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Beyond hypomethylating agents failure in patients with myelodysplastic syndromes

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Abstract

Purpose of review—Although hypomethylating agents (HMAs) significantly improve outcomes in myelodysplastic syndromes (MDS), only half the patients achieve objective responses, and most responders lose response within 1–2 years. Azacitidine prolongs survival by a median of only 9.5 months. Failure of HMA therapy is associated with a very dismal prognosis. Therefore, novel therapeutic approaches are clearly needed.

Recent findings—The sequential use of the alternative HMA after failure of first line HMA is associated with modest efficacy. The improved understanding of the biologic underpinnings of the disease have opened the door to study investigational agents that target disrupted molecular pathways critical to the pathogenesis of MDS. Combination treatment strategies using an azacitidine backbone are demonstrating promising early results. Expanding the applicability of allogeneic stem cell transplantation (alloSCT), the only curative modality, by reducing toxicity and relapse rates is another area of active research.

Summary—Sequential switching to the alternative HMA, clinical trials of novel targeted therapies, azacitidine-based combination therapeutic strategies, and improvements in the alloSCT platform are the main directions in improving outcomes of MDS post HMA failure.

Keywords

allogeneic hematopoietic stem cell transplantation; azacitidine; decitabine; hypomethylating agents; myelodysplastic syndromes

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Conflicts of interest

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INTRODUCTION

Myelodysplastic syndromes (MDS) include a group of hematopoietic neoplasms characterized by ineffective hematopoiesis and dysplasia that manifest clinically as cytopenias and a variable tendency for leukemic progression [1▪▪,2]. Because of the biological heterogeneity of the disease, the clinical manifestations and outcomes of patients with MDS vary significantly [3]. Therefore, the management paradigm for MDS typically follows a risk-adaptive strategy that aims to balance the risk/benefit ratio of any potential therapeutic intervention against the prognostic outlook for the individual patient [4]. Using a number of validated prognostic schemes, of which the most commonly used is the International Prognostic Scoring System (IPSS), patients with MDS are typically grouped into two major risk groups: higher risk and lower risk [5,6].

Using the IPSS, higher risk-myelodysplastic syndromes (HR-MDS) includes patients in the risk classes of intermediate-2 and high (i.e., IPSS score of >1) [5]. Patients with HR-MDS have a median survival of less than 1 year if untreated. Therefore, the goal of therapy is the alteration of the natural history of the disease by prolonging survival and delaying progression to acute myeloid leukaemia (AML) [1▪▪,5]. Only two treatment modalities have been shown to prolong survival in patients with MDS: allogeneic stem cell transplantation (alloSCT) and azacitidine. alloSCT is the only treatment modality with a known curative potential [7]. Nonetheless, with a median age at diagnosis of 76 years, frequent presence of comorbidities, limited allogeneic graft sources, concerns over excessive toxicity and limited efficacy, financial and insurance considerations, physician-preference and patient-preference and other factors, only a minority of MDS patients undergo alloSCT [8–11,12▪]. Intensive chemotherapy is not usually given to MDS patients except for younger fit patients as a bridge to alloSCT. For the vast majority of HR-MDS patients who do not undergo alloSCT, the approved standard approach is the use of hypomethylating agents (HMAs). Additionally, patients who belong to the IPSS lower risk group who have severe thrombocytopenia or neutropenia and those who do not respond to growth factors or lenalidomide are also candidates for HMA therapy in the United States [13].

LIMITATIONS OF HYPOMETHYLATING AGENTS THERAPY IN MYELODYSPLASTIC SYNDROMES

Of the two approved HMAs for MDS (azacitidine and decitabine), only azacitidine has been shown to prolong survival in comparison to conventional care regimens [14]. Although HMA therapy leads to significant clinical benefits including improving blood counts and delaying leukemic progression, the outcomes associated with the use of these agents are still far from optimal. The median survival advantage associated with azacitidine use in HR-MDS is only 9.5 months [14]. Objective clinical responses are seen in only about half of the patients treated with HMAs, and the complete response (CR) rate is only 10–20% [14–17]. Even among patients with initial responses to HMAs, the median response duration is only 9–15 months with the vast majority of patients losing response within 2 years [14–16]. If they live long enough, ultimately all HMA responders will require further therapy.

Moreover, clinical responses to HMAs might not become apparent for 4–6 months of therapy, and no biomarkers or clinical predictors have been widely validated to select patients for HMA therapy [6]. This means that many patients with HR-MDS will be subjected to a prolonged period of HMA therapy with its associated costs and possible toxicity without gaining clinical benefit. Such patients will be also losing valuable time before HMA failure is realized to be considered for alternative approaches. In order to improve outcomes of HR-MDS patients, there have been ongoing efforts at identifying patients with low probability of achieving clinical benefit from HMAs who would be candidates for upfront aggressive or investigational approaches. Clinical tools such as the French Prognostic Scoring System and genetic alterations such as *TET2* mutations have been proposed to select patients based on likelihood of achieving clinical benefit from azacitidine therapy, but further validation is needed before they can be clinically used for this purpose [6,18–21].

FAILURE OF HYPOMETHYLATING AGENTS THERAPY IS ASSOCIATED WITH VERY POOR PROGNOSIS

Primary and secondary resistance to HMA therapy are the harbingers of dismal prognosis. After azacitidine or decitabine failure, patients with MDS have an estimated 1-year survival probability of 28% and 21–24-month survival probability of 15% [22–24]. The median overall survival (OS) after azacitidine or decitabine failure in patients with MDS is 5.6 and 4.3 months, respectively [22,23]. It has been reported that MDS patients with HMA failures are divided into three groups: one third with leukemic progression, a second third with worsening cytopenias due to disease progression, and a last third of patients who refuse more therapies or succumb to complications [25]. Outcomes after HMA failure in patients with IPSS lower risk-myelodysplastic syndromes (LR-MDS) are also poor. In a report from the Moffitt group, the median OS after azacitidine failure in 280 patients with LR-MDS was 18.5 months (95% confidence interval, 13.5–23.5 months), and it was specially worse for patients with IPSS intermediate-1 risk group (median OS 15 months) [26]. Another retrospective analysis of 59 IPSS LR-MDS patients with primary or secondary azacitidine failure reported a similarly poor median OS after azacitidine failure of 16.7 months [27].

AML arising from MDS is also characterized by a particularly poor prognosis, especially if prior HMA has been received [28,29]. The median OS in 74 patients with MDS who developed secondary AML after azacitidine failure was a dismal 3.4 months with a 1-year survival probability of only 8% [28]. In another report, prior therapy with HMA in patients with MDS who progressed to AML was independently associated with inferior response and survival after intensive chemotherapy [29].

WHAT ARE THE CURRENT OPTIONS AFTER FAILURE OF HYPOMETHYLATING AGENTS IN MYELODYSPLASTIC SYNDROMES?

There are no standard of care options for second-line treatment in MDS after HMA failure. Despite the limited published experience, sequential use of the alternative HMA is not an uncommon practice considering the limited availability of other options and the possibly

distinct cellular resistance mechanisms between the two drugs [26]. The use of combination treatment strategies such as azacitidine and lenalidomide combinations is also showing promising early results [30,31▪]. Clinical trial enrollment when available is always the preferred option after HMA therapy failure. The improved understanding of the genetic heterogeneity and the biologic underpinnings of MDS has led to the initiation of a large number of clinical trials to evaluate investigational agents that target disrupted molecular pathways central to the disease pathogenesis [12▪].

Modification of the biologic pathways to prevent development of resistance or restore sensitivity to HMAs is unlikely to be possible without detailed dissection of the poorly understood mechanisms of primary and secondary resistance to HMAs. For example, Cluzeau *et al.* [32] showed that increased expression of BCL2L10 (an antiapoptotic Bcl-2 family member) significantly correlated with azacitidine resistance and that the proportion of BCL2L10+ cells in bone marrow can predict OS in MDS or AML patients. Based on their findings, the authors proposed a flow cytometric assay of the percentage of BCL2L10+ cells to predict patients who will become resistant to azacitidine. Additionally, these findings suggest that targeting BCL2L10 could be evaluated as a new strategy to prevent or overcome azacitidine resistance [32]. Finally, efforts at expanding the applicability of alloSCT by reducing toxicity and improving efficacy are also important areas of research. In the next few sections, we will briefly discuss these approaches to improve outcomes of MDS patients who fail HMA therapy. Suggested treatment options for patients with MDS with failure of HMA therapy are as follows:

1. enrollment in clinical trials when feasible;
2. alloSCT (±intensive chemotherapy);
3. sequential switching to the alternative HMA (decitabine if azacitidine used initially and vice versa);
4. addition of lenalidomide;
5. best supportive care.

SEQUENTIAL USE OF THE ALTERNATIVE HYPOMETHYLATING AGENTS

Whether MDS patients who develop primary or secondary resistance to azacitidine derive a benefit from sequential decitabine therapy and vice versa is a controversial issue [25,33]. The mechanisms of resistance to azacitidine and decitabine might not be overlapping in terms of changes in transport proteins, alterations in the enzymes involved in phosphorylation and catabolism of the two agents or in their target enzymes [25]. A small prospective study of 14 MDS patients who were switched from azacitidine to decitabine after primary or secondary failure or intolerance to azacitidine has been reported [34]. Decitabine was well tolerated and resulted in a CR rate of 21% and hematologic improvement in 7%. In the four responders, initial azacitidine therapy was terminated because of skin toxicity (one patient), disease progression (two patients), and lack of response (one patient) [34].

A retrospective analysis from the Moffitt Cancer Center presented only in an abstract format identified 21 patients who received decitabine after azacitidine [26]. The initial azacitidine therapy was discontinued because of lack of response (33%), loss of response (43%), progressive disease (5%), and adverse events (19%). Decitabine was initiated after a median of 118 days of azacitidine discontinuation, and a mean of four cycles of decitabine therapy were delivered (range, 1–18). The overall response rate (ORR) to decitabine was 19% (5% CR and 14% hematologic improvement), whereas 67% had progressive disease and 14% were unevaluable. The median OS from decitabine initiation and from diagnosis was 17.8 and 48 months, respectively. The investigators also identified a second cohort of 10 patients who received azacitidine after decitabine failure. The initial decitabine therapy was discontinued due to lack of response (10%), loss of response (30%), progressive disease (20%), toxicity (30%), and physician choice (10%). Azacitidine was initiated after a median of 179 days after decitabine discontinuation, and the patients received a mean of six azacitidine cycles (range, 2–12). The ORR to azacitidine was 40% (20% CR, 20% hematologic improvement), whereas 20% had stable disease, and 40% had progressive disease. The median OS from azacitidine initiation and from diagnosis was 22 and 100 months, respectively. The authors concluded that sequential use of alternative HMA after failure of first line might be a viable treatment option outside of clinical trials [26].

LENALIDOMIDE THERAPY AFTER HYPOMETHYLATING AGENTS FAILURE

Prebet *et al.* [35] reported the outcomes of 10 MDS patients with azacitidine failure who received salvage lenalidomide therapy. The median number of initial azacitidine cycles received was eight. All these patients received other therapy prior to azacitidine but none of them received prior lenalidomide. Half of the patients had primary azacitidine failure whereas the other half had secondary azacitidine failure. Lenalidomide was administered at 10 mg dose for 21 days in 28-day cycles (five patients) and 5 mg daily in 21-day cycles (five patients) with a median of three treatment cycles. The ORR was 40% [CR, 30%, hematologic improvement-erythroid (HI-E), 10%]. All three patients who achieved CR had del5q and two of them also developed a complete cytogenetic response. The median response duration was 6 months, whereas the median OS after azacitidine failure was 19.5 months. As expected, the presence of del5q even within a complex karyotype was associated with a higher probability of response (60%). These data combined with documented efficacy of lenalidomide in the upfront treatment of HR-MDS with del5q [36] suggest that lenalidomide should be studied further in this setting and may be considered after azacitidine failure in HR-MDS with del5q [35].

COMBINATION STRATEGIES

As azacitidine is the only drug shown to prolong survival in patients with MDS, using an azacitidine-based platform for combination strategies is a major focus of active research [37]. The goals of this strategy would be to increase the frequency, quality, and duration of clinical responses and ultimately delay/prevent development of resistance and prolong survival [38]. For patients in whom HMA therapy has already failed, a combination strategy might be one way to re-sensitize the tumor cells to therapy.

Lenalidomide has been combined with azacitidine with promising early results [30,31▪, 39,40]. The complementary mechanisms of action of the two drugs against the neoplastic clones and their bone marrow microenvironment provoked a question of possible synergistic or additive effects if they were used concurrently or sequentially in patients with HR-MDS with and without del5q [30,31▪,39,41]. An impressive ORR of 72% was reported in an early phase trial of 36 HR-MDS patients who received azacitidine at a standard dose of 75 mg/m^2/day concurrently with lenalidomide [31▪]. Forty-four percent achieved CR with a median duration of at least 17 months (range, 3 to ≥39 months) and a median OS of ≥37 months (range, 7 to ≥55 months). The other 28% achieved hematologic improvement. This ORR of 72% is significantly better than that seen with azacitidine monotherapy, although these findings await confirmation in the ongoing randomized phase 3 trials. Interestingly, CR was restored in three initial complete responders to the combination regimen who relapsed after they were switched to single agent azacitidine maintenance [42]. This observation suggest an additive effect of the combination over azacitidine, and that adding lenalidomide to azacitidine nonresponders might have a beneficial effect, though this requires further confirmation [42]. Another early phase study of sequential azacitidine–lenalidomide in HR-MDS and AML with del5q reported a lower ORR (26%) [41]. It is noteworthy that real-life analyses using US Medicare claims data of MDS patients showed that lenalidomide is frequently used in the community concurrently with other agents including erythropoiesis-stimulating agents (ESA) and azacitidine [43].

Histone deacetylase inhibitors (HDACIs) are another group of agents that have been combined with azacitidine. Azacitidine–vorinostat combination did not improve OS over azacitidine monotherapy in a randomized phase 2 trial of 150 patients [44]. An early phase study of nine patients using an azacitidine combination with the novel HDACI pracinostat reported a combined CR + CR with incomplete blood count recovery (CRi) rate of 78%. Based on encouraging early phase data, azacitidine-based combination regimens might improve outcomes over azacitidine monotherapy in patients with HR-MDS. Another phase 1 trial combined cytarabine with vorinostat in various regimens of concomitant or sequential therapy in 40 MDS patients with azacitidine failure. The combination was tolerable and resulted in an ORR of 15% (better in concomitant arm, ORR, 25%) [45].

In a retrospective French analysis of 32 HR-MDS who received a concurrent combination regimen of azacitidine with ESA, 44 and 48% reached HI-E and transfusion-independence, respectively, in comparison to 29% ($P = 0.07$) and 20% ($P = 0.01$) in a cohort of azacitidine-treated HR-MDS patients who did not receive ESA therapy [46]. Moreover, the median OS was 19.6 vs. 11.9 months ($P = 0.04$), respectively, and ESA use was independently associated with improved overall survival ($P = 0.03$). These findings suggest a potential benefit for the combination and the need to evaluate this question prospectively [46].

Combinations of azacitidine with cytarabine [47] and anti-CD33-conjugate gemtuzumab ozogamicin [48,49] and others were also evaluated in HR-MDS. Whether adding lenalidomide, a HDACI, ESA, or other agents to HMA nonresponders would sensitize patients to therapy and improve their outcomes remains to be determined. Randomized trials of some of these combinations are ongoing [e.g., a randomized phase 3 trial comparing

azacitidine + lenalidomide combination, azacitidine + vorinostat combination, and azacitidine monotherapy (NCT01522976)].

NOVEL TARGETED THERAPIES

Many agents have been studied empirically for the management of HR-MDS such as clofarabine [50,51], farnesyl-transferase inhibitors [52–54], and arsenic trioxide [55,56]. Recent years have witnessed an explosive increase in the understanding of the genetic basis of MDS, the molecular alterations in signaling pathways, critical enzymes, and other aspects of the complex pathophysiologic mechanisms of MDS. Although therapeutic translation of these important findings is still in its infancy, the increasing knowledge is allowing a more rational approach for drug discovery. Many ongoing clinical trials study agents which target key regulators and critical pathways that contribute to disease maintenance and progression and mediate resistance to current therapies [57]. Although a detailed discussion of the large number of compounds in various stages of preclinical and clinical development for MDS is beyond the scope of this article, we will overview some of the more promising agents in advanced stages of clinical evaluation for MDS after HMA failure (Table 1 [51,58–62]).

Rigosertib (ON-01910) is a multikinase inhibitor that showed activity in early phase trials in HR-MDS after HMA failure, and is currently undergoing evaluation in a randomized phase 3 trial in this setting [59,63,64]. Tosedostat, a novel oral amino-peptidase inhibitor, has shown activity in HR-MDS post azacitidine failure and is undergoing further testing [65]. Sapacitabine, a novel oral deoxycytidine nucleoside showed promising activity in HR-MDS [60]. SGI-110 is another novel potent azanucleoside that is resistant to cytidine deaminase [58,66]. Tyrosine kinase inhibitors such as erlotinib and dasatinib showed modest activity in this setting [61,62,67].

Effector regulatory T cells (Tregs-effs) and the myeloid-derived suppressor cells (MDSCs) are important in the pathogenesis of MDS as key effector elements that mediate immune tolerance to the neoplastic cells [68]. INCB24360 is an oral indoleamine 2,3 dioxygenease inhibitor that alters the bone marrow microenvironment by targeting Tregs-effs and MDSCs by interfering with the vital tryptophan metabolism [69,70]. Inhibiting critical survival and self-renewal pathways in MDS stem cells [e.g., Wnt/β-catenin, sonic hedgehog (shh), and Notch pathways] might overcome resistant disease in MDS [70,71]. PF-04449913, for example, is an inhibitor of smoothened which is a downstream effector in the shh pathway that has shown early evidence of activity in refractory hematologic malignancies [72].

INDUCTION CHEMOTHERAPY

For patients who progress to AML or HR-MDS, intensive chemotherapy is often attempted. Data suggest poor outcome and less chances of complete remission for secondary AML from antecedent MDS. Response rates are reported in the range of 20–30% only [22,28,29]. The Moffitt Cancer Center group reported higher response rates and better OS in a retrospective case–control study in patients who were treated with CLAG-M induction regimen compared with the standard 7 +3 regimen [73]. Intensive chemotherapy preferably should be offered in the context of clinical trials. For those patients with no access to an

intensive clinical trial, only those with proliferative disease or noncomplex karyotype should probably be offered intensive chemotherapy.

alloSCT FOR TREATMENT OF RELAPSED MYELODYSPLASTIC SYNDROMES AFTER 5-AZACITIDINE

As mentioned earlier, alloSCT remains the only known treatment modality to offer a possibility of cure in patients with MDS whether in front line or in the relapsed/refractory setting [74]. Recent improvements related to the introduction of reduced-intensity conditioning regimens has expanded applicability of this procedure to patients of more advanced age or those with less than optimal performance status who were not eligible to undergo myeloablative conditioning in the past [75]. As a result, the number of allografts performed for patients with MDS, mainly for those older than 60 years, has significantly increased over the past decade [76]. Following availability of HMAs, a large number of MDS patients, considered eligible for an alloSCT, have been exposed to these agents beforehand. Field *et al.* [77] compared outcomes of 54 patients (MDS = 48, chronic myelomonocytic leukemia = 4, other = 2) who underwent alloSCT after prior azacitidine (*n* = 30) or not (*n* = 34). No difference in 1-year OS was reported despite addition of pretransplant azacitidine (60 vs. 47%, *P* = 0.25) [77]. Similarly, a phase 2 study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies evaluated 265 consecutive patients who received an alloSCT between 2005 and 2009 [78▪]. There was no difference in 3-year OS whether patients received azacitidine, intensive chemotherapy, or azacitidine preceded or followed by intensive chemotherapy (55 vs. 48 vs. 32%, *P* = 0.07). Moreover, cumulative incidence of relapse at 3 years postallografting was not different among the groups (19 vs. 20 vs. 35%, *P* = 0.24) [78▪]. Also, Gerds *et al.* [79] showed no difference in 1-year OS after alloSCT regardless of receiving azacitidine or conventional induction chemotherapy preallografting.

No randomized controlled trials, evaluating alloSCT vs. nontransplant strategies, in the setting of azacitidine failure are available to our knowledge. An analysis of 435 patients from four data sets (AZA001, Johns Hopkins Univ. Trials 9950 and J0443, and a compassionate use program in France) with HR-MDS who failed azacitidine demonstrated that individuals offered an alloSCT or investigational agents had better survival compared with those offered supportive care or conventional chemotherapy, whether low or intensive-dose [22]. For instance, the median OS after best supportive care, low-dose, intensive-dose, investigational therapy, or alloSCT was 4.1 months, 7.3 months, 8.9 months, 13.2 months, and 19.5 months, respectively [22].

de Lima *et al.* [80] demonstrated that maintenance therapy with low-dose azacitidine (32 mg/m^2 for 4 cycles) is feasible to administer in the post-alloSCT setting for recurrent AML or MDS. It is unclear, however, if these patients had been exposed to azacitidine prior to alloSCT [80]. Whether adoptive immunotherapy, mediated by donor T cells, is capable of altering the biologic milieu to render MDS sensitive to azacitidine after previous failure remains an interesting research question.

Studies comparing alloSCT vs. novel therapies for MDS patients who fail azacitidine or other HMAs are needed. Until such studies become available MDS patients who relapse or progress after treatment with HMAs should be considered for alloSCT if a suitable donor is available and if deemed suitable candidates for the procedure.

CONCLUSION

Patients with MDS and HMA failure have a dismal prognosis and no standard second line therapy. New options for the management of these patients are a clear unmet medical need. Clinical trial enrollment and alloSCT are the preferred therapeutic modalities, but both are unfortunately not available or feasible for the majority of patients who fail HMA therapy. Other options that can be considered include the sequential switching to the alternative HMA and addition of lenalidomide especially for patients with del5q. A large number of experimental agents are undergoing clinical evaluation and hopefully will become available soon to improve the outcomes of these unfortunate patients.

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KEY POINTS

- Patients with MDS who develop primary or secondary failure of HMA have a very dismal prognosis.
- The preferred management options include clinical trial enrollment or allogeneic hematopoietic stem cell transplantation when feasible.
- The sequential use of the alternative HMA after failure of first-line HMA is associated with modest efficacy and can be considered for these patients.
- The improved understanding of the biologic underpinnings is allowing the evaluation of many promising agents that target disrupted molecular pathways critical to the pathogenesis of MDS.
- Azacitidine–lenalidomide combination regimens showed encouraging results and currently are being evaluated in randomized trials. Therefore, addition of lenalidomide to azacitidine might be considered in patients without other alternatives.

Table 1

Selected novel agents under active investigation for patients with myelodysplastic syndromes

Agent	Patient population	Response
Clofarabine [51]	Higher-risk MDS (*n* = 58)	ORR: 29–41% Median OS with response: 13.4 months Median OS: 7.4 months
Oral azacitidine [58]	MDS, CMML, AML (*n* = 41)	ORR (previously-treated): 35% (6/17) ORR (treatment-naive): 73% (11/15)
Rigosertib [59]	MDS (*n* =60) HMA failure (*n* =39)	31% (16/51) ≥ 50% blast decrease Median OS with response: 11 months
Sapcitabine [60]	Phase 1 refractory AML/MDS (*n* = 47)	ORR: 28%
Erlotinib [61]	HMA failure higher-risk MDS (*n* = 35)	ORR (evaluable): 19% (5/26) Median OS with response: 16.8 months Median OS: 6.8 months
Dasatinib [62]	HMA failure higher-risk MDS, CMML, AML (*n* = 18)	ORR: 16.7%

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; HMA, hypomethylating agents; MDS, myelodysplastic syndromes; ORR, overall response rate; OS, overall survival.