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HYPOMETHYLATING AGENTS (HMA) TREATMENT FOR MYELODYSPLASTIC SYNDROMES: ALTERNATIVES IN THE FRONTLINE AND RELAPSE SETTINGS

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Abstract

Introduction—Hypomethylating agents (HMA) have played a pivotal role for treating myelodysplastic syndromes (MDS) over the past decade, inducing sustained hematological responses and delaying progression to leukemia. However, a vast majority of patients will experience treatment failure within 2 years, with poor prognoses and limited options, and management of this growing patient population remains unclear.

Areas Covered—With the introduction of new agents in the MDS field, a better understanding of the biology of MDS, and updated information on standard of care options (including allogeneic transplantation), we re-evaluate the global treatment strategy in MDS via novel agents, focusing in particular on investigational approaches for patients who fail to respond to HMA when applicable. This review aims to address two questions: what are reasonable alternatives to HMA in MDS, and what strategies can be used for patients experiencing HMA failure.

Expert Opinion/Commentary—HMA therapy remains a mainstay of treatment, even if additional research is still warranted to maximize its benefits for the different groups of patients. The outcome of patients experiencing HMA failure remains grim, without standard of care, but

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several new approaches seem promising, as there is an increasing focus on studying treatments for patients refractory to HMA treatment.

Keywords

Disease Management; epigenetic modification; hypomethylating agents; hypomethylating agent failure; IPSS; investigational agents; myelodysplastic syndrome; treatment failure

1. Introduction

Myelodysplastic syndromes (MDS) are hematopoietic disorders featuring clonal defective hematopoiesis and peripheral blood cytopenias. The clonal process is thought to develop from a single transformed hematopoietic progenitor cell, acquiring multiple mutations resulting in dysplasia, ineffective hematopoiesis, and ultimately progression to acute myeloid leukemia (AML) with myelodysplastic related changes [1, 2, 3]. The pathogenesis of MDS is incompletely understood; it may occur de novo or arise after chemotherapy, environmental exposures to toxins or radiation; like most malignancies, it involves the stepwise acquisition of oncogenic driver mutations. These mutations may be clonal or sub-clonal and affect several distinct cellular processes including splicing machinery (SF3B1, SRSF2, U2AF1, and others), epigenetic regulation (TET2, DNMT3A, IDH1/2, ASXL1, and others), apoptosis (TP53), or cell proliferation (RAS)[3].

In addition to DNA mutations, aberrant DNA methylation (including global DNA hypomethylation as well as hypermethylation of cell regulatory genes) represent hallmarks of cancer genetic changes [4]. Methylation of cytosine in DNA at C-5 of CpG base pairs catalyzed by 3 major DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) is the most abundant epigenetic modification altering gene expression [4]. The reversible nature of DNA methylation provides an opportunity for DNA hypomethylating agents (HMA) to re-express genes silenced by promoter methylation. 5-azacytidine (azacitidine) and 5-aza-2′-deoxycytidine (decitabine)are the 2 registered HMA used worldwide, including in the US, Brazil, and Korea. They are cytidine analogs that inactivate DNMT-1 to demethylate DNA;decitabine is incorporated only into DNA while azacitidine is incorporated into the RNA as well as DNA in a 2:1 ratio in a cell cycle dependent manner [5]. Low doses of azacitidine or decitabine induce re-expression of previously silenced genes by degrading previously formed adducts between DNA and DNMT-1, after which DNA synthesis resumes in the absence of DNMT-1. Thus, aberrant DNA methylation patterns can no longer be reproduced in the daughter strands [4]. Modification of DNA methylation is believed to alter gene expression, leading to cellular apoptosis in abnormal hematopoietic cells, although the methylation status of specific genes does not guarantee HMA response [3]. Few studies have highlighted distinctions of azacitidine and decitabine as non-equivalent agents due to their distinct effects on cell viability, protein synthesis, cell cycle and gene expression profiles in malignant clones [6, 7]. Mechanisms that may explain differences in their clinical activities have not yet been clearly defined, notably, the potential additional mechanisms of azacitidine activity mediated via incorporation into newly synthesized RNA, including rRNAs, tRNAs, mRNAs, and miRNAs [5]. This non-equivalency due to their distinct effects on gene expression profiles in malignant cells may explain differences in overall survival

rates with azacitidine and decitabine, despite similar overall response rates in phase 3 RCTs [8, 9].

Nonetheless, these HMA are able to trigger sustained improvement of cytopenias in 40% of treated MDS patientsand delay progression to acute myeloid leukemia (AML) in intermediate-2 and high risk MDS patients [9, 10]. Azacitidine, shown to improve overall survival in higher risk patients compared to conventional care [8], is the only approved HMA in Europe, and hence accounts for its more widespread use than decitabine [11, 12]. No direct comparison from clinical trials on azacitidine and decitabine in MDS patients has shown differences in survival although data is lacking; both are accepted as the standard first line treatment [13]. Unfortunately, only 40–50% of patients respond to HMA treatment; complete response is lower at a mere 10–20%. Among clinical responders, the majority will experience loss of response and disease progression, with mean duration of response of 11–15 months [13, 14, 15]. A large number of investigational agents are currently combined with HMA and investigated in clinical trials, but to date none has demonstrated improvements in outcome [16]. Following HMA failure, patients have poor prognosis and limited options [17], and there is no consensus on how to manage this patient population [18].

In summary, HMA, which have been registered for a decade, represent an important, but not optimal, standard of care for MDS patients. In the present article, we address alternatives to HMA as frontline treatment investigated in clinical trials, potential second line therapy after failure of HMA, and highlight future areas of research.

2. Risk stratification and outcome prognostication

The heterogeneous natural history of MDS patients reflects differences in the pathobiology of disease specific factors and patient related characteristics. A number of prognostic models have been developed to risk stratify patients with MDS such as the International Prognostic Scoring System (IPSS) [19], World Health Organization classification-based Prognostic Scoring System [20], MD Anderson Prognostic Scoring System [21] and the revised IPSS (IPSS-R) [2]. These take into account variables such as age and sex, morphologic features, blast percentage, clinical characteristics, cytopenias, transfusion requirements, and cytogenetic abnormalities. These models are prognostic tools at diagnosis when used for de novo disease or when patients have not undergone a single line of therapy. However, this does not reflect treatment approaches for the majority of MDS patients in the era of modern therapy, particularly as molecular abnormalities are increasingly identified and used for prognosis and treatment determination [3, 22]. Additionally, none of the aforementioned scoring systems address patient related factors such as comorbidities, which have a significant independent impact on survival and prognostic scores [12, 23]. Hence, the integration of these factors (comorbidities and genetic defects) into existing classification and scoring systems will provide a more accurate prediction of prognosis [24].

Altogether, the general approach is to dichotomize MDS patients into two main categories defined by the risk of progression to AML and consequently overall survival. Lower risk patients have more indolent disease characterized by prolonged survival, lower risk of AML

progression, and often chronic transfusion dependence. Transfusion dependence strongly influences outcome and quality of life in this group of patients; the treatment goals are to correct the cytopenias. In the higher risk population, the majority of patients progress to AML within 2 to 3 years, and survival is shorter. The treatments are more aggressive, overlapping with approaches used in AML, and aim to delay progression and improve overall survival. Finally, it is important to keep in mind that all of the registered medications, including HMA, have been developed using the first generation IPSS as the inclusion or stratification factor, and that the application of new prognostication tools influences the expected results of treatment groups.

3. Alternatives in the frontline and relapse settings in lower-risk MDS

In lower risk MDS patients (Revised IPSS very low, low or intermediate), the therapeutic goals are treatment of cytopenias (predominantly anemia), improving quality of life, and minimizing treatment toxicities and transfusion burden. Several treatment options are already available, and many new agents are currently investigated (Table 1). While there is no consensus on optimum treatment, evidence suggests that a more personalized approach, carefully choosing the most appropriate frontline treatment and the sequence of subsequent therapies, can impact outcomes.

3.1. Frontline treatment

Since anemia is the primary challenge in MDS, erythrocyte stimulating agents (ESA) are generally the first line therapy recommended by international guidelines [25, 26] for symptomatic MDS patients with low serum EPO levels (≤500 mU/mL). While many patients respond to higher doses of ESA [27], the effect is transient for most, with a mean duration of 18 to 24 months [28]. Early failure to ESA and a baseline diagnosis of refractory anemia with excess blasts are believed to be independent prognostic factors for AML progression. Lower risk patients with early or primary failure to ESA have a relatively unfavorable outcome, including higher risk of progression to AML, and more intensive additional treatments may be considered [29, 30].

In frontline settings, the options for any other treatment seem limited, although there are notable exceptions. In the context of patients harboring isolated del(5q), lenalidomide is remarkably effective in altering the disease natural history. Long term follow-up on the MDS-003 trial demonstrated that OS was improved in RBC-TI (≥ 8 weeks with hemoglobin increase ≥ 1g/dl) responders (4.3 vs 2.0 yrs in nonresponders), in complete responders (4.9 vs 3.1 yrs in non-complete responders), and in isolated del(5q) (3.9 isolated vs 2.7 yrs if additional cytogenetic abnormalities). A trend for progression delay to AML was found patients with any response [31]. Practices differ on the frontline use of lenalidomide vs the initiation of lenalidomide after ESA failure for this group of patients.

3.1.1 Immunosuppression Therapy—In hypoplastic MDS, immunosuppressive therapy (IST) may be considered in patients with select characteristics, notably age <60, low risk MDS, hypocellularity, and HLA-DR15 type [25, 26]. In a randomized phase 3 trial, 13/45 patients on antithymocyte globulin (ATG) + cyclosporine (CSA) had a hematologic response compared with 4/43 patients on best supportive care (BSC); however, there was no

impact on OS (1.9 in ATG+CSA vs 2.8 yrs in BSC) [32]. The combination ATG + tumor necrosis factor receptor inhibitor, Enteracept, was evaluated in a phase 2 trial in low risk patients, in which 13/19 patients had hematological improvement, and 70% of those hematological responses lasted ranging from 5 – 36 months. [33]. Alemtuzumab, the CD52 monoclonal antibody, was evaluated as monotherapy in 32 MDS patients selected for favorable characteristics for IST response; seventeen (77%) intermediate-1 patients and 4 (57%) intermediate-2 patients responded [34].

Altogether, patients with intermediate risk diseases based on revised IPSS, might represent the most accepted indication of frontline HMA among lower risk MDS patients.

3.2 Second line treatment and beyond

Therapies beyond first line for lower risk MDS have been a prolific area of research over the last 5 years. The biggest challenges are determining the drug with the higher probability of response in a specific patient and, on a long-term perspective, what may be the best sequence of treatments. The majority of clinical trials performed so far have been focused on patients experiencing ESA failure; patients previously treated with HMA often are not addressed (Table 1). A study in 438 patients with IPSS low risk (145 patients) and intermediate-1-risk (293 patients) disease following HMA failure found that factors associated with disease progression from lower-risk to higher-risk MDS categories included baseline neutropenia, intermediate-risk and poor-risk baseline, and lack of response to HMAs [35].

3.2.1 Transplantation—Allogeneic transplantation may be considered when feasible [25]. Models have shown that in unselected lower risk MDS patients, the benefits of allogeneic transplantation outweigh risks when transplantation is delayed until disease progression [36, 37]. A retrospective analysis found that lower risk patients have better outcomes than higher risk patients following transplant, with a 3 year OS probability of 58%. Interestingly, a majority of the lower risk patients in this series harbored some high risk features (bone marrow fibrosis, poor prognosis somatic mutations patients), and many were reclassified to a higher risk category using the newer IPSS-R [38].

3.2.2 Non targeted investigational approaches—Although lenalidomide has not been approved by FDA for this indication, its benefit may extend beyond del(5q) patients, as recent studies have shown efficacy in non-del(5q) MDS. In non-del(5q) patients refractory to ESAs, 27% of lenalidomide-treated patients (43 patients) achieved TI compared to 2.5% in a placebo group (2 patients) [39]. In vitro data suggests that lenalidomide stabilizes the EPO-R at the cell membrane leading to potential synergism with ESA [40]. A RCT phase 3 found that HI-E and TI were higher in patient with lenalidomide+ EPO (23.1% and 39.4% respectively) compared with lenalidomidealone (13.8% and 24.2% respectively) [41]. The role of lenalidomide in the context of HMA resistance remains under investigation; a retrospective study suggested that response in lower risk MDS patients treated with lenalidomide followed by HMA is better than azacitidine followed by lenalidomide [11]. Larger retrospective studies show improved OS (mean of 51 months) when HMA was used

after lenalidomide failure [42]. The optimal use and timing of lenalidomide treatment has yet to be evaluated in larger trials.

In patients with ring sideroblasts MDS and/or SF3B1 mutations, the TGF beta family inhibitors (Luspatercept and Sotatercept) seem to be promising alternatives to HMA. TGF beta impacts terminal erythropoiesis, and both drugs are designed as trap proteins (modified activin receptor IIB fused with IgG Fc), inhibiting Smad 2/3 signaling. In a phase 2 study (Phase 2 PACE-MDS Extension Study), patients refractory to ESA were administered Luspatercept once every 3 weeks at dose levels ranging from 0.125 to 1.75 mg/kg. There was a high response rate (48% HI-E) for increasing hemoglobin and decreased transfusion burden, particularly in patients with ring sideroblasts and splicing factor mutations (notably SF3B1) [43]. Patient who received continuous Luspatercept in the extension study had sustained HI-E with a favorable safety profile [44]. Currently, a phase 3 study compares Luspatercept to placebo for treatment of anemia in patients with IPSS-R Very Low-, Low-, or Intermediate-risk MDS and ring sideroblasts who require regular RBC transfusions [45]. Sotatercept has a similar profile but has not been further developed. The data on the use of TGF beta inhibitors after HMA or lenalidomide are limited.

3.2.3 Novel Agents—Many new agents are currently under investigation for lower risk MDS. Ezatiostat is a glutathione analog prodrug glutathione S-transferase P1-1 (GSTP1-1) inhibitor, which promotes hematopoietic progenitor maturation of normal cells and induces apoptosis in malignant cells through the jun-N-terminal kinase/c-Jun pathway. RNA studies have shown that genes in these molecular pathways, known to be activated by ezatiostat, are under-expressed in patients who respond to the drug [46]. In a phase 1 trial with 19 patients, oral ezatiostat led to reductions in transfusions as well as bilineage [HI-E and HI-P (60%), HI-E and HI-N (33%), and HI-N and HI-P (33%)] and trilineage responses (3%); it has been proposed to potentially counter the myelosuppressive side effects of other front line treatments [47]. In the phase 2 trial, ezatiostat again showed transfusion reduction and multilineage responses, but interestingly, also suggested that prior therapy impacted efficacy; lenalidomide and HMA naïve patients achieved 28% (5/18) HI-E rate while a 40% (6/15) HI-E rate was observed in patients with prior lenalidomide but were HMA naïve. Furthermore, prior HMA treatment 34/89 (47%) was associated with increased ezatiostat-related AEs [48].

Imetelstat is a telomerase activity inhibitor; transcriptional regulation of the TERT gene is a rate-limiting determinant of telomerase activity, and high TERT expression is seen in malignant cells. As telomerase has been suggested be associated with higher-risk AML/MDS, methylation of the TERT promoter may be a potential biomarker for high risk AML/MDS [49]. A pilot study of imetelstat treatment in patients with refractory anemia with ring sideroblasts (RARS) or RARS with thrombocytosis (RARS-T) suggests potential efficacy. Three of 8 transfusion-dependent patients became TI, lasting a median of 28 weeks, although response was not as robust as seen in other hematologic diseases such as myelofibrosis [50].

Panobinostat and Belinostat are both class I/II HDACi shown to have antitumor activity in preclinical data. Unfortunately, both had phase 2 studies which were terminated early due to lack of efficacy with 0% ORR in Panobinostat [51] and 5% ORR in Belinostat [52].

CC-486 is an oral version of the azacitidine; prolonged exposure at lower doses via oral formulation is hypothesized to enhance DNA hypomethylation. Patients had a 12/55 (38%) ORR with once daily dosing in extended dosing regimens. Reduced global DNA methylation was associated hematologic response to CC-486, although the relationship needs to be elucidated [53]. A phase 3 RCT comparing oral azacitidine with placebo is currently underway (NCT01566695).

The multi-kinase inhibitor rigosertib (ON 01910.Na), a Ras mimetic that inhibits the phophoinositide 3-kinase and polo-like kinase pathways, induces mitotic arrest and apoptosis in myeloblasts while sparing normal cells. Both IV and oral rigosertib suppress bone marrow blasts without causing severe myelosuppression, which is particularly beneficial in the MDS population [54]. A phase 1 study in predominantly lower risk MDS patients, most with HMA failure, showed some improvement in this population with 4/12 reaching TI, and 1/12 with HI-E, 2/15 with HI-N, and 2/26 with HI-plt [54]. An abstract for a phase 2 study dosing rigosertib showed 15/33 achieving TI with median duration of 17 weeks, nearly all responders taking ESA concomitantly, suggesting potential synergy over the effects of ESA alone. As DNA hypermethylation was associated with rigosertib response, genomics may possibly preselect patients in the future [55].

Oral ARRY-614 is a novel oral dual inhibitor of the p38 MAPK/Tie2 signal pathways studied in inflammation models. A phase 1 trial in lower risk MDS, majority treated with HMA prior, found responses in 14/44 patients. Interestingly, of the 14 who responded, 13 had been treated previously with an HMA, suggesting interactions between ARRY-614 and HMA therapy [56].

4. Alternatives in the frontline and relapse settingsin higher-risk disease

The natural history of higher risk MDS is dominated by increasingly severe bone marrow failure that translates in short survival with median survival of 12 to 18 months. The goal of treatments, current and those under investigation (Table 2), is therefore to alter the natural disease course and to provide hematological improvements.

4.1. Frontline treatment

Allogeneic hematopoietic stem cell transplantation (AlloSCT) remains the only curative option but is associated with a significant mortality and morbidity in an elderly population such as MDS. In the context of higher risk MDS, transplantation should be considered at diagnosis; based on Markov models, early transplantation in higher-risk MDS has been associated with longer survival both in myeloablative and RIC treatment [12, 57]. In the absence of a significant excess of bone marrow blasts, alloSCT may be considered as an upfront treatment, but this represents a small group of patients. The majority of transplant-eligible patients need some degree of cytoreduction before alloSCT, as excess of blasts before transplant has been reported as a major risk factor for relapse [12]. The threshold

varies based on conditioning regimen and from one institution to the other, but a commonly accepted, though arbitrary, bone marrow blast limit is 10%.

Although prospective data is lacking, most guidelines recommend cytoreductive therapy before alloSCT (so called “bridge to transplant.”). Studies have demonstrated that the outcomes of MDS patients after alloSCT with various bridging therapies (i.e. HMA vs intensive chemotherapy) are similar [58]; choices for bridging therapy may involve compromises between optimal cytoreduction and minimal treatment-induced toxicity which may interfere with alloSCT. Based on data with both azacitidine and decitabine [59, 60], patients with complex cytogenetics should proceed with HMA while for patients with non-complex cytogenetics, the decision must integrate the morbidity and mortality risk of induction therapy.

Based on our current knowledge, there is no other active treatment that represent a valid alternative to HMA for those not eligible for transplant. However, several currently investigational drugs may represent a valid alternative in the future, for instance IDH inhibitors or new HMA such as SGI-110. Most of the current efforts are focused on optimizing treatment while using HMA as a backbone of combination therapy [16].

4.2. Second line treatment and beyond

Once MDS patients are refractory to HMA, the outcome is dismal with median survival of 6 months after azacitidine failure [17] and a median survival of 4 months after decitabine failure [35]. Clinically, risk factors for worse survival include age, male sex, high-risk cytogenetics, higher blast count, and lack of prior response to azacitidine [17, 61]. Eligible patients may attempt transplant; however, many patients are not candidates due to comorbidities and poor performance status. Trials are difficult since HMA refractory patients are a challenging population, and selecting the optimal next line options remains undetermined [13].

4.2.1 Conventional treatments—Second-line intensive chemotherapy, although often limited by toxicities, can reduce disease burden and serve as a bridge to alloSCT. A large retrospective, multicenter study evaluated 366 patients after HMA failure, whose treatments include 7+3, IDAC, or a nucleoside based regimen. The ORR to chemo was 39.6%; 8-week mortality was 7.9%, and the median OS was 10 months. Unfortunately, the relapse rate was 50% at 1 year and 71% at 2 years. No chemotherapy was superior or more toxic; so while chemotherapy after HMA failure is a valid option, overall outcome remains poor [62].

In patients unable to tolerate intensive chemotherapy, sequential use of the alternative HMA after initial HMA failure (i.e. azacitidine followed by decitabine) has had questionable efficacy, with minimal results and no clear effect on OS [63][64, 65]. Of note, trials using the new generation of HMA like guadecitabine (SGI-110), which have a longer half-life, are ongoing [66] (NCT02907359).

4.2.2 Targeted approaches—Given lenalidomide’s efficacy in lower risk del(5q) patients, it was hypothesized to also be active in del(5q) patients after HMA failure. Lenalidomide treatment for patients after azacitidine failure has been studied retrospectively

with 10 patients; four patients responded, with 3 achieving a CR [all had del(5q)], and 1 a major HI-E in a patient with trisomy 8 for a median response duration was 6 months [67]. A phase 2 study on lenalidomide in higher risk MDS with del(5q) patients (some pre-treated, though none with HMA prior) had an ORR of 14/47 (27%), and OS was 560 days for those with hematologic response and not reached for those with CR. In patients with additional chromosomal abnormalities, response rate was only 7/38 (18%), most of very short duration with rapid progression; median survival was only 5.5 months in this subgroup [68]. A phase 2 study on lenalidomide in relapsed/refractory AML and high-risk MDS with del(5q) found limited clinical efficacy. Out of 9 MDS patients, 2 had stable disease at best, and lenalidomide did not have responses any AML or MDS patients with complex cytogenetics [69]. Lenalidomide in studies evaluating patients in general, beyond del(5q), has not been as efficacious when given as salvage therapy vs upfront, often because of side effects are prohibitive for continuing treatment [70, 71].

In the subset of patients harboring IDH mutations, there is a relatively paucity of data on the impact of IDH inhibitors, particularly the first in class AG221 and AG120. For patients with IDH2 mutation, AG221 triggered responses in 8/16 (50%) patients based on the ASH 2016 presentation [72]. Half of the overall responses were hematologic improvement, and little is known on response duration. Of the 10 evaluable patients previously treated with HMA, 50% responded, including 1 CR [72]. Other IDH targeted agents are currently developed in these settings. IDH305 is an oral mutant-selective, allosteric IDH1 inhibitor that suppresses mutant IDH1-dependent 2-HG production and cell proliferation, and has antitumor activity in preclinical studies. A phase 1 abstract on multiple types of malignancies, including refractory AML and MDS, with IDH1R132 mutations only had 3 MDS patients; the drug had a favorable safety profile and potential activity in AML with responses in 7/21 (33%) [73].

4.2.3 Non targeted investigational approaches

4.2.3.1 Histone deacetylase inhibitors (HADCi): HDACi result in hyperacetylation of histones, and its functions include modulating the immune system, cell differentiation, cell cycle arrest, apoptosis, and tumorigenesis [74]. HMA have been frequently studied in combination with a HDACi, which includes entinostat (SNDX275), vorinostat (SAHA), belinostat (PDX101), panobinostat (LBH589), mocetinostat (MGCD0103), and pracinostat (SB939). Efficacy of these combinations has not shown improvement over HMA monotherapy in initial treatment studies, and studies of this class on patients with HMA failure are limited [13]. Combination therapies with HMA are reviewed by Ball, et al [16]. In a phase 1 trial, 40 refractory higher risk MDS patients (nearly all after azacitidine failure) were treated with a cytarabine and vorinostat combination with an ORR of 15% [75]. Abexinostat was evaluated in 17 relapsed MDS, AML, ALL patients in a phase 1 study, but all 17 withdrew due to disease progression or adverse effects. Despite promising potential in preclinical studies, it was found to have no clinical benefit as monotherapy [76]. Of note, add-on strategies (adding an HDAC inhibitor while continuing HMA in a patient with no response or a loss of response) are currently being investigated [77]. Overall, efficacy from either monotherapy or combination therapy has been limited, and the pleiotropic effects of HDACi makes it difficult to determine the biological consequences of HDAC inhibition [74].

4.2.3.2 Nucleoside analogues: Clofarabine is a second generation purine nucleoside analogue that inhibits ribonucleotide reductase, is incorporated into DNA, and induces apoptosis [78]. In 32 patients, oral clofarabine achieved a response rate of 43% in patients with higher-risk MDS, with median OS of 9.2 months; lower doses were better tolerated without significant differences in response [79]. A phase 2 trial administered low dose clofarabine to 10 patients ranging from low to high risk MDS who were 5-azacytidine-refractory. Four out of 10 patients responded (1 CR, 1 PR, and 2 HI); all responders had low risk disease [80]. A phase 1 trial studying low-dose oral clofarabine (1mg po daily for 7 days) in 9 higher risk patients who had not responded to first line therapy demonstrated responses in 3 patients (2 with responses lasting up to 21 and 51 cycles) [78].

Clofarabine has also been studied in combination with chemotherapeutic agents. A phase 2 study looked at low-dose clofarabine and cytarabine in 70 higher risk MDS patients that relapsed after HMA. The ORR was 44%, with median OS of 22 months for responders, and 10 months for the cohort. Thirteen percent of the patients underwent allogeneic stem cell transplantation, suggesting this may be an option as a bridging therapy [81]. Similarly, out of 84 patients treated with clofarabine +/− cytarabine combination for relapsed or refractory AML or MDS, 12 patients who were able to undergo transplantation had an 18-month median survival [82]. A review on 84 patients treated with clofarabine for relapsed or refractory AML or MDS, either with clofarabine as monotherapy (n=19) or in combination with cytarabine (n=65) argued that clofarabine's efficacy in a "real-world" setting is lower than reported in clinical trials, with a median survival of 3 months and a high early mortality rate (30-day mortality of 21%) [82].

Sapacitibine, an oral nucleoside analogue that is converted into CNDAC, which creates single-stranded DNA breaks which then converts into double stranded DNA breaks after replication, inducing G2 cell cycle arrest [83]. A phase 1 trial found sapacitibine to have a favorable safety profile with 13/47 (28%) ORR in a cohort of mostly pretreated AML, ALL, and MDS [83]. A phase 2 sapacitibine dosing study had a 14% (9/63) ORR (2 CR, 2 CRp, and 5 HI), with 21 patients achieving stable disease lasting longer than 16 weeks. Median OS was 8.6 months, and clinical activity was noted in all three dosing schedules[84]. A more recent phase 2 abstract enrolled 60 higher risk MDS patients had ORR of 13% (1 CR, 8 HI-E) and found the most effective dosing so far to be 300mg BID ×7 days, although data analysis was still in process [85].

4.2.3.3 Kinase inhibitors: Rigosertib has been studied in higher risk MDS populations specifically, in the context of its use as a next agent after HMA. A series of phase 1–2 studies on IV rigosertib found a favorable safety profile and activity in patients after HMA failure. Early BM response was suggested as a biomarker of rigosertib activity predicting survival [86]. The most comprehensive study was a phase 3 RCT with 299 patients testing rigosertib vs conventional care. However, rigosertib did not significantly improve OS (median OS = 8.2 months in the rigosertib group vs 5.9 months in BSC). There was no CR or PR in the rigosertib group, nor was there a significant difference in improvement in platelets, neutrophils, or RBC. Analysis suggested a potential survival benefit in several subgroups, including patients with monosomy 7 or trisomy 8, patients younger than 75 years, patients with primary HMA failure (vs secondary failure), and patients who received

< 9 months of prior HMA [87]. A randomized phase 3 trial of rigosertib is underway in patients with HMA failure with very high risk features (NCT02562443).

Erlotinib is an oral EGFR inhibitor approved in lung and pancreatic cancers which has been studied in higher risk MDS and AML. Interestingly, erlotinib ex vivo studies have demonstrated an antineoplastic activity on MDS and AML cells, causing a proapoptotic effect even in EGFR-negative cell lines due to inhibitory effects on JAK2 [88]. Case reports in patients with concurrent non-small cell lung cancer and AML or MDS treated with erlitonib demonstrated some activity against hematologic malignancies [89]. In a phase 1/2 trial, 30 patients (18 MDS and 12 AML) with azacitidine failure received 100mg/day or 150mg/day of Erlotinib orally. Response was observed in 6 patients including 1 CR, 1 mCR and 4 HI. Median duration of response was 5 months. Median OS for responders was 12.3 months compared with the cohort's median OS of 7 months [90]. In another phase 2 trial, 35 MDS patients who failed HMA (76% higher risk) received erlotinib; ORR was 14% (3 patients having mCR and 2 HI-E) and OS for the entire cohort was 6.8 months. Survival was greatest in responding patients (16.5 months) less in patients with stable disease (7.1 months), and least in patients with progressive or inevaluable disease (5 months) [89].

The oral multi-kinase inhibitor dasatinib has efficacy against a broad range of tyrosine kinases, including SFKs, BCR-ABL, cKIT, platelet-derived growth factor receptor, and EphA; SFKs, in particular Lyn kinase, have been implicated in myeloblast proliferation [91]. A phase 2 trial evaluated 18 higher risk MDS, CMML, or transformed AML patients with azanucleoside failure; 3/18 responded, two of which had mCR but no HI-E, and one proceeded to alloSCT. The 7 patients who either responded or maintained stable disease had better OS (28.5 months) compared to the 11 who progressed (4 months), and median OS of the whole cohort was 7.6 months. The trial was terminated early, as there was no HI-E even among "responders" [91]. Given the increased phosphorylation in SFK's, dasatinib was thought to block proliferative response of myeloid leukemia cells, but studies have shown limited activity so far.

4.2.3.4 Immunotherapy: The new generation of immunotherapy has been much less studied in hematologic malignancies compared to solid tumors. Studies have demonstrated PD-1, PD-L1 and CTLA-4 upregulation in MDS CD34+ cells in context with loss of response to HMA [92] A phase I trial on Ipilimumab (Ipi) found limited efficacy after HMA failure, with best response being mCR in 2/29 (7%) although 5/29 (17%) subsequently underwent alloSCT [93]. Preliminary results of a phase 2 study on Nivolumab (Nivo) and Ipi, monoclonal antibodies targeting PD-1 and CTLA-4 respectively, suggest a favorable safety profile with Nivo and azacitidine in HMA naïve higher-risk MDS. In patients with HMA failure, Ipi monotherapy induced some response in 2/9 (22%); however, Nivo monotherapy did not show clinical activity [94]. Ongoing clinical trial include Durvalumab (Durva, or MEDI4736) in combination with azacitidine and tremelimumab, (NCT02117219), CC-486 with Durva (NCT02281084), and azaditidine and Durva in untreated high risk MDS (NCT02775903).

5. CONCLUSION

HMA therapy had been a major breakthrough for MDS management; however, the majority of patients eventually relapse over the course of 2 years, with poor prognosis and limited options. With better understanding of the biologic mechanisms underlying MDS, improved standard of care options, and more data on patient outcomes, the current approach for low and high risk MDS patients is evolving, as reflected by more recent guidelines and clinical trials on investigational agents targeting molecular pathways involved in the disease pathogenesis [15].

Once limited, the therapeutic options in lower risk MDS are now more developed, and the use of HMA frontline may be limited to a smaller group of patients with more aggressive presentation. HMA therapy remains one of the most commonly agents used in second line treatment in the absence of validated biomarkers. Selected studies on lower risk MDS HMA alternatives, including drugs for targeted mutations (lenalidomide and TGF beta inhibitors), and novel agents (ezatiostat, imetelstat, HDACi, oral azacitidine, and rigosertib), are listed in Table 1. In higher risk disease, HMA and HMA based combinations are the gold standard. Alternatives after HMA failure in patients not eligible for AlloSCT are limited and participation in clinical trials is strongly encouraged [14]. Different approaches under investigation include chemotherapy, sequential additional HMA agents, novel HMA agents (CC-486 and guadecitabine), and drugs for targeted mutations (lenalidomide and IDH2 inhibitors). There are a growing number of non-targeted investigational approaches, such as HDACi, nucleoside analogues (clofarabine and sapacitibine), and kinase inhibitors (rigosertib, erlotinib, and dasatinib). Selected studies on high risk HMA alternatives are listed in Table 2. While these HMA alternatives offer some potential, much of the data is mixed or preliminary, highlighting a need for further research.

6. EXPERT OPINION

The clinical landscape of MDS had been deeply modified over the last 15 years by the introduction and development of HMA and lenalidomide in patients with del(5q). No new agent has been registered since. Recent years have shown exciting developments that will hopefully lead to the registration of a new wave of agents and optimize the use of HMA in the global long-term strategy of MDS treatment.

One key issue (and remaining challenge) is understanding the biological mechanisms driving HMA response, disease resistance, and ultimately, defining prognostic models validated in lower-risk and higher-risk patients. The classical response criteria (age, adverse cytogenetic, blast count) may only partially apply to HMA therapy. Several groups have also presented potential candidates as prognostic biomarkers, for example, data on HMA metabolism [18] or methylation profile [18, 95], but large scale validation of the prognostic value and accessibility of the techniques remain issues. The impact of mutational spectrum is also debated, with several groups showing that TET2, or DNMT3A mutated patients may have a higher probability of response [96]. More recently it has been shown that mutations such as TP53 do not seem to negatively impair outcome [60]. The above mentioned study also illustrates an important point of actual debate: the optimal regimen of HMA. In the

contribution of Welch and colleagues, decitabine has been given over a 10-day schedule, which is hypothesized as one of the factors that favorably influenced the outcome and made a difference as compared to prior negative studies. The E1905 clinical trial [97] showed similarly that 10 days of AZA may allow a higher rate of hematologic normalization. In contrast, the MDS consortium described surprisingly good results of low dose decitabine (3 days) in the context of lower-risk disease [98]. Another challenge is the optimization of HMA through combination strategies. Until now, we lack evidence in any randomized study that combination arms are doing better. Overlapping toxicities [99] and potential pharmacodynamics antagonism [100] are possible explanations for lack of success so far. Again, a better clinical/molecular definition of the target population may improve results of combinations. As an example, in AML patients with IDH or FLT3 mutations, combinations studies of HMA+ specific inhibitors are currently investigated (NCT02752035) and may improve the results of the single agent treatments. Similarly, developing agents that can be effective on non-cycling MDS cells, like presumably most of MDS initiating cells, will allow to overcome one of the major caveat of HMA therapy. So far, we did not have significant positive clinical signal from these approaches (hedgehog targeting and others) but a newer generation of agents, such as IL3-R targeted antibodies, is currently under investigation. At the other end of the spectrum, the development of checkpoint blockade inhibitors alone or in combination may represent a new hope, in particular, in patients that do not present any actionable mutation. Phase 1 data had just been presented last year, and it remains to be confirmed if the potential of these agents is as promising as it is in solid tumors [93, 94].

Overall, we cannot rely today on a “one-size-fits-all” approach for MDS management and we should not consider as a dogma that HMA is the only way in either lower risk or higher risk settings. Conventional approaches should not be considered as completely obsolete but could be applied carefully in selected population of patients (IST, induction chemo, allo). In parallel, the new generation of investigational agents, built on our more comprehensive knowledge of the disease, offer new avenues of treatment, particularly in second line of treatment. The choice of treatment may be facilitated by validated biomarkers (SF3B1 mutation and Luspatercept), but this is only a minority of cases. The question is not only to develop new options, but also to better define how to use them by a comprehensive evaluation of responses in new agents.

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ARTICLE HIGHLIGHTS

- HMA therapy has been a major breakthrough for MDS management; however, the majority of patients eventually relapse over the course of 2 years, with poor prognosis and limited options
- With better understanding of the biologic mechanism of MDS and improved standard of care options, including transplant, along with the development of novel agents, the current approach for low and high risk MDS patients is being re-evaluated as seen with new scoring systems.
- HMA alternatives for lower and higher risk MDS patients include current therapy, such as transplantation, chemotherapy, immunosuppression, and alternative HMA agents, as well as a growing number of both targeted and non-targeted investigational approaches.
- Recent years have shown exciting developments as we optimize dosage, sequence of agents, and combination therapies with current and emerging drugs that, in the future, may serve as frontline alternatives to HMA or second-line line therapy after HMA failure.

TABLE 1

Selected clinical trials on HMA alternatives in lower risk MDS populations

Drug	Design	Population	N	Prior HMA failure	ORR	CR	Median OS	author
lenalidomide	phase 2, RCT	lower risk del(5q)	148	0	97/148 (65.5%) RBC TI	40/88 (60.3%) CyR and 23/88 (26.1%) pCyR	4.3 years (RBC-TI responders)	[30]
lenolidomide	phase 3, RCT	lower risk non-del(5q) MDS	239	0	43/160 (26.9%) RBC TI; 57/160 (36.5%) HI-E	9/27 (33.3%) CyR	NR	[35]
lenolidomide +/− EPO	phase 3, RCT	lower risk non-del(5q) MDS	131	0	HI-E: 15/65 (23.1%) Len vs 26/66 (39.4%) Len+EPO TI: 9/65 (13.8%) Len vs 16/66 (24.2%) Len+EPO	0	NR	[37]
luspatercept	phase 2	lower risk MDS refractory to ESA (83% RS+)	58	0	48% (19/40) HI-E, HI-N 4/8 (50%) patients	NR	NR	[39]
ezaziostat	phase 2	lower risk MDS	89	34 (47%)	overall HI-E rate 13/75 (17%), 6/15 (40%) HI-E rate HMA naïve, 5/18 (28%) HI-E rate Len and HMA naïve	1/28 (3%) CyR (del5q)	NR	[43]
imetelstat	pilot	RARS-T (5), RARS (3) or MDS/MPN with spliceosome mutation (1)	9	NR	3/8 (38%) TI	NR	NR	[44]
panobinostat (LBH589)	phase 2	lower risk, del(5q) (5)	34	NR	0	NR	NR	[45]
belinostat	phase 2	lower risk (14) and higher risk (7) MDS	21	7 (33%)	1/21 (5%)	0	17.9 months	[46]
oral azacitidine	phase 2	lower risk MDS	55	0	21/55 (38%), 17/55 (31%) HI-any	1/12 (8%) CR 3/12 (25%) mCR	NR	[47]
oral rigosertib	phase 2	lower risk MDS	33	NR	17/48 (35%)	NR	NR	[49]
oral ARRY-614	phase 1	lower risk MDS	45	36 (80%)	14/44 (32%) HI-any	NR	NR	[50]

CR: complete remission; CyR: cytogenetic response; ESA: erythrocyte stimulating agent; HI-E: hematologic improvement-erythroid; mCR: marrow CR; NR: not reported; pCyR: partial cytogenetic response; RBC TI: RBC transfusion independence.

TABLE 2

Selected clinical trials on HMA alternatives in higher risk MDS populations

Drug	Design	Population (n subgroup)	N	Prior HMA failure	ORR	CR	Median OS	author
salvage chemotherapy	retrospective	AML (59), high risk MDS (307)	366	100%	145/336 (39.6%)	145/336 (39.6%) CR+mCR	10.1 months	[56]
decitabine after azacitidine	retrospective	high risk MDS and CMML	36	100%	7/36 (19.4%), including 3 mCR	3/36 (8%) mCR	7.3 months	[57]
decitabine after azacitidine	retrospective	MDS, MPN, AML after azacitidine failure	25	100%	0	0	5.9 months	[59]
guadecitabine	phase 1	AML (74) and MDS (19)	93	100% (MDS)	MDS: 6/19 (32%), including 4 HI	MDS: 2/19 (10%) mCR	282 days MDS	[61]
lenalidomide	retrospective	MDS after aza failure, del(5q)(5)	10	100%	4/10 (40%)	3/10 (30%) CR [all del(5q)]	19.5 months	[62]
lenalidomide	phase 2	higher risk MDS 5q(del)	47	0	13/47 (27%), including 7 CR, 2 mCR, 4 HI-E	4/47 (9%) CR, 3/47 (6%) PR, 2/47 (4%) mCR	560 days (hematologic response) and not reached (CR)	[63]
lenalidomide	phase 2	higher risk MDS (11), del 5q (3), CMML (1)	24	100%	8/24 (33%)	0 CR, 8/24 (33%) mCR	172 days	[65]
lenalidomide	phase 2	relapsed/refractory MDS and AML-TD; no isolated del5q	27	100%	0/9 low dose; 2/18 (11%) high dose	0	114 days, 19% surviving ≥1 year.	[66]
Enasidenib (AG-221) IDH inhibitor	phase 1	relapsed/refractory MDS or poor candidates, higher risk (8)	16	11/16 (69%)	8/15 (53%)	1/9 (11%) CR, 1/9 (11%) PR, 2/9 (22%) mCR	not reached after a median follow-up of 4.7 months	[67]
IDH305 IDH inhibitor	phase 1	relapsed/refractory AML (21) and MDS (3)	81	NR	0 MDS, 7/21 AML	2/21 (10%) CR, 1/21 (10%) iCR, 4/21 (19%) PR	NR	[68]
vorinostat + cyratabine	phase 1	higher risk MDS after azacitidine	40	39/40 (98%)	6/40 (15%), including 2 CR, 3 HI-any, 2 mCR	2 CR, 2 mCR	16.2 months	[69]
abexinostat	phase 1	relapsed/refractory AML (13), MDS (2), ALL (2)	17	NR	0	0	NR	[70]
clofarabine	phase 2	higher risk MDS (22), CMML/AML (8)	32	20/32 (60%)	14/32 (43%), including 8 CR, 3 HI	8/32 (25%) CR	9.2 months	[73]
clofarabine	phase 2	higher risk MDS	10	100%	4/9 (44%), including 1 CR, 1 PR, and 2 HI	1/9 (11%) CR, 1/9 (11%) PR	12 months	[72]
clofarabine + cytarabine	phase 2	higher risk MDS (59)	70	100%	31/70 (44%), including 13	13/70 (19%) CR, 15/70 (21%) mCR, 1/70 (1%) PR	22 months (responders)	[74]

Drug	Design	Population (n subgroup)	N	Prior HMA failure	ORR	CR	Median OS	author
					CR, 15 mCR, 1 PR, 2 HI			
sapacitabine	Phase 1	refractory/relapse AML (42), ALL(1), and MDS (4)	47	NR	13/47 (28%)	4/47 (9%) CR, 2/47 (4%) CRp	6 months (per Kaplan Meier curve)	[76]
sapacitibine	phase 2	higher risk MDS	63	100%	9/63 (14%)	2/63 (3%) CR, 2/63 (3%) CRp	8.6 months	[77]
sapacitidine	phase 2	higher risk MDS	60	100%	8/60 (13%), including 1 CR and 8 HI	1/60 (2%) CR	NR	[78]
IV rigosertib	phase 1–2 (pooled)	higher risk MDS (35) after HMA	39	100%	15/39 (39%), including 5 HI-any, 5 mCR, 1 CyR	5/30 (17%) mCR, 1/30 (3%) CyR	35 weeks	[79]
IV rigosertib	phase 3, RCT	higher risk MDS after HMA	299	100%	rigosertib: HI-plt 5/199 (3%), HI-E 4/199 (2%)	0 CR, 0 PR, 39/199 (20%) mCR rigosertib vs 14/100 (14%) mCR BSC	8.2 months rigosertib vs 5.9 months BSC	[80]
erlotinib	phase 2	34 MDS, higher risk (26)	39	100%	5/26 (19%) 3 mCR and 2 HI-E	3/26 (11%) mCR	6.8 months overall; 16.5 months (responders)	[81]
erlotinib	phase 1/2	MDS (18), AML (12)	30	100%	6/30 (20%), including 1 CR, 1 mCR, 4 HI-any	1/30 (3%) CR, 1/30 (3%) mCR	12.3 months	[82]
dasatinib	phase 2	MDS (12), CML (3), AML (3) after azacitidine	18	100%	3/18 (17%)	2 mCR (11%)	28.5 months (responders/stable)	[83]

BSC: best supportive care; CR: complete remission; CRp: complete remission without platelet recovery; CyR: cytogenetic response; ESA: erythrocyte stimulating agent; HI-E: hematologic improvement-erythroid; HI-plt: hematologic improvement-platelets; iCR: incomplete CR; mCR: marrow CR; NR: not reported; pCyR: partial cytogenetic response; RBC TI: RBC transfusion independence.