

Recent advances in stem cell therapy for myelodysplastic syndromes

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Abstract: Many reports have emphasized the potential of stem/progenitor cells as intervention strategy to repair damaged tissue, providing new hope for the treatment of various diseases and conditions previously intractable like myelodysplastic syndromes, clonal hematopoietic disorders where blood-forming cells are damaged in the bone marrow. Early experimental evidence and growing clinical evidence strongly suggest that transplantation of allogeneic hematopoietic stem cells can repair the bone marrow and even cure myelodysplastic syndromes, with a reduced risk of rejection and manageable side effects. These findings have opened new avenues for cell-based cancer therapies, which have been providing very encouraging results in myelodysplastic syndromes and a number of blood cancers. However, though relatively minimal toxicity is reported in young adult patients, allogeneic stem cell transplantation still associates with life threatening undesired effects in pediatric and senior patients. In addition, a considerable fraction of these patients may also develop graft-versus-host disease. Recent advances in allogeneic stem cell transplantation in myelodysplastic syndrome as therapeutic strategy are herein briefly discussed, as well as newly proposed strategies to overcome the drawbacks of this technique.

Keywords: Stem Cells, Myelodysplastic Syndrome, Microenvironment, Signaling Pathways, Therapy

1. Background

Hematopoiesis is a continuous process in which progenitor cells, i.e. hematopoietic stem cells (HSCs), develop into mature blood cells, in hematopoietic organs like the bone marrow, which is the major site of hematopoiesis in the adult. HSCs have the ability to self-renew, thanks to the microenvironment created by stromal cells. A huge body of experimental and clinical evidence strongly suggests that embryonic stem cells and some adult stem cells (like HSCs), can repair damaged tissues in the body, partly by differentiating in the lost cell type and replacing lost cells, with a reduced risk of rejection and manageable side effects [1-3]. These findings have opened new avenues for cell-based cancer therapies in the last decades, which have been providing very encouraging results in clinical settings [4-6]. Herein, we will briefly present and discuss recent reports on such therapies and their outcomes in myelodysplastic syndromes (MDSs), which are clonal hematopoietic disorders where blood-forming cells are damaged in the bone marrow [7, 8].

2. Pathogenesis of Myelodysplastic Syndromes

MDSs encompass a number of hematopoietic neoplasms with a characteristic bone marrow dysplasia resulting in an ineffective hematopoiesis and cytopenias [8, 9], with progression to acute myeloid leukemia (AML) in a third of patients [10, 11]. Except for cases resulting from treatment of aggressive blood cancers [12, 13], the etiology of MDSs is still unclear. Cytogenetic aberrations like chromosomal aberrations with a random loss of chromosomal material were reported in bone marrow stem cells of MDS patients, including hematopoietic stem cells (HSCs), and bone marrow mesenchymal stem cells (BM-MSCs) [14]. The latter cells are multipotent non hematopoietic progenitor cells that supports hematopoiesis and give rise to different stromal cell lineages [15, 16]. An enhancement of genetic susceptibility in BM-MSCs of MDS patients was also reported [14], suggesting that genetic alterations in these cells may be a

pathogenic mechanism of MDSs and of subsequent myeloproliferative malignancies. Possible mechanisms for high-risk MDS determination by such genetic alterations in MSCs are numerous, and may include, for instance, reduced ability of hematopoietic support and aberrantly increased immunosuppressive abilities [17], considering also that BM-MSCs express various proto-oncogenes crucial for HSC maintenance, such as Notch ligands and Wnt [18].

Aberrant activation of these proto-oncogenes may also play a pivotal role in MSC pathogenesis and development [19, 20] as observed for instance in acute lymphoblastic leukemia (ALL) and B-cell chronic lymphoblastic leukemia (CLL), where BM-MSCs promote the neoplastic tissue survival partly via these signaling pathways [21, 22]. Thus, it appears that at least part of MDS patient condition improvement following bone marrow transplantation reported in early studies [23-25] emerged from the adjunction of healthy BM-MSCs that probably rescued affected BM-MSC cell populations, restored hematopoietic support, and suppressed cancer-promoting signaling in the bone marrow microenvironment [19, 20, 26, 27].

3. Allogeneic Stem Cell Transplantation in MDSs

Partly due to epigenetic alterations [9, 28, 29], MDS clinical manifestations present with an important inter-individual heterogeneity, which also reflects on therapy outcomes and seriously undermines efforts for new drug development [30, 31]. Consequently, MDS management strategies are risk-adaptive strategies balancing the risk/benefit ratio of potential therapeutic intervention against patient prognostic [32, 33], using commonly accepted prognostic schemes like the International Prognostic Scoring System (IPSS) that classifies patients into higher risk and lower risk groups [10, 34]. Considering that high risk patients have a short survival time (about a year if untreated) and a higher risk for developing acute myeloid leukemia (AML) [10, 12], the main objectives of therapy are patient survival increase and AML progression delay. To date, allogeneic stem cell transplantation is the only treatment modality with established curative potential, though various approaches have been tested (for review see [6, 9, 31, 35]).

Basically stem cell transplantation includes two phases. First, abnormal bone marrow cells are killed either by patient exposed to total body irradiation or by administering high-dose chemotherapy. Afterwards, patients are transplanted with healthy HSCs. Autologous stem cell transplantation after the bone marrow is destroyed is not commonly used for MDS treatment, because this strategy implies giving back their own stem cells to patient, which will not bear any benefit in this context as MDS patient bone marrow contains pathogenic abnormal stem cells [8], unlike allogeneic stem cell transplantation therapy that is providing very encouraging results, with minimal toxicity and improved quality of life [4-6]. During allogeneic stem cell transplant,

patients receive HSCs from a healthy donor, preferentially closely matched to patient cell types such as siblings and other close relatives [36-38]. However, though less often, not related donors may also match to the patient [39-42].

4. Current Limits of HSC Therapy

Due to the complexity of blood cancer pathogenesis and clinical features also shared by MDS, many patients remain non-eligible for HSC transplantation or do not show any improvement following such treatment [9, 43, 44], underlining the need for more research aimed at providing insights in stem cell behavior upon transplantation, particularly the interactions of allogeneic stem cells with the diseased hematopoietic niche. Notably, a majority of senior patients are not eligible for HSC therapy due to their inability to sustain intensive treatment associated with allogeneic cell transplantation [9, 45]. Considering that the incidence and severity of MDSs increase with age [46], i.e. that MDSs are more common in older people, improvements in transplantation strategies in use are mandatory for making this therapeutic approach also suitable for senior patients.

For a number of senior [11] and pediatric [47] patients HSC therapy-associated risk of serious undesired effects result, first, from an emphasis of undesired effects of the prior chemotherapy and radiation, such as absence or marked reduction in hematopoietic processes resulting in serious cytopenia, anemia, and immune system deregulation favoring development of opportunistic life threatening infections [48-52]. To reduce or prevent these undesired effects, improvement in conditioning regimens of patients undergoing allogeneic stem cell transplantation were proposed [53-56], as well as a reduction in allogeneic peripheral blood stem cell transplantation intensity [57, 58]. Development and use of more targeted chemotherapy drugs would also represent good strategies for improving patient condition following allogeneic stem cell transplantation in MDSs, considering that they are less toxic, and thus, associated with less marked undesired effects [59-62]. For instance, encouraging results were reported using hypomethylating agents before allogeneic HSC transplantation in MSC patients [63, 64]. In addition, allogeneic HSC transplantation without myeloablative conditioning, which accounts for a number of undesired effects of the therapy [48-52], successfully cured high risk MDS senior patients [65-68]. However, all these approaches only reduce the severity of undesired effects, thus further studies are still needed to improve patient conditions.

Unfortunately, some MDS patients may develop graft-versus-host disease (GVHD) [69, 70], a condition originating from the rejection of allogeneic cells by host immune system. GVHD is a serious, and potentially fatal condition, in particular in pediatric patients [47, 71]. Attempts to prevent such unfortunate outcome include clinical studies assessing potential risk factors for developing GVHD [53, 72], and those aimed at elucidating variables affecting the outcome of this condition after diagnosis [47, 73], in particular relapse

[70]. Pathogenic mechanisms of GVHD in MDSs are still puzzling, particularly in patients with immune deregulation [74, 75] and those receiving immunosuppressive agents [76, 77].

5. Concluding Remarks and Perspectives

Allogeneic HSC transplantation is currently the only treatment able to cure MDS patients, partly due to the functional loss of HSCs during disease pathogenesis.

However, not all patients are eligible to this treatment, a number is not cured, and potentially fatal complications are still associated with this treatment despite recent improvements, particularly in senior and pediatric patients. Such drawbacks limit the use of this therapeutic approach to only advanced stage and high risk patients. Future studies aimed at understanding the interactions of transplanted allogeneic HSCs with normal and affected host bone marrow cells are mandatory, considering the potential for improving MDS treatment.

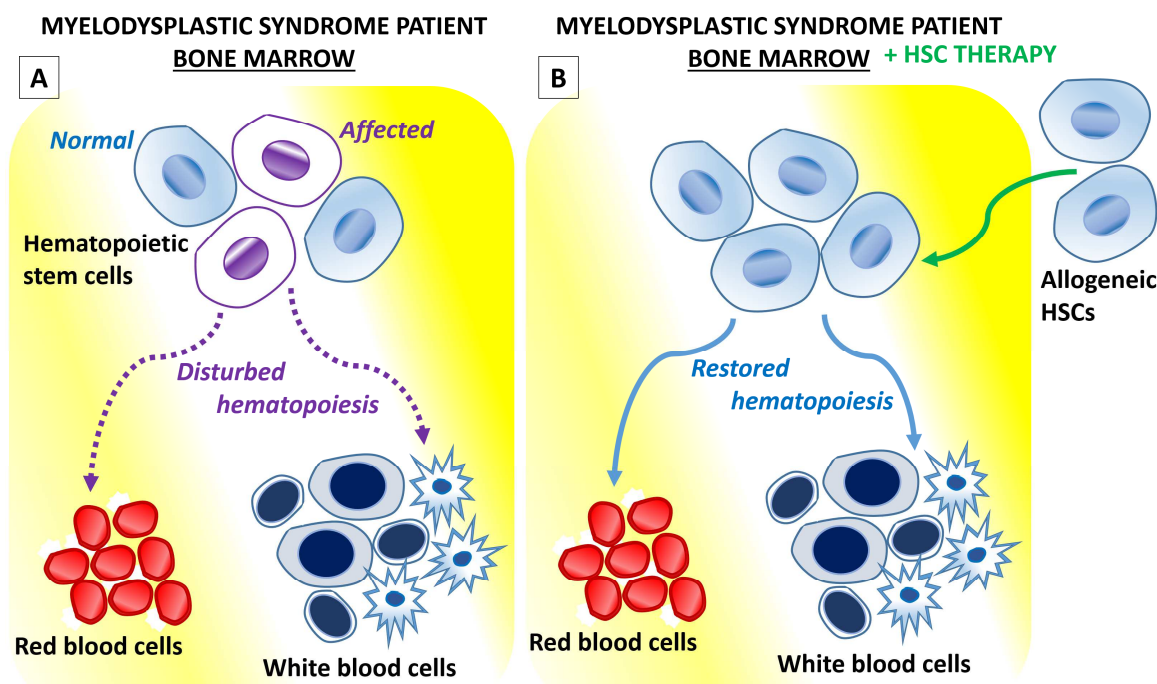


Figure 1. Transplantation of allogeneic hematopoietic stem cells has therapeutic and restorative effects on affected bone marrow in myelodysplastic syndrome patients.

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