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REVIEW ARTICLE

Haploidentical bone marrow transplant with posttransplant cyclophosphamide for sickle cell disease: An update

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Abstract

Hematopoietic cell transplant (HCT) can cure both children and adults with sickle cell disease. Outcomes have historically been poor for the vast majority of patients who lack a matched sibling donor. However, the development of haploidentical HCT (haplo-HCT) with high doses of posttransplant cyclophosphamide (PTCy) has allowed for curative long-term potential with favorable transplant-related outcomes, though this has not obviated the potential for graft rejection from human leukocyte antigen mismatch and repeated red blood cell transfusions. Accordingly, multiple strategies have been developed to improve outcomes, the majority of which are based on the Johns Hopkins platform from 2012. Presently, we aim to discuss results from pertinent studies and compare outcomes with the two most recent approaches involving either thiotepa plus 200-cGy total body irradiation or 400-cGy total body irradiation. Direct comparisons are required to determine the optimized curative potential. Transplant-eligible patients must be referred to tertiary medical centers for consideration of haplo-HCT.

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Introduction

Sickle cell disease is a life-threatening hemoglobinopathy that leads to poor quality and expectancy of life in children and adults [1–4]. The condition is caused by a single missense mutation in codon six of the beta globin gene, resulting in increased clumping of hemoglobin in red blood cells, particularly in conditions of low oxygen tension with chronic hemolysis of small and large vessels highlighting the pathophysiology [1,2]. Clinical manifestations, while highly variable between patients, include debilitating pain from vaso-occlusive crises, strokes with associated disability, cardiopulmonary abnormalities, vision impairment, priapism in males, chronic kidney disease, hepatobiliary disease, osteonecrosis of long bones, splenic infarction, and an overall increased risk of infections complications [1,2,5–7]. Sickle cell disease also negatively impacts the health-care system in terms of cost and work productivity resulting from mental and physical disabilities [1,2]. Current management strategies, most commonly hydroxyurea and red blood cell transfusion therapy as well as crizanlizumab and L-glutamine, are disease modifying rather than curative and are each associated with unique challenges that often potentiate multiorgan system disease [7–10]. Gene therapy has been shown to be successful, though not available on a broad scale and is associated with potentially severe toxicities [11,12]. As a result, the condition is presently incurable without allogeneic hematopoietic cell transplant (HCT) [7,13,14].

Historically, optimal HCT-related outcomes have been seen in children who receive myeloablative conditioning regimens followed by infusion of marrow allografts from human leukocyte antigen (HLA)-matched related donors [13]. Cumulative data on over 500 children between the ages of 2 and 20 years who underwent matched related donor HCT are notable for sickle cell-free survival of 90%, transplant-related mortality of 6–7%, incidences of acute and chronic graft versus host disease (GvHD) of 10–20% and less than 5%, respectively, and graft rejection rates of less than 10% [13]. However, patients have at most a 25% chance of having a matched sibling donor, and ethnic minorities have a 6–10% chance of finding a fully matched unrelated donor in the United States registry, meaning that most patients are ineligible for curative therapy, thereby necessitating the development of alternative donor platforms [15,16].

The most successful and widely adopted alternative donor approach for the cure of sickle cell disease involves haploidentical grafts from family donors, who share 5/10 HLA loci or more by definition [17–20]. Haploidentical-HCT (haplo-HCT) provides near-universal donor availability for transplant-eligible patients, though historically has been limited due to high transplant-related mortality [21]. Pioneering work in drug-induced immunologic tolerance with administration of high doses of posttransplant cyclophosphamide (PTCy) has mitigated severe acute and chronic GvHD and reduced, though not eliminated graft rejection, a problem that is more severe in patients with transfusion-dependent hemoglobinopathies due to alloimmunization from recurrent transfusions (Fig. 1) [21–24]. Accordingly, we want to share progress with PTCy-based haplo-HCT platforms with an emphasis on competing strategies to improve transplant-related outcomes including graft rejection [2].

Materials and methods

Relevant articles were obtained from extensive PubMed and MEDLINE searches using the following keywords and phrases: sickle cell disease haploidentical, posttransplant cyclophosphamide, graft rejection, thiotepa, and total body irradiation. The ClinicalTrials website, www.clinicaltrials.gov, was also searched using the same keywords.

Haplo-HCT with PTCy: Proof of principle

The majority of haplo-HCT strategies are based on variations of the protocol created at Johns Hopkins University [21–24]. The administration of PTCy on Days 3 and 4 post-haplo-HCT induced favorable rates of GvHD and graft rejection for patients with hematologic malignancies, though was first shown to be effective also in individuals with inherited genetic disorders [20,21]. Seventeen patients were screened for enrollment and 14 were considered eligible [20]. The median age was 23.5 years. The conditioning regimen was reduced intensity and included cyclophosphamide, fludarabine, rabbit antithymocyte globulin, and
2-Gy total body irradiation, as depicted in Fig. 2, with the exception of thiotepa [25]. Patients received granulocyte colony-stimulating bone marrow allografts followed by GVHD prophylaxis with PTCy, sirolimus, and mycophenolate mofetil (Fig. 2). The results were favorable in that no transplant-related mortality was seen. In addition, 43% of patients had full myeloid chimerism and were off sirolimus at last follow-up. However, graft rejection occurred in 57% (8/14) of patients, reflective of inherent alloreactivity. Clinically, those who fully engrafted experienced resolution of vaso-occlusion, indicating the importance of mitigating graft rejection for improving transplant-related outcomes. Despite the high graft rejection rate, Bolanos-Meade et al. [20] demonstrated that less toxic nonmyeloablative regimens and haploidentical grafts with PTCy could reverse the sickle cell disease phenotype.

Modifications to the PTCy-based approach with peripheral blood allografts

Fitzhugh and colleagues [26] sought to further improve eligibility for haplo-HCT by enrolling adults with multiple comorbidities to an early phase study of alemtuzumab and total body irradiation-based conditioning followed by infusion of granulocyte colony-stimulating factor-primed peripheral blood allografts (Table 1). Twenty-one included patients had sickle cell disease and two had transfusion-dependent beta-thalassemia. The median age was 36 years. Participants were split into three cohorts that differed by doses of PTCy given (no PTCy, 50 mg/kg, or 100 mg/kg, respectively), with the goal of determining the benefit of cyclophosphamide for improving engraftment rates. No patient had grades moderate-to-severe acute GVHD or severe chronic GVHD, which likely reflects that PTCy reduces alloreactivity. Furthermore, 86% (18/21) of the non-beta thalassemia patients survived, though 14% of patients with rejection (3/21) died. Engraftment rates and chimerism were highest in cohort three, though rejection was still 50% (4/8). One potential explanation is that the conditioning regimen was skewed toward tolerability rather than recipient immunosuppression given the advanced age and increased number of comorbidities in the adult patients.

Saraf et al. [27] also sought to determine the optimal conditioning regimen to boost engraftment using peripheral blood stem cells. The authors conducted a single-institution retrospective study on 10 patients (range, 20–38 years), with the first two receiving the regimen developed by Fitzhugh et al. [26] and the remaining eight receiving the Bolanos-Meade et al. [20] protocol with 3-Gy total body irradiation rather than 2 Gy as initially studied. The results provide evidence for a multiagent cytotoxic-based regimen rather than nonchemotherapy-based regimens alone, as the first two patients did not engraft while 88% (7/8) of the remaining patients did long term with over 95% donor cell chimerism at 1 year. One case of secondary graft rejection occurred. Rates of moderate-to-severe acute GVHD and extensive chronic GVHD were 25% (2/8) and 13% (1/8), respectively. Based on the findings, it was suggested that an increased dose of total body irradiation may contribute to improved engraftment, albeit at the cost of increased acute and chronic GVHD.
Myeloablative regimens and bone marrow allografts

While the Bolanos-Meade et al. [20] protocol utilized non-myeloablative conditioning to spare toxicity, Wiebking et al. [28] administered a myeloablative regimen with alemtuzumab, fludarabine, treosulfan, thiotepa, and cyclophosphamide with the goal of ablating the recipient immune system to reduce graft rejection (Table 1). Notably, individuals did not receive total body irradiation. All three patients (age range, 8.5–20.3 years) included had disease that was refractory to hydroxyurea. The results were favorable in terms of absence of graft rejection, full donor chimerism, and absence of disease-related symptoms or GvHD at 11, 14, and 30 months post-haplo-HCT, respectively. While the small sample size limits generalizability and warrants validation in larger prospective clinical trials, the results highlight the impact of total body irradiation on long-term outcomes.

Nonmyeloablative regimens and bone marrow allografts

Pawlowska and colleagues [29] retrospectively assessed pretransplant immune suppression with two courses of fludarabine and dexamethasone prior to haplo-HCT with PTCy (Table 1). Four patients with a median age of 19 years received reduced intensity conditioning with rabbit antithymocyte globulin, busulfan, and fludarabine without total body irradiation. All survived at a median follow-up of 5–11 months in part due to 99.9–100% donor engraftment. No moderate-to-severe acute or extensive chronic GvHD grades were noted (Table 1). In addition, two of four patients were noted to have high anti-HLA titers, for which plasmapheresis, intravenous immune globulin, and rituximab were given for desensitization prior to the conditioning regimen. The results suggest that the novel approach of pretransplant immune suppression should be further investigated with more patients. In addition, the results demonstrate that desensitization is beneficial for patients who lack better donor options.

Results from collaborative consortiums: Benefit of addition of thiotepa

To improve enrollment of transplant-eligible individuals with sickle cell disease and improve generalizability of findings, an international team-based learning collaboration was established between centers in the United States, United Kingdom, and France [30]. With a focus on haplo-HCT, the group hypothesized that nonmyeloablative conditioning with the addition of thiotepa followed by infusion of marrow allografts and PTCy-based GvHD prophylaxis regimen would reduce graft rejection and improve transplant-related outcomes (Fig. 2). Eligibility criteria, similar to the aforementioned studies, included patients between 1 and 70 years of age with at least one criteria for severe disease, including cerebrovascular event lasting longer than 24 hours, magnetic resonance imaging evidence of strokes, recurrent acute chest syndrome or vaso-occlusive crises, repeated hospital stays, or chronic lung conditions. Included participants had a favorable performance status and must not have had a matched donor.

The Phase II study was conducted by de la Fuente et al. [30] with the primary end point being 1-year event-free survival, which included primary or secondary graft rejection, stroke, or death (Table 1). Eighteen patients with a median
### Table 1 Outcomes of Haplo-HCT with PTCy-Based Approaches.

| Author and year | Graft source | Conditioning regimen [36]                                                                 | N / age range (y)          | OS (%) (n) [36] | GvHD (%) (n) [36] | Engraftment (%) (n) [36] | Sickle cell-related and transplant outcomes [36] |
|-----------------|--------------|------------------------------------------------------------------------------------------|----------------------------|-----------------|---------------------|---------------------------|------------------------------------------------|
| Bolanos-Meade et al. [20] 2012 | G-BM (3), BM (11) | Nonmyeloablative ATG (12 patients), fludarabine, cyclophosphamide, 200-cGy total body irradiation | 14/15–42                  | 100 (14/14) at 7.5–66 mo | 0 (0/14) acute GvHD | 57 (8/14)                 | 50% (7/14) alive and without sickle cell-related symptoms |
| Fitzhugh et al. [26] 2017 | PBSC         | GyHD prophylaxis: PTCy, FK, sirolimus, MMF                                              | 12/20–56                  | 92 (11/12)       | 8 (1/8) acute GyHD  | 70                        | No new strokes, acute chest syndrome, priapism infections |
| Bolanos-Meade et al. [31] 2019 | BM           | Nonmyeloablative ATG, fludarabine, cyclophosphamide, 400-cGy total body irradiation    | 17/6–31 (median age 16 years) | 100 (17/17)      | 29 (5/17) acute GyHD | 94 (16/17)                | Three CMV reactivation, one EBV reactivation, one with RSV upper respiratory infection, and mycobacterium lung infection |

Note: We thank the editors for careful review of our article. Table 1 shares similarities with our aforementioned published work, namely Patel et al. [36]. ATG = antithymocyte globulin; BM = bone marrow; cGy = centigray; CMV = cytomegalovirus; EBV = Epstein-Barr virus; EFS = event-free survival; G-BM = granulocyte colony-stimulating factor primed bone marrow; GyHD = graft versus host disease; Haplo = haploidentical; HCT = hematopoietic cell transplant; HLA = human leukocyte antigen; MMF = mycophenolate mofetil; OS = overall survival; PBSC = peripheral blood stem cell; PTCy = post-transplant cyclophosphamide; PTIS = pretransplant immune suppression; PTLD = post-transplant lymphoproliferative disorder; RIC = reduced intensity conditioning.
age of 20.9 years were included, the first three of whom received the Johns Hopkins platform, the remaining 15 received thiotepa for conditioning due to graft rejection seen in 66% (2/3) initial patients. Greater than 95% myeloid engraftment was noted after at least 6 months of follow-up in 93% (14/15) patients. No further graft rejection was detected. All patients were alive at study completion. GvHD rates were favorable, with 13% (2/16) acute and 6% (1/16) extensive chronic GvHD noted. In addition, preconditioning did not appear to impact transplant-related outcomes on patients who received thiotepa. Importantly, all patients were off immunosuppression by 1 year follow-up. The findings indicate the potential for a single dose of thiotepa to improve the efficacy of haplo-HCT based on improved engraftment.

Competing strategy for improving engraftment: 400-cGy total body irradiation

Bolanos-Meade et al. sought to improve the main problem of primary graft rejection noted in their initial report in 2012 by increasing the dose of total body irradiation in the non-myeloablative conditioning regimen to 400 cGy from 200 cGy in transplant-eligible patients with severe hemoglobinopathies in a Phase II clinical trial [31]. The conditioning regimen and GvHD prophylaxis regimen were otherwise the same. The primary objective was assessment of engraftment based on donor chimerism, which notably was a new end point. However, enrollment was stopped in 2017 following recruitment of 17 participants when funding was stopped. Of the 17 participants enrolled, 71% (12/17) had sickle cell disease and 29% (5/12) beta-thalassemia major. Both children and adults were included, with a median age of 16 years (range, 6–31 years). Engraftment results were favorable in that 76% (13/17) had full myeloid chimerism with 18% (3/17) having mixed chimerism and 6% (1/17) having primary graft failure. The continued benefit of PTCy on GvHD outcomes was seen, as evidenced by 24% (4/17) of participants with Grade II acute GvHD and 6% (1/17) with Grade III disease. No participant had Grade IV acute GvHD. Eighteen percent (3/17) developed limited chronic GvHD. Importantly, at the time of last follow-up, no participant had documented GvHD and none were on immunosuppression therapy.

Conclusions and future directions

Sickle cell disease leads to age-dependent chronic organ dysfunction, resulting in decreased survival in affected individuals [4]. The main limitation for the application of HCT is principally donor availability and toxicity of conditioning. Initial approaches using a combination of recipient immunoablation with conditioning chemotherapy and total body irradiation appear too toxic. Thus, most affected individuals are not candidates for myeloablative conditioning due to age, comorbidities, including dosing issues related to renal or hepatic dysfunction, risks of infertility, especially for younger patients, and fear of developing acute or chronic GvHD, which remains one of the reasons that patients and family decline potentially curative therapy [17–19,32]. Nonmyeloablative haplo-HCT appears to address these limiting factors. Since 2012, multiple approaches have been utilized to combat the primary issue associated with haplo-HCT with PTCy regimens, namely graft rejection, which is partially inherent to the high degree of alloreactivity in the setting of HLA mismatch compounded by alloimmunization from high numbers of transfusions [33–35].

Notably, patients in the de la Fuente et al. study had more comorbidities at baseline, namely moyamoya, cerebrovascular infarcts, and acute chest syndrome, compared with those in the Bolanos-Meade et al. study [30,31]. Incidence of moderate-to-severe acute GvHD and subsequently chronic GvHD were also greater in the participants who received higher doses of total body irradiation. Both regimens were comparable in terms of graft rejection and overall survival, which is encouraging in terms of increasing future enrollment of patients on trials. Ultimately, regimens containing thiotepa plus 200-cGy total body irradiation and 400-cGy total body irradiation without thiotepa must be compared head to head in a prospective randomized trial to know the optimal approach to cure patients.

Declaration of Competing Interest

The authors do not have any competing interests to disclose.

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