

Therapy for the Myelodysplastic Syndromes

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Hormone Therapy

Corticosteroids have been used to treat most hematologic malignancies, but limited in vitro data and anecdotal cases contraindicate the use of these drugs because they increase the susceptibility to infections in patients with MDS. Androgens do not appear to have a beneficial effect on the clinical course.^(1,2) Activity for danazol in a small number of patients with an associated immune-mediated cytopenia was not noted in other patients.^(3,4)

Single Agent Chemotherapy

Based on its activity in acute myeloid leukemia (AML), cytarabine has been the most widely used agent. Anecdotal reports and small series suggested that cytarabine administered at 10-20% of the standard dose used in the treatment of AML either subcutaneously or by continuous intravenous infusion might be effective therapy for MDS by inducing cellular differentiation,⁽⁵⁻¹⁶⁾ although other reports did not support the activity of this approach.^(2,17-19) In a literature review, the complete remission rate was only 17%, with 19% partial remissions. The median survival was only 15 months. Myelosuppression was reported in 88% of cases, with 15% treatment-related deaths.^(18,19)

Table 1. Intensive Chemotherapy Regimens for MDS

Investigator	Pts	Regimen	CR (%)	Deaths (%)	Toxic
Mertlesmann ⁽³⁸⁾	45	A-T-D	NR		
Armitage ⁽³⁹⁾	20	OAP;ROAP;AdOAP	15	NR	
Kantarjian ⁽⁴⁰⁾	57	AMSA/OAP			
Preisler ⁽²¹⁾	15	HiDAC	13	40+	
Tricot ⁽²⁴⁾	15	HiDAC;D/A	53	33+	
Fenaux ⁽²³⁾	20	R/A;HiDAC	50	30	
Aul ⁽¹⁷⁾	16	DAT	56	13	
De Witte ⁽⁴¹⁾	14	D or Ad/A	64	20	
Estey ⁽⁴²⁾	74	FA;FLAG	58	23	

Abbreviations used in Tables: A - cytarabine; T -6-thioguanine; D - daunomycin; HiDAC - high-dose cytarabine; R- rubidazole; O - vincristine; P - prednisone; Ad - adriamycin; AMSA - amsacrine; FA - fludarabine + cytarabine; FLAG - FA + G-CSF

In a randomized study conducted by the Eastern Cooperative Oncology Group and the Southwest Oncology Group,⁽²⁰⁾ the response rate to cytarabine of 23%, including eight complete remissions, and the median duration of response (8 months) were comparable to

published data.^(18,19) Infections were more frequent in the treatment arm. There was a similar frequency of transformation to AML and no difference in survival.

High doses of cytarabine (e.g., 2-3 g/m² every 12 hours for 6 days)⁽²¹⁻²⁵⁾ have resulted in responses of brief duration.

Anthracyclines and related compounds have had limited study as single agents.^(26,27) Anecdotal activity with azathioprine,⁽²⁸⁾ carboplatin and other cisplatin analogues⁽²⁹⁻³¹⁾ and with etoposide, notably in patients with CMML,^(32,33) have not been substantiated in larger trials.

Recent trials with topoisomerase I-inhibiting agents, such as topotecan, have shown activity in refractory acute leukemia^(34, 35) and appear to be quite active in MDS.

Combination Chemotherapy

Since patients with MDS tend to be elderly, attenuated dose combination chemotherapy has been attempted^(36,37) with low response rates of brief duration

Intensive multi-drug regimens generally induce lower response rates in patients with MDS than with AML, and with greater toxicity (Table 1).

Mertlesmann et al⁽³⁸⁾ performed a retrospective analysis of 263 cases of AML treated with cytarabine, daunorubicin and 6-thioguanine; 45 were reclassified as MDS, and 16 as AML that had evolved from MDS. Of these 61 cases, 48% achieved a complete remission, similar to the 50% for the less differentiated cases of AML but lower than the 59% for AML cases with differentiation. Armitage et al⁽³⁹⁾ treated 20 patients with MDS with daunorubicin and cytarabine, with only three complete remissions and five treatment-related deaths; this treatment appeared to be detrimental. Better results with chemotherapy in MDS are achieved in younger patients and those with more aggressive subtypes of MDS (RAEB, RAEB-T) who have not received prior therapy for their MDS.

Treatment of patients with AML that has evolved from MDS has generally been unsuccessful, with lower response rates, higher mortality and shorter survival than de novo AML^(25,38,43-47) (Table 2).

Whether AML following an antecedent hematologic disorder has a different prognosis from AML secondary to cytotoxic chemotherapy or other toxin exposure is controversial.⁽⁴³⁻⁴⁶⁾ Kantarjian et al⁽⁴⁰⁾ described 112 patients who developed MDS or AML following chemotherapy or radiation therapy for a prior malignancy. In 51% of the patients, MDS was the first presentation, although 55% of these cases subsequently progressed to AML. The CR rate was 15% for patients with MDS and 37% for those with AML. The median survival was significantly shorter for patients with AML than MDS at presentation, and was not different for patients whose MDS progressed to AML. The Medical Research Council's 9th Acute Myeloid Leukemia trial⁽⁴⁵⁾ included 688 patients with primary AML, and 66 with AML following either cytotoxic chemotherapy (n=20), MDS (n=36), or a myeloproliferative disorder (n=10). Induction therapy involved daunorubicin, cytarabine, and 6-thioguanine with a post-remission randomization to either MAZE (amsacrine, 5-azacytidine, etoposide) or COAP (cyclophosphamide, vincristine, cytarabine, prednisolone). The complete remission rate for patients with primary AML was 66%, compared with 25% and 42% for the postcytotoxic therapy and prior MDS patients, respectively. This difference was explained, in part, by a high rate of

resistant disease in the latter two groups. Moreover, the median survival for the post-cytotoxic therapy group was only 58.5 days compared with 125.5 days in the post-MDS group. Neither the duration of remission nor the overall survival of the secondary AML patients were different from the patients with primary AML when stratified for age.

Newer regimens are in development to improve on these results. In vitro data suggest that fludarabine prior to cytarabine markedly augments incorporation of arabinosylcytosine 5'-triphosphate (ara-CTP) into DNA.⁽⁴⁹⁾ Pretreatment of cells with G- or GM-CSF may also increase their sensitivity to subsequent cytarabine. Estey et al⁽⁴²⁾ combined fludarabine (30 mg/m² daily for 5 days) and cytarabine (2 gm/m² over 4 hours beginning 3-1/2 hours after completion of fludarabine (FA)), or FA plus G-CSF (FLAG). Of 43 patients with

Table 2. Chemotherapy for AML Following MDS

Investigator	Pts	Regimen	CR (%)	Deaths (%)	Toxic
Mertlesmann ⁽³⁸⁾	3	ROAP	53		
Keating ⁽⁴³⁾	2	HiDAC	64		
Preisler ⁽⁴⁴⁾	11	D/A	44		
Martiat ⁽⁴⁸⁾	25	R/A;HiDAC	44	44	
Fenaux ⁽²³⁾	9	DAT	21		
Gajewski ⁽⁴⁶⁾	44	D or Ad/A	62		
De Witte ⁽⁴¹⁾	22	DAT	42	25	
Hoyle ⁽⁴⁵⁾	36				

MDS (mostly RAEB and RAEB-T) with adverse cytogenetic abnormalities or an antecedent hematologic abnormality, the CR rate was 55% and 60% with FA and FLAG, respectively.

Multi-drug resistance is present in almost half the cases evaluated^(50,51); however, the clinical relevance of this observation is unknown.

Bone Marrow Transplantation

Allogeneic bone marrow transplantation is the only curative therapy for MDS in both adults and children^(24,52-63) (Table 3).

Unfortunately, most patients with MDS are elderly and, therefore, few are suitable candidates for this procedure. Anderson et al⁽⁵²⁾ described 93 patients with a median age of 29 years (range 4-54 years). Disease recurred in eight patients, for an actuarial probability of relapse of 23%. Relapses occurred only in patients with RAEB and RAEB-T. At the time of the report, 28 of the 59 patients were alive and free of disease 12-215 months after transplant. Twenty-three patients (39%) died from transplant-related complications, most often interstitial pneumonia and graft-versus-host disease. O'Donnell et al⁽⁶¹⁾ treated 20 patients; 45% died of transplant-related complications. Three patients relapsed at 67, 462, and 2922 days following transplant, one of whom underwent a second, successful transplant. Eight patients remained alive and well from 108+ to 3359+

days posttransplant. The European Bone Marrow Transplant Group (EBMTG) published their retrospective experience with 78 patients with MDS or secondary AML,⁽⁵⁶⁾ using various preparative regimens. Disease status at the time of transplant was highly predictive for survival; patients transplanted while in complete remission had a 60% two-year disease-free survival compared with 18% for those who only partially responded to prior intensive chemotherapy. The disease-free survival at two years for previously untreated patients was 58% for RA or RARS, 74% for RAEB, 50% for RAEB-T, and 18% for secondary AML.

Table 3. Bone Marrow Transplantation for MDS

Author ⁽⁶⁴⁾	Regimen	Pts	DFS (mos)	Deaths(%)
O'Donnell ⁽⁶¹⁾	Cy+/-A/TBI	20	8(3+-120+)	45
Belanger ⁽⁵³⁾	Cy/TBI;BuCy	8	5(9+-35+)	25
Bunin ⁽⁵⁵⁾	Cy/Bu/A/MP/TBI	6	3(8+-18+)	33
Kolb ⁽⁵⁹⁾	Cy/TBI;BuCy	7	5(6-34)	29
Longmore ⁽⁶⁰⁾	Cy+/-A/TBI	23	12(6+-102+)	22
De Witte ⁽⁵⁶⁾	Variable	65	32(6+-91+)	31
Gajewski ⁽⁵⁷⁾	BuCy ± TBI	6	3(4-5)	50
Anderson ⁽⁵²⁾	Cy/TBI	93	41%, 4 yrs	43

Thirty-five of the 78 patients were disease-free at 2-91 months; 25 (32%) died of transplant-related complications.

Factors predicting a poor outcome following BMT include extensive bone marrow fibrosis, age greater than 40 years, chemotherapy-resistant disease, longer disease duration and the presence of excess blasts.^(52,56) The use of hematopoietic growth factors and the donor peripheral blood stem cells may reduce the treatment-related morbidity from infections.

Matched unrelated donors and partially matched family members have also been used.^(52,55,57,65) In a report from the National Marrow Donor program of the first 462 cases of matched-unrelated donor transplants, 32 (7%) were for MDS. The median age of these patients was 24 years. The probability of survival at two years was 24%; however, the probability of disease-free survival was only 18%. A matched unrelated transplant is a therapeutic option to be considered for a younger patient (under 40 years) without a suitable family donor, who is experiencing progressive disease.

Biological Approaches

Differentiating Agents

Retinoids have been the most widely studied potential differentiating agents. Initial reports suggested response rates to 13-*cis*-retinoic acid or isotretinoin in MDS from 0% to approximately 20%. Two randomized trials failed to demonstrate any efficacy for

13-*cis*-retinoic acid compared with no treatment.⁽⁶⁶⁻⁶⁸⁾ All-*trans* retinoic acid exhibits a high level of activity in patients with acute promyelocytic leukemia; however, studies in MDS have failed to demonstrate clinically meaningful activity.⁽⁶⁹⁻⁷¹⁾ Both *in vitro* data and anecdotal reports suggest that retinoids may actually accelerate transformation to acute leukemia.^(72,73)

Vitamin D3 induces hypercalcemia but is without clinical activity.⁽⁷⁴⁾

5-Azacytidine, a pyrimidine analogue, is active in AML, but with considerable toxicity. Since the drug also induces *in vitro* cellular differentiation in association with hypomethylation of DNA, it was of interest for study in MDS. Chitambar et al⁽⁷⁵⁾ used a relatively low dose (10-35 mg/m²/d for 14 days) to treat

Table 4. Hematopoietic Growth Factors in MDS

Factor	Reference source not found	Per Cent Increase
GM-CSF	69	28
G-CSF	58	20
IL-3	65	19
EPO	-	-

13 patients, three of whom achieved a partial response. CALGB investigators⁽⁷⁶⁾ conducted a phase II trial of 5-azacytidine at 75 mg/m²/day by continuous infusion for 7 days every 28 days in 48 patients with MDS. They noted 11% complete remissions and 25% partial remissions. Major toxicities included nausea and vomiting; one patient died from neutropenic sepsis. Subcutaneous administration resulted in slightly lower response rates.⁽⁷⁷⁾ A randomized trial is comparing 5-azacytidine with supportive care.

Interferons

Limited activity has been observed with interferon (IFN), along with considerable toxicity.⁽⁷⁸⁻⁸⁵⁾

Hematopoietic Colony-Stimulating Factors

Myeloid growth factors have been extensively evaluated in MDS to decrease the morbidity and mortality associated with prolonged neutropenia and, perhaps, to induce *in vivo* cellular differentiation.⁽⁸⁶⁻⁹⁹⁾

An increased neutrophil count has been observed in 60-70% of patients treated with G-CSF, GM-CSF, or IL-3. Platelet counts improve in 10%; however, a decrease in platelet count, with clinical bleeding, has also been observed. Increased reticulocyte counts have rarely been accompanied by an elevation in hemoglobin or decreased transfusion requirement.

In more than a quarter of cases of MDS treated with G- or GM-CSF, increased bone marrow blasts are observed, with AML developing in a similar number, often with rapid onset and generally not reversible when the growth factor was stopped. Preliminary results from a multi-center randomized trial⁽¹⁰⁰⁾ noted significantly higher neutrophils in the treated group, with no differences in hemoglobin, platelet count, or frequency of transfusions. Frequency of transformation to AML was similar. The cross-over design of

the study confounded any comparison of survival. Myeloid growth factors should be reserved for patients who experience infections with neutropenia.

Serum erythropoietin (EPO) levels are very variable in patients with MDS and do not correlate with erythropoiesis^(101,102); therefore, it is not clear that recombinant erythropoietin will be effective in this disease.⁽¹⁰³⁻¹⁰⁶⁾ Whether combinations including EPO and a myeloid growth factor can improve on these results is under study.⁽¹⁰⁷⁾

Newer hematopoietic growth factors such as PIXY321 (GM-CSF/IL-3 fusion protein), stem cell factor, IL-6, IL-11, and IL-12 are still in early stages of clinical development.⁽¹⁰⁸⁻¹¹²⁾ There has been considerable interest in the recent availability of thrombopoietin.⁽¹¹³⁻¹¹⁶⁾

Conclusions

New treatment approaches are urgently needed for patients with MDS. The results of published studies in MDS are often difficult to interpret because of difficulties in establishing an accurate diagnosis, heterogeneity within MDS subtypes, and the lack of standardized response definitions for MDS.⁽¹¹⁷⁾

The standard therapy for MDS remains supportive care, with judicious use of red cell and platelet transfusions to minimize the risk of alloimmunization, and antibiotics when indicated. Progress towards improved therapy for patients with MDS requires carefully designed and conducted clinical trials addressing important biologic and therapeutic questions.

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