INTRODUCTION

Mesenchymal stromal cells (MSCs), designated mesenchymal stem cells by some investigators [1], are a heterogeneous population of spindle-shaped, plastic-adherent cells isolated from bone marrow, adipose tissue, and many other tissue sources [2,3]. These intriguing cells have been widely studied for many disorders in both hematopoietic cell transplantation and regenerative medicine.

Although MSC research continues along many avenues, this article will focus on the MSCs in close relation to hematopoietic cell transplantation (HSC). To assist the nonexpert, we have divided the article into 3 sections discussing (I) the current view of the MSC mechanisms of action for most applications, (II) MSCs as adjunct therapy to foster HSC engraftment and hematopoietic reconstitution, and (III) MSCs for prophylaxis and therapy of graft-versus-host disease (GVHD).

SECTION I: A NEW VIEW OF MSCS

Mesenchymal stromal cells (MSCs) were originally identified by Friedenstein et al. [4] as the stromal cells of the marrow microenvironment that support hematopoiesis. Soon thereafter, MSCs were shown to differentiate into bone and have an immense capacity for growth in cell culture in vitro. Friedenstein et al. [5] further showed that a subset of the cells had a high proliferative potential, generating clonal colonies when plated in tissue culture at low density, the so-called fibroblast colony-forming cells (CFU-F). It was then discovered that MSCs could differentiate in vitro into fat and cartilage as well as bone. At that time, the only widely recognized stem cells were the HSCs, and based largely on that model, adult stem cells were generally defined as cells that could undergo self-renewal and differentiation into at least 2 lineages. As there was no clear distinction between in vivo and in vitro differentiation capacity, MSC seemed to fulfill those criteria. Owen [6] then proposed the existence of stromal stem cells, analogous to the HSCs, that could reconstitute the hematopoietic microenvironment, and suggested the CFU-F may represent such cells. Later, Caplan [7] noted that MSCs fulfilled the self-renewal and multilineage differentiation criteria and proposed that these cells were actually MSCs, with the capacity to differentiate into a wide variety of mesenchymal tissues. According to this concept, these MSCs could serve as a broadly applicable stem cell source for regenerative medicine, repopulating injured tissues and clinically ablated diseased tissues with healthy, terminally differentiated, tissue-specific cells [8,9].

The New Paradigm of the MSC Mechanism of Action

It has now been 15 years since the first report of MSC infusion into humans [10]. Several thousand patients have received systemically infused MSCs for various indications. Interestingly, in all of these studies, the documented engraftment of donor cells at the presumed site of activity is low or even completely absent. Even in preclinical models, the engraftment is exceedingly low. Despite our preconceived notions, the most appropriate conclusion seems to be that, after systemic infusion, there is no definitive evidence of a therapeutic effect being mediated by engraftment and terminal differentiation of MSCs to the cells of the resident tissue. In other words, there is no evidence of MSCs acting as “building blocks” to rebuild tissue after systemic infusion. Given their feeble and transient engraftment, nevertheless resulting in substantial clinical benefit, what molecular and cellular mechanism may account for the striking biologic activity of MSCs? An emerging body of data suggests that soluble...
factors released by the MSCs are key elements in their mechanism of action for most, if not all, of the systemic effects [11].

MSCs secrete stromal-derived factor-1 [12], which plays a vital role in HSC homing to the niche in the marrow microenvironment [13]. In vitro, MSCs constitutively secrete interleukin (IL)-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, macrophage-colony-stimulating factor, Flt-3 ligand, and stem cell factor. Upon IL-1α stimulation, MSCs are induced to express further IL-1α, leukemia inhibitory factor (LIF), granulocyte-macrophage-colony-stimulating factor (G-CSF), and granulocytemacrophage-colony-stimulating factor (GM-CSF) [14]. Finally, MSCs can secrete several chemokine ligands, including CCL2, CCL4, CCL5, CCL20, CX3CL1, and CXCL8 [15].

The search for soluble mediators generated by MSCs is an active area of investigation and will probably reveal a new array of important secreted signaling molecules. These observations, together with the finding that local engraftment and differentiation, is an uncommon event, suggest a new general paradigm for MSC therapeutic activity. Systemically infused MSCs exert a therapeutic effect primarily through the release of soluble mediators that act on local and distant target tissues. Rather than serving as stem cells to repair tissues, they serve as cellular factories secreting mediators to stimulate the repair of tissues or modulate the local microenvironment to foster requisite beneficial effects.

**The Impact of the New Paradigm**

There are 2 key implications to the idea that the principal mechanism of biologic activity after systemic infusion of MSCs, in virtually all applications, is the secretion of soluble mediators. First, the tissue source of the MSCs may be critically important in determining biologic activity. Despite the uniform morphology and cell-surface marker expression, gene expression studies show that populations of MSCs are heterogeneous [16,17]. Whereas MSCs are often considered to be the same general population of cells regardless of the tissue source, recent data suggest that MSC gene expression reflects their tissue of origin, indicating that MSC tissue heterogeneity is biologically relevant [18,19]. Thus, different tissue sources may generate MSC products with different cytokine expression profiles. Hence, different MSC tissue sources may be especially suited for specific clinical applications. Second, isolation and culture expansion conditions may significantly affect gene expression, and therefore the bioactivity, of the cells. Such conditions include the seeding density, culture media, serum supplementation, and extent of ex vivo expansion. Furthermore, bioreactors, in contrast to conventional plastic culture flasks, may affect gene expression. These observations suggest that the cell processing protocols can be modified to enhance or repress expression of specific genes in order to optimize the cytokine profile for a given clinical indication.

What are the implications for the use of MSCs as adjunct therapy in HCT? The 2 principle applications are to enhance HSC engraftment and as prophylaxis and/or therapy for GVHD. The work investigating the use of MSCs to foster HSCs, which will be discussed in the next section, initially focused on repairing the cellular constituency of the microenvironment after radiochemotherapy conditioning. Use of MSCs to foster engraftment may merit a reexamination based on the idea that MSCs may release mediators that facilitate engraftment and hematopoietic reconstitution without actually rebuilding the microenvironment. The use of MSCs in GVHD, which is also discussed later in this article, is currently 1 of the most widely studied applications of MSCs. These studies are consistent with the secreted mediator proposal, and the approaches being studies are likely to yield optimal results.

**SECTION II: MESENCHYMAL STEM CELLS (MSCS) AND HEMATOPOIESIS**

The biologic relationship of stromal adherent stem cells/MSCs and hematopoiesis has been long recognized [5,20]. A variety of in vitro analyses have clearly demonstrated augmentation of hematopoietic stem cell (HSC) expansion upon coculture with ex vivo-expanded MSCs, with contributions from trophic factors and secreted cytokines as well as from direct cellular interaction in which stromal stem cells and their specific progenitors may provide a scaffold for HSC growth and expansion [1,14,21-23]. All lineages including lymphocyte expansion have been observed, with megakaryocyte expansion most heralded given the relative scarcity of these cells within the bone marrow environment [24].

What remains to be determined is whether hematopoiesis can truly be augmented in vivo by application of MSC in the human transplant setting [25,26]. Significant effort has focused on exploiting the paracrine effect of stromal adherent stem cells on the HSCs, with particular attention to the various secreted growth factors and matrix components that have agonistic effects on promoting HSC growth and differentiation as well as cellular expansion [1,14,21,22,24]. Additionally, the immune suppressive potential of MSCs has also been highlighted, not only for therapeutic interventions, but also for providing immune protection to potential targeted HSCs [27-32]. Recent demonstration that adherent stromal stem cells can modulate inflammatory cytokine-mediated tissue injury suggests that hematopoiesis augmentation by MSC may not be confined to growth promotion but also include injury protection processes.
Increased levels of tumor necrosis factor (TNF)-
à or interferon (INF)-ß associated with the inflammatory state have been known to hinder HSC growth and expansion, as has been demonstrated within the Fanconi anemia model of bone marrow failure [37,38]. This potential novel mechanism of MSC impact on hematopoiesis has not yet been scrutinized to any significant degree and remains a subject of intense investigation.

Despite the encouraging observations of augmented hematopoiesis by MSCs in vitro with confirmation of these principles with multiple preclinical animal models [39-43], there still remains a dearth of human studies that clearly document successful clinical augmentation of hematopoiesis by MSCs. Clinical application of MSCs could target enhancement of primary engraftment, or conversely, for application in patients experiencing or at risk for graft failure, recently shown in a retrospective analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) to be associated with over 90% mortality [44]. The first studies of interest were first published over 15 years ago, and subsequently, several small studies have been completed that confirm safety of MSC infusion and perhaps demonstrate some utility, but as of yet, no phase III randomized trials have materialized. In patients undergoing peripheral blood stem cell transplantation (PBSCT) for rescue after high-dose myeloablative chemotherapy for breast cancer, coinfusion of autologous, ex vivo expanded MSC was found to be safe, and interestingly, demonstrated both neutrophil engraftment at a median of 8 days and platelet engraftment at 8.5 days [45]. MSC were also used specifically to target enhanced engraftment in a study reported by LeBlanc et al. [46]. Seven patients, 3 of whom had already experienced graft failure/graft rejection, and 4 patients for whom hematopoietic engraftment were targeted for enhancement, were transplanted with HSCs and haploidentical MSCs, and all 7 achieved 100% donor chimerism with a median time to both neutrophil and platelet engraftment of 12 days. Subsequently, several other small studies in haploidentical HSC transplantation and of cord blood transplantation cotransplanted with MSC have suggested engraftment benefit, although this has not been universally confirmed [47-49].

What is intriguing is whether or not MSC transplantation by itself can provide therapeutic benefit. Certainly, this approach is being highlighted in the field of regeneration medicine using MSC both for immunomodulatory therapeutics as well as for assisting in tissue repair [32]. In HSCT, there have been isolated reports in which solitary MSC infusion may have provided therapeutic benefit. Specifically, Fouillard et al. [50] reported a single patient who underwent autologous stem cell transplantation for acute myelogenous leukemia (AML) who subsequently experienced partial graft failure, requiring ongoing growth factor in transfusion support. Even after an interval of over 2 years had passed, infusion of haploidentical MSCs from her brother was associated with reversal of the defect in hematopoiesis. Short-term but not long-term evidence of MSC engraftment was identified. Additionally, 6 patients with poor hematopoietic recovery after autologous transplantation were infused with donor-expanded MSC only [51]. It was a suggestive result that 2 of the 6 patients experienced rapid recovery of donor hematopoiesis, although the other 4 failed to demonstrate benefit. Observations such as these have led to great interest in MSCs being considered for use as primary therapy for hematopoietic injury. There have been animal studies to suggest that cotransplantation of MSC with limiting doses of HSC after radiation injury can lead to enhanced survival of the animals associated with more rapid platelet and neutrophil recovery [52,53]. Given these considerations, MSC therapy has emerged as a potential therapeutic maneuver for treatment of acute radiation syndrome, in the event of nuclear accidents or potential nuclear terrorist events, with a plan to stockpile for the Department of Defense large quantities of cryopreserved MSC. If FDA approval for MSC for treatment of acute radiation syndrome is eventually obtained, a staggered plan for delivery of 20,000 cryopreserved doses for the United States Emergency Preparedness Network has been put in place (Osiris, Inc., Website, announcement, 1/3/08).

Significant work remains to be performed to actually confirm that MSCs should be utilized routinely to support hematopoiesis with enough efficiency to demonstrate a therapeutic benefit. Many questions remain regarding efficacious dose, optimized and targeted delivery, and relevant efficacy measurements. Recently, there have been interesting observations that umbilical cord HCT directly transplanted within the medullary cavity has been associated with improved engraftment [54-56]. Certainly, many of the regeneration medicine efforts surrounding neurologic or cardiac repair have focused on issues of direct implantation versus systemic intravenous delivery. Trafficking of MSCs to relevant target areas is clearly confounded by pulmonary vascular bed retention, and whether augmentation of efficacy within the HSCT arena can be improved upon by direct implantation within the marrow cavity needs to be studied. A single case report provides tantalizing data on this subject [57]. A 3-year-old child with Wiscott-Aldrich syndrome underwent haploidentical HSCT from his mother with direct intraosseous injection of preexpanded, donor MSCs unilaterally into the iliac crest at 6 different sites. No clinical benefit could be documented, although posttransplant assessment at day 60 with bilateral bone marrow biopsies revealed markedly improved donor cellularity on the treated hemipelvis compared to the untreated side. Additionally, further efforts on using adherent stromal...
stem cell platforms for ex vivo expansion of stem cell products in limited supply such as for cord blood transplantation needs to be assessed [58-62]. Similarly, it remains to be determined if MSCs can effectively support haploidentical HSC transplantation perhaps by taking advantage not only of the support for hematopoiesis but also for protection of the donor graft from host T cell destruction, as has been proposed [47].

Finally, the characterization of MSC has been defined by consensus as a result of a recent effort by investigators supported by the International Society for Cellular Therapy (ISCT) [61]. However, no one questions that multiple adherent stromal stem cell populations have been identified, isolated from multiple tissue sources and captured potentially at multiple differentiation states [62]. Biologic properties may vary between these various MSC sources, but to date, side-by-side comparative trials have not yet been performed nor has it been determined whether or not autologous or allogeneic MSCs will be preferentially utilized. What has been demonstrated is that delivery can be performed safely, but all also agree that delivery to tissue target areas have not yet been optimized [63], and that long-term effects such as a deleterious effect on the graft-versus-leukemia response remain a concern [64]. Obviously, this would not be an issue if MSC are proven to ultimately be best used in the autologous setting or as a solitary product for defective hematopoiesis, but it does remain an important but unanswered issue in the setting of allogeneic HSCT. Ultimately, we anticipate that these will be the novel studies that will emerge over the next few years, recognizing that the cost of product will necessarily dictate close attention to viable and valid endpoints of trial design.

SECTION III: MSCS AND GVHD

Mesenchymal stromal cells (MSCs) are a population of phenotypically heterogeneous cells marked by an absence of hematopoietic markers (CD34−, CD45−), and expression of CD73, CD90, and CD105 surface markers, that can differentiate in vitro into osteoblasts, chondroblasts, and adipocytes [65-68]. Furthermore, MSC do not express HLA class II histocompatibility antigens, or accessory molecules, CD40, CD80, and CD86, required for immune cell activation, and thus, histocompatibility matching is not required for therapeutic effect [69]. Subpopulations may contribute directly, and via paracrine effects, to immunomodulation [70-73] and tissue repair [74-76]. Finally, MSCs can be readily expanded and purified ex vivo from bone marrow mononuclear cells obtained from animals and humans [77,78]. These unique properties make MSC a rationale agent to investigate for the treatment of graft-versus-host disease (GVHD), which results in significant morbidity and mortality following allogeneic hematopoietic cell transplantation (HCT).

Immunomodulation

MSCs possess intrinsic immunoregulatory activities that are still not fully characterized, but broadly modulate innate and adaptive immune responses [72,79]. Within the context of innate immunity, MSC alter antigen-presenting cell (APC) development, maturation, and function. Dendritic cells (DCs) are potent APC for naïve T cells, and are critical in donor T cell activation during acute GVHD [80]. MSC inhibit differentiation of monocytes to DC, and furthermore, affect DC differentiation, activation, and function [72]. MSCs also inhibit natural killer (NK) cell proliferation and cytokine production, and could potentially modulate DC function through their effects on NK cells [81]. Therefore, MSCs should suppress alloreactivation of donor T cells against the host in the setting of GVHD. However, this is with the caveat that acute GVHD (aGVHD) typically results in high levels of interferon (INF)-γ that may increase MHC class II expression on MSC [80,82], and could paradoxically augment GVHD.

Within the context of adaptive immunity, MSC inhibit alloreactive T cell responses via contact-dependent mechanisms and soluble factors [72,83], and some studies suggest a shift in T cell function toward a more regulatory phenotype [84]. Importantly, the effects of MSC on T cells are independent from HLA matching between MSC and lymphocytes [69]. Sundin and colleagues [85] evaluated the immunogenicity of HLA-mismatched MSC infused after HCT. Recipient lymphocyte response to MSC and peripheral blood lymphocytes from the MSC or third party donors was measured before and after MSC infusion. Transplant recipients given MSC showed an allo-response to the third party and MSC donor, but no immune response to infused MSCs, suggesting immune unresponsiveness restricted to the MSCs, rather than tolerance to the MSC donor; this lack of immune response was sustained after repeated MSC infusions [85].

Tissue Repair

The role of MSC in tissue repair is under extensive study. Of relevance to GVHD, a number of animal models of injury including cerebral ischemia [86], total-body irradiation (TBI) [87,88], and myocardial infarction [89] have demonstrated a chemotactic response of MSC to the site of injury. Once at the site of injury or inflammation, it has been proposed that MSC stimulate tissue repair of the affected organs. This likely occurs via the paracrine effects of MSC [90], rather than through direct MSC-mediated tissue repair [91].
Clinical GVHD Trials

Thus far, the majority of data for MSC are derived from tissue culture experiments and nonhuman animal models. However, some compelling clinical results have been noted in therapeutic trials for GVHD (Table 1). MSC have been most extensively studied in steroid-refractory GVHD. LeBlanc and colleagues [92] reported the first case of successful treatment of severe refractory aGVHD of the gut and liver in a pediatric patient using ex vivo expanded haploidentical human MSC. Prompt response was observed after the addition of MSC to the existing immunosuppressive regimen, but symptoms recurred after discontinuation of immunosuppression. Symptoms were responsive to a repeat dose of MSC [92]. Eight patients with steroid refractory GVHD were subsequently treated with complete response (CR) noted in 6 patients, and DNA from the MSC donor detected in the colon of 1 patient 1 month after MSC infusion [31]. These positive results were corroborated in a nonrandomized, multicenter trial reported by the European Blood and Marrow Transplant MSC consortium, using a shared expansion protocol for the cells and common reagents [93]. Twenty-five pediatric and 30 adult patients were treated with sibling HLA-identical, haploidentical, or third-party mismatched, bone marrow–derived MSC for steroid-refractory GVHD. A single MSC infusion, with median dose 1.4 × 10⁶ MSC/kg, was infused into 27 patients and the remaining patients were treated with 2 or more infusions. The initial response rate was 70% (30 CR, 9 partial response [PR]). The median time from infusion of first MSC to response was 18 days, with 19 patients with sustained CR at 6 weeks following infusion. Patients with a CR had a statistically significant lower treatment-related mortality (TRM) at 1-year and overall survival (OS) at 2 years following transplant compared to nonresponders, 37% versus 72%, P = .002, and 53% versus 16%, P = .018, respectively [97]. The infusions were well tolerated with no significant adverse events noted. There was a trend for better response in the pediatric patients, with a statistically better survival. The majority of patients received third-party donors, precluding an efficacy analysis for MSC match grade. Similar positive findings were noted in a large, pediatric phase II study of third-party, mismatched MSC (Prochymal®) for steroid-refractory aGVHD. Fifty-nine patients, with median age 8 years received 8 biweekly infusions of 2 × 10⁶ MSCs/kg for 4 weeks, followed by additional 4 infusions weekly as “maintenance” in patients with PR. The majority of patients had severe gut and liver GVHD, and had progressed through a median of 3.2 lines of prior therapy for GVHD. At day 28, the overall response rate, defined as organ improvement of at least 1 stage without worsening in any other, was 64%. These patients had a significantly better survival at 100 days compared to patients who did not achieve response at day 28, 76% versus 9% [94]. Similar findings have been noted in the remaining, smaller patient series using MSCs for GVHD, with transiently higher response rates noted than compared with historic data, and no significant adverse effects noted with MSC infusion (Table 1) [95–98].

There are fewer investigations of MSC for de novo aGVHD. Kebriaei and colleagues [99] reported the results of a phase II trial designed for patients with grades II-IV, de novo aGVHD. Thirty-two adult patients received 2 treatments of MSC (Prochymal®) at a dose of either 2 or 8 × 10⁶ MSCs/kg in combination with a conventional corticosteroid regimen. Patients continued to receive GVHD prophylaxis with tacrolimus, cyclosporine, or mycophenolate mofetil. Thirty-one patients were evaluable, with 94% initial response noted (21 CR, 5 PR). Nineteen of 24 CR were maintained for at least 90 days. No infusional toxicities or ectopic tissue formation were reported. The trial was not designed to detect a difference between the 2 different MSC doses, but no obvious differences were observed [99].

Preliminary results from 2 multicenter, randomized, Phase III clinical trials for de novo acute and steroid-refractory aGVHD have been reported (September 8, 2009 http://investor.osiris.com/release detail.cfm?ReleaseID5408763). In both studies weekly or biweekly MSC (Prochymal®) were administered for 4 weeks with individual dosing at 2 × 10⁶ MSCs/kg. Neither the steroid-refractory nor the newly diagnosed GVHD trials reached the primary endpoint of durable CR ≥28 days. However, select patients with either steroid-refractory liver or gastrointestinal GVHD were reported to have significantly improved response rates (81% versus 68%, P = .035). No significant difference was noted with respect to toxicity or recurrent malignancy rates [100]. Experience with MSCs for the treatment of chronic GVHD (cGVHD) is more limited. Three pediatric patients were treated with MSC for cGVHD, with 1 patient showing slight improvement after infusion of 3 million MSCs/kg administered at 7 months and again at 26 months following transplant [96]. One patient with extensive cGVHD was treated with 0.6 × 10⁶ haploidentical MSCs/kg at 5 months following transplant, with no response [31]. Of note, both this patient, and 1 of the cGVHD patients in the previous study, died eventually of EBV-PTLD related complications [31,96].

In conclusion, the clinical experience with MSC for the treatment of GVHD is encouraging, but incomplete. Significant questions remain regarding the optimal culture conditions, biodistribution, and persistence of MSC, as well as potential long-term toxicities and risk for infection. Future clinical trials should be designed to determine the optimal dose
<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>N</th>
<th>Med Age (Range)</th>
<th>GVHD</th>
<th>MSC Regimen (M, 10^6 MSC)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kebriaei et al., 2009 [33]</td>
<td>De novo acute GVHD</td>
<td>32</td>
<td>52 (34-67)</td>
<td>Grade II: 21</td>
<td>2 or 8 M/kg at 1 and 3 days after GVHD + steroids; mismatched MSC</td>
<td>94% initial response (77% CR, 16% PR), 61% sustained CR; No difference b/w high/low MSC dose; No infusional toxicity</td>
</tr>
<tr>
<td>Ringden et al., 2006 [26]</td>
<td>Steroid refractory, acute GVHD</td>
<td>8</td>
<td>56 (8-61)</td>
<td>Grade II: 2</td>
<td>1 M/kg (range: 0.7-9); 1 dose (range: 1-2); mismatched/sib/haplo MSC</td>
<td>6/8 CR; 5/8 survival; No infusional toxicity</td>
</tr>
<tr>
<td>Fang et al., 2007 [31]</td>
<td>Steroid refractory, acute GVHD</td>
<td>6</td>
<td>39 (22-49)</td>
<td>Grade III: 5</td>
<td>1 M/kg adipose MSC; 1 dose (range: 1-2); mismatched/haplo MSC</td>
<td>5/6 CR, 4/6 survival; No infusional toxicity</td>
</tr>
<tr>
<td>Le Blanc et al., 2008 [27]</td>
<td>Steroid refractory, acute GVHD</td>
<td>55</td>
<td>22 (5-64)</td>
<td>Grade II: 5</td>
<td>1.4 M/kg (range: 0.4-9); 1 dose (range: 1-5); mismatched/sib/haplo MSC</td>
<td>71% initial response (55% CR, 16% PR); 2-year survival benefit for CR, 53% versus 16%; No infusional toxicity</td>
</tr>
<tr>
<td>Von Bonin et al., 2009 [29]</td>
<td>Steroid refractory, acute GVHD</td>
<td>13</td>
<td>58 (21-69)</td>
<td>Grade III: 2</td>
<td>0.9 M/kg (range: 0.6-1.1); 2 doses; mismatched MSC expanded in platelet lysate-containing medium</td>
<td>2/13 CR, 5/13 mixed response; 4/13 alive at median 237 days; No infusional toxicity</td>
</tr>
<tr>
<td>Kurtzburg et al., 2010 [28]</td>
<td>Steroid refractory, acute GVHD</td>
<td>59</td>
<td>8</td>
<td>Grade II: 6</td>
<td>2 M/kg; 8 biweekly x4 weeks, followed by 4 infusions weekly x4 if PR; mismatched MSC</td>
<td>64% ORR at day 28; 76% versus 9% survival at day 100; No infusional toxicity</td>
</tr>
<tr>
<td>Martin et al., 2010 [34]</td>
<td>Steroid refractory, acute GVHD</td>
<td>244</td>
<td>44 MSC; 40 control</td>
<td>Grade II: 38 vs control III: 88 vs control IV: 47 vs control</td>
<td>2 M/kg; 8 biweekly x4 weeks, followed by 4 infusions weekly x4 if PR; mismatched MSC</td>
<td>significantly better response 81% versus 68%, ( P = .035 )</td>
</tr>
<tr>
<td>Muller et al., 2008 [30]</td>
<td>Acute/chronic GVHD</td>
<td>5</td>
<td>14 (4-17)</td>
<td>Grade II: 2</td>
<td>0.4-3 M/kg 1 dose (range: 1-3); haplo MSC</td>
<td>2/2 acute GVHD did not progress; 1/3 chronic GVHD improvement; No infusional toxicity</td>
</tr>
</tbody>
</table>

GVHD indicates graft-versus-host disease; MSC, mesenchymal stromal cells; GI, gastrointestinal; CR, complete response; PR, partial response; ORR, overall response rate; M, million.
and schedule of MSC administration, so that MSC are used most effectively.

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