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Mesenchymal Stromal Cell Product "MSC-FFM" for Treatment of Severe Multi-Organ Steroid Refractory Acute Graft-Versus-Host Disease in an Infant with Congenital Dyserythropoietic Anemia

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Abstract

Steroid-Refractory acute Graft-*versus*-Host disease (SR-aGvHD) remains a therapeutic challenge and carries a devastating prognosis especially in infants and small children where no treatment is available yet. Through various studies Mesenchymal Stromal Cells (MSCs) have been proposed but definitive studies are pending. A specific off-the-shelf preparation of Bone Marrow (BM)-derived MSCs, "MSC-FFM" has previously been described and is currently being tested in a multicenter trial. Nevertheless, more insight into the clinical application of "MSC-FFM" in different patient populations is needed. Especially in those with disease constellations that prompt Hematopoietic Stem Cell Transplantation (HSCT) but that haven´t been studied as extensively yet.

We report the case of a 1-year-old girl with transfusion-dependent Congenital Dyserythropoietic Anemia (CDA) type 2 who developed severe multi-organ SR-aGvHD following allogeneic HSCT. The aGvHD reached an overall grade IV according to the Glucksberg grading system with severe gastrointestinal hemorrhage which led to admission to the Pediatric Intensive Care Unit (PICU). AGvHD progressed despite treatment with Cyclosporine A (CsA), Methylprednisolone and Mycophenolate-Mofetil (MMF). Administration of weekly doses of "MSC-FFM" was initiated after 15 days (d) of futile methylprednisolone treatment and resulted in Partial Resolution (PR) at d+28 and Complete Resolution (CR) at d+34 after the start of MSC treatment. No toxicities were detected, and steroids were weaned on d+38 after the first dose of "MSC-FFM". MMF was stopped on d+93 and CsA is being tapered. She shows a promising course of immune cell recovery and no chronic GvHD; she is a full donor chimera.

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Introduction

Acute Graft-versus-Host Disease (aGvHD) remains a challenging complication after Hematopoietic Stem Cell Therapy (HSCT)[1]. Although the incidence and severity varies greatly the mortality of aGvHD remains considerable [2] especially with intestinal and/or liver involvement [1]. First line therapy continues to be corticosteroids [1-3], but in spite of their potent anti-inflammatory activity only about half of aGvHD patients experience CR through this Standard of Care (SOC) [1,3-5], and immunosuppressive treatment predisposes to various, especially infectious, complications [3]. Due to the multicausal dismal prognosis of SR-aGvHD [6,7], several strategies for secondary treatment are under investigation [8], but so far not one of them could establish itself as SOC in young children [1,7,9,10]. In some quite the opposite appears true as they show potent toxicities and side effects [1,8]. This leaves an urgent need for new treatment strategies [7].

Since their first description [11] MSCs have been studied extensively [7]. With their broad immunosuppressive capacities [4,10,12-14], as well as regenerative properties [4,15-17] and their ability to migrate to distant and thus possibly inflamed tissues [4,18] they seem an ideal treatment element for SR-aGvHD therapy [19].

While many clinical studies report clinical effectiveness in SR-aGvHD [8,12,20-23], confirmation by way of randomized controlled trials is still lacking [20,24]. Regardless, all studies describe their

favorable toxicity profile: application of MSCs was reported to be safe [7,8,12,21,22,25].

Furthermore, ambiguous results have been published regarding the amount of resolution that can be achieved by MSC therapy [7]. On d+28 after start of MSC therapy 58% [24] to over 80% [26-28] of SR-aGvHD patients had improved; how much of this is attributable to the MSCs is, by necessity, debatable. The high variability was proposed due to different preparation techniques and donor heterogeneity, all affecting the potency of the cell product [10,29]. By creating a MSC bank from pooled BM mononuclear cells of random BM donors Kuci et al. [27] established a standardized off-the-shelf cell product, "MSC-FFM" [30], which received national marketing authorization and was, applied clinically [27]. The encouraging results warrant further studies and application of this product [27,30]. Meanwhile multicenter trials have started.

Case Presentation

Herein, we report the case of a 1-year-old girl whose severe SR-aGvHD was treated with "MSC-FFM". Past medical history is pertinent for intra-uterine anemia (minimal Hb 2.9 mg/dl) with hydrops fetalis requiring 2 intrauterine Red Blood Cell (RBC) transfusions (SSW21+4 and 28+6). She was born by Caesarean delivery after a concerning cardiotocography at 29 weeks. After birth bi-nuclearity of erythroblasts, increased ferritin levels and evidence of SEC23B mutation led to a rapid diagnosis of CDA type 2, which was managed conservatively with monthly RBC transfusions. Concurrently, she faced several other life-threatening complications of prematurity like an intraventricular hemorrhage and respiratory distress syndrome.

The ongoing transfusion dependency led to the early decision for HSCT with a conditioning regimen of Treosulfan (3 × 12 g/m^2), Thiotepa (2 × 4 mg/kg Body Weight (BW)), Fludarabin (4 × 40 mg/m^2) and ATG (20 mg/kg BW). She was transplanted with a BM graft containing 7.66 × 10^6 CD34+ cells/kg BW of a 10/10 matched unrelated donor. As aGvHD prophylaxis our patient received CsA (initially 3 mg/kg BW), as well as methotrexate (10 mg/m^2) on d+1, +3 and +6 after HSCT.

Initially, a timely regeneration with thrombocyte and leukocyte take on d+23 and +24, respectively, was seen. Unfortunately, severe aGvHD compromised the engraftment, and led again to transfusion dependency of thrombocytes and RBCs until d+100 after HSCT.

One week prior to engraftment (d+15), she developed aGvHD of the skin, prompting treatment with methylprednisolone (initially 2 mg/kg BW) under which skin aGvHD worsened to generalized erythrodermia with strong pruritus (grade III by Glucksberg grading [31]) (Figure 1A)). The pruritus led to our patient developing rocking movements, which only ceased after administration of clonidine.

Signs of liver and Gastrointestinal (GI) aGvHD arose on d+29 and progressed rapidly. Liver aGvHD reached grade III [31] (d+40) with a bilirubin of up to 7.2 mg/dl and maximum liver transaminases of 304 U/l (GOT), 810 U/l (GPT), and GGT values of up to 1767 U/l (d+27, 28, 51, respectively). Upper GI aGvHD was noticeable by frequent vomiting for which we implemented a feeding tube. Lower GI aGvHD presented with increased volumes of diarrhea and hematochezia (grade IV [31] on d+47-51). The overall grading of aGvHD reached grade IV [31] (d+31-34 and +39-52). On d+21 MMF (30 mg/kg BW) was added for aGvHD control without relevant therapeutic benefit, yet further progression of aGvHD.

On d+30 (d+15 after start of aGvHD and methylprednisolone treatment) a first dose of "MSC-FFM" was administered; a total of six doses (2 × 10^6 cells/kg BW) were given at weekly intervals, meanwhile maintaining the triple immunosuppression. Subsequently, skin responded by d+44 and was in CR from d+48 onward (d+14 and +18 after first dose of "MSC-FFM", respectively). Liver showed an objective response by d+46, CR by d+64 (d+16 and +34 after first dose of "MSC-FFM", respectively).

Parallel to the resolving skin and liver aGvHD she had an acute duodenal hemorrhage (Forrest Ib), which was clipped and injected with suprarenin. Multiple ulcers and vulnerable mucosa were found in the immediate vicinity on endoscopy – consistent with aGvHD. Differential diagnoses like CMV were ruled out hereafter. The diffuse and heavy intestinal hemorrhage led to a five-day stay at the PICU. Although the intestinal bleeding was controlled, GI aGvHD reached CR only at d+64 (d+34 after first dose of "MSC-FFM") (Figure 1B)). From d+68 onward, first methylprednisolone was weaned, then MMF was discontinued (d+93) and tapering of CsA has already begun.

During her long hospitalization our patient developed additional complications in the form of infections, which were treated with various antibiotic regimens. Whilst receiving immunosuppressive treatment she had recurrent fevers and once a *Staphylococcus haemolyticus* was detected in her blood culture. Her CRP levels reached a maximum of 28.73 mg/dl. As the methylprednisolone was tapered and subsequently stopped, so did the infections. Her immune system shows a continuous increase in all cell lines.

Her nutrition buildup proved difficult, as she was losing weight despite eating adequate amounts even after CR of GI aGvHD.

She was discharged with additional parental nutrition but otherwise in good general condition. Today, the patient gained 2 kg BW, is in excellent clinical condition and free of acute and chronic GvHD at d+151 post-transplant, with her underlying disease being in remission and complete donor chimerism in all lineages.

Discussion

The case of our 1-year-old patient with CDA warrants reporting as it represents a course of severe SR-aGvHD in a very young patient with a rare non-malignant disease. Severe SR-aGvHD has a devastating prognosis [6] and as no SOC is currently available in this particular age group [10] and second-line options carry several toxicities and side effects [1,7,8,32], the need for new treatment options is immense.

MSCs have distinguished themselves in terms of efficacy and safety [7,8,20,21] and "MSC-FFM" in turn has erased the variable of cell donor heterogeneity and implemented an off-the-shelf product [27,30]. The absence of infusion-related toxicities [5,33] combined with the confirmed short- and long-term safety even after multiple infusions [8] underline the advantage in heavily pre-treated patient populations.

So far, in clinical MSC studies patients with rare and non-malignant diseases like CDA [34] were enrolled less frequently [8,35,27], justifying the specific interest in this case.

In transfusion-dependent severe CDA allogeneic HSCT is the only curative treatment option [34,36]. Yet, aGvHD is the main reason of death [36]. As our patient developed multi-organ SR-aGvHD the decision for treatment with "MSC-FFM" was made. Interestingly, MSCs seem more effective in severe aGvHD [21], as they are

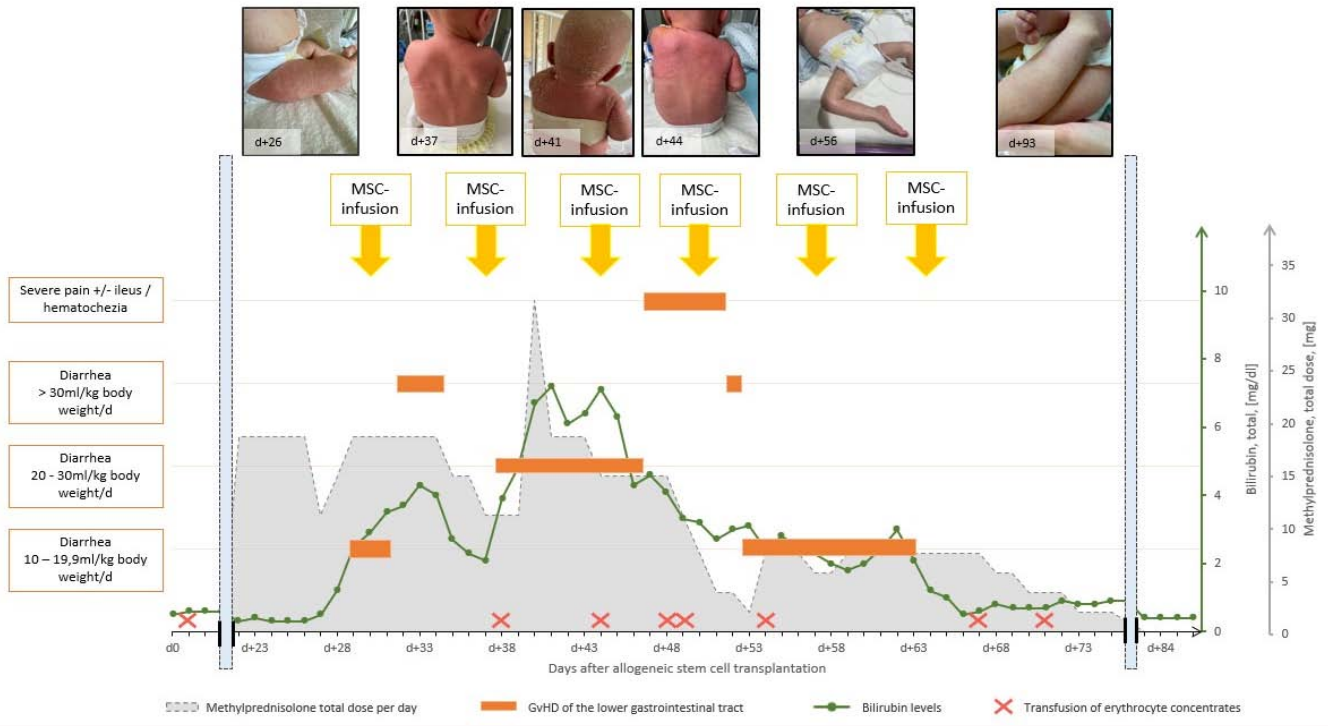

Figure 1: Evolution of SR-aGvHD. A) Development and resolution of skin aGvHD. The time given on the pictures corresponds to the number of days after HSCT. B) Course of liver and lower GI aGvHD together with the application of steroids and "MSC-FFM" doses. The four stages of GI tract aGvHD on the left correspond to the Glucksberg grading system [34].

activated by their inflammatory environment [37]. Accordingly, an earlier administration during the acute phase of inflammation seems advantageous [8,14,27]. Here, our patient received "MSC-FFM" on d+15 after the start of steroid therapy.

The d+28 after start of MSC therapy is perceived as predictive for survival as non-responders at d+28 rarely respond afterwards and most die [21,27,30]. In this case, our patient showed a very good overall PR on d+28, with CR of skin and upper GI tract. At this time, liver and lower GI aGvHD were subsiding but overall CR took one more week until d+34, which we still consider as fast in such a severe manifestation of SR-aGvHD. The rapid response of the skin and the protracted response of liver and gut are a known phenomenon [8]. Persistence of GI symptoms is attributed to post-inflammatory villous atrophy rather than ongoing aGvHD [8], explaining the protracted course of diarrhea and absence of weight-gain in our patient. As previously reported, MSCs emit trophic factors which may help rebuild the endothelial damage in aGvHD of the bowel [33].

The only adverse events during MSC treatment, albeit likely not attributable, were several bacterial infections, which stopped after tapering of steroids. Most strikingly, no viral reactivations were observed, which contrasts with other studies where T-cell toxic treatments were being used [32,38].

Conclusion

The excellent outcome in this case of severe multi-organ SR-aGvHD in a toddler with an underlying non-malignant marrow failure adds to the body of data supporting tolerability and effectiveness of treatment with "MSC-FFM".

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