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Meeting Report

Challenges and Opportunities for International Cooperative Studies in Pediatric Hematopoeitic Cell Transplantation: Priorities of the Westhafen Intercontinental Group

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A B S T R A C T

More than 20% of allogeneic hematopoietic cell transplantations (HCTs) are performed in children and adolescents at a large number of relatively small centers. Unlike adults, at least one-third of HCTs in children are performed for rare, nonmalignant indications. Clinical trials to improve HCT outcomes in children have been limited by small numbers and these pediatric-specific features. The need for a larger number of pediatric HCT centers to participate in trials has led to the involvement of international collaborative groups. Representatives of the Pediatric Blood and Marrow Transplant Consortium, European Group for Blood and Marrow Transplantation's Pediatric Working Group, International Berlin-Frankfurt-Munster (iBFm) Stem Cell Transplantation Committee, and Children's Oncology Group's Hematopoietic Stem Cell Transplantation Discipline Committee met on October 3, 2012, in Frankfurt, Germany to develop a consensus on the highest priorities in pediatric HCT. In addition, it explored the creation of an international consortium to develop studies focused on HCT in children and adolescents. This meeting led to the creation of an international HCT network, dubbed the Westhafen Intercontinental Group, to develop worldwide priorities and strategies to address pediatric HCT issues. This review outlines the priorities of need as identified by this consensus group.

INTRODUCTION

Approximately 20% to 25% of allogeneic hematopoietic cell transplantations (HCTs) worldwide are performed in children and adolescents [1]. Unlike in adults, at least one-third of the HCTs in children are performed for rare, nonmalignant indications, including immune deficiencies, immune dysregulation, marrow failure syndromes, metabolic syndromes, and hemaglobinopathies, as well as a number of inherited disorders, such as osteoporosis and ostogenesis imperfecta. In addition, the distribution of hematopoietic malignancies

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treated with HCT differs between children and adults, with relatively more children with such diseases as acute lymphoblastic leukemia and juvenile myelomonocytic leukemia. There are unique issues associated with HCT in children with leukemia, including the fact that we are treating a developing individual with greater susceptibility to the some of the toxicities of myeloablative preparative regimens. Overall, there are many major questions and issues unique to pediatric HCT that need to be considered separately in clinical trials. Moreover, the rare nature of many of the pediatric disorders treated by HCT require a large number of transplantation centers and international trials to address some of these questions and issues. This conclusion is well supported by the difficulties that have been encountered by the Blood and Marrow Transplant Clinical Trials Network in North America in attempting to develop a clinical trial aimed at improving HCT for treating hemophagocytic lymphophistiocytosis.

Given this clear need to develop a structure for international trials in pediatric HCT, the 4 largest pediatric clinical trials groups in North American and Europe met to begin the process of developing trials to address the most compelling questions for HCT. The groups at this meeting included the International BFM Stem Cell Transplantation Strategy Group, the Pediatric Blood and Marrow Transplantation Consortium (PBMTC), the Children's Oncology Group (COG) Hematopoietic Stem Cell Transplantation Discipline Committee, and European Group for Blood and Marrow Transplantation (EBMT) Pediatric Working Group. The consensus group first met on October 3, 2013, in Frankfurt, Germany. That meeting focused on reviewing the current status of pediatric HCT worldwide and identifying the critical areas of need that can be addressed only by larger multicenter studies.

HCT IN PATIENTS WITH PRIMARY IMMUNE DEFICIENCY

Outcomes of HCT in patients with primary immune deficiency (PID) have improved significantly over the last several decades in both Europe and the United States [2]. Collaborative studies evaluating outcomes by stem cell source as well as disease-specific outcomes from centers within the EBMT Inborn Errors Working Party (IEWP), the European Society for Immunodeficiency (ESID), and the Center for International Blood and Marrow Transplant Research (CIBMTR) have had a positive impact on these outcomes [2-4]. Conclusions from these studies include the following: (1) Patients with non–severe combined immunodeficiency (SCID) T cell deficiencies have poorer outcomes compared with all others; (2) patients with SCID B^+ deficiencies have the best outcomes; (3) the overall survival (OS) is similar with matched related donors and matched unrelated donors and better with both compared with haploidentical donors; and (4) a shorter time from diagnosis to HCT is associated with better OS. Furthermore, in Europe, studies of reduced-toxicity regimens in phagocytic disorders, such as chronic granulomatous disease (CGD) and leukocyte adhesion deficiency, are reporting apparent good results [4,5]. Such results may impact the choice of conditioning regimens HCT for CGD in the United States. In addition, antibody-based conditioning regimens, such as monoclonal antibody targeting CD45, are now under evaluation [6]. Collaborative studies are currently open within the EBMT, and a new North American consortium, the Primary Immune Deficiency Treatment Consortium (PIDTC), has been created.

The major problem faced when studying children with PID in North America is that owing to the rarity of these disorders, as no single institution treats a sufficient number of patients to be able to implement anything other than pilot or observational studies. Despite this limitation, over the years centers have developed their own institutional protocols and reported on their own experiences, with less emphasis on multi-institutional trials. The PIDTC was formed to overcome this deficiency and ro replicate the achievements of the EBMT/ESID IEWP, which has been well established for 2 decades.

The PIDTC is a group of 33 transplantation centers in the United States and Canada that is focused on 3 PIDs: SCID, CGD, and Wiskott-Aldrich syndrome (WAS) [7,8]. PIDTC retrospective, cross-sectional, and prospective studies of SCID hope to determine the optimal conditions for HCT in children with SCID, including donor type, donor source, donor match, minimal conditioning regimen, and supportive care guidelines, that result in the best long-term survival with minimal toxicity. In addition, these studies are assessing for unique biomarkers that can predict outcome and identify the optimum approaches for the various SCID genotypes and phenotypes. Finally, other research studies in long-term survivors include quality of life, T cell tolerance mechanisms, B cell reconstitution and function, and donor stem cell chimerism. Studies of WAS and CGD are focused on the extent of donor chimerism necessary to correct the disease and avoid post-transplantation autoimmunity and inflammatory disease, as well as the indications for HCT. Updates on the outcomes of these studies are presented during annual meetings of both the IEWP and PIDTC with representative of each group participating, but joint meetings are currently lacking. Although a growing number of collaborations have developed on an ad hoc basis, no formal collaborative multi-institutional studies have been conducted to date.

New challenges and opportunities to improve the outcomes for patients with PID are newborn screening programs (already open in some US states) and emerging therapies (eg, gene therapy, antibody-based conditioning). Although SCID, WAS, and CGD are relatively more frequent among the rare PIDs, many other serious primary disorders of the immune system are even less common ($<$1/100,000 population). For many of these, even studies in Europe or North America would enroll relatively few patients, and joint collaborative efforts would be much more effective. Moreover, to test important therapeutic approaches, enrolling sufficient numbers of patients in a timely manner to answer definitive questions will require collaborative efforts between the PIDTC and IEWP. At a minimum, we need to standardize data collection and PID definitions to compare outcomes. Only then we can begin to work together to develop not only collaborative retrospective analyses, but also prospective phase III intervention trials to further improve transplantation outcomes and, perhaps even more importantly, long-term outcomes. After the last PIDTC meeting in Houston, a potential PIDTC/IEWP collaborative analysis of Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome was proposed.

The conclusions can be summarized as follows:

1. Conducting randomized controlled trials will be difficult without standardization of data collection and disease definitions.
2. Clear treatment guidelines should be developed for patients identified in newborn screening programs. A prospective intervention study is being planned by the PIDTC pending funding. As European countries institute newborn screening for SCID, it is hoped that

a collaboration with the PIDTC protocol will be possible.
3. Efforts to homogenize the conditioning regimens are supported by research data from retrospective and prospective studies.
4. The EBMT guidelines (www.ebmt.org) may be a good platform for the PIDTC centers. This will be discussed within the group.
5. There is the need for a joint statement on the importance of standardized treatment guidelines for the various disease groups. For specific diseases, special recommendations may be needed (eg, X-linked lymphoproliferative disease) [9].
6. Data collection and registration are important, especially for long-term functional outcomes. Characterizing the long-term outcomes and late effects in children with, for example, SCID, WAS, or CGD who underwent HCT is important. At present, we are using standard registries to report these data, but a critical review is needed to homogenize the endpoints in the EBMT PROMISE and SCETIDE, PIDTC, and CIBMTR registries.
7. Joint meetings (once every 2 to 4 years) between EBMT IEWP and PIDTC would be of use to further homogenize HCT practice and follow-up.

OVERVIEW OF EBMT/IBFM STUDIES FOR LEUKEMIA

The major European-based cooperative groups active in the field of HCT for children with leukemia are the iBFM Study Group and the EBMT's Pediatric Disease Working Party. Ongoing and recent European studies involving this patient population include the following:

- CML-SCT iBFM, a study of imatinib and HCT for children and adolescents with CML using reduced-intensity conditioning (RIC) (ongoing, open in some European countries only; challenged by low accrual)
- AML SCT 2007, a study of HCT in pediatric AML with busulfan-cyclophosphamide-melphalan conditioning for patients in complete remission with a matched donor (ongoing)
- IntReALL, a study of frontline protocol for relapsed acute lymphoblastic leukemia (ALL) in children
- Allogeneic Stem Cell Transplantation for Children and Adolescents with Acute Lymphoblastic Leukaemia–FORUM (For Omitting Radiation Under Majority age) trial, a study of HCT in pediatric ALL.

The ALL-SCT BFM 2003 trial accrued 452 patients with childhood ALL. The conditioning regimen was TBI/etoposide for children age >2 years and busulfan/cyclophosphamide/etoposide in younger patients and those with a contraindication to TBI. Graft-versus-host disease (GVHD) prophylaxis was cyclosporin A only for matched sibling donor (MSD) HCT and cyclosporin A/methotrexate/antithymocyte globulin (ATG) for matched unrelated donor (MUD) HCT. High-resolution typing and allele matching of 9/10 or greater was required for the MUD group. The protocol was amended to remove peripheral blood stem cells (PBSCs) as a stem cell source, owing to an increased risk of extensive chronic GVHD (cGVHD) after MSD HCT. Outcomes were equivalent for patients undergoing HCT with either an MSD or an MUD, using either bone marrow (BM) or PBSCs as the stem cell source, with no difference between 9/10 and 10/10 matches, with a low 3-year TRM of 5% for MSD HCT and 10% for MUD HCT. Poor outcomes were reported for those with MUD or matched related donors with no difference in stem cell source, but significantly better OS was seen in patients at very high risk for relapse who underwent HCT while in first remission.

A new trial, ALL SCTped entitled FORUM, is being conducted by the EBMTG pediatric working group. This trial, a joint effort of the EBMTG, iBFM-SG, and the IntReALL known as the "Open, Randomized, Multicenter, Controlled, Prospective Phase III Study For Therapy And Therapy Optimization in Patients with ALL and an Indication for Allogeneic HSCT," is sponsored by St Anna Kinderkrebsforschung, Vienna, Austria. Recruitment will be 1000 patients over 5 years, with 10 years of observation. Inclusion criteria will allow any patient age <18 years at the time of conditioning and in complete remission. The overall goal of the study will be to show that non–TBI-containing conditioning (fludarabine/thiotepa/bulsulfan or fludarabine/thiotepa/treosulfan) will result in noninferior survival compared with conditioning with TBI/etoposide in children age >4 years after (HCT) using BM or PBSCs from MSDs or MUDs. The study will also evaluate event-free survival (EFS) after HCT in patients who receive an HLA-mismatched transplant from a mismatched MUD, mismatched umbilical cord blood, or an HLA-haploidentical family member with a non–TBI-conditioning regimen.

OVERVIEW OF COG AND PBMTC STUDIES FOR LEUKEMIA

The largest pediatric HCT cooperative groups in North America include the COG SCT Committee [10] and the PBMTC [11]. Whereas the COG focuses on oncology, supportive care, and phase III trials, the PBMTC performs trials in nonmalignant disorders and early-phase pilot studies that could go on to become phase III trials in the COG. The PBMTC functions as a core center in the National Cancer Institute/National Heart, Lung, and Blood Institute–sponsored BMT Clinical Trials Network (BMT CTN), and represents pediatric transplantation interests in that forum.

The COG SCT Committee and the PBMTC have numerous individual and joint projects. Selected studies from these groups include the following:

- For the COG alone: ASCT1221, a comparative trial of busulfan/fludarabine versus busulfan/cyclophosphamide/melphalan for children with JMML
- Joint COG and PBMTC trials: ASCT0431 (recently completed), a phase III trial comparing sirolimus containing GVHD prophylaxis with standard regimens, and ASCT0521, a phase II trial assessing the role of entanercept in the treatment of idiopathic pneumonia syndrome
- For the PBMTC alone: ONC1001, a study comparing pre- and post-HCT minimal residual disease measurements for patients with AML undergoing HCT; ONC1101, a phase II study of treosulfan in children with AML/MDS; and ONC1201, a phase II trial of moxetumomab for reduction of minimum residual disease (MRD) in patients with ALL before HCT
- For the COG and PBMTC with the BMT CTN: 0501, a comparison of 1 unit and 2 unit umbilical cord blood transplantation in children with hematologic malignancies; 0601, a reduced-intensity approach to children with sickle cell disease; and 1204, a study of optimized timing of alemtuzumab for RIC in children with HLH and selected immune deficiencies.

Another important effort of the PBMTC was an international conference on late effects in pediatric HCT held in April

2011. The key consensus publications from this effort form a foundation for continued international cooperation in late effects research [12-18].

MRD IN LEUKEMIA

The predictive value of MRD and chimerism post-HCT for ALL has been shown to enable potential interventions to avert a pending relapse [19-21]. Patients with rising donor chimerism were found to have better outcomes when a therapeutic intervention, such as withdrawal of immune suppression and/or donor lymphocyte infusion (DLI), was performed. MRD $<10^{-4}$ versus $\geq 10^{-4}$ was used as cutoff for ALL (based on pretreatment marrow). There was no benefit of DLI intervention at MRD $>10^{-3}$. Chimerism used for studies was on whole-cell populations. One emerging standard practice is analysis of MRD in BM, with proposed time points of 30, 60, 100, 150, 200, and 300 days and 12 and 18 months after HCT. Either cessation of immunosuppression or DLI is considered at MRD $\geq 10^{-4}$ or if chimerism is observed with >1% recipient.

CELLULAR AND IMMUNE THERAPIES FOR ALL

Currently, there are no leukemia-specific cellular therapy options broadly available, so cellular therapeutic options are limited to DLI, CIK cells, and natural killer cells. The group proposed that studies be developed based on MRD analysis in BM using the timing described above, plus chimerism performed in peripheral blood at weekly intervals until day 200 and monthly thereafter. An intervention with withdrawal of immune suppression and DLI or possibly another immune intervention would be based on either an MRD $\geq 10^{-4}$ or mixed chimerism of >1%.

There is a broadly held belief that ALL is not susceptible to the graft-versus-leukemia (GVL) effect, because DLI does not improve outcome in ALL. The ASCT0431/ONC051NCONC051 trial, "A Randomized Trial of Sirolimus-Based GVHD Prophylaxis after HSCT in Selected Patients with CR1 and CR2 ALL," demonstrated in a prospective, multicenter, phase III randomized trial that the GVL effect is important in preventing relapse after transplantation for pediatric ALL. Although sirolimus has potent antileukemic activity in ALL [22-24], the addition of this medication after transplantation did not decrease relapse, because it also decreased acute GVHD (aGVHD). The strongest association with decreased relapse in this trial was noted with any occurrence of aGVHD. In addition, a very significant risk was conferred by the presence of MRD before or after transplantation, and this risk was greatly increased in patients who did not experience aGVHD. However, patients who were MRD-positive before HCT were found to be at high risk for relapse when analyzed by the presence or absence of aGVHD; those with aGVHD had a relatively low risk of relapse, whereas those without aGVHD had a 3-fold increased relapse risk. Almost all relapses occurred by day +400 after HCT, but a relatively small number occurred within the first 50 to 200 days after HCT. This means that there is a small window of opportunity in the immediate post-HCT period for interventions aimed at preventing relapse. Especially good target populations for relapse intervention studies include MRD-positive patients pre-HCT who do not develop aGVHD by day +55 and any patient with any level of MRD noted after HCT [25]. A first step when giving an agent to prevent relapse is withdrawing or decreasing immune suppression. This by itself has been documented to salvage a percentage of patients and will be further explored in an upcoming COG trial. Possible agents to use in interventions for these patients after HCT include blinatumomab, moxetumomab, TLR9 agonists, and leukemia-specific chimeric antigen receptor (CAR)-armed T cells [26-29].

Blinatumomab is available in the clinical trial setting and is now being explored in much larger studies in children [26]. A total of 9 patients have been treated, including 1 in first relapse, 6 in second relapse, 1 in third relapse, and 1 in fourth relapse [30]. Blinatumomab induces a generalized inflammatory response with elevation of C-reactive protein. This is due to cytokine release, which may be mediated by IL-6 in some patients and may respond to IL-6–directed cytokine blockade [31]. Treatment commonly caused weight gain (6 of 9 patients) and AST/ALT elevation (9 of 9). Mild central nervous system toxicities (3 of 9; ataxia, tremor), and peripheral neuropathy has been observed. Major toxicities, such as seizures, were relatively infrequent (1 of 9). Management of toxicities include antipyretics (eg, metamizole, paracetamole), fluid support and pressors as needed for hypotension, and dexamethasone prophylaxis and treatment in the event of developing cytokine release syndrome. Of the 9 patients treated under compassionate use, 6 achieved complete remission. The long-term outcome with blinatumomab is unclear, but that it is effective for remission induction. It is probably effective in patients with frank relapse, but may have the highest efficacy in MRD-positive patients.

Another approach to controlling disease in ALL involves the use of CAR-armed T cells. In B cell malignancies, such as CLL [32,33] and now pediatric ALL [29], these genetically engineered T cells have shown signficant activity against relapsed/refractory disease. In addition, some early cases treated with CAR T cells have shown long persistence and disease control for up to 2.5 years. Studies with engineered T cells are being pursued in several instutions, with multi-institutional trials now in the planning stages. The role of CAR T cells in ALL and lymphoma will be further clarified in these trials, particularly in terms of whether cell therapy can act as a bridge to allogeneic HCT, or perhaps even a replacement for it.

WHICH ALL GROUPS SHOULD BE UNDERGO HCT?

There is a paucity of randomized clinical trials that have rigorously evaluated HCT versus intensive chemotherapy for ALL; however, some common practice patterns have emerged over the past few years. In de novo ALL, patients with high-risk cytogenetic abnormalities, including *BCR/ABL*, hypodiploid ALL, and *MLL* rearrangements are considered candidates for HCT in first clinical remission (CR1). However, with the recent results from the COG using TKIs versus HSCT in patients with Philadelphia chromosome–positive (Ph^+) ALL provide interesting insights into the role of HCT in this disease [34]. Updates from COG study AALL0031 revealed no significant differences ($P = .93$) in the estimates of EFS for patients with Ph^+ ALL enrolled on cohort 5 receiving imatinib (EFS, 84% ± 7%) versus patients who underwent MSD HCT (EFS, 77% ± 12%) versus those who received a MUD HCT (EFS, 83% ± 15%) [35]. This was not a randomized comparison, and an additional caveat is that the cohort who received HCT was small. More recently, a joint European/COG study (AALL1122/BMS CA180-372) is currently assessing outcomes in patients with Ph^+ ALL treated with dasatinib and the EsPhALL chemotherapy backbone; however, a slow response to induction and/or consolidation therapy are criteria for proceeding to allogeneic HCT in that study. Although the foregoing studies may call into question the role of HCT as

the primary treatment modality for patients with Ph^+ ALL, socioeconomic factors also also contribute to this decision making process, especially when considering concerns about compliance over years of therapy and the cost of prolonged TKI therapy versus the proven long-term success of HSCT as a curative treatment strategy for patients with Ph^+ ALL.

Similarly, other small molecules are currently being developed for other gene targets in ALL. Recently, cytogenetic abnormalities that involve genes signaling in the Ras/MAPK pathway have been identified in hypodiploid ALL and may be targets for novel therapies [36]. The discovery of mutations activating the Janus kinase (JAK) pathway in patients with high-risk ALL have raised the possibility that JAK inhibitors such as ruxolitinib may be useful in this subset of patients [37,38]. Importantly, a high rate of *TP53* mutations has been identified in patients with low hypodiploid ALL (32 to 39 chromosomes). Approximately 45% of these patients were subsequently found to have germline events, thus firmly establishing this subtype of childhood ALL within the Li-Fraumeni syndrome. Thus, the discovery of germline *TP53* mutations supports referral for assessment of genetic risk, to allow initiation of early monitoring for other cancers in the patient and family members. Nevertheless, until the safety and efficacy of novel targeted therapies are evaluated in vivo, it will remain common practice to proceed to allogeneic HCT in CR1 for these high-risk patients.

Older patients with *MLL* rearrangements have been reported to do less well with current conventional therapies. Thus, the general recommendation is to refer these patients for HCT while in CR1. However, recent data presented at the 2012 SIOP meeting suggest that patients with *MLL* rearrangements who respond rapidly to induction therapy may achieve durable responses with intensive BFM-style therapy. In particular, for the NCI-HR group, patients with *MLL* rearrangements without evidence of residual BM disease at day 29 using flow cytometric methods (MRD $<0.1\%$) had a 5-year EFS of 77.7% (SE 0.07).

Finally, slow response to induction therapy has been the single most important risk factor for relapse [39]. Many centers pursue HSCT early for patients with frank induction failure (day 29 BM with $>25\%$ lymphoblasts) after reinduction strategies. A recent report from the Ponte di Legno group published outcomes for patients with induction failure [40]. Out of a total of 44,017 patients, 1041 patients failed induction (2.4%). Of the 198 patients who underwent HCT, transplantation was beneficial for those with T cell ALL ($n = 71$) who were considered induction failures. However, this study suggested that HCT might not be beneficial for children with B-lineage ALL age <6 years at diagnosis and who do not have an *MLL* gene rearrangement, although the number of these children was relatively small ($n = 32$). Furthermore, the benefit of HSCT could not be confirmed in patients with *MLL* rearrangements, owing to the small number of patient. In summary, indications for HCT in CR1 appear to be evolving as upfront therapy intensifies or incorporates molecular targets. However, for many high-risk patients, HCT currently remains the only readily available and potentially curative treatment option. Thus, novel approaches focused on conditioning regimens, graft sources, and post-HSCT supportive care strategies should be considered as priorities for development to improve outcomes in high-risk patients with ALL.

HCT FOR HEMOGLOBINOPATHIES

The probability of survival with HLA-matched sibling transplants reported by the Pesaro group in more than 900 patients with thalassemia age <35 years is 73% [41]. Risk factors validated in pediatric patients and predictive of poor outcomes include irregular chelation, presence of hepatomegaly, and hepatic fibrosis. Considering these risk factors, 3 classes of risk have been identified with different outcomes: class I, in which none of these 3 risk factors is present, associated with disease-free survival (DFS) of 87% and treatment-related mortality (TRM) of 8%; class II, including children with 1 or 2 risk factors, associated with DFS of 84% and TRM of 14%; and class III, including children with all 3 risk factors, associated with DFS of 65% and TRM of 25% [41]. Outcomes of adults with thalassemia major undergoing HCT with a graft from an HLA-identical sibling are comparable to those of class III pediatric patients. The majority of TRM is toxicity-related (organ damage).

Bernardo et al. [42] recently reported results obtained using a treosulfan-based regimen for thalassemia. Their regimen, consisting of thiotepa, treosulfan, and fludarabine followed by 9-10/10 HLA-matched allogeneic HCT from either a related or an unrelated donor resulted in survival in the 80% range for all risk classes. Outcomes were comparable in related and unrelated donor HCT recipients. In view of these results, this preparative regimen merits further investigation. A French study of sickle cell disease evaluated patients who underwent HLA-identical sibling HCT or cord blood transplantation after a busulfan/cyclophosphamide preparative regimen [43]. The update of the original analysis was presented; a large proportion of patients also received rabbit ATG. The combination of cyclosporine and short-term methotrexate was used for GVHD prophylaxis. The 5-year OS was 95%. The addition of ATG significantly reduced the rejection rate, from 35% to 2%.

There is a high potential for international interaction for transplantation studies in hemoglobinopathies. In this regard, it is noteworthy that the Eurocord and EBMT have performed a joint retrospective study comparing the use of cord blood with HCT in patients with hemoglobinopathies. The CIBMTR has examined similar analyses in North America. In Europe, France, the United Kingdom, and Monte Carlo were funded for an International Observatory on Sickle Cell Disease grant from Monaco to establish a group of experts (leader, Eliane Gluckman). A recent evaluation of HCT performed in adults with sickle cell disease (SCD) in Europe based on the EBMT registry identified 35 adults with SCD who had undergone HCT, 10 of whom received an RIC regimen and 25 of whom received myeloablative conditioning, and found an OS of 81%. Opportunities for international studies in hemaglobinopathies include quality of life studies; comparative effectiveness research (HCT versus no HCT); randomized clinical trials evaluating treosulfan-based versus busulfan-based regimens; introduction of ATG to the conditioning regimen, tested in a randomized fashion; long-term outcomes for SCD/thalassemia; strategies to enhance survival of alternative donor recipients, such as mismatched donors, cord, and haploidentical donors; and evaluation of stable donor chimerism in patients with SCD/thalassemia [44,45].

HCT for treating hemoglobinopathies in North America has pursued similar strategies. MSD, umbilical cord blood, and BM transplantation after primarily busulfan-based myeloablative regimens have shown good outcomes. Reports from multicenter trials and the CIBMTR registry have shown good efficacy, with DFS of 79% to 90% in Pesaro low-risk and 62% in high-risk class III thalassemia [46,47]. The small number of actual transplantations despite no lack

of eligible patients is related to such limitations as lack of an MSD, organ toxicities (eg, hepatic sinusoidal obstruction syndrome, seizures, gonadal failure, growth inhibition in adolescent recipients), and worse outcomes/toxicities in vulnerable subgroups (eg, older patients, advanced disease, unrelated donors) [48-50]. Transplant trials focusing on these obstacles are moving forward. Although graft rejection is a risk owing to immune competency, nonablative immunosuppression (eg, alemtuzumab, low-dose TBI) before receipt of a mobilized PBSC graft from an MSD was found to support long-term mixed chimerism in 74% of adults with SCD when sirolimus was continued for tolerance induction. Successful engraftment (6 of 7) has been reported with MSD marrow after an RIC regimen of busulfan, fludarabine, ATG, and total lymphoid radiation [51,52]. RIC (with ATG, fludarabine, cyclophosphamide, and 2 Gy TBI) HLA-haploidentical HCT with cyclophosphamide-based GVHD prophylaxis resulted in engraftment in 57% of SCD recipients, including adults [53]. Based on successful RIC HCT with alemtuzumab, fludarabine, and melphalan in nonmalignant disorders (NCT00920972), a national unrelated trial is currently in progress for children with severe SCD (0601; the sickle cell unrelated donor transplant [SCURT] trial) but is restricted to BM because of graft rejection with cord blood as the stem cell source [54,55]. This trial is a cooperative effort of the National Marrow Donor Program, BMT CTN, Sickle Cell Disease Clinical Research Network, and PBMTC. Subsequently, a similar RIC trial (supported by the Thalassemia Clinical Research Network and PBMTC) for thalassemia-included hydroxyurea and thiotepa has completed enrollment with unrelated BM and cord (the URTH trial). RIC HCT aims to achieve stable full or mixed donor chimerism and is under evaluation for safety and success.

Cautious expansion of donor sources with formal protocols that explore reduced intensity and/or toxicity are justified in hemoglobinopathy. As the North American studies are concluded, there is a general consensus that international trials for both thalassemia and in particular SCD should be considered using a RIC approach with alternative donors. Areas of promise for cooperative international efforts include the following:

1. Comparing long-term outcomes and quality of life among various transplantation approaches to continue to improve on existing results
2. Defining acceptable levels of mixed chimerism with longitudinal follow-up studies
3. Defining the population of patients (particularly those with SCD) best served by early transplantation planning based on outcome analyses.

HCT IN METABOLIC DISEASES

During 3 decades of HCT for inborn errors of metabolism (IEM), important lessons have been learned about transplantation- and disease-specific factors that affect engrafted survival and long-term outcomes. Children with MPS IH (Hurler's disease) have benefited from many advances, including the development of worldwide guidelines for evaluation and treatment [56,57]. The importance of early diagnosis and prompt HCT, using cord blood as the cell source, for patients with excellent performance scores is clear [58]; outcomes are worse in symptomatic patients (usually associated with poor performance scores) [59]. Efforts aimed at early diagnosis and treatment have had favorable affects in all children with IEM. This should be the focus in the future as well. Developments in newborn screening and therapy will facilitate early diagnosis and direct greater attention to genotype/phenotype correlation.

The rare nature of these disorders necessitates a worldwide network for a collaborative international, multicenter, and interdisciplinary research approach. This is of utmost importance given the development of new treatment modalities, including gene therapy and combined HCT and enzyme replacement therapy. Especially for these rare diseases, data collection and registration need to be homogenized between the EBMT and CIBMTR registries, to facilitate comparison of outcomes and reasonable discussions. Furthermore, collaborative longitudinal studies can provide a better understanding not only of survival, but also of functional ability and quality of life after HCT for patients with IEM.

The conclusions can be summarized as follows:

1. The rare nature of these disorders necessitates a worldwide network for collaborative international, multicenter, and interdisciplinary research.
2. Clear treatment guidelines should be developed for patients identified in newborn screening programs.
3. Efforts should be undertaken to homogenize data collection, especially regarding long-term functional outcomes. Currently, standard registries are used for reporting data, but a critical review is needed to homogenize the endpoints in the EBMT and CIBMTR registries.
4. Joint meetings (once every 2 or 4 years) of the EBMT IEWP and Working Committee of the CIBMTR will be important to further homogenization of HCT practices and follow-up.

CHALLENGES FOR INTERNATIONAL GVHD STUDIES

GVHD remains a leading cause of morbidity and mortality for children who undergo allogeneic HCT, with the ongoing critical need for more effective preventive and treatment strategies. Although clinical characteristics, such as donor type and donor–recipient HLA mismatch, predict an elevated risk of GVHD, there are currently no diagnostic tests that can reliably predict occurrence, severity, or response to therapy. Recent compelling results from single-center studies suggest that biomarkers (protein, DNA, RNA, and cellular) can be identified to stratify patients into discrete risk groups for outcomes and overall mortality; however, these relatively small studies generally lack the necessary statistical power or validation to allow the incorporation of their results into practice. A future focus of GVHD research will be on developing biomarker-based strategies that allow for individualized treatment assignments based on the likelihood of GVHD or response to therapy [60].

One key factor in the success of biomarker studies is the quality of clinical outcomes data linked to the specimens being analyzed. Most international clinical registries include mostly GVHD data limited to the presence of aGVHD and cGVHD and maximum grade of aGVHD. Information such as date of onset, date of response or resolution, and management strategies is scarce or absent in these registries. Moreover, existing GVHD staging and grading definitions often lack clarity and reproducibility. For example, a patient with gastrointestinal GVHD experiencing occasionally bloody, low-volume diarrhea may be categorized as GVHD stage 0 (absent) or stage 4 (life-threatening) on different days in the same week with no significant change in treatment or

condition. Deaths are inconsistently categorized as related to GVHD, infection, or multiorgan system failure, leading to misunderstanding of the specific barriers to success in various scenarios. Another major barrier is that data at the onset of symptoms and after initiation of treatment lack sufficient detail and consistency to enable comparison of results among different centers. All of these data-related problems impair the integration of laboratory values into overall schema that can predict clinical outcomes.

To maximize the benefit of potential GVHD biomarkers, it will be necessary to standardize data collection strategies internationally to make granular GVHD data available. Furthermore, expert consensus panels need to adjudicate "gray areas" to develop consistent definitions for the complex clinical scenarios not envisioned when the current GVHD staging and grading system was initially proposed nearly 20 years ago [61]. It is anticipated that these expert panels will function best when the data are reviewed in near real time, when memories are fresh and feedback to centers supplying the data can be given. Although effort-intensive, a strategy of this nature will speed the adoption of harmonized data strategies across the many centers worldwide that perform pediatric allogeneic HCT.

EBMTG/IBFM GVHD TRIALS (IN STEROID-REFRACTORY GVHD)

In addition to causing direct target organ toxicity, GVHD and its treatments are associated with infections and long-term side effects. In children with hematologic malignancies, GVHD may be beneficial to some extent because of its associated (albeit limited) GVL effect. However, the immunosuppressive treatment required to control GVHD may interfere with or preclude potential post-transplantation immunotherapeutic interventions. Prevention and rapid recognition and control are important goals in the management of GVHD. Systemic treatment with high-dose steroids is very effective and remains the first-choice treatment; however, approximately half of patients experience steroid refractoriness or dependency. Evidence of the efficacy of second-line treatment modalities is limited, and studies are often hampered by small numbers of patients and single-arm study designs [62].

Along with immunosuppressive and modulatory drugs, the potential of 2 novel therapies, extracorporeal photopheresis (ECP) and in vitro expanded mesenchymal stromal cells (MSCs), has been reported in some recent studies. Clinical outcomes with ECP in children with aGVHD have been evaluated in 7 single-arm studies with a total of 155 patients. The response rate (CR/partial response [PR]) was 74%, with steroid reduction in responding patients. OS was 57%, and was significantly higher in ECP responders compared with nonresponders [63]. Predictive clinical/biological markers for response to treatment have not yet been identified.

Following the initial study reported by le Blanc et al. [64] on behalf of the EBMT Developmental Committee, clinical experience with MSC treatment in children with steroid-refractory GVHD has been evaluated in several single-arm studies with a total of 61 patients. Three additional studies are now closed, with reports expected soon. The response rate (CR/PR) in the published studies is 82% [65]. So far, there is no evidence of increased rates of relapse or infection, ectopic tissue formation, or MSC transformation. Similar to the experience with ECP, there is currently a lack of data on reliable predictive clinical/biological parameters for MSC-treated patients. Overall, both ECP and MSC treatment appear to be feasible and safe therapeutic modalities in children, with promising efficacy in steroid-resistant aGVHD. Several registered ECP and MSC therapeutic trials are currently recruiting, including a randomized ECP trial. Randomized trials of MSC treatment of steroid-refractory GVHD in both children and adults are underway.

Randomized controlled trials, preferably multicenter and multinational, to evaluate the therapeutic efficacy of ECP, MSC, and pharmacologic agents as second-line treatment modalities in steroid-refractory GVHD are clearly needed. Biological monitoring is pivotal in these studies and should involve evaluation of both soluble and cellular biomarkers, as well as histological analysis of GVHD-affected tissues [66].

CHRONIC GVHD BIOMARKER TRIALS

Various adult studies have demonstrated a predominance of B cell activation markers and autoantibody production as markers for cGVHD [67-69]. Pediatric cGVHD biomarkers were first studied on a multicenter basis in the COG ASCT0031 trial. That study reported 6 biomarkers that were identified in the smaller multicenter study, including the cellular markers CpG ODN-responding/TLR9-expressing B cells (with cGVHD) and INF-γ $CD4^+$ T cells (tolerance), as well as plasma biomarkers, including sBAFF, anti-dsDNA antibody, sIL-2Rα, and sCD13 [70,71]. A combination of these 4 plasma-based biomarkers resulted in an overall diagnostic sensitivity of 84% when 1 or more of the 4 markers were positive and 56% when 2 or more of the 4 markers were positive. The specificity was 100% when 1 or no biomarkers was positive, and the positive predictive value was 100% when 2 or more of the 4 biomarkers were positive. Future studies are needed to validate biomarkers for their ability to diagnose cGVHD; to evaluate the ability of biomarkers to predict therapeutic response, allowing for development of a risk and therapy assignment strategy; and to evaluate the ability of biomarkers to predict later onset of cGVHD. Current studies in Canada of 250 adults are aiming to validate the pediatric-based biomarkers in adults with patients from the CBMTG 0601 and 0801 clinical trials and from Stephanie Lee's U01-funded trial. These studies are evaluating these biomarkers for their ability to diagnose cGVHD and to predict therapeutic response, with the goal of developomg risk and therapy assignment strategies. Discovery-based assays (proteomics and microarrays) are being performed to identify new biomarkers that can be used to diagnose or classify the risk of cGVHD. A new pediatric cGVHD biomarker study, Applied Biomarkers in Long-Term Effects of Children and Adolescents treated for Cancer (ABLE), is being opened in Canada by the PBMTC. This study will enroll 300 pediatric allo-HSCT recipients prospectively over the next 3 years.

The conclusions can be summarized as follows:

1. There was general consensus that standardized approaches for the collection of samples and the type of clinical data collected need to be standardized to allow for future studies and sharing among biorepositories.
2. A working group should be formed to further develop these approaches. There will be a expert consensus meeting aimed at promulgating standards in pediatric ECP on behalf of the EBMT's Pediatric Disease Working Party.
3. To enhance pediatric data, a questionnaire on centers' strategy for pediatric ECP will be circulated upfront, and some US centers will join in.

CONCLUSION

The Westhafen Intercontinental Group has concluded that international studies are essential to further the practice of pediatric HCT owing to the complexity, diversity, and rarity of pediatric disorders treated by HCT worldwide. An initial step of merging the activities of the largest cooperative groups, including the PBMTC, EBMTG Pediatric Working Group, iBFM SCT Group, and the COG HSCT Strategy Group, is critical. Such a consortium will allow for database-driven studies using the EBMT and CIBMTR registries, as well as the implementation of international trials focused on rare diseases that can be addressed only by larger international consortia. This international pediatric HCT group formed at the meeting in Frankfurt chose a name, the Westhafen Intercontinental Group, reflective of that city and the importance of multinational collaboration.

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