GvHDHub

cGvHD, aGvHD

Impact of mesenchymal stem cells in the hematopoietic stem cell transplantation on prevention and treatment of GvHD

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A systematic literature review on the role of mesenchymal stem cells (MSC) in the prevention and treatment of graft-versus-host disease (GvHD) by Zhao and colleagues was published in the June issue of Stem Cell Research and Therapy.[1] It aimed to evaluate whether the efficacy of MSC-based therapy on the prevention and treatment of GvHD was greater than conventional therapy.

The use of hematopoietic stem cell transplantation (HSCT) for treatment of hematologic malignancies and genetic disorders is increasing, with the number of unrelated donors expected to double in the next 5 years. Unfortunately, this therapy is associated with as much as 50% risk of GvHD,[2] an immune response where donor cells attack healthy tissue of the recipient. The complication can manifest itself as acute (aGvHD) or chronic (cGvHD).[3]

The preventative strategies include pharmacological manipulation of T cells after transplantation which reduces the frequency of GvHD but does not enhance long-term survival. Therapy of choice for GvHD are steroids, but many patients become refractory.[4-7] Over the years, there has been little improvement in the mortality and morbidity of the disease and patients with severe chronic GvHD have long-term survival rates of 25–5%.[8] Recently, use of MSCs, immunosuppressive fibroblast-like cells with the self-renewal capacity and ability to differentiate into multiple mesenchymal cell lineages, has become an exciting tool for treating and prophylaxis of GVHD in the HSCT setting[9] and have been approved for use in clinical trials as immunomodulators[10] and in some countries gained approval for the treatment of children with steroid-refractory GvHD.

Multiple studies have explored the possible benefits of MSCs in GvHD with conflicting results.[11-14] This systematic review and meta-analysis selected 10 studies out of 413 candidates published between 2008 and 2017. The design of the prevention and treatment studies are presented in tables 1 and 2 respectively.

Meta-analysis of MSC for prevention

Among seven randomized clinical trials listed in Table 1, a total of 402 patients underwent HSCT, of whom 205 were in control group undergoing conventional GVHD prevention and 197 patients in the MSC group received MSC infusions.

Table 1. Design of studies using MSC for prevention of GvHD.

Study	Patient populations	Sample size (MSC/ control)	Average age (MSC/ control)	Male % (MSC/ control)	MSC source and dose (cells/kg)	MSC infusion timing	Maximum follow-up (month)
Xiang J, 2017[15]	ALL	32/32	5.5/5.2	56/53	UC 1.0×10^6	4 h after HSCT	12
Gao L, 2016[16]	AML, MDS, ALL,	62/62	18–40/ 18–40	47/48	UC 3.0×10^7	Monthly after HSCT*	70
Shipounova IN, 2014[17]	Leukemia	39/38	17–63	NR	BC $(0.9–1.65) \times 10^6$	19–54 days after HSCT	55
Liu, K, 2011[14]	ALL, AML, CML, high-risk patients	27/28	30/31.5	74/68	BC $(3–5) \times 10^5$	Within 24 h after HSCT	33.5
Ning H, 2008[13]	AML, CML, MDS, ALL, NHL	10/15	38/37	90/87	BC 3.4×10^5	4 h before HSCT	36
Kuzmina L A, 2012[2]	AML,MDS, ALL, CML, CLL	19/18	34/29	42/39	BC 1.1×10^6	19-54 days after HSCT	32
Wu K H, 2013[18]	ALL, AML	8/12	9.8/8.5	63/50	UC 7.2×10^6	4 h before HSCT	27

ALL, acute lymphoid leukemia; AML, acute myeloid leukemia; BM, bone marrow; CLL chronic lymphoid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NR, not reported; UB, umbilical cord; *, up to 4 doses

Engraftment

Only three studies reported the median time to neutrophil engraftment for both groups. Analysis showed shorter time to neutrophil engraftment in the MSC group (syndrome myelodysplastic (SMD) = - 1.20; 95% CI, 2.57–0.17; I^2= 88%; p < 0.01)). The large heterogeneity was likely to be due to different sources of MSCs. After excluding the most heterogenic study the heterogeneity was significantly reduced (SMD = -1.89; 95% CI, -2.42– -1.37; I^2= 0%; p = 0.91).

A subgroup analysis based on the source of MSCs revealed that the UB-MSC subgroup had a significantly shorter time to neutrophil engraftment in the MSC group compared with the control group (SMD = -1.89; 95% CI, -2.42– -1.37).

According to a subgroup analysis based on MSC infusion time, the subgroup which received the infusion after HSCT showed a significantly shorter latency to neutrophil engraftment compared with the control group (SMD = -1.91; 95% CI, −2.51− -1.31).

aGvHD

The meta-analysis of the five studies, which reported the number of patients who developed aGVHD within 100 days after HSCT, showed a trend towards lower risk of aGVHD in the MSC group patients (RR = 0.59; 95% CI, 0.34–1.03; I^2 = 39%; p = 0.16) independent on the MSCs source and time of infusion.

cGvHD

The meta-analysis of the six studies which reported the number of patients who developed cGVHD showed, a significantly lower risk of cGVHD in the MSC group patients (RR = 0.61; 95% CI, 0.45–0.83; I2 = 0%; p = 0.59). The subgroup analysis showed the result was driven by the UB-MSC subgroup (RR = 0.49; 95% CI, 0.28–0.85), while there were no significant differences in the BM-MSC subgroup.

Similar to the aGvHD, the subgroup which received the MSCs infusion after the HSCT (RR = 0.63; 95% CI, 0.46–0.86) had a significantly lower risk of cGVHD compared with the control group; the subgroup with the infusion before HSCT did not show significant differences between MSC and control groups.

Relapse

Based on the analysis of seven studies, there was a trend towards lower risk of relapse in the MSC group compared to patients receiving conventional treatment (RR = 0.98; 95% CI, 0.70− 1.39; I^2 = 0%; p = 0.46). The subgroup analysis showed a not-significantly lower risk of relapse in the patients receiving MSC from UB (RR = 0.90; 95% CI, 0.581–1.41) and not significantly higher risk using BM-derived MSC (RR = 1.20; 95% CI, 0.59–2.41), compared to control group. Patients with the MSC infusion after the HSCT had decreased RR compared to controls (RR = 0.86; 95% CI, 0.59–1.24), while MSCs infusion before the HSCT had a negative impact (RR = 2.44; 95% CI, 0.95–6.31), both differences were not statistically significant.

Death

In the meta-analysis of the seven studies, patients in the MSC group showed a trend towards a lower risk of mortality (RR = 0.84; 95% CI, 0.61–1.15; I^2 = 1%; p = 0.41) compared to control group. Both BM and UC sources of MSC were associated with a non-significant lower risk of mortality compared with the control group (RR = 0.83; 95% CI, 0.43–1.61 and RR = 0.85; 95% CI, 0.55–1.31).

While the subgroup analysis based on MSC infusion time, showed a lower (but not statistically significant) risk of death in the ‘after’ subgroup (RR = 0.75; 95% CI, 0.54–1.06) compared with the control group, whereas the risk was higher (but not statistically significant) in the ‘before’ subgroup (RR = 1.40; 95% CI, 0.64–3.08).

Death due to relapse

The analysis based on the five studies which reported the number of patients who died after relapse for both groups, MSC was associated with a trend towards higher risk of death due to relapse, was (RR = 1.16; 95% CI, 0.93–1.46; I^2 = 0%, p = 0.77) compared with the control group. Moreover, both sources of MSC had not significantly increased the risk of death

due to relapse compared with the control group (BM RR = 1.28; 95% CI, 0.76–2.15 and UC RR = 1.19; 95% CI, 0.81–1.77). Similar effect was seen independent of the MSC infusion time before HSCT (RR = 1.57; 95% CI, 0.89–2.80) and after (RR = 1.10; 95% CI, 0.86–1.41)

Death due to infection

Meta-analysis of four studies showed non-statistically significant decreased risk of death due to infection in patients receiving MSC (RR = 0.70; 95% CI, 0.31–1.60; I2 = 0%, $p = 0.61$) compared to conventional treatment. Concordantly, both the BM-MSC (RR = 0.65; 95% CI, 0.11–3.75) and UC MSC (RR = 0.60; 95% CI, 0.19–1.94) subgroups showed a trend towards the decreased risk of death due to infection compared with the control group. Similar, impact was also seen in subgroup analysis by time of infusion with both the 'before' (RR = 0.25; 95% CI, 0.04–1.72) and 'after' (RR = 0.88; 95% CI, 0.35–2.20) subgroups having lower (not statistically significant) risk of death caused by infection compared with the control group.

Meta-analysis of MSC for treatment

A total number of 103 patients with aGVHD from the 3 non-randomised clinical trials listed in Table 2 were included in the analysis; 57 of whom underwent conventional treatment (control group), and 46 received additional MSC infusions (MSC group).

Table 2. Design of studies using MSC for the treatment of acute GvHD.

Study	Sample size (MSC/ control)	Median age (MSC/ control	Male (%) (MSC/ control)	Meantime of aGVHD diagnosis after HSCT (days)	aGvHD grade	MSC source and dose (cells/kg)	Median duration of GVHD prior to enrolment (range)	Max follow-up (days)
Zhao K, 2015[19]	28/19	26/29	68/63	37/33	II-IV	BM 1×10^6	17 (11–55)	1312
Szabolcs P, 2010[20]	14/14	7/10	50/71	NR	II-IV	UC 2×10^6	20/8	139
Remberger, M, 2012[21]	15/13	57/48	NR	63/56	III-IV	NR 3×10^7	8(0–37)	730

Complete response (CR)

- In two of the three groups which reported CR, the relative rate (RR) of CR was higher in the MSC group compared to control (RR = 2.28; 95% CI, 1.24–4.18; $I^2 = 0\%$; $P = 0.97$)

Overall survival (OS)

- Based on the results from three studies patients in the MSC group had a higher rate of survival (RR = 1.93; 95% CI, 1.12–3.32; I^2= 41%; P = 0.18)

Conclusion

The authors conclude that their systematic review of randomized clinical trials suggests the efficacy of MSC treatment in improving CR rates and overall survival for cGvHD. Prevention of cGVHD and the promotion of engraftment were optimal with UC MSCs and when the infusion was performed after HSCT. The BM MSCs infusion before HSCT may be harmful to patients and thus should be considered carefully. The main limitations of this meta-analysis were the small number of included studies and their small number of patients. Therefore, the results would need to be validated in further studies. This would allow to more accurately determining the clinical impact of MSC infusion for treating and preventing GVHD.

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