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Myelodysplastic syndromes - Section 14

High-risk MDS after HMAs

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Take home messages

- How to define HMA failure.
- Know the prognosis of patients having failed HMAs.
- What are the current recommendations for the treatment of high-risk MDS after HMAs.
- What are the future perspectives.

Introduction

Allogeneic stem cell transplantation (ASCT) remains, when feasible, the only curative treatment option of higher-risk myelodysplastic syndrome (MDS) with prolonged disease-free survival observed in 35% to 50% of the patients.[1] Based on the recommendation from an international expert panel, it is recommended in high-risk MDS patient (1) to proceed to transplant as soon as possible and (2) to reduce tumor burden in patients with >10% blasts using either hypomethylating agent (HMA) or chemotherapy HMA.[2] However, as MDS mainly occurs in the 7th and 8th decade of life, only a limited number of patients are eligible for ASCT. Moreover, comorbidity is common among the elderly such as heart disease, renal insufficiency, and vascular disease decreasing the ability to withstand the exhausting transplantation procedures. Currently, HMAs—azacitidine (AZA) and decitabine (DAC)—are the first-line treatment in higher-risk MDS cases.[1] Indeed, in a randomized trial, a survival benefit with AZA was demonstrated over conventional care regimens (including best supportive care, low-dose AraC or intensive chemotherapy), with a median survival of 24.4 months versus 15 months, while progression to AML was delayed and significantly more frequent RBC transfusion independence was obtained.[*3] Nevertheless, the 50% response rate obtained with AZA is low and the median survival of about 2 years remains short, suggesting that HMA effect is only transient, and that the majority of the patients will require second-line therapy. However, survival of refractory/relapsed patients is extremely short with a median survival of 4 to 6 months and no current recommendation has been made to treat these patients.[*4] As most of the available scoring systems were inadequate to determine the prognosis of patients after HMA failure, the MDS Clinical Research Consortium developed a specific scoring system (based on ECOG performance status, very poor cytogenetic, age, bone marrow blast >20%, platelet count <30, and transfusion dependency) to discriminate a group of patients with a better outcome (low score median overall survival (OS) of 11 months, high score median OS of 4.5 months) highlighting the heterogeneity of the disease, even after HMA failure.[5] Despite of its ability to predict OS after HMA failure, this score is not helpful to guide the decision making for patients, in the absence of molecular data that may further enhance the predictability of the model and in the absence of a clear therapeutic strategy that might also modify this model. Consequently, it is strongly recommended to enroll patients with HMA failure in clinical trials, even if clinical trials are only available for a small minority of the patients, leaving the majority of the patients without therapeutic options outside best supportive care.

Current state of the art

Definition of HMA failure

In the AZA001 trial, the survival advantage with azacitidine was seen irrespective of age, marrow blast percentage and karyotype and responses were often delayed, some patients responding only after 6 cycles, suggesting that patients should not be considered as primary resistant before 6 cycles, unless they clearly progress.[*3] Any type of response was associated with a survival advantage, supporting that treatment can only be discontinued if the absence of hematological improvement. Secondary HMA failure is defined as loss of response and/or progression of MDS. The outcome of primary and secondary resistances to HMA is different and median OS is 4.6 months in patients with primary resistance compared to 7.4 months in patients with secondary resistance ($P=0.007$) that the mechanism of resistance is scarce and

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probably different from one patient to another.[*4] Altogether, these results demonstrate that it is crucial to maximize the benefit of HMAs by continuing therapy until clear evidence of lack of response or failure of therapy.

Despite the use of HMA for more than 15 years, timing of evaluations of response and subsequent clear definition of resistance remained unclear. Premature evaluation of response, before 6 cycles, might lead to inappropriate diagnosis of HMA failure, even if, before cycle 6, it might be difficult to decipher between cytopenia related to HMA and cytopenia related to MDS. Thus, in the absence of clear response or subsequent cytopenia after initial response, delaying cycles, especially beyond cycle 6, waiting for hematological recovery might help to decide whether a patient experienced toxicity of HMA or relapse, in the absence of a marked marrow response. Moreover, new criteria for the evaluation of response in MDS were recently proposed to clarify the definition of hematological improvement and the loss of hematological response in MDS, at least for clinical trial.[*6]

Current management of HMA failures

The therapeutic options after HMA failure are scarce, but, outside a clinical trial, several options including ASCT, high- and low-dose chemotherapy, switch of HMA can be considered. the best outcomes after HMA failure are reported with ASCT, but, as for first-line therapy, it can be offered to a small minority of the patients based on criteria such as age and availability of donors.[*4] Similarly, induction chemotherapy is able to induce 41% of response but seems to have a limited impact on survival without subsequent allogeneic transplantation.[7] The role of CPX-351, a new formulation of 7+3 (daunorubicin and aracytine), approved in the United States for the treatment of AML-MRC (AML with myelodysplastic-related changes) is under investigation in this poor risk population. The switch from one HMA to another after initial failure gave limited response, inferior to 30%[8] and short survival and even if the mechanism of action of AZA and DAC is rather different, this option might not be longer recommended.

Future perspectives

Promising new therapy

Even if it is strongly recommended to enroll these patients in clinical trials, during the past 10 years, no investigational agent has demonstrated any relevant major clinical activity, but recent clinical trial suggested that the end of the tunnel might be close, at least for selected patients.

Guadecitabine, also known as SGI-110, is a new HMA with extended biological activity. In a phase II study in HMA failure patients, Sebert et al (Haematologica 2019) reported a response rate of 26% in primary refractory and of 9% in relapsing patients, with median duration of response of 9 months.[9]

Rigosertib, a multikinase inhibitor, has been tested in a phase III randomized trial versus BSC in patients with higher-risk MDS after HMAs failure.[10] If there was no significant survival advantage in the whole cohort, a potential survival benefit with rigosertib was observed only in patients with primary HMA (compared with secondary HMA failure). Even though the place of rigosertib in the therapeutic armamentarium of MDS remains to be determined in future subsequent clinical trials.[10]

Venetoclax is a BH3 mimetic that binds to and inhibits the antiapoptotic Bcl-2 protein family. Recently, venetoclax was tested in combination with HMAs or low-dose AraC in AML and yielded very encouraging results,[*11] but no clinical trial was specifically published in higher-risk MDS so far even if, in vitro, inhibition of Bcl-2 pathway efficiently induces apoptosis in progenitor cells from higher-risk MDS.[12]

Mutation-driven therapies

IDH1/2 are found in 5% to 10% of MDS and IDH inhibitors are currently evaluated as single agents or in combination with

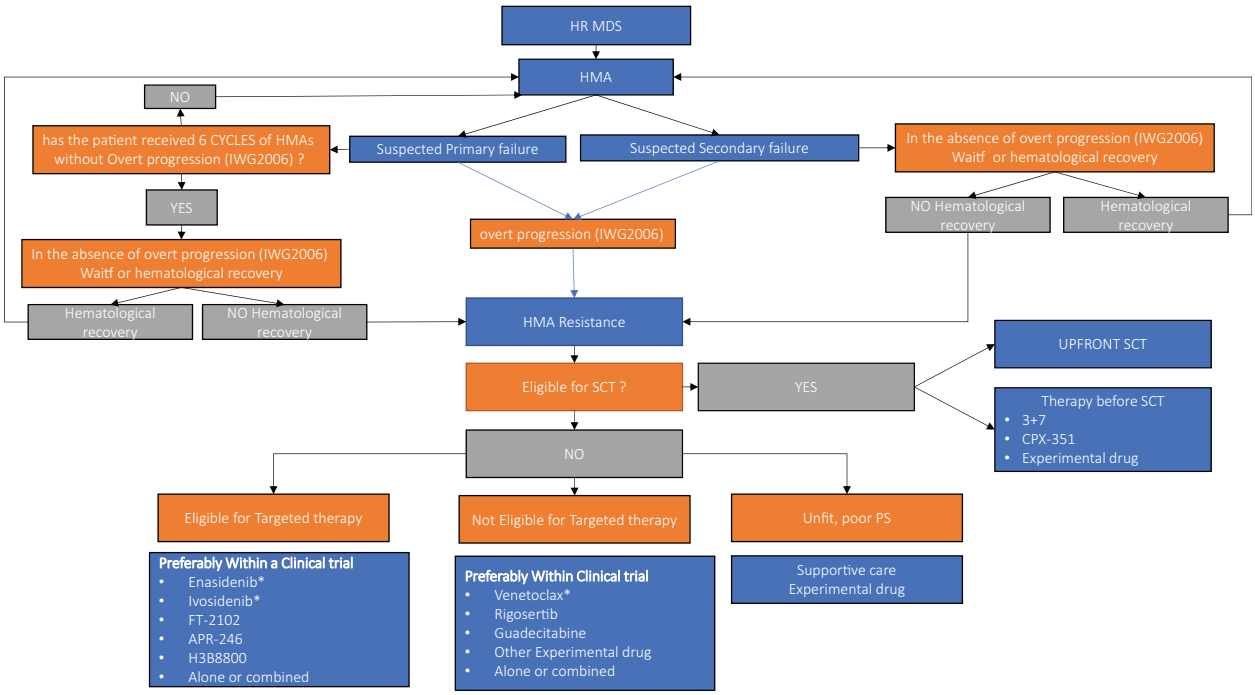

Figure 1. Algorithm for treatment choice in MDS patients after failure of HMA. HMA = hypomethylating agent, MDS = myelodysplastic syndrome.

AZA in MDS and AML. Stein et al reported the results of a phase I study of enasidenib (AG-221), a potent oral inhibitor of mutant IDH2 enzyme, in 16 refractory/relapsed (r/r) high-risk MDS patients, two-thirds of whom had failed prior HMA treatment.[*13] The overall response rate was 53% including 1 patient who achieved complete remission (CR). More recently, ivosidenib, an IDH1 inhibitor, has been evaluated in patients with r/r AML, including patients with prior history of MDS. More recently, ivosidenib, an IDH1 inhibitor, has been evaluated in patients with r/r AML, including patients with prior history of MDS, with a CR rate of 21.6% and an overall response rate of 41.6%. Given these very encouraging results in AML, the potential therapeutic role of ivosidenib and enasidenib in MDS is currently under investigation, either as a single agent or in combination with HMAs.

Besides, small molecule inhibitors that target components of the spliceosome have demonstrated selective toxicity to MDS cells in preclinical models.[14,15] They may benefit to a large number of patients given the high prevalence of mutations in genes involved in the splicing machinery in MDS. A phase I trial (NCT02841540) is presently being conducted to evaluate the safety of the splicing modulator H3B-8800 in higher-risk MDS and AML.

Finally, an ongoing phase Ib/II evaluating the role APR-246—a reactivating compound of mutant TP53 protein—in combination with AZA for the treatment of TP53-mutated myeloid neoplasms has shown very promising data with not only an 82% CR rate but also deep molecular responses assessed by serial next generation sequencing.[16]

Based on these preliminary results, an algorithm for treatment choice in MDS patients after failure of HMA therapy might be suggested (Fig. 1).

Conclusion

HMA relapsed/refractory MDS patients should always be considered for clinical trials and, outside a clinical trial, only stem cell transplantation seems to induce sustained response. During the past 10 years, the results of phase I/II and III studies were unimpressive in terms of response or survival but new investigational agents are under investigation with potential more potent activity.

References

1. Adès L, Itzykson R, Fenaux P. Myelodysplastic syndromes. *Lancet Lond Engl*. 2014;383:2239–2252.
2. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129:1753–1762.

*3. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol*. 2009;10:223–232.

This paper highlight the role of azacytidine as the reference treatment for first line therapy in patient with higher risk MDS.

*4. Prébet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol*. 2011;29:3322–3327.

The outcome after AZA failure is poor. this results serve as a basis for designing second-line clinical trials in this population.

5. Nazha A, Komrokji RS, Garcia-Manero G, et al. The efficacy of current prognostic models in predicting outcome of patients with myelodysplastic syndromes at the time of hypomethylating agent failure. *Haematologica*. 2016;101:e224–e227.

*6. Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood*. 2019;133:1020–1030.

The IWG 2006 criteria for response in MDS have been used prospectively in many clinical trials but proved challenging in several of them. This report provide rationale for modifications (IWG 2018) of these recommendations

7. Ball B, Komrokji RS, Adès L, et al. Evaluation of induction chemotherapies after hypomethylating agent failure in myelodysplastic syndromes and acute myeloid leukemia. *Blood Adv*. 2018;2:2063–2071.
8. Harel S, Cherait A, Berthon C, et al. Outcome of patients with high risk myelodysplastic syndrome (MDS) and advanced chronic myelomonocytic leukemia (CMML) treated with decitabine after azacitidine failure. *Leuk Res*. 2015;39:501–504.
9. Sebert M, Bally C, Peterlin P, et al. Results of a phase II study of guadecitabine (SGI-110) in higher risk MDS, CMML or low blast count AML patients refractory to or relapsing after azacitidine (AZA) treatment. *Blood*. 2016;128:347.
10. Garcia-Manero G, Fenaux P, Al-Kali A, et al. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2016;17:496–508.

*11. DiNardo CD, Pratz KW, Letai A, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol*. 2018;19:216–228.

Venetoclax plus hypomethylating agent therapy seems to be a promising regimen in elderly patient with AML. Its role in MDS remain to be determined.

12. Jilg S, Reidel V, Müller-Thomas C, et al. Blockade of BCL-2 proteins efficiently induces apoptosis in progenitor cells of high-risk myelodysplastic syndromes patients. *Leukemia*. 2016;30:112–123.

*13. Stein EM, DiNardo CD, Pollyea DA, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood*. 2017;130:722–731.

Enasidenib seems to be a promising drug in elderly patient with AML and IDH2 mutation. Its role in MDS remain to be determined.

14. Lee SC-W, Dvinge H, Kim E, et al. Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal proteins. *Nat Med*. 2016;22:672–678.
15. Seiler M, Yoshimi A, Darman R, et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. *Nat Med*. 2018;24:497–504.
16. Sallman DA, DeZern AE, Steensma DP, et al. Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with TP53 mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML). *Blood*. 2018;132:3091.