

Outlook and Management of Patients with Myelodysplastic Syndromes Failed by Hypomethylating Agents

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Abstract The DNA hypomethylating agents (HMAs) azacitidine and decitabine are currently the most frequently administered disease-modifying therapies for patients with higher-risk myelodysplastic syndromes (MDS). However, azacitidine and decitabine are not curative, the median response duration is 11–15 months, and only 10–20 % of patients experience complete hematologic and cytogenetic response. Moreover, once an HMA fails the patient, the prognosis is poor, with a median survival of less than 6 months unless the patient undergoes hematopoietic stem cell transplantation (HSCT). Recent insights into the genetic basis of MDS have enhanced biological understanding and prognostication accuracy, but these developments have not yet led to regulatory approval of new therapies. While there are multiple potential approaches to patients with MDS for whom HMAs have failed, including supportive care alone, cytotoxic therapy, lenalidomide, histone deacetylase inhibitors, and HSCT, favorable responses to these approaches are limited and new therapies are greatly needed. Here, we review clinical and biological data about the population of patients failed by HMAs, evaluate currently available approaches to patients in this clinical situation, and discuss prospects for development of novel active agents.

Keywords Myelodysplastic syndromes · Azacitidine · Decitabine · DNA methyltransferase inhibitor

Introduction

Treatment of patients with myelodysplastic syndromes (MDS) has been augmented by development of two clinically active DNA methyltransferase inhibitors, azacitidine (Vidaza; Celgene, Summit, NJ) and decitabine (Dacogen; Eisai, Woodcliff Lake, NJ), sometimes called “hypomethylating agents” (HMAs) because of their effect on global cytosine 5' methylation. These drugs were approved by the US Food and Drug Administration (FDA) for all French-American-British (FAB) Co-operative Group subtypes of MDS in 2004 and 2006, respectively, and are now recommended by consensus guidelines for treatment of International Prognostic Scoring System (IPSS) intermediate-2- and high-risk MDS and certain populations of IPSS low- and intermediate-1-risk MDS patients [1]. Before the introduction of HMAs, the only treatment approach that could favorably influence the natural history of MDS (i.e., increase overall survival or delay progression to acute myeloid leukemia (AML)) was allogeneic hematopoietic stem cell transplantation (HSCT) [2].

The most compelling evidence of azacitidine's disease-modifying benefit in MDS comes from the AZA-001 study, an international, multicenter trial that randomized 358 patients to receive either “conventional care” ($n=179$) or azacitidine ($n=179$) [3]. Conventional care included supportive care alone, low-dose cytarabine, or anthracycline-cytarabine AML induction chemotherapy. In the AZA-001 study, azacitidine was administered subcutaneously at 75 mg/m² per day for 7 days every 28 days for a minimum of six treatment cycles. The primary endpoint was overall survival (OS), with secondary endpoints including time to AML progression,

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responses assessed with International Working Group (IWG) 2000 criteria [4], and adverse events. The study met the primary endpoint, as the azacitidine group experienced a median OS of 24 months compared to 15 months in the conventional care group (hazard ratio (HR) 0.58). AML transformation was also delayed, with the azacitidine group diagnosed with AML a median of 18 months after enrollment compared with 12 months for the conventional care group.

Although no survival advantage has been formally demonstrated with decitabine, it remains unclear whether that is because of differences in drug action between decitabine and azacitidine or is instead due to differences in clinical trial design and enrolled populations. Two randomized controlled trials and other prospective studies have demonstrated hematological improvement, cytoreduction of clonal cells, and improved progression-free survival (PFS) with decitabine, which is an established alternative to azacitidine in higher-risk MDS [5–10].

HMA is now a standard first-line therapy in patients with IPSS intermediate- and high-risk MDS [11–13]. However, HMA is not curative, and even when a complete remission (CR) is achieved, the median duration of response is only about 1 year [14]. There is no current consensus on management strategies after HMA failure. Here, we review patterns of HMA failure and potential approaches to patients who have been failed by an HMA.

Hypomethylating Agent Failure Patterns and Prognosis

Understanding the nature of HMA response and failure is necessary before planning management after failure. A recent meta-analysis reported a 73 % overall response rate (ORR) during azacitidine treatment; however, most azacitidine responses are hematologic improvement (HI) rather than deeper remission (pooled CR rate of only 12 %, partial response (PR) 12 %, and HI 46 %, based on IWG 2000 and 2006 or similar custom response criteria, depending on the specific trial). Similar CR rates but lower ORR are suggested when pooling decitabine MDS trial data: an ORR of 42 % with CR 13 %, PR 5 %, and HI 23 % [15]. The median number of treatment cycles until any IWG qualifying response has been reported to be 2–4 with HMAs, with 75 % of patients who will achieve response to decitabine doing so by cycle 3 and the median time to response with azacitidine about one cycle longer (i.e., 4 cycles). In a few cases, initial responses have been described only after more than 1 year of azacitidine therapy [16].

Failure of HMAs can be categorized as “primary” (i.e., no response seen) or “secondary” (i.e., loss of response or disease progression after a period of improvement). A third category of failure occurs if the HMA is stopped before a full course of

therapy due to intolerable adverse events, regardless of clinical response. Data on failure patterns and prognosis of such patients comes primarily from two retrospective studies: a multicenter study from Johns Hopkins University and the Groupe Francophone des Myélodysplasies (GFM) and a single-center study from the MD Anderson Cancer Center [17, 18].

Prebet from the GFM and his colleagues retrospectively assessed 435 patients from three clinical trials of azacitidine (J9950, J0443, AZA-001) and the French azacitidine compassionate use program. Twenty percent of patients received combination therapy, most commonly with a histone deacetylase inhibitor (HDACi). Primary failure in this analysis was defined as either IWG-defined progressive or stable disease [4, 18]. Secondary failures included those patients who achieved IWG 2000 qualifying response during azacitidine therapy but then lost response or experienced disease progression. Primary failure, secondary failure, and intolerance were observed in 55 % ($n=229$), 36 % ($n=164$), and 9 % ($n=42$) of patients, respectively. Thirteen of the 42 patients intolerant to azacitidine experienced their adverse effect during a period of response. OS for the cohort was 5.6 months. Predictors of better OS included female gender, younger age, favorable cytogenetics, lower bone marrow blast count before azacitidine treatment, and response to azacitidine.

The best subsequent outcomes in this cohort were in patients who underwent HSCT (median OS 19.5 months), who were likely the group with fewest comorbid conditions and destined to live longer anyway, while those who received only palliative or supportive care did the most poorly (median OS 3 to 4 months). Poor outcomes were also seen with low-dose chemotherapy (e.g., hydroxyurea, mercaptopurine, cytarabine, melphalan) with no patients in this group achieving IWG qualifying response and median OS of 7.3 months. Intensive AML-like chemotherapy was associated with a median OS of 8.9 months, while investigational therapies, which included HDAC inhibitors, thalidomide derivatives, and various nonregistered drugs, did slightly better with median OS of 13.2 months—again, likely due to a selection bias for healthier or younger patients. Similar poor results after azacitidine failure were also demonstrated in a single institution retrospective review of 59 patients, with a median OS of 5.8 months and 12-month survival of 17 % [47].

In an analogous paper, Jabbour and colleagues reviewed outcomes in 87 patients with intermediate- or high-risk MDS or chronic myelomonocytic leukemia (CMML) evaluated at MD Anderson Cancer Center after decitabine failure [17]. In contrast to the study of Prebet et al., patients who discontinued decitabine therapy due to adverse events were not included in this analysis, and IWG 2006 criteria were applied for response [48]. Forty-three percent ($n=37$) of the 87 evaluable patients had primary failure while 57 % ($n=50$) had secondary failure [17]. The median OS was 4.3 months, with 1-year survival of

28 %. At the time of treatment failure, 25 % had transformed into AML and 75 % had persistent MDS. Among the 65 patients with MDS rather than AML, 10 received idarubicin and cytarabine, with 2 patients achieving decrease in blasts to <5 % (i.e., marrow CR), 30 patients were put on a clinical trial with an ORR of 20 % (most of the trial patient responses were with clofarabine), 4 patients received HSCT with 2 patients achieving a CR lasting over 24 months, 6 patients received unknown therapies, and 15 elected not to receive further treatment beyond supportive care. Comparative survival data were not reported for these subgroups.

Molecular and Clinical Predictors of Hypomethylating Agent Response and Failure

The mechanism of the clinical activity of HMAs in MDS is unclear. Proposed mechanisms include alteration of DNA methylation and, consequently, change in gene expression (either leading to cellular apoptosis or triggering an immunological response) or cytotoxicity akin to other DNA nucleoside analogues such as cytarabine. Aberrant DNA methylation has been described recurrently in MDS, though whether methylation is a pathophysiologic driving mechanism or epiphenomenon remains unclear, and methylation status of specific genes does not predict HMA response [49, 50]. Nonetheless, both clinical and more recently specific molecular genetic markers have been able to predict the likelihood of HMA response with modest success.

Clinical Predictors of Hypomethylating Agent Response

Clinical predictors of HMA response are best described by Itzykson and colleagues in an analysis of 282 IPSS intermediate-2- or high-risk MDS patients from the French compassionate use program [51]. In this series, prior treatment with low-dose cytarabine, bone marrow blasts >15 %, and abnormal karyotype were all associated with decreased HMA response rate. A complex karyotype was associated with a decreased response duration on multivariate analysis. Prognostic factors for decreased OS were Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2 , unfavorable IPSS cytogenetic risk, heavy transfusion dependence (defined ≥ 4 RBC units/8 weeks), and presence of peripheral blasts. Additionally, for patients who failed to achieve CR or PR, achieving HI with erythroid-predominant response predicted a better OS.

A scoring system was developed consisting of these factors and validated using patient data from the AZA-001 trial. Patients could be placed into low-, intermediate-, and high-risk groups with a median OS of not reached, 6.1 months, and 15 months, respectively [52]. This scheme has been validated

retrospectively in two smaller cohorts but has not yet undergone prospective validation [53].

Factors that predicted a lower likelihood of achieving response with decitabine in another series were longer duration of MDS and previous MDS therapy [54]. OS was negatively impacted by chromosome 5 or 7 abnormalities, older age, and prior MDS therapy (excluding growth factors). However, a large pooled analysis of 177 patients, mostly from European trials, did not reveal any predictive factors for decitabine response [55]. Predictive factors for OS in decitabine-treated patients in that analysis included an inferior survival in elderly patients (over 75) and those with elevated serum lactate dehydrogenase (LDH), while, surprisingly, high-risk cytogenetics conferred better OS when compared to lower-risk karyotypes. Lastly, response duration was inversely correlated with increasing IPSS risk. Chromosome 5 or 7 abnormalities (specifically isolated monosomy 7) have been linked to a better likelihood or response to decitabine treatment in several studies, but other analyses have not shown a predictive value of chromosome 7 abnormalities [56–58].

Molecular Predictors of Response

Somatic point mutations are detectable in more than 90 % of patients with MDS, and among the ≥ 40 recurrently mutated genes are several influencing DNA methylation patterns or chromatin conformation, including *TET2*, *DNMT3A*, *ASXL1*, *EZH2*, and *IDH1/IDH2*. As a class, this group of “epigenetic” mutations is second in frequency only to those in genes encoding RNA splicing factors (e.g., *SF3B1*, *SRSF2*, *ZRSR2*, *U2AF1*) [59–61]. There has been wide interest in linking epigenetic abnormalities to specific genetic mutations for therapeutic targets, and several investigative groups have also explored whether mutation results predict HMA response and OS [62, 63].

TET2 mutations have most consistently been associated with HMA response. *TET2* encodes an enzyme that converts 5-methyl-cytosine to 5-hydroxy-methyl-cytosine. A subset of other mutations listed above has been linked to poorer OS and worse prognosis in MDS but has not clearly shown a specific predictive value for HMA response rate, depth, or duration [53].

Recently, Bejar and colleagues published results on 40 sequenced genes in primary cell DNA from 213 MDS patients collected prior to treatment with either azacitidine or decitabine. The cohort demonstrated ORR (41 %) similar to previous HMA trials. A *TET2* mutation with at least 10 % allelic burden predicted a higher likelihood of response to HMA (adjusted odds ratio 1.98); this effect was more pronounced if *ASXL1* mutations were absent (adjusted odds ratio 3.64). The presence of other mutations (*TP53*, *PTPN11*, and others) was associated with shorter OS, but not HMA ORR.

To investigate these results mechanistically, Bejar and colleagues introduced *TET2* knockout or wild-type donor marrow into murine recipients, which were then treated either with azacitidine or control. An engraftment advantage in the *TET2*-null cells over *TET2* wild-type cells was observed by chimerism studies [62••]. A previous French study of 86 patients treated with azacitidine supported these findings; investigators observed a higher likelihood of response in *TET2*-mutated patients (82 % ORR in mutant vs. 45 % for WT) [63]. While *TET2* mutation status is likely a reliable marker of response to HMAs, this difference is still not striking enough to influence prescribing patterns.

At this time, no mutation is known to predict lack of response to HMA or impending treatment failure, and no other mutation besides *TET2* is known to be related to HMA monotherapy response rate or duration. In a phase 2 study of azacitidine and lenalidomide combination therapy in higher-risk MDS, patients with *TET2*, *DNMT3A*, or *IDH1/2* mutations appeared to achieve a higher response rate than those without these mutations, although the sample size did not reach statistical significance [34]. Detailed information on the genetic mutations involved in the pathogenesis and influencing prognosis of MDS outside the HMA context is beyond the scope of this article and has been recently reviewed elsewhere [59, 64, 65].

Treatment Options After Hypomethylating Agent Failures

Best Supportive Care

Data from the analysis by Prebet and colleagues described above indicate that patients treated with supportive care alone after HMA have a poor overall prognosis, with a median OS of 4.1 months [18] (Table 1). However, this is the default strategy for patients who are too sick or choose not to receive other therapies.

Low-Dose Cytarabine and Other Cytotoxic Agents

Low-dose cytarabine (LDAC) has modest efficacy in MDS and was the most commonly used cytoreductive agent for MDS patients with excess blasts before HMAs were developed. In a phase III trial conducted in the 1980s by ECOG and the Southwest Oncology Group (SWOG), which evaluated LDAC administered at a dose of 10 mg/m² twice daily versus best supportive care alone, LDAC was associated with an ORR of 32 % (trial-specific response criteria), but there was no difference in time to leukemic transformation or OS between the two groups [19]. LDAC has not been studied systematically for post-HMA therapy. Although there have been several attempts to use LDAC in combination therapies in

higher-risk MDS, these strategies have not yet proven benefit [66, 67].

Intensive AML-like induction chemotherapy for untreated higher-risk MDS is often poorly tolerated, with a high likelihood of early disease recurrence, poor hematopoietic recovery, and treatment-related mortality, despite blast reduction rates of up to 50 % in some series [1, 68, 69]. In the AZA-001 study, while HMA treatment was superior to intensive chemotherapy in higher-risk MDS, only a small number of patients ($n=25$) in the control arm chose to receive intensive therapy. To our knowledge, just as for LDAC, there are no studies that prospectively assess the outcomes of intensive therapy after HMA failure, and the Prebet et al. reported relatively poor outcomes in people treated with this approach [18]. One study suggested that in patients with AML arising from MDS in whom azacitidine had failed, cladribine, cytarabine, filgrastim, and mitoxantrone (CLAG-M) were superior to the standard “7+3” with cytarabine plus daunorubicin or idarubicin, but this has not been validated in other trials [70].

Switching to Another Hypomethylating Agent or Lenalidomide

A few small retrospective studies have examined the effects of switching to decitabine after azacitidine failure; none has yet reported cohorts of azacitidine after initial loss of response to decitabine therapy (SGI-110, a novel HMA not yet approved by the FDA, is described below). In one analysis of 25 patients with MDS, AML, or MDS/myeloproliferative neoplasms treated with decitabine after primary or secondary azacitidine failure, the results were discouraging, with no patients achieving CR, PR, or HI; five patients achieved stable disease. Median OS was 5.9 months and most patients discontinued decitabine after 1 or 2 cycles [23].

Slightly more favorable results with switching were reported in a 2008 study, where 14 patients for whom azacitidine had failed or not been tolerated were treated with decitabine and the ORR was 28 % (3 CR, 1 HI) [22]. One of the four responding patients had stopped azacitidine for side effects, rather than lack of response. Similarly, investigators at the Moffitt Cancer Center reviewed 21 patients who received decitabine for a median of 4 cycles after azacitidine failure; 19 % of these patients had stopped azacitidine for adverse events, while the rest did not respond. The ORR was 19 % (5 % CR, 14 % HI), but there was a small subgroup within the cohort ($n=10$) who restarted azacitidine after discontinuation of decitabine for a drug holiday, and these patients achieved 40 % ORR (20 % CR, 20 % HI) with a median OS of 22 months from azacitidine initiation [21].

Finally, a cohort of ten patients received single-agent lenalidomide for a median of 3 cycles after azacitidine failure. ORR was 40 % (3 CRs, 1 HI), the median response duration

Table 1 Efficacy of selected therapeutic agents after hypomethylating agent failure

Treatment modality	Study design	Results	Comments
Best supportive care	Retrospective [17]	Median OS 4.1 months	
Low-dose cytarabine	Phase III [19]	ORR 32 %, CRR 11 %, OS 6.8 months [20]	No difference in time to leukemic transformation or overall survival between the two groups
Intensive chemotherapy	Retrospective [17, 18]	ORR 14–20 %, median OS 8.9 months	
Sequential HMA	Retrospective [21–23]	ORR 0–28 %; median OS 5.9–22 months [24–26]	
Combination with HDACi	Phase I-II [27, 28, 29••, 30, 31]	ORR 5–89 %; median OS (13 months with entinostat, 17.9 months with belinostat)	Pracinostat showed the highest efficacy with ORR 89 %, belinostat 5 % ORR, 27 % entinostat, 27 % HN ^a , vorinostat up to 60 %, panobinostat 50 %
Combination with lenalidomide	Phase I-II [32–34]	ORR 59–72 %; CRR 14–44 %; median OS 37+months	
Clofarabine	Phase II; Retrospective [17, 35–38]	ORR 17–50 %; CRR 6–25 %; median OS 5–12 months	Including studies assessing clofarabine in combination with cytarabine
HSCT	Retrospective [17, 18]	ORR 50–68 %; median OS 19.5–24 months	
Rigosertib	Phase I-III [39•, 40, 41]	ORR 31 %, OS 8.2 months	No statistically significant difference in OS in the phase III trial
Sapacitabine	Phase II [42]	ORR 14 %, median OS 8.6 months	30-day mortality rate 5 % in all three dosing arms
SGI-110	Phase I-II [43••, 44]	ORR 25 %, CRR 16 % in relapsed/refractory, 47 % treatment-naïve	
AG-221	Phase I [45••]	ORR 60 % (n=10)	Severe adverse events included leukocytosis, confusion, and death from sepsis
ARRY-614	Phase I [46•]	HI 22 %	All responding patients had been treated with prior HMA

ORR overall response rate, CRR complete response rate, OS overall survival, HDACi histone deacetylase inhibitor, HSCT hematopoietic stem cell transplantation, HI hematologic improvement

^a HN hematologic normalization = CR, PR, or major trilineage response rate

was 6 months, and median OS was 20 months. Half of this cohort harbored del(5q) at baseline [71].

Combination Strategies

Addition of a Histone Deacetylase Inhibitor

Understanding of potential gene expression regulation synergy between histone modification and cytosine methylation has prompted clinical interest in HDACi—which also inhibits deacetylation of other cellular proteins—in MDS and other diseases. HDACi that has recently been investigated or is currently undergoing trials in MDS includes entinostat (SNDX275), vorinostat (SAHA), belinostat (PDX101), panobinostat (LBH589), mocetinostat (MGCD0103), and pracinostat (SB939). These agents collectively have had limited activity as single agents in myeloid neoplasms. For instance, belinostat monotherapy induced an ORR of 5 % and was poorly tolerated [27].

Results with HDACi monotherapy in patients for whom HMAs have failed, or adding HDACi to an incompletely effective HMA as an “add-on” strategy, have not been systematically

reported. However, up-front combinations of HMA plus HDACi have not shown superiority to HMA alone, suggesting that there may be limited clinical efficacy with this combination approach despite the in vitro synergy.

A randomized phase II comparison of entinostat with entinostat plus azacitidine, E1905, was disappointing, failing to reach the primary objective of improved hematological normalization (monotherapy 32 %, combination therapy 27 %). Adverse events including fatigue and thrombocytopenia, which are HDACi class effects, were more common in the combination arm. Additionally, the combination arm exhibited less treatment-associated demethylation, suggesting an antagonistic effect of entinostat, which is a cell cycle inhibitor (azacitidine requires cells to undergo cycle to have an effect) [29••].

Similarly, the randomized US/Canadian intergroup S1117 trial (NCT01522976) compared azacitidine monotherapy with two combination approaches: azacitidine plus vorinostat, and azacitidine plus lenalidomide, for patients with higher-risk MDS or CMML. The study did not meet its primary endpoint of superior ORR with combination therapy compared to monotherapy, but the combination arms did have longer PFS at the cost of greater toxicity.

Other agents are at an earlier stage of development. Panobinostat was evaluated in a phase Ib/II study assessing 39 patients with AML ($n=29$) or MDS ($n=10$) in combination with azacitidine, with ORR 50 % in the 10 MDS patients [31]. Pracinostat plus azacitidine combination was associated with a striking 89 % ORR in a small number of patients [30]. Randomized data with pracinostat, however, showed no benefit (<http://investor.meipharma.com/2015-03-23-MEI-Pharma-Announces-Top-Line-Data-From-Randomized-Phase-II-Clinical-Study-Of-Pracinostat-In-Front-Line-Myelodysplastic-Syndrome>).

Vorinostat was evaluated with decitabine in a phase 1 dose escalation study in 34 patients with relapsed/refractory AML, newly diagnosed AML, or intermediate to HR-MDS; 11 of the patients had MDS. Decitabine was given at 20 mg/m² for 5 days plus vorinostat 400 mg daily for 14 days. Responses were observed in those who received the drugs in a “concurrent” schedule with 60 % of MDS patients responding in this group ($n=5$). Only one patient had dose-limiting toxicity—an individual enrolled in the “sequential” schedule arm [28].

Addition of Lenalidomide

Lenalidomide, the cereblon/ubiquitin ligase modulator that is a standard first-line therapy for lower-risk MDS patients with anemia and deletion of chromosome 5q, has been examined in several studies in combination with HMAs, but not as a post-HMA strategy. In a phase 1 and an extension phase 2 trial conducted by the now-defunct Bone Marrow Failure Consortium, 36 HMA-naïve patients received azacitidine at 75 mg/m²/day and oral lenalidomide 5–10 mg daily in 4-week cycles. Results were encouraging with a median OS of over 37 months, with ORR of 72 %, and with CRR 42 % [33, 34]. However, this combination was not superior to azacitidine monotherapy in the S1117 trial described above. [32].

Clofarabine

Clofarabine, a second-generation nucleoside analog active in AML and MDS, is sometimes used as post-HMA salvage therapy [35, 72]. Clofarabine’s use in the specific population of HMA failures was described in abstract form in 2014 [37]. Fifty-two patients with higher-risk MDS who had received at least 4 cycles of azacitidine or decitabine were given clofarabine 15 mg/m² IV daily \times 5 days in combination with LDAC 20 mg SC twice daily \times 7 days, followed by consolidation therapy with the same regimen if an initial response was achieved. An ORR of 48 % was obtained, with a CRR of 17 %, and HI/stable disease of 12 %. Median OS was only 4.8 months, with febrile neutropenia rates of 38 % and 4-week mortality of 12 %. Oral clofarabine was tested in 32 MDS patients, 20 of whom had prior failure with an HMA. Using nonstandard response criteria, ORR was reported as 43 %

(25 % CR, 9 % HI, 9 % “clinical benefit”). Median OS for the cohort that had received prior HMA therapy was 7.8 months, with 50 % of patients in the entire group experiencing at least one infectious episode [36].

We recently published results from 84 patients with AML ($n=81$) and MDS ($n=3$) receiving clofarabine either as monotherapy or in combination with cytarabine in the relapsed/refractory setting. The ORR was 21 %, which was lower than previous published studies of clofarabine’s activity in this setting. Median OS was 3 months for the entire cohort, with a small subgroup taken to transplant that had a median OS of 18 months. Unfortunately, the 30-day mortality or induction death rate was equally as high as the response rate at 21 % with 70–80 % experiencing a documented infection or febrile neutropenia, respectively [38]. The ORR for the 30 patients that had previously received HMAs was poor: only 4 patients responded to clofarabine (ORR 17 %); most patients who had received HMAs were given clofarabine alone ($n=19$) as opposed to combination therapy with cytarabine.

Hematopoietic Stem Cell Transplant

The topic of HSCT in MDS is complex, with many patient-specific variables to consider, including which patients are suitable transplant candidates, the best timing of transplant in the disease course, the optimal conditioning regimen, and post-HSCT management [73, 74]. Nevertheless, HSCT remains the only possible cure for patients with MDS and should be considered in all potentially transplant-eligible patients after failure of HMAs [13, 75].

Lim and colleagues reviewed 1333 MDS patients undergoing HSCT and observed a 4-year OS of 31 %, with the most important predictor of relapse and nonrelapse mortality being “advanced disease state,” defined as >5 % marrow blasts at the time of conditioning [76]. These and other data showing poorer outcomes in patients going into transplant with excess blasts have argued in favor of pretransplant cytoreduction with HMAs or, if HMAs have already failed, cytotoxic drugs such as clofarabine or induction chemotherapy. Even though patients with MDS without excess blasts have a high clonal burden, this seems to be less of a consideration in transplant outcomes than blast proportion or other disease characteristics such as karyotype. Patients who have been failed by azacitidine can be reassured that should they undergo a transplant; their prognosis is similar to untreated patients undergoing transplant as long as their blast proportion is low, which has been demonstrated in multiple studies [77–79].

Given that most patients with MDS are at least age 70, additional data are needed regarding transplant outcomes and mortality in the elderly population [20]. Comorbid conditions are especially important in transplant decisions in this group, as numerous studies indicate that a higher

hematopoietic cell transplant-comorbidity index (HCT-CI) is associated with inferior nonrelapse mortality and survival [24–26].

Most recently, genetic mutations have been shown to influence prognosis after an allogeneic stem cell transplant. Bejar and colleagues reported HSCT outcomes on 87 patients in whom 40 recurrently mutated genes were sequenced by massive parallel sequencing before HSCT. The median age was 58, 71 % of patients underwent reduced intensity conditioning, and prior HMA therapy did not influence results. On univariate analysis, only *TP53* mutations conferred a worse median OS and PFS. However, after adjustment of clinical factors associated with these endpoints, *TET2* and *DNMT3A* were additionally associated with poor OS. Three-year OS in patients with one of these mutations was 19 versus 59 % in patients without the mutations [80•]. Furthermore, outcomes with *TP53* mutations were particularly grim; all 18 *TP53* mutants died before 5 years, with a median OS of 4.6 months, and 83 % had active disease at time of death. It is questionable whether the enormous resource expenditure, risks, and patient lifestyle changes required for transplant are justified in such patients, unless they are part of a clinical trial of a novel approach. Efforts at preventing or aborting relapse with post-HSCT azacitidine and other drugs, donor lymphocyte infusion (DLI), and adaptive immunotherapy vaccines are all being explored [81–85].

Novel Therapeutics

A recent review outlining new developments for MDS highlights the broad range of approaches currently being explored in clinical trials [86]. As new recurrently mutated genes are discovered, yielding additional insight into the pathophysiology of MDS, additional investigational agents targeting these mechanisms will be tested. Below, we highlight several recent developmental programs of special interest for the HMA failure space in MDS.

Rigosertib (ON 01910.Na)

Rigosertib is a multikinase inhibitor with myeloblast-reducing activity in MDS, including in the post-HMA setting [40]. Unfortunately, this agent did not show an OS benefit in a randomized controlled trial versus best supportive care (BSC) in higher-risk MDS patients who had previously been failed by an HMA: OS was 8.2 in the rigosertib arm versus 5.8 months in the BSC arm (not statistically significant) [39•]. Specific subgroups, including primary HMA failures, may have experienced greater benefit with rigosertib [87]. A phase I study evaluating oral rigosertib has been completed. Oral rigosertib demonstrated efficacy in terms of marrow response, hematological improvement, and transfusion independence in a subset of patients, but minor adverse events such as dysuria were common [41].

Sapacitabine

Sapacitabine is a nucleoside analog that generates a small single-stranded break in DNA, which, on subsequent rounds of DNA replication, leads to double-stranded breaks and cell death; additionally, a palmitoyl side chain allows oral absorption and protects the molecule from inactivation. A phase II study of 63 patients with MDS for whom HMAs had failed randomized enrolled subjects to three dose regimens (200 mg BID \times 7 days, 300 mg QD \times 7 days, or 100 mg QD \times 5 days per week for 2 weeks). Responses were seen in 14 % (two CRs, two CRp, and five HI), with 21 patients achieving stable disease lasting longer than 16 weeks; clinical activity was noted in all three schedules. Median OS was 8.6 months with 30-day mortality rate of 5 % in each arm [42].

SGI-110

SGI-110 is a novel dinucleotide HMA that complexes decitabine with deoxyguanosine, inducing resistance to degradation by cytidine deaminase and providing a longer in vivo half-life than decitabine. In a phase I/II study, subcutaneous SGI-110 was administered to 78 patients with AML ($n=64$) or MDS ($n=14$); phase II schedules included 60 mg/m²/day or 90 mg/m²/day \times 5 days. Twenty of 45 patients who were previously treated with HMAs had at least 10 % long interspersed nuclear element demethylation, with over 20 % demethylation in 11/45; more clinical responses (4/11) were seen in the latter group. The ORR, which was not dose-dependent, was 25 %, with eight CRs in 50 relapsed/refractory AML and eight CRs in 17 treatment-naïve AML patients. Febrile neutropenia, thrombocytopenia, anemia, and leukopenia were the most common adverse events and were more frequent with the 90 mg/m² dose [43•, 44].

AG-221

A primary goal of current cancer genetics efforts is to distinguish biologic subtypes of disease in order to apply more narrowly targeted therapeutics to the subset of patients most likely to benefit. AG-221, an oral, reversible, selective IDH2 inhibitor, which is an exciting new compound with activity in AML, is an example of genotype-directed therapy. In a phase I study, AG-221 was delivered orally at doses ranging from 30 to 100 mg BID in continuous 28-day cycles to 18 AML patients and 1 MDS patient harboring an IDH2 mutation. Pharmacodynamic studies showed sustained reduction in levels of the oncometabolite generated by IDH1 or IDH2 mutations, 2-hydroxyglutarate. At the time of release of preliminary data, ten AML patients were evaluable for response and six had objective responses, including two CRs. There were no dose-limiting toxicities reported, but severe adverse events included hyperleukocytosis, confusion, and death from sepsis [45•]. An inhibitor of IDH1 is in an earlier phase of development.

ARRY-614

ARRY-614 is a dual inhibitor of both p38 and Tie2 kinases that has showed activity in a phase 1 trial enrolling patients with MDS who met criteria for IPSS low- or intermediate-1-risk disease (although the IPSS was meant to apply only at diagnosis and not subsequent in the disease course). Sixty-two patients were treated at escalating doses for a median of 13 weeks, and the most common treatment-related adverse events were rash, nausea, atrial fibrillation, decreased appetite, fatigue, and vomiting. The rate of HI was 22 % (12/54) across all cell lines, and several patients achieved platelet transfusion independence. Curiously, all of the responding patients had been treated with a HMA [46•].

Other Agents

Several kinase inhibitors approved for other malignancies, such as erlotinib and dasatinib, have been studied in MDS populations including patients for whom HMAs failed but had limited efficacy [88, 89]. An oral formulation of azacitidine (CC-486) has activity in both untreated and previously treated patients with MDS; diarrhea and febrile neutropenia were observed in up to 20 % [90]. Further studies with CC-486 are underway. Newer drugs such as INCB024360, an oral inhibitor of indoleamine 2, 3-dioxygenase, and birinapant, a second mitochondrial activator of caspases (SMAC) peptidomimetic, are in early stages of investigation (NCT01822691 and NCT01828346).

Conclusion

Although HMAs have improved MDS care, the high failure rate and uncertainty about how to best proceed once an HMA has failed the patient remain major challenges. For now, patients for whom HSCT remains a feasible option should be offered transplantation, but it is unclear how to proceed with other patients. Improved understanding of the molecular pathophysiology underlying MDS may eventually yield novel targeted agents that will move treatment forward.

Compliance with Ethics Guidelines

Conflict of Interest Daniel A. Roberts declares no potential conflicts of interest.

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