

New therapeutic options in myelodysplastic syndrome: literature review and single-center treatment results

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Summary

Myelodysplastic syndromes (MDS) comprise a group (continuum) of clonal hematopoietic diseases associated with high risk of transformation into acute myeloid leukemia (AML) and unfavorable prognosis. Compared to the other hematologic malignant diseases, there was only a modest improvement in survival of MDS patients over the last years. Allogeneic stem cell transplantation remains the only curative option for these patients, however, most of them are not candidates for transplantation. This review focuses on the long-term outcomes of existing therapies and novel agents that are currently

tested at different stages of clinical trials. These include inhibitors of TGF β , various kinase inhibitors, and immune checkpoint inhibitors. Administration of new therapies in the patients with different pathogenetic MDS variants is discussed.

Keywords

Myelodysplastic syndrome, treatment, checkpoint inhibitors, luspatercept, glasdegib, venetoclax, IDH inhibitors.

Introduction

Myelodysplastic syndrome (MDS) represents a heterogeneous group of clonal diseases caused by alterations in hematopoietic stem cells due to hereditary predisposal, along with variable somatic gene mutations, and/or abnormal epigenetic regulation, including those induced by altered microenvironment and disrupted immune surveillance [1].

Pre-leukemic features of MDS were explored since early 80's based on atypical *in vitro* growth of hematopoietic precursor cells from MDS patients [2-4]. Further on, some newer laboratory techniques, like flow cytometry and next-generation sequencing (NGS), allowed better insight into the distinct pathological events underlying MDS development. Over last decades, with increased lifespan, a number of peripheral blood cytopenias were found to precede clinical MDS,

especially, in the patients >65 years old, i.e., ICUS (idiopathic cytopenia of undetermined significance); CHIP (Clonal hematopoiesis of indeterminate potential); CCUS (clonal cytopenia of undetermined significance). Such conditions are determined by the age-dependent accumulation of somatic mutations which may play a role in subsequent MDS development.

These disorders may be transformed to hematological malignancy at a frequency of ca. 0.5-1% *per year* [5-7]. The majority of associated gene mutations (e.g., DNMT3A, TET2, ASXL1, TP53, and JAK2) affect RNA splicing or epigenetic regulation. However, patients with long-term cytopenias and somatic mutations do not always exhibit morphological changes of blood cells corresponding to MDS criteria. Moreover, only distinct cytogenetic aberrations (del5q) and point mutations (*SF3B1*) are considered specific for MDS, whereas other mutations are relatively non-specific and could be

revealed in other pathologies, e.g., in the myeloproliferative disorders [8] or aplastic anemia (Fig. 1). In the latter case, MDS frequency was demonstrated to be sufficiently higher than in general population which is determined by the mutational profile [9].

Occurrence of additional potentially pathogenic mutations is associated with increased MDS risk [10]. At diagnosis, two or more marker somatic mutations can be determined in most MDS patients [11]. In parallel to additional mutagenesis and clonal evolution of hematopoietic cells, the clinical manifestations undergo several stages, from a cytopenia of undetermined significance to MDS, and, in some cases, to leukemic transformation into acute myeloid leukemia (AML) [12]. Due to this complex pathogenesis effective target therapy is still not available for this group of diseases despite better awareness of MDS development mechanisms.

Hematopoietic cell transplantation and current therapeutic options

At the present time, allogeneic HSCT is the only curative treatment method for MDS. However, patients with MDS still remain the most complicated candidates for allo-HSCT, due to a number of additional unfavorable factors, including advanced age of the patients. MDS is more common in the patients over 65 years old, which determines a sufficient number of co-morbidities. In addition, preceding prolonged therapy is associated with significant number of blood transfusions with high frequency of clinical and laboratory signs

of iron overload, as well as immunization due to these transfusions. In clinical practice, reduced-intensity conditioning regimens are often applied, taking into account somatic state of patients [14]. However, hematological remission is not achieved at the time of allo-HSCT in the majority of patients.

Along with gene mutations in stem cells, a special feature of MDS pathogenesis are certain defects of hematopoietic microenvironment, which alter functioning of hematopoietic niches [15]. These alterations contribute to higher incidence of graft failure, including primary graft failure and severe poor graft function after engraftment, as well as increased probability of early relapse. Long cytopenias after allo-HSCT is associated with higher risk of infectious complications, which are the main cause of posttransplant mortality in MDS patients. All issues described above determine higher post-transplant mortality in MDS compared to the other groups of HSCT recipients [16, 17]. Moreover, a significant proportion of patients is lacking HLA-compatible related or unrelated donor, and efficiency of haploidentical HSCT in MDS is still not supported by large studies [18]. According to the current European Blood and Marrow Transplantation (EBMT) guidelines, allo-HSCT from haploidentical donor is a clinical option and could be considered only after thorough evaluation of potential risks and benefits associated with this procedure.

Nonetheless, allo-HSCT facilitates cure in 30-40% of MDS patients. Several studies are ongoing aiming to improve allo-HSCT outcomes with posttransplant relapse preventive strategies [19, 20].

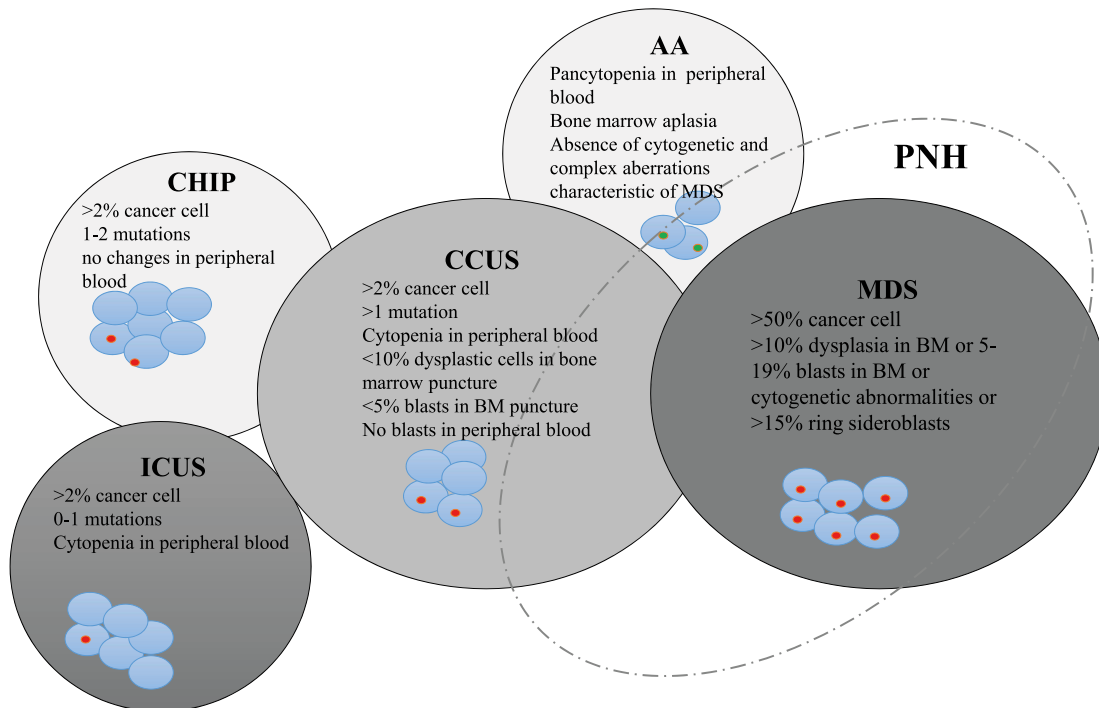


Figure 1. Interactions and characteristic features of clonal hematopoiesis of indetermined potential (CHIP), idiopathic cytopenia of undetermined significance (ICUS), clonal cytopenia of undetermined significance (CCUS), aplastic anemia (AA), and myelodysplastic syndrome (MDS). Adapted from Young N., 2002 [13]

Due to clinical heterogeneity of MDS and risks associated with HSCT procedure, the strategy of treatment is largely personalized, dependent on the prognostic group, according to national and international recommendations [21, 22].

In low- and very low-risk patients with predominant clinical signs of anemia, the main therapeutic goal is to reduce transfusion dependence and to prevent organ damage caused by iron overload. Erythropoiesis-stimulating agents (ESA) could be administered, which, however, are clinically effective in about 1/3 of the patients, according to the multicenter studies [23]. The responders are predominantly those with initially low erythropoietin levels (<200 ng/ml) and the median duration of clinical response is about 1 year. Some studies suggest the possibility of decreased transfusion requirements with chelator therapy [24]. However, a randomized study did not show any improvement of erythropoietic response compared to ESA monotherapy [25].

In low-risk MDS cases with 5q- chromosomal aberration, immunomodulating therapy may result into cytogenetic remission in about 50% of the patients, with 2/3 of cases becoming transfusion-independent [26, 27]. In other low-risk MDS variants, there are only several single-center studies, where transfusion independence was achieved after short courses of hypomethylating agents (HMA) [28], and immunosuppressive treatment (IST), including cyclosporine A and anti-thymocyte globulin [29]. The median duration of clinical response using these therapies was, respectively, 16 and 18 months. Only small proportion of MDS patients has long-term remissions, either with HMA or IST protocols. However Kokhno A. et al. have shown that IST proved to be more effective in the patients with hypocellular bone marrow, or non-uniform cellularity with hypoplastic/aplastic areas, in absence of poor and very poor karyotype abnormalities according to IPSS-R scale, or without 7q-, i(17q) aberration [30].

In high-risk MDS, low-dose cytosine arabinoside (LDAC) treatment was a long-standing approach to therapy in myeloid dysplasia since mid-80's [31]. Median survival time in clinical studies was ca. 8 months for these cohorts, with maximal lifespan of 2-3 years and frequency of clinical

responses of 15 to 30%. However, some studies did not show any differences in survival rates between LDAC protocol and best supporting therapy [32-34]. At the present time, HMA became another standard of therapy in high-risk MDS. In registration randomized studies, decitabine and 5-azacitidine were associated with prolonged median survival by 2.7 and 10 months, respectively, compared with best available treatment [35, 36]. Nevertheless, large clinical studies, e.g., Surveillance, Epidemiology, and End Result-Medicare database embracing 532 MDS high-risk patients, have shown somewhat higher results, i.e., median overall survival (OS) of, respectively, 11 and 12 months for decitabine and 5-azacitidine [37]. Despite MDS complete remissions are rare in HMA-treated MDS patients, these drugs enable temporary control of the disease with good quality of life and low hematological toxicity. Moreover, in the context of allo-HSCT, HMA may be effective in the pre-transplant period, by improving the patient's state during search and activation of potential donors without increase of hematological toxicity [38].

There also are some studies on improvement of platelet counts with supplementary treatment with Eltrombopag, however, without evidence of higher response rate [39, 40].

Despite improvements with HMA introduction, recent studies in fundamental biology and pathogenesis of MDS revealed potential opportunities for studying novel treatments able to modify specific signaling and metabolic pathways, as well as hematopoietic and immune microenvironment.

Transforming growth factor-beta (TGFβ) antagonists

TGFβ antagonists, e.g. luspatercept, proved to be potentially effective in low-risk MDS with transfusion dependence, given the key role of TGFβ ligands in hematopoiesis. This drug represents a recombinant protein able to bind the TGFβ superfamily ligands, thus blocking SMAD2 and SMAD3 signaling pathways, regulating differentiation and maturation of erythroid precursors [41, 42]. These pathways play an

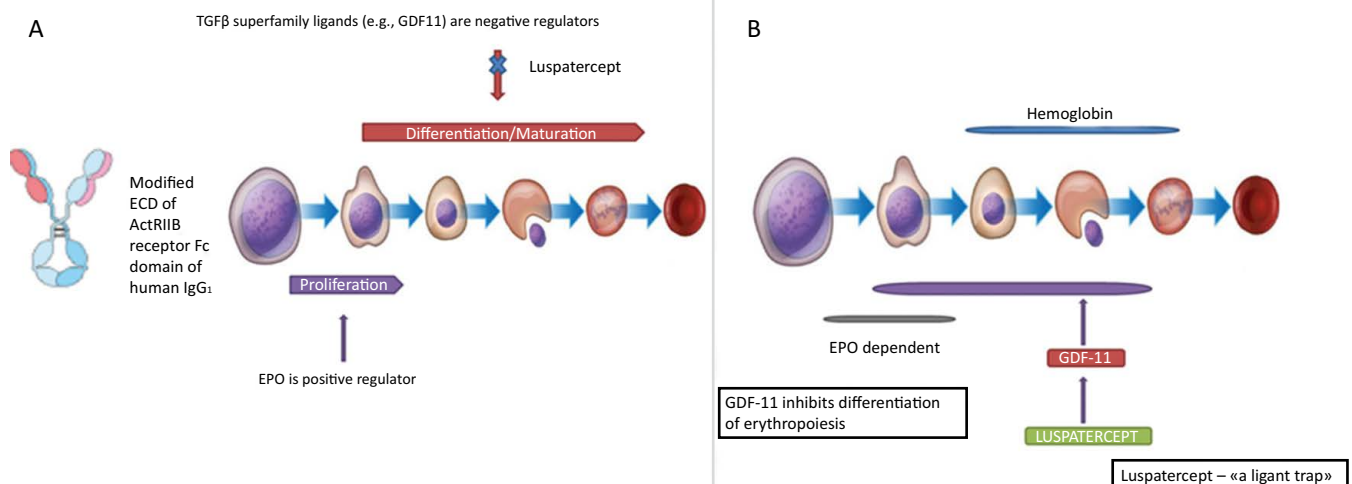


Figure 2. Hematopoietic effects of luspatercept (A); Molecular mechanisms of luspatercept action (B)

important role in MDS pathogenesis by inhibition of SMAD7 and SKI expression [43, 44]. Luspatercept binds TGFβ ligands, that abrogating negative erythropoiesis regulation, accelerating events during late RBC maturation, unlike erythropoietin which regulates early stages of erythropoiesis [45], as shown in Fig. 2.

A general reduction in transfusion dependence was demonstrated in phase II clinical trial PACE-MDS with 29% of cases being with high transfusion requirements. Independence of blood transfusions was achieved in 36% of the cases. In particular, clinical responses were more often observed among patients with marrow ring sideroblasts and SF3B1 mutation [46].

In the phase 3 MEDALIST study, 37.9% of low-risk MDS patients became transfusion-independent in the treatment with luspatercept compared to 13.2% in the placebo group. According to the results of longitudinal observation (MEDALIST study), independence on red blood cell (RBC) transfusions maintained for at least 8 weeks at any period of treatment, and it was more frequent among patients treated with luspatercept (47.7%) than in placebo group (15.8%). Approximately 1 year after initiation of luspatercept, 31.4% did not require RBC transfusions, against 0% in placebo group. Among luspatercept-treated patients, the overall transfusion-free period and clinical improvement was observed, independent on previous transfusion burden. Transfusion independence persisted in 12 cases (7.8%) out of 153 patients who received luspatercept after 48 weeks of follow up. Some adverse effects associated with luspatercept administration rarely caused early discontinuation of therapy, and their occurrence decreased over time. Frequency of progression to AML (5%) was similar for luspatercept-treated patients and placebo group [47].

Another randomized phase III study COMMANDS is ongoing, where a comparison is made between luspatercept and erythropoietin α, the current standard of therapy [48]. The results of this study may influence the subsequent treatment standards in low-risk MDS patients. Similarly, some preclinical and clinical studies of kinase inhibitors involved into the TGFβ signal pathway are currently underway.

Galunisertib, an inhibitor of ALK5 kinase related to the signal transduction for TGFβ receptor activation, was studied in phase 2 clinical trials in low- and intermediate risk MDS, according to the IWG 2000 criteria. In 43.9% of patients, erythroid response was observed, hematological improvement was registered in 24.4% of cases, along with reduction of weakness in 44% of the patients. The results may justify its application in transfusion-dependent MDS patients who are non-responding to ESA [49]. Thus, a new class of TGFβ-directed drugs can be registered in the near future. The ongoing studies will show if these drugs are applicable only in MDS with ring sideroblasts, or they could be extended to other subgroups of low-risk MDS patients.

Another agent for low-risk MDS in late clinical trials is Roxadustat. It is a protein factor regulating HIF-1α (hypoxia-inducible factor-α) [50]. The drug influences erythropoietin production and iron uptake from macrophages, enhances iron metabolism, stabilizes blood HIF levels and prevents its degradation, thus promoting erythropoiesis [51]. Interim results of a multicenter study involved 24 patients with low-risk MDS and demonstrated a decrease of transfusion dependence by 50% [52]. Roxadustat inhibits HIF-α decay followed by its dimerization with HIF-β and nuclear translocation to cellular nucleus where the response to hypoxia is mediated at the transcriptional level (Fig. 3).

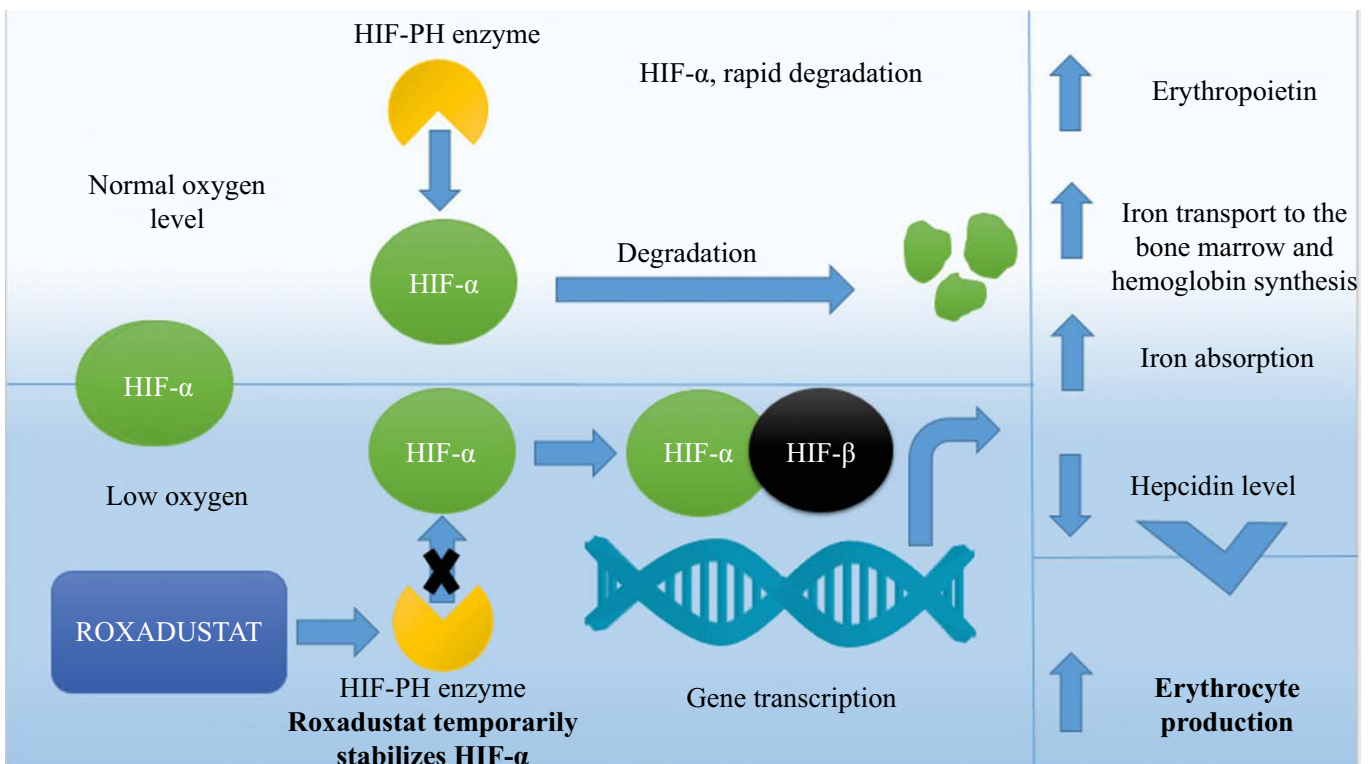


Figure 3. Main effects of roxadustat upon different organs and cells

Immune checkpoint inhibitors

The inhibitors of immune checkpoints (ICP) are highly effective in a treatment of some solid tumors. Their versatile effects are based on reactivation of exhausted immune cells via blocking appropriate inhibitory signal, leading to a recovery of antitumor immunity. Nevertheless, the characteristics and expression of different ligands of ICP strongly depends on the type of malignancy. Pronounced clinical response to ICP is prominent in tumors with high neo-antigen contents, or amplification of genes encoding ICP ligands. Highest sensitivity to ICP treatment was demonstrated for Hodgkin's lymphoma, melanoma, cancers of urinary tract, lung cancer, head and neck malignancies, solid cancers with microsatellite instability [53]. There are usually only a small number of somatic mutations in MDS patients despite variable mutation profile [11], however hematopoietic cells in MDS exhibit high expression of the ICP ligands which may be increased during HMA therapy [54, 55].

Nonetheless, the ICP monotherapy was not associated with significant response in clinical trials [56]. The failure of nivolumab or ipilimumab monotherapy may be due to simultaneous expression of several inhibitors of immune response as confirmed by experimental data, including our own results [57]. Garcia-Manero G. et al. have shown the overall response rate (69%) to 5-azacitidine+nivolumab treatment in MDS, including complete remission in 2 patients. Higher response rate in this combined treatment schedule correlates with induction of neoantigen expression in tumor cells under HMA, thus enhancing the T cell immune response.

Failure of ICP therapy in MDS could be also determined by immunosuppressive effects in the hematopoietic niches. As possible mechanisms, one may consider high indoleamine-pyrrole 2,3-dioxygenase (IDO) expression in cellular microenvironment, T cell differentiation towards regulatory T cells, low interferon- α expression by T cells, induction of

T cell apoptosis due to activation of CD33-S100A9 signaling, increased levels of myeloid suppressor cells [58-68]. In future, ICP-based treatment seems to enter the standards of MDS therapy, however, not as monotherapy, but as combined therapeutic schedules, e.g., with PD-1, CTLA4 and TIM3 inhibitors [69]. Clinical trials with anti-TIM3 monoclonal antibodies are underway now. A multicenter study has shown that combined treatment with MBG453B, an anti-TIM3 antibody, and decitabine resulted into hematological or molecular remission in 50% of high-risk MDS patients [70].

Macrophage ICPs represent a fundamentally new class of such regulatory molecules. CD47, being expressed on macrophages, is a key molecule able to inhibit their response, and its interaction with SIRP α ligand protein causes suppression of phagocytic function. This effect is called a blocking "don't eat me" signal of CD47-SIRP α . This signal pathway is active during interactions between hematopoietic cells and macrophages, also serving as a tolerance mechanism in hematopoietic malignancies [71]. Magrolimab, or 5F9 antibody, is a humanized monoclonal antibody (MAb) which blocks CD47 and activates SIRP α pathway, promotes phagocytosis of tumor cells. Combined application of this drug with 5-azacitidine in preclinical model of acute myeloid leukemia (AML) has shown high survival rates in laboratory animals [72]. During the Phase 1 clinical trial, 5-azacitidine and Magrolimab was administered to 35 high-risk MDS patients. The response was evaluated in 24 patients, with hematological response in 92% and complete remission in 50% of the cases. Further observations are required to assess duration of the responses [73].

Distinct effects of the CD47-blocking antibodies are considered, as follows: (a) under normal conditions, both healthy and malignant cells are avoiding phagocytosis by CD47 expression. CD47 is overexpressed by cancer cells for protection from *eat me/prophagocyte* signals. (b) After the

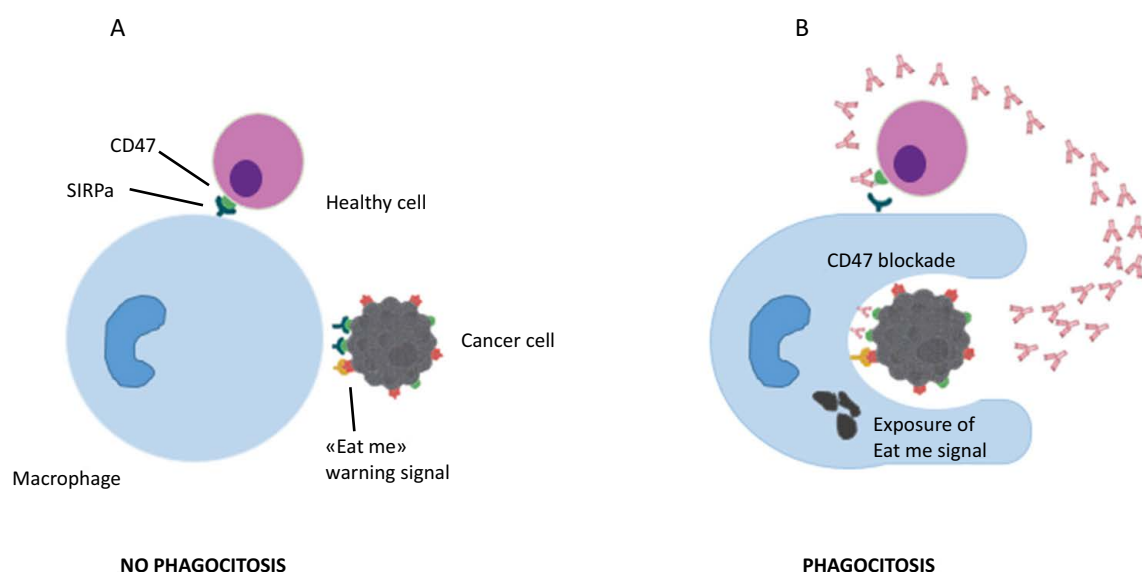


Figure 4. Possible effects of CD47-blocking antibodies upon immune cells

Mab-induced CD47 blockage, the malignant cells are phagocytized, thus causing exposure of the *eat me* signal. By contrast, normal cells remain intact due to absent expression of prophagocytic signals.

Inhibitors of bcl2, hedgehog, IDH and other molecular targets

Over last years, a significant role of bcl2 in AML progression and drug resistance was elucidated. Venetoclax, a specific bcl2 inhibitor, was shown to increase the rates of complete remission in combination with LDAC or HMA [74, 75]. However, the results observed in AML cannot be blindly extended to MDS. BCL2 inhibition in an MDS models leads to suppression of apoptosis in hematopoietic cells and transition to the resting phase of a cell cycle. As a result a reduced DNA damage of erythropoietic precursors was observed. However, some doubts exist since apoptosis blockage may promote faster transition to AML [76].

Overall response to venetoclax was 21% in a group of chemotherapy-refractory AML and MDS patients [77]. Clinical studies are ongoing with early venetoclax and HMA administration in MDS. So far only the results of non-randomized studies are published demonstrating promising overall and complete remission rates (59% and 14%, respectively) even in HMA-exposed patients [78].

Glasdegib, another inhibitor of signaling pathways, was registered in 2019 for therapy of AML and high-risk MDS in combination with chemotherapy. The drug inhibits Hedgehog (Hh) pathway previously described as an embryogenesis regulator, since Hh proteins are involved in cell and tissue differentiation. Like other intracellular signaling systems, the Hh pathway plays an important role in cell cycle regulation of malignant cells and is involved into the mechanisms of chemotherapy resistance [79].

In a Phase I study, 31% of AML and high-risk MDS patients have achieved complete remission during the glasdegib therapy combined with LDAC and decitabine [80]. Complete remission was achieved in 46% of the patients with similar disorders in another study using glasdegib combined with systemic 7+3 chemotherapy [81]. In a randomized study comparing glasdegib plus LDAC against LDAC a 3-month increase in OS was demonstrated, along with long-term stabilization of the disease in some patients. The rates of response to glasdegib monotherapy in refractory MDS comprise only 6% [82]. Chaudhry et al. noted that therapeutic activity of glasdegib requires expression of GLI3 suppressor gene which may be hypermethylated in MDS and AML. Determination of GLI3 expression may serve as predictor of response to glasdegib treatment [83]. Despite relatively low efficiency, glasdegib is well tolerated, thus allowing to suggest it as a component of combined therapy in MDS.

About 5% of MDS cases are associated with IDH1 and IDH2 gene mutations. The mutated IDH variants are associated with excessive production of R2-hydroxyglutarate which causes functional insufficiency of TET2 gene [84, 85]. Presently, two IDH inhibitors for oral administration are under clinical trials, enasidenib, and ivosidenib (respectively for

IDH2 and IDH1 inhibition). The Phase II study in AML and high-risk MDS patients, enasidenib therapy was associated with response in 53% of the patients including complete remission in 7% [86]. There are no preliminary results on ivosidenib in MDS at the present moment. However, in elderly AML ivosidenib induced complete remission, including one with partial hematologic recovery, in 42.4% of patients and median duration of remission was not reached with 2-year follow up [87].

Rigosertib is another clinically tested inhibitor of signal pathways which is able to suppress several kinases, e.g., Akt, PI3K. A clinical study in MDS patients has demonstrated reduction of blastosis [88]. However, Phase III study in HMA-resistant patients did not show any differences in survival between Rigosertib treatment and best available therapy [89]. At present, Rigosertib is tested in combination with 5-azacitidine [90].

A small group of MDS patients exhibits FLT3 mutation [11]. These patients are prone to rapid transformation to AML, thus precluding data accumulation on clinical efficiency of FLT3 inhibitors in this MDS variant. Nevertheless, the MDS experience shows that addition of Midostaurin to chemotherapy is associated with 8% increase in relapse-free survival [91]. The response rate in combined therapy with 5-azacitidine was 26% [92]. Meanwhile, the second-generation FLT3 inhibitors (Gilteritinib and Quizartinib) demonstrate more optimistic results [93, 94], thus creating the basis for addition of these agents to standard therapy in MDS patients with FLT3 mutations.

Summarizing the overview of developing targeted therapies, it is important to mention that few of them induce high complete remission rate and these complete remissions are not durable in the high proportion of the patients. When keeping in mind the complex pathogenesis of this disease, it is clear that complex approaches to therapy are required. The successful examples of other hematological diseases give us hope for long-term improvement of survival in MDS (Fig. 5).

Allogeneic HSCT as a platform for immune therapy in MDS patients

Along with development of novel therapeutic molecules, some feasible options of cellular therapy are under investigation in MDS [95]. At the moment, allo-HSCT is the only cellular therapy in MDS which is widely used in clinical practice. However, allo-HSCT is a high-risk procedure with potentially severe complications that may cause sufficiently decreased quality of life and shorter survival of the patients. This issue is especially important due to advanced age of most MDS patients, thus increasing risk for dismal outcome.

To evaluate the impact of allo-HSCT on survival in MDS we compared the survival of two contemporary cohorts of patients treated at RM Gorbacheva Research Institute. The first cohort agreed to allograft procedure while the second refused to undergo allo-HSCT and was treated with available therapies. Although the groups were not well matched, however represent the real life clinical practice at large HSCT

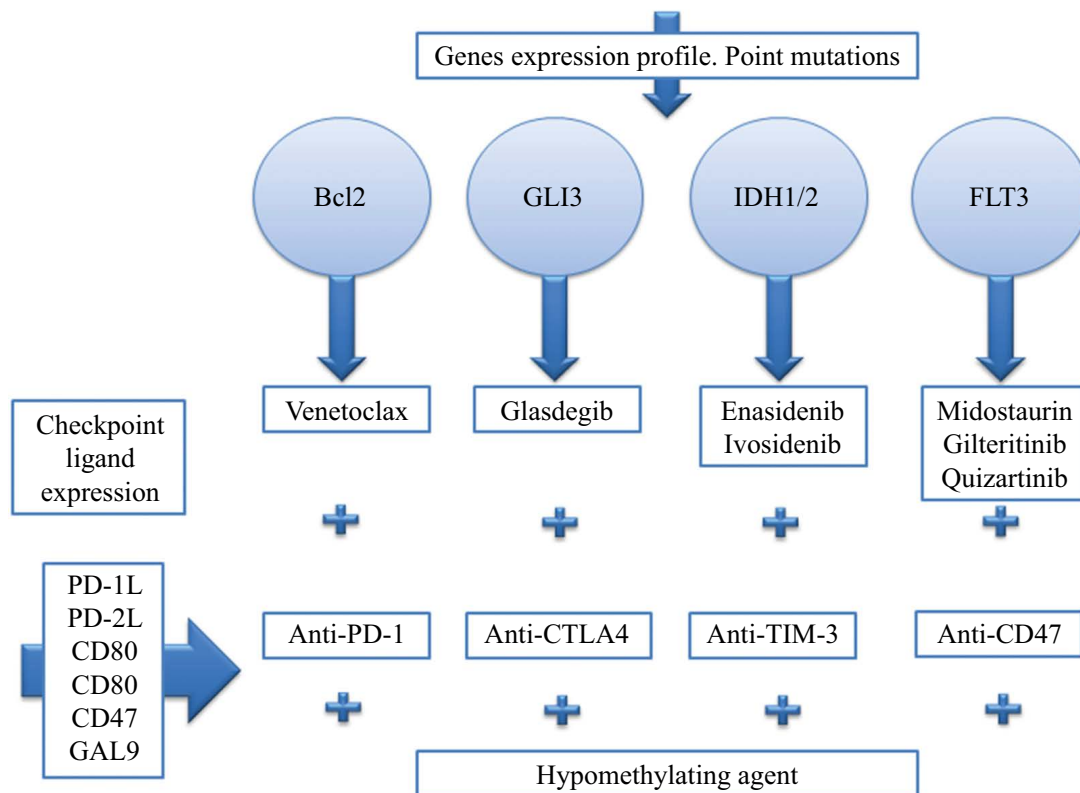


Figure 5. Potential drug combinations in personalized therapy of high-risk MDS

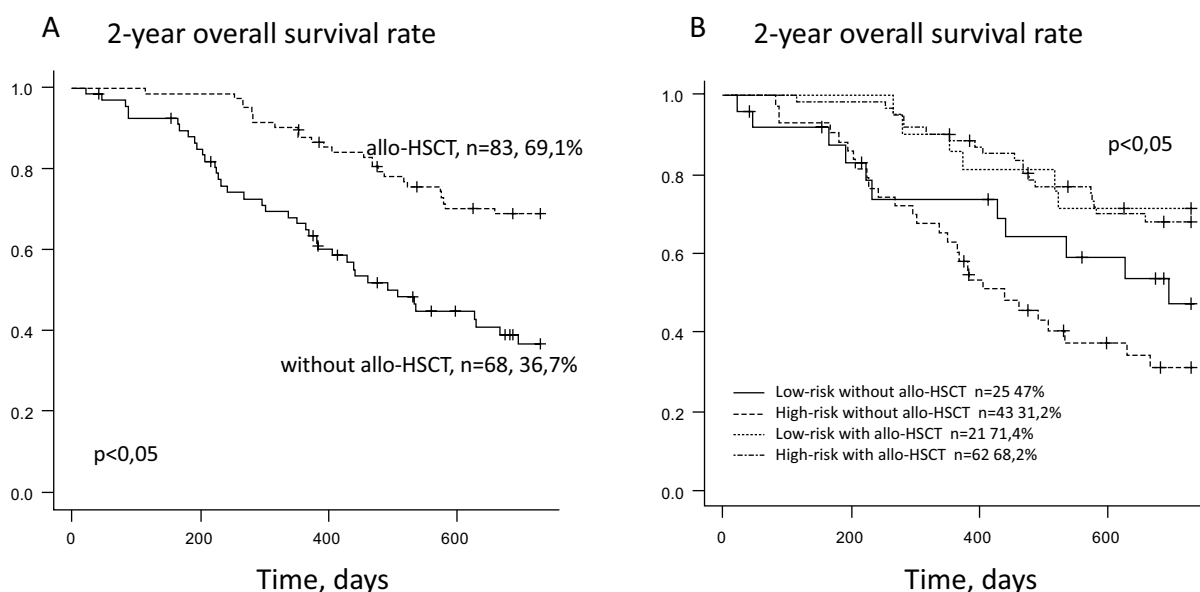


Figure 6. Two-year overall survival of MDS patients depending on allo-HSCT performed (A). The two-year overall survival of MDS patients depending on allo-HSCT performed and IPSS risk group (B)

center. The comparison of these two groups revealed that two-year OS in MDS patients without allo-HSCT was 36.7% (n=68), while it was 69.1% (n=83) among the patients after HSCT ($p < 0.05$) (Fig. 6A). In allo-HSCT group, the 2-year OS was comparable in IPPS-R intermediate-2 *versus* high-risk groups (n=62), and intermediate-1 *versus* low-risk groups (n=21, 68.2% *vs* 71.4%, respectively). Two-year overall survival was lower in similar patient groups without allo-HSCT:

31.2% (n=43) and 47% (n=25, $p < 0.05$), respectively (Fig. 6B). The survival rates following HSCT depended on the following items: disease status, graft composition, infectious complications, acute GvHD grade I-II [16]. Interestingly, the evaluation of all existing MDS prognostic scales in our MDS allo-HSCT group did not exert any significant effects on survival after allo-HSCT. This observation highlights a necessity to validate developing scales in the center- or country-

stratified manner. Hence, it is clear that the risk-adapted strategies in MDS patients are of extreme importance.

So far, it is unclear how the role of allo-HSCT in MDS will change. It can follow the track of chronic lymphocytic leukemia [96] and Hodgkin's lymphoma [97] where effective bridging before allo-HSCT brought the results of allo-HSCT in refractory disease close to the results of primary treatment in these malignancies. In this situation, allo-HSCT will be more broadly used in MDS. On the other hand, combination therapies can bring durable remissions to this difficult population of patients. In this case allo-HSCT will be brought from first line to second or subsequent lines of therapy like it happened with chronic myeloid leukemia [98]. Given the preliminary favorable results of allo-HSCT in MDS after therapy with ICPs [99], it is likely that at least the first scenario with effective bridging therapies will be implemented in the near future.

Conclusion

With respect to recent findings and genetic studies made by means of NGS techniques, some radical changes are expected in MDS therapies. The drug selection will be based on evaluation of mutational profile, expression of checkpoint molecules and methylation profile. The results of these studies will determine a combination of target agents, ICP inhibitors and hypomethylating agents. It is also clear that allo-HSCT will remain in MDS clinical practice, however its place in a sequence of therapies will be rapidly changing.

Acknowledgements

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Conflict of interest

The authors declare no conflicts of interest.

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Новые опции лечения пациентов с миелодиспластическим синдромом: обзор литературы и результаты одноцентрового исследования

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Резюме

Миелодиспластический синдром (МДС) – это гетерогенная группа клональных заболеваний, в основе которой находится поражение гемопоэтической стволовой клетки, как следствие наследственной предрасположенности, а также соматических мутаций различных генов и/или эпигенетической регуляции, в том числе индуцированных нарушением микроокружения и нарушениями в иммунной системе противоопухолевого надзора.

В обзоре освещаются долгосрочные результаты существующих методов лечения МДС, а также эффективность новых препаратов, находящихся на различных стадиях клинических испытаний, включая

ингибиторы сигнальных путей, ингибиторы контрольных точек, антагонисты трансформирующего ростового фактора бета. Характеризуется взаимосвязь новых методов терапии с патогенетическими основами МДС.

Ключевые слова

Миелодиспластический синдром, терапия, ингибиторы контрольных точек, луспатерцепт, гласдегиб, венетоклакс, IDH ингибиторы.