Chemotherapy and Bone Marrow Transplantation for Myelodysplastic Syndromes

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THE MYELODYSPLASTIC syndromes (MDS) are a heterogeneous group of disorders that form a spectrum that ranges from diseases that are relatively indolent (refractory anemia with [RARS] or without [RA] ringed sideroblasts) to those that are more aggressive (refractory anemia with excess blasts [RAEB] and RAEB in transformation [RAEB-t]. Indeed, the line separating RAEB-t and acute myeloid leukemia (AML) is somewhat arbitrary, being primarily based on histopathologic features (30% blasts or the presence of Auer rods), and not clinical features.'.' Variability in bone marrow sampling or counting of bone marrow cells can even shift a patient between the diagnosis of MDS to AML. Moreover, some patients who present with MDS can develop a clinical picture with rapidly increasing numbers of blasts, consistent with AML although not yet demonstrating the requisite number of bone marrow blasts to be called AML.

Although the French, American and British (FAB) subtypes vary in their duration of survival and frequency of progression to AML, MDS are uniformly fatal disorders. Even those cases of MDS that do not progress to AML have a poor prognosis as the result of complications from infection and bleeding?

Chemotherapy has often been used to treat MDS patients because of the similarities to AML, and the lack of effective alternative treatments (eg, retinoids, androgens, vitamin D_3).[4] The chemotherapeutic approaches have ranged from single cytotoxic agents, to attenuated doses of multi-agent regimens, to standard therapy for AML.

SINGLE AGENTS

Most of the chemotherapy drugs that have been evaluated in MDS were selected because of their activity in AML. It is, therefore, no coincidence that cytarabine (Ara-C) has been the agent that has been most extensively used to treat patients with MDS. In contrast to the use of Ara-C in AML, however, this agent has been most often administered at 10% to 20% of standard dose Ara-C (LoDAC). This approach is based on in vitro data suggesting that low-dose Ara-C is a potent inducer of human leukemia cell differentiation? In 1968, Ellison and her Cancer and Leukemia Group B coworkers[6] first reported results in patients with AML using various doses of the new antileukemic agent, Ara-C. Although complete responses (CR) were observed at dose levels as low as 10 mg/m^2 per day, more myelosuppression was observed at 50 to 100 mg/m^2; therefore, lower doses were abandoned. A decade later, Baccarani and Tura[7] described a previously untreated patient with AML treated with 0.7 mg/kg of Ara-C by a 24-hour continuous infusion for 7 days. A partial remission was achieved and maintained for 6 months. They interpreted an increase in the number of bone marrow myelocytes and neutrophils in the setting of persistent, although milder, dyserythropoiesis to indicate that differentiation had occurred. The same investigators subsequently reported their additional experience with "subacute myeloid leukemia" and MDS using 20 to 30 mg/m^2 per day of Ara-C for 7 to 10 days.' A partial response (normal blood counts, but a slight increase in bone marrow blasts) was achieved in 1 of 11 patients with MDS. Transient increases in a single cell line were noted in 3 additional patients (hemoglobin in 1, neutrophils in 2). Wisch et al[9] also reported responses to LoDAC in 8 patients with MDS. Despite the large number of publications that followed, there is a limited role for LoDAC in the treatment of MDS. In a review of over 250 published cases of MDS treated with LoDAC, the CR rate was only 17%, with an additional 19% qualifying as partial remissions (PR).[10,11] Response was not influenced by age, FAB subtype, prior therapy

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for MDS, or schedule of administration (subcutaneous v continuous infusion). The median survival was 15 months, which does not support an impact of therapy on survival. Despite the low dose of Ara-C, myelosuppression was reported in 88% of cases, with more than 15% toxic deaths. Based on clinical features and laboratory correlative studies, the data support LoDAC as a cytotoxic agent, without clinical differentiating activity. A large number of subsequent reports has served only to confirm these impressions. Moreover, combining LoDAC with other putative differentiating agents has not improved on these results."

In a recent intergroup study conducted by the Eastern Cooperative Oncology Group and the Southwest Oncology Group, 140 patients were randomized to either LoDAC or supportive care.[13] Central pathology review excluded 25 cases on the basis of an incorrect diagnosis, 20 of which were reclassified as AML. The overall response rate to LoDAC was 23%, of which 8% were CRs. These results are consistent with the summarized published data." The highest response rate was seen in RAEB-t, with 17% CRs and 25% PRs. The median duration of response was less than 8 months. More infections were noted in the LoDAC arm. The frequency of transformation to AML was similar in the two arms. Most important, there was no difference in survival (8.7 months for LoDAC *v* 6.9 months for supportive care). This study provides convincing data that LoDAC should not be considered standard therapy for MDS.

At the other end of the dose intensity range is the use of high-dose Ara-C (HiDAC) in MDS. Preisler et al[14] treated 15 patients with 3 g/m² (2 gm/m² for patients older than 70 years of age) of Ara-C every 12 hours for 6 days. Complete remissions were achieved in only 2 cases (13%). Peripheral blood counts normalized in 2 other patients, but extensive bone marrow fibrosis precluded CR status. The treatment-related death rate exceeded 40%, and the median duration of survival was only 43 days.

Despite the activity of daunomycin in AML, there has been only limited testing of other anthracycline analogues or related drugs in MDS. Shibuya et al[15] used low doses (3 to 14 mg/m² daily for 7 to 10 days for 2 courses) of aclarubicin to treat 15 patients with MDS or MDS that had transformed into AML. Of the 11 with MDS, 3 patients all with RAEB-t (1 AML) achieved a CR lasting 2 months, 2 months, and 11 months. The use of oral idarubicin has been reported in 14 patients with RAEB (n = 8) or RAEB-t (n = 6), with 1 CR in each subtype.[16]

5-Azacytidine is an antimetabolite that has activity in AML. The drug also induces in vitro cellular differentiation in association with hypomethylation of DNA. Cancer and Leukemia Group B investigators conducted a phase II trial of continuous infusion 5-azacytidine in 48 patients with MDS and noted 11% CRs and 25% PRs.[17] The major toxicity was nausea and vomiting with one patient dying from neutropenic sepsis. Studies to determine if the effect were the result of cytotoxicity or differentiation were not presented. A subsequent study using a more convenient subcutaneous schedule is being pursued. Any enthusiasm for these results should be tempered by the fact that the response rate is similar to the results achievable with LoDAC, although substantial palliative benefit was observed, primarily a reduction in transfusion requirements. Moreover, interpretation of these results is further confounded by the lack of a randomized trial. The analogue 5-aza-2′deoxycytidine has been administered as an intermittent intravenous infusion to eight patients with MDS; one patient with CMML achieved a CR and another a PR, whereas two patients with RAEB-t achieved PRs.[18] Based on alterations in blast cell immunophenotype and a decrease in *c-myc* expression in responders, the authors speculated that the responses were the result of cellular differentiation. However, the lack of two-channel flow cytometry makes this conclusion difficult to support. Moreover, grade 4 neutropenia was encountered in almost half of the responders, and grade 4 thrombocytopenia in over 70% of patients.

Homoharringtonine is a cephalotaxine ester with activity in AML and chronic myelogenous leukemia (CML).[19] Feldman et al[20] treated 11 patients with MDS or AML that had transformed from MDS using a 9-day continuous infusion. There were two CRs and one PR (response by histology was not provided). Other drugs, including oral 6-thioguanine or etopo-

side, have not demonstrated sufficient promise to pursue in large-scale clinical trials.[21,22]

Carboplatin is an analogue of cisplatin that differs from the parent drug primarily in its toxicity spectrum; carboplatin is less neurotoxic and nephrotoxic, but is more myelotoxic. Several recent reports have demonstrated that this agent is active and well tolerated in relapsed AML[23,24] and it merits evaluation in MDS.

COMBINATION CHEMOTHERAPY

Combination chemotherapy for MDS has primarily included traditional regimens for AML (Table 1). Mertlesmann et al[25] conducted a retrospective analysis of 263 cases of AML treated between 1970 and 1978 with Ara-C, daunomycin, and 6-thioguanine. When the blood and bone marrow samples were subsequently reclassified blindly according to the FAB system, 45 cases were believed to be more consistent with the diagnosis of MDS. The CR rate was 48% in this subset of patients, compared with 59% for the AML patients whose leukemia cells exhibited some degree of differentiation, and the survival duration was similar. Armitage et al[26] treated 20 patients with MDS using daunorubicin and Ara-C. They observed only three CRs (15%), all in previously untreated patients with RAEB, and 5 patients died as a result of therapy. A concurrent cohort of 15 patients was managed with supportive care alone because they were believed to be a poor risk for intensive chemotherapy; those with RAEB lived a median of 14 months compared to 1 month for the treated patients, suggesting that the chemotherapy was detrimental. In general, the best results with aggressive chemotherapy in MDS tend to occur in patients who are younger and have not received prior therapy for their MDS.[26-30]

Table 1. Intensive Chemotherapy Regimens for Myelodysplastic Syndromes

Author	PTS	Regimen	CR (%)	Toxic Deaths (%)
Preisler"	15	HiDAC	13	40+
Mertlesmann"	45	AT ± D	51	NR
Armitage[26]	20	DNR/A	15	25
Tricot[27]	15	HiDAC;DNR/A	53	33
De Witte[28]	14	D or Ad/A	64	20
Fenaux[30]	20	R/A;HIDAC	50	30
Aul[34]	16	DAT	56	13

Abbreviations: A, cytarabine; T, 6-thioguanine; D, daunomycin; HiDAC, high-dose cytarabine; R, rubidazone; Ad, Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH).

Table 2. Chemotherapy for Acute Myeloid Leukemia Following MDS

Author	PTS	Regimen	CR (%)	Toxic Deaths (%)
Mertlesmann[25]	16	AT ± D	31	NR
De Wine"	22	D or Ad/A	62	15
Fenaux[30]	9	RIA;HiDAC	44	44
Gajewski[31]	44	DAT	41	21
Keating[32]	32	ROAP	22	53
Martiat[33]	25	DNR/A	24	44
Preisler[37]	11	HiDAC	18	64
Hoyle[38]	36	DAT	42	25

Abbreviations: A, cytarabine; T, 6-thioguanine: D. daunomycin; HiDAC, high-dose cytarabine; R, rubidazone; Ad, Adriamycin; O, vincristine.

The use of multi-agent antileukemia therapy for AML that has evolved from MDS has generally been less effective than for de novo patients with AML (primary AML). Complete remission rates are lower and treatment-related deaths are more frequent than with primary AML (Table 2).[30,31] Both of these factors contribute to the shorter overall survival. Keating et al[32] used rubidazone, vincristine, Ara-C, and prednisone (ROAP) to treat 91 patients with AML, a third of whom had an antecedent hematologic disorder, mostly MDS. The CR rate for the primary AML group was 63% compared with 22% for the secondary leukemias. Martiat et al[33] treated 25 patients with MDS that had transformed into AML, with no antecedent toxin exposure, using daunomycin and Ara-C. A CR was achieved in only 24% of patients, whereas 44% died of complications of treatment-induced myelosuppression. The median survival for this series was 5 months. Gajewski et al[31] treated 196 patients with AML using daunomycin, Ara-C, and 6-thioguanine; CR rates for the 44 patients with AML following a prior hematologic disorder and the 111 patients with primary AML were 41% and 73%, respectively. Moreover, it took longer for bone marrow recovery for the post-MDS patients. Aul and Schneider[34] treated 16 patients with MDS with daunomycin, Ara-C, and thioguanine. There were 9 (56%) CRs and 2 (13%) PRs; all 5 RAEB-t patients achieved CRs compared with 4 of 11 AML with a prior history of MDS. Two patients (13%) died from infection during neutropenia. They treated another cohort of 31 patients with MDS

and 20 with MDS that had transformed into AML with LoDAC. The CR rate for the MDS patients was 16%, 20% for the secondary AML group. The induction death rate was 16% and 35%, respectively. The survival of these patients was similar to their historical controls treated with supportive care only. They concluded that aggressive treatment is more effective than LoDAC in MDS.

Larson et al[35] treated 17 patients with therapy-related MDS or AML with 1 to 3 g/m^2 of HiDAC every 12 hours for 12 doses, followed by intensive consolidation with HiDAC. Death from treatment-induced marrow hypoplasia occurred in 5 patients (27%). Of 8 patients who achieved a CR, cytogenetic analysis was repeated in 7, and a previously existing abnormality was no longer detectable in 6 of these. Nevertheless, the median remission duration was only 5 months, with 7 of the 8 relapsing within 8 months. In contrast is the report by De Witte et al[28] who treated 126 patients with primary AML, 22 patients with secondary AML, and 14 with MDS. Complete remission rates were 67%, 62%, and 64%, respectively. It is likely that the younger age of the patients (median age AML—44 years, secondary AML 47 years, MDS 42 years) was responsible, to a large extent, for the favorable results.

Kantarjian et al[36] described 112 patients who developed AML or MDS 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 for the two groups was 29%; 15% for patients with MDS and 37% for those with AML. The overall median survival was 30 weeks, and was significantly shorter for those patients with AML than MDS at presentation (21 *v* 45 weeks), and did not appear to be different for those patients whose MDS progressed to AML.

Whether AML following MDS and AML following cytotoxic chemotherapy or toxin exposure differ in their responsiveness to chemotherapy is controversial. Preisler et al[37] treated 67 patients with poor risk *AML* (age > 70 years, unable to receive anthracyclines, prior toxin exposure, or a hematopoietic disorder lasting longer than 3 months) with HiDAC. The CR rate for the 23 patients with prior toxin exposure was 61% compared to 18% for the 11 patients with an antecedent hematologic disorder. The difference in response rate reflected an induction death rate of 22% in the former group and 64% in the latter. The Medical Research Council (MRC) 9th Acute Myeloid Leukaemia Trial[38] accrued 688 patients with primary AML and 66 with AML following either cytotoxic chemotherapy (n = 10), MDS (n = 36), or a myeloproliferative disorder (n = 10). For induction therapy, patients were randomized between two schedules of daunomycin, Ara-C, and 6-thioguanine. Patients were again randomized postremission to either MAZE (amsacrine, 5-azacytidine, etoposide) or COAP (cyclophosphamide, vincristine, Ara-C, prednisolone). The CR 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 postcytotoxic therapy group was only 58.5 days compared with 125.5 days for the post-MDS group. However, the duration of remission was not different when stratified for age. The discrepancy between the results from Preisler et al[37] and the MRC may be explained by the small sample sizes, the routine use of consolidation in the MRC trial, or other unspecified patient characteristics.

The negative influence of age has also been observed by other investigators.[27,28,31] The patients reported by Gajewski et al[31] who had post-MDS AML and who were ≥ 64 years of age experienced a 23% CR rate, compared with 48% for the younger patients, although the difference was not significant. However, none of their 13 patients in the older group survived beyond a year, compared with 12% of the younger patients ($P < 0.01$). De Witte et al[28] treated 22 patients with either secondary AML or poor prognosis MDS with aggressive combination chemotherapy; CR rates for those who were 15 to 45 years of age were 75% and 71%, and for those older than 45 years 50% and 57%, respectively.

Although patients with MDS most commonly fail to respond to therapy because of death from marrow hypoplasia, many exhibit clinical drug resistance. *An* interesting observation is that

the gene that codes for the p-glycoprotein has been localized to the long arm of chromosome 7,[39] which is commonly involved in cytogenetic abnormalities in MDS and secondary leukemias. Holmes et al[40] evaluated 19 cases of MDS for the presence of the multi-drug resistance (mdr) phenotype associated with the p-glycoprotein using the mdrl gene probe. Southern blot analysis failed to detect gene amplification; however, 7 patients showed an increase of mdr messenger RNA expression. List et al[41] used a monoclonal antibody reactive with the surface epitope or the cytoplasmic domain of p-glycoprotein to demonstrate p-glycoprotein expression in 7 of 32 cases of primary MDS, and in 4 of 7 cases with leukemia secondary to MDS, and in 5 of 6 cases of therapy-related hematologic disorders. The clinical relevance of these observations remains to be determined.

Less often, attenuated dose chemotherapy has been used for MDS. The rationale for attenuated doses is based on the generally older age of patients with MDS, and their tendency to die from marrow hypoplasia following intensive treatment. Letendre et al[42] treated 18 patients (RAEB-9, RAEB-t-7, CMML-2) with 100 mg/m^2 of Ara-C and 60 mg/m^2 of etoposide (VP-16) as a 1-hour infusion every 12 hours for 5 days. All patients developed severe neutropenia and thrombocytopenia. Nevertheless, there were two unspecified responses lasting 2 and 6 months, and three patients progressed to AML within a month of therapy. Owens and Bennett[43] treated five elderly men (median age 64 years) with RAEB or CMML with attenuated doses of DAT, which required hospitalization. Four of the patients responded with an improvement in blood counts, although with less than would be classified as a CR or PR, lasting 1.5 to 9 months. One patient experienced an early death.

BONE MARROW TRANSPLANTATION

Allogeneic bone marrow transplantation is a rational approach for stem cell disorders such as MDS. One of the earliest reports was published in 1979 of a successful syngeneic BMT followingcyclophosphamide and total body irradiation (TBI).[44] At 6 weeks there was complete hematologic and cytogenetic remission. Unfortunately, no long-term follow-up data were provided. Subsequent studies in both adults and children demonstrating prolonged disease-free survival of greater than 10 years confirm that BMT is the only currently available curative approach for MDS (Table 3).[45-54] Appelbaum et al[50] recently updated their experience with 59 patients, most of whom were treated with cyclophosphamide and TBI. The median age was 29 years (range, 4 to 54 years). At the time of the report, 28 of the 59 patients were alive and disease-free from 12 to 215 months after transplant. Disease recurred in 8 patients, between 14 days and 783 days following transplant, for an actuarial probability of relapse of 23%. The highest relapse rate was observed in patients with RAEB and RAEB-t. Twenty-three patients (39%) died from transplant-related complications, most often interstitial pneumonia and graft-versus-host disease (8 patients each). Younger age was a favorable prognostic factor by impacting on nonmalignant deaths, but not on relapse rates. The degree of marrow cellularity or fibrosis did not appear to influence outcome, consistent with the results of other investigators. An unexpected finding was that patients with clonal cytogenetic abnormalities

Table 3. Bone Marrow Transplantation for MDS

Author	Regimen	PTS	DFS(mos)	BMT-Related Deaths(%)
Tricot[45]	ARA-C/TBI+/−Cy	7	4 (5+-32+)	29
O'Donnell[46]	Cy+/−A/TBI VP-16/TBI;BuCy	20	8 (3+-120+)	45
Belanger"	Cy/TBI;BuCy	8	5 (9+-35+)	25
Bunin"	Cy/Bu/A/MP/TBI	6	3 (8+-18+)	33
Appelbaum[50]	Cy+/−TBI;BuCy	59	28 (12+-215+)	39
Longmore[51]	Cy+/−A/TBI	23	12 (6+-102+)	22
DeWitte[52]	Variable	65	32 (6+-91+)	31
Kolb[53]	Cy/TBI;BuCy	7	5 (6-34)	29
Gajewski[55]	BuCy ± TBI	6	3 (4-5)	50

had a significantly longer disease-free and overall survival than those without such an abnormality. The meaning of this observation is not clear because it has not been verified by other investigators. O'Donnell et al[46] from the City of Hope (Duarte, CA) treated 20 patients (age 4 to 48 years, median 36) with one of four preparative regimens. Nine (45%) patients died of transplant-related complications including interstitial pneumonia (n = 6), gastrointestinal bleeding (n = 2), and fungal sepsis (n = 1). Eight patients remain alive and well from 108+ to 3,359+ days posttransplant. Three patients relapsed at 67, 462, and 2,922 days following transplant, one of whom had a second, successful transplant. Although the number of patients in the series was small, there was no apparent correlation between outcome and FAB subtype, marrow fibrosis, cytogenetic abnormalities, or preparative regimen.

DeWitte et al[52] recently published the retrospective experience from the European Bone Marrow Transplant Group (EBMTG) of 78 patients with MDS or secondary AML. The preparative regimens varied among the institutions, although 69 patients received TBI in addition to chemotherapy. Disease status at the time of transplant was highly predictive for survival; those patients transplanted while in CR had a 60% 2-year disease-free survival compared with 18% for those who only partially responded to prior intensive chemotherapy. The disease-free survival at 2 years for previously untreated patients was 58% for RA or RARS, 74% for RAEB, 50% for RAEB-t, and 18% for secondary AML. Thirty-five of the 78 patients were disease-free at 2 to 91 months; 25 (32%) died of transplant-related complications, mainly interstitial pneumonitis (n = 9) and GVHD (n = 7); and 18 patients relapsed. None of the 8 patients transplanted with chemotherapy-resistant disease survived; 4 died of transplant-related complications, 4 from relapse. Longmore et al[51] transplanted 23 patients with MDS and secondary AML. Of the 12 patients with MDS, 8 were alive with a median follow-up of 2 years, 7 of whom were disease-free. They suggested that T-cell depletion should be avoided in patients with marrow fibrosis because of an increased incidence of graft failure. The authors also concluded that attempts to induce remission prior to BMT were unnecessary based on their success in 10 patients with secondary MDS/AML. The contrast with the conclusions of DeWitte et al[52] may reflect the small sample size, patient characteristics, or other factors that have not been identified.

Sources of bone marrow other than HLA-identical sibling have also been attempted in MDS.[48,53,55,56] Bunin et al[48] described 6 patients treated with BMT using T-cell–depleted bone marrow from a partially matched relative (n = 3) or unrelated donor (n = 3). Four patients engrafted without difficulty. One patient required a second graft because of initial graft failure. Three patients died, 1 prior to engraftment from aspergillosis, 1 at day 257 of recurrent disease, the third at day 515 of pancreatitis and respiratory failure. Three patients are disease-free at 240, 395, and 560 days. Gajewski et al[55] transplanted six patients with MDS with bone marrow from an unrelated donor, three of whom were alive 4, 4, and 5 months after transplant.

Though allogeneic BMT achieves prolonged disease-free survival in approximately 40% of patients with MDS, deaths can be attributed to the transplant in 30% to 40%. The recent availability of hematopoietic growth factors may abbreviate the period of neutropenia and reduce the treatment-related morbidity from infections. However, there is limited evidence currently available to support an improvement in survival. On the other hand, hematopoietic growth factors may also delay consideration of BMT until the patient has developed a more progressive disease, reducing the likelihood of a successful BMT. Although allogeneic BMT has been successful in MDS, the majority of patients with this disorder are elderly and, therefore, only a small proportion of patients would be suitable candidates for this procedure.

Autologous BMT has been used in only a few patients with MDS or AML and a preexisting MDS. Gribben et al[57] reported five cases of secondary AML, all of whom relapsed within 1 year of either a single or double graft. A recent study by the Children's Cancer Study Group identified 18 cases of MDS in a series of 137 patients with MDS or AML referred for allografting or autografting.[58] Patients received a 5-drug induction program of dexamethasone,

Ara-C, 6-thioguanine, etoposide and daunomycin, followed by busulfan and cyclophosphamide as a conditioning regimen. Eight of the 18 patients with MDS underwent successful autografting (W. Woods, personal communication). Long-term follow-up information on these cases will be of interest.

CONCLUSIONS

The optimal therapy for patients with **MDS** is not yet known. Although a substantial number of trials with cytotoxic, biologic, and differentiating agents have been reported: the results of these published studies are often difficult to interpret. One problem is whether all of the cases have been accurately diagnosed. In multi-institutional trials in which central review of bone marrow samples is required, almost 25% of cases diagnosed locally as MDS are rendered ineligible for the protocol because of misdiagnosis; those cases have generally been reclassified as AML.[13] Moreover, there is considerable clinical and biological heterogeneity even within MDS subtypes. Studies are also difficult to compare because there are no standardized response definitions for **MDS.** These issues will become even more problematic as more effective treatments are developed.

The accepted standard therapy for **MDS** has been supportive care, with red cell and platelet transfusions, and antibiotics when indicated. This approach may change markedly, however, with the recent commercial availability of erythropoietin, G-CSF, and **GM-CSF.** There are at least three ways in which these agents may alter the pattern of care. First, they may be used individually or in combination with each other as primary therapy for patients with **MDS.** Unfortunately, as currently used, these agents are palliative; they do not induce CRs, a necessary factor in achieving cure. Whether or not the use of growth factors to reduce the cytopenias will improve survival is being addressed by ongoing trials comparing these agents with either supportive care or placebo. Nevertheless, the cross-over design in one of these trials has made survival comparisons impossible to interpret.[59] Hematopoietic growth factors may also be used to synchronize the malignant cells, making them more sensitive to chemotherapy. For example, both GM-CSF and IL3 preferentially increase the uptake of Ara-C in leukemic cells compared with normal cells.[60-63] Third, growth factors could make intensive chemotherapy an option for a larger number of patients; these agents may ameliorate the toxicities of aggressive chemotherapy, reducing the treatment-associated death rate and, therefore, permitting a greater number of CR.

Whether hematopoietic growth factors will become standard treatment for patients with **MDS** remains to be determined. These agents are expensive, and they are associated with some side effects.[64] There is also the potential for stimulating progression to **AML.** Another consequence of the routine use of growth factors is that there will be an increased number of patients who will not be referred for a clinical trial until they require therapy for secondary AML. It is imperative that a patient who is a suitable candidate for allogeneic bone marrow transplantation be considered for that procedure as soon as possible.

The current recommended treatment strategy for newly diagnosed, asymptomatic patients with MDS involves observation for several weeks, when possible, to assess the biologic activity of the disease. Patients who are clinically stable can be managed with supportive care (eg, intermittent antibiotics and blood components as needed). Initiation of systemic treatment should be considered when there is evidence of clinical deterioration as manifested by repeated infections, a requirement for increasing red blood cell or platelet transfusions, or progression to a more unfavorable histologic subtype. When indicated, treatment should be dictated by clinical and laboratory factors. An occasional patient whose clinical picture is characterized by symptomatic anemia may benefit from erythropoietin, although, to date, responses to this factor have been infrequent.[64,65] Those patients with neutropenia and recurrent infections as their primary feature may respond to **G-CSF, GM-CSF,** or **IL3.** Patients with RA or **RARS** or CMML with favorable prognostic features can be considered for treatment with potential differentiating agents, hematopoietic growth factors, or various combination approaches, or possibly bone marrow transplantation. Unfortunately, none of the currently avail-

able hematopoietic growth factors is associated with a consistent improvement in thrombocytopenia, and they may even worsen thrombocytopenia in a small proportion of patients. Patients with RAEB or RAEB-t, CMML, or others with poor risk features are candidates for cytotoxic therapy, either combination chemotherapy with or without the use of growth factors, or, if eligible, allogeneic bone marrow transplantation.

Whatever therapy is most appropriate for a particular patient, based on clinical and biologic characteristics, should be delivered in the context of a carefully designed and conducted clinical trial. These trials should include biologic correlates such as cytogenetics, oncogenes, and growth factor receptors so that we may increase our understanding of the biology of these disorders leading to a more rational approach to therapy.

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