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Insurance approval of mesenchymal stem cell for acute GVHD in Japan: need of follow up for some remaining concerns

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Abstract Acute graft-versus-host disease (aGVHD) is a major obstacle following allogeneic hematopoietic stem cell transplantation. Steroid is the standard treatment for aGVHD grade II-IV; however, nearly half of patients do not respond to the therapy. Many drugs have been proposed, but no standard therapy has been determined. This is because of the resistance to these drugs and of infections due to prolonged immunosuppressive states. Over the past decade a new approach using mesenchymal stem cells (MSCs) has been emerging in Japan and western countries. MSCs have unique characteristics such as specific immunosuppressive properties, no immunogenicity on their own and supportive activity for hematopoiesis. Most of the published trials have reported a favorable effect in acute GVHD, but a phase III trial failed to reach the primary endpoint, although, subgroup analyses found significant effects on gut and liver GVHD in the patients with MSCs infusion. In Japan several institutes are trying to develop MSC for clinical use in post HSCT patients. However, several limitations make it difficult to use MSC in clinical practice. Recently we conducted a phase II/III study using MSC (JR-031) for patients with steroid-refractory grade III or IV aGVHD. From the feasible clinical results, JR-031 was approved by PMDA as the first product which meets the Act to Revise the Pharmaceutical Affairs Act and the Act to Ensure the Safety of Regenerative Medicine. The cost of one series of the treatment is more than ten million yen. Now we encounter new issues such as cost, indication, safety and efficacy. The mechanism of MSC is still unclear and potential concerns about ectopic tissue formation and MSC related malignancy in vivo remain. In conclusion, MSC infusions are well tolerated and show benefit in some patients without adverse safety effects; however, long-term follow-up is needed to be more certain of this.

Keywords Mesenchymal stem cell · Graft-versus-host disease · Safety · Cost · Follow-up

Introduction

Allogeneic hematopoietic stem cell transplantation (Allo-HSCT) is a curative therapeutic option for hematopoietic malignancies and hematopoietic stem cell disorders [1]. Graft-versus-host disease (GVHD) is a major obstacle following allogeneic HSCT. Acute GVHD (aGVHD) develops in a significant number of patients who receive Allo-HSCT despite GVHD prophylaxis [2]. Once aGVHD grade II–IV develops, standard initial therapy is systemic administration of methylprednisolone. However, about half of the patients do not respond to this therapy [3, 5]. Despite nearly 40 years of clinical experience and developing new agents, the treatment of steroid refractory aGVHD still needs to be improved [6–20]. Hitherto no standard strategy has been established [4].

Mesenchymal stem cells (MSCs) were originally identified in mouse bone marrow and were well characterized for their multi-potentialities [19]. Recent studies have shown that MSCs are a strong modulator of both acquired and natural immune systems. Thus, MSCs would seem to be promising for the treatment of excessive immune responses.

Since the first results of dramatically improvement with treatment using BM-MSCs in a 9-year-old boy with refectory GVHD, there have been several reports on the

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effectiveness of MSCs against steroid refractory aGVHD [20–39]. In Japan, several institutes have carried out clinical studies of MSCs for complications after HSCT. Previously, we reported a phase I/II study using MSCs (JR-031) derived from bone marrow of unrelated healthy subjects for patients with steroid-refractory grade II or III acute GVHD [40]. Subsequently, we conducted a phase II/III study using JR-031 for patients with steroid-refractory gradeIII or IV acute GVHD [41]. From the feasible clinical results, JR-031 was approved by PMDA as the first product which meets the Act to Revise the Pharmaceutical Affairs Act and the Act to Ensure the Safety of Regenerative Medicine.

Now we encounter old and new concerns such as cost, indication, safety and efficacy. In this review, I will discuss the current status of MSC treatment and future direction of cell therapy.

Mesenchymal stem cell

MSCs and MSC-like cells can be isolated from many different tissues, including bone marrow, adipose tissue, placenta, amniotic fluid, and umbilical cord blood [19]. All MSCs are phenotypically and functionally equivalent, and it is not known how in vitro expansion affects these features. MSCs have unique characteristics, such as specific immunosuppressive properties, no immunogenicity, and supportive activity for hematopoiesis. MSCs are thought to accumulate at injury sites and help to repair them. MSCs have strong immunosuppressive actions on many kinds of acquired or innate immune cells, in vitro, although the mechanism for this is unclear. PGE2, TGF-B1, HGF and others are reported to be key molecules for their function [19]. It has also been suggested that cell–cell direct contact is needed. They differentiate into fibroblasts; chondroid, muscle, tendon, bone blasts and endothelial cells. In bone marrow, they construct the environment. MSCs are considered be have immunogenicity, displaying low expression levels of human leukocyte antigen (HLA) major histocompatibility complex (MHC) class I and no expression of costimulatory molecules. In vitro studies have demonstrated that MSCs do not elicit a proliferative response from allogeneic lymphocytes [42]. This evidence supports the possibility of exploiting third party donor MSCs for therapeutic applications.

However, recent findings indicate that MSCs can function as APCs and activate immune responses under appropriate conditions [19, 43]. It has been hoped that MSCs would reach sites of inflammation, but evidence for this is lacking. Transfused MSCs are trapped in the lungs and then remain in the liver and spleen [42]. The possibility that some may reach sites of inflammation cannot be ruled out, but that action may be a paracrine function.

To some extent, concerns about the ectopic formation and transforming to malignancy during the passage of MSC remain [44].

Taken together, the mechanisms of MSC in acting against GVHD remain unclear. It is speculated that allogeneic MSCs can engraft in immunocompromised hosts or at immune-privileged sites but trigger an immune response in hosts with an intact immune system, resulting in elimination. On the other hand, elimination of allogeneic MSCs might be profitable. It is hoped that MSCs only temporarily suppress the immune system, thereby reducing the risk of infection, malignant transformation, or suppression of a graft-versus-tumor effect.

GVHD

Donor-versus-host alloreactivity may always be directed towards all recipient tissue and cells (GVHD) in addition to leukemia cells (GVL effect). GVHD has been classically divided into aGVHD, occurring within 100 days after transplantation, and chronic GVHD developing thereafter. However, aGVHD may occur beyond day 100 after HCT [3], often upon discontinuation of immunosuppression [45, 46]. In the new GVHD classification proposed by the National Institutes of Health Consensus Conference [47], aGVHD is defined as GVHD without features consistent with chronic GVHD, even occurring after day 100. aGVHD is a severe and potentially life-threatening complication after transplantation. The most common primary therapy for aGVHD consists of methylprednisolone, 2 mg/kg/day for 7–14 days, followed by gradual dose reduction if the GVHD improves. However, almost half of patients are thought to be resistant to this primary steroid therapy. A wide variety of second-line treatments such as ATG, MMF, daclizumab, alemuzmab, infliximab, pentostatin, etanercept, sirolimus, low-dose MTX and ECP, are reported from western [5–10, 48, 49] countries as well as Japan [12–18]. Mostly they found some merits but substantial portion of patients die because of high risk of infectious complications, immunosuppression-mediated toxicity and often incomplete GVHD remission. Further more recently endothelial damage in refractory GVHD has been well documented. Transplantation associated microangiopathy (TAM) may explain the steroid refractoriness in part [50, 51]. In addition, immunosuppressive therapy for GVHD is associated with deterioration of the GVL effect, resulting in the risk of relapse of malignant disease. Thus the improved second line treatments are desired.

MSCs for GVHD: Institution oriented studies

Le Blanc first reported the transplantation of haploidentical mesenchymal stem cells in a patient with severe treatment-resistant grade IV aGVHD of the gut and liver, which resulted in a striking clinical response [20].

Following the initial success, European Group for Blood and Marrow Transplantation conducted a phase II clinical study aiming to assess whether mesenchymal stem cells could ameliorate GVHD after HSCT [24]. Fifty-five patients with steroid-resistant, severe, aGVHD received 1-3 infusions of bone-marrow derived mesenchymal stem cells from HLA-identical siblings, haploidentical donors, and third party donors (1.4×10^6/kg). Three patients had recurrent malignant disease and one developed de-novo acute myeloid leukemia of the recipient origin. Complete responders had lower transplantation-related mortality 1 year after infusion than did patients with partial or no response (11 [37 %] of 30 vs. 18 [72 %] of 25; $p = 0.002$) and higher overall survival 2 years after transplantation (16 [53 %] of 30 vs 4 [16 %] of 25; $p = 0.018$). They concluded that infusion of mesenchymal stem cells expanded in vitro, irrespective of the donor, and might be an effective therapy for patients with steroid-resistant, aGVHD. However, 33 patients had already received second-line therapy for aGVHD before MSCs infusion.

Introna et al reported that fourty patients with steroid refractory grade II to IV aGVHD received bone marrow-derived MSCs [36]. Patients received a median of 3 MSCs infusions after having failed conventional immunosuppressive therapy. A median cell dose of 1.5×10^6/kg per infusion was administered. No acute toxicity was reported. Overall, 86 adverse events and serious adverse events were reported in the study, most of which (72.1 %) were of infectious nature. The overall response rate, measured at 28 days after the last MSCs injection, was 67.5 %, with 27.5 % complete response. The latter was significantly more frequent in patients exhibiting grade II GVHD as compared with higher grades (61.5 vs. 11.1 %, $p = .002$) and was borderline significant in children as compared with adults (46.7 vs. 16.0 %, $p = .065$). Overall survival at 1 and 2 years from the first MSCs administration was 50.0 and 38.6 %, with a median survival time of 1.1 years. They concluded that MSCs can be safely administered on top of conventional immunosuppression for steroid resistant GVHD treatment.

Sanchez-Guijo et al reported that 25 patients with steroid refractory aGVHD received four infusions (days 1, 4, 11, 18) with 1.1×10^6 MSC/kg bone marrow-derived MSCs [37]. There were no adverse events related to the MSCs infusion in the 99 procedures performed. The response to MSCs at 60 days after the first dose was evaluable in 24 patients. Seventeen patients (71 %) responded (11 complete and 6 partial responses), with a median time to response of 28 days after the first MSCs dose, whereas 7 patients did not respond. They concluded that sequential cryopreserved third-party MSCs therapy is a safe procedure for patients with steroid-refractory aGVHD.

Wernicke et al reported the metaanalysis of 183 cases that nearly half patients with steroid refractory aGVHD had complete response [32]. Other reports have been from small clinical studies, including phase I or phase I/II studies to treat steroid refractory aGVHD with MSCs [20–39] (Table 1). Caution is needed when assessing the efficacy and adverse events of MSCs treatment because in all of these studies, second- or third line immunosuppressive agents in combination with MSCs were allowed.

Clinical studies using MSCs made by Osiris Therapeutics, Inc. (Prochymal)

Prochymal is MSCs manufactured by Osiris Therapeutics Inc. (Columbia, MD, USA) derived from bone marrow of unrelated healthy donor [52]. There are several reports on the effects of MSCs on patients with steroid-refractory GVHD [25, 30, 38].

Kebriaeir et al. reported that among 31 patients the CR rate was 77 % and the survival rate in the patients who achieved CR was 88 %. They showed that there was no difference in effects between a high-dose (8×10^6/kg) and low-dose (2×10^6/kg) [25]. Prasad et al. [30] showed the efficacy of MSCs for pediatric patients with severe refractory aGVHD. Most patients received MSCs at a dose of 2×10^8 cells/kg.

From the favorable results in these two studies, Osiris conducted a double-blind randomized placebo-controlled phase III study to treat steroid-refractory acute GVHD in the United States, Canada, and Australia [52–54]. Patients were randomized at a 2:1 ratio for either MSCs or a placebo. MSC was given in a dose of 2×10^6/kg twice a week for 4 weeks, for a total 8 times. It should be noted that most patients had already received a second-line therapy before MSC therapy. This trial enrolled 260 patients. The primary endpoint was durable CR for 28 days. Unfortunately, the phase III trial did not prove the superiority of MSCs over the placebo (MSCs 35 % vs. placebo 30 %). However, subpopulation analysis at day 100 showed that MSCs significantly improved the response in liver aGVHD (76 vs. 47 %) and gastrointestinal aGVHD (82 vs. 68 %), especially in children (71 vs. 50 %). Infection rates were not different between the MSCs and placebo groups. Rates of severe adverse effects associated with MSCs administration were not different in the two arms. MSCs are now approved for use in pediatric steroid-refractory aGVHD in Canada and New Zealand as a cell-based medicine [51].

Prochymal studies in Japan

JCR Pharmaceutical Co. Ltd. conducted a phase I/II clinical study [40]. At that time, it was anticipated that MSCs would be approved by the FDA after the phase III study in the USA and bridging study style might be considered and that this

Table 1 Summary of MSC studies for aGVHD

	References	Subjects	Origin	No. of patients (Grade IV GVHD)	Results
1	Le Blanc et al. [20]	Grade IV SR aGVHD	BM(mother)	1(1)	Well after 1 year
2	Ringden et al. [21]	SR II-IV aGVHD	BM(MSD, Haplo, UR)	8 (2)	CR 6/8
3	Fang et al. [22]	SR III-IV aGVHD	Adipose(Haplo, UR)	6	CR 5/6
4	Le Blanc et al. [24]	SR II-IV aGVHD	BM(MSD, Haplo, UR)	55(25)	CR 30, PR 9
5	Kebriaei et al. [25]	SR II-IV aGVHD	Prochymal	31(3)	CR 77 %, PR 16 %
6	Prasad et al. [30]	SR III-IV aGVHD	Prochymal	12(1)(children)	CR 58 %, PR 17 %
7	Perez-Simon et al. [31]	SR II-IV aGVHD cGVHD	BM	18(4)	aGVHD(CR 1/10, PR 6/10), cGVHD(CR 1/8, PR 3/8)
8	Wernicke et al. [32]	SR aGVHD		183	CR:children 57.4 %, adults 45.1 %
9	Herrmann et al. [33]	SR III-IV aGVHD cGVHD	BM	19((4)	aGVHD(CR 7/12, PR 4/12), cGVHD(CR 2/7, PR 2/7)
10	Ball et al. [34].	SR III-IV aGVHD	BM(Haplo, UR)	37(child)	CR 65 %
11	Resnick et al. [35]	SR II-IV aGVHD n	BM(3rd party, HSCT donor)	50(48)	CR 34 %
12	Muroi et al. [40]	SR II-IV aGVHD	Prochymal	14(0)	CR 50 %
13	Introna et al. [36]	SR aGVHD/cGVHD	3rd BM	40	PR + CR 67.5 %(CR 27.5 %)
14	Sanchez-Guijo et al. [37]	SR aGVHD	3rd BM	25(4)	CR 44 %
15	Kurtzberg et al. [38]	SR aGVHD	Prochymal	75	PR + CR 61.3 %
16	Zhao et al. [39]	SR aGVHD	3rd BM	28(16)	CR 60.7 %
17	Muroi et al. [41]	SR III-IV aGVHD	Prochymal	25(3)	CR 48 %

SR: steroid refractory, Haplo: haploidentical donor, MSD: matched sibling donor, Prochymal: MSCs made by Osiris Therapeutics, Inc

study was mainly to confirm safety and feasibility. However, the study failed to reach the endpoint and was not approved in the USA, and the PMDA requested that we perform a more rigorous study using only grade III-IV aGVHD [41].

In multicenter phase I/II study [40], 14 patients with hematological malignancies who suffered from grade II (9 patients) or III aGVHD [6] were treated. Affected organs were the gut (10 patients), skin (9 patients), and liver (3 patients). Seven patients had two involved organs. The median age was 52 years. No other second-line agents were given. MSCs were given at a dose of 2×10^6 cells/kg in each infusion twice a week for 4 weeks. If needed, patients were continuously given MSCs weekly for an additional 4 weeks. By week 4, 13 of 14 patients (92.9 %) had responded to MSCs therapy with a complete response (CR; $n = 8$) or partial response (PR; $n = 5$). At 24 weeks, 11 patients (10 with CR and 1 with PR) were alive. At 96 weeks, 8 patients were alive in CR. A total of 6 patients died, attributable to the following: underlying disease relapse (2 patients), breast cancer relapse (1), venoocclusive disease (1), ischemic cholangiopathy (1), and pneumonia (1). No clear adverse effects associated with MSCs infusion were observed. We concluded that third party-derived bone marrow MSCs may be safe and effective for patients with steroid-refractory aGVHD.

Following the phase I//II study a phase II/III study with the cells focused on steroid-refractory grade III or IV aGVHD was conducted [41]. Twenty-five patients (grade III, 22 patients and grade IV, three patients) were enrolled in this study. The cumulative incidence from the first MSC infusions to the achievement of CR is shown in Fig. 1. A 50 % CR was obtained around at 6 weeks after the first MSC infusions. The steroid dose from the start of MSC therapy to 24 weeks was plotted (Fig. 2). Steroid dose was reduced in about two-thirds at 4 weeks and about half at 8 weeks, thereafter nearing to the base line of 0 mg/day. Overall survival after the first infusions of MSCs was plotted (Fig. 3). Taken together, our two clinical trials suggest MSCs to be effective for steroid-refractory aGVHD.

Academic studies in Japan

Currently, three clinical trials of MSCs for HSCT patients are listed or recruiting on the web site of the UMIN clinical trials registry. Hyogo College of Medicine is conducting a study entitled "Amniotic membrane-derived mesenchymal stromal cells for the treatment of steroid-resistant acute GVHD." Jichi Medical University is conducting a study entitled "Efficacy of mesenchymal stem cells for treatment of refractory acute GVHD after stem cell transplantation." Recruiting is already finished and they reported that 10 patients are enrolled and 3 patient received third

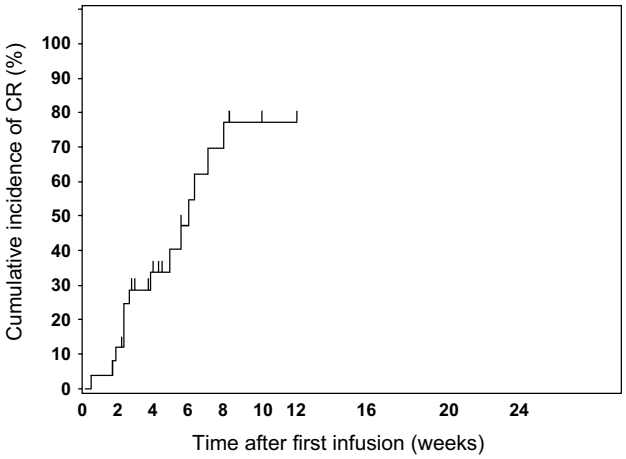

Fig. 1 Cumulative incidence of complete response after the first infusions of MSCs [41]

party MSCs resulting in mixed responses. They concluded that further studies are needed [55]. Nagoya University launched a clinical trial, but it is for engraftment not for GVHD. All in all, it seem to be still some distance from clinical practice in the HSCT centers in Japan.

Insurance approval of TEMCELL® HS Injection

Following the favorable outcome of clinical studies, the PMDA approved MSCs. The indication is, "acute graft-versus-host disease after hematopoietic stem cell transplantation." It is accompanied with the special precautions that "this product should be used only in a case where a sufficient therapeutic effect cannot be obtained even with steroid therapy," and "on using this product, the patients to be administered should be selected carefully after becoming fully aware of the severity of acute GVHD as well as the contents of the section of clinical studies and understanding the efficacy and safety of this product."

Also, a notification from the Minister's Secretariat Counsellor, Ministry of Health, Labor and Welfare (in charge of medical device/regenerative medicine review control) has been issued (http://www.jshct.com/pdf/2015925.pdf).

Cost

MSCs cost more than ten million yen (approximately $100,000) per course of MSCs therapy for refractory GVHD. From the database of the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT), the number of cases of aGVHD more than the grade II is approximately 1000 and at least 40 % are steroid refractory. If half of them are candidates for MSCs therapy, it would be at a total cost of ¥2.6 billion.

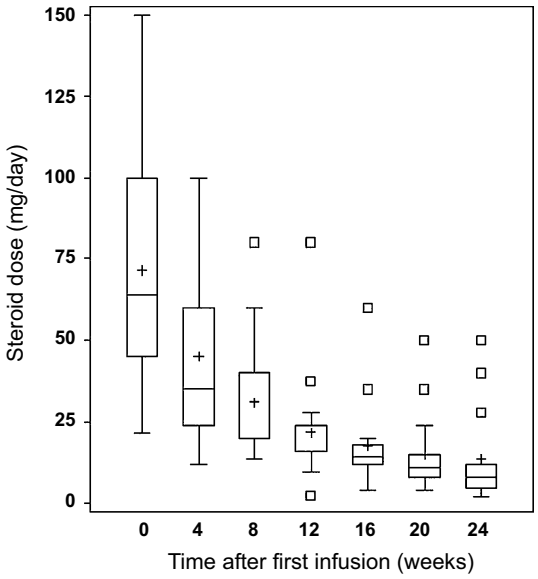

Fig. 2 Steroid doses after MSC administration displayed by the boxplot method. *Plus signs* and *squares* indicate mean and extreme outliers, respectively [41]

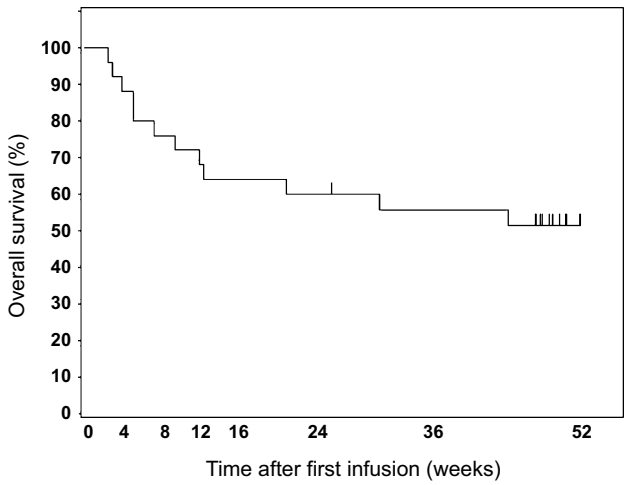

Fig. 3 Overall survival after the first infusions of MSCs. At 52 weeks, 12 patients (48 %) were alive [41]

The methods of production

The methods of production is open. Briefly, an aliquot of bone marrow obtained from healthy volunteers was cultured in a medium supplemented with 10 % fetal bovine serum from New Zealand (Life Technologies, New York, USA). The fetal bovine serum products were free of bacteria, viruses, mycoplasma, and endotoxins in the checking tests. The products met standards for Code of Federal Regulations 9CFR113.53 and the United States Department of Agriculture. Adherent cells were expanded by culture and used as MSCs. Before freezing, cells were examined in the terms of MSCs characteristics [40]. Isolated cells showed positivity for CD73, CD90, CD105, and CD166 and negativity for CD34, CD45, and HLA-DR. The cells inhibited the mixed-lymphocyte reaction and differentiated to fat cells, chondrocytes, and osteoblasts. The cells had the ability to produce prostaglandin E2. Multicolor-fluorescence in situ hybridization showed that the cells had no chromosomal abnormalities. No infectious agents such as bacteria, mycoplasma, or viruses were detected in the supernatants of the cells or the cells themselves. No endotoxin was detected in the supernatant. Number of passage was not open to the public.

Discussion

Clinical issues

Several studies have demonstrated the merits of MSCs for steroid refractory aGVHD treatment. However, because a majority of patients had already received one or more immunosuppressant before MSCs administration, it is difficult to evaluate the effectiveness of MSCs. A commercially sponsored, randomized Phase III study in steroid-refractory acute GVHD (NCT00366145) apparently did not reach significance in its primary endpoint, failing to show a difference in complete response rate in those receiving MSCs. This study suggested that MSCs therapy might be more useful for certain groups of patients such as those with liver and gut GVHD or pediatric patients [53, 54]. It might be certain that in some patients MSCs is useful and only curable management.

Scientific concerns

As mentioned above, the evidence that MSCs reach sites of inflammation is lacking [42]. The mechanism for improvement of GVHD by MSCs remains unclear, although several in vitro studies have been reported. Transfused MSCs are trapped in the lungs, liver and spleen. The possibility that some may reach sites of inflammation cannot be ruled out, but that action may be a paracrine function. Further investigations are needed in clinical setting, e.g. immunohistochemical analysis of biopsy, autopsy specimens.

The donor source in these studies was heterogeneous and included autologous, related donor and unrelated healthy donor (including HLA mismatch third-party). MSCs sources are variable such as bone marrow, adipose tissue, placenta, amniotic fluid and cord blood. Some concerns about purity and cell function have been raised with regard to the production of MSCs in different institutes. Efficacy has apparently not depended on whether

HLA-matched haploidentical or third party donor cells were used [24]. The age and gender of the donor may be a cause of variability in growth potential as well as culture conditions, such as choice of media and seeding density [56]. The number of MSCs infused, the number of MSCs infusions, and infusion intervals also varied among the clinical trials.

Safety issues

Manufacture under good manufacturing practices (GMP) is important in the prevention of contamination of products with microorganisms. In Japan, MSCs are produced according to GMP both in academic setting and in companies.

Because of the immunosuppressive effect of MSCs, it might be reasonable to expect that a smaller GVL effect could induce a recurrence of the treated hematologic malignancy in recipients treated with MSCs. Currently, however, there are no reports of such, although it must be admitted that the numbers are small.

Compounding the risk of opportunistic infection in an already heavily immune-deficient host is the immunosuppressive function of MSCs. Decreased immunoglobulin activity is reported in MSCs. There are also reports of increases in EBV-PTLP and fungal infections, and reports of increased occurrence of cancer. On the other hand, a German group has published an intriguing in vitro study of the antimicrobial effect of human and murine MSCs [57].

Histological studies of autopsies and tissues in patients who had received MSCs for steroid-refractory acute GVHD did not find any evidence of MSC-related malignancy nor ectopic bone formation [58]. As chromosomal changes leading to malignancy are possible but not shown in man. The expantion of cells for therapeutic use is considered important because of the potential risk of malignant transformation in culture through many passages [59, 60]. The possibility of change in feature of MSC through passage is also unclear [61]. According to TEMCELL®, the detailed number of passages is not available to the public.

Economic issue

The Japan pharmaceutical products trade deficit was ¥162 billion in 2012. It estimated that MSCs treatment will increase the medical cost ¥2.6 billion. Following, MSCs, clinical study of ECP (extracorporeal photopheresis) is running and that of CAR, cord blood cell expansion are now planning by pharmaceutical companies. Along with emerging molecular targeting drug, cell therapies are advancing at tremendous speeds with the increasement of medical cost.

Future direction and perspective

In just the field of HSCT, a fair number of academics in Japan are pursuing research with the aim of clinical applications of cell therapy. Academics have been making cell therapies for more than the past decade. There is a path laid out for academics that leads to insurance coverage for a medical technology. After they have completed an initial feasibility institutional clinical study, they can then move on to advance medical technology “Koudo Sennshinn Iryou”. However, this is a very daunting process or at least it is time consuming, and over the past decade not a single treatment has reached this point in the field of hematopoietic stem cell transplantation

One other way forward is to work for pharmaceutical approval as a product for regenerative medicine, but this requires the steady continuation of research to support technical development and clinical trials by companies and academic support is needed. In this case, there are also points that need to be sorted out with regard to the profitability of companies that contract cell culture work and investment in companies when they aim to develop regenerative medicine products. Some of the basic technology for this has been patented by foreign companies and measures are also needed in terms of avoiding or adopting patents.

TEMCELL® was approved by PMDA in September 2015. At first, it will be used only in the 20 institutes that were involved in the clinical studies. The government ask the company and JSHCT for comprehensive data collection. The total cost is estimating to be 2.6 billion. Japan’s pharmaceutical products trade deficit was ¥162 billion in 2012. Cell therapy and molecular targeting agents are increasing and there are some concerns about the trade deficit and increasing the medical costs are proposed. However, the most important issue is the development of effective treatment and supply to those patients who need them. It may be great undertaking to balance the benefit and cost.

Finally even though the clinical feasibly was confirmed in phase II studies, several concerns are remaining. Thus TEMCELL® should be used only in restricted well trained institutes and the patients should be selected carefully with informed consent regarding the severity of acute GVHD and the efficacy and safety of this product.

Conclusion

1. Most of the published trials have reported a favorable effect in acute GVHD, but no randomized phase III trial confirmed this.
2. The mechanism of how MSCs works for GVHD has not been clarified and the nature of MSCs after infusion remain unknown.

3. MSCs (TEMCELL®) is approved for severe GVHD by the Japanese PMDA, along with restricted institutions and data collection is being planned.
4. Registration of all patients in the post marketing study is mandatory and long term follow up to confirm the efficacy and adverse events is recommended.
5. Commercial MSCs is very expensive but have the merit of easy supply to larger numbers of patients and the practice field and constancy.
6. Academic production of MSCs are less expensive and have some advantages, and national strategies for developing new agents by collaboration between academics and companies are being promoted in Japan.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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