PBMTC).

2.1. Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

BMT CTN is an NIH-funded consortium that was established in 2001 with the aim of conducting multi-institutional clinical trials on both a national and international level. Since its establishment, BMT CTN has implemented over 30 cooperative group clinical trials at over 100 institutions across the world. The development of clinical trials in the BMT CTN group is guided by a series of State of the Science Symposia where experts discuss pressing clinical questions in the field of bone marrow transplantation in order to plan for new and relevant cooperative group clinical trials [9,10]. Over the past decade, BMT CTN has developed a series of prospective clinical trials for eligible pediatric patients undergoing alloHCT, many of which have impacted clinical practice and furthered the field. The questions addressed in these trials range from comparisons of conditioning regimens to questions about stem cell sources to approaches to post-transplant GVHD treatment and prophylaxis [9]. Key clinical trials conducted by BMT CTN are presented in Table 1.

2.2. Children's Oncology Group (COG)

In the year 2000, the COG was formed out of the joining of the Pediatric Hematology/Oncology Group (POG), the Children's Cancer Group (CCG), the National Wilm's Tumor Study Group and the International Rhabdomyosarcoma Study Group. Prior to this, the POG had developed group-wide criteria for performance of bone marrow transplantation in pediatric patients. Between 1990 and 2000 the group performed two pivotal studies investigating the utility of transplant in both AML and ALL patients. Simultaneously, the CCG ran a study investigating the use of matched sibling versus autologous transplant in AML patients in first remission [11,12]. Both the CCG and the POG studies revealed that certain patients who received matched sibling donor transplants for these diseases had superior disease-free survival than those who did not [13]. Today, the COG continues to focus on developing groundbreaking phase II and phase III trials for pediatric oncology patients undergoing alloHCT. Key clinical trials conducted by COG are outlined in Table 2.

2.3. Pediatric Blood and Marrow Transplantation Consortium (PBMTC)

PBMTC was founded in 1989 as a core member of the BMT CTN and includes over 100 pediatric BMT centers in the United States, Canada, New Zealand and Australia with affiliates in Europe and Asia as well. It is currently the largest cooperative group that exclusively focuses on stem cell transplantation in pediatric and adolescent patients. The PBMTC has developed a program aimed at running developmental and early-phase trials with a special focus on rare and non-malignant diseases. These early phase trials function to provide preliminary data to the group's partner networks, the BMT CTN and the COG.

3. The past decade in pediatric allogeneic stem cell transplantation

There are myriad details that contribute to the overall transplant plan for a given patient. More broadly, however, one can consider a few key areas, all of which are components of the transplant process and all of which are areas of developing research.

These are the following:

1. Donor selection and stem cell source;
2. Primary disease and diseases status at the time of transplant;
3. Conditioning regimens;
4. Supportive care therapies;
5. Acute and chronic graft-versus-host disease (GVHD); and
6. Long term survivorship.

3.1. Donor selection and stem cell source

For a patient in need of alloHCT, donor hematopoietic cells are collected from the best available identified donor. These cells may be obtained either from the donor's bone marrow, peripheral blood or umbilical cord blood. Donors may be HLA-matched siblings, HLA mismatched family members or HLA matched/mismatched unrelated persons (umbilical cord blood (UCB)/volunteer adult). HLA-matched sibling transplants historically have the best outcomes and, if feasible, these related donor cells are considered the best donor option due to ease of cell availability and a theoretically lower risk of GVHD post-transplant [13]. While matched-sibling alloHCT has been the gold standard for decades, recent advances in HLA typing have enabled expansion of the donor pool to unrelated options while still maintaining the excellent outcomes seen in matched sibling transplants. A recent prospective study in children with ALL demonstrated that patients had similar outcomes whether they had a matched sibling or an unrelated donor alloHCT [14].

Unrelated umbilical cord blood (UCB) is a valuable donor source for alloHCT, especially in pediatrics. The number of patients undergoing UCB Transplantation has increased steadily over the last few decades [15]. There are several advantages to using UCB, namely ease of cell collection and less stringent need for perfect HLA match due to low allogenicity of the cord-blood donor cells. Challenges with UCB include the fact that the number of T-cells and hematopoietic progenitor cells in a single cord blood unit may be relatively low thus resulting delayed neutrophil and platelet recovery and resultant prolonged infection risk [16]. To circumvent the issue of cell dose in UCB, adult patients often receive two UCB units which, in some cases, has resulted in overall improvement in outcomes [17,18]. In conjunction with the Children's Oncology Group, a BMT CTN study 0501 investigated outcome differences in children receiving single or double UCB transplantation. In this study, investigators found that a single-unit UCB transplant was associated with better platelet recovery and a lower risk of GVHD [19] but ultimately, survival rates were similar after either a single or double-UCB transplant.

One of the major limitations of cord blood transplantation is limited number of hematopoietic progenitor cells resulting in delayed immune reconstitution, especially for older children and adolescents. Various promising strategies have recently demonstrated that cord blood hematopoietic progenitor cells can be successfully expanded resulting in faster neutrophil and platelet engraftment [20]. It is anticipated that