Emerging Treatment Options for Adult MDS: A Clinical Perspective

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Introduction

The incidence of myelodysplastic syndromes (MDS) is increasing in tandem with our aging population. In turn, the disease burden on the patient and the health care system is increasing exponentially. New treatment options must be assessed with this in mind.

This paper briefly reviews the clinical features and classification of adult MDS and focuses on existing and emerging treatment options for patients who are *not* candidates for either hematopoietic stem cell transplant (HSCT) or high intensity chemotherapy, which are usually appropriate only for relatively young patients with good performance status. Although a number of exciting investigative treatments are currently being evaluated in MDS, this paper discusses the three pharmacologic therapies furthest along in clinical testing.

The current standard of care for MDS patients who are not candidates for HSCT is supportive care — antibiotics as needed and red blood cell (RBC) and/or platelet transfusions [1-4]. RBC transfusions are the most frequent interventions for the majority of MDS patients, especially those with relatively good prognosis. Importantly, repeated RBC transfusions are associated with risks (e.g., iron overload, febrile reactions, transmission of viral infections) that impact the overall quality of life (QOL) of MDS patients and overall survival. Platelet transfusions

carry similar risks, including viral transmission, transfusion reactions, alloimmunization, and induction of transfusion resistance.

Several emerging therapies that target one or more pathogenic processes involved in the development and maintenance of MDS lead to hematologic responses and attendant clinical benefits characterized by transfusion independence, cytogenetic remissions, improved QOL, and/or delay in disease progression. There is a need for new effective MDS therapies that will provide clinical benefit and lessen the substantial disease burden for patients, even if not accompanied by a survival advantage. Due to the chronic nature and symptomatology of MDS, which primarily affects the elderly (median age: 65-70) [4,5], improvement of persistent cytopenia(s) and related complications are considered valid clinical endpoints in studies of new therapies [6].

Disease Course and Etiology

MDS is a heterogeneous clonal, mostly acquired, hematopoietic stem cell disorder, characterized by ineffective and dysplastic hematopoiesis. Patients with MDS have widely variable cellular hematopoietic (morphologic) features, chromosomal abnormalities, clinical manifestations, and prognoses. The disease course may be indolent or aggressive. Overall, progression to acute myeloid leukemia (AML) occurs in approximately one-third of adult MDS patients and is associated with poor prognosis (median survival: 6-12 months) [7,8].

Primary, or *de novo*, MDS accounts for the majority of adult MDS cases and is largely idiopathic. However, MDS may develop following exposure to chronic or

high levels of environmental toxins (i.e., leukemogens), cytotoxic chemotherapy, and/or ionizing radiotherapy. This is referred to as secondary MDS and includes therapy-related, or t-MDS, which generally rapidly transforms to therapy-related AML (t-AML). Approximately one-half of patients with *de novo* MDS have chromosomal abnormalities (e.g., partial or complete deletions or gains involving chromosomes 5, 7, 8, 20), whereas almost 95% of patients with t-MDS have abnormal bone marrow cytogenetics, which are considered complex in the majority of cases [9,10].

Clinical Presentation

Most adult patients with de novo MDS are asymptomatic or present with symptoms associated with anemia — fatigue, weakness, dyspnea [11,12]. Anemia that is refractory to iron, folate, and vitamin B_{12} supplementation dominates the early course of disease in approximately 80% of adult MDS patients [11,12]. More than 40% of MDS patients require RBC transfusions at some stage of the disease [13]. Moreover, a substantial proportion of MDS patients of all prognostic risk groups are transfusion-dependent and approximately 30% of these patients require iron chelation therapy to limit iron overload due to repeated transfusions [13]. Multiply transfused anemic MDS patients have decreased survival compared with transfusion independent patients [12]. The burden associated with anemia, in terms of reduced QOL and economic cost, is much greater than generally appreciated [14,15]. Anemia and its associated symptoms, particularly fatigue, are debilitating for MDS patients [16]. In a multicenter survey study of cancer patients, fatigue was found to affect

QOL more than any other cancer-associated symptom, including pain and nausea [17].

Manifestations of the underlying hematopoietic stem cell defect in MDS other than symptomatic anemia include signs and symptoms of neutropenia and thrombocytopenia. Although uncommon at presentation, approximately 60% of MDS patients develop neutropenia or thrombocytopenia in the course of their disease. Recurrent bacterial infections in neutropenic MDS patients may be prolonged. Abnormal hemostasis, due to reduced platelet aggregation and/or other platelet dysfunction, with or without thrombocytopenia, frequently complicates the disease course and must be managed with platelet transfusions. Patients with platelet alloantibodies may require single donor or compatible blood product transfusions to avoid reactions to platelet transfusions. At least 30% of platelet transfusions result in complications, usually febrile reactions but occasionally bacteremia or acute pulmonary injury related to transfusion [18]. The cause of death for the majority of MDS patients is infection (up to 50% of cases) or other cytopenic complications, due to the underlying bone marrow failure [19].

Diagnosis and Classification

MDS is a diagnosis of exclusion, based on the existence of one or more persistent cytopenias ($\geq$6 months) and the presence of dysplastic hematopoietic cells in one or more hematopoietic lineages, with or without an increased percentage of bone marrow blasts [20-22]. Recognition of the heterogeneous

morphologic, cytogenetic, and clinical features of MDS and the variability in disease course and prognosis led to the proposal of the French-American-British Cooperative Group (FAB) classification system in the late 1970's [23], the International Prognostic Scoring System (IPSS) in 1997 [7], and the World Health Organization (WHO) classification system in 2000 [20-22]. (Table 1; Table 2)

The IPSS is widely used in conjunction with the FAB and WHO classification systems for predicting transformation to AML and survival in MDS patients. The IPSS score estimates time to leukemic progression and survival by weighing three disease variables: cytogenetic abnormalities of the bone marrow cells, percentage of bone marrow blasts, and number of affected lineages (cytopenias) [7]. (Table 2) The predicted median survival, as determined by IPSS, in the study cohort of untreated MDS patients was found to range from almost 6 months (high-risk category) to almost 6 years (low-risk category). (Table 2)

Treatment Response Criteria

To provide uniformity in the comparative analysis of the efficacy of new therapies, a set of standardized treatment response criteria has been established by an international group of experts in MDS (International Working Group, IWG) [6]. The IWG recognized that MDS differs from other hematologic malignancies in that the morbidity and mortality associated with chronic cytopenias in MDS are frequently unaccompanied by disease progression, and therefore specific evaluation criteria for MDS therapies were needed. The IWG acknowledged that the goals of non-curative therapy in MDS are to alleviate disease-related

complications and improve QOL, thereby establishing the need to objectively measure these clinical benefits. Although survival is a preferred endpoint in the clinical testing of potential therapies for MDS, there are multiple practical reasons (i.e., co-morbidities, elderly patient population, small number of eligible clinical trial participants) for establishing response criteria based on endpoints other than survival. To date, no randomized studies have demonstrated a survival benefit for any therapeutic intervention in MDS.

The response criteria (objective measures of treatment efficacy), established by the IWG, for potential MDS therapies are grouped into four categories:

- Altering disease natural history

  Complete or partial remission (normalization (CR) or improvement (PR) in bone marrow blast count, dysplasia, and peripheral blood absolute values lasting $\geq$2 months); stable disease; failure; relapse after CR or PR; disease progression; transformation to AML; survival; progression-free survival

- Hematologic improvement (HI)

  Major or minor erythroid, neutrophil, platelet responses in the absence of therapy (changes in absolute peripheral blood values lasting $\geq$2 months)

- Cytogenetic response

  Major or minor cytogenetic responses: reversal of cytogenetic abnormalities or reduction in cytogenetic abnormalities

- Quality of Life

  Measured by standardized instruments such as FACT, HRQoL Questionnaire (physical, functional, emotional, social, spiritual aspects)

Clinically meaningful improvement in persistent cytopenia(s) and related complications in MDS include a reduced need for or independence from RBC and/or platelet transfusion, iron chelation therapy, and myeloid growth factors. The attainment of transfusion independence is of significant benefit to MDS patients because it eliminates the risk of transfusion-related complications [24], and it can enhance the resumption of normal daily living activities. Transfusion independence or a reduced frequency of transfusions lowers the disease burden for patients in terms of QOL and both direct and indirect costs (reduced frequency of office/hospital visits, reduced need for care providers and daily living assistance). The healthcare delivery system would also realize direct and indirect cost savings (reduced resource utilization, reduced healthcare staffing).

Clinical Practice Guidelines

Evidence-based treatment guidelines for MDS from the Italian Society of Hematology, the United Kingdom, and the United States (National Comprehensive Cancer Network) have been drafted to assist clinicians in the use of current therapeutic options [1-3]. These guidelines indicate that IPSS risk category, patient age, and performance status are major determinants for treatment decision-making.

Treatment Options

Hematopoietic Stem Cell Transplantation (HSCT)

Currently, only HSCT offers a potential for cure in MDS, but it is appropriate for only a portion of MDS patients (i.e., younger age, histocompatible donor, no significant comorbidities). Several studies have confirmed the existence of a graft-versus-MDS effect; thus, allogeneic HSCT is the preferred approach, predominantly for IPSS Intermediate-2 and High risk patients [1-3,25-27]. Myeloablative and reduced intensity conditioning regimens, consisting of total body irradiation, immunosuppressive therapy, and/or cytotoxic chemotherapy, are used in allogeneic HSCT to eradicate the MDS clone [1,2,27-29]. Autologous HSCT following intensive chemotherapy (see below) has also shown some benefit for treating selected MDS patients [27,28]. The majority of MDS patients do not have the option of HSCT and therefore are reliant upon non-curative treatment interventions and supportive care to alleviate cytopenic complications and improve QOL.

Intensive Chemotherapy

Intensive antileukemic chemotherapy is only recommended for high-risk MDS patients who have good performance status [1-3]. Among this group, the highest CR rate is achieved in relatively young patients [30]. The use of intensive chemotherapy in MDS is associated with increased mortality, low remission rates (<50%), and short duration of remission (<12 months) [26,27]. Nevertheless,

such chemotherapy may delay progression to leukemia and may improve cytopenias in selected patients [26].

Supportive Care

The vast majority of MDS patients are clinically managed with supportive care: broad-spectrum antibiotics and RBC/ platelet transfusions. MDS patients who require repeated RBC transfusions may be treated with an iron chelating agent to prevent or reduce iron overload. In addition to parenteral deferoxamine, the only iron chelation agent approved by the U.S. Food & Drug Administration (FDA), oral iron chelating agents, such as the investigative agents deferiprone and deferasirox (formerly ICL670), have proven effective in treating iron overload in thalassemia major patients [31-36]. Ongoing studies seek to determine whether deferasirox, administered once daily as an oral suspension, or deferiprone, administered thrice daily orally, will extend the benefits of iron chelation to more transfusion-dependent MDS patients. This will be especially germane for those patients not currently receiving iron chelation therapy due to logistical difficulties, local reaction, discomfort or pain associated with subcutaneous deferoxamine, and/or adverse effects (visual impairment, hearing loss, allergic reactions).

Growth Factors

Recombinant human erythropoietin (EPO), with or without granulocyte colony-stimulating factor (G-CSF), is used to treat the dyserythropoiesis in MDS patients with symptomatic anemia, specifically those with serum EPO <500 U/L and limited transfusion requirement [24]. EPO in combination with G-CSF relieves

anemia and produces a synergistic effect enhancing erythroid response rates: 40-50% for EPO + G-CSF *vs.* 10-20%, for EPO alone [15,37]. EPO + G-CSF are extremely active pro-erythroid agents; however, they are expensive. Recently, the durability of response achieved with EPO + G-CSF was assessed in a study of 129 MDS patients and was found to be significantly greater in IPSS Low/Intermediate-1 risk patients versus Intermediate-2/High risk patients: 25 months *vs.* 7 months, respectively; P=0.002 [38]. No difference in survival was noted between risk groups.

Emerging Therapies

While a growing number of drugs from different therapeutic categories are being evaluated for the treatment of MDS [5,11,39-43], those furthest along in the development process include 5-azacitidine, which has been approved by the U.S. FDA and is under review in Europe, and decitabine and lenalidomide, which are under review by both U.S. and European regulatory agencies. Ongoing clinical investigations will identify optimal use of these drugs in this difficult-to-treat patient population.

5-azacitidine (azacytidine)

The methyltransferase inhibitor 5-azacitidine promotes the hypomethylation of DNA and produces re-expression of inactivated genes [44]. In a randomized, controlled, phase III clinical trial conducted by the Cancer and Leukemia Group B (CALGB 9221), 191 patients of all FAB subtypes and IPSS categories received either a 16-week course of subcutaneous 5-azacitidine, 75 mg/m^2 for 7 days

every 4 weeks, with supportive care (n=99), or supportive care alone (n=92) [45]. Study participants who received supportive care alone were allowed to cross over to the 5-azacitidine arm after 16 weeks or sooner if disease progression occurred. The majority of patients were elderly (median age: 68), male (69%), and required regular RBC transfusions (65%). The distribution of IPSS categories for those patients who had bone marrow cytogenetics assessments was Low risk: 9%, Intermediate-1: 45%, Intermediate-2: 27%, and High risk: 19%.

Intent-to-treat analysis revealed that treatment with 5-azacitidine produced a significantly higher response rate (CR + PR: 21%) than supportive care alone (0%) ($P < 0.0001$; Chi square test) [45]. During the period of CR or PR, patients who had been dependent on RBC and/or platelet transfusions became transfusion independent, and responses were long lasting (median response duration: 15 months). Hematologic improvement was noted in 37% of patients in the 5-azacitidine treatment arm and 5% of supportive care alone arm. 5-azacitidine therapy was also associated with significant improvement in the following QOL measures: fatigue, dyspnea, physical functioning, affect and psychological distress [46]. Although Kaplan-Meier analysis showed 5-azacitidine to be associated with a significantly longer median time to AML progression (12 months *vs.* 21 months; $P = 0.007$) [44], this endpoint was not a factor in the drug approval because of the study cross-over design (49 patients crossed over to 5-azacitidine treatment) [47]. The most common toxicity associated with 5-azacitidine was myelosuppression [45]. Using standard CALGB criteria, grade 3 or 4 leukopenia occurred in 59%, granulocytopenia in 81%, and

thrombocytopenia in 70% of 5-azacitidine-treated patients [45]. The FDA, in approving 5-azacitidine, concluded that the clinical benefit of response was shown in long-lasting increases in peripheral blood cell counts, which made transfusions unnecessary [47].

5-aza-2'-deoxycytidine (decitabine)

Decitabine is more potent than 5-azacitidine as an inducer of differentiation and as an inhibitor of DNA methylation [48]. Decitabine has been shown to affect the tumor suppressor gene promoter, p15INK4B, which is commonly hypermethylated and silenced in MDS and AML [49,50]. Hypomethylation of other critical genes, global DNA hypomethylation, and mechanisms other than hypomethylation have also been proposed to be responsible for clinical responses in decitabine-treated MDS patients [51-53].

In phase II studies, decitabine treatment of MDS patients led to CR, PR, and hematologic improvement (IWG criteria), as well as major cytogenetic responses (IWG criteria) [54-57] which were more frequent in high- than intermediate-risk cytogenetic sub-groups. In a randomized, controlled phase III trial, 170 MDS patients (IPSS Intermediate-1: 31%, Intermediate-2: 44%; High risk: 26%) received either decitabine (3-hr infusion, 15 mg/m^2/hr q 8 hrs for 3 days q 6 wks) plus supportive care (n=89) or supportive care alone (n=81) [58-60]. Response rates were established following a blinded, centralized bone marrow review. In the decitabine group, the overall response rate was 17% (CR, 9%; PR, 8%), compared with 0% in the supportive care alone group ($P < 0.001$). In addition,

hematologic improvement was noted in 13% of patients in the decitabine group (7% in the supportive care alone group) [60]. Responses were observed in all IPSS groups, and the median response duration was 9 months. Patients treated with decitabine had a non-significant trend toward longer median time to AML or death than patients treated with supportive care alone: 340 days for decitabine *vs.* 219 days for supportive care alone (P = 0.160; log-rank test) [59]. Decitabine responders remained or became RBC/platelet transfusion independent during response. Quantitative QOL instruments showed decitabine to be associated with reduced fatigue and dyspnea, and improved global health status and physical functioning. The incidence of grade 3/4 toxicity (febrile neutropenia, myelotoxicity) was higher in the decitabine arm; however, overall, decitabine was found to be well tolerated, with a manageable toxicity profile.

Recently reported findings from an open-label randomized study that evaluated three daily dose schedules of decitabine in 64 Intermediate-1, Intermediate-2, and High risk patients showed favorable results (CR: 15/32 patients [47%]) with decitabine 20 mg/m^2 IV over 1 hr qd for 5 days [61,62]. This dosage also had the best side effect profile. Retreatment of 22 MDS patients (Intermediate-1, Intermediate-2, or High risk) who had responded to initial treatment with decitabine (median of 6 courses, range: 2-6), with CR (n=12), PR (n=6), or HI (n=4), produced responses (CR, PR, or HI) in 47% of patients after a median of 3 courses [63].

Lenalidomide (CC-5013)

Lenalidomide is an analog of thalidomide, but is a more potent angiogenesis inhibitor and immunomodulator and has a more favorable toxicity profile (no reported teratogenicity at therapeutic doses in any of the animal models treated) than thalidomide. Recent findings from a single-institution study of 43 MDS patients (all FAB subtypes, all IPSS risk categories: Low/Intermediate-1: n=38, Intermediate-2/High: n=5) showed that treatment with this oral agent was associated with hematologic improvement [64]. At baseline, all patients had symptomatic or transfusion-dependent anemia and most were either not responsive to treatment with recombinant EPO or had an endogenous serum EPO >500 mU/mL. Lenalidomide was administered orally once daily (25 mg/d or 10 mg/d or 10 mg/d for 21 days of a 28-day cycle). Hematologic responses were assessed after 16 weeks. Overall, 24 (56%) patients had an IWG erythroid response: 20 patients had sustained independence from transfusion, 1 patient had an increase in the hemoglobin level >2 g/dL, and 3 patients had >50% reduction in the need for transfusions. After a median follow-up of 81 weeks, the median duration of transfusion independence or hemoglobin increase greater than 2 g/dL had not been reached (>48 weeks; range: 13-101 weeks) and the median hemoglobin level was 13.2 g/dL. Patients with lower risk MDS had a greater response rate than higher risk MDS patients: 60% *vs.* 20%, Low/Intermediate-1 *vs.* Intermediate-2/high, respectively. The response rate was highest among patients with deletion 5q, a clonal interstitial deletion involving the long arm of chromosome 5. The most common adverse events were neutropenia and thrombocytopenia. Severe but reversible myelosuppression was dose-

dependent and required temporary interruption of treatment in 47%, 62%, and 77% of patients receiving 10 mg/d for 21 days, 10 mg/d, and 25 mg/d, respectively. In these patients, therapy was resumed at a median of 22 days in each dose group.

In a multicenter phase II trial of lenalidomide, given at a dose of 10 mg/d for 21 days or 10 mg/d, in 148 transfusion-dependent MDS patients with deletion 5q, with or without additional cytogenetic abnormalities, transfusion independence was achieved in 66% of patients with confirmed Low/Intermediate-1 (80/122) compared with 52% of patients with higher risk (13/25) [65]. Responses were assessed after 24 weeks of treatment. A cytogenetic response was achieved in 76% of patients; 55% had a CR. The most common adverse events that required a treatment interruption or dose reduction were neutropenia and thrombocytopenia.

Summary

Currently, there is an urgent need for therapies for MDS patients who are not candidates for HSCT or high intensity cytotoxic chemotherapy. Recent findings from clinical testing of potential therapies in such patient populations demonstrate that 5-azacitidine, decitabine, and lenalidomide, provide clinical and QOL benefits, *and hope*, for a significant number of MDS patients.

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Table 1. World Health Organization (WHO) Classification for MDS

MDS Subtype	PB Blasts	BM Blasts	BM Ringed Sideroblasts	Dysplasia
Refractory anemia (RA)	<1%	<5%	<15%	Dyserythropoiesis alone (>10% dyserythropoietic cells)
Refractory anemia with ringed sideroblasts (RARS)	<1%	<5%	≥15%	Dyserythropoiesis alone (>10% dyserythropoietic cells)
Refractory cytopenia with multilineage dysplasia (RCMD)	<1%	<5%	<15%	>10% dysplastic cells/ line in ≥2 hematopoietic lineages
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	<1%	<5%	≥15%	>10% dysplastic cells/ line in ≥2 hematopoietic lineages
Refractory anemia with excess blasts (RAEB)				
RAEB Type 1	1-4%	5-9%	*	>10% dyplasia in any lineage; no Auer rods
RAEB Type 2	5-19%	10-19%	*	>10% dyplasia in any lineage; Auer rods may be present
5q- Syndrome	<5%	<5%	*	Dyplasia in any lineage (e.g., large mononuclear megakaryocytes)
Unclassifiable MDS	<1%	<5%	0%	Single lineage (not erythroid): ≥10% dysgranulopoiesis or ≥10% of dysmegakaryocytopoiesis

PB: peripheral blood; BM: bone marrow

* Presence of ringed sideroblasts do not influence classification for this subtype

Table 2. International Prognostic Scoring System (IPSS)[1]

Variable	**Points**				
	0	**0.5**	**1**	**1.5**	**2**
BM blasts	<5%	5-10%	—	11-20%	21-30%
Karyotype[2]	Good	Intermediate	Poor		
Cytopenias[3]	0-1	2-3			
	Risk Score				
	0	**0.5 – 1**	**1.5 – 2**	**>2.5**	
Risk Category	Low	Intermediate -1	Intermediate-2	High	
	Predicted Median Survival				
	Low Risk 5.7 years	INT-1 3.5 years	INT-2 1.2 years	High Risk 4.8 months	

[1] Modified from Greenberg P, Cox C, Le Beau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079-2088.

[2] Good = normal, -Y, del(5q) alone, del (20q) alone
Poor = complex (≥3 abnormalities) or chromosome 7 abnormalities
Intermediate = trisomy 8, miscellaneous isolated deletions or gains, double abnormalities

[3] Neutrophils <1.8 x 10^9/L, hemoglobin <10 g/dL, platelets <100 x 10^9/L