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Treatment of Higher-Risk Myelodysplastic Syndromes After Failure of Hypomethylating Agents

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Abstract

Outcome after hypomethylating agents failure in higher risk MDS is poor and treatment represents an unmet clinical need. The best outcomes after HMA failure are achieved among those patients who proceed to allogeneic stem cell transplant or enroll on clinical trials.

Hypomethylating agents (HMAs) are the standard of care for higher-risk myelodysplastic syndrome (MDS) patients in whom azacitidine was the only treatment to demonstrate an overall survival advantage in a randomized clinical study. Only 40% to 50% of patients typically will respond to HMAs, with a median duration of response < 1.5 years and eventually all patients will lose initial response. Outcome after HMA treatment failure is poor and represents an unmet need. In this article we review the definition of HMA failure in higher-risk MDS patients and its outcome. We highlight options of treatment including sequential use of HMAs, add-back strategies, other palliative chemotherapy options, and provide an overview for several promising investigational agents. Understanding mechanisms of resistance and molecular changes at the time of HMA failure will be a key to development of further therapies.

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Introduction

Myelodysplastic syndromes (MDS) are a spectrum of bone marrow failure neoplasms resulting in peripheral cytopenia and a tendency to progress to acute myeloid leukemia (AML).[1] Patients are risk-stratified according to several clinical models into lower- and higher-risk disease based on features such as myeloblast percentage, severity of cytopenia, and cytogenetic abnormalities.[2-4] The clinical phenotype observed and behavior reflects the underlying disease biology and molecular abnormalities.

The International Prognostic Scoring System (IPSS) is still widely used to identify patients with higher-risk features.[2] New risk models such as the revised IPSS or global M.D. Anderson model refine the prognostic utility of the IPSS and upstage almost 20% of patients to higher-risk categories.[3-5]

Allogeneic stem cell transplantation (ASCT) remains the only curative option for MDS patients. For patients with higher-risk MDS proceeding early to ASCT yields maximum gain in survival.[6] However, only ≤ 10% of all MDS patients proceed to ASCT because of their age, comorbidities, donor identification, and disease status. Hypomethylating agents (HMAs) are considered the standard of care for higher-risk MDS patients. The AZA-001 study demonstrated an overall survival (OS) advantage for azacitidine over conventional care regimens (CCRs). HMAs are effective in 30% to 40% of patients with duration of response typically < 1.5 year.[7]

Outcome after HMA failure is poor.[8-10] There is an unmet need for patient treatment. We discuss herein the current available options and some of the promising investigational agents in the setting of higher-risk MDS after HMA treatment failure.

Definition of HMA Failure

There is no consensus definition on HMA failure in higher-risk MDS. One could divide treatment failure into primary HMA failure, which is a lack of initial response including clear evidence of progressive disease or death during study. Stable disease (SD) is more controversial, in which there is no definitive increase in myeloblasts observed, but also no hematological improvement (HI) is achieved by the International Working Group (IWG; 2006) criteria.[11] In a landmark analysis of the AZA-001 study, patients who achieved HI or better response at 3, 6, and 9 months had better OS with azacitidine treatment compared with CCRs. For patients with SD, OS was the same for azacitidine and CCR. However, 19%

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of patients treated with azacitidine who had SD at 3 months, achieved HI at 6 months compared with 13% for those treated with CCR. At the 9 month follow-up, only 14% of patients who had SD with azacitidine at 6 months achieved HI and none of those who received CCRs achieved HI.[12] The median OS for primary HMA failure was 5.5 months in the rigosertib randomized clinical study.[13] Secondary HMA failure is defined as clear loss of initial response (HI or better according to IWG 2006 criteria) and SD after 9 months.

Outcome After Failure of HMA

It is well recognized that outcome after azacitidine failure is poor.[8-10] The median OS ranges from 4 to 6 months after HMA failure in higher-risk MDS patients. Almost 20% to 30% of patients progressed to AML. The best outcome was achieved if patients proceeded to ASCT (median OS of 19.5 months) or enrolled in investigational clinical trials (median OS, 13.2 months).[8]

Recently, outcome after HMA treatment failure was also reported to be poor in lower-risk MDS patients by the MDS clinical consortium group. The median OS was 17 months.[14]

Standard Treatment Options for Failure of HMA Treatment

The standard of care for MDS patients with HMA treatment failure should be investigational therapy. However, in the absence of clinical trial few options are available, but unfortunately with limited success.

Sequential Treatment With Azanucleosides: "HMA Cross-Over"

There are currently 2 HMA agents available, azacitidine and decitabine. Scarce data exist on the activity of sequential use of those treatments. Borthakur et al reported in a 14-patient study that 28% responded to decitabine after azacitidine treatment failure.[15] In another study, 19% of patients responded to decitabine after azacitidine failure (n = 21) and 40% responded to azacitidine after decitabine failure (n = 10; Table 1).[16] Those studies were limited by their retrospective nature, lack of standard definition of HMA treatment failure, and inclusion of patients who were nontolerant to the first agent.

Table 1 Sequential Use of Azanucleosides

	Group 1; DAC After AZA (n = 21)	Group 2; AZA After DAC (n = 10)
Median Time To First-Line HMA From Diagnosis (months)	10	2.4
Mean First-Line Cycles	8	4
First-Line Best Response (High or Better), %	63	50
Lag Between First- and Second-Line Treatment, Days	118	179
Second-Line Cycles	4	6
Second-Line Best Response (High or Better), %	19	40
Median OS, Months		
From start of second-line treatment	17.8	22
From time of diagnosis	48	100
AML Transformation, %	29	20

Abbreviations: AML = acute myeloid leukemia; AZA = azacitidine; DAC = decitabine; OS = overall survival.

"Add-Back Strategy"

In the context of phase I azacitidine/lenalidomide study, in 3 patients who relapsed during aza monotherapy after cycle 6 lenalidomide was resumed in combination. Each patient recaptured a complete response (CR) that was sustained for 5, 7, and ≥ 7 months.[17] There is an ongoing study in which the combination of pracinostat with HMAs in patients with MDS who failed to respond to single-agent HMAs is being investigated (NCT01993641).

Low-Dose Chemotherapy: "Older Drugs"

In Table 2, selected lower-dose chemotherapy agents used for treatment of MDS are summarized. In one study combining low-dose ara-c and vorinostat after HMA failure, a 15% response rate was reported.[18] Low-dose melphalan, etoposide, and topotecan were used in the pre-HMA era with limited success.[19-21] The Groupe-Francophone des Myélodysplasies reported no response to low-dose chemotherapy after azacitidine failure among 18 evaluable patients.[8]

Selected Investigational Agents for HMA Treatment Failure

A detailed discussion of investigational agents is beyond the scope of this review. In Table 3 selected investigational agents tested after HMA treatment failure are highlighted.

SGI-110

SGI-110 is a dinucleotide of decitabine and deoxyguanosine that protects it from deamination. In a phase I study that included 14 MDS patients after HMA treatment failure, SGI-110 had a 4.5-fold longer half life than decitabine. Equivalent or higher area under the

Table 2 Efficacy of Selected Low-Dose Chemotherapy in MDS

Drug	Dose	Response (%)	Notes
Low-Dose ara-c (n = 40)	10-20 mg/m2 for 14 days with vorinostat 400 mg	15	After HMA treatment failure
Melphalan (n = 21)	2 mg orally daily	40	Normo- or hypocellular bone marrow and absence of complex karyotype predicted response
Etoposide (n = 43)	50 mg orally daily for 21 of 28 days	40	CMML
Topotecan (n = 90)	1.2 mg/m2 twice daily for 5 days or once daily for 10 days	30	CMML; high toxicity

The Groupe-Francophone des Myélodysplasies experience after failure of HMA; no responses observed with low-dose chemotherapy.
Abbreviations: CMML = chronic myleomonocytic leukemia; HMA = hypomethylating agent; MDS = myelodysplastic syndrome.

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