

Therapeutic Options in Myelodysplastic Syndromes: Established and Emerging Therapies

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Abstract

Although hypomethylating agents (HMA) have revolutionised the treatment of myelodysplastic syndromes (MDS), a significant proportion of patients either fail to respond to HMA or their disease progresses after an initial response. Established therapeutic options for these patients remain limited. Fortunately, recent advancements in the knowledge of MDS pathogenesis have allowed for the development of many targeted therapies, including epigenetic regulators, signal transduction regulators, immune checkpoint inhibitors, cell apoptosis regulators, and novel cytotoxic agents. These novel therapeutics have shown varying degrees of promise in clinical trials. Epigenetic regulators, such as second-generation HMA and isocitrate dehydrogenase inhibitors, have shown modest efficacy in early studies, while histone deacetylase inhibitors have, thus far, failed to show significant clinical benefit. Signal transduction modulators, such as transforming growth factor (TGF)- β inhibitors and toll-like receptor inhibitors, appear to alleviate anaemia symptoms, but further studies are needed to determine their effect on survival. Rigosertib, a multikinase inhibitor, improved survival in a small subset of patients with very high-risk MDS. Immune checkpoint inhibitors have shown mixed results. Agents that have recently been approved for use in specific types of high-risk acute myeloid leukaemia, including FMS-like tyrosine receptor kinase 3 inhibitors and CPX-351, are also being studied for use in MDS, with early studies suggesting efficacy. Several other agents are also under investigation with results pending. These novel agents represent potential therapeutic options for patients who have failed HMA and for whom no currently established therapies are available.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders resulting from the clonal expansion of a haematopoietic progenitor, leading to bone marrow dysplasia, ineffective haematopoiesis, and increased risk of transformation to acute myeloid leukaemia (AML). Risk factors include older age, male sex,

and prior exposure to radiation or chemotherapy.¹ Treatment selection is generally based on calculated risk. The International Prognostic Scoring System (IPSS), which stratifies patients with MDS into four risk categories (low, intermediate-1 [INT-1], intermediate-2 [INT-2], and high-risk) based on blast percentage, number of cytopenias, and cytogenetic profile, is the most commonly used risk stratification tool for treatment selection (Table 1). Of note, an

updated scoring system, the IPSS-R, is available (Table 2); however, all currently established therapies were approved using the older IPSS system.² This paper will review both established and emerging therapeutic options for both lower and higher-risk MDS, with an emphasis on novel therapies.

ESTABLISHED THERAPIES FOR LOWER-RISK MYELODYSPLASTIC SYNDROMES

For patients with lower-risk MDS (INT-1), the decision to treat is often based on the degree of anaemia and transfusion dependence. Patients who are transfusion independent may simply be observed; however, for those who become transfusion dependent, therapy is often warranted. Standard options include erythropoiesis-stimulating agents (ESA), lenalidomide, hypomethylating agents (HMA), and immunosuppressants (Table 3). Of these options, ESA, such as recombinant erythropoietin and darbepoietin, are generally considered first-line therapy in lower-risk MDS, having been shown to alleviate anaemia and possibly overall survival (OS) in this population.³⁻⁵ Granulocyte-colony stimulating factor improves

the efficacy of ESA through a synergistic effect without increasing the risk of leukaemic transformation; as a result, granulocyte-colony stimulating factor has gained wide clinical acceptance in most countries.⁵⁻⁷ Lenalidomide is considered first-line therapy for those with del(5q), having been shown in clinical trials to produce haematologic improvement (HI) in 56.0% of lower-risk MDS patients, transfusion independence (TI) in 46.0%, and partial or complete cytogenetic response in 71.6%, with best response in those with del(5q).^{8,9}

HMA have shown efficacy in lower-risk MDS, particularly after ESA and/or lenalidomide failure. In a Phase II clinical trial, low-dose 5-AZA and decitabine showed good overall response rates (ORR) (49% and 70%, respectively), cytogenetic response rates (61% and 25%, respectively), and achievement of TI (32% and 16%, respectively) in this lower-risk population.¹⁰ However, further studies are needed to determine whether HMA alter the natural history of lower-risk MDS. Immunosuppressants, including antithymocyte globulin, cyclosporine, and steroids, are also used in lower-risk MDS and have been associated with haematologic response in clinical studies, though no survival benefit has been found (Table 3).¹¹

Table 1: International prognostic scoring system for the stratification of myelodysplastic syndromes.

		Value	IPSS Score
Blasts (%)		<5	0
		5-10	0.5
		11-20	1.5
		21-30	2.0
Cytogenetics	<ul style="list-style-type: none"> > Normal > -Y only > Del(5q) only > Del(20q) only 	Good	0.0
	> Abnormalities other than good or poor	Intermediate	0.5
	<ul style="list-style-type: none"> > Complex > 3 or more abnormalities > Abnormal chromosome 7 	Poor	1.0
Cytopenias	<ul style="list-style-type: none"> > Haemoglobin <10 g/dL > Absolute neutrophil count <1,500 cells/μL > Platelet count <100,000/μL 	0 or 1	0.0
	Each cytopenia counts as a value of 1	2 or 3	0.5

IPSS risk score interpretation: low risk: 0; intermediate-1 risk: 0.5-1.0; intermediate-2 risk: 1.5-2.0; high risk: \geq 2.5.
Del: deleted; IPSS: International Prognostic Scoring System.

Table 2: Revised international prognostic scoring system for the stratification of myelodysplastic syndromes.

		Value	IPSS-R Score
Blasts (%)		≤2	0.0
		>2-<5	1.0
		5-10	2.0
		>10	3.0
Cytogenetics	> -Y > Del(11q)	Very good	0.0
	> Normal > Del(5q) > Del(12q) > Del(20q) > Double including del(5q)	Good	1.0
	> Del(7q) > +8 > +19 > i(17q) > Any other single or double independent clone	Intermediate	2.0
	> -7 > Inv(3)/+(3q)/del(3q) > Double including -7/del(7q) > Complex: 3 abnormalities	Poor	3.0
	> Complex: >3 abnormalities	Very poor	4.0
Cytopenias	Haemoglobin (g/dL)	≥10.0	0.0
		8.0->10.0	1.0
		<8.0	1.5
	Absolute neutrophil count (x10 ⁹ /L of blood)	≥0.8	0.0
		<0.8	0.5
	Platelet count (x10 ⁹ /L of blood [μL])	≥100.0	0.0
		50-<100	0.5
		<50	1.0

IPSS-R risk score interpretation: very low risk: ≤1.5; low risk: >1.5 to 3.0; intermediate risk: >3.0-4.5; high risk: >4.5-6.0; very high risk: >6.

Del: deleted; IPSS-R: International Prognostic Scoring System-Revised

ESTABLISHED THERAPIES FOR HIGHER-RISK MYELODYSPLASTIC SYNDROMES

For patients with higher-risk MDS (INT-2), HMA are considered the standard of care. 5-AZA has been particularly well-studied in this population by two multicentre randomised trials. In the CALGB 9221 trial,¹² 191 patients with higher-risk MDS were randomised to 5-AZA or best supportive care. Treatment with 5-AZA was associated with 7% complete response, 16% partial response, longer median time to leukaemic transformation (21 months versus 13 months; p=0.007), and improved survival

(18 months versus 11 months). Similarly, the AZA-001 trial¹³ showed that, compared to supportive care and low-dose cytarabine (araC), 5-AZA treatment is associated with longer median survival (24.5 months versus 15.0 months; p=0.0001), delayed progression to AML, decreased transfusion requirements, and decreased rate of infections. Decitabine has also demonstrated a modest clinical benefit in clinical trials, with a multicentre Phase II trial (ADOPT)¹⁴ showing an ORR of 32%, with 17 patients having complete responses. However, unlike 5-AZA, decitabine has not demonstrated significant survival benefit in a randomised trial.¹⁵

Table 3: Established and emerging therapies for myelodysplastic syndromes.

Mechanism of action	Agents
Immunosuppressants	<ul style="list-style-type: none"> ➤ Antithymocyte globulin ➤ Cyclosporine ➤ Steroids
Epigenetic regulators	<p>Hypomethylating agents</p> <ul style="list-style-type: none"> ➤ Azacitidine (5-AZA), administered via IV, SC, PO ➤ Decitabine, administered via IV, SC, PO ➤ Guadecitabine, administered via SC <p>Histone deacetylase inhibitors</p> <ul style="list-style-type: none"> ➤ Sodium phenylbutyrate ➤ Valproic acid ➤ Romidepsin ➤ Vorinostat ➤ Mocetinostat ➤ Panobinostat ➤ 4SC-202 <p>Mutant IDH1 and IDH2 inhibitors</p> <ul style="list-style-type: none"> ➤ Enasidenib ➤ Ivosidenib <p>PDH inhibitors</p> <ul style="list-style-type: none"> ➤ CPI613 <p>BET inhibitors</p> <ul style="list-style-type: none"> ➤ CPI-0610
Signal transduction regulators	<p>Growth factors</p> <ul style="list-style-type: none"> ➤ Erythropoiesis-stimulating agents ➤ Granulocyte-colony stimulating factor ➤ Thrombopoietin agonists - Romiplostim - Eltrombopag <p>TGF-β signalling modulators</p> <ul style="list-style-type: none"> ➤ Luspatercept (ACE-536) ➤ Sotatercept (ACE-011) ➤ Galunisertib <p>Toll-like receptor inhibitors</p> <ul style="list-style-type: none"> ➤ OPN-305 <p>Multi-kinase inhibitors</p> <ul style="list-style-type: none"> ➤ Rigosertib <p>FLT-3 inhibitors</p> <ul style="list-style-type: none"> ➤ Midostaurin ➤ Sorafenib
Immune checkpoint inhibitors	<p>PD-1 inhibitors</p> <ul style="list-style-type: none"> ➤ Nivolumab ➤ Pembrolizumab ➤ Durvalumab <p>CTLA-4 inhibitors</p> <ul style="list-style-type: none"> ➤ Ipilimumab
Cell death inhibitors	<p>Proteasome inhibitors</p> <ul style="list-style-type: none"> ➤ Bortezomib <p>BCL-2 inhibitors</p> <ul style="list-style-type: none"> ➤ Venetoclax
RNA splicing modulators	H3B-8800
Cytotoxic agents	<ul style="list-style-type: none"> ➤ Standard anthracycline-araC-based chemotherapy ➤ Low-dose clofarabine ➤ CPX-351

BCL: B cell lymphoma; BET: bromodomain and extraterminal domain; FLT: FMS-like tyrosine receptor kinase; IDH: isocitrate dehydrogenase; IV: intravenous; PD: programmed cell death protein; PDH: pyruvate dehydrogenase; PO: per os (oral administration); SC: subcutaneous.

Standard AML-based chemotherapy (classically, an anthracycline-araC combination) can also be used in higher-risk MDS, but this therapeutic strategy is associated with significant morbidity, due to prolonged cytopenias and poor long-term survival.¹⁶ Therefore, its use is generally limited to younger patients with a favourable karyotype.^{2,16} Allogeneic stem cell transplantation remains the only curative treatment for higher-risk MDS, and has been associated with prolonged disease-free survival in about 30–50% of patients.¹⁷ Although allogeneic stem cell transplantation use has historically been limited to younger patients due to significant toxicities and poor tolerability in older patients,^{18,19} the emergence of reduced-intensity conditioning allogeneic stem cell transplantation has improved its availability to older patients in recent years.

EMERGING THERAPIES FOR MYELODYSPLASTIC SYNDROMES

Despite the aforementioned advancements, there remain limitations to established therapies. ESA can improve symptoms in low-risk patients with MDS, but do not provide definitive treatment. Lenalidomide has shown efficacy in low-risk MDS with del(5q), but no clear survival benefit has been found. Although HMA have revolutionised the treatment of MDS, only about half of patients treated with HMA achieve objective responses, and most responders eventually lose response within 1–2 years.²⁰ Unfortunately, there remains a lack of therapeutic options for those who fail HMA. Use of conventional chemotherapy in the elderly MDS population is limited by toxicities. Allogeneic stem cell transplantation remains the only curative option, but is limited by donor availability and tolerability. As a result, prognosis for patients with MDS who fail HMA remains poor. For patients with lower-risk MDS who have failed HMA, survival is estimated to be between 14 and 17 months.²¹ Those with higher-risk MDS who have failed HMA have an even poorer prognosis, with an estimated survival of 4–6 months.²² Fortunately, several novel therapeutics are now being investigated for use in MDS, either as first-line or salvage treatments after HMA failure.

Oral Hypomethylating Agents

Oral azacitidine and decitabine are being explored as alternatives to the more conventional intravenous and subcutaneous administration formulation HMA in ongoing Phase III clinical trials.²³ Benefits of an oral formulation include increased patient convenience and the feasibility of an extended drug dosing schedule. Oral azacitidine has already been shown in Phase I and II trials to be bioavailable, clinically active, and well-tolerated, with an ORR, defined as complete response, HI, or TI, of 35% in previously treated patients and 73% in previously untreated patients.²⁴ An extended dosing schedule has also been found to be beneficial, with improved ORR after a 14-day dosing schedule (ORR: 36%) versus a 21-day dosing schedule (ORR: 41%) in those with lower-risk MDS.²⁴

Oral decitabine is the subject of clinical trials as part of a combination agent called ASTX727, which includes a novel cytidine deaminase inhibitor, cedazuridine (E7727). Cedazuridine inhibits cytidine deaminase, thereby inhibiting decitabine degradation in the gut and liver. Initial results from a Phase II study²⁵ of ASTX727 in intermediate and higher-risk MDS were presented at the American Society of Hematology (ASH) Congress 2017, and reported a clinical benefit in 31 out of 50 patients (62%), with 8 (16%) patients in complete remission (CR), 14 (28%) patients with marrow CR, and 9 (18%) individuals with HI.²⁵ A Phase III randomised, open-label, crossover pharmacokinetic study of ASTX727 versus intravenous decitabine is underway to demonstrate comparable exposures of decitabine.

Guadecitabine

Guadecitabine (SGI-110) is a next-generation, subcutaneous, small volume dinucleotide of decitabine and deoxyguanosine currently in clinical trials for higher-risk MDS and AML. Unlike decitabine, guadecitabine is resistant to deamination by cytidine deaminase, allowing prolonged *in vivo* exposure to the active ingredient decitabine.^{26–29} A Phase I study has confirmed that a dose of 60 mg/m² guadecitabine for 5 days is clinically active and well-tolerated in

patients with relapsed or refractory MDS or AML that failed HMA.²⁶ Preliminary results of Phase II trials in various MDS cohorts have demonstrated efficacy of guadecitabine as both an initial therapy in higher-risk HMA-naïve MDS patients (ORR: 50–60%)^{27,29} and as a salvage therapy in higher-risk MDS patients who have failed prior therapy with 5-AZA (ORR: 16%).²⁸ A Phase III randomised open-label study comparing guadecitabine to standard therapy in patients with MDS and chronic myelomonocytic leukaemia after HMA failure is currently underway.³⁰

Histone Deacetylase Inhibitors

Histone deacetylase inhibitors (HDACi) are similar to HMA in that they target epigenetic dysregulation, albeit through a different mechanism. HDACi modulate gene expression by inhibiting the deacetylation of histone lysine tails, relaxing chromatin structure. Secondary mechanisms of action include direct acetylation of nonhistone proteins, alterations to the NFκB signalling pathway, and upregulation of the death receptor pathway.³¹ Several different HDACi, including sodium phenylbutyrate, valproic acid, romidepsin, vorinostat, mocetinostat, panobinostat, and 4SC-202, have been tested in clinical trials, with many trials still ongoing. Despite robust preclinical data suggesting benefits, Phase I and II clinical trials of HDACi have shown only a modest effect at best.^{31,32} Notably, none of these agents used alone or in combination with other therapeutic agents have been shown to be superior to HMA monotherapy.^{33–35}

Mutant Isocitrate Dehydrogenase 1 and 2 Inhibitors

Isocitrate dehydrogenase (IDH)1 and IDH2 are enzymes involved in histone demethylation. Recurrent mutations are detected in *IDH1/2* genes in about 5% of MDS patients and 20% of AML patients. These are typically gain-of-function mutations that result in increased enzymatic activity, leading to DNA and histone hypermethylation and a blockade of haematopoietic cellular differentiation.³⁶ Several mutant IDH (mIDH) inhibitors are currently being investigated in clinical trials (most of which are still in Phase I or II) for use in patients with relapsed or refractory MDS or AML. The most promising results thus far have

been seen with enasidenib (a mIDH2 inhibitor) and ivosidenib (a mIDH1 inhibitor).³⁶ In a recent Phase I and II trial of enasidenib in relapsed and refractory AML, the ORR was 40.3%, with 19.3% of patients achieving CR.³⁷ A significant survival benefit was also demonstrated in those who achieved CR (median OS: 19.7 months in those who achieved CR versus 9.3 months in others).³⁷ Preliminary results of a Phase I and II study, including 17 patients with *IDH2*-mutated MDS, suggested that enasidenib also has activity in MDS, with a reported OSS of 59%.³⁸ Similarly, ivosidenib has been suggested to have efficacy in patients with advanced haematologic malignancies, including MDS, with 36% ORR in a Phase I study.³⁹

Pyruvate Dehydrogenase and Bromodomain and Extraterminal Domain Inhibitors

Pyruvate dehydrogenase inhibitors (e.g., CPI613)⁴⁰ and bromodomain and extraterminal domain inhibitors (e.g., CPI-0610) also target epigenetic dysregulation. These inhibitors are currently being studied in Phase I clinical trials with results pending.⁴¹

DRUGS TARGETING ABNORMAL SIGNAL TRANSDUCTION

Thrombopoietin Agonists

Thrombopoietin agonists have also been explored for use in lower-risk MDS patients with thrombocytopenia and have shown some benefit. Unfortunately, widespread use has been limited by concern for increased risk of leukaemogenesis. This fear is based on early studies showing a transient increase in blast percentage in 15% of patients treated with high-dose romiplostim, despite a recently published follow-up study reporting no difference in the risk of transformation to AML or mortality with romiplostim versus placebo at 5 years.⁴² Eltrombopag is an alternative thrombopoietin agonist that has shown efficacy in treating aplastic anaemia and, unlike romiplostim, is not associated with an increase in blast percentage. A recently published Phase II clinical trial (ASPIRE) showed that eltrombopag improved platelet counts and reduced clinically relevant thrombocytopenic events compared to placebo

in high-risk MDS and AML patients with thrombocytopenia who are ineligible for other treatment or not receiving disease-modifying treatment.⁴³ Clinical trials to investigate the efficacy of eltrombopag in lower-risk MDS are ongoing; however, preliminary results show efficacy in improving thrombocytopenia and reducing bleeding events in this population as well.⁴⁴

Transforming Growth Factor- β Signalling Modulators

TGF- β signalling modulators have been developed for treatment of MDS with the aim of inhibiting TGF- β -mediated myelosuppression,⁴⁵ thereby promoting maturation of haematopoietic progenitors in bone marrow. Luspatercept (ACE-536) is a selective activin receptor ligand that traps GDF11, blocking TGF- β signalling and promoting late-stage erythropoietic maturation. It has shown promising activity in preliminary results of an ongoing Phase II multicentre study in patients with lower risk MDS with anaemia (PACE-MDS): 53% of patients showed erythroid response and 38% of patients achieved TI.⁴⁶ In this study, particularly high response rates were observed among patients with refractory anaemia with ring sideroblasts, *SF3B1* mutation, and/or low transfusion burden, leading to the development of a randomised trial of luspatercept for patients with refractory anaemia with ring sideroblasts.⁴⁷ Sotatercept (ACE-011), which functions through a very similar mechanism, has also shown promising evidence of clinical activity in ESA-refractory lower-risk MDS patients in an ongoing Phase II study, with 49% of patients showing improvement in anaemia.⁴⁸ Galunisertib, an agent that inhibits the kinase activity of TGF- β receptor Type 1, also known as ALK5, is also currently in Phase II and III clinical trials, with preliminary results showing HI in 21% of the 38 lower-risk MDS patients studied.⁴⁹

Toll-Like Receptor Inhibitors

TLR signalling is abnormally activated in MDS, especially after HMA therapy, leading to activation of the NF- κ B pathway and inhibition of haematopoiesis.⁵⁰ OPN-305 is a fully humanised IgG4 κ monoclonal antibody against TLR2 that is currently being investigated in Phase I and II clinical trials for the treatment of low or INT-1

risk MDS after HMA failure.⁵¹ Preliminary results in 21 patients have shown haematologic improvement in 53% of patients, with 20% achieving TI.⁵² Further studies are necessary to confirm this response and evaluate effect on survival.

Rigosertib

Rigosertib is a multikinase inhibitor that induces mitotic arrest and apoptosis in neoplastic cells while sparing normal cells. It has been explored for use in patients with refractory MDS with excess blasts or treatment-related MDS who have failed HMA.⁵³ In a Phase III study (ONTIME)⁵⁴ comparing rigosertib to best supportive care with or without low-dose araC in this population, rigosertib was not shown to improve OS. However, in a post-hoc analysis, patients with very high-risk IPSS-R scores and monosomy 7 or trisomy 8 were found to have significant improvement in survival with rigosertib compared to supportive care (median OS: 7.6 months versus 3.2 months, $p=0.015$).⁵⁴ A second Phase III study in this smaller cohort of very high-risk patients is now underway to further evaluate this effect.⁵⁵

FMS-like Tyrosine Receptor Kinase Inhibitors

Midostaurin is a FMS-like tyrosine receptor kinase (FLT) 3 inhibitor that was recently approved for use in combination with 7+3 chemotherapy for patients with newly diagnosed *FLT3* mutation-positive AML, based on clinical trial data showing improved OS and event-free survival in patients treated with midostaurin.⁵⁶ Though not formally approved for use in MDS as of yet, FLT3 inhibitors (i.e., midostaurin, sorafenib) have also demonstrated efficacy in Phase I and II clinical trials when used in combination with HMA (i.e., 5-AZA, decitabine) in patients with *FLT3*-mutated MDS.^{57,58} Notably, although *FLT3* mutations are seen in <1% of patients with newly diagnosed MDS, they have been observed in up to 5% of patients at the time of MDS transformation to AML and are associated with much poorer outcomes.⁵⁹ The hope is that mutation-targeted therapy will improve these outcomes.

Immune Checkpoint Inhibitors

Several monoclonal antibodies against immune checkpoint regulators, both alone and in combination with HMA, are being tested in clinical trials. These include nivolumab (a programmed cell death protein [PD-1] inhibitor), ipilimumab (a CTLA-4 inhibitor), pembrolizumab (a PD-1 inhibitor), and durvalumab (blocks interaction of PD ligand-1 with PD-1 and CD80 molecules). Early results of these studies have been mixed. Preliminary results from a Phase Ib study of pembrolizumab in 27 patients with MDS after HMA failure (KEYNOTE-013) show only modest response to therapy, with no CR, 1 partial remission, 3 marrow CR, and 3 HI.⁶⁰ However, 2-year survival was reportedly 57% in those treated with pembrolizumab, which is considerably superior to that typically expected in MDS patients after HMA failure.⁶⁰ A Phase II study evaluating nivolumab and ipilimumab as single agents or in combination with AZA for patients with MDS (as initial or salvage therapy) is also ongoing, with preliminary results in 39 patients showing an ORR of 69% in the AZA plus nivolumab cohort, 22% in the ipilimumab monotherapy cohort, and no response in the nivolumab monotherapy cohort.⁶¹ Further follow-up is needed to clarify efficacy and safety.

Proteasome Inhibitors

Proteasome inhibitors inhibit cell death by preventing degradation of proapoptotic proteins. The proteasome inhibitor, bortezomib, has recently been explored as a therapeutic option in MDS. In a limited study of 15 patients with low or INT-1 MDS after HMA failure, bortezomib showed only modest effect, with HI observed in 20% of patients.⁶² However, an unexpected significant reduction of ring sideroblasts was seen in 70% of patients treated with bortezomib in this study, suggesting potential benefit specifically in MDS patients with ring sideroblasts.⁶² Further studies are necessary to better evaluate this effect.

B Cell Lymphoma-2 Inhibitors

Antiapoptotic resistance due to B cell lymphoma (BCL)-2 overexpression has been reported in higher-risk MDS and may contribute to disease

pathogenesis. As a result, BCL-2 inhibitors have been explored as a therapeutic option in higher-risk MDS after HMA failure and in relapsed and refractory AML. Venetoclax is the best studied BCL-2 inhibitor thus far, and has shown modest efficacy (ORR: 19%) as monotherapy in patients with high-risk relapsed or refractory AML.⁶³ Venetoclax has also shown significant efficacy in combination with araC for patients with treatment-naïve AML (including those with previously treated MDS) in a Phase I trial of 20 patients, with 14 out of 20 patients (70%) achieving CR or CR with incomplete marrow recovery.⁶⁴ The presence of mutations in chromatin-RNA splicing genes (*ASXL1*, *EZH2*) or *NPM1* correlated with a higher likelihood of response in a separate analysis.⁶⁵ A Phase I clinical trial evaluating venetoclax alone and in combination with azacitidine in higher-risk MDS after HMA failure is ongoing.⁶⁶

RNA Splicing Modulators

Genes encoding various spliceosome components (*SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*) are frequently mutated in patients with MDS.^{67,68} While the precise mechanism by which abnormal RNA splicing leads to the development of MDS is unknown, the association is clear. Based on this knowledge, H3B-8800, a potent and orally bioavailable SF3b complex modulator, was developed and is now being studied in a Phase I clinical trial for use in patients with MDS and AML with splicing mutations, with results pending.^{69,70}

Cytotoxic Agents

Although many patients with MDS cannot tolerate standard AML-based chemotherapy, less intensive cytotoxic agents can be considered. Cytotoxic agents that have been explored for use in MDS patients include low-dose clofarabine and CPX-351. Low-dose clofarabine is currently under investigation for both higher-risk MDS and AML, with promising results. A Phase II study evaluating the safety and efficacy of low-dose clofarabine in combination with araC in patients with MDS who have failed HMA has reported an ORR of 44%, median OS of 10 months overall, and median OS of 22 months in responding patients (versus 4 months in non-responding patients).⁷¹ CPX-351, a liposomal formulation of araC and daunorubicin in a 5:1

molar ratio, was recently U.S. Food and Drug Administration (FDA) approved as front-line therapy for patients with therapy-related AML and AML with MDS-related changes based on a Phase III randomised trial reporting a survival advantage compared to standard 7+3 chemotherapy (OS: 9.6 months versus 5.9 months).⁷² However a subsequent Phase II randomised trial testing attenuated doses of CPX-351 in a small cohort of less fit adults with untreated AML or MDS with 10% or more blasts in peripheral blood or bone marrow did not show much efficacy.⁷³

CONCLUSION

Although HMA have changed the landscape of MDS therapy in the past decade, they have limitations and are not curative. There remains a significant proportion of patients who simply do not respond to HMA, or who develop resistance to HMA after initial response. Unfortunately, established therapeutic options for patients with MDS who have failed HMA therapy are limited, and these patients have very poor prognosis. Thus, multiple novel agents are being developed in clinical trials with the aim of improving symptoms and OS in patients with MDS.

References

- Rollison DE et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood*. 2008;112(1):45-52.
- Montalban-Bravo G, Garcia-Manero G. Myelodysplastic syndromes: 2018 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2018;93(1):129-47.
- Fenaux P, Adès L. How we treat lower-risk myelodysplastic syndromes. *Blood*. 2013;121(21):4280-6.
- Moyo V et al. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: A meta-analysis. *Ann Hematol*. 2008;87(7):527-36.
- Jädersten M et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. *J Clin Oncol*. 2008;26(21):3607-13.
- Hellström-Lindberg E et al. Scandinavian MDS Group; A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: Significant effects on quality of life. *Br J Haematol*. 2003;120(6):1037-46.
- Santini V. Treatment of low-risk myelodysplastic syndrome: Hematopoietic growth factors erythropoietins and thrombopoietins. *Semin Hematol*. 2012;49(4):295-303.
- List A et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med*. 2005;352(6):549-57.
- List A et al. Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS. *Leukemia*. 2014;28(5):1033-40.
- Jabbour E et al. Randomized Phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. *Blood*. 2017;130(13):1514-22.
- Passweg JR et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: A prospective randomized multicenter Phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care - SAKK 33/99. *J Clin Oncol*. 2011;29(3):303-9.
- Silverman LR et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the cancer and leukemia group B. *J Clin Oncol*. 2002;20(10):2429-40.
- Fenaux P et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, Phase III study. *Lancet Oncol*. 2009;10(3):223-32.
- Steensma DP et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: The alternative dosing for outpatient treatment (ADOPT) trial. *J Clin Oncol*. 2009;27(23):3842-8.
- Lübbert M et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomized Phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *J Clin Oncol*. 2011;29(15):1987-96.
- Wattel E et al. Long-term follow-up of de novo myelodysplastic syndromes treated with intensive chemotherapy: Incidence of long-term survivors and outcome of partial responders. *Br J Haematol*. 1997;98(4):983-91.
- Chang C et al. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: Similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic. *Blood*. 2007;110(4):1379-88.
- Koreth J et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: An international collaborative decision analysis. *J Clin Oncol*. 2013;31(21):2662-70.
- Cutler CS et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: Delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood*. 2004;104(2):579-85.
- Zeidan AM et al. Beyond hypomethylating agents failure in patients with myelodysplastic syndromes. *Curr Opin Hematol*. 2014;21(2):123-30.
- Jabbour E et al. Outcome of patients with low-risk and intermediate-1-risk myelodysplastic syndrome after hypomethylating agent failure: a report on behalf of the MDS Clinical Research Consortium. *Cancer*. 2015;121(6):876-82.

22. Harel S et al. Outcome of patients with high risk myelodysplastic syndrome (MDS) and advanced chronic myelomonocytic leukemia (CMML) treated with decitabine after azacitidine failure. *Leuk Res.* 2015;39(5):501-4.
23. Celgene. The efficacy and safety of oral azacitidine plus best supportive care versus placebo and best supportive care in subjects with red blood cell (RBC) transfusion-dependent anemia and thrombocytopenia due to International Prognostic Scoring System (IPSS) low risk myelodysplastic syndrome (MDS). NCT01566695. <https://clinicaltrials.gov/ct2/show/NCT01566695>.
24. Garcia-Manero G et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol.* 2011;29(18):2521-7.
25. Garcia-Manero G et al. A Phase 2 dose-confirmation study of oral ASTX727, a combination of oral decitabine with a cytidine deaminase inhibitor (CDAi) cedazuridine (E7727), in subjects with myelodysplastic syndromes (MDS). Abstract 4274. ASH 2017, 9-12 December, 2017.
26. Issa JJ et al. Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: A multicentre, randomized, dose-escalation Phase 1 study. *Lancet Oncol.* 2015;16(9):1099-110.
27. Montalban-Bravo G et al. Initial results of a Phase 2 study of guadecitabine (SGI-110), a novel subcutaneous (sc) hypomethylating agent, for patients with previously untreated intermediate-2 or high risk myelodysplastic syndromes (MDS) or chronic myelomonocytic leukemia (CMML). *Blood.* 2016;128(22):346.
28. Sebert M et al. Results of a Phase II study of guadecitabine (SGI-110) in higher risk MDS, CMML or low blast count AML patients refractory to or relapsing after azacitidine (AZA) treatment. *Blood.* 2016;128(22):347.
29. Kantarjian HM et al. Guadecitabine (SGI-110) in treatment-naive patients with acute myeloid leukaemia: Phase 2 results from a multicentre, randomised, Phase 1/2 trial. *Lancet Oncol.* 2017;18(10):1317-26.
30. Astex Pharmaceuticals. Guadecitabine (SGI-110) vs treatment choice in adults with MDS or CMML previously treated with HMAs. NCT02907359. <https://clinicaltrials.gov/ct2/show/NCT02907359>.
31. Griffiths E et al. DNA methyltransferase and histone deacetylase inhibitors in the treatment of myelodysplastic syndromes. *Semin Hematol.* 2008;45(1):23-30.
32. Stahl M et al. Lost in translation? Ten years of development of histone deacetylase inhibitors in acute myeloid leukemia and myelodysplastic syndromes acute myeloid leukemia and myelodysplastic syndromes. *Expert Opin Investig Drugs.* 2016;25(3):307-17.
33. Prebet T et al.; Groupe Francophone des Myélodysplasies. Addition of suberoylanilide hydroxamic acid (Vorinostat) to azacitidine for patients with higher risk myelodysplastic syndromes and azacitidine failure: A Phase II add-on study from the Groupe Francophone des Myelodysplasies. *Br J Haematol.* 2016;180(5):735-7.
34. Sekeres MA et al. Randomized Phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. *J Clin Oncol.* 2017;35(24):2745-53.
35. Garcia-Manero G et al. Phase 2, randomized, double-blind study of pracinostat in combination with azacitidine in patients with untreated, higher-risk myelodysplastic syndromes. *Cancer.* 2017;123(6):994-1002.
36. Medeiros BC et al. Isocitrate dehydrogenase mutations in myeloid malignancies. *Leukemia.* 2017;31(2):272-81.
37. Stein EM et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood.* 2017;130(6):722-31.
38. Stein E et al. Enasidenib (AG-221), a potent oral inhibitor of mutant isocitrate dehydrogenase 2 (IDH2) enzyme, induces hematologic responses in patients with myelodysplastic syndromes (MDS). Abstract 343. Present 58th ASH Annu Meet Expo San Diego, 2016.
39. DiNardo C et al. Molecular profiling and relationship with clinical response in patients with IDH1 mutation-positive hematologic malignancies receiving AG-120, a first-in-class potent inhibitor of mutant IDH1, in addition to data from the completed dose escalation portion. Abstract 1306. 57th Annual Meeting & Exposition, Orlando, 5-8 December, 2015.
40. Pardee T et al. A Phase I study of the safety, efficacy and pharmacokinetics of the first-in-class anti-mitochondrial metabolism agent, CPI-613, in patients with advanced hematologic malignancies. *Clin Cancer Res.* 2013;122(21):486.
41. Chaidos A et al. Inhibition of bromodomain and extra-terminal proteins (BET) as a potential therapeutic approach in haematological malignancies: Emerging preclinical and clinical evidence. *Ther Adv Hematol.* 2015;6(3):128-41.
42. Kantarjian HM et al. Long-term follow-up for up to 5 years on the risk of leukaemic progression in thrombocytopenic patients with lower-risk myelodysplastic syndromes treated with romiplostim or placebo in a randomised double-blind trial. *Lancet Hematol.* 2018;5(3):e117-26.
43. Mittelman M et al. Eltrombopag for advanced myelodysplastic syndromes or acute myeloid leukaemia and severe thrombocytopenia (ASPIRE): A randomised, placebo-controlled, Phase 2 trial. *Lancet Haematol.* 2018;5(1):e34-43.
44. Oliva E et al. Eltrombopag versus placebo for low-risk myelodysplastic syndromes with thrombocytopenia (EQoL-MDS): Phase 1 results of a single-blind, randomised, controlled, Phase 2 superiority trial. *Lancet Hematol.* 2017;4(3):e127-36.
45. Zhou L et al. Inhibition of the TGF-beta receptor I kinase promotes hematopoiesis in MDS. *Blood.* 2008;112(8):3434-44.
46. Platzbecker U et al. Luspatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes (PACE-MDS): A multicentre, open-label Phase 2 dose-finding study with long-term extension study. *Lancet Oncol.* 2017;18(10):1338-47.
47. Celgene. A study of luspatercept (ace-536) to treat anemia due to very low, low, or intermediate risk myelodysplastic syndromes (medalist). NCT02631070. <https://clinicaltrials.gov/ct2/show/NCT02631070>.
48. Komrokji R et al. A Phase 2, dose-finding study of sotatercept (ACE-011) in patients with lower risk myelodysplastic syndromes (MDS) or non-proliferative chronic myelomonocytic leukemia (CMML) and anemia requiring transfusion. *Leuk Res.* 2015;39(Suppl 1):S5-6.
49. Valcarcel D et al. Phase 2 study of monotherapy galunisertib (LY2157299 Monohydrate) in very low-, low-, and intermediate-risk patients with myelodysplastic syndromes. *Blood.* 2015;126(23):1669.
50. Wei Y et al. Toll-like receptor alterations in myelodysplastic syndrome. *Leukemia.* 2013;27(9):1832-40.
51. Opsona Therapeutics Ltd. A Phase I/II study of opn-305 in second-line lower risk myelodysplastic syndrome. NCT02363491. <https://clinicaltrials.gov/ct2/show/NCT02363491>.
52. Garcia-Manero G et al. Phase II Study OPN-305, a (TLR-2) Antibody, in patients with lower risk

- myelodysplastic syndromes with prior hypomethylating agent (HMA) therapy. Abstract P317. EHA22 Friday 23, 2017.
53. Silverman LR et al. Clinical activity and safety of the dual pathway inhibitor rigosertib for higher risk myelodysplastic syndromes following DNA methyltransferase inhibitor therapy. *Hematol Oncol*. 2015;33(2):57-66.
 54. Garcia-Manero G et al. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): A randomised, controlled, Phase 3 trial. *Lancet Oncol*. 2016;17(4):496-508.
 55. Onconova Therapeutics, Inc. Controlled study of rigosertib versus physician's choice of treatment in MDS patients after failure of an HMA (INSPIRE). NCT02562443. <https://clinicaltrials.gov/ct2/show/NCT02562443>.
 56. Stone RM et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med*. 2017;377(5):454-64.
 57. Strati P et al. Phase I/II Trial of the combination of midostaurin (PKC412) and 5-azacytidine for patients with acute myeloid leukemia and myelodysplastic syndrome. *Am J Hematol*. 2015;90(4):276-81.
 58. Ravandi F et al. Phase 2 study of azacytidine plus sorafenib in patients with acute myeloid leukemia and FLT-3 internal tandem duplication mutation. *Blood*. 2013;121(23):4655-62.
 59. Badar T et al. Detectable FLT3-ITD or RAS mutation at the time of transformation from MDS to AML predicts for very poor outcomes. *Leuk Res*. 2015;39(12):1367-74.
 60. Garcia-Manero G et al. Pembrolizumab, a PD-1 inhibitor, in patients with myelodysplastic syndrome (MDS) after failure of hypomethylating agent treatment. *Blood*. 2016;128(22):345.
 61. Garcia-Manero G et al. A Phase II study evaluating the combination of nivolumab (Nivo) or ipilimumab (Ipi) with azacitidine in Pts with previously treated or untreated myelodysplastic syndromes (MDS). *Blood*. 2016;128(22):344.
 62. Daher M et al. An exploratory clinical trial of bortezomib in patients with lower risk myelodysplastic syndromes. *Am J Hematol*. 2017;92(7):674-82.
 63. Konopleva M et al. Efficacy and biological correlates of response in a Phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov*. 2016;6(10):1106-17.
 64. Wei A et al. Safety and efficacy of venetoclax plus low-dose cytarabine in treatment-naive patients aged ≥ 65 years with acute myeloid leukemia. *Blood*. 2016;128(22):102.
 65. Chyla B et al. Correlative biomarkers of response to venetoclax in combination with chemotherapy or hypomethylating agents in elderly untreated patients with acute myeloid leukemia. *Blood*. 2016;128(22):1709.
 66. AbbVie. A study evaluating venetoclax alone and in combination with azacitidine in subjects with higher-risk myelodysplastic syndromes (mds) after hypomethylating agent-failure. NCT02966782. <https://clinicaltrials.gov/ct2/show/NCT02966782>.
 67. Papaemmanuil E et al. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. *N Engl J Med*. 2011;365(15):1384-95.
 68. Yoshida K et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature*. 2011;478(7367):64-9.
 69. Seiler M et al. H3B-8800, an orally bioavailable modulator of the SF3b complex, shows efficacy in spliceosome-mutant myeloid malignancies. *Blood*. 2018;131(24):497-504.
 70. H3 Biomedicine Inc. Phase 1 trial to evaluate the safety, pharmacokinetics and pharmacodynamics of splicing modulator h3b-8800 for subjects with myelodysplastic syndromes, acute myeloid leukemia, and chronic myelomonocytic leukemia. NCT02841540. <https://clinicaltrials.gov/ct2/show/NCT02841540>.
 71. Jabbour E et al. Phase 2 study of low-dose clofarabine plus cytarabine for patients with higher-risk myelodysplastic syndrome who have relapsed or are refractory to hypomethylating agents. *Cancer*. 2017;123(4):629-37.
 72. Talati C, Lancet JE. CPX-351: Changing the landscape of treatment for patients with secondary acute myeloid leukemia. *Future Oncol*. 2018;14(12):1147-54.
 73. Walter RB et al. Unsatisfactory efficacy in randomized study of reduced-dose CPX-351 for medically less fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm. *Haematologica*. 2018;103(3):e106-9.