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Allogeneic Human Mesenchymal Stem Cell Therapy (Remestemcel-L, Prochymal) as a Rescue Agent for Severe Refractory Acute Graft-versus-Host Disease in Pediatric Patients

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A B S T R A C T

Severe steroid-refractory acute graft-versus-host disease (aGVHD) is related to significant mortality and morbidity after allogeneic stem cell transplantation. Early clinical trials of therapy with human mesenchymal stem cells (hMSCs) in pediatric patients with severe aGVHD resistant to multiple immunosuppressive agents showed promising results. In this study, we evaluated the risk/benefit profile of remestemcel-L (Prochymal), a third-party, off-the-shelf source of hMSCs, as a rescue agent for treatment-resistant aGVHD in pediatric patients. Children with grade B-D aGVHD failing steroids and, in most cases, other immunosuppressive agents were eligible for enrollment. Patients received 8 biweekly i.v. infusions of 2×10^6 hMSCs/kg for 4 weeks, with an additional 4 weekly infusions after day +28 for patients who achieved either a partial or mixed response. The enrolled patients compose a very challenging population with severe disease that was nonresponsive to the standard of care, with 88% of the patients experiencing severe aGVHD (grade C or D). Seventy-five patients (median age, 8 yr; 58.7% male; and 61.3% Caucasian) were treated in this study. Sixty-four patients (85.3%) had received an unrelated hematopoietic stem cell graft, and 28 patients (37.3%) had received a cord blood graft. At baseline, the distribution of aGVHD grades B, C, and D was 12.0%, 28.0%, and 60.0%, respectively. The median duration of aGVHD before enrollment was 30 d (range, 2 to 1639 d), and patients failed a median of 3 immunosuppressive agents. Organ involvement at baseline was 86.7% gastrointestinal, 54.7% skin, and 36.0% liver. Thirty-six patients (48.0%) had 2 organs involved, and 11 patients (14.7%) had all 3 organs involved. When stratified by aGVHD grade at baseline, the rate of overall response (complete and partial response) at day +28 was 66.7% for aGVHD grade B, 76.2% for grade C, and 53.3% for grade D. Overall response for individual organs at day +28 was 58.5% for the gastrointestinal system, 75.6% for skin, and 44.4% for liver. Collectively, overall response at day +28 for patients treated for severe refractory aGVHD was 61.3%, and this response was correlated with statistically significant improved survival at day +100 after hMSC infusion. Patients who responded to therapy by day +28 had a higher Kaplan-Meier estimated probability of 100-d survival compared with patients who did not respond (78.1% versus 31.0%; $P < .001$). Prochymal infusions were generally well tolerated, with no evidence of ectopic tissue formation.

INTRODUCTION

The success of allogeneic hematopoietic stem cell transplantation (HSCT) and its ultimate therapeutic effect depends on the control of acute graft-versus-host disease (aGVHD). Depending on various risk factors and the administration of prophylactic agents, 30% to 80% of recipients will develop aGVHD [1,2]. Corticosteroids are the initial intervention for controlling aGVHD; however, in 30% to 50% of patients, aGVHD is not controlled with first-line therapy and requires additional therapeutic intervention [3]. In a recent retrospective analysis of 864 patients with aGVHD [4], patients who failed to respond to therapy at day +28 after initiation were 2.78 times more likely to experience treatment-related mortality (TRM) compared with those who demonstrated response. Thus, the outcomes for nonresponders are poor. Various agents have been added to

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steroid therapy in an attempt to treat steroid-resistant aGVHD, including polyclonal and monoclonal antibodies, immunotoxins, immunosuppressive agents, chemotherapeutic agents, and phototherapy. Overall, responses to these agents and outcomes in salvage therapy for steroid-refractory aGVHD have been disappointing [5-7].

Clinically, patients who fail to respond to steroids and additional immunosuppressive agents are at increased risk for morbidity associated with infections and uncontrolled aGVHD, as well as an increased risk of mortality. The poor prognosis of severe aGVHD is well documented, with long-term survival probabilities of 20% for grade III and <5% for grade IV [8]. Thus, steroid-refractory aGVHD represents a significant clinical challenge.

Previous studies have demonstrated the potential of human mesenchymal stem cells (hMSCs) as an effective treatment for aGVHD. Recent reviews indicate that hMSCs down-regulate immune and inflammatory responses, providing therapeutic potential for treating diseases characterized by the presence of an inflammatory component [9,10]. The production of anti-inflammatory cytokines and growth factors by hMSCs can promote a favorable environment and facilitate tissue repair. Clinical improvement in aGVHD after i.v. infusion of hMSCs has been reported in single case reports [11], pilot studies [12-15], and phase II studies [16,17]. In these studies, the vast majority of patients received 1 or 2 infusions of hMSCs. Clinical experience and pilot investigations have indicated that for the most severe cases of refractory aGVHD, a greater number of treatments may be required to reverse the course of one of the most severe complications of HSCT [14]. Here we present the findings of a study of severe, multiline refractory aGVHD in pediatric patients treated with multiple infusions of allogeneic culture-expanded adult hMSCs (remestemcel-L [Prochymal]; Osiris Therapeutics, Columbia, MD).

METHODS

Study Design

This was an open-label, single-arm, prospective multicenter study of male and female pediatric patients between age 2 mo and 17 yr (inclusive) with grade B-D aGVHD [18] who were nonresponsive to steroids and, in most cases, other immunosuppressive therapies. The objectives were to evaluate whether the treatment plan (8 infusions of 2×10^6 hMSCs/kg) could induce an objective response in patients with severe refractory aGVHD, and also to assess the safety and tolerability of remestemcel-L infusion for the given dosing scheme.

As part of this trial, aGVHD prophylactic agents, concomitant therapies, and other supportive therapies were administered at the investigator's discretion in accordance with site-specific institutional practices and policies. Safety assessments included 12-lead electrocardiography, and monitoring for infusional toxicity, ectopic tissue formation, relapse of underlying malignancy, and survival. Serious adverse events (SAEs) were recorded throughout the study. Patients were evaluated for the efficacy and safety of remestemcel-L until death, withdrawal, or 100 d after the first infusion (day 0), whichever occurred first.

Study Population

Pediatric patients (age 2 mo to 17 yr; median age, 7.8 yr) with aGVHD secondary to allogeneic HSCT or donor lymphocyte infusion who had failed to respond to systemic steroid therapy for grade B-D aGVHD (using the Center for International Blood and Marrow Transplant Registry grading scheme [18]) were eligible. Failure to respond to steroid treatment for aGVHD was defined as any grade II-IV aGVHD that did not improve after at least 3 d of treatment with methylprednisolone (≥1 mg/kg/d) or equivalent. Exclusion criteria included known allergy to bovine or porcine products and most recent HSCT performed to treat a solid tumor. In addition, patients must not have had evidence of a pulmonary infiltrate or diffuse alveolar hemorrhage, and must have been deemed unlikely to require more than 2 L of oxygen via face mask or an estimated fraction of inspired oxygen of 28% via other delivery methods to maintain oxygen saturation of 92% for the 3 d after screening.

The protocol was submitted for ethics review, and approval or acknowledgment of treatment was obtained in writing from the Institutional Review Board or Ethics Committee of each institution. Parental signed informed consent and patient assent, when applicable, were required before any study-specific procedures were undertaken. The study was registered with www.ClinicalTrials.gov (NCT00759018).

Failed aGVHD Therapy

The number of therapies beyond systemic steroid therapy that each patient received before the start of remestemcel-L was recorded. Previous aGVHD therapies included systemic steroids (methylprednisolone or equivalent), infliximab, etanercept, pentostatin, daclizumab, rituximab, denileukin diftitox, alemtuzumab, mycophenolate mofetil, tacrolimus, and antithymocyte globulin. Nonsystemic steroids, such as budesonide and beclamethasone, were not counted as second-line therapy for aGVHD treatment, nor were prophylactic treatments, such as cyclosporine, sirolimus, and methotrexate. If an agent was used for aGVHD prophylaxis, discontinued, and then restarted for treatment, therapy must have been initiated after the onset of aGVHD for the agent to be counted as a second-line agent for aGVHD.

The effect of aGVHD therapies before the introduction of remestemcel-L was characterized as improving, unchanged, or worsening. Improving aGVHD was defined as at least a 1-grade reduction in aGVHD between disease onset and study baseline, worsening GVHD was defined as an increase in aGVHD grade, and maximal aGVHD was defined as grade D at both onset and study baseline.

Treatment Regimen

Remestemcel-L was given i.v. at a dose of 2×10^6 hMSCs/kg of body weight twice weekly for 4 consecutive wk. Patients received all 8 infusions in the initial treatment plan by day +28. Infusions were administered at least 3 d apart. During the course of remestemcel-L treatment, all other aGVHD therapies were administered at the discretion of the investigator according to institutional practice.

Patients who demonstrated a partial response (PR) or mixed response (MR) to remestemcel-L at study day +28 and had no safety issues related to therapy after the first 8 doses were eligible for continued therapy with an additional 4 infusions of 2×10^6 hMSCs/kg administered once weekly for 4 wk.

Within 30 min before remestemcel-L infusion, patients were premedicated with hydrocortisone (0.5-1.0 mg/kg, up to 50 mg/dose) and diphenhydramine (0.5-1 mg/kg, up to 50 mg/dose). The product was thawed and reconstituted with PlasmaLyteA (Baxter, Deerfield, Illinois) to a final cell concentration of 2.5×10^6 hMSCs/mL. The dimethyl sulfoxide (DMSO) concentration of the final infused product was 3.75%. The infusion was given i.v. at a controlled rate of 4-6 mL/min in patients weighing ≥35 kg and over 60 min in those weighing <35 kg. The total volume administered to each patient was dependent on body weight. Vital signs and oxygen saturation were monitored during each infusion. Oxygen saturation was monitored by pulse oximetry for at least 30 min before and up to 2 hr after the start of infusion.

All patients received standard of care treatment with corticosteroids, as well as other second-line agents at the discretion of the investigator.

Source of hMSCs, Remestemcel-L

The product lots of remestemcel-L used in this study were derived from the bone marrow of 7 different donors, age 18-30 yr, who had been screened and tested in accordance with Food and Drug Administration requirements for blood and tissue-based products. The product lots were manufactured using a scaled adaptation of the technique described by Pittenger et al. [19] in accordance with good manufacturing practices, as described previously [17]. All lots met established quality release criteria for viral pathogens, mycoplasma, sterility, endotoxin, cell identity, purity, viability, and potency before use.

GVHD Assessment

The severity of aGVHD was assessed using the Center for International Blood and Marrow Transplant Research grading system [18]. Patients were evaluated by the treating physician for the presence or absence of aGVHD of the skin, liver, and gastrointestinal (GI) system. Organ stage and overall grade were recorded. aGVHD assessments were performed at baseline before initiation of remestemcel-L, at day +28 after initiation, and at day +100/end of treatment.

Response to treatment was evaluated based on established clinical criteria [4]. Overall response (OR) was either a complete response (CR) or a PR. No response (NR) was defined as a MR, stable disease, or worsening disease. Definitions of responses are summarized in Table 1.