International Journal of Biomedical Science and Engineering
2014; 2(6-1): 1-6
Published online November 09, 2014 (http://www.sciencepublishinggroup.com/j/ijbse)
doi: 10.11648/j.ijbse.s.2014020601.11

Recent advances in stem cell therapy for myelodysplastic syndromes

Armel Herve Nwabo Kamdje[1], Paul Faustin Seke Etet[2]

[1]Department of Biomedical Sciences, University of Ngaoundere, Ngaoundere, Cameroon
[2]Department of Basic Health Sciences, College of Applied Medical Sciences, Qassim University, Buraydah, 51452, Saudi Arabia

Email address:
kamdjewa@yahoo.fr (A. H. N. Kamdje), armel.nwabo@gmail.com (A. H. N. Kamdje), Paul.seke@gmail.com (P. F. S. Etet)

To cite this article:
Armel Herve Nwabo Kamdje, Paul Faustin Seke Etet. Recent Advances in Stem Cell Therapy for Myelodysplastic Syndromes. *International Journal of Biomedical Science and Engineering.* Special Issue: Cancer Research. Vol. 2, No. 6-1, 2014, pp. 1-6.
doi: 10.11648/j.ijbse.s.2014020601.11

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.

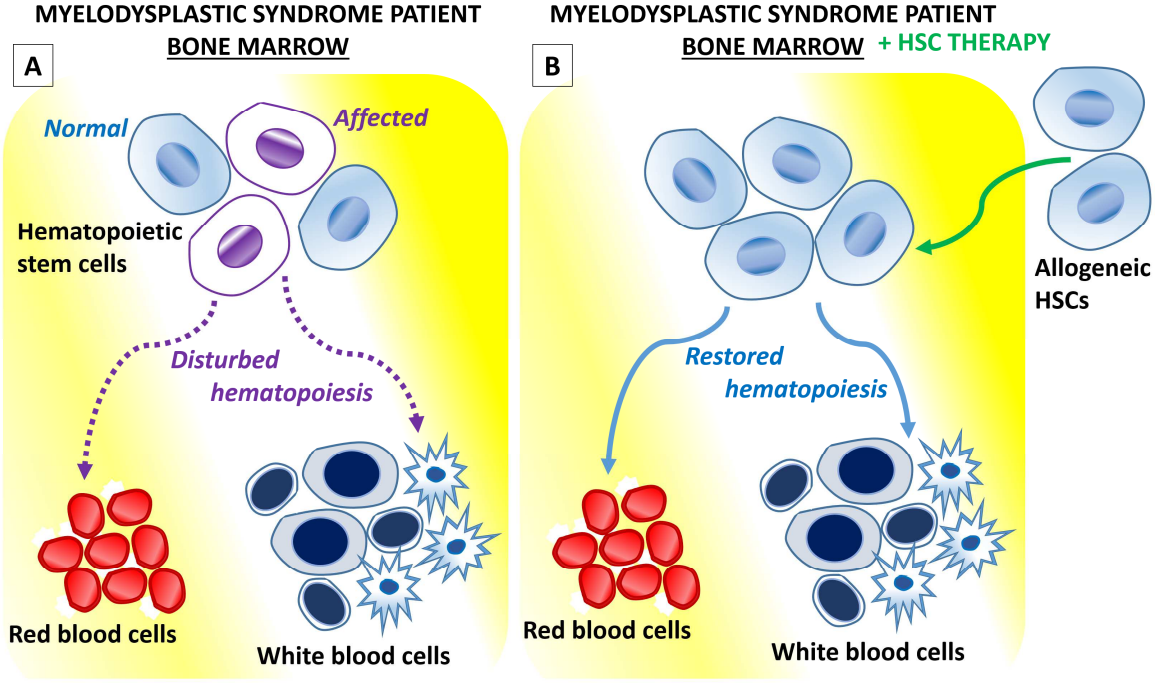

Figure 1. *Transplantation of allogeneic hematopoietic stem cells has therapeutic and restorative effects on affected bone marrow in myelodysplastic syndrome patients.*

References

[1] Dimarino AM, Caplan AI, Bonfield TL. Mesenchymal stem cells in tissue repair. Front Immunol. 2013; 4:201.

[2] Wang Y, Yuan M, Guo QY, Lu SB, Peng J. Mesenchymal stem cells for treating articular cartilage defects and osteoarthritis. Cell Transplant. 2014;

[3] Eseonu OI, De BC. Homing of mesenchymal stem cells: mechanistic or stochastic? Implications for targeted delivery in arthritis. Rheumatology.(Oxford) 2014;

[4] Mufti GJ, Potter V. Myelodysplastic syndromes: who and when in the course of disease to transplant. Hematology.Am.Soc.Hematol.Educ.Program. 2012; 2012:49-55.

[5] Platzbecker U, Mufti G. Allogeneic stem cell transplantation in MDS: how? When? Best.Pract.Res.Clin.Haematol. 2013; 26:421-429.

[6] Garcia-Manero G. Myelodysplastic syndromes: 2014 update on diagnosis, risk-stratification, and management. Am.J.Hematol. 2014; 89:97-108.

[7] Davids MS, Steensma DP. The molecular pathogenesis of myelodysplastic syndromes. Cancer Biol.Ther. 2010; 10:309-319.

[8] Serio B, Risitano A, Giudice V, Montuori N, Selleri C. Immunological derangement in hypocellular myelodysplastic syndromes. Transl.Med.UniSa. 2014; 8:31-42.

[9] Zeidan AM, Kharfan-Dabaja MA, Komrokji RS. Beyond hypomethylating agents failure in patients with myelodysplastic syndromes. Curr.Opin.Hematol. 2014; 21:123-130.

[10] Kao JM, McMillan A, Greenberg PL. International MDS risk analysis workshop (IMRAW)/IPSS reanalyzed: impact of cytopenias on clinical outcomes in myelodysplastic syndromes. Am.J.Hematol. 2008; 83:765-770.

[11] Ades L, Itzykson R, Fenaux P. Myelodysplastic syndromes. Lancet 2014; 383:2239-2252

[12] Gertz MA, Terpos E, Dispenzieri A, Kumar S, Shah RA, Orlowski R, Kastritis E, Dimopoulos MA, Shah J. Therapy-Related Myelodysplastic Syndrome/Acute Leukemia After Multiple Myeloma in the Era of Novel Agents. Leuk.Lymphoma 2014; 1-16.

[13] Pemmaraju N, Shah D, Kantarjian H, Orlowski RZ, Nogueras Gonzalez GM, Baladandayuthapani V, Jain N, Wagner V, Garcia-Manero G, Shah J, Ravandi F, Pierce S, Takahashi K, Daver N, Nazha A, Verstovsek S, Jabbour E, De LM, Champlin R, Cortes J, Qazilbash MH. Characteristics and Outcomes of Patients With Multiple Myeloma Who Develop Therapy-Related Myelodysplastic Syndrome, Chronic Myelomonocytic Leukemia, or Acute Myeloid Leukemia. Clin.Lymphoma Myeloma.Leuk. 2014;

[14] Song LX, Guo J, He Q, Yang LP, Gu SC, Zhang X, Wu LY, Li X, Chang CK. Bone marrow mesenchymal stem cells in myelodysplastic syndromes: cytogenetic characterization. Acta Haematol. 2012; 128:170-177.

[15] Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. Science 1999; 284:143-147.

[16] Phinney DG, Prockop DJ. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair--current views. Stem Cells 2007; 25:2896-2902.

[17] Zhao Z, Wang Z, Li Q, Li W, You Y, Zou P. The different immunoregulatory functions of mesenchymal stem cells in patients with low-risk or high-risk myelodysplastic syndromes. PLoS.One. 2012; 7:e45675.

[18] Calvi LM, Adams GB, Weibrecht KW, Weber JM, Olson DP, Knight MC, Martin RP, Schipani E, Divieti P, Bringhurst FR, Milner LA, Kronenberg HM, Scadden DT. Osteoblastic cells regulate the haematopoietic stem cell niche. Nature 2003; 425:841-846.

[19] Nwabo Kamdje AH, Mosna F, Bifari F, Lisi V, Bassi G, Malpeli G, Ricciardi M, Perbellini O, Scupoli MT, Pizzolo G, Krampera M. Notch-3 and Notch-4 signaling rescue from apoptosis human B-ALL cells in contact with human bone marrow-derived mesenchymal stromal cells. Blood 2011; 118:380-389.

[20] Seke Etet PF, Vecchio L, Bogne KP, Nchiwan NE, Krampera M, Nwabo Kamdje AH. Normal hematopoiesis and hematologic malignancies: role of canonical Wnt signaling pathway and stromal microenvironment. Biochim.Biophys.Acta 2013; 1835:1-10.

[21] Nwabo Kamdje AH, Bassi G, Pacelli L, Malpeli G, Amati E, Nichele I, Pizzolo G, Krampera M. Role of stromal cell-mediated Notch signaling in CLL resistance to chemotherapy. Blood Cancer J. 2012; 2:e73.

[22] Seke Etet PF, Vecchio L, Nwabo Kamdje AH. Interactions between bone marrow stromal microenvironment and B-chronic lymphocytic leukemia cells: any role for Notch, Wnt and Hh signaling pathways? Cell Signal. 2012; 24:1433-1443.

[23] Belanger R, Gyger M, Perreault C, Bonny Y, St-Louis J. Bone marrow transplantation for myelodysplastic syndromes. Br.J.Haematol. 1988; 69:29-33.

[24] Bunin NJ, Casper JT, Chitambar C, Hunter J, Truitt R, Menitove J, Camitta BM, Ash R. Partially matched bone marrow transplantation in patients with myelodysplastic syndromes. J.Clin.Oncol. 1988; 6:1851-1855.

[25] Selby GB, Saez RA, Epstein RB, Slease RB, Confer DL. Allogeneic bone marrow transplantation: experience with 92 patients. J.Okla.State Med.Assoc. 1993; 86:599-603.

[26] Seke Etet PF, Vecchio L, Nwabo Kamdje AH. Interactions between bone marrow stromal microenvironment and B-chronic lymphocytic leukemia cells: any role for Notch, Wnt and Hh signaling pathways? Cell Signal. 2012; 24:1433-1443.

[27] Seke Etet PF, Vecchio L, Nwabo Kamdje AH. Signaling pathways in chronic myeloid leukemia and leukemic stem cell maintenance: key role of stromal microenvironment. Cell Signal. 2012; 24:1883-1888.

[28] Raza A, Galili N. The genetic basis of phenotypic heterogeneity in myelodysplastic syndromes. Nat.Rev.Cancer 2012; 12:849-859.

[29] Vecchio L, Seke Etet PF, Kipanyula MJ, Krampera M, Nwabo Kamdje AH. Importance of epigenetic changes in cancer etiology, pathogenesis, clinical profiling, and treatment: what can be learned from hematologic malignancies? Biochim.Biophys.Acta 2013; 1836:90-104.

[30] Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. Blood 2014;

[31] Musto P, Simeon V, Guariglia R, Bianchino G, Grieco V, Nozza F, La RF, Marziano G, Lalinga AV, Fabiani E, Voso MT, Scaravaglio P, Mecucci C, D'Arena G. Myelodysplastic disorders carrying both isolated del(5q) and JAK2(V617F) mutation: concise review, with focus on lenalidomide therapy. Onco.Targets.Ther. 2014; 7:1043-1050.

[32] Faltas B, Zeidan A, Gergis U. Myelodysplastic syndromes: toward a risk-adapted treatment approach. Expert.Rev.Hematol. 2013; 6:611-624.

[33] Zeidan AM, Linhares Y, Gore SD. Current therapy of myelodysplastic syndromes. Blood Rev. 2013; 27:243-259.

[34] Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T, Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997; 89:2079-2088.

[35] Elli EM, Belotti A, Aroldi A, Parma M, Pioltelli P, Pogliani EM. Iron chelation therapy with deferasirox in the management of iron overload in primary myelofibrosis. Mediterr.J.Hematol.Infect.Dis. 2014; 6:e2014042.

[36] Di Stasi A, Milton DR, Poon LM, Hamdi A, Rondon G, Chen J, Pingali SR, Konopleva M, Kongtim P, Alousi A, Qazilbash MH, Ahmed S, Bashir Q, Al-Atrash G, Oran B, Hosing CM, Kebriaei P, Popat U, Shpall EJ, Lee DA, De LM, Rezvani K, Khouri IF, Champlin RE, Ciurea SO. Similar Transplantation Outcomes for Acute Myeloid Leukemia and Myelodysplastic Syndrome Patients with Haploidentical versus 10/10 Human Leukocyte Antigen-Matched Unrelated and Related Donors. Biol.Blood Marrow Transplant. 2014;

[37] Hu C, Lv L, Liu D, Huo J. Treatment of Crohn's disease complicated with myelodysplastic syndrome via allogeneic hematopoietic stem cell transplantation: case report and literature review. Clin.J.Gastroenterol. 2014; 7:299-304.

[38] Oran B, Kongtim P, Popat U, De LM, Jabbour E, Lu X, Chen J, Rondon G, Kebriaei P, Ahmed S, Andersson B, Alousi A, Ciurea S, Shpall E, Champlin RE. Cytogenetics, donor type, and use of hypomethylating agents in myelodysplastic syndrome with allogeneic stem cell transplantation. Biol.Blood Marrow Transplant. 2014; 20:1618-1625.

[39] Stamatovic D, Balint B, Tukic L, Elez M, Tarabar O, Todorovic M, Ostojic G, Tatomirovic Z, Ljubenov M, Marjanovic S, Malesevic M. Impact of stem cell source on allogeneic stem cell transplantation outcome in hematological malignancies. Vojnosanit.Pregl. 2011; 68:1026-1032.

[40] Battiwalla M, Ellis K, Li P, Pavletic SZ, Akpek G, Hematti P, Klumpp TR, Maziarz RT, Savani BN, Aljurf MD, Cairo MS, Drobyski WR, George B, Hahn T, Khera N, Litzow MR, Loren AW, Saber W, Arora M, Urbano-Ispizua A, Cutler C, Flowers ME, Spellman SR. HLA DR15 antigen status does not impact graft-versus-host disease or survival in HLA-matched sibling transplantation for hematologic malignancies. Biol.Blood Marrow Transplant. 2012; 18:1302-1308.

[41] Yabe M, Shimizu T, Morimoto T, Koike T, Takakura H, Tsukamoto H, Muroi K, Oshima K, Asami K, Takata M, Yamashita T, Kato S, Yabe H. Matched sibling donor stem cell transplantation for Fanconi anemia patients with T-cell somatic mosaicism. Pediatr.Transplant. 2012; 16:340-345.

[42] Horowitz MM. Does matched unrelated donor transplantation have the same outcome as matched sibling transplantation in unselected patients? Best.Pract.Res.Clin.Haematol. 2012; 25:483-486.

[43] Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, Gau JP, Chou WC, Buckstein R, Cermak J, Kuo CY, Oriol A, Ravandi F, Faderl S, Delaunay J, Lysak D, Minden M, Arthur C. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J.Clin.Oncol. 2012; 30:2670-2677.

[44] Oki Y, Kondo Y, Yamamoto K, Ogura M, Kasai M, Kobayashi Y, Watanabe T, Uike N, Ohyashiki K, Okamoto S, Ohnishi K, Tomita A, Miyazaki Y, Tohyama K, Mukai HY, Hotta T, Tomonaga M. Phase I/II study of decitabine in patients with myelodysplastic syndrome: a multi-center study in Japan. Cancer Sci. 2012; 103:1839-1847.

[45] Platzbecker U, Mufti G. Allogeneic stem cell transplantation in MDS: how? When? Best.Pract.Res.Clin.Haematol. 2013; 26:421-429.

[46] Shadman M, Deeg HJ. Hematopoietic Cell Transplantation for Older Patients with MDS. Mediterr.J.Hematol.Infect.Dis. 2014; 6:e2014056.

[47] Jacobsohn DA, Arora M, Klein JP, Hassebroek A, Flowers ME, Cutler CS, Urbano-Ispizua A, Bolwell BJ, Antin JH, Boyiadzis M, Cahn JY, Cairo MS, Herzig RH, Isola LM, Klumpp TR, Lee SJ, Petersdorf EW, Santarone S, Gale RP, Schouten HC, Spellman SR, Weisdorf DJ, Wingard JR, Horowitz MM, Pavletic SZ. Risk factors associated with increased nonrelapse mortality and with poor overall survival in children with chronic graft-versus-host disease. Blood 2011; 118:4472-4479.

[48] Shao L, Wang Y, Chang J, Luo Y, Meng A, Zhou D. Hematopoietic stem cell senescence and cancer therapy-induced long-term bone marrow injury. Transl.Cancer Res. 2013; 2:397-411.

[49] Bhattad D, Kulkarni V, Bhave A, Balasubramanian M, Upase DP, Khude S. Refractory anaemia in an immunocompromised patient--what is it? J.Assoc.Physicians India 2013; 61:673-675.

[50] Dietz AC, DeFor TE, Brunstein CG, Wagner JE, Jr. Donor-derived myelodysplastic syndrome and acute leukaemia after allogeneic haematopoietic stem cell transplantation: incidence, natural history and treatment response. Br.J.Haematol. 2014; 166:209-212.

[51] Tacke D, Buchheidt D, Karthaus M, Krause SW, Maschmeyer G, Neumann S, Ostermann H, Penack O, Rieger C, Ruhnke M, Sandherr M, Schweer KE, Ullmann AJ, Cornely OA. Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Ann.Hematol. 2014; 93:1449-1456.

[52] Duggleby RC, Madrigal JA. Methods of detection of immune reconstitution and T regulatory cells by flow cytometry. Methods Mol.Biol. 2014; 1109:159-186.

[53] Li QB, Li L, You Y, Chen ZC, Xia LH, Zou P. A comparative study of outcomes of idarubicin- and etoposide-intensified conditioning regimens for allogeneic peripheral blood stem cell transplantation in patients with high-risk acute leukemia. Acta Pharmacol.Sin. 2009; 30:1471-1478.

[54] Hong M, Wu Q, Hu C, Fang J, You Y, Zhong Z, Zou P, Hu Y, Xia L. Idarubicin-intensified BUCY2 regimens may lower relapse rate and improve survival in patients undergoing allo-SCT for high-risk hematological malignancies: a retrospective analysis. Bone Marrow Transplant. 2012; 47:196-202.

[55] William BM, De LM. Advances in conditioning regimens for older adults undergoing allogeneic stem cell transplantation to treat hematologic malignancies. Drugs Aging 2013; 30:373-381.

[56] Sebert M, Porcher R, Robin M, Ades L, Boissel N, Raffoux E, Xhaard A, Dhedin N, Larghero J, Himberlin C, Delmer A, Fenaux P, Dombret H, Socie G, de Latour RP. Equivalent outcomes using reduced intensity or conventional myeloablative conditioning transplantation for patients aged 35 years and over with AML. Bone Marrow Transplant. 2014;

[57] Chen YB, Coughlin E, Kennedy KF, Alyea EP, Armand P, Attar EC, Ballen KK, Cutler C, Dey BR, Koreth J, McAfee SL, Spitzer TR, Antin JH, Soiffer RJ, Ho VT. Busulfan dose intensity and outcomes in reduced-intensity allogeneic peripheral blood stem cell transplantation for myelodysplastic syndrome or acute myeloid leukemia. Biol.Blood Marrow Transplant. 2013; 19:981-987.

[58] Le Bourgeois A, Mohr C, Guillaume T, Delaunay J, Malard F, Loirat M, Peterlin P, Blin N, Dubruille V, Mahe B, Gastinne T, Le GS, Moreau P, Mohty M, Planche L, Lode L, Bene MC, Chevallier P. Comparison of outcomes after two standards-of-care reduced-intensity conditioning regimens and two different graft sources for allogeneic stem cell transplantation in adults with hematologic diseases: a single-center analysis. Biol.Blood Marrow Transplant. 2013; 19:934-939.

[59] Melchert M, List A. Targeted therapies in myelodysplastic syndrome. Semin.Hematol. 2008; 45:31-38.

[60] Lainey E, Thepot S, Bouteloup C, Sebert M, Ades L, Tailler M, Gardin C, de BS, Baruchel A, Fenaux P, Kroemer G, Boehrer S. Tyrosine kinase inhibitors for the treatment of acute myeloid leukemia: delineation of anti-leukemic mechanisms of action. Biochem.Pharmacol. 2011; 82:1457-1466.

[61] Li KK, Luo LF, Shen Y, Xu J, Chen Z, Chen SJ. DNA methyltransferases in hematologic malignancies. Semin.Hematol. 2013; 50:48-60.

[62] Ishikawa T. Novel therapeutic strategies using hypomethylating agents in the treatment of myelodysplastic syndrome. Int.J.Clin.Oncol. 2014; 19:10-15.

[63] Cogle CR, Imanirad I, Wiggins LE, Hsu J, Brown R, Scornik JC, Wingard JR. Hypomethylating agent induction therapy followed by hematopoietic cell transplantation is feasible in patients with myelodysplastic syndromes. Clin.Adv.Hematol.Oncol. 2010; 8:40-46.

[64] Kim DY, Lee JH, Park YH, Lee JH, Kim SD, Choi Y, Lee SB, Lee KH, Ahn SY, Lee YS, Seol M, Kang YA, Jeon M, Jung AR, Lee YJ, Lee KH. Feasibility of hypomethylating agents followed by allogeneic hematopoietic cell transplantation in patients with myelodysplastic syndrome. Bone Marrow Transplant. 2012; 47:374-379.

[65] Gurman G, Arat M, Ilhan O, Konuk N, Beksac M, Celebi H, Ozcan M, Arslan O, Ustun C, Akan H, Uysal A, Koc H. Allogeneic hematopoietic cell transplantation without myeloablative conditioning for patients with advanced hematologic malignancies. Cytotherapy. 2001; 3:253-260.

[66] Valcarcel D, Martino R, Caballero D, Martin J, Ferra C, Nieto JB, Sampol A, Bernal MT, Pinana JL, Vazquez L, Ribera JM, Besalduch J, Moraleda JM, Carrera D, Brunet MS, Perez-Simon JA, Sierra J. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. J.Clin.Oncol. 2008; 26:577-584.

[67] Warlick ED, Cioc A, Defor T, Dolan M, Weisdorf D. Allogeneic stem cell transplantation for adults with myelodysplastic syndromes: importance of pretransplant disease burden. Biol.Blood Marrow Transplant. 2009; 15:30-38.

[68] Davies JK, Taussig D, Oakervee H, Smith M, Agrawal S, Cavenagh JD, Gribben JG. Long-term survival with low toxicity after allogeneic transplantation for acute myeloid leukaemia and myelodysplasia using non-myeloablative conditioning without T cell depletion. Br.J.Haematol. 2013; 162:525-529.

[69] Zhou X, Di SA, Tey SK, Krance RA, Martinez C, Leung KS, Durett AG, Wu MF, Liu H, Leen AM, Savoldo B, Lin YF, Grilley BJ, Gee AP, Spencer DM, Rooney CM, Heslop HE, Brenner MK, Dotti G. Long-term outcome after haploidentical stem cell transplant and infusion of T cells expressing the inducible caspase 9 safety transgene. Blood 2014; 123:3895-3905.

[70] Kim JH, Stein A, Tsai N, Schultheiss TE, Palmer J, Liu A, Rosenthal J, Forman SJ, Wong JY. Extramedullary relapse following total marrow and lymphoid irradiation in patients undergoing allogeneic hematopoietic cell transplantation. Int.J.Radiat.Oncol.Biol.Phys. 2014; 89:75-81.

[71] Arora M, Klein JP, Weisdorf DJ, Hassebroek A, Flowers ME, Cutler CS, Urbano-Ispizua A, Antin JH, Bolwell BJ, Boyiadzis M, Cahn JY, Cairo MS, Isola L, Jacobsohn DA, Jagasia M, Klumpp TR, Lee SJ, Petersdorf EW, Santarone S, Gale RP, Schouten HC, Spellman S, Wingard JR, Horowitz MM, Pavletic SZ. Chronic GVHD risk score: a Center for International Blood and Marrow Transplant Research analysis. Blood 2011; 117:6714-6720.

[72] Bruserud O, Reikvam H, Kittang AO, Ahmed AB, Tvedt TH, Sjo M, Hatfield KJ. High-dose etoposide in allogeneic stem cell transplantation. Cancer Chemother.Pharmacol. 2012; 70:765-782.

[73] Petersen SL. Alloreactivity as therapeutic principle in the treatment of hematologic malignancies. Studies of clinical and immunologic aspects of allogeneic hematopoietic cell transplantation with nonmyeloablative conditioning. Dan.Med.Bull. 2007; 54:112-139.

[74] Voulgarelis M, Giannouli S, Ritis K, Tzioufas AG. Myelodysplasia-associated autoimmunity: clinical and pathophysiologic concepts. Eur.J.Clin.Invest 2004; 34:690-700.

[75] Kotsianidis I, Bouchliou I, Nakou E, Spanoudakis E, Margaritis D, Christophoridou AV, Anastasiades A, Tsigalou C, Bourikas G, Karadimitris A, Tsatalas C. Kinetics, function and bone marrow trafficking of CD4+CD25+FOXP3+ regulatory T cells in myelodysplastic syndromes (MDS). Leukemia 2009; 23:510-518.

[76] Nakamura R, Palmer JM, O'Donnell MR, Stiller T, Thomas SH, Chao J, Alvarnas J, Parker PM, Pullarkat V, Maegawa R, Stein AS, Snyder DS, Bhatia R, Chang K, Wang S, Cai JL, Senitzer D, Forman SJ. Reduced intensity allogeneic hematopoietic stem cell transplantation for MDS using tacrolimus/sirolimus-based GVHD prophylaxis. Leuk.Res. 2012; 36:1152-1156.

[77] Zeighami S, Hadjibabaie M, Ashouri A, Sarayani A, Khoee SH, Mousavi S, Radfar M, Ghavamzadeh A. Assessment of cyclosporine serum concentrations on the incidence of acute graft versus host disease post hematopoietic stem cell transplantation. Iran J.Pharm.Res. 2014; 13:305-312.