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Enrollment Lessons from a Biologic Assignment Study of Marrow Transplantation vs Standard Care for Adolescents and Young Adults with Sickle Cell Disease: Considerations for Future Gene and Cellular Therapy Trials

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Abstract

Background.—We previously conducted a single-arm feasibility study (STRIDE1) of myeloablative bone marrow transplantation (BMT) in adolescents and young adults with sickle cell disease (SCD). The trial identified donors before entry, enrolled well and found no unexpected regimen-related toxicity. While many single arm studies have been published, there are no controlled trials of either BMT or gene therapy in SCD. Therefore, we designed a comparative trial by biologic assignment (available donor vs no donor). This multicenter NIH-funded study (BMT CTN 1503, STRIDE2) enrolled between 2016 and 2021 at 35 sites. Lagging recruitment led to study closure and we report here the impediments to accrual.

Methods.—The transplant regimen and entry criteria were from STRIDE1 and two-year survival was the primary endpoint. To minimize selection bias due to prior HLA typing, STRIDE2 excluded individuals with previously identified donors.

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Author Statement

All authors have made substantial contributions to the conception or design of the work, and the acquisition, analysis, and interpretation of data for the work. All authors drafted the work or revised it critically for important intellectual content. All authors gave final approval of the version to be published. All authors confirm that they had full access to all the data in the study and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Findings.—Accrual was stopped at 69% of target (138 enrolled; assigned 28 donor, 96 no donor). Barriers to enrollment included: lower than expected frequency of HLA-matched related and unrelated donors; loss of enrollees due to previously identified donors; conventional care arm dissuaded some who were seeking BMT; short-term endpoints in SCD were a challenge, including incomplete documentation of sickle pain episodes; state Medicaids (primary insurers of SCD) denied BMT coverage for adult SCD despite the study having secured Coverage with Evidence Development from federal CMS; accrual slowed in 2019–2021 during COVID-19; academic medical (cancer) centers restricted BMT resourcing for non-malignant diseases; social obstacles and access to BMT centers limited entry as did practitioner and participant concerns over suitability, cost and toxicity.

Conclusions.—Planning for future controlled trials of curative therapy in SCD and other non-malignant diseases will likely meet these enrollment challenges. Lessons from this trial may assist development of future comparative studies.

Keywords

Bone Marrow Transplantation; Sickle Cell Disease; Comparative Studies

Introduction

Comparisons of curative therapies in sickle cell disease (SCD) have been elusive since published studies of bone marrow transplantation (BMT) have largely focused on uncontrolled trials in children[1]. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) protocol 1503 is an attempt to bridge this gap. We highlight lessons learned, and barriers observed in implementing a a prospective biologic assignment comparative phase II trial of BMT. The multi-level barriers observed in this trial offer insight when designing future trials of curative therapy for SCD including particularly those that seek to compare curative therapies with standard of clinical care..

The study question of BMTCTN 1503 is whether older sickle patients benefit from BMT from of an HLA-matched related or unrelated donor compared with standard of care (SOC). Assignment to treatment arm was determined by the availability of a suitably matched donor. Those with a donor were given BMT and those without a donor received SOC. The primary outcome is 2-year survival from the date of biologic assignment with the expectation that most transplant-related mortality occurs in the initial two years and that standard care disease-related mortality in SOC would continue beyond 2 years.

The study opened in October 2016 and enrollment at the 35 sites was closed with the last enrollment on 19 Mar 2021 and last assignment to study arm on 18 Jun 2021 due to lagging accrual after enrolling 138 participants (69% of target). Herein we describe lessons learned about barriers to recruitment, steps taken to mitigate these difficulties and speculate about implications in the design of future trials of curative therapies for SCD.

Study Launch

A single-arm pilot trial (STRIDE1) to test the safety and efficacy of the transplant conditioning regimen preceded the BMT CTN 1503 study (STRIDE2) [2]. The pilot trial

enrolled patients after a suitable donor had been identified. To reduce selection bias, STRIDE2 excluded participants who had a donor identified before enrollment. Thus, enrollment was more easily completed in the pilot investigation because patients considering BMT were seeking a curative option. The possibility of being assigned to a 'non-curative' no-donor arm in STRIDE2, made recruitment in a comparative study difficult, especially as other options such as haploidentical donor HCT[3–5] and autologous gene therapy [6,7] became available. In retrospect, this was probably the greatest impediment to study enrollment. The study team had considerable experience conducting clinical trials in SCD and BMT but was not alone in under-estimating this important barrier to study accrual. Experts who conducted multiple peer reviews (U01 HL 128568 and U01 HL 128566), the BMT CTN steering committee with NHLBI program membership, a Data Safety Monitoring Board, and the Adult Sickle Cell Provider Network all endorsed the study design.

Difficulties of comparative clinical trials of curative therapies for SCD

Many publications of BMT in SCD are single-center case series that generally show promising results in children. How to transform these small trials into a generalizable body of evidence to guide the implementation of curative therapy in clinical practice is an unresolved issue. Ideally, a comparative trial of curative therapy would show benefit compared with to standard care treatment. However, this path to generalizable knowledge has been elusive in SCD and identifying suitable short-term outcomes has been challenging. Moreover, the design and implementation of contemporary control cohorts with similar characteristics poses logistic problems and challenges for those seeking curative treatment.

Patient and practitioner concerns

Based on informal feed-back from steering committee, coordinator, and investigator meetings, we identified key factors that contributed to the slow pace of enrollment (Table 1). These included impediments to easy access to clinical trial sites and/or comprehensive care in SCD for potential participants; concerns among hematologists and transplant physicians about the suitability of potentially eligible participants; concerns about the risk of toxicity following myeloablative conditioning; distrust of clinical trials among potential participants; and the low priority for a clinical trial targeting a non-malignant disease at clinical transplant sites situated in comprehensive cancer centers.

Patients and their physicians consult BMT physicians when they have arrived at decisional readiness to seek a potentially curative approach[8]. As mentioned above, the BMT CTN 1503 with its best available standard of care "no donor" arm may not have appealed to patients searching for a curative option. The availability of single-arm clinical trials of alternative donor allogeneic HCT might also have negatively impacted participation. Alternatively, potential participants in BMT trials may have limited access to centers capable of delivering curative therapy. Moreover, serial assessments of physical functioning, pain, health related QoL, and disease complications were study requirements and appeared more difficult in those in the SOC group. Scheduling return visits proved difficult for them, as did navigating the logistics of travel to a distant institution in an unfamiliar setting.

This study team engaged the Adult Sickle Cell Provider Network in discussions on study design and their willingness to refer patients. We speculate that we failed in our outreach efforts beyond a select group of physicians and did not more broadly engage community physicians who care for adult patients with SCD. Since there is no national registry, it is challenging to identify a comparable cohort of SCD patients who met eligibility based on eligibility criteria. BMTCTN 1503 was open to enrollment between October 2016 and March 2021. According to data retrieved from curesickle metadata catalog during the period of January 2016 to December 2020 of the 677 first HCTs reported to CIBMTR in patients with SCD, 299 (44%) were carried out in patients 15–40.99 years the age of eligibility for BMT CTN 1503 (Krishnamurti, personal communication).

Availability of a suitably HLA-matched related or unrelated donor is a challenge. Of those enrolled in STRIDE2, only 22% had a suitable marrow donor. In planning, we had estimated 33% would have a donor: 19% with an matched unrelated donor[9] and ~14% with a matched sibling[10]. A 200-participant trial was statistically powered based on accruing 60 patients to the donor arm and 140 to the no donor arm. Assumptions on donor availability proved incorrect and far less than published data. This was another major contributor to enrollment shortfall.

Health insurance coverage

Coverage denial was particularly pertinent to Medicaid health insurance plans, which insures more than 55%[11] of the estimated 100,000 patients in the U.S. with SCD[12]. To mitigate this potential barrier, the study team petitioned the Center for Medicare and Medicaid Services (CMS) about allogeneic HCT for SCD in January 2016. Their national coverage determination for HCT for SCD stated that CMS would cover items and services necessary for the study for BMT using the Coverage with Evidence Development (CED) paradigm. In addition, it stipulated that a prospective clinical study seeking Medicare coverage of allogeneic HCT for SCD under CED must have a comparator arm of subjects who share comparable eligibility for HCT but are treated according to accepted “standard of care.”. The BMT CTN 1503 protocol was approved for CMS coverage under CED in June 2016 (https://www.com.gov; NCT02766465).

Despite the approved CED from CMS for this trial, insurance authorization by state Medicaid plans remained a barrier. The CMS guidance was not universally adopted or interpreted favorably by individual plans[13]. Some state plans excluded coverage for participating in a “research study” while other state plans provided coverage for BMT for SCD, but excluded those enrolled in a clinical trial. Moreover, some transplant centers did not accept Medicaid reimbursement as a business policy, especially for out-of-state plans. This was balanced by other transplant programs that accommodated the additional costs of care to promote access to study participation and BMT for donor-arm participants. This experience underscores the multifaceted difficulties in access to health care that are prevalent structural obstacles to equitable access to care experienced by Americans with SCD[14]. The absence of federal policy on coverage of treatments on clinical trials likely suppressed the representation of low-income and minority populations in the clinical research thus, limiting equitable access to novel therapies and compromising the generalizability of research

findings[15]. Beginning in January 2022, coverage of the "routine costs" associated with clinical trial participation is guaranteed for all Medicaid beneficiaries for the first time in the program's history[15]. Further, while the upfront costs of BMT are substantial for any yearly Medicaid revenue cycle, the SCD-attributable costs to commercial insurers over 0–64 years of age is $1.6 Million, a 907% increase over matched controls.[16]

Competing clinical trials and emergent therapeutic options for SCD

Enrollment on this trial may also have been impeded the FDA approved three new disease-modifying therapies--L-Glutamine[17], Voxelotor[18], and Crizanlizumab[19] during the BMT CTN 1503 trial period. L-Glutamine was studied in a clinical trial from 2010–2014 and approved by the FDA in 2017. The FDA approved Voxelotor in 2019 after it was studied in a clinical trial from 2017–2019.

Similarly, Crizanlizumab was studied in a clinical trial from 2013–2015 and approved by the FDA in 2019. An exclusion criterion for BMT CTN 1503 study was participating in a clinical trial in which the patient receives an investigational drug or device. These drugs were required to be discontinued prior to the date of enrollment. For patients undergoing HCT, hydroxyurea was required to be discontinued at least one week before initiation of the conditioning regimen. Thus, it is likely that some patients who may have been eligible for enrollment on BMT CTN 1503 may instead have been enrolled in a clinical trial of one of the novel agents in a clinical trial at that time.

Impact of the pandemic.

COVID-19 pandemic severely disrupted life worldwide in 2020. Many institutions limited clinical trials or deferred 'elective' BMT, and patients stayed away from hospitals out of fear of contracting COVID-19.

Concerns about treatment related toxicities.

In previous qualitative research, studies of patient and parent perspectives on decision-making about BMT, concerns about short and long-term sequelae were cited as the most significant and perhaps the most critical barriers to BMT[20,21]. We proposed a conditioning regimen in STRIDE2 to generate an acceptable event-free survival (EFS) of≥70%, based upon our pilot data. The acceptability of this approach was based upon queries of adult providers, who agreed that a long-term EFS of ≥70% was acceptable because it exceeded long-term survival estimates in adults with severe disease treated by supportive care. However, subsequent transplant registry data suggested a poorer outlook after adult unrelated transplants in SCD. Brazauskas analyzed 1425 transplants between 2008 and 2017 and reported EFS of 50% and 49% EFS in SCD recipients ≥13 years old given matched and mismatched unrelated transplants[22]. This report of poor outcomes after unrelated marrow grafts possibly diminished enthusiasm for enrollment.

Patients with chronic disabling pain may not satisfy eligibility criteria.

The Ellipsis study[23] reinforced findings of the PISCES study[24] that most acute pain episodes in SCD are treated outside the hospital setting and that a sizable proportion of adults with SCD have daily pain or pain on most days. In addition, pain is a major biomarker of disease

severity and impacts QoL and healthcare utilization. In 2019, we expanded eligibility criteria to include high-impact chronic pain (HICP)[25,26] as defined by criteria described in Table 2, even in the absence of frequent healthcare utilization. Despite informing investigators through a series of communications about this new inclusion criterion, we did not enroll any participants for high-impact chronic pain. This was often due to medical encounters not routinely using HICP.

A suitable primary endpoint in trials with curative intent in SCD has been elusive

A survival advantage after BMT is a compelling reason to recommend it, especially if the toxicity profile is manageable and short-lived. Unfortunately, it is not feasible to determine survival advantage in the course of a typical clinical trial. Experience in hydroxyurea trials suggested that survival as a primary endpoint may require an observation period of 10 years or more[27]. Thus, long-term survival, projected from the 2-year survival observed in both study arms, was judged as the most readily adaptable and clinically meaningful endpoint to assess the impact of BMT. While survival is an important endpoint, is it practical for this study design? Or is 'event'-free survival, with a sickle-related event defined as a severe pain treated in the hospital or an episode of acute chest syndrome, sufficient to show safety and efficacy? Or should EFS without graft-vs-host disease be used? Endpoint selection requires further careful thought. Recently, however, increased risk of myelodysplastic syndrome/acute myelogenous leukemia following autologous transplantation of genetically modified hematopoietic cells on a lentiviral gene therapy trial, as well as in some patients following allogeneic HCT, has been observed [28,29]. Thus, after allogeneic HCT or autologous gene therapy, long-term survival without malignancy or other late effects of chemotherapy or radiation may become an essential endpoint.

Conclusions:

The study team pursued innovative recruitment strategies that were not previously reported in trials of SCD and allogeneic transplant. These might be applied to future controlled studies of curative trials in SCD. These steps included:

1. Secured CMS approval under Coverage with Evidence Determination
2. Conducted a published pilot study that showed the feasibility and acceptable short-term outcomes
3. Secured multiple peer reviews and NIH grant support
4. Obtained support by the adult SCD provider network
5. Amended the protocol in several ways to overcome perceived recruitment issues

Yet, is it feasible to conduct controlled prospective trials in curative therapies for adults with severe SCD? This question reflects socioeconomic realities in SCD that will continue to challenge study planning. Approximately 80% of patients with SCD receive health coverage through Medicaid or other government-sponsored insurance. Medicaid in many US states will authorize transplant for children since outcomes in children are broadly excellent[22,30–34]. However, results in adults are largely unknown. Single institution, single-arm BMT trials in adults with SCD take five years to recruit even a small number of

participants[35]. In addition, academic medical centers and their embedded comprehensive cancer centers, commonly support BMT and cellular therapy programs, but do not wish to support research for transplant or gene therapy for morbid non-malignant diseases such as hemoglobinopathies and autoimmune disorders which lay outside funding mandates of cancer research and treatment.

We have attempted to share a *rear view* (what we did and what happened) on BMT CTN 1503 and a *forward view* (what will make controlled curative trials in SCD more successful) to stimulate ideas about how to move the field forward. For greatest effect, these discussions will include industry, academic centers and investigators, providers, patients, families, health care providers, and research funding agencies.

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Table 1.

Barriers to enrollment in STRIDE2

1.	Assignment to a conventional care comparative arm discouraged some patients seeking curative therapy.
2.	The pilot study (STRIDE1) enrolling participants *after* a donor was identified did not predict enrollment rates in the comparative trial (STRIDE2) which excluded individuals who had donors identified *before* enrollment.
3.	The likelihood of finding an HLA-matched related or unrelated marrow donor in this prospective trial was only 22%, far less than expected.
4.	Follow-up of enrollees assigned to conventional care was fraught with dropouts and missing data.
5.	Identification of suitable short-term endpoints in sickle cell disease remains challenging, and tracking episodes of sickle pain was complicated by poor medical documentation.
6.	State Medicaids routinely denied coverage of BMT for adults with sickle cell disease despite the trial being approval by the federal Centers for Medicare and Medicaid Services.
7.	Priority in academic medical (cancer) centers for research support for BMT performed for non-malignant diseases was low.
8.	Concern about intensive BMT therapy raised doubts for sickle cell practitioners and patients about treatment risk, cost and suitability for enrollment.
9.	Social issues and ease of access to research centers appeared to limit enrollment and follow-up.
10.	At the onset of the pandemic, recruitment and follow-up were challenged by COVID-19 restrictions.

Table 2.

Screening for High Impact Chronic Pain (HICP)[26,36]

Patient reports pain on a majority of days per month for six months
Review three HICP assessment questions with the patient and document the response in the medical record A) Over the past six months, have you had pain on at least half the days? 1) Yes 2) No B) Over the past six months, how much has pain interfered with your life activities? 1) No interference 2) Mild interference 3) Moderate interference 4) Severe interference C) Over the past six months, how often did pain limit your life or work activities, including household chores? 1) Never 2) Rarely 3) Sometimes 4) Usually 5) Always For the patient to be considered to have HICP, Q1 should be answered Yes AND either Q2 or Q3. Must be answered with responses numbered 4 or 5
The patient meets the requirement for HICP based on mixed pain types. Chronic pain is also occurring at sites (e.g., arms, back, chest, or abdominal pain) unrelated to sites with contributory SCD complications (e.g., avascular necrosis)