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SUPPLEMENT ARTICLE

# Allogeneic Hematopoietic Cell Transplantation for Chronic Granulomatous Disease: Controversies and State of the Art

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Chronic granulomatous disease (CGD) is a congenital disorder characterized by recurrent life-threatening bacterial and fungal infections and development of severe inflammation secondary to a congenital defect in 1 of the 5 phagocyte oxidase (*phox*) subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Hematopoietic cell transplant (HCT) is a curative treatment for patients with CGD that provides donor neutrophils with functional NADPH and superoxide anion production. Many characteristics of CGD, including preexisting infection and inflammation and the potential for cure with mixed-donor chimerism, influence the transplant approach and patient outcome. Because of the dangers of short-term death, graft-versus-host disease, and late effects from chemotherapy, HCT historically has been reserved for patients with high-risk disease and a matched donor. However, as advances in CGD and HCT treatments have evolved, recommendations on transplant eligibility also must be amended, but the development of modern guidelines has proven difficult. In this review, we provide an overview of HCT in patients with CGD, including the debate over HCT indications in them, the unique aspects of CGD that can complicate HCT, and a summary of transplant outcomes.

**Keywords.** chronic granulomatous disease; hematopoietic cell transplant.

Chronic granulomatous disease (CGD) is a life-threatening primary immunodeficiency caused by mutations in genes that encode proteins that are critical components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex. Mutations in these genes lead to crippling of neutrophil-killing mechanisms that depend on NADPH oxidase activity. Because of the severe defects in neutrophil function, patients with CGD are at high risk for life-threatening infections with organisms such as *Staphylococcus aureus* and *Aspergillus fumigatus*. Patients also can suffer from a variety of inflammatory complications.

Because of the life-threatening nature of CGD, allogeneic hematopoietic cell transplantation (HCT) is a curative option for many patients; however, HCT is a high-risk procedure and is associated with significant risks for morbidity and death. Deaths that occur after transplant in many patients with CGD (and other primary immunodeficiencies) are related most often to complications of graft-versus-host disease (GVHD) or infection. These risks can be mitigated, however, because transplant outcomes are influenced greatly by the type of pretransplant conditioning, the HLA match, patient age, and the overall clinical condition of the patient.

## CHARACTERISTICS AND RISKS OF HCT CONDITIONING REGIMENS

With regard to the risks conveyed by the conditioning regimen, more intensive fully myeloablative conditioning (MAC) regimens are associated with higher acute toxicities, such as pulmonary hemorrhage and hepatic veno-occlusive disease. An example of a fully MAC regimen would be full-dose (16 mg/kg) or high area under the curve (AUC)–targeted busulfan with cyclophosphamide and anti-thymocyte globulin (ATG). On the other end of the conditioning-intensity spectrum are nonmyeloablative regimens, which can consist of serotherapy or serotherapy coupled with "milder" chemotherapeutic agents such as fludarabine or cyclophosphamide. The effect on marrow function by a nonmyeloablative approach is mild and not irreversible, and toxicities are rare, but the ability to achieve sustained engraftment is extremely limited and therefore is rarely used in HCT for the treatment of CGD.

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In between these 2 extremes lie reduced-intensity conditioning (RIC) and reduced-toxicity conditioning (RTC) regimens. RIC regimens can be thought of as those that are neither myeloablative nor nonmyeloablative and have various degrees of myelosuppression [1]. An example of an RIC regimen used in patients with CGD is alemtuzumab (or ATG), fludarabine, and melphalan.

RTC is a term that we prefer to use for regimens that include the use of alkylating agents that have been reduced in dose or targeted AUC or are inherently associated with lower toxicity profiles and are combined with nucleoside analogs (such as fludarabine) rather than additional alkylating agents or radiation yet are most often myeloablative in nature [2]. Thus, RTC can be thought of as a subcategory of either MAC or RIC. In the reduced-toxicity category, we include 2 regimens that have been used in many patients with CGD, treosulfan and fludarabine (with or without alemtuzumab or ATG) and busulfan and fludarabine (with alemtuzumab or ATG).

RIC and RTC regimens are generally associated with less toxicity than are MAC regimens. These regimens are often associated also with lower rates of acute GVHD but increased rates of infection, and both of these effects are influenced by the serotherapy (alemtuzumab or ATG) that is usually included in these approaches. It should be noted that RIC regimens can be complicated by high rates of mixed donor and recipient chimerism and increased rates of graft loss. "Mixed chimera" is the term used to describe patients who have blood cells that are derived from both the patient and the donor. This situation is acceptable for many patients with a primary immunodeficiency, because 100% correction of any immune defect usually is not needed. However, a decrease of donor-derived cells below somewhat ill-defined thresholds (generally estimated to be near 20%) results in a risk of disease relapse; the patient ultimately might require a second transplant. The high incidence of mixed chimerism and possibility of low myeloid donor chimerism that can be associated with RIC regimens potentially makes them a less attractive option than RTC regimens for patients with CGD.

## HUMAN LEUKOCYTE ANTIGEN MATCH AND OTHER PATIENT-SPECIFIC CHARACTERISTICS

Another factor that affects patient outcomes after allogeneic HCT is the human leukocyte antigen (HLA) match between the patient and donor. The HLA match greatly influences the risk of GVHD and ultimate survival. Over time, advances in HLA-typing techniques have led to better outcomes because patients can be better matched with potential donors. In the current era, patients who receive a graft from an HLA-matched unrelated donor (MUD) can be expected to do nearly as well as those who receive a graft from an HLA-matched related donor (MRD). The source of the graft also can affect transplant success, and the options for graft source include bone marrow, peripheral blood stem cells, and cord blood. A variety of graft-manipulation techniques also can affect outcomes by altering risks for GVHD and infection, but that subject is beyond the scope of this review.

Patient-specific factors also affect transplant outcomes. For patients with CGD, increasing age and the accumulation of preexisting infection, inflammation, and organ compromise can have key detrimental effects, and special considerations sometimes are required for these patients. Thus, the decision of whether a patient with CGD should undergo a transplant is not always straightforward. Controversy regarding the indications for transplantation in patients with CGD still lingers and relates to the long-standing difficulty of weighing the risks and benefits.

## CONUNDRUM OF USING CONVENTIONAL THERAPY OR HCT FOR PATIENTS WITH CGD

Although allogeneic HCT is an established curative treatment for CGD with reasonably widespread availability, HCT is not performed for all patients with CGD. Concerns are related mostly to unnecessary risk of death in patients with relatively "mild disease" and higher risks of complications in patients with underlying organ dysfunction and preexisting inflammation that can lead to an added danger of conditioning regimen toxicity and GVHD [3]. Because of these concerns, some clinicians have attempted to identify patients with CGD who would most benefit from HCT and to not recommend transplant for patients with so-called mild CGD. Several aspects of CGD that make the task of outlining HCT indications very difficult have emerged. First, it is challenging to predict the future outcome of patients diagnosed with CGD given continuously improving treatment modalities [4]. Conventional therapy aimed at preventing infection includes antibacterial prophylaxis, antifungal prophylaxis, and interferon γ therapy (see Slack M et al, this supplement). These interventions have led to significant improvements in survival for this disease once considered lethal. A recent review of patients who have not undergone a transplant and are followed by the National Institutes of Health found decreased risks of death over time with a median age of death in their cohort before 1991 of 15.53 years and improvement to 28.12 years by 2012 [5]. Longer survival time is attributed also to the earlier recognition and diagnosis of CGD, better management of autoinflammatory and autoimmune disease with immunosuppressive agents, and also the increased use of HCT for patients at high risk.

Similar to conventional therapy outcomes, mortality rates of patients with CGD who have undergone HCT have decreased also [6]. High-resolution molecular HLA typing has improved unrelated outcomes across a spectrum of diseases, and advances in umbilical cord and haploidentical donor transplantation have expanded the donor pool so that HCT candidacy is no longer considered limited by the availability of a matched donor. RIC/RTC regimens have lessened organ damage in comparison to MAC, which expanded the use of allogeneic HCT in sicker

patients with CGD and reduced long-term effects, including preserving fertility in some transplant recipients. Further advances in the field are expected to continue to reduce transplant-related morbidity and death and further compel patients and physicians to consider HCT a reasonable treatment option.

Given these medical advancements, it is now expected that most patients with CGD will survive into adulthood with or without a transplant. As a growing population of adult patients with CGD develops, a better understanding of long-term morbidity related to chronic infections and inflammation in patients who have not undergone a transplant has surfaced. A recent French study detailed common complaints in adult patients with CGD who have not undergone a transplant, including growth failure, chronic dyspnea (23.5% after the age of 30 years), chronic digestive complications (eg, inflammatory enteritis/colitis), and poor educational achievement (only half of the patients were attending high school at the age of 16 years) [7]. A second study focused on the pulmonary manifestations of adult patients with CGD, and only 25% of them had normal pulmonary function testing results; 58% and 17% were found to have a restrictive or obstructive physiology, respectively [8]. Lifelong use of antimicrobial agents also can result in medical problems (see Slack M et al, this supplement; see also references 8–12). Still, how much these present and future health and quality-of-life concerns should be weighed in developing a transplant-decision algorithm is uncertain, because most published HCT indications have been focused primarily on factors known to affect the risk of death.

As the number of chronically ill adult patients with CGD continues to expand, another consideration in developing criteria for transplant candidacy is whether traditional pediatric CGD HCT criteria should be applied equally to older patients. Physicians historically have been hesitant to offer a transplant to patients with organ dysfunction, which is a common finding in adults with CGD. HCT outcome data for guiding decision making for adults with CGD are limited, but a recent HCT trial using a reduced-toxicity busulfan-fludarabine-serotherapy approach in patients at high risk resulted in excellent outcomes in adults (survival in 12 of the 13 adult patients) [13]. Although it is uncertain if chronic organ damage in adults with CGD can be reversed by HCT, the authors of this study documented improvement in pulmonary functioning after transplant in adults, and 2 male patients went on to father children.

In attempts to provide better clarity for developing pediatric and adult criteria for HCT, a comparison of the effects of HCT versus those of conventional treatment on survival, quality-of-life measures, and overall cognition from the UK CGD registry was reported in a series of publications [14–16]. The first study involved a cohort of 62 patients with CGD aged 16 years or less; 30 (48%) patients had undergone HCT, and 32 (52%) had not [14]. These 2 groups of patients had similar overall survival rates (90%) at 15 years of age or after their transplant [14]. However, children in the transplant group experienced significantly fewer episodes of infection/admission/surgery per year (0.15 events per transplant-year [95% confidence interval, 0.09–0.21 events per transplant-year]) than those in the nontransplant group (0.71 events per CGD-life-year [95% confidence interval, 0.69–0.75 events per CGD-life-year]). Patients in the nontransplant group also had significantly lower *z* scores for height and body mass index than those in the transplant group. A second study from the UK cohort compared health-related quality of life and emotional well-being of patients who had and of those who had not had undergone HCT and found that quality-of-life and emotional-difficulty assessments from parent and self-reports were significantly worse for children who had not undergone a transplant than healthy norms, but the scores of children who had undergone a transplant were not significantly different that those of healthy norms [16]. In contrast, a third cognition study did not identify a difference in intelligence quotients (IQs) between the treatment groups, and the mean IQs for both groups were within the normal range [15].

Overall, these data seem to indicate improved outcomes with HCT, but inherent issues with these types of analyses that hinder us from forming sound conclusions exist. First, HCT historically has been performed on the most severely affected patients, which leaves a biased population of healthier patients in the cohort of patients who had not undergone a transplant. Second, most deaths of patients after a HCT occur within the first 2 years after transplant, and longer-term follow-up would be expected to cause a divergence of mortality curves once pediatric patients reach adulthood. Last, these smaller studies were limited geographically and therefore exclude variances in medical care access and types of treatment in other regions that might affect mortality rates in both treatment groups [17].

A final consideration in developing HCT inclusion criteria is that HCT outcomes are improved when patients can be identified before disease progression produces organ damage. The addition to or even replacement of clinical-severity criteria with prognostic biomarkers would potentially abrogate sick children with CGD undergoing a transplant. It has long been recognized that genotype has typically correlated with outcome because patients with *gp91$^{phox}$* (X-linked) mutations result in inferior survival compared to those with autosomal recessive mutations. However, a study by Kuhns et al [18] found that survival was independently associated with residual reactive oxygen intermediate production and that the remaining oxidase activity correlated with the type of mutation in NADPH oxidase genes. A study in 89 Turkish patients with CGD found similar results; survival probabilities were 0.93 in the oxidase-residual population and 0.38 in the oxidase-null population [19]. Although prospective studies of residual oxidase activity and CGD are lacking, these 2 studies identified the most promising biomarker to date that correlates with disease outcomes.

It is clear that the challenge of developing HCT criteria for patients with CGD is controversial, but it is immensely important

to create standard recommendations to guide treatment decisions. Wide variability in published indications for transplant in patients with CGD currently exists. On one extreme, given the apparently better outcomes with HCT over those with conventional therapy, some authors have recommended a transplant to all patients if a matched donor can be identified [20]. A more commonplace recommendation is that patients with X-linked or autosomal recessive CGD should be offered a transplant if a matched donor is identified and if no residual oxidase activity is noted or if severe disease complications develop [4, 21]. The European Society for Immunodeficiencies (ESID) and the European Blood and Marrow Transplantation (EBMT) current indications for HCT in patients with CGD includes patients with a matched donor or mismatched unrelated donor plus 1 clinical or social complication [22]. The ESID/EBMT defines transplant-eligible complications as (1) nonavailability of a medical care specialist, (2) noncompliance with prophylactic medications, (3) 1 or more life-threatening infections, (4) severe granulomatous disease with progressive organ dysfunction, (5) steroid-dependent granulomatous disease, (6) therapy-refractory infection, or (7) emergence of premalignant or myelodysplastic clones after gene therapy. Although more specific than most recommendations, these criteria remain purposefully vague to avoid overly strict guidelines. However, given that severe infection is found in 97% of patients surveyed by National Institutes of Health [5] and progressive organ dysfunction is very common in adult patients [14], most if not all patients with CGD will eventually meet ESID/EBMT HCT criteria.

The good news is that the current challenges and arguments in the development of HCT criteria for patients with CGD have occurred, in part, as a result of better survival in conventionally treated patients and those who have undergone a transplant. Although accumulating data suggest a benefit of HCT in preventing long-term morbidity, the prospect of subjecting a patient to a procedure with a notable risk of death over the first 2 posttransplant years should not be overlooked. Also, there certainly are some patients with mild CGD in whom the risk of HCT likely outweighs the benefits gained. Much more research in this area is necessary before exact recommendations on HCT candidacy can be made. Such research will need to include study on long-term treatment outcomes, manifestations of disease and outcomes of HCT in adults with CGD, and prospective validation of residual oxidase activity as a predictive biomarker.

## DONOR SELECTION FOR HCT RECIPIENTS

For children with CGD who undergo HCT, the donor preference should be a matched sibling donor, and if not an option, a MUD. Beyond that, the use of a mismatched unrelated donor, haploidentical donor, or umbilical cord blood donor depends on center expertise and open clinical trials. In the haploidentical-donor setting, a maternal donor is recommended for patients with autosomal recessive CGD, because maternal grafts in HCT in general have been associated with less GVHD than paternal grafts [23]. However, in the more common X-linked CGD in boys, one should be cautious with the use of a female related donor who might well be a carrier of the disease. Secondary to lyonization (random inactivation of the X chromosome), female carriers of X-linked CGD have a mixed population of neutrophils, 1 population with normal NADPH activity and 1 population with a CGD phenotype. Thus, one should preferentially use a paternal donor in the haploidentical setting or, at a minimum, confirm when possible that a non–X-linked CGD carrier female donor is being used to avoid reduction in the number of functioning neutrophils derived from the graft. However, if no other matched donor is available other than a carrier sibling, the desire to avoid donor graft neutrophil lyonization should be heavily weighed against the increased risks of GVHD associated with the use of alternative donors.

## CHALLENGES OF PERFORMING A TRANSPLANT IN PATIENTS WITH ACTIVE INFECTION AND/OR AUTOIMMUNITY OR INFLAMMATION

In patients with CGD, reduction of infection and active autoimmunity or inflammation before transplantation is ideal, but often, complete resolution is impossible to attain. Transplantation outcomes are better before infectious and inflammatory damage accumulates. For example, patients who develop severe granulomatous disease of the lung can develop pulmonary restrictive disease. The most common inflammatory disease in patients with CGD is inflammatory bowel disease, which affects almost 20% of these patients [24]. Some patients have a preexisting complication from this disease (eg, gastrointestinal fistula) that makes the decision regarding timing of an HCT difficult. Delaying an HCT offers additional time for fistula treatment, but a delay also offers an unfortunate opportunity for further complications. The challenge is to time the HCT before irreversible organ dysfunction. Autoimmune diseases, including immunoglobulin A nephropathy, antiphospholipid syndrome, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and juvenile idiopathic arthritis, can provide another challenge to successful HCT in patients with CGD [20].

Patients who have ongoing infection that cannot be resolved should be considered for an RIC or RTC regimen. Common sites of infection include the lung, liver, and skin. RIC and RTC regimens enable transplantation during ongoing infection and result in potentially fewer infection-related deaths. One should try also to avoid granulocyte transfusions of leukocytes from unrelated donors before transplantation, because it can cause the development of HLA alloimmunization and increase the rate of rejection. However, granulocyte transfusions might be helpful during the transplantation period for those with active infection and do not seem to affect engraftment [25].

Additional considerations for patients with X-linked CGD include the possibility for McLeod phenotype, a disorder secondary to deletion of the *XK* gene that results in absent production of the XK protein [26]. The XK protein is essential for Kell antigen presentation on red cells, and patients with McLeod phenotype have a Kell-negative red cell phenotype. McLeod phenotype is found in some patients with X-linked CGD from a contiguous gene deletion of *XK* and the neighboring *CYBB* gene that encodes $gp91^{phox}$ [27]. Patients with McLeod phenotype can have red cell antigen sensitization from previous Kell and XK-positive red cell transfusions and require special attention when an HCT is planned for them. Such considerations include pretreatment with rituximab to reduce anti-Kell and anti-Kx (an antigen on the XK protein) immunoglobulin production, conditioning with an MAC regimen with immune ablation to prevent persistent posttransplant recipient anti-Kell and anti-Kx B and T cells, red cell reduction for Kell/Kx-positive stem cell products, and planned availability of Kell/Kx-negative (McLeod phenotype) blood to support the patient until donor hematopoiesis is established [28].

Because CGD is a nonmalignant disorder, we also prefer to schedule the transplant to be performed in a summer month when possible to avoid the risk of influenza and other respiratory viruses and to allow well patients to finish their school year before the HCT, which can greatly improve their quality of life.

## IMPORTANCE OF MYELOID CHIMERISM FOR CURE

The question of how many donor myeloid cells and, alternatively, how few recipient myeloid cells are necessary to cure CGD has not yet been answered satisfactorily. Marciano et al [29] evaluated 162 female carriers of X-linked CGD. Although this clinical scenario is not the same as recovery from HCT, in some aspects, X-linked carriers with lyonization have similarities to posttransplant patients with mixed-donor chimerism in the myeloid lineage (with 1 population of CGD neutrophils and 1 population of normal neutrophils). In these X-linked carriers, females with less than 20% dihydrorhodamine (DHR)-positive neutrophils had a significantly increased infection risk. Autoimmune/inflammatory manifestations, however, did not depend on the percentage of DHR-positive neutrophils, which implies that the mere presence of CGD neutrophils can result in abnormal immune reactions. These data suggest that patients with low donor myeloid chimerism (<20%) might be at continued risk of infection and that the continued presence of recipient CGD neutrophils can impart a lifelong risk of inflammation. In a study that specifically examined posttransplant chimerism in patients with CGD, Parta et al [30] found statistical significance for improved outcomes with increased donor myeloid and NK cell chimerism but not with CD3 cell chimerism. Additional research in this area is needed to determine whether mixed chimerism is associated with the risk of persistence, or de novo development, of inflammatory and autoimmune manifestations and whether it is sufficient to attain full correction of the disease phenotype. Such data are being collected in Primary Immune Deficiency Treatment Consortium (PIDTC) Protocol 6903, in which the baseline incidence of autoimmune/inflammatory complications is being recorded and compared with the posttransplantation incidence. These outcomes will be used to develop hypotheses regarding the relation of myeloid and/or $CD3^+$ donor chimerism to autoimmune/inflammatory events for patients with CGD, and the best approach to transplantation, to be addressed in future prospective clinical studies.

## CURRENT PROGRESS IN HCT FOR PATIENTS WITH CGD

Given the rarity of CGD, HCT outcome data typically span years to decades of patient treatment. However, as data have amassed over time, we are gaining a better understanding of the effects of conditioning intensity and, to some extent, the type of donor in patient survival. The initial attempts at HCT in patients with CGD primarily included MAC regimens, given the lack of experience with RIC and RTC regimens. However, data on modern RIC and RTC regimens in patients with CGD have been accrued, and these data have indicated that these regimens result in survival rates similar to and short- and long-term toxicities less than those with MAC regimens. The success of RTC regimens has led some transplant physicians to consider RTC preferable for modern transplant recipients with CGD who have a matched bone marrow donor. For umbilical cord transplants and those with a haploidentical donor, which present greater risk of graft rejection, MAC still remains the preferred regimen. However, well-designed head-to-head trials in which MAC is compared with RTC or RIC have not been developed, leaving the question of what the most appropriate conditioning intensity is unanswered.

## EXPERIENCE WITH MAC HCT

MRD HCT from an unaffected person is considered the gold standard for transplants for a variety of disorders. Seger et al [31] reported historical outcomes of HCT in patients with CGD from European centers spanning a period if 1985 to 2000. Twenty-seven patients, predominantly with X-linked CGD, underwent a transplant with mostly MRDs (n = 25). Two patients received a graft from an MUD. Bone marrow was the predominant graft source. The majority of the patients underwent busulfan-based MAC (n = 23). Four patients with a poor performance status underwent RIC. Nine patients had active treatment-refractory infection at the time of their transplant, 7 of whom received additional supportive care in the form of granulocyte transfusions during the period of posttransplant aplasia. All evaluable patients who underwent an MAC regimen engrafted and maintained full donor chimerism (n = 22), whereas only 2 of 4 patients

who underwent RIC had engraftment with full donor chimerism. Severe acute GVHD, grades III to IV, developed in 4 patients, all of whom had either a preexisting overt infection or acute inflammation. At a median follow-up of 2 years, the overall survival rate was 85%, and the event-free survival rate was 81%. In patients without a preexisting infection at the time of transplant (n = 18), the survival rate was 100%. All patients with full donor engraftment were noted to have resolution of previous infections and inflammatory disorders, such as colitis and pulmonary granulomas. Catch-up growth was observed in 2 patients.

For patients who lack an MRD, HCT from a MUD is increasingly being used for patients with a variety of disorders. Soncini et al [6] described outcomes of a severe CGD cohort of 20 patients, 10 of whom underwent a transplant from an unrelated donor. Unrelated donors for 2 of the patients were mismatched at 1 allele. All except for 1 of the patients had X-linked CGD. Myeloablative busulfan-based conditioning, with addition of alemtuzumab for donors other than matched siblings, was used for the majority of patients. Granulocyte transfusions were used for 3 patients. In this cohort, excellent outcomes (90% event-free survival rate), similar to those described with an MRD, were noted. The incidence of severe acute GVHD was low (~10%) despite the use of an unrelated donor for half of the patients. Similar to a previous report [31], resolution of infections and inflammation in the surviving patients and significant improvement in growth in patients who had growth failure before their transplant were noted. Both patients who died had previous invasive fungal infections. Similar survival outcomes were reported by several other groups that used MRD and MUD bone marrow transplantation, including Martinez et al (Texas Children's Hospital) [32], Schuetz et al (University Hospital Ulm) [33], and Tewari et al (Duke University) [34] (Table 1).

Several lessons can be learned from those studies. An MAC transplantation scheme with a busulfan-based regimen and using HLA-matched bone marrow donors is very effective in curing patients with CGD and thus providing them with an alternative to conventional therapy. Significant infections, inflammatory complications, and end-organ damage at the time of transplant were observed to be associated with a higher risk of posttransplant complications, including severe acute GVHD and death, which suggests that patients with an available matched donor should undergo transplantation earlier in the course of their disease. Transplantation in patients with an active infection patients with an active infection is feasible with aggressive supportive care, although risks are significantly higher with a myeloablative regimen. RIC/RTC regimens are desirable because of their potential to decrease treatment-related toxicity, especially for patients with an active infection and poor performance status at the time of transplant. However, graft rejection is an important challenge with this approach that has been addressed in more recent studies [13, 30, 35].

## EXPERIENCE WITH NONMYELOABLATIVE, RIC, AND RTC HCT

Earlier nonmyeloablative transplantation regimens were associated with an increased incidence of graft failure [36]. A more recent RIC regimen that consisted of alemtuzumab, fludarabine, and melphalan has often been used successfully in patients with a primary immunodeficiency such as hemophagocytic lymphohistiocytosis [38]. However, RIC data on patients with CGD are limited and these regimens seem to lead to suboptimal engraftment for this disease [37].

On the basis of 2 recently published studies, RTC seems to be a better alternative for patients with CGD. A multicenter study by Güngor et al [13] of RTC in patients with CGD resulted in

**Table 1. Summary of Published HCT Outcomes in Patients With CGD Based on Intensity of Conditioning Therapy**

| Reference | Year | N | Age (Median [Years]) | X Linked (%) | Regimen | Donor Type | OS Rate(%) | EFS Rate(%) | F/U Duration (Median [Years]) |
|---|---|---|---|---|---|---|---|---|---|
| Myeloablative regimen studies | | | | | | | | | |
| Seger et al [31] | 2002 | 27 | 8 | 85 | Bu/Cy/ATG | MRD | 85 | 81 | 2 |
| Soncini et al [6] | 2009 | 20 | 6.25 | 95 | Bu/Cy/ alemtuzumab | MRD/MUD | 90 | 90 | 5 |
| Schuetz et al [33] | 2009 | 12 | 8.5 | 92 | Bu/Cy/ATG | MRD/MUD | 75 | 75 | 4.4 |
| Martinez et al [32] | 2012 | 11 | 3.8 | 82 | Bu/Cy/ alemtuzumab | MRD/MUD | 100 | 100 | 4 |
| Tewari et al [34] | 2012 | 12 | 5 | 67 | Bu/Cy/ATG | MRD/UCB | 100 | 100 | 5.8 |
| RTC regimen studies | | | | | | | | | |
| Güngor et al [13] | 2013 | 56 | 12.7 | 61 | Bu/Flu/ serotherapy | MRD/MUD | 93 | 89 | 1.75 |
| Morillo-Gutierrez et al [35] | 2016 | 70 | 8.9 | 80 | Treo/Flu ± thiotepa ± serotherapy | MRD/MUD | 91 | 81 | 2.8 |
| Nonmyeloablative and RIC regimen studies | | | | | | | | | |
| Horwitz et al [36] | 2001 | 10 | 15 | 80 | Flu/Cy/ATG (NMA) | MRD | 70 | 60 | 1.4 |
| Khandelwal et al [37] | 2016 | 4 | 14 | 75 | Alemtuzumab/ Flu/Mel (RIC) | MUD | 100 | 50 | 1.65 |

Abbreviations: ATG, anti-thymocyte globulin; Bu, busulfan; CGD, chronic granulomatous disease; Cy, cyclophosphamide; EFS, event-free survival; Flu, fludarabine; F/U, follow-up; HCT, hematopoietic cell transplantation; MEL, melphalan; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; NMA, nonmyeloablative; OS, overall survival; RIC, reduced-intensity conditioning; RTC, reduced-toxicity conditioning; Treo, treosulfan; UCB, umbilical cord blood.

excellent outcomes. Fifty-six patients with a median age of 12.7 years, the majority (75%) of whom had high-risk CGD (ie, intractable infection or autoinflammation), underwent bone marrow transplantation using RTC consisting of busulfan, fludarabine, and serotherapy (ATG or alemtuzumab). Patients received grafts from either an MRD (n = 21) or an MUD (n = 35). The busulfan dose was 55% to 75% of the myeloablative dose (target cumulative AUC, 45–65 mg/L·h). None of the patients received a granulocyte transfusion. No episodes of veno-occlusive disease, interstitial pneumonitis, or severe mucositis were observed. The transplant-related mortality rate was low (7%). The cumulative incidence of acute GVHD, grades III to IV, was 4%, and that of chronic GVHD was 7%. The 2-year overall survival and event-free survival rates were 93% and 89%, respectively, for the entire cohort. The event-free survival rate for MRD recipients was 95%. All surviving patients had stable myeloid donor chimerism (>90%) and were reported to have cleared all infectious and autoinflammatory complications. In peripheral blood lymphocytes, donor chimerism ranged between 70% and 100%. An important observation is that the optimal busulfan exposure was critical. Patients who had a lower busulfan exposure (<45–65 mg/L·h) had a lower probability of engraftment (or higher chance of graft failure), which highlights the role of busulfan pharmacokinetic monitoring and avoidance of significant reduction of conditioning intensity for HCT in patients with CGD.

Another emerging reduced-toxicity approach is based on a bifunctional alkylating agent, treosulfan, which has both myeloablative and immunosuppressive effects. HCT conditioning regimens based on treosulfan were recently shown to be effective in achieving engraftment with fewer adverse effects, especially with a decreased risk of veno-occlusive disease compared to that with traditional busulfan- and cyclophosphamide-based regimens in children with nonmalignant disease [39, 40]. Morillo-Gutierrez et al [35] reported outcomes of treosulfan-containing conditioning regimens in 70 pediatric patients with CGD from Europe. The majority of these patients (>90%) had high-risk features, defined as ongoing or previous infection or autoinflammation. The donor types were HLA-matched related (n = 13), HLA-matched unrelated (n = 56), and haploidentical (n = 1). Patients underwent the transplant at a median age of 8.9 years with a regimen consisting of fludarabine and treosulfan with or without thiotepa and with or without serotherapy. Most of the patients had >95% donor chimerism in myeloid and lymphoid cells. Graft failure was noted in 11% (n = 8), but 7 of 8 patients with graft failure were still alive at the time the report was written after a boost or second bone marrow transplant, which resulted in an effective 2-year probability of cure of >90% at a median follow-up time of 34 months. Six patients died, the majority as a result of GVHD or viral infection after 100 days, which indicates the low toxicity of these regimens. The cumulative incidence of acute GVHD grade III or IV was 12% and that of chronic GVHD was 13%.

## EXPERIENCE WITH ALTERNATIVE DONORS

Often, patients with CGD in need of transplant do not have a suitable HLA-matched donor. For such patients, alternative donor transplantation can be of great interest. Unrelated umbilical cord blood has been used successfully in transplants to treat a variety of malignant and nonmalignant diseases in children and adults [41–44]. Partially mismatched donors are feasible with unrelated cord blood grafts because of the decreased risk of GVHD, because of which the donor availability increases. Cord blood grafts are also readily available. Potential challenges with cord blood transplantation (CBT) include delayed engraftment and an incidence of graft failure higher than that after bone marrow grafts. Successful CBT for patients with CGD has been described in a few case reports [45–48]. Seven patients with CGD were also included in a larger analysis of patients undergoing CBT for a primary immunodeficiency disorder (n = 88). It should be noted that 5 out of the 7 patients in this study had failed 1 or 2 prior HCTs and were given a RIC for their cord transplant [49]. The cumulative incidence of neutrophil engraftment was 43%, and only 3 of 7 patients survived. These results most likely reflect the high-risk status of patients in this cohort. At Duke University, 14 patients underwent umbilical cord blood transplantation to treat CGD after MAC with busulfan/cyclophosphamide/ATG with or without fludarabine (data on a subset of 7 patients was published by Tewari et al [34], and data on the remaining subset are unpublished, J Kurtzberg and V Prasad, 2017). The first 2 patients experienced graft rejection and underwent a successful retransplantation after additional RIC with second CBTs [50]. At the time the report was written, 13 (93%) of 14 patients were alive and disease free at a median follow-up of 7 years. Thus, with adequate supportive care, CBT can be feasible in patients with CGD. In addition, some novel reports have noted other HCT regimens using a haploidentical donor and T-cell depletion of grafts or posttransplantation cyclophosphamide, which might have use in patients with CGD in the future [51, 52].

## CONCLUSIONS AND FUTURE DIRECTIONS

Allogeneic HCT for patients with CGD has improved greatly over recent years. One can generally estimate the HCT event-free survival rate for patients with CGD to be greater than 80% with improved quality of life in this current era, and transplant outcomes are likely to continue improving over time. As HLA typing and donor selection become even more sophisticated, the risks of GVHD and patient death are expected to decrease further. Advances in graft manipulation should similarly continue to decrease the incidence of GVHD and better protect patients from infection. Likely also is that RIC and RTC approaches will continue to be improved. Head-to-head trials of different conditioning regimens are needed, as are trials of precision dosing approaches for both chemotherapeutic and

lymphodepleting agents. Nontransplant advances also should continue to improve patient outcomes. Patients are already benefitting from antifungal and antibacterial treatment options that are better than those in previous decades, and the routine use of donor-derived or third-party infection-specific cytotoxic T cells is on the horizon. In addition, general continued advances in medical and critical care should contribute to improved patient outcomes. As both conventional and HCT treatments continuously improve, a better understanding of HCT indications in patients with CGD that reflect current outcomes is necessary, and such recommendations for pediatric and adult patients might be different. As gene correction strategies continue to advance, decisions on treatment options will need to include this emerging therapy (see Keller M et al, this supplement). The future is certainly looking brighter for patients with CGD, and we hope that survival for every patient can be realized one day.

## Notes

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