Treatment options for patients with myelodysplastic syndromes after hypomethylating agent failure

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The treatment of patients with myelodysplastic syndromes (MDSs) has hinged primarily on supportive care (ie, blood transfusions, colony stimulating agents, iron chelation, etc.) and the US Food and Drug Administration-approved agents, including 5-azacytidine, deoxyazacytidine, and lenalidomide. For patients no longer benefitting from these agents, there is a paucity of effective therapies. The challenges at this time include our limited understanding of the mechanisms of resistance to these therapies and the variables employed to select next best therapies for patients based on: (1) their performance status and medical comorbidities; (2) the molecular feature(s) of their MDS; (3) the prior treatments they have received; and (4) the long-term goal(s)/possibilities for their future treatment (ie, transplant vs no transplant).

Learning Objectives
- Annotate the mechanisms of action of hypomethylating (HMT) therapy
- Annotate the mechanisms of resistance to HMT
- Define “failure” of HMT
- Review the prognosis for patients with relapsed MDS post-HMT
- Identify options for therapeutic treatment post-HMT

Hypomethylating agents (HMTs) such as 5-azacytidine (5AC) and deoxyazacytidine (DAC) are the current mainstay of treatment of patients diagnosed with high-risk myelodysplastic syndromes (MDS). It is paramount that these agents be delivered to patients, such that maximal benefit is obtained using optimal dosing and schedule until loss of response to the agent(s) or the presence of intolerable side effects. The majority of patients (50% to 60%) (frontline-treated patients) will have some response to HMT, but these responses are not durable. Unfortunately, when MDS progresses despite these agents, the clinical outcome for patients is dismal (low-risk MDS patients have a median overall survival [OS] of 17 months1 and for high-risk MDS patients it is 5.6 months2). Treatment approaches in this situation focus on available clinical trials and expeditious transition to bone marrow transplant (BMT) if at all possible. The focus of this study is to review the mechanism of action of HMT, as well as the mechanism(s) of resistance. The definition of failure of HMT will be discussed, as well as options for therapy in this setting including the use of selected novel agents.

In phase 1 trials conducted in the 1970s, patients with MDS were administered 5AC at cytotoxic doses (double or higher the current US Food and Drug Administration [FDA]-approved doses), as a single agent or in combination with other cytotoxic agents. Von Hoff et al3 published the first review article documenting the first 200 relapsed acute myeloid leukemia (AML) patients treated with 5AC in this manner, demonstrating an overall response rate (ORR) of 36% (complete remission = 20% and partial remission = 16%). Given the challenges of toxicity, these cytotoxic doses were significantly reduced with a corresponding increase in the frequency of administration and culmination to the current (lower) FDA-approved epigenetic dosing regimens. This historical experience highlights the rationale for why significantly higher doses of HMT are not a logical approach for when MDS progresses.

HMTs 5AC and DAC are nucleoside analogs that mimic physiological cytidine to exert their pharmacologic actions.5,6 Nucleoside transporter proteins mediate the transport of 5AC and DAC across cell membranes,6,8 where they are activated through phosphorylation by uridine-cytidine kinase (UCK) and deoxycytidine kinase (DCK), respectively (Figure 1). Phosphorylated DAC is incorporated into newly synthesized DNA with block of DNA methylation in the newly synthesized DNA strand (hypomethylation). 5AC works through the same mechanism of action to affect DNA after being converted to DAC by ribonucleotide reductase (RR). However, the majority (80% to 90%) of 5AC preferentially incorporates into RNA, thereby inhibiting RNA synthesis and protein metabolism. Additionally, 5AC is a potent inhibitor of RR, which leads to depletion of the deoxyribonucleotide triphosphate stores and inability to repair DNA.9 Notably, increased expression of genes relevant in immune checkpoint modulation post-HMA exposure has been noted in samples from MDS patients and suggests that programmed cell death protein 1 (PD-1) signaling may be involved in MDS pathogenesis and resistance mechanisms to HMT. Specifically, upregulation of programmed death ligands 1 and 2 (PD-L1 and PD-L2) and cytotoxic T-lymphocyte-associated antigen 4 was observed in MDS patients with greater gene expression in patients resistant to HMT (vs responders to HMT).10 This suggests that in higher risk MDS, a suppressive microenvironment protects cells from immune destruction and substantiates the proposed combination therapy of HMT with immune checkpoint inhibitors discussed later in this study.

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Proposed mechanisms of resistance to HMT include: (1) decreased transportation of HMT into the cell through altered function/capacity of the human nucleoside transporters; (2) disruption of the activating enzymes UCK/DCK; (3) augmented elimination of HMT out of the cell as a result of increased cytidine deaminase (CDA) activity; (4) immune modulation; and (5) inability to eradicate the leukemia stem cell due to stem cell quiescence.\textsuperscript{11,12}

Some hypothesize that resistance to HMT can also be due to heavy or dense presence of methylation at promoter sites of tumor suppressor genes that are more resilient to reversal by HMT.\textsuperscript{13} Others, however, suggest that differentially methylated regions in nonpromoter regions may be unique in nonresponders and associate with overexpression of CXCL4/CXCL7, and contribute to primary HMT resistance.\textsuperscript{14}

With regard to the mechanisms of resistance mentioned in the paragraph above, the decreased cellular transport of HMT across the cell membrane can be caused by alterations of the human nucleoside transport enzymes hCNT3 and human equilibrative nucleoside transporter 1 (for 5AC and DAC, respectively).\textsuperscript{15} It is thought that decreasing levels of human nucleoside transporters can impact resistance to HMT and distinct human nucleoside transportability profiles exist for 5AC as compared with DAC.

Inactivation or altered phosphorylation of 5AC/DAC by UCK or DCK can also lead to resistance to HMT. In leukemia cell lines (HL60), point mutations in DCK are a key resistance mechanism for DAC, although these point mutations are incredibly rare in MDS patients. However, levels of DAC and associated DCK enzyme levels have been measured in samples from MDS patients, and decreased levels of both have been associated with clinical nonresponders. Similarly, UCK point mutations have been seen in 5AC-resistant cell lines (THP-1 and HL60).\textsuperscript{16}

Valencia et al\textsuperscript{8} assessed whether the expression of nucleoside metabolizing enzymes predicted response to 5AC therapy in 57 MDS patients. Expression level by quantitative polymerase chain reaction was performed for human equilibrative nucleoside transporter 1, UCK1, UCK2, DCK, and the 2 subunits of the RR gene (RRM1 and RRM2). In this 1 study, higher UCK1 messenger RNA expression levels were detected in MDS patients responding to 5AC compared with nonresponders. More importantly, patients with lower UCK1 expression had a shorter median OS than those with a high expression (19 months vs 49 months, respectively).

Increased CDA activity is another manner by which effective HMT can be sabotaged. CDA is the enzyme that deaminates 5AC and DAC, and alters the cytidine to a uridine moiety. Accordingly, elevated CDA expression/activity decreases HMA plasma half-life. It has been suggested that CDA expression and enzyme activity is significantly higher in males as compared with females, and this may contribute to the lower response rates in males.\textsuperscript{17,18}
Epigenetic silencing can be due to dense methylation or other post-translational modifications, such as methyl binding proteins, chromatin compaction, or other transcription factors. Epigenetic signaling may be directly or indirectly involved with immune pathway upregulation. Consequently, immune checkpoint inhibitors have emerged as a novel approach to MDS therapy.

Additional proposed mechanisms of resistance include whether DNA methyltransferase inhibitors are unable to eradicate the malignant clone due to deactivation of an apoptotic pathway or continuous activation of cellular signaling pathways. Cluzeau et al. demonstrated that increased expression of BCL2L10 (an antiapoptotic Bcl-2 member) was linked to resistance in a 5AC-resistant cell line (SKM1-R). Importantly, the mode of resistance may be different between patients who are “never-responders” to HMT and those who are “partial/complete responders.” The larger “resistant” population of patients is comprised of “never-responders,” although only 1 clinical trial to date focuses on investigating these subset target populations and is currently evaluating response to therapy with a multikinase inhibitor, rigosertib (NCT02562443; Controlled study of rigosertib versus physician choice of treatment in MDS patients after failure of an HMT [INSPIRE]). Notably, in the ONTIME phase 3 trial for MDS patients (who previously progressed on, failed, or relapsed despite HMT), 299 patients were treated with rigosertib vs best supportive care (BSC), and the study concluded that there was no improvement in OS with rigosertib (compared with BSC). However, a subset analysis demonstrated that there was a potential survival benefit to those patients receiving rigosertib if they had primary HMT failure (as opposed to secondary HMT failure), or had received <9 months of prior HMT drug treatment (as opposed to >9 months), or had a revised International Prognostic Scoring System (IPSS) very high risk or cytogenetic abnormalities of either monosomy 7 or trisomy 8. These subset analyses led to the current trial design for the INSPIRE study noted earlier.

The proposed mechanisms of resistance are thought to explain how patients with MDS experience either upfront resistance HMT-directed therapy or eventually progress after some period of clinical response to HMT. The definition of HMT treatment failure is when the patient has progression of MDS at any time after initiation of 5AC/DAC treatment (according to International Working Group [IWG] criteria) or failure to achieve hematologic improvement (HI), partial response (PR), or complete response (CR) (according to IWG criteria) after at least 4 to 6 cycles of therapy with DAC/5AC at standard dosing. Additionally, patients can also be considered a treatment failure if they have progression of disease after initial response (HI/PR/CR) to therapy, based on IWG criteria. Once HMT therapy is initiated, some patients are unable to achieve the same complete blood count level that they enjoyed prior to initiation of the HMT. Initially, patients may also require increased transfusion support in the first number of cycles. In others, the complete blood count demonstrates increasing blasts in the peripheral blood (or bone marrow [BM]) despite therapy. Finally, failure of HMT also includes patients who were unable to tolerate the chemotherapy due to unmanageable toxicities (ie, severe and repeated infection, bleeding, intractable nausea, diarrhea, and others).

Ultimately, despite any clinical response to HMT therapy, we expect that all patients will eventually relapse at some point given that HMT is not curative. Although patients with MDS can have a meaningful benefit from this therapy, these agents do not completely eradicate the BM neoplasm. Patients need to remain on active therapy without stopping in order to maintain the benefit. Thus, if HMT therapy is stopped or interrupted, MDS will ultimately recur in all patients. Upon re-introduction of HMT, typically the MDS is less or no longer HMT responsive. Furthermore, it is thought that the only curative option for MDS patients is a hematopoietic stem cell transplant (HSCT) once disease has been controlled, with a likelihood of >50% chance of cure with at least 20% treatment associated mortality. In the AZA001 study, there was an improvement in OS for MDS patients receiving 5AC vs a conventional care regimen, although it is important to highlight that there was no plateau in the Kaplan-Meier curve. Furthermore, patients who fail HMT have a poor survival based on retrospective studies; 17 months for low-risk and 5.6 months for high-risk patients. Prébet et al. compiled the outcomes for MDS patients failing HMT from: (1) 2 studies at Johns Hopkins University (J0443 and J9950); (2) the AZA001 study; and (3) the French ATU Compassionate Use study, and found the median OS for any therapy (supportive care, low-dose or intensive or investigational chemotherapy, or HSCT) was 5.6 months. Similar examination of 438 low-risk MDS patients failing HMT was performed and the median OS was 17 months. In MDS patients who failed HMT, outcome was improved in those who enrolled in a clinical trial or received an HSCT. Cabrero et al evaluated the outcomes for 16 MDS patients who stopped HMT therapy electively (for any reason) while having a clinical response to the agent (excluding BMT). Median OS and progression-free survival were 15 months and 4 months, respectively. They reported that for those MDS patients who received >12 cycles of therapy or did not have high-risk cytogenetics, there was a significantly longer OS and they tended to have a longer progression-free survival as well.

Traditionally, prognostic scoring systems like IPSS and revised IPSS help physicians guide patients with therapeutic decision-making, based on the predictive power of these algorithms to determine low- or high-risk phenotype. Data show that these prognostic scoring systems are at their best predictive power at the time of initial MDS diagnosis, particularly for low-risk MDS patients. Nazha et al has proposed a prognostic algorithm that may be better for prediction for MDS patients at the time of HMT failure. These tools may aid in making optimal recommendations for patients based on improved prognostic ability, although this prognostic scoring system still requires validation in a prospective trial.

In order to optimize therapeutic selection(s), it is desirable to predict response to HMT prior to initiating this therapy. This would facilitate rational treatment selections, and spare unnecessary exposure and toxicity to agents that are not beneficial. Currently we do not have the ability to identify these patients, but future studies may help with this vision given the promise of next-generation sequencing. In this regard, identification of biomarkers that aid with better patient selection to identify those patients who are more likely to achieve a complete response, long duration of response, or benefit from certain combinations of therapy would be ideal. As just mentioned, little data exist to predict who might benefit from therapy vs those who should forego this option. The ability to predict response to HMT using karyotypic information appears to be relevant if the patient’s MDS harbors deletions with 5q or a trisomy 8 abnormality. In these 2 scenarios, patients appear to have a better CR rate in response to HMT (18% and 21%, respectively) than was otherwise appreciated in the entire group (N = 800 patients). Unfortunately, MDS presenting with a cytogenetic abnormality including 3q26, is associated with a lower ORR and OS. Moreover, this study reported there was no baseline karyotype associated with an improved
It would also be ideal if we could use our understanding of mechanisms of resistance to HMT to inform the strategy of an MDS patient’s next best chemotherapy. Several approaches might arise with this tactical approach. For example, a patient’s UCK or DCK activity level might help select the 5AC- (vs DAC)-directed approach. Increased transport of HMT into the cellular compartment by adding an agent to increase NT activity might also optimize delivery and drug effect. Alternatively, maybe there is a technique to stimulate activation of 5AC/DAC by increasing UCK or DCK activity. When CDA activity is blocked with tetrahydroeuridine, the exit of active HMA out of the cellular compartment is reduced, thus increasing the effect of the HMA. Finally, epigenetic targeting can be enhanced by the addition of other novel agents (histone deacetylase [HDAC], BCL-2, and bromodomain and extra-terminal [BET] inhibitors, or DOL1L inhibitors) with intention about dosing, timing, and sequencing of therapies. Notably, limited data exist with clinical use of BET and DOT1L inhibitors, but the biologic impact of these agents is thought to be similar. Improvement with HDAC inhibitors (HDACi) added to HMT therapy has also been, thus far, unimpressive and will be discussed in the next section.

Clinical trials serve as the best option for almost all MDS patients who have had disease progression despite an adequate trial of HMT. First steps in addressing the MDS patient who has progressed on epigenetic therapy is to ensure adequate trial (duration) of the upfront HMT and appropriate dosing, including avoiding drug interruptions and delays, as well as the potential consideration to increase 5AC from 75 mg/m² to 100 mg/m² over 7 days once a month if less than stable disease was obtained. Specifically, delivery of 5AC is often not administered as per standard of care, given the challenges of a 7-day schedule in the community setting. Despite the common practice in general oncology of switching to a “sister agent” (ie, carbo- and cisplatin, daunorubicin, and mitoxantrone) to determine if there is a possible additive class effect, a patient who has failed 5AC has a very low likelihood of having any meaningful benefit from DAC (and vice versa). However, in the E1905 study, Prébet et al demonstrated that longer duration and decreased dose of 5AC in the upfront setting for high-risk MDS patients doubled tri-lineage response rates (30%) compared with historical controls (15%). In this trial, a 10-day duration of 5AC as single agent was compared with combination therapy with the same dose 5AC and the HDACi entinostat. The total monthly dose of 5AC was 500 mg/m² (as compared with 525 mg/m² with standard 7-day therapy per month). No appreciable difference in response rates was noted with single agent compared with combination therapy, although this might be explained by the overlapping delivery of agents, because the HDACi is known to stop cells from cycling (static agent), which decreases incorporation of 5AC. Studies comparing the variation of sequencing (overlapping vs sequential administration of combination therapy) are ongoing. Interestingly, in an unplanned subset analysis of E1905, 47 patients with treatment-related MDS had a tri-lineage response rate of 46%, which is quite impressive compared with the 30% response rate of the whole MDS population. Alternative dosing schedules of 5AC and DAC have been proposed to increase duration of exposure of cells to HMT, while decreasing the effective daily doses and achieving similar total monthly exposure as standard-of-care dosing. As referenced above, Steensma et al demonstrated in the alternate dosing for outpatient treatment trial that decreased total monthly dose and increased duration of decitabine (100 mg/m² over 5 days vs 135 mg/m² over 3 days) was comparable in efficacy (two- to threefold improvement in MDS remission and HI rates). It was demonstrated that longer duration and decreased dose of DAC to ~10% to 25% of FDA-recommended doses with an administration frequency of 1 to 3 times per week to increase DNA methyltransferase 1 depletion, although this has yet to be tested in a prospective randomized clinical trial setting.

Importantly, the delivery of novel agents is paramount in treating this relapsed and refractory MDS population because there are limited benefits to previously studied combinations. Notably, combination studies have been attempting to improve on ORRs by addition of second agents to HMT. Overall, most combinations demonstrate added toxicities with combination approaches with minimal to limited benefit. One example of which is the S1117 study led by Sekeres et al, which evaluated high-risk MDS patients treated by either single-agent 5AC, or combination with either vorinostat (HDACi) or lenalidomide (immunomodulatory agent). This study was based on prior work demonstrating ORRs as high as 72% with these combination therapies. Unfortunately, patients in this study who received combination therapy had no benefit compared with monotherapy and they more often suffered side effects/toxicities. Sadly, ~35% to 40% of patients/physicians stopped therapy in combination arms and did not follow protocol guidelines for taking patients off study, thus limiting true exposure to combination agents and potentially confounding results. Unfortunately, the study was not powered to evaluate OS end points, despite rapid accrual and high interest across the nation.

Another way to modulate epigenetic therapy other than the addition of other epigenetic approaches such as HDACi or immunomodulatory agents is to pursue a novel formulation of HMT. One such agent, guadecitabine (SGI-110), is thought to increase in vivo exposure of DAC by blocking deamination (Table 1). SGI-110 is a dinucleotide of DAC (and deoxyguanosine) that has been tested in the phase 1 setting, CC-486 was bioavailable, clinically active, and well tolerated with an ORR of 35% in previously treated MDS/AML patients. In this multicenter, open-label phase 1 study, 31% (6/19) of the MDS patients had a clinical response to this agent. This study determined that the maximal-tolerated dosage was 90 mg/m² × 5 days in the MDS cohort and that there was potent dose-related DNA demethylation that occurred in the daily × 5 days dosing with a plateau at the 60 mg/m². This agent, as well as an oral version of 5AC (CC-486), is being evaluated in ongoing phase 1 and 2 clinical trials in adults with high-risk MDS and low-risk MDS, respectively. In the phase 1 setting, CC-486 was bioavailable, clinically active, and well tolerated with an ORR of 35% in previously treated MDS/AML patients. An oral formulation with decitabine plus a CDA inhibitor E7727 is called ASTX727 and is currently being tested in patients with MDS. These novel formulations may allow for improved ability to deliver combination epigenetic-directed therapies in the future.

We also expect that novel combinations will emerge and/or be optimized. Questions around sequencing of epigenetic therapy continue regarding overlapping vs sequential delivery of agents. Novel formulations of HDACi are emerging, such as tenfinostat (CHR-2845 and CHR-2845), mocetinostat, and pracinostat. CHR-2845, a novel monocyte macrophage-targeted HDACi is
cleaved by human carboxylesterase-1, which is an intracellular esterase found only in cells of monocytoid lineage and hepatocytes. Thus, delivery of this agent primarily targets the cells of interest and spares the normal BM reserve.

As noted before, it is essential that novel therapies be identified for MDS patients failing HMT therapy. Rigosertib, an inhibitor of phosphatidylinositol 3-kinase and polo-like kinase was evaluated in a phase 3 study (ONTIME), where patients with high-risk MDS after failure of HMT were randomized in a 2:1 fashion to rigosertib or BSC. Unfortunately, rigosertib did not significantly improve OS compared with BSC after a median follow-up of 19.5 months. For patients receiving rigosertib, median OS was 8.2 months and 5.9 months in the BSC arm. Another clinical trial with this same agent is underway in specific subgroups of MDS patients deemed to be high risk (ie, high blasts % and other predefined high-risk populations such as HMT never-responders) (Table 1).

Not surprisingly, efforts to understand the BM milieu have also provided novel approaches to treat myeloid disorders. Krevvata et al54 posit that osteoblastic cells are decreased in patients with increased myeloid disease burden, and that the malignant myeloid cells destroy the niche components, which contributes to the suppression of normal hematopoiesis. They suggest that future work should be focused on additional manipulation of the tumor’s stromal environment, with agents such as abexinostat.55 Other broadly targeted agents that are only available to patients on a clinical trial include the anti–CD33-directed therapies (SGN-CD33a, TandAbs)56,57 and anti-angiogenic agents (Oxi4503),58 which are promising.

If reprogramming of the immune system by a BMT is not plausible, then using checkpoint inhibitors to modify the host’s immune response is another therapeutic strategy. Immunologic tolerance to cancer has major implications for the ability of MDS to persist despite a variety of therapies. Tumor cells can block immune checkpoints through the expression of proteins that interfere with normal immune effector function. Increased relative expression of PD-L1 was found in 124 samples from patients with myeloid neoplasms (MDS/AML/chronic myelomonocytic leukemia) with greater increments in gene expression in patients who were clinical nonresponders to HMT. Notably, in vitro treatment of KG1 and THP1 leukemia cell lines with DAC resulted in a dose-dependent upregulation of these same checkpoint genes and this was not appreciated with cytarabine (Ara-C). Work from Meldi et al also suggests

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CDAi, CDA inhibitor; CTLA-4, T-lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; LSD-1, lysine-specific demethylase 1; MOA, mechanism of action; MPN, myeloproliferative neoplasm; PDH, pyruvate dehydrogenase; PLK-1, polo-like kinase 1.
that patients with chronic myelomonocytic leukemia who are non-responders to HMT have upregulation of CXCL4, CXCL7, and integrin B3.14 It remains to be seen whether upregulation of these genes can be modified by combination therapy using immune blockade plus HMA-directed therapy. The addition of PD-1 and PD-L1 inhibition to chemotherapy (cytotoxic and/or epigenetic-based) is investigational, and several prospective clinical trials with monotherapy and combination therapy (ie, pembrolizumab, nivolumab, ipilimumab, etc) are ongoing (Table 1). Determination of efficacy of these agents, as well as the interplay of immune regulation and pathogenesis of MDS, will be paramount in understanding and optimizing these therapies. Another means to disrupt the effector T-cell function and proliferation in the BM environment can be caused directly by myeloid-derived suppressor cells (MDSCs), which are found in the marrow parenchyma in MDS patients. Expansion of the MDSC population correlates with progression of MDS.59-61 Targeting of MDSCs to improve the immune function of the MDS patients can be performed with novel approaches (ie, by natural killer cells activated by a CD16xCD33 bispecific killer engager).62

Our understanding of the dynamic nature of the molecular profile in the progression of MDS remains challenging and its elucidation is currently costly (both time-intensive and financially prohibitive). The importance of molecular mutational data (pre-/post-therapy and at relapse) may inform patterns of upfront resistance to chemotherapy (vs sensitivity to therapy) or if one therapy is superior to another (or best if given in advance of another agent). Molecular mutation profiling will hopefully appraise data regarding driver mutations and ultimate progression of disease (clonal evolution). It is possible that in the future these molecular data may contribute to the essence of rational sequencing of therapy for MDS patients, but we are not currently able to make these determinations.

Given the complexity of data that is provided with mutational analyses, it is not uncommon for multiple coactive deregulated pathways to occur, and this can lead to confusion about best design and testing of a novel agent (ie, which patient is the best suited for therapy and what end points are optimal). Isolation of specific populations for testing “targeted” therapies may under (or over) estimate their true efficacy and benefit. It is conceivable that some of these novel agents might need to be combined and innovative clinical trial designs might be transformative. For example, if an MDS patient’s myeloid sample harbors a mutation in TET2, the patient has an increased likelihood of responding to HMT and patients who harbor isocitrate dehydrogenase (IDH) mutations have a higher likelihood of benefit from targeted therapy (ie, AG-120 and AG-221) with IDH1/2 inhibitors that block cellular metabolism. Other possible actionable mutations are those genes mutated around the spliceosomal machinery such as SRSF2 and SF3B1, where novel inhibitors are being introduced into clinical trials. Understanding the clonal architecture of myeloid neoplasms at dynamic times in disease progression will help direct rationally designed approaches to therapy. It may be that myeloid disorders that harbor mutations with IDH1/2 may respond best upfront to IDH1/2 inhibitors (or BCL2 inhibitors) and EVI1-mutated lesions will respond to BET inhibitors. These targeted agents may be able to eliminate one clone, but if it is only a subclone and not the founder clone then the effectiveness of these agents is limited. Future clinical trials will likely need to focus on what clones are eradicated and how the epigenetic machinery (chromatin and methylome) dictates response/nonresponse.65

If optimization of epigenetic therapy does not result in acceptable treatment outcomes, another option for MDS patients failing HMT is to escalate to an intensive induction chemotherapy approach (ie, “7+3” with cytarabine and an anthracycline, single-agent cytarabine at high/intermediate dosing, or single-agent clofarabine or fludarabine),66-68 as a bridge to HSCT as if treating de novo AML. Prébet et al12 evaluated 435 MDS patients who failed HMT and information collected on chemotherapy given after 5AC failure was available in 270 patients. Poor outcome was seen in those who received low-dose chemotherapy (N = 32) with a 0% response rate and median survival of 7.3 months. For the 35 patients treated with intensive chemotherapy (IC), the ORR was 14% and median survival was 8.9 months. There was no statistical difference in survival between the 2 groups, although the patients treated with IC had a better outcome than those treated with BSC. As previously noted, for those patients who underwent a clinical trial, the median OS was 13 months, which was statistically better than each of the other arms (BSC, low-dose chemotherapy, and IC). Several regimens have been used in MDS patients progressing despite HMT and which regimen is optimal is unclear, and is often guided by present comorbidities and if transition to an HSCT is actually timely and feasible. Because patients with MDS have a median age of >65 years, the risk-benefit ratio of HSCT remains questionable due to the high frailty index, ongoing comorbidities, and high-risk karyotypes (complex cytogenetics), which predict for resistance. However, for some patients HSCT is a viable, curable, and meaningful option. Feasibility of HSCT is often limited by proximity to a qualified cancer center that can offer alternative transplant options such as reduced-intensity or haplo-identical HSCT. In the Prébet study noted earlier, 37 patients proceeded to HSCT with allogeneic SCT and the median OS was 19 months. Again, for those MDS patients with progression and an active plan to move forth with HSCT, the best pretransplant regimen is not well established,69 and preferences for chemotherapy can depend on type of transplant, timing of transplant, and hospital center performing the HSCT.

In conclusion, we are still working on optimizing the delivery of HMT by dosing appropriately, sequencing appropriately, and using thoughtful combinations; as well as improving drug formulations (oral formulations and/or novel formulations) and working toward better selection of patients for best upfront mutation-directed therapy. Hopefully, with improvement in our understanding of the mechanisms of action (and resistance) of these agents, we will improve drug targeting and patient selection for optimal HMT treatment of MDS. Furthermore, ongoing research is focused on identifying unique agents to rescue MDS patients who have progressed despite HMT. Agents such as rigosertib are now focused on its application in specific MDS populations who might most likely benefit from this therapeutic approach (primary refractory and high-risk IPSS patients). Given the significant progress to overcome immune evasion in solid tumor malignancies, we eagerly await results of single-agent PDL-1 and PD-1 inhibitors, or combination with HMT to the upfront and relapsed MDS setting. For the minority of patients who have specific targetable mutations, there are selective agents (IDH1/2) that are highly promising. BMT remains the only offer for cure, but is depressingly unrealistic given the majority of the elderly and frail patients at the time of MDS progression.

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