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Therapeutic options in high-risk myelodysplastic syndrome

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Abstract

Myelodysplastic syndromes (MDS) constitute a heterogeneous group of diseases characterised by ineffective haematopoiesis, dysplasia and cytopenias. The treatment for high-risk MDS (HR-MDS) depends on individual factors such as the stage of the disease, age, comorbidities, and infections.

Allogeneic haematopoietic stem cell transplantation (allo-HSCT) with reduced intensity conditioning has allowed more HR-MDS patients to be transplant-eligible, regardless of age. Hypomethylating agents, including azacitidine and decitabine, remain the standard of care for HR-MDS patients who are not qualified for curative allo-HSCT. Combination therapy of azacitidine with some new drugs resulted in higher response rates than azacitidine in monotherapy. Other targeted therapies are under investigation. They include HMA with different antibodies targeting immune checkpoints — programmed cell death (ligand) 1, cytotoxic T lymphocyte antigen 4, T-cell immunoglobulin mucin-3 or cluster of differentiation 47. Larger studies are necessary to confirm their efficacy in the treatment of HR-MDS.

Key words: myelodysplastic syndromes, MDS, hypomethylating agent, combination therapy, immune checkpoint inhibition, targeted therapies

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Introduction

Myelodysplastic syndromes (MDS) constitute blood cancers distinguished by dysfunction of production of blood cells, cytopenias, and frequent transformations to acute myeloid leukaemia (AML) [1]. The risk of MDS development is increased among the elderly, men and patients previously receiving cytotoxic chemotherapy or irradiation therapy [1].

The severity of the disease, prognosis and type of treatment methods for patients with MDS are assessed by International Prognostic Scoring System (IPSS) and its revised version (IPSS-R) [2–4]. Categories based on peripheral blood cytopenias, bone marrow blast percentage, and cytogenetic alterations allow the classification of MDS patients into low-risk MDS (LR-MDS) or high-risk MDS (HR-MDS) [3]. In the treatment of patients with HR-MDS, the main challenge is prolonging survival and inhibiting progression to AML [2]. The only effective method of treating patients with HR--MDS, allowing for recovery, is allogeneic stem cell transplantation (allo-HSCT) [3]. Due to the toxicity of this treatment, particularly elderly patients with comorbidities are not qualified for this treatment. Alternatives — hypomethylating drugs (HMAs), chemotherapy or other new agents such as venetoclax, CPX-351(cytarabine and daunorubicin), ATG (anti-thymocyte globulin), and immune checkpoint inhibitors (ICIs) are being investigated to improve outcomes in HR-MDS [2, 3].

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Moreover, the group of patients with targetable driver mutations require other specified therapeutic methods. Choice of therapy is dependent on such factors as age, comorbidities, the severity of cytopenias, transfusion needs, per cent of bone marrow blasts, the potential for allo-HSCT, and prior exposure to HMAs.

Pathogenesis

The underlying pathophysiology of MDS is the growth and spread of a mutant multipotent stem cell [2, 5]. Conventional karyotyping should be performed in all patients diagnosed with MDS to better understand the pathogenesis of the disease. Advances in the identification of genetic and immunological factors in the development of MDS allow for targeted and individualized treatments. A study performed on 944 patients with MDS revealed that the most common mutated genes included: *TET2, SF3B1, ASXL1, SRSF2, DNMT3A* and *RUNX1* [5]. *RUNX1, ASXL1,* and *TP53* mutations, as well as monosomal karyotype and high complexity, have been shown to be associated with poorer survival and risk factors linked to leukaemia progression [6, 7], while *SF3B1* mutations are found to be associated with more favourable outcomes [8].

Recently, new insights into the biology of MDS have helped to describe immune dysregulation in the disorder. Nielsen et al. [9] observed increased levels of tumor necrosis factor α (TNF-α), interleukin (IL)-6, CXCL10, IL-10 and decreased levels of transforming growth factor β_1 (TGF-β_1), regulated on activation, normal T-cell expressed and secreted (RANTES), and S100A4. Additionally, IL-10 and IL-8 levels were higher in HR-MDS, compared with LR-MDS. Immune factors are also thought to be involved in the pathogenesis of MDS — which is exploited in therapy with ICIs. HR-MDS have been shown to have higher CD47 expression on leukemic stem cells compared to control and LR--MDS [10]. Additionally, increased expression of programmed cell death 1 protein (PD-1) was also demonstrated in MDS [11]. Other studies have reported modified expression of PD-1 and other molecules such as PD1, programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4) in the bone marrow progenitor cells and T lymphocytes of patients with MDS and AML [12]. Additionally, increased expression of these proteins has been detected among patients treated with HMA or after HMA failure [13]. Another potential marker for targeted therapy of MDS is T cell immunoglobulin mucin-3 (TIM-3), the expression of which has been linked to leukemic transformation [14]. A dysregulated balance between pro- and anti-apoptotic factors is at play in the progression to HR-MDS. Acquired apoptotic resistance is correlated with the presence of B-cell lymphoma-2 (Bcl-2), the expression of which is increased in HR-MDS [15].

Clinical manifestation and diagnosis

MDS can be asymptomatic for a long time until cytopenias are noted in laboratory findings. Instead, clinical manifestations of symptomatic MDS are nonspecific. They are related to cytopenias — anaemia, neutropenia and/or thrombocytopenia and manifest as fatigue, bleeding, or infections. Anaemia is the most frequent clinical manifestation among MDS patients [2, 7]. It manifests as easy fatigue, palpitations, chest pains, dizziness, symptoms of heart failure, or pale skin. Usually, neutropenia and thrombocytopenia are noted later. Neutropenia disturbs immunity leading to infections. Thrombocytopenia manifests as haemorrhagic diathesis: petechiae to the skin or mucous membranes, bleeding from the mucous membranes of the nose, gastrointestinal tract, urinary tract, and genital tract in women.

The course of the disease is variable. It depends on differences in symptom burden, comorbidities, and rates of progression [1]. IPSS or R-IPSS scoring system helps to assess the intensification of symptoms and potential morbidity of the disease. As described, these two systems allow for dividing patients with MDS into two groups — lower- and higher-risk diseases.

The initial examination is the morphology of peripheral blood with light microscopy smear evaluation. In MDS, results of the study reveal disorders of blood — the presence of cytopenias — normocytic or more frequent — macrocytic anaemia and/or neutropenia and/or thrombocytopenia, duopenia, or pancytopenia. Moreover, it identifies immature forms of leukocytes – myeloblasts and/ /or promyelocytes. Neutrophils can be hypogranular and have hyposegmented neutrophils [4]. Reticulocytosis is reduced. Anaemia requires additional testing including iron and ferritin levels, lactate dehydrogenase (LDH), haptoglobin and Coombs testing, serum protein electrophoresis (SPEP) and immunofixation (IFE) due to the necessity to exclude multiple myeloma [16]. Macrocytic anaemia requires checking levels of vitamins B12 and folic acid. After basal examination — morphology of peripheral blood and exclusion of nonhematologic

reasons of anaemia and other cytopenias, bone marrow should be examined in more detail — by aspiration and biopsy. In MDS with multilineage dysplasia, dysplasia affects 10% of the cells of 2 or 3 cell lines (red cells, white cells and/or megakaryocytes) in the bone marrow. Histopathologic examination of bone marrow refers to the bone marrow architecture disorders, features of dysplasia of individual cell lines, percentage of blasts, and marrow fibrosis.

Furthermore, cytochemical examination and iron staining with Prussian blue reaction allow the identification of iron deposits around the nuclei of the erythroblasts — cells called sideroblasts. Diagnostic workups such as cytogenetic examination of bone marrow can confirm the diagnosis of MDS, and the changes found are a prognostic factor. Approximately 50% of MDS patients have abnormal karyotypes. The finding of a change in chromosome 5, namely 5q–, allows for the identification of the 5q– syndrome and is very important for the therapeutic process. As described, peripheral blood counts and cytologic, histopathologic, cytogenetic and cytochemical examination of the bone marrow are necessary for the diagnosis. Molecular tests are performed more and more often, which makes it possible to identify gene mutations, such as *SF3B1, TET2, SRSF2, ASXL1, DNMT3A, RUNX1, U2AF1, TP53,* and *EZH2* [16, 17]. Other new tests are crucial for the description of the phenotype of bone marrow cells with the presence of appropriate surface antigens.

Classification and prognosis

The current classification of MDS is based on World Health Organization (WHO) criteria from 2016. This system divides MDS into types based mainly on such features as cytogenetic, marrow blast and peripheral blood parameters [17, 18]. Furthermore, to predict clinical outcomes among MDS cases, the system called molecular IPSS (IPSS-M) can be useful [19]. Due to recent updates on mutations and their role in prognosis for MDS patients, the next classification systems should also include molecular aspects and divide into molecular subtypes.

The prognosis of patients with MDS depends upon factors such as cytogenetics and severity of cytopenias, the percentage of blasts in the bone marrow and peripheral blood/number of cytopenias in peripheral blood. The most common scoring system — Revised International Prognostic Scoring System (IPSS-R) — is based on the number of cytopenias in peripheral blood, their severity, blast percentage, absolute neutrophil count, haemoglobin value, and platelet value [17]. LR-MDS group includes low- and intermediate-1-risk disease and very low-, low- and some subsets of intermediate--risk MDS by IPSS-R. HR-MDS include patients from intermediate-2 and high-risk diseases by IPSS, and some subsets of intermediate-, high- and very high-risk diseases by IPSS-R [16]. Approximately one-third of MDS patients transform into AML, which is related to a poor prognosis. Prognosis is also worse in patients with mutations, even with normal karyotypes, independently from IPSS and IPSS-R [20].

The scoring system is used in prognosis, but also it plays a role in the selection of therapy. LR--MDS and HR-MDS differ in overall survival (OS) and the probability of transformation to AML. Patients with HR-MDS — intermediate, high and very high-risk MDS have a median OS of 0.8 to 3.7 years [21]. The risk of transformation to AML within 0.2 to 1.1 years is 25% [22]. In the treatment of patients with HR-MDS, the main challenge is prolonging survival and inhibiting progression to AML [2].

Therapeutic methods

Hypomethylating drugs

The introduction of hypomethylating drugs (HMAs) influenced the prognosis of MDS patients [23]. They remain the mainstay of therapy in newly diagnosed HR-MDS patients ineligible for allo-HSCT [2, 24]. They are effective and less toxic, compared to intensive chemotherapy. HMAs such as 5-azacitidine (5-AZA) and its analogue decitabine (DEC) inhibit DNA methyltransferase activity leading to inhibiting cell proliferation. DNA demethylation leads to restoring the expression of tumour-suppressive genes silenced by promotor hypermethylation [25, 26]. Expression of these genes and synthesis of proteins are involved in angiogenesis, apoptosis, differentiation, and DNA repair. The results of the drugs are epigenetic changes and clinical improvement [27].

AZA and DEC are administered every 28 days — subcutaneously at a dose of 75 mg/m^2 for 7 days every 28 days and intravenously at 20 mg/m^2, respectively [28]. In a 3-phase, randomized study, AZA led to 50.8% survival at 2 years, compared with 26.2% in conventional care regimens [29]. Moreover, the advantage of 5-AZA is delaying disease progression, prolonging survival and suppressing transformation to AML [4, 23]. It also caused reduced transfusion needs. In the

systematic review including 237 studies, Garcia et al. [30] noted that HR-MDS patients treated with HMA monotherapy achieved complete remission (CR) rate of 17% and a median OS of 18.6 months. HMAs are recommended to use for patients with HR-MDS who are not eligible for intensive treatment, resistant to immunosuppressive schemes, or as a bridging treatment before allo-HSCT. However, in the meta-analysis of Liu et al. [31], they observed no differences between OS in patients with HMAs bridging to allo-HSCT and best supportive care before transplantation [hazard ratio (HR) = 0.86, 95% confidence interval (CI): 0.64–1.15, p = 0.32]. Evaluation of the effect of this therapeutic method on OS requires further prospective studies with a longer observation period. Although the toxic effect of AZA manifests as myelosuppression, the addition of eltrombopag, lenalidomide or vorinostat to AZA therapy can worsen the effect and aggravate the toxicity [2]. To prevent progression, it is suggested to check serum albumin level, because its low level can increase the risk of infections and can be used as a prognostic factor in AZA therapy [32].

AZA was also assessed as maintenance therapy post-allogeneic bone marrow transplantation (post-allo-BMT) in MDS patients. I/II phase studies had promising results, which encouraged researchers to conduct further studies. Unfortunately, in the III phase study, there was no observed beneficial effect of AZA on the median relapse-free survival (RFS) and OS, compared with standard care [33].

Unlike AZA, DEC has not improved OS in the RCT study conducted by Kantarjian et al. [34]. However, the overall response rate (ORR) rate was 17% with a CR of 9% in DEC ARM, compared with the supportive care group with an ORR of 0%. DEC is considered the drug with durable responses — a median of 10.3 months. Modification of dosing schedules of DEC in the following studies increased the efficacy of DEC [2]. According to studies with DEC assessed as therapy for HR-MDS, ORR was 30% to 50%. The randomized trial compared DEC to supportive care, which demonstrated improvement in progression-free survival (PFS) but no difference in OS. Although gender is not a standard prognostic factor or response indicator, in the study with 642 HR-MDS patients, in the female group, OS was higher in the DEC group compared to the AZA group [23]. In the systematic review of Ma et al. [35], both AZA and DEC were effective in AML and HR-MDS treatment. Concerning safety, it was noted that severe cytopenias were more common in the DEC group than in the AZA arm.

Although standard use of HMA in first-line treatment of HR-MDS, complete response is noted only in < 20% of patients and is typically not durable [36]. Patients with relapsed or refractory HR-MDS achieve a median OS of fewer than 6 months, and there are no approved second-line treatments for this subset of difficult-to-treat patients [37, 38]. HMA failure is associated with a poor prognosis for the patient. According to some studies, HMA failure can be associated with high expression of PD-1, PD-L1, PD-L2 and CTLA-4 [28].

Several novel HMAs (e.g. guadecitabine and the oral ASTX727 and CC-486) are in development [36]. Due to the short half-life of AZA and DEC, guadecitabine – DEC analogue resistant to deamination by cytidine deaminase (CDA), and probably a longer time of action was evaluated in II phase trial with patients with HR-MDS resistant to AZA. It resulted in an ORR of 14.3% [28]. On the other hand, the randomized phase III ASTRAL-3 trial did not confirm benefits — there was no improvement in the survival of resistant patients with MDS [39]. Severe toxicities of guadecitabine use were: febrile neutropenia, myelosuppression, and infections [40].

CC-486 is an oral form of AZA, while ASTX727 is an oral decitabine analogue combined with cedazuridine — the cytidine deaminase inhibitor. They are characterized by other, more convenient methods of administration and give more comfort to the patient due to fewer visits and time at the hospital [36, 41].

ASTX727 is an oral form of DEC combined with the cytidine deaminase inhibitor cedazuridine and is indicated in HR-MDS and CMML. Food and Drug Administration (FDA) approval of ASTX727 or treatment of HR-MDS patients was based on studies comparing ASTX727 with parenteral DEC. The phase 3 ASCERTAIN study resulted in 64% ORR, including a CR of 12%. CR rates of 11–21% and transfusion independence in 30–53% of patients in the respective trials [42–44]. The main toxicities of the drug are neutropenia and thrombocytopenia.

According to Komrokiji's study [45], initiating HMA treatment 90 days after diagnosis in HR-MDS patients with adequate haematopoiesis does not negatively affect OS or transformation to AML. Earlier start of therapy was associated with a higher CR rate but did not affect ORR [45]. The main adverse events of HMAs use are grade 3–4 peripheral cytopenias: neutropenia, thrombocytopenia, anaemia, and grade 3–4 infections. It is worth noting that most infections observed in MDS, are

associated with the first three weeks of therapy with AZA. In the retrospective study of Schuck et al. [46], they noted that infectious complications were associated with age and longer hospital stays, but not with comorbidities. The infections presented mostly as fever of unknown origin or pneumonia. Therefore, therapy with AZA requires considering the administration of antibiotics or antifungal prophylaxis.

Lenalidomide

Lenalidomide is a thalidomide derivative, currently used in LR-MDS with del(5) patients. This is an oral agent given daily, with responses typically noted after 3 months of treatment and often allows patients to become independent of blood transfusions [47].

According to some studies, the use of lenalidomide in first-line therapy causes more benefits than salvage therapy. In the multicentre randomized, II phase study of the combination of lenalidomide and AZA and AZA monotherapy in patients with HR-MDS, there was no improvement in responses and clinical benefit [48]. In another study, conducted by Adès et al. [49], the combination of AZA + lenalidomide resulted in a response rate of 38.8%, compared to 42.0% for AZA alone [49]. Similarly, the addition of the drug did not improve EFS (15.6 vs. 19 months) or OS (17.5 vs. 23.1 months).

Immunotherapy

Due to the potential role of cellular and innate immunity in the development of MDS, it was suspected that drugs with an impact on the immune system can be used in the treatment of this disorder. ICIs constitute breakthrough therapy in many solid tumours [2]. As evidenced, programmed death-1 — PD-1 expression was higher in HR-MDS compared to LR-MDS, which suggested the efficacy of PD-1 blockers in HR-MDS treatment [50]. The benefit of synergistic therapy of HMA with ICIs is associated with increased expression of leukaemia-associated antigens and PD-1 and its ligand (PD-L1) and CTLA-4 during treatment with HMA. Several studies demonstrated induction expression of PD-1, PD-L1, PD-L2 and CTLA-4 and partial demethylation of PD-1 [51] after HMAs use in MDS. Dysregulation of the PD-1/PD-L1 pathway plays a role in HMA resistance [52]. HMAs can promote PD-1 expression on T cells, which disturbs immune response against the blasts. Therefore, the combination of HMAs with ICIs can have a synergistic anticancer effect. In the 2-phase study assessing nivolumab and ipilimumab in MDS patients after HMA failure, 13% of the nivolumab group had a response but the non-achieved CR and 35% of ipilimumab had a response and achieved CR [13]. It is well known that these agents are more successful in combination therapy than monotherapy. It was confirmed by results of a combination of AZA and nivolumab or ipilimumab in first-line treatment — response rates were 75% and 71%, respectively, with CR rates of 50% and 38%. Pembrolizumab — an anti-PD1 agent was assessed in combination with AZA in patients with intermediate-1 or HR-MDS. The ORR was 76% in the front-line setting and 25% in the HMA failure group [53].

Notably, the addition of the anti-PD-L1, durvalumab, to AZA improved the ORR in HR-MDS, as demonstrated in a 2-phase study performed by Zeidan et al. [54] (ORRs: 61.9% vs. 47.6%). However, it did not influence positively on median OS in AZA + durvulumab and AZA in monotherapy (11.6 months vs. 16.7 months).

Promising results were presented after the use of PD-1/PD-L1 inhibitors with intensive chemotherapy regimens. In a 2-phase study including 42 patients with AML and 2 with HR-MDS, therapy consisting of cytarabine, idarubicin and nivolumab led to the ORR of 80% with CR of 78%. [55]. Median OS was 18.54 months, with no significant improvement compared to a contemporary cohort examining cytarabine plus idarubicin [55, 56].

Further studies evaluate antibodies in different combinations and different sequences — in the first line, after allo-HSCT or HMAs. It also requires checking doses due to the potential risk of graft-versus-host disease (GvHD) after allo-HSCT in this group of patients [57].

MDS cells in HR-MDS overexpress such molecules as CD47, which was evaluated as a checkpoint for magrolimab — CD47 inhibitor. Binding CD47 to signal regulatory protein α (SIRPα) prevents macrophage phagocytosis of MDS cells while targeting CD47 leads to phagocytosis of cancer cells [58]. AZA is also engaged in this prophagocytic pathway, inducing signals. In the 1b phase study including subjects with HR-MDS treated with magrolimab + AZA, the ORR rate was 91%, while CR was 42%. The toxicity profile was acceptable. The response was also noted in patients with *TP53* mutated MDS, which is important due to the worse prognosis for this cytogenetic disorder compared with other MDS patients. The 3-phase, ongoing study compared magrolimab + AZA with that of AZA + placebo in the first line of treatment of HR-MDS.

Another drug in development in the therapy of HR-MDS is MBG423 — sabatolimab. This agent targets T-cell immunoglobulin and TIM-3 — molecules expressed on immune cells and myeloid leukemic progenitors. In the Ib phase study evaluating Sabatolimab combined with HMA in the treatment of 51 patients with very-high risk (vHR)/HR-MDS, ORR was 56.9%, with a median DOR (mDOR) of 16.1 months [59]. Additionally, patients with mutations such as *TP53* developed durable responses.

Venetoclax

Bcl-2 is an anti-apoptotic protein that is overexpressed in many cancers, also in MDS [24, 60]. Venetoclax — an oral inhibitor targeting Bcl-2, known as an effective drug in the treatment of AML, has been used as the drug of HR-MDS, de novo MDS and MDS patients which are ineligible for intensive chemotherapy. It disturbs the binding of BH3 proteins to Bcl-2, leading to the release of pro-apoptotic BAK and BAX proteins [61, 62]. The effect is a disturbance of mitochondrial membranes and apoptosis of cancer cells. Moreover, it was suggested that venetoclax with AZA inhibits amino acid metabolism and apoptosis. In the 1b phase study conducted on 57 patients with untreated previously HR-MDS, venetoclax in combination with AZA, the ORR was 77% [1, 63]. Unfortunately, after the combination of venetoclax with AZA, the patients with MDS resistant to HMAs did not achieve median PFS and OS with a 9-month estimate for OS of 83% (95% CI: 55%, 95%). This therapy might contribute to prolonged aplasia in MDS patients and affect the course of the disease [64]. The toxicity of this method is associated with the combination with other drugs affecting granulopoiesis in the bone marrow and altered drug metabolism by the CYP3A4 inhibitors, such as triazole.

Isocitrate dehydrogenase inhibitors

Isocitrate dehydrogenase (IDH) mutations are rare among MDS, but patients with HR-MDS are more prone to the incidence of this mutation, compared to LR-MDS patients [65]. In addition, these genetic changes increase the risk of progressing to AML [2]. Ivosidenib — an oral IDH1 inhibitor directed against mutant IDH1, synthesis of oncometabolite D-2-hydroxyglutarate (2-HG), which disturbs myeloid lineage differentiation and the progress of leukaemia. It was evaluated in mutated newly diagnosed and relapsed/refractory (R/R) AML and HR-MDS. An ORR of 91.7% was entailed and 60% of patients remained in CR at 12 months, revealing the favourable response of ivosidenib in R/R MDS patients [66-68]. Enasidenib – an agent directed against IDH2 was approved for the treatment of MDS with IDH mutation in 2017. The ORR was 67–100% in first-line treatment. The drug was effective in monotherapy of MDS resistant to HMA (AZA) — ORR was 50% [69]. Moreover, combination therapy consisting of AZA — enasidenib led to high response rates and accepted toxicity [28].

FMS-like tyrosine kinase 3 inhibitors

As FMS-like tyrosine kinase (FLT3) mutation is associated with leukemogenesis, therefore it has been suggested that the most prominent effect of treatment with the FLT3 inhibitor, midostaurin, is a reduction in the number of blasts. Midostaurin is a first-generation type 1 FLT3 inhibitor targeting both *FLT3*-ITD and *FLT3*--TKD mutations. Concomitant use of midostaurin and AZA only showed an ORR of 26% in a phase 1/2 study in FLT3-positive HR-MDS and AML patients [70].

Rigosertib

Rigosertib is a multikinase inhibitor with an impact on the PI3K pathway. It has been demonstrated that it induced selective apoptosis in MDS primary CD34+ cells and MDS cell lines [71]. Rigosertib was assessed in HMA-refractory HR-MDS in comparison with the best supportive care group [72]. In the 3-phase study median OS was similar — 8.2 months in the rigosertib group and 5.9 months in the second group ($p = 0.33$). In a phase 1/2 study of 9 patients with HR-MDS, rigosertib demonstrated biological activity in the form of partial or complete marrow response in 5 patients; in addition, in one patient, drug supplementation resulted in haematologic improvement regarding erythroid and neutrophil lineages [73].

Rigosertib was also evaluated as an oral form combined with AZA in first-line therapy for patients with HR-MDS in a II phase study [74]. It resulted in an ORR of 92% (CR 34%). Rigosertib will be further tested in the INSPIRE trial (NCT02562443) to evaluate it in pod types of MDS.

Eprenetapopt

It is well known that patients with *TP53* mutated MDS/AML have a poor prognosis. Eprenetapopt (APR-246) — a methylated derivative of PRIMA-1 stabilizes chemically mutant p53 protein [24]. Eprenetapopt is converted to methylene quinuclidinone (MQ), which binds changed p53 resulting in confirmation change and apoptosis [75].

Eprenetapopt with AZA used in MDS with *TP53* mutations resulted in higher response rates than AZA used in monotherapy [76]. The efficacy of using the combination of eprenetapopt with AZA was demonstrated in a phase-2 study, which reported that 62% of patients with *TP53*-mutated MDS responded to this treatment, and among these subjects, 47% achieved complete remission [77]. The most frequent adverse effects were neurologic adverse events, but they were resolved. Although these results of the II phase study were promising, in the III phase study, the statistically significant CR was not reached.

Pevonedistat

Pevonedistat is the next potential drug which can be used as a treatment for HR-MDS after HMA failure. It inhibits neural precursor cell expressed, developmentally downregulated 8 (NEDD8)-activating enzyme (NAE) and disrupts the degradation of proteins in the proteasome [78, 79]. In a 2-phase study, in patients with HR-MDS, the addition of Pevonedistat to AZA improved both time to treatment failure (TTF) (median 19.7 vs. 13.6 months; HR: 0.521, $p = 0.025$) and the rate of transfusion independence (69.2% vs. 47.4%, $p = 0.228$). Despite these promising results, in the study completed in May 2021, pevonedistat did not improve ORR, or OS.

Intensive chemotherapy

Intensive chemotherapy (IC) is used as a bridge therapy — induction treatment before allo-HSCT in transplant-eligible HR-MDS patients, or option after HMA failure [2]. Regimens based on anthracycline/ cytosine arabinoside (Ara-C) are used in AML therapy and can be considered in MDS treatment [16]. However, intensive AML-like chemotherapy lead to CR rates of 56–60%, while early death incidence was 20–25% [24]. Duration of remission was at a median of 8 months. Additionally, in the study comparing decitabine treatment with IC in HR-MDS patients, OS was higher in the DEC group [34]. Due to the high toxicity and not enough benefits of anthracyclines and cytarabine-based IC, their use in HR-MDS treatment is limited. The CR rate was 36–60%. Response to AML-like treatment can be predicted by karyotype and some mutations [1]. In the case of −7/del7q or complex karyotype or *TP53* mutations, CR rates were lower. Similarly to allo-HSCT, elderly patients are not the best candidates for this therapy. In contrast, IC seems to be a better option for young patients — up to 65–69 years, without comorbidities and with favourable cytogenetics according to IPSS and IPSS-R (at least in those with *NPM1* mutations) [24].

Allogeneic haematopoietic stem cells transplantation

It is well known that allo-HSCT is one potentially curative method of treatment for patients with HR-MDS – disorder with poor prognosis [16, 36].

As evidenced, allo-HSCT improved survival in HR-MDS [16, 24]. Therefore, it should be considered in the first line of HR-MDS. However, it is mostly used in patients with < 10% bone marrow blasts and medically fit, which is based individually considering age, performance status psychosocial status, comorbidities, and disease features — IPSS-R score, bone marrow blast percentage, cytogenetic and molecular features [2, 8, 16]. However, transplant eligibility should not be considered only for young patients. Allo-HSCT improved event-free survival (EFS) in comparison with continuous AZA treatment in a group of older patients with HR-MDS [80]. Following recent studies, transplantation contributed to OS benefits in patients up to 75 years [7, 81]. Therefore, allo-HSCT should be an option considered during choice therapy among both young and older patients.

The efficacy of allo-HSCT in HR-MDS probably depends on the timing of receiving therapy, induction treatment and conditioning drugs. As described, early allo-HSCT at diagnosis is related to longer survival among HR-MDS patients [24]. Best long-term results were noted when pre-transplant blasts were < 5%. When blasts are > 10% in bone marrow, it is recommended to use cytoreduction before transplantation with the aim to reduce the risk of recurrence [24]. Cytoreduction is performed using HMA or intensive chemotherapy [82, 83]. As described, chemotherapy is more toxic than HMA, so reduced-intensity conditioning (RIC) is beneficial for young patients. RIC and increasing donor availability contribute to more frequent transplantations among MDS patients [84]. Compared with myeloablative conditioning regimens (MACs), RIC can increase the risk of relapse of disease but lower the risk of nonrelapse mortality (NRM). Following recent studies, induction therapy consisting of conventional cytoreductive chemotherapy or HMA did not improve results compared to direct HCT [85]. In the randomized, multicentre clinical study, the use of RIC and MAC led to similar outcomes, with 2-year survival rates of 76.3% and 63.2%, respectively [86]. Wedge et al. [87] evaluated new regimens including fludara-

Table 1. Reported results of studies evaluating new agents for high-risk myelodysplastic syndrome (HR-MDS)

Drug	Agent	Mechanism of action	Phase + treatment regimen	Study group	Results	Reference
HMAs — azanucleosoides	AZA	Inhibition of DNA methyltransferase activity	III, AZA monotherapy vs. conventional care group	HR-MDS	Median OS 24.5 months for AZA vs. 15.0 months for the conventional care group 2-year OS 50.8% (95% CI 42.1–58.8) for AZA vs. 26.2% (18.7–34.3) for conventional care group	Fenaux et al. [29]
	DEC		III, DEC monotherapy vs. supportive care	MDS with intermediate-1 disease and above	ORR 17% (9% CR) with DEC vs. 0% with supportive care (0%) Durable responses (median, 10.3 months) and prolonged AML progression time (12.1 months vs. 7.8 months)	Kantarjian et al. [34]
			III, DEC monotherapy vs. BSC	Patients with HR-MDS, aged ≥ 60 years	DEC improved OS (10.1 vs. 8.5 months), median PFS, (6.6 vs. 3.0 months) and AML transformation (22% vs. 33%), and QoL parameters	Lübbert et al. [93]
	Guadectiabine — dinucleotide of DEC and deoxyguanosine		I/II, randomization to subcutaneous guadecitabine 60 or 90 mg/m^2	Intermediate-1 risk, intermediate-2 risk, or HR-MDS or CMML, treatment-naive, 27 R/R disease after previous HMA treatment	ORR 40% and 55% in the combined front-line and HMA-refractory cohort when used at 60 mg/m^2 and 90 mg/m^2, respectively Median OS 611 days, 399 days, respectively, response independent of dose groups [21 of 53 with 60 mg/m^2 and 27 of 49 (55%, 95% CI 40–69) with 90 mg/m^2] ORR: 51% in treatment-naive patients and 43% in R/R disease	Garcia-Manero et al. [94]
			II	HR-MDS/low-blast count AML after AZA therapy	ORR 27 and 12% in patients with primary and secondary failure, respectively	
	ASTX727 (DEC and cedazuridine)	Cedazuridine — cytidine deaminase inhibitor	II	Intermediate or HR-MDS or CMML	ORR 62% [32 pts, with 8 (16%) CR, 14 (28%) mCR, and 9 (18%) HI]	Garcia-Manero et al. [42]
	CC-486 (oral AZA)		II	MDS, CMML, AML	ORR 32% in MDS/CMML subgroups Red blood cell transfusion independence rate: 33% in MDS/CMML	Savona et al. [44]
Immunomodulatory drugs	Lenalidomide	Cell cycle arrest and modulatory effect on immune cells	II	Low or intermediate-1 risk MDS associated with the del 5q abnormality	ORR of 76% of patients with 67% that became transfusion independent	NCT00065156
			II, AZA + lenalidomide	HR-MDS and AML with a karyotype including del 5(q)	ORR 44% vs. 39% for AZA monotherapy, CR 6% vs. 11%, marrow CR 28% vs. 17%	Rasmussen et al. [95]
			II, AZA + lenalidomide vs. AZA	HR-MDS, CMML and low-blast count AML	ORR 38.8% vs. 42.0% for AZA monotherapy	Adès et al. [49]

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Table 1 (cont.). Reported results of studies evaluating new agents for high-risk myelodysplastic syndrome (HR-MDS)

Drug	Agent	Mechanism of action	Phase + treatment regimen	Study group	Results	Reference
BCL-2 inhibitor	Venetoclax	Inhibition of the antiapoptotic factor Bcl-2	Ib, non-randomized, multicentre study	Treatment-naïve HR-MDS	ORR 77%, CR 42%, mCR 35%	Garcia et al. [63]
			Ib, ventoclax + AZA vs. AZA monotherapy	R/R MDS	mORR 38.3%, median PFS 8.6 months, median OS 12.6 months	Zeidan et al. [96]
			I/II, venetoclax + AZA	Treatment-naïve and R/R HR-MDS, CMML	ORR 93%, median PFS and OS = 8.4 months and 13 months	Bazinet et al. [97]
Liposomal cytarabine and daunorubicin (cytotoxic chemotherapy)	CPX 351		II, CPX-351 induction treatment	Untreated HR--MDS	CR 52%, CRi 13%	Peterlin et al. [98]
			I/II	HMA-refractory HR-MDS and CMML	ORR 71%, median OS 12.6 months	Montalban--Bravo et al. [99]
Neddylation inhibitor	Pevonedistat		II, pevonedistat + AZA	MDS/MPN refractory to DNMTi treatment	ORR 42% (CR, mCR, HI)	Moyo et al. [100]
			II, pevonedistat + AZA vs. AZA	HR-MDS	ORR 79.3% vs. 56.7%, OS 23.9 vs. 19.1 months, EFS median 20.2 vs. 14.8 months	Sekeres et al. [78]
IDH inhibitors	Ivosidenib	IDH1 inhibitor	I, ivosidenib monotherapy	R/R MDS with IDH1 mutations	ORR 75%, CR 42%	DiNardo et al. [68]
	Enasidenib (ENA)	IDH2 inhibitor	II, AZA + ENA vs. ENA	HR-MDS with *IDH1* mutation	ORR of 67%, including 100% among previously untreated MDS for combination therapy and ORR of 50% in HMA-failure cases receiving ENA alone	Richard--Carpentier et al. [69]
	Olutasidenib	IDH1 inhibitor	I/II, olutasidenib vs. olutasidenib with AZA or cytarabine	MDS with *IDH1* mutation	ORR 33%, CR 17% as monotherapy and 73%, CR 55% as combination therapy	Cortes et al. [101]
FLT3 inhibitors	Midostaurin	Inhibition of FLT3 receptor signalling	I/II	HR-MDS, *FLT3* mutated	ORR 26%	Strati et al. [70]
RAS pathway affector inhibitor: PI3K and PLK	Rigosertib	Multikinase inhibitor	II, rigosertib + AZA (I line)	HR MDS	OR 92% (CR 34%)	Navada et al. [73]
			III, rigosertib vs. BSC	HMA R/R	Median OS 8.2 months vs. 5.9 months	Garcia-Manero et al. [72]

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Table 1 (cont.). Reported results of studies evaluating new agents for high-risk myelodysplastic syndrome (HR-MDS)

Drug	Agent	Mechanism of action	Phase + treatment regimen	Study group	Results	Reference
p53 reactivator	Eprenetapopt (APR-246)	Restoring p53 function	Ib/II, eprenetapopt + AZA	*TP53*-mutant MDS	OR 73%, CR 50%, CCR 58%	Salmann et al. [76]
ICIs	Nivolumab	Anti-PD-L1 monoclonal antibody	II, nivolumab monotherapy	R/R MDS	ORR 0%	NCT02530463
			I/II, nivolumab + idarubicin + cytarabine	Front-line AML and HR--MDS eligible for intensive therapy	Median OS 18.5 months	Ravandi et al. [55]
	Pembrolizumab	Anti-PD-1 antibody	II, pembrolizumab + AZA	Intermediate-1 or HR--MDS, HMA--naïve and failure	ORR 76% in previously untreated patients and 25% in the HMA failure cohort	Chien et al. [53]
	Ipilimumab	Anti-CTLA-4 monoclonal antibody	II, monotherapy	R/R MDS	ORR 30%	Zeidan et al. [102]
	Durvulumab	Anti-PD-L1 monoclonal antibody	II, durvulumab + AZA vs. AZA monotherapy	HR-MDS, I line	ORR 61.9%, median OS 11.6 months vs. 16.7 months	Zeidan et al. [54]
Macrophage ICIs	Magrolimab	Anti-CD47 monoclonal antibody	Ib, magrolimab + AZA	Intermediate and HR-MDS, I line	OR 92%, CR 50%	Sallman et al. [58]
TIM-3	MBG453		Ib, sabalitomab + HMA	HR-MDS, AML	HR-MDS: ORR 62.9%	Brunner et al. [59]

AML — acute myeloid leukemia; AZA — azacitidine; BSC — best supportive care; CD47 — cluster of differentiation 47; CI — confidence interval; CMML — chronic myelomonocytic leukemia; CR — complete remission; CRi — CR with incomplete hematologic recovery; CTLA-4 — cytotoxic T lymphocyte antigen 4; DEC — decitabine; DNA — deoxyribonucleic acid; DNMTi — DNA methyltransferase inhibitor; ENA — enasidenib; FLT3 — FMS-like tyrosine kinase 3; HI — hematological improvement; HMA — hypomethylating agents; ICI — immune checkpoint inhibitor; IDH — isocitrate dehydrogenase; mCR — marrow CR; mORR — modified overall response rate; MPN — myeloproliferative neoplasm; ORR — overall response rate; OS — overall survival; PD-(L)1 — programmed cell death (ligand) 1; PFS — progression-free survival; PI3K — phosphatidylinositol 3-kinase; PLK — polo-like kinase; QoL — quality of life; R/R — relapsed/refractory; TIM-3 — T-cell immunoglobulin mucin-3

Table 2. New potential drugs for high-risk myelodysplastic syndrome (HR-MDS) treatment

Target	Agents	Clinical trials
MCL-1	S64315	NCT02979366
TIM-3	MBG453	NCT03940352, NCT03066648
CD47	TTI-621 (SIRPαFc)	NCT02663518
Smoothened (SMO) protein	Glasdegib	NCT02367456
Cyclins A, B1, H, and cyclin-dependent kinase 2 (CDK2)	Indisulam	NCT01692197
SF3b complex inhibitor	H3B-8800	NCT02841540

CD47 — cluster of differentiation 47; MCL-1 — myeloid cell leukaemia 1; TIM-3 — T-cell immunoglobulin mucin-3

bine/treosulfan as a conditioning regimen and it resulted in quite satisfying efficacy. It is worth noting that new drugs are characterised by lower toxicity and can be used in a more extended group of patients — also with comorbidities. 3-year OS rate was 71%, 52.8% and 62% (p = 0.075) after fludarabine/treosulfan-based conditioning, in the group treated with the standard MAC regimen [total body irradiation (TBI)/cyclophosphamide or busulfan/cyclophosphamide], and in the group receiving RIC, respectively [87]. However, these outcomes should be assessed in future studies in the context of possible resistant clones.

Due to limited therapeutic options for HR--MDS cases with relapse after HMA, allo-HSCT can be considered in patients with HR-MDS resistant to HMA. However, it is suspected, HMA failure increases the risk of relapse after transplantation, compared to patients with response to treatment [88]. According to some studies, patients with mutations in such genes as *RAS, TP53, RUNX1, ASXL1* and *JAK* are a group of patients with worse chances of therapeutic success [89, 90]. Relapse after allo-HSCT in the therapy of MDS is related to poor results. Potential therapeutic methods are unmanipulated donor cell infusion (DLI) and the second allo-HSCT [91, 92].

Other new therapeutic targets

In recent years, novel agents have shown promising results in clinical trials as HR-MDS treatment. They are effective with HMAs or other drugs or in monotherapy. Increased expression of myeloid cell leukaemia 1 (MCL-1) is associated with chemotherapy resistance and BCL-1 inhibition. Due to its frequent noting in haematological cancers, MCL-1 inhibitors have been investigated as agents in the treatment of MDS. The next example agent which was approved for therapy of AML and is investigated for HR-MDS is CPX--351 — a liposomal formulation of cytarabine and daunorubicin at a synergistic 5:1 molar ratio. Other drugs with potential anticancer action are histone deacetylase inhibitors (HDCAi) (Tables 1, 2).

Conclusions

HSCT is still the only curative therapy for HR-MDS. Due to the new conditioning regimen, transplantation is possible among a wider group of people. Despite the promising results of research on new drugs, the HMA — AZA and DEC constitute the standard of care for HR-MDS cases. Further studies and genetic tests will allow to identify new pathomechanisms of MDS and allow for more individualized treatment of HR-MDS patients. Larger, randomized trials are required for confirming the use of new promising and investigational agents.

Conflict of interest

The authors declare no conflict of interest.

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