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REVIEW

Mesenchymal stroma/stem cells: Haematologists' friend or foe?

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Summary

Mesenchymal stromal cells (MSCs) are non-haematopoietic cells found in fetal and adult organs, that play important roles in tissue repair, inflammation and immune modulation. MSCs residing in the bone marrow interact closely with haematopoietic cells and comprise an important component of the microenvironment supporting haematopoiesis, in both health and disease states. Since their identification in 1970, basic scientific and preclinical research efforts have shed light on the role of MSCs in the regulation of haematopoiesis and evoked interest in their clinical application in haematopoietic stem cell transplantation (HSCT) and malignant haematology. Over the last two decades, these research efforts have led to numerous clinical trials, which have established the safety of MSC therapy; however, the optimal mode of administration and the benefit remain inconclusive. In this paper, we will review the clinical experience with use of MSCs in HSCT for enhancement of engraftment, prevention and treatment of graft-versus-host disease and haemorrhagic cystitis. Then, we will discuss the contradictory evidence regarding tumour-promoting versus tumour-suppressing effects of MSCs in haematological malignancies, which may have relevance for future clinical applications.

KEYWORDS
engraftment, GVHD, mesenchymal cells, tumorigenesis

INTRODUCTION

Mesenchymal stromal cells (MSCs), interchangeably referred to as mesenchymal stem cells, are non-haematopoietic cells of mesodermal origin that are found in numerous tissues and organs, and have the capacity to both self-renew and differentiate into various cell lineages including adipocytes, osteocytes, chondrocytes and skeletal myocytes.[1] However, according to the International Society for Cell & Gene Therapy (ISCT), the term stromal cells refers to a mixed population of stroma cells demonstrating secretory properties as well as immunomodulation and homing, and is not interchangeable with the term stem cells referring to a more unified population of progenitor cells capable of self-renewal and differentiation.[2,3] Since most manuscripts do not refer to these functional definitions, for the purpose of this review we will use the acronym MSC interchangeably. MSCs residing in the bone marrow (BM-MSCs) comprise a multifunctional tissue that provides a specialized microenvironment involved in the regulation of haematopoiesis.[4,5] BM-MSCs are thought to promote haematopoiesis via both proximal and remote interactions. They provide an anatomic scaffold for haematopoietic precursors and secrete cytokines and extracellular matrix components that support haematopoietic stem cell (HSC) survival and proliferation.

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Despite their heterogeneity and lack of a discrete immunophenotype, MSCs are characterized by their plastic adherence *in vitro* and share typical phenotypic markers and various surface antigens allowing their antibody-based isolation.[6] MSC progenitors can be readily isolated from bone marrow, adipose tissue and umbilical cord blood (UCB) and expanded *ex vivo* while maintaining their phenotype and function.[7] These features have led many investigators to explore the ability of MSCs to support bone marrow engraftment of HSCs following haematopoietic stem cell transplantation (HSCT), especially in conditions associated with poor engraftment outcomes.[8,9]

Moreover, MSCs have been shown to possess immunomodulatory and anti-inflammatory properties, mainly by regulating the maturation, proliferation and activation of lymphocytes. They have been shown to inhibit allogeneic $CD4^+$ and $CD8^+$ T-cell proliferation, impair proliferation and differentiation of B cells, inhibit differentiation of $CD14^+$ monocytes towards $CD1a^+$ dendritic cells (DCs) and downregulate expression of costimulatory molecules and cytokine secretion from mature DCs.[10–13] The inhibitory effect of MSCs is not necessarily dependent on cell–cell contact, suggesting soluble factors may also mediate these effects. The exact mechanisms governing these inhibitory effects are not known, and multiple factors [e.g., transforming growth factor (TGF)-β1, interleukin (IL)-10 and galactins] have been implicated. Due to their regulatory effects, it has been postulated that MSCs can serve as possible immune modulators in patients with immune-associated diseases including acute and chronic graft-versus-host disease (GVHD), inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis and others.[14–17]

Graft-versus-host disease is a major complication of allogeneic haematopoietic stem cell transplantation (alloHSCT) and remains a significant limitation of this procedure accounting for decreased quality of life and increased lethality. The pathobiology of acute GVHD (aGVHD) is attributed to activation of recipients' antigen-presenting cells initiating donor T-cell activation, proliferation, differentiation and migration, leading in turn to target tissue destruction. The pathophysiology of chronic GVHD (cGVHD) is less clear and is believed to involve both cellular and humoral immunity. Due to the immune nature of GVHD there has been a vast interest in the use of MSCs for both prevention and treatment of this devastating condition.

MSCs used in HSCT are almost exclusively allogeneic, and can be derived from either the allogeneic HSC donor, or a separate, related or unrelated, 'third-party' donor. As with other allogeneic cellular product, concerns were raised with regards to MSC haemocompatibility and potential immunogenicity leading to thrombo-inflammation. However, over two decades of clinical experience have established the overall safety of MSC therapy in most clinical settings. Administration of MSCs is associated with a remarkably low risk of infusion reactions and minimal long-term toxicity, as these cells generally do not persist in the recipients.[8,18–20] Clinical trials evaluating the use of allogeneic MSCs to improve HSCT outcomes vary greatly in MSC source, *ex vivo* expansion methods, cell dose and number of doses, timing of MSC administration, patient population and the transplantation protocols used.[8,21] Despite this perplexing variation, strategies employing MSCs in HSCT can be divided broadly to two main approaches: co-administration of MSCs along with HSCs on the same day of HSC transplantation, usually in the context of enhancement of engraftment and/or GVHD prophylaxis, and independent administration of MSCs weeks or months following HSCT, at presentation of transplant-related complications such as GVHD and haemorrhagic cystitis.

The role of MSCs in tumorigenesis of haematological cancers is under intense investigation. MSCs have been shown on the one hand to decrease proliferation of tumour cells by induction of cell cycle arrest and upregulation of T regulatory cells, but on the other hand to promote tumorigenesis by suppression of apoptosis, enhancement of angiogenesis, downregulation of Treg cells and mediation of drug resistance. Most intriguing is how the close interaction between MSCs and leukaemia cells generates a cross-talk that may drive the leukemogenic process.

The goal of this review is to summarize the updated available knowledge regarding the role of MSCs in haematological diseases including their potential role in cellular therapies, as well as their potential for tumour promotion.

COTRANSPLANTATION OF MSCS FOR ENHANCEMENT OF ENGRAFTMENT AND GVHD PROPHYLAXIS

Graft failure (GF), poor graft function and delayed engraftment are complications of alloHSCT that contribute to increased post-transplantation morbidity and mortality. The incidence of GF is less than 3%–5% in autologous and matched alloHSCT but can increase to up to 10% in haploidentical or UCB transplantations. Risk factors associated with GF include human leukocyte antigen (HLA) mismatched or haploidentical donors, a low $CD34^+$ cell dose (characteristic of UCB transplantations), a severely compromised host microenvironment such as in myelofibrosis or heavily pretreated leukaemia, and reduced-intensity or non-myeloablative conditioning.[22] Due to their supportive effects towards HSCs within the bone marrow microenvironment, in addition to their immunomodulatory and anti-inflammatory properties, MSCs have emerged as candidate agents to enhance engraftment and prevent GF.

In pre-clinical studies, *in vivo* co-infusion of human MSCs with unrelated human stem cells supported multilineage haematopoietic reconstitution in immunodeficient mice[23–25] and fetal sheep.[26] Two early clinical studies demonstrated the safety and feasibility of isolating autologous BM-MSCs from haematological malignancy and breast cancer patients, expanding them in *ex vivo* culture, and re-infusing them alone or along with autologous HSCs.[27,28] Robinson et al. showed that expansion of haematopoietic progenitors from UCB was markedly enhanced in ex vivo coculture with

MSCs.[29] These findings led to two clinical trials in humans that evaluated transplantation of UCB units expanded *ex vivo* with MSCs; both studies showed improved engraftment outcomes, including a remarkable shorter time to neutrophil engraftment as compared with historical controls.[30,31] However, this strategy was not further pursued owing to advances in the use of small molecules for UCB expansion.[32] Collectively, the above observations supported the clinical evaluation of cotransplantation of MSCs along with HSCs, as an approach to enhance engraftment after autologous or allogeneic HSCT, particularly in conditions associated with a high risk of graft failure or delayed engraftment.

The first example of co-infusion of donor MSCs with HSCs in the setting of alloHSCT was reported by Lazarus et al. in 2005. In 46 adult patients with haematological malignancies who received myeloablative conditioning culture-expanded MSCs were cotransplanted along with HSCs, both from HLA-identical siblings, with the aim of preventing GVHD and facilitating engraftment. MSCs were administered at a dose of 1–2.5 $\times 10^6$/kg, four hours prior to infusion of either BM or peripheral blood HSCs. The *ex vivo* culture duration required for sufficient MSC expansion ranged from 21 to 48 days, hence did not enable the evaluation of a higher dose of MSCs (5×10^6/kg) that was originally planned. Median times to neutrophil (>0.5 $\times 10^3$/l) and platelet (>20 $\times 10^3$/l) engraftment were 14 and 20 days respectively. Grade II–IV aGVHD was observed in 28% of the patients, while cGVHD was found in 61% of 36 patients who survived at least 90 days, comparable to previously reported rates. The authors concluded that this treatment strategy was feasible and safe, and merited further evaluation.[33] Another study employing cotransplantation of MSCs along with same-donor HSCs to enhance engraftment, was reported by Le Blanc et al. in 2007. Seven paediatric and adult patients were included, three received MSCs along with a second or third alloHSCT for the treatment of GF, and four were cotransplanted as part of a pilot study. Donors were HLA-matched siblings in three cases and haploidentical in four. A cell dose of 1 $\times 10^6$/kg was infused to each patient within four hours of HSC infusion. There were no toxicities related to the MSC infusions. Remarkably, the median time to both neutrophil engraftment and platelet engraftment was 12 days, 100% donor chimaerism was reached in all patients at 30 days post transplantation, and rates of GVHD were lower than expected. The authors concluded that cotransplantation of MSCs may have positive effects towards both engraftment and GVHD prevention and should be evaluated in larger studies.[34]

Three pilot studies initially used third-party donor MSCs in adult patients undergoing HSCT in different clinical settings. In a study by Gonzalo-Daganzo et al., nine patients who received UCB transplants along with third-party mobilized HSCs as 'bridge to engraftment', were also co-infused with MSCs derived from the third-party donors (administered immediately after UCB and HSC infusions). No differences in CB engraftment or incidence of aGVHD were observed, in comparison to historical controls who did not receive MSCs.[35] Baron et al. co-infused third-party culture-expanded MSCs to 20 patients with haematological malignancies undergoing non-myeloablative HSCT from HLA-mismatched donors. MSCs were administered 30–120 min before infusion of HSCs. Rates of grade IV aGVHD, one-year non-relapse mortality (NRM) and one-year overall survival (OS) compared favourably with historical controls receiving a similar HSCT. Importantly, MSC infusion did not abrogate the graft-versus-tumour effect, in a transplant setting that solely relies on this effect.[36] Finally, a multicentre study from China examined the effect of unrelated donor MSCs with or without UCB for the treatment of engraftment failure following autologous HSCT (an event which rarely occurs in the era of mobilized peripheral blood grafts). Twenty-two adult or adolescent patients with haematological malignancies who developed engraftment failure following auto-HSCT were randomized to receive either MSCs alone (in 2–4 separate doses) or MSCs co-infused with UCB. Both strategies led to various degrees of engraftment in most patients, with an apparent advantage to the MSC and UCB co-infusion.[37]

Several studies evaluated the cotransplantation of donor MSCs in small series of paediatric patients, in the context of UCB[38,39] and haploidentical donor transplantations,[40] both associated with a higher risk of GF. These studies showed inconsistent results with regard to both engraftment outcomes and GVHD prevention. A recent meta-analysis detected eight single-arm studies evaluating the co-infusion of MSCs with haploidentical donor HSCT in paediatric and adult patients with severe aplastic anaemia (SAA) and compared their results to those of 11 studies reporting outcomes of haploidentical transplants for SAA without the use of MSCs. No significant differences were found in the pooled incidence of acute or chronic GVHD; and there were no differences in time to neutrophil and platelet recovery, achievement of 100% donor chimaerism and two-year OS.[41] Conversely, a recently published study reporting the cotransplantation of donor or third-party MSCs along with allogeneic HSCs in a series of 17 patients with primary myelofibrosis, a condition associated with a high risk of graft failure following alloHSCT, showed encouraging engraftment outcomes. In this retrospective study, median time to neutrophil and platelet engraftment was 13 and 21 days respectively and there were no cases of primary or secondary GF, suggesting that cotransplantation of MSCs may represent an effective treatment approach for patients with primary myelofibrosis undergoing HSCT.[42]

In recent years, the focus of clinical studies evaluating the cotransplantation of MSCs with allogeneic HSCs has shifted from enhancement of engraftment to GVHD prophylaxis, perhaps owing to the inconsistent engraftment outcomes in previous studies along with the more encouraging outcomes in GVHD treatment (see below). Several randomized controlled studies have been conducted in this context, evaluating incidence and severity of GVHD as the primary outcome.[43–45] Despite varying widely in modes of MSC harvesting and expansion, transplant protocols and patient population, these studies showed evidence for benefit of MSC administration in the prevention of acute and/or chronic GVHD. Two recently published meta-analyses reviewed the outcomes of cotransplantation of MSCs for GVHD prophylaxis in HSCT recipients, using different methodological approaches. A Cochrane

Collaboration review limited its analysis to randomized controlled trials (RCTs) in patients with haematological conditions who had undergone an HSCT and were randomized to MSCs versus no MSCs, or to different MSC protocols, for GVHD prophylaxis. In seven RCTs detected, the administration of MSCs had little or no influence on the risk of relapse, incidence of aGVHD and OS, but reduced the risk of cGVHD [risk ratio (RR) 0.66].[46] In contrast, a meta-analysis by Morata-Tarifa et al., that used more liberal criteria to include 16 studies encompassing 356 patients who were treated with MSCs for GVHD prophylaxis, showed a 17% increase in OS and a significantly reduced incidence of aGVHD (RR, 0.22) in patients treated with MSCs, as compared to those transplanted without MSCs. Furthermore, a positive correlation was observed between the MSC dose and survival of aGVHD patients.[47] Engraftment outcomes were not addressed in both above studies. In summary, the therapeutic use of MSCs for enhancement of engraftment and GVHD prophylaxis has not yet shown a consistent and robust benefit. Larger and better-designed clinical trials are merited to establish a clear benefit and elucidate the ideal mode of cotransplantation of MSCs with HSCs.

MSCS FOR THE TREATMENT OF GVHD AND HAEMORRHAGIC CYSTITIS

Both acute and chronic GVHD are treated with a variety of immunosuppressive agents, with limited efficacy.[48] Steroids are the first-line therapy for aGVHD. Approximately 35%–50% of the patients have a steroid-refractory (SR) disease associated with a high mortality risk (two-year NRM of 65% and a four-year OS of 15%).[49] Numerous medications and treatment strategies have been used and proposed as second-line therapies for SR-aGVHD, with limited success. While recent advances are encouraging, there is still an unmet need for innovative treatment approaches for this devastating condition. Since Le Blanc and coworkers reported on their first successful experience in treating a patient with grade IV acute gastrointestinal (GI) and liver GVHD with third-party haploidentical MSCs,[1,50] more than 35 studies have reported the use of allogeneic MSCs for the treatment of aGVHD and cGVHD, in both paediatric and adult patient populations.[47]

Haemorrhagic cystitis (HC) has been shown to occur in at least 10% of patients undergoing HSCT.[51,52] The pathogenesis of this potentially life-threatening complication is multifactorial, including: chemotherapy and radiotherapy used in the conditioning regimen, viruses with a high rate of replication (such as polyomavirus BK) and alloimmune effects.[53] *In vitro* and *in vivo* animal models have shown that MSCs can diminish HC through activation of Wnt pathways and inhibition of mast cell infiltration and degranulation.[54,55] Consequently, MSCs have been reported to be helpful in resolving HC in patients undergoing HSCT in several small studies.[56–59] Recent pilot studies have shown efficacy of placenta-derived decidual stromal cells (DSCs), a unique source of MSCs, for the treatment of HC, as well as aGVHD.[60–62] Studies by Ringden and coworkers have revealed increased expression of tissue factor (TF), a key factor in the initiation of the coagulation cascade, on the surface of DSCs, as compared to MSCs from other sources. Increased TF expression was associated with a stronger procoagulant activity observed in DSCs, providing a mechanistic explanation for their apparent efficacy in the treatment of HC, and supporting the evaluation of DSCs for the treatment of other bleeding disorders.[8,63,64]This interesting observation serves as an example for the growing diversity of MSC sources and products, and their potential uses in various indications.

MSCs for the treatment of acute GVHD

In the aGVHD setting, the vast majority of studies administering MSCs used third-party BM-MSCs for the treatment of grade III–IV SR/resistant patients. These studies ranged in size from small patient series in most cases to larger cohorts of as many as 241 and 91 paediatric and adult patients respectively. Moreover, these studies varied greatly in the cell preparation method used, the number of administered doses,[1–12] and the number of infused cells ($0.22–6.81 \times 10^6$ MSCs/kg), which even varied between patients within each study (Table 1). These differences hamper the ability to draw practical conclusions regarding the benefit of this treatment approach. In 2020, two phase 3 studies reported the use of a commercial product, Remestemcel-L (Prochymal, Osiris Therapeutics, Columbia, MD, USA), in paediatric (n = 55) and adult (n = 149) patients. In the paediatric setting, in 2014 Osiris Therapeutics reported on their experience treating 75 patients, across seven countries, of whom 88% suffered from grade II–IV aGVHD, the majority involving more than two organs and failing three immunosuppressive agents (IST). Cell dose was 2×10^6 hMSCs/kg and the number of administered doses ranged from 1 to 20. Ten serious adverse events were reported, but none were considered related to the treatment. The overall response rate (OR) at day 28 was 61% and the OS by day 100 was 57.3%, with a better OS in those responding by day 28. This report was updated in 2020, showing similar results among 241 paediatric patients treated in an expanded-access protocol.[65,66] Concurrently, Osiris Ltd. reported a phase 3 single-arm study designed to evaluate the efficacy and safety of Remestemcel-L in 54 paediatric patients with primary SR-aGVHD in the absence of an additional IST for aGVHD, compared to historical results of second-line treatments in this population. The OR at day 28 was 70% with complete response raising from 29.6% on day 28 to 44.4% on day 100 and OS rates of 74.1% and 68.5% at day 100 and 180 respectively.[67] Three acute infusion reactions were documented, infections were the most commonly reported adverse events, and 14 deaths were recorded within the first 100-day period, none of which were attributed to the treatment. These results are in agreement with the larger non-commercial studies by Ball et al. in 2013 and Erbey et al. in 2016 reporting on 37 and 33 paediatric patients respectively; The former administered MSCs in two paediatric

HSCT centres in Leiden and Pavia and the latter in Istanbul, achieving ORs of 86% and 76% respectively, with an OS of 65% (at a median follow-up of 2.9 years, in the Leiden and Pavia group) and 63% (two-year OS, in the Istanbul group) in patients achieving CR.[68,69]

In the adult setting, a phase 3 study reported their experience in 2019 administering Remestemcel-L (n = 163;149 adults, 14 children) versus placebo (n = 81), added to a second-line therapy in for SR-aGVHD. One hundred and forty-nine[149] adult patients received Remestemcel-L in 72 centres across seven countries. Durable CRs (for at least 28 continuous days) were documented in 34% of treated patients compared to 29% in the placebo group. Durable CRs were significantly improved in patients with any liver involvement (29% vs 5%; p = 0.05). The proportion of patients with grade IV aGVHD and high-risk disease (as defined by the Minnesota risk scoring for aGVHD) was higher in the Remestemcel-L group compared to the placebo group (27% and 64% vs 16% and 53%).[70] There was a low rate of infusion-related reactions, probable treatment-related adverse events (AEs) and serious AEs in the treatment and placebo groups, with a trend towards a higher rate of deaths associated with infections in the Remestemcel-L group (p = 0.07). On 2021 Murata et al. published the Japanese real-world experience with Temcell (the Remestemcel-L equivalent in Japan), which was approved in Japan for treatment of aGVHD at all ages. For OS analysis, 381 patients were analysed, but due to missing data only 309 were available for the rest of the analysis. The majority of patients (84%) were over 18 years old. MSC cell dose ranged from 0.7 to 3×10^6/kg and administered doses ranged from 1 to 12. OR was 56% by day 28 and 63% by day 100. Higher non-relapse mortality (NRM) was seen with older age (>18 years), higher aGVHD grade, multiple previous treatments for aGVHD and no OR by day 28. OS at one year in the entire population was 27% (41% in the responders compared to 16% in the non-responders). Relapse rate of the underling malignancy in the first year was 21%. Infection rate at any point after MSC administration was 47%.[71]

The literature on non-commercial studies in the adult population is scarce and inconsistent, reflecting reports of small numbers of patients, often a mixture of paediatric and adult patients, receiving treatment for either acute and/or chronic GVHD. Stoma et al. reported an observational study performed to estimate the risk factors for infections in 24 patients receiving MSCs as a treatment for aGVHD. They showed a trend towards clinical efficacy in patients with SR grade II–IV aGVHD, with a marginal six-month OS difference between those receiving MSCs and the historical control group (58.82% vs 38.24%; p = 0.0678). In this relatively small study, no statistically significant risk of bacterial infections, cytomegalovirus (CMV) disease and invasive fungal disease was observed.[72] Cetin et al. treated 17 patients with aGVHD; survival rate at six months was 69.2% in the responder group (n = 13) compared with no survival in the non-responder group (n = 4).[73] Bonig et al. reported real-world experience in treating 92 patients across six countries with MSCs produced in Germany (Frankfurt-am-Main), generated from pooled bone marrows of multiple third-party donors. The majority of patients (66%) were over 18 years old, had higher than grade II aGVHD (96%) and received more than five prior IST therapies. MSC cell dose ranged from 0.6 to 4.5×10^6/kg and administered doses ranged from 1 to 9. OR was comparable in the adult and paediatric population, reaching 81% at last follow-up (35% and 59% reached CR respectively). Patients receiving higher numbers of prior IST were less likely to achieve CR. Six-month OS was 64% (69% and 54% in the paediatric and adult population respectively).[74] Others have reported similar results.[75,76]

In 2020, Morata-Tarifa et al. published a meta-analysis on MSCs administered for the prophylaxis and treatment of GVHD.[47] They analysed 35 studies treating acute and/or cGVHD. From a total number of 887 patients treated for aGVHD, 67% responded to the treatment while 39% achieved CR, with no difference shown between the adult and paediatric population, and a lower CR rate in the grade III–IV group compared to the grade II group. A higher OR and CR rate was calculated in patients with skin compared to liver or gut involvement and a lower GI-involved aGVHD response in the paediatric compared with the adult population.

MSCs for the treatment of chronic GVHD

Notably, there are fewer reports on the role of MSCs in patients with cGVHD, and these are limited to small series. Jurado et al. reported treating 14 patients with cGVHD (seven moderate, seven severe) with adipose tissue-derived MSCs. CR was achieved in 57% of patients and 71% were off steroids by week 56. During the follow-up, no cases of underlying disease relapse nor mortality due to infection were observed.[77] Weng et al. reported 19 patients treated with multiple doses (1-5) of MSCs for refractory cGVHD (73% severe, 26% moderate), on a compassionate basis, reporting an OR of 73.7%. Again, no underlying disease relapses were observed, and the two-year survival rate was 77.7% with no immediate adverse effects noted.[78] Morata-Tarifa et al. in their meta-analysis reviewed 10 studies (n = 75, total number of patients) with an OR of 66% and a CR of 23%.[47]

In conclusion, MSCs can serve as a second-line treatment for acute and chronic GVHD, but study heterogeneity and lack of suitable controls hinders the ability to draw definite conclusions. Since there are profound differences in patients' response to treatment, specific MSCs and patients' properties should be explored in order to define better criteria for more successful prediction of efficacy.

Extracellular vesicles as substitute for MSC therapy

Extracellular vesicles (EVs) have been shown to play an important role in cell-to-cell communication. They contain

TABLE 1 Characteristics of the studies included in the section on mesenchymal stromal cells (MSCs) for the treatment of graft-versus-host disease (GVHD)

Author, year	Study description	Product/location	No. of pts	GVHD
Kurtzberg et al. [65] 2014	Paediatric <18 years; open-label; single-arm; prospective	bmMSC; Remestencel-L[a] [Prochymal]; Osiris Therapeutics, Columbia, MD, USA	75	Grade II–IV
Kurtzberg et al.[66] 2020	Paediatric <18 years; open-access	bmMSC; Remestencel-L[a] [Prochymal]; Osiris Therapeutics, Columbia, MD, USA	241	Grade II–IV
Kurtzberg et al.[66] 2020	Paediatric <18 years; phase-3; single arm vs historical cohort	bmMSC; Remestencel-L[a] [Prochymal]; Osiris Therapeutics, Columbia, MD, USA	54	Grade II–IV
Ball et al.[68] 2013	Paediatric <18 years; experience of two centres	bmMSC; Leiden University Medical Centre, Netherlands	37	Grade III–IV
Erbey et al.[69] 2016	Paediatric <18 years; retrospective; single-centre	Third-party or haploidentical family donor bmMSC; Atakent hospital, Istanbul, Turkey	33	grade III–IV aGVHD
Kebriaei et al.[70] 2020	Adult and paediatric <18 years; phase 3 randomized	Remestencel-L[a] (Prochymal) Mesoblast (USA) bought Prochymal (Osiris, USA)	244 MSC-treated 163 (paediatric = 14 adults = 149) placebo 81	Grade II–IV
Murata et al.[71] 2021	Adult and paediatric <18 years; real-world	Temcell (JCR Pharmaceuticals Co. Ltd, Hyogo, Japan)[b]	309 Adults = 259 Paediatric = 50	Any Grade
Stoma et al.[72] 2018	Adult; observational study	bmMSC and AT-MSC; Minsk, Republic of Belarus	24	Grade II–IV
Cetin et al.[73] 2017	Adult	Genome and Stem Cell Center of Erciyes University (Genkok), Turkey	22	Grade II–IV
Bonig et al.[74] 2022	Adult and paediatric <18 years; real-world	MSC-Frankfurt am Main[c]	92 61 paediatric, 31 adults	Grade II–IV
Jurado et al.[77] 2017	Adult; open, prospective, multicentre, randomized phase I/II clinical trial	Third party, AT- MSCs	14	Moderate–severe cGVHD
Weng JY[256] 2010	Adult; compassionate treatment	Third-party bmMSC donors; Guangdong General Hospital,	19	

Abbreviations: aGVHD, acute graft-versus-host disease; AT-MSC, adipose-tissue-derived MSC; bmMSC, bone-marrow-derived MSC; CR, complete response; cGVHD, chronic graft-versus-host disease; FU, follow-up; IST, immunosuppressive therapy; MSC, mesenchymous stromal cell; NR, non-responders/no response; OS, overall survival; PR, partial response; R, responders; SR, steroid-refractory.

[a]Remestencel-L — human culture-expanded bone-marrow-derived MSCs of unrelated, HLA-unmatched donors. Cell products were harvested at passage 5 from 4 male donors and 1 female donor, 19–27 years of age, with each infusion product derived from a single donor.

[b]Temcell — a manufactured MSC product equivalent to remestemcel-L, approved in Japan in 2016. Cryopreserved, from unrelated adult human bone-marrow-derived MSCs.

[c]MSC-FFM – MSCs generated from pooled, previously cryopreserved mononuclear cells from eight random donor of bone marrow.

various molecules [such as cellular proteins, soluble factors, mRNA and microRNA (miRNA)] originating from the parent cells, which are able to change protein expression in targeted cells. This has led many investigators to explore the immunomodulatory function of MSCs via excretion of small EVs (e.g. exosomes), and study their effects on the function of neutrophils, B cells, T cells, macrophages and DCs.[79,80] These findings supported the evaluation of MSC-derived small EVs for the treatment of immune disorders, including GVHD. Several GVHD mice models treated with human BM-derived MSC EVs have reported improvement in mice GVHD clinical scores and OS.[81,82] However, until now only a single report has described the treatment of a heavily pretreated patient suffering from advanced-stage aGVHD with four doses of EVs derived from 4×10^6 cells/kg. Although the patient died seven months later from pneumonia, he shown a remarkable skin and GI response, enabling steroid reduction.[83] Thus, EVs may serve as an adequate substitute to MSC application for treatment of GVHD. However, many issues are yet to be settled, including tissue source, isolation methods, acceptance criteria, dosing and treatment schedule.

Criteria for treatment	Cells dose (cells/kg)	No. of doses	Overall response	Overall survival
SR-GVHD	2×10^6	1–20	61% at day 28	57.3% at day 100 78.1% in R vs 31.0% in NR
SR-GVHD	2×10^6	1–24	65.1% at day 28	66.9% at day 100 82% in R vs 38.6% in NR
SR-aGVHD	2×10^6	1–16	70% at day 28 (CR 29.6%)	74.1% at day 100 68.5% at day 180
SR-aGVHD	$0.9–3.0\times10^6$	1–13	86%	After a median follow-up of 2.9 years 65% vs 0 in those achieving vs not achieving CR
SR-aGVHD and at least one second-line therapy.	$0.54–2.80\times10^6$	1–4	75.75% (CR 54.5%)	57.6% at day 335; 63.8% vs 29.4%, in those achieving CR vs PR/NR
SR-GVHD,MSC given together with a second-line treatment	2×10^6	1–16	58% in the treated vs 54% in the placebo group; at day 28	34% (56/163) for treated vs 42% (34/81) for placebo at day 180
aGVHD	$0.71–3.01\times10^6$	1–12	56% at day 28 63% at day 100	27% 1 year OS; 41% in R vs 16% in NR
SR-aGVHD	$0.87–2.16\times10^6$	1–5	Not reported	58.8% vs 38% in historical cohort at 6 months OS
Acute[17] or chronic[5] SR-GVHD,	$0.84–2.54\times10^6$	2–7	79.1% at 6 months of FU	63.6% survived 6 months; 76.5% in R vs 20% in NR
SR-aGVHD	$0.6–4.5\times10^6$	1–9	81% at last FU; paediatric 84% and adults 77%	64% at 6 months; paediatric 69%; adult 54%
cGVHD	1 or 3×10^6		71.4% at week 20	78.57% at 60-week FU
IST refractory cGVHD	$0.23–1.42\times10^6$	1–5	73.7% at a median FU of 697 days	77.7% 2-year OS

MESENCHYMAL CELLS' SIGNIFICANCE IN HAEMATOLOGICAL MALIGNANCIES

MSCs are involved in many key aspects of tumour development, such as immunomodulation, inflammation, angiogenesis and microenvironment support.[84,85] These findings combined with the proximity of MSCs to tumour cells, prompted numerus studies to try and utilize MSCs as therapeutic leverage against various tumours. Results from these studies are often contradictory and must be reviewed in the context by which activity was assessed. As such, direct cell–cell contact versus paracrine effect, ratio of tumour to MSC cells, the source of MSCs and most importantly, the presence of stroma and a functioning immune system all dramatically affect the impact of MSCs on the tumour. Thus, *in vitro* experiments often miss immunomodulatory or tumour vasculature effects of MSCs, as well as possible effects on drug metabolism and delivery.[86]

Growth and viability — in vitro lessons

One of the more consistent observations is the ability of MSCs to decrease proliferation of tumour cells by induction of cell cycle arrest. This finding was consistent across several studies in leukaemia of myeloid and lymphoid lineages as well as lymphoma cell lines.[87–89] The inhibitory effect was highly dependent on the ratio between the MSCs and tumour cells,[87,90,91] and irrespective of the MSC source.[87,88,92] However, it was not cell-specific, as a similar inhibitory effect was observed in tumour cells of various lineages and in non-haematopoietic cells. Furthermore, it is not clear whether the inhibitory effect is contact-dependent and/or induced via paracrine signalling, with conflicting reports. Song et al. reported that the anti-proliferative effect of MSCs on leukaemia cells was lost when separated by a permeable membrane,[92] while other studies demonstrated a clear paracrine effect. MSCs derived from adipose tissue were able to inhibit proliferation of haematopoietic tumour cell lines, such as K562 and HL-60 cells, showing cell cycle arrest in the G0/G1 phase. The effect was not influenced by a permeable membrane precluding direct cell–cell contact, and was reversed by neutralizing antibodies against Dickkopf-related protein (DKK1).[93] DKK1 is a regulator of the Wnt signalling pathway, involved in the proliferation of leukaemia cells.[94] Others have shown that MSCs derived from cord blood induce a similar cell cycle arrest in K562 and HL-60 cells, via phosphorylation of p38 MAPK.[95]

In seeming contradiction to the cell cycle arrest triggered by MSCs, consistent reports indicate suppression of apoptosis by MSCs in solid tumours as well as haematological malignancies.[86] This raises the question of whether MSCs promote or negate tumour growth. Wei et al. demonstrated the cell cycle arrest of K562 cells cultured with MSCs, concomitant with the reduction of apoptotic cells and the upregulation of p-Akt and p-Bad levels.[89] A similar anti-apoptotic effect in leukaemia cells was described with MSCs derived from bone marrows of chronic myeloid leukaemia (CML) patients in the blast phase[96] and in Jurkat leukaemia cells.[97] Culture of primary B-acute lymphoblastic leukaemia (ALL) cells with autologous MSCs was able to rescue the leukaemia cells from apoptosis. Coculture significantly increased the expression of Notch ligands on the leukaemia cells, while blocking this pathway eliminated the suppression of apoptosis by the MSCs.[98] A different study also demonstrated the ability of bone-marrow-derived MSCs to protect B-ALL cells from DNA damage-induced p53-mediated cell death. This effect was dependent on the production of prostaglandin E_2 (PGE_2) and signalling of the protein kinase A (PKA).[99]

Growth and viability — in vivo lessons

Limited numbers of studies have demonstrated reduced tumour growth in *in vivo* models utilizing co-injections of MSCs and tumour cells. Inhibition of murine leukaemia cell lines' growth was observed by syngeneic MSC injections,[92] and by co-injection of MSCs with lymphoma cells intraperitoneally.[100] In contrast, many studies reported a pro-tumorigenic effect of MSCs. Ramasamy et al. demonstrated that while incubation of MSCs *in vitro* with leukaemia cell lines reduced proliferation and induced cell cycle arrest, co-injection of MSCs and leukaemia cells in a NOD-SCID mouse favoured tumour generation, with a marked difference of 75% compared to 12% in tumour development with or without MSCs respectively.[87] The authors suggest that MSCs decrease the residual immunity of the NOD-SCID mice, promoting tumour growth. Similarly, co-injection of ALL cells of NOD/SCID mice with adipose tissue stem cells intraperitoneally resulted in a marked increase in tumour growth. Interestingly, the effect was dependent on the number of adipose stem cells injected.[101]

MSCs influence tumour growth through immune modulation

Several reports further highlighted the effect of MSCs on the immune response as a significant mechanism that promotes tumour growth (Figure 1). MSCs were shown to modulate the immune response both by cell–cell contact-dependent and -independent mechanisms,[102] affecting both the innate and adaptive immune systems. The effects of MSCs on T-cell activation, proliferation and cytokine secretion are not well determined, although a plethora of studies demonstrate variable and often contradictory inhibitory effects of MSCs. Evidence suggests that MSCs can regulate T-cell differentiation and T-cell subpopulation ratios,[103] and specifically T regulatory (Treg) cells, allowing the leukaemia cells to better evade the immune system.[104,105] Several mechanisms have been suggested for the increase in Treg population observed in acute myeloid leukaemia (AML). Indoleamine 2,3-dioxygenase (IDO) expressed by leukaemia calls or by MSCs has been recognized as a key regulator of Tregs, with a correlation between higher expression of IDO and Treg percentage.[106,107] MSCs' production of prostaglandins (PDs) increases the secretion of IL-5, which in turn expand the Treg population, with a pro-leukaemia effect.[108] Other reported mechanisms includes Programmed death (PD-1) signalling, exosome secretion[109] and tumour necrosis factor (TNF)-α.[110,111] MSCs have also been shown to affect other participants of the adaptive immune system, such as B cells, reducing proliferation, differentiation and chemotactic properties.[112] Natural Killer (NK) cells are part of the innate immune system with key functions in cancer surveillance. Studies revealed that MSCs can modulate NK function by direct cell–cell contact as well as secretion of soluble factors [indoleamine 2,3-dioxygenase (IDO), TGF-β1, nitric oxide and PGE2] allowing immune evasion by the tumour cells.[113–116]

MSCs' impact on angiogenesis

MSCs have been reported to directly support tumour vasculature, by differentiating into pericytes and endothelial

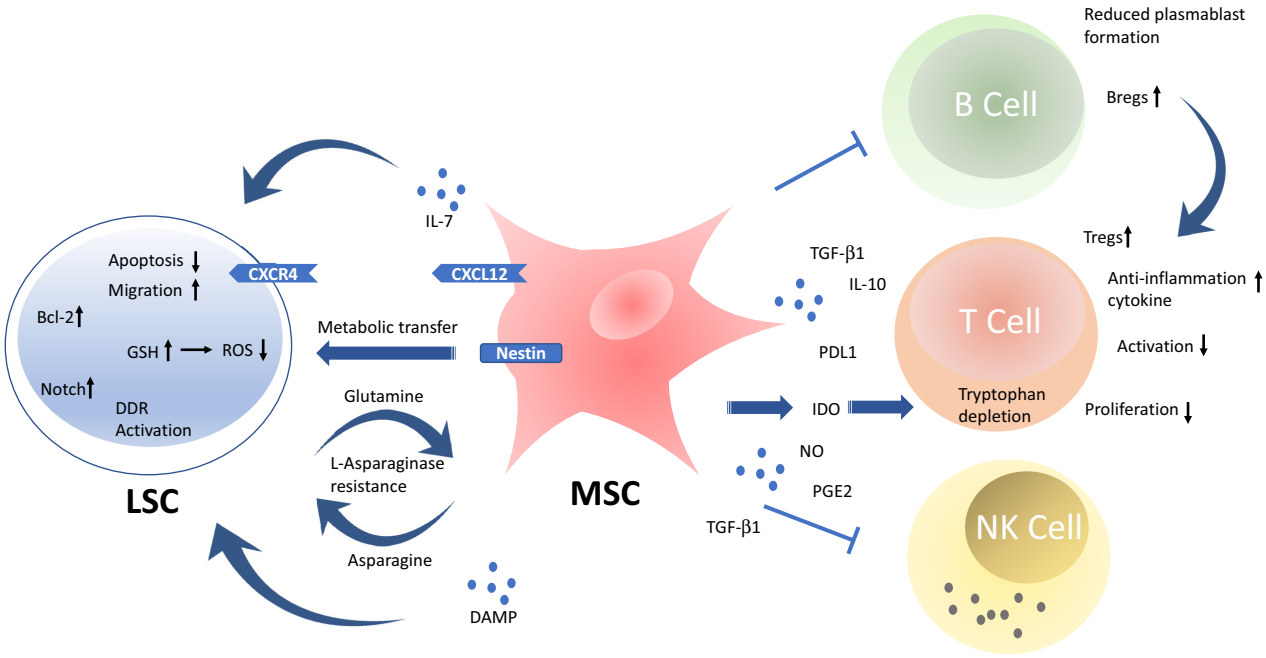

FIGURE 1 The cross-talk between MSCs, LSCs and cells of the immune system. The close interaction between MSCs and LSCs in bone marrow niche generates a cross-talk via direct contact as well as soluble factors. The effects are often bidirectional and signals from the LSCs affect the function of MSCs, which often further support the LSCs' survival. One example is the metabolic transfer between MSCs and LSCs which allows leukaemia to resist treatment with asparaginase and reduce the oxidative stress by reducing levels of reactive oxygen species (ROS) (please see text for more details). MSCs have also wide immunomodulatory effects on cells of the adaptive and innate immune system. These effects include reduction in proliferation and inflammatory cytokine release, as well as changes in the subpopulations of the immune systems, such as an increase in numbers of T regulatory cells (Tregs). Abbreviations: CXCL12: chemokine receptor ligand 12; CXCR4: chemokine receptor type 4; DAMP, damage-associated molecular pattern; DDR: DNA damage response; GSH: glutathione; IDO: indoleamine 2,3-dioxygenase; IL, interleukin; LSC, leukaemia stem cell; MSC, mesenchymal stromal cell; NK, natural killer; NO: nitric oxide; PDL1: programmed death ligand 1; PGE2: prostaglandin E2; ROS: radical oxygen particles; TGF-β1: transforming growth factor beta 1; Tregs, regulatory T cells.

cells[86,117] and through indirect mechanisms, by secreting vasculogenic growth factors, such as vascular endothelial factor (VEGF), hepatocyte growth factor and IL-6, among others.[118–120] MSCs' secretion of interleukin-6 (IL-6) increases the secretion of endothelin-1 (ET-1) by colon cancer cells, which induces the activation of protein kinase B (Akt) and extracellular-signal-regulated kinase (ERK) in endothelial cells, thereby enhancing angiogenesis and tumour growth.[121] A few reports suggested a negative effect of MSCs on tumour vasculature, again demonstrating the complexity of these interactions. MSCs were shown to migrate towards capillaries and induce apoptosis of endothelial cells, resulting in tumour inhibition by ablating necessary vasculature.[91,122,123]

MSCs enhance tumour-cell-mediated drug resistance

Being part of the tumour stroma and microenvironment, MSCs have the potential to alter drug delivery and metabolism or promote drug resistance in tumour cells. This might allow the survival of tumour cells residing in such a specialized niche, eventually leading to disease relapse. Several studies illustrated the pathways by which bone marrow MSCs can promote resistance of acute and CML to various treatments. CXCL12, a C-X-C chemokine ligand, is a major chemoattractant for HSCs. Deletion of CXCR4, a receptor for CXCL12, resulted in severe reduction of HSC numbers and increased sensitivity to myelotoxic injury in adult mice.[124] MSC coculture protected CML cells from imatinib-induced apoptosis in a CXCR4-dependent manner.[125] Furthermore, CML cells exposed to imatinib retained the ability to engraft in a mouse xenograft model, again in relation to CXCR4,[126] suggesting the CXCR4–CXCL12 cross-talk between leukaemia stem cells (LSCs) and MSCs is significant.

Interestingly, deletion of CXCL12 from mesenchymal progenitors enhanced CML stem cell numbers and function. In accordance, sensitivity to treatment with tyrosine kinase inhibitors was enhanced following CXCL12 loss.[127] Another study demonstrated that the Apoptosis repressor with caspase recruitment domain (ARC) protein induces IL-1β expression in AML cells and increases CCL2, CCL4 and CXCL12 expression in MSCs, with enhanced migration of AML cells to MSCs. Inhibition of IL-1β protected AML cells from cytarabine-induced apoptosis.[128] IL-7 levels were shown to be higher in the bone marrow of CML patients in blast crisis, as compared to healthy individuals and CML

patients in chronic and accelerated phases. The increased IL-7 was mediated by MSCs in the bone marrow, and was shown to protect CML stem cells from imatinib-induced apoptosis.[129] Others have demonstrated that the close interaction of leukaemia cells with MSCs protected from mitoxantrone-induced apoptosis in a c-MYC-dependent mechanism.[130] Similar reports included resistance to anthracyclines with evidence of the Notch-signalling pathway,[131] and Bcl-2 upregulation.[132,133]

Asparagine is a vital amino acid, required for several key cellular processes. The only enzyme able to synthetize asparagine is asparagine synthetase (ASNS). The majority of B-cell ALL blasts lack the expression of ASNS and largely depend on extracellular asparagine. This observation led to the wide incorporation of L-asparaginase, which rapidly hydrolyzes plasma asparagine (and at a lower rate glutamine), as a drug in ALL therapy. The metabolic cross-talk between MSCs and ALL blasts was shown to promote resistance of the leukaemia cells to L-asparaginase treatment.[134,135] Primary human MSCs from the bone marrow of ALL patients use glutamine produced by ALL blasts to synthetize and excrete asparagine, which in return supports the ALL blasts and protects them from L-asparaginase. Higher expression levels of SNAT5, the exporter of asparagine in MSCs, were reported in ALL patients compared to their normal counterparts.[136]

Chronic lymphocytic leukaemia (CLL) cells cocultured *in vitro* with MSCs showed a reduced apoptosis rate in response to fludarabine, with upregulation of Bcl-2. Furthermore, the MSCs–CLL interaction resulted in an increase in CD38 expression and activation markers such as CD71.[137] Taken together, these findings demonstrate how the intimate cross-talk of MSCs with leukaemia cells in a specific BM niche promotes tumour resistance. Additional mechanisms of tumour–stroma interactions in drug resistance are described in length by Ni et al.[138]

In summary, MSCs have been found to play a role in the resistance of various leukaemia cells to imatinib, asparaginase and chemotherapeutic agents.

The role of MSCs in leukemogenesis

Accumulating evidence reveals the bidirectional interaction of leukaemia cells and MSCs in specialized bone marrow niches (Figure 1). Certain studies demonstrate that MSCs also bear genetic abnormalities that suggest a common stem cell aberration leading to leukaemia;[139] however, in most cases the AML clone affects the MSC gene expression and activity, in favour of the leukaemic development.[140] These novel insights promote our understanding of the biology of leukaemia cells and offer new avenues of therapy.

In a seminal work by Raaijmakers et al. it was shown that disrupting mesenchymal cell osteoprogenitors disrupts the integrity of haematopoiesis with resulting myelodysplasia and AML development.[141] Kode et al. also demonstrated how manipulation of osteoblasts alters the differentiation potential of myeloid and lymphoid progenitors, leading to the development of AML.[142] Another such example was described using the leukaemia predisposing disorder Shwachman–Diamond Syndrome (SDS), which is characterized by the loss of function of the *SBDS* gene. However, loss of *SBDS* in haematopoietic progenitor cells does not result in myelodysplasia or leukaemia. Strikingly, deletion of *SBDS* from MSCs in the bone marrow induces apoptosis and myelodysplasia in haematopoietic stem cells. This effect was later attributed to the secretion of endogenous damage-associated molecular pattern (DAMP) molecules by the MSCs, which resulted in activation of the DNA damage response in HSCs.[143]

Leukaemia stem cells are a subset of leukaemia cells with a unique stem-like transcriptional signature with self-renewal ability, specific metabolic features and resistance to chemotherapy. LSC largely rely on mitochondrial oxidative phosphorylation (OXPHOS) for their metabolic needs. As this is often accompanied by high numbers of radical oxygen particles (ROS), it was not completely understood how leukaemia cells avoid ROS toxicity. Recently, it was demonstrated that Nestin$^+$ MSCs can stimulate the tricarboxylic acid (TCA) cycle and glutathione (GSH)

TABLE 2 Defining the features that need to be explored in future clinical studies

	Characteristic	Experimental approach
MSC features	Source of MSC	Explore the best available source: bone marrow, adipose tissue, umbilical cord
	Proportions of MSC subpopulations	Better defined by single-cell RNA (scRNA)
	Cell dose	Determine the most effective cell dose
	Repeated doses	Explore the number of doses and interval between doses
	No. of donors	Single vs multiple grouped donors
Recipient–donor features	Recipient immune state	Assessment of recipients' baseline immune state as a predictor of response
	In vitro assessment of the combined immune response	Development of laboratory tools predicting *in vivo* response to MSC injection
	Development of better response assessment tools	Accurate quantifiable tools such as cell-free (cf) DNA

availability and utilization by the leukaemia cells, allowing leukaemia cells to reduce chemotherapy-induced ROS levels.[144] Nestin is a filament protein, which forms a specialized niche, shown to be increased in AML patients.[144,145] Laminin α4 (Lama4) is an extracellular matrix protein also linked to bone marrow niches. Remarkably, deletion of Lama4 in MSCs resulted in the upregulation of inflammatory cytokines, increased antioxidant activity and promoted myeloid LSC proliferation and chemoresistance. This effect was accompanied by increased mitochondrial transfer from MSCs to AML cells, similar to what was reported with Nestin$^+$ MSCs above.[146]

As described, most changes in MSCs from leukaemia patients are dependent on the interaction with the leukaemia cells, suggesting that these effects are reversible or amenable to intervention. Recently, it was shown that MSCs from AML patients upregulate the Notch-signalling pathway. Remarkably, treatment with dexamethasone supressed Notch signalling in MSCs to levels comparable to that in MSCs with no exposure to leukaemia cells. Correspondingly, treatment with dexamethasone augmented the effect of Notch inhibitor in a mouse xenograft leukaemia model with prolonged survival of the mice.[147] This finding might explain evidence suggesting a clinical benefit in treating AML with dexamethasone,[148] and might also partially explain the efficacy of dexamethasone in ALL, given the significance of Notch signalling in ALL.[98,149] Another example of how the cross-talk between MSCs and leukaemia cells can serve as a target for novel therapy was reported with the CXCR-4 inhibitor AMD300. Treatment with AMD300 blocked the leukaemia growth and migration of leukaemic cells enhanced by MSCs.[150]

Finally, MSCs have been shown to modulate AML cell proliferation by the release of miRNA in small EVs. This has been shown to affect key regulatory pathways in leukaemia including PI3K/AKT/mTOR, affecting both proliferation and resistance to chemotherapy.[151,152]

Taken together, these studies strengthen our understanding that the BM niche and the cross-talk between the MSCs and the leukaemia cells play a crucial role in the leukomogenic process, and thus offer new targets for future drug development.

In conclusion, MSCs are an important part of the haematopoietic niche, and as such, play a pivotal role in HSC tumorigenesis, engraftment and immune modulation. There is a profusion of contradictory literature regarding their tumorigenic effects and their role in HSCT. Despite the conflicting evidence, many of the aforementioned studies did suggest a benefit of MSCs for the treatment and prevention of GVHD and/or for enhancement of engraftment while there was no clinical evidence for tumorigenesis. Based on the currently available basic scientific data and clinical experience, there is still a valid rationale for the continued investigation of the utility of MSC therapy in the field of HSCT. Well-planned randomized controlled studies are needed. In addition to clinical outcomes, these trials should also assess potential predictors of response, an assessment that has been lacking in most studies to date (Table 2). Such efforts may likely lead to the successful and standardized incorporation of MSCs in clinical haematology.

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