Therapy of Myelodysplastic Syndrome

a report by
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Myelodysplastic syndrome (MDS) has evolved from an entity for which no treatment options were available 10 years ago to one where several treatment options are now beneficial. These include:

- growth factors—erythropoietin (EPO) ± granulocyte colony-stimulating factor (G-CSF);
- lenalidomide—US Food and Drug Administration (FDA)-approved for low-risk MDS transfusion dependence and 5q abnormality;
- immunotherapy with anti-thymocyte globulins (ATG), cyclosporine A, and steroids;
- decitabine and azacitidine—FDA-approved for MDS and chronic myelomonocytic leukemia (CMML);
- intensive chemotherapy with topotecan and cytarabine or other anti-acute myeloid leukemia (AML) regimens;
- allogeneic stem cell transplant (SCT);
- oral chelation therapy (to prevent iron overload); and
- imatinib for translocations involving 5q33.

Investigational approaches of significant potential include clofarabine, homoharringtonine, AMG531 (a thrombomimetic agent), and others.

Treatment of MDS depends on patient age, prognostic risk, and comorbid conditions. The availability of these options has resulted in an increase in the documented incidence of MDS from 12,000 cases per year in the US to more than 20,000 cases. This is because more bone marrow studies are now performed in elderly patients with mild cytopenias to obtain a precise diagnosis, which may document MDS and allow early interventions.

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Myelodysplastic Syndrome Classifications

Of several proposed classifications (French–American–British (FAB), World Health Organization (WHO), and International Prognostic Scoring System (IPSS)),[1–3] the IPSS is now commonly used. It divides patients based on the percentage of marrow blasts, karyotype, and degree of cytopenias, into low-, intermediate-1-, intermediate-2-, and high-risk groups, with median survival of 5.6, 3.1, 1.2, and 0.4 years, respectively (see *Table 1*).[1] The IPSS excludes CMML and secondary MDS, and applies only to newly diagnosed MDS.

When previously treated MDS cases referred to tertiary centers following failure of 'standard options' are considered, patient outcome even within 'lower-risk' groups is worse.[4] In general, 'lower-risk' MDS refers to the refractory anemia (RA) and refractory anemia with ringed sideroblasts (RARS) FAB categories, or to low- and intermediate-1-risk IPSS groups. 'Higher-risk' MDS refers to refractory anemia with excess of blasts (RAEB) and efractory anemia with excess of blasts transformed (RAEBT) FAB categories or to intermediate-2- and high-risk IPSS groups. A simple categorization considers higher-risk MDS when the percentage of blasts is ≥10%.

General Treatment Principles in Myelodysplastic Syndrome

Lower-risk MDS constitutes 60–70% of newly diagnosed MDS and 40–50% of treated MDS referred to specialized centers. Here, the initial approaches include: observation; transfusions; growth factors (EPO, G-CSF); immune therapies (e.g. ATG, steroids, cyclosporine); 5-azacytidine or decitabine (more for IPSS intermediate-1-risk or worse), or low-intensity investigational strategies including histone deacetylate inhibitors (e.g. valproic acid (VPA), depsipeptide, suberoylanilide hydroxamic acid (SAHA)); farnesyl transferase inhibitors (FTI) (e.g. tipifarnib, lonafarnib); and angiogenesis inhibitors (tumor necrosis factor alpha (TNF-α)/cytokine inhibitors such as thalidomide or lenalidomide) (see *Table 2*).

Higher-risk MDS is usually treated with decitabine or azacitidine as an initial approach in older patients. Intensive chemotherapy and/or allogeneic SCT are considered in younger patients with favorable karyotypes. The general strategies in MDS are listed in *Table 2* and discussed in more detail below.

Growth Factors

Growth factors with EPO with or without G-CSF reduce transfusion needs, produce responses in 30–50% of patients that are durable for a median of 2.5 years, and improve quality of life (see *Table 3*).[5–9]

Therapy with longer-acting EPO, e.g. darbepoetin (glycosylated form of EPO, longer T1/2), were reported to be associated with erythroid response rates of 35–70%.[9–11] However, on average, all EPOs appear to produce similar results.

Immune Therapy

Immunotherapy with intravenous immunoglobins, ATG, cyclosporine, or steroids appears to produce significant and durable responses in MDS. For example, a recent study by Lim et al. using ATG in 68 patients with MDS resulted in a response rate of 43%. This included major erythroid responses in 20/30 patients, and platelet responses in 20/30 patients (12 major, eight minor).

Responses were durable for a median of 29 months, and were independent of human leukocyte antigen (HLA)-DR status.[13] Responses appear to be better in patients with hypoplastic marrow and normal karyotypes (i.e. situations close to aplastic anemia). However, by multivariate analysis, only younger age and thrombocytopenia were independent good prognostic factors for response.[14] Thus, immunotherapy in early MDS may be a reasonable option after growth factor failure and before low-intensity chemotherapy (e.g. decitabine, azacitidine) is considered.

Farnesyl Transferase Inhibitors

Following several encouraging pilot trials of tipifarnib (Zarnestra, R115777) in MDS, Kuzrock et al.[15] conducted a multi-institutional study of tipifarnib 300mg orally BID x three weeks every four weeks in 82 patients. Their median age was 67 years; 83% had IPSS intermediate-2 or high-risk MDS; 37% had prior therapies.

> Treatment of myelodysplastic syndrome depends on patient age, prognostic risk, and comorbid conditions.

Overall, seven patients achieved complete remission (CR), four had complete remission with low platelets, two had partial remission (PR), and 13 had hematological improvement, for an overall response in 26/82 patients (32%).

The median time to AML transformation was 14 months, and to AML or death 6.4 months; median survival was 12 months. Severe side effects included myelosuppression in 24–37% and fatigue, nausea, diarrhea, or rashes in fewer than 5%. Thus, FTI should be further pursued in investigational studies in MDS.

Table 1: International Prognostic Scoring System Classification

	Score				
Variable	0	0.5	1.0	1.5	2.0
% marrow blasts	<5	5–10	–	11–20	21–30
Karyotype*	Good	Intermediate		Poor	
Cytopenias+	0/1	2/3			

			IPSS Study Group	MD Anderson Study Group[4]	
IPSS Risk	Score	%	Median Survival (years)	Transformation to Acute Leukemia (%)	Median Survival (years)
Low	0				
Intermediate-1	0.5–1.0	33	5.7	19	2.1
Intermediate-2	1.5–2.0	38	3.5	30	1.2
		22	1.2	33	0.7
High	>2.0	7	0.4	45	0.4

* *Good, normal, -Y, del(5q), del(20q); poor, complex (>3 abnormalities) or chromosome 7 anomalies; intermediate, other abnormalities.*

\+ *Definitions of cytopenias: hemoglobin <10g/dl, granulocytes <1.5 x 109/l, platelets <100 x 109/l.*

• *IPSS risk applies to only to newly diagnosed MDS and excludes secondary MDS.*

Table 2: Treatment of Myelodysplastic Syndrome by Risk Category

Lower Risk (blasts <10%)	Higher Risk (blasts ≥10%)
Growth factors—EPO ± G-CSF	5-azacytidine, decitabine
Immune therapy—steroids, cyclosporine, ATG	Investigational—clofarabine
Lenalidomide (5q31)	Intensive chemotherapy (younger, diploid karyotype)
5-azacytidine, decitabine	Allogeneic transplantation
Investigational—tipifarnib, clofarabine, homoharringtonine	

→ *Iron chelation.*

→ *t(5;12) or 5q33 variant (PDGFR-B) - imatinib.*

Thalidomide and Lenalidomide (Revlimid, CC5013)

Thalidomide has previously shown modest activity in MDS with a response rate of 10–20%.[16] Bouscary et al.[17] updated their experience using thalidomide 100–400mg orally daily in 82 patients with MDS, mostly with lower-risk disease (IPSS risk low in 21, intermediate-1 in 44). After three months, 47 of 72 patients continued therapy for three months and only one (2%) had a response.

Thirty-three patients continued therapy beyond six months: six had a major erythroid response and eight a minor erythroid response for a response rate of 28% (14 of 50 evaluable).

Neutrophil and platelet responses were uncommon. The authors concluded that thalidomide may be used at low doses (50–100mg daily) in patients with low-risk MDS/refractory anemia with red cell transfusion dependence.

Lenalidomide is an immunomodulatory inhibitory derivative (IMID) of thalidomide. It is 3,000 times more potent than thalidomide in suppressing TNF-α in pre-clinical models. Unlike thalidomide, it is rarely associated with neurotoxicity and is not teratogenic in one animal model. However, it is myelosuppressive. In a pilot study by List et al.,[18] 45 patients with lower-risk MDS received lenalidomide 10–25mg orally daily. Responses, mostly

Table 3: Growth Factors in Lower-risk Myelodysplastic Syndrome

Study (reference)	No.	G-CSF (mcg)	EPO (u/wk)	% Erythroid response
Negrin[5]	55	150–300/day	50–150,000	48
Hellstrom[6]	63	75–300 TIW	50,000	42
Mantovani[7]	33	100/day	45–80,000	80
Casadevall[8]	30	105 TIW	60,000	58
Literature	340			

G-CSF = granulocyte colony-stimulating factor; EPO = erythropoietin; TIW = three times weekly.

Table 4: Decitabine versus Supportive Care in Myelodysplastic Syndrome

Parameter	Decitabine	Supportive Care	Log Rank (p value)
No. treated	89	81	
% complete response	9	0	<0.001
% partial response	8	0	
Median time to event (months)			
Overall	12.1	7.8	0.16
Intermediate-2 high-risk (n=118)	12.0	6.8	0.03
Treatment-naïve (n=124)	12.3	7.3	0.08

erythroid, were encouraging. Erythroid response was noted in 24 patients (53%; 67% of 36 evaluable patients), and was major in 21 patients. Impressively, 10 of 11 patients (91%) with 5q31 abnormality had erythroid response, and nine of them (82%) had a complete cytogenetic response.

Responses were durable (48+ weeks; range 13+ to 101+ weeks). This encouraging pilot study resulted in two FDA pivotal trials of lenalidomide 10mg orally daily, or daily x 21 every month, in (a) low-risk MDS with transfusion dependence (n=215); and (b) low-risk MDS with 5q abnormality with transfusion dependence (n=148). The results in the low-risk MDS with 5q abnormality were impressive:

- a major erythroid response rate of 66%;
- a complete cytogenetic response rate of 44%; and
- durable responses for a median of two years.[19]

This resulted in the FDA approval of lenalidomide for lower-risk MDS with 5q abnormality and red cell transfusion dependence. Future studies will evaluate lenalidomide + EPO in lower-risk MDS and transfusion dependence and lenalidomide in higher-risk MDS and AML with 5q abnormality, alone, as maintenance post-chemotherapy-induced CR, and in combination with chemotherapy.

> Immunotherapy with intravenous immunoglobins, ATG, cyclosporine, or steroids appears to produce significant and durable responses in MDS.

Hypomethylating Agents and Histone Deacetylase Inhibitors

Global and site-specific DNA methylation induces suppression of regulatory genes, which promotes tumor progression and resistance. This mechanism is shared by many tumors, including hematological cancers.

Protein or histone deacetylation also contributes to this process. Two classes of agents may suppress these processes: hypomethylating agents (5-azacytidine, decitabine) and histone deacetylase inhibitors (valproic acid, depsipeptide, SAHA, and others).

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5-azacytidine

Silverman et al. investigated 5-azacytidine in a series of phase II studies. This led to the phase III study of azacitidine 75mg/m^2 subcutaneously (SQ) daily x seven every four to six weeks versus supportive care.

The final analysis showed an advantage for azacitidine in relation to response rates, time to transformation or death, and quality of life.[20–21] 5-azacytidine resulted in significantly higher CR (7 versus 0%) and overall response rates (63 versus 7%), longer time to transformation or death (median 22 versus 12 months; p<0.01), and a trend for better survival (median 18 versus 14 months, p=0.1), particularly compared with patients who did not cross over from supportive care to 5-azacytidine (by landmark analysis).[20] Of note, 35% of patients had intermediate-2 or high-risk MDS; 15% had prior therapies; and the median MDS duration was two months. The median number of 5-azaycytidine courses was nine.

These results led to the FDA approval of 5-azacitidine for the treatment of MDS and CMML in May 2004. The approval decision was detailed in a recent publication.[22]

Decitabine

Wijermans et al. developed several decitabine studies in MDS, using decitabine 45–50mg/m^2 by continuous infusion daily for three days every 4–6 weeks (135–150mg/m^2 per course).[23] One hundred and sixty-nine patients treated were reviewed. Their median age was 70 years. By IPSS, 48 had intermediate-1, 50 had intermediate-2, and 71 had high-risk disease. Overall, the CR rate was 20%, PR rate 10%, and hematological improvement rate 19%, for an overall response rate of 49%. Platelet increases were observed after one course in 42%, and after two courses in 63%. Median response duration was nine months and median survival 15 months.

Based on these findings, a multi-institutional study was initiated in the US randomizing patients to decitabine 50mg/m^2 daily x three every four to six weeks versus supportive care.[24] One hundred and seventy patients were randomized: 125 had intermediate-2 and high-risk, 45 had intermediate-1-risk, and 124 were-treatment naïve. The results showed a benefit for decitabine in relation to response rates, time to AML or death in higher-risk and treatment-naïve subsets, and improved transfusion needs (see *Table 4*).

This study resulted in the FDA approval of decitabine for the treatment of MDS in CMML in May 2006. The median number of decitabine courses in the above study was three; 43 of 89 patients (48%) received two courses or fewer. In contrast, the median number of courses in the azacitidine study was nine, and the range of courses to CR was 5–15.[22] This suggested that part of the optimization of decitabine and hypomethylation strategies requires timely and repealed courses of therapy before declaring response or failure in MDS.

Following the above experience, the authors sought to optimize the dose schedule of decitabine by investigating, in a Bayesian randomized design, three schedules of decitabine in MDS (total 100 mg/m^2/course in all three arms; 2/3 of the phase III randomized study).[25] Ninety-five patients have been treated; median age 65 years (range 39–90); 67% were >60 years old. IPSS risk was intermediate-1 (33%), intermediate-2 (46%) or high (19%). Cytogenetic abnormalities were present in 56%; secondary MDS in 32%; marrow blasts ≥10% in 45%; and prior therapy in 61%. The median number of decitabine courses was ≥7.

Response by International Working Group (IWG) criteria were: CR 34%, PR 1%, marrow CR 11%, marrow CR + HI 14%, HI 13%; overall response 73%. Compared with an historical group of patients with MDS who received intensive chemotherapy (2000–2004), the CR rate was lower with decitabine, but the overall response rate was favorable; the six-week mortality was also lower with decitabine (2% versus 21%); and estimated survival favorable (p<0.001). The rate was highest with the five-day intravenous (IV) schedule; this schedule also induced the best degree of hypomethylation. There was more myelosuppression with the 10-day IV schedule.

> In leukemia, vorinostat administration resulted in a 15% response rate (four out of 27 patients), including two complete remissions in patients with advanced acute myeloid leukemia.

It was concluded that: decitabine at this low-dose schedule had significant anti-MDS activity in the setting of poorer-risk MDS; the optimal dose was 20mg/m^2 IV daily x five; side effects were acceptable; and timely and repeated courses of decitabine therapy were required for optimal response results.

Table 5: Life Expectancy Estimates (in Years) for Allogeneic SCT in MDS by IPSS Risk and by Whether it was Performed Immediately, Two Years into MDS, or at Progression

	Median Survival (years) if SCT Performed:		
IPSS Risk	Immediately	Two Years Later	At Progression
Low	6.5	6.9	7.2
Intermediate-1	4.6	4.7	5.2
Intermediate-2	4.9	3.2	2.8
High	3.2	2.7	2.7

Current Research with Decitabine and Azacitidine

Ongoing studies include decitabine combinations, particularly with VPA and other histone deacetylase inhibitors. VPA as a single agent has resulted in a response rate of 42% in lower-risk MDS. Among 119 patients treated by Kuendgden et al.[26] with VPA ± all trans-retinoic acid, 25 (21%) had a response: one CR, one PR, and 23 HIs. Response rate was 42% in patients with blasts <5% and 44% in IPSS low-risk.[26] Studies of the combinations are ongoing.[27–29]

> Non-ablative allogeneic stem cell transplant is gaining popularity in the context of myelodysplastic syndrome therapy.

Future studies include combinations of decitabine with vorinostat (formerly SAHA) and LBH589. Both agents are potent hydroxamic acid derivatives with activity in cutaneous lymphoma. In leukemia, vorinostat administration resulted in a 15% response rate (four out of 27 patients) including two CR in patients with advanced AML.[30] LBH589 has also been studied in a phase I study in leukemia.[31] Its administration resulted in rapid control of peripheral blasts but the duration of drug administration was limited by significant QT interval prolongation. An oral schedule of LBH589 is currently being studied.

Another ongoing study includes the combination of 5-azacitidine with MGCD0103, an oral isotype specific histone deacetylase inhibitor. In a phase I study, the maximum tolerated dose (MTD) of MGCD0103 was 60mg/m^2 orally three times a week. Complete marrow responses were observed in three out of 22 patients (13%) with advanced refractory AML.[32] Gore et al. used a combination of 5-azacitidine and phenylbutyrate with encouraging results: 11 of 29 evaluable patients with MDS or AML had a response, including four CRs and one PR.[29]

Intensive Chemotherapy and Allogeneic Transplants

Intensive chemotherapy is associated with CR rates of 40–60% in high-risk MDS, but also with a mortality rate of 20%. Response duration and survival remain poor.[33] In an update of the Memorial Sloan-Kettering experience, 99 patients (median age 43 years)

received intensive chemotherapy for higher-risk MDS. The CR rate was 60%. Allogeneic SCT was performed in 49%. Cure rates post-SCT were 47% in patients transplanted in CR versus 0% in others.[34] This suggest that induction of minimal residual disease pre-SCT in MDS may be beneficial.

Results of allogeneic stem cell transplant (SCT) in MDS remain poor and are limited by patient age, comorbid conditions, and donor availability. The timing of SCT in MDS is also controversial since the potential for long-term event-free survival in 30–40% may be offset by the high early and one-year mortality (about 30%).

Cutler et al.,[35] using Markov modeling, evaluated the benefit–risk of allogeneic SCT versus standard therapy in early or late MDS by whether SCT is performed at MDS diagnosis, two years into MDS, or at the time of transformation. The results suggested that the best survival overall was obtained when patients underwent allogeneic SCT early in higher-risk MDS, but later in lower-risk MD.[35] For example, the estimated median survivals in lower-risk MDS were 4.7–7.2 years if SCT was performed later versus 4.6–6.5 years if it was carried out earlier. In higher-risk MDS, the opposite was true: the estimated median survivals were 3.2–4.9 years if SCT was performed earlier versus 2.7–3.2 years if it was carried out later.

Several studies have updated the results of non-ablative allogeneic SCT in MDS.[36,37] The general trends with non-ablative sibling or unrelated SCT were: it could be performed safely in older age groups (average five to 10 years older); it was associated with less acute graft-versus-host disease (GVHD), and with a lower early (100-day and one-year) mortality rate and with lower rates of severe organ complications (cardiac, gastrointestinal, hepatic, pulmonary); but it resulted in similar rates of chronic GVHD and long-term outcome (considering the older age of patients). Thus, non-ablative allogeneic SCT is gaining popularity in the context of MDS therapy. ■

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