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Recent Advances in Myelodysplastic Syndromes

Guest Editors: Miguel Angel Sanz, Guillermo Sanz & Teresa Vallespí

Prognosis and therapy of secondary myelodysplastic syndromes

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Abstract

This is an invited review of a condition that is likely to become increasingly frequent in coming years. The objective is to define the varying prognoses of the condition and to discuss treatment options for patients with better and worse prognoses. The source of the data is the literature. Of particular note are the paper by Greenberg *et al.* describing the International Prognostic Scoring System for MDS and that by Estey *et al.* describing the similar response of AML, RAEB-t, and RAEB to AML-type chemotherapy. The *state of the art* is that no satisfactory therapeutic options exist; consequently, the majority of patients with secondary MDS should participate in clinical trials.

Key words: International Prognostic Scoring system, erythropoietin, G-CSF, AML-type chemotherapy, topotecan, allogeneic transplant

Secondary myelodysplastic syndromes (secondary MDS) are those that present in patients who have received chemotherapy ± radiation therapy, generally for a malignancy such as Hodgkin's disease or breast cancer. The review immediately preceding this one deals with chromosome abnormalities and their relationship to prior therapy in patients with secondary MDS, as well as clinical characteristics of secondary MDS. This review will focus on prognosis and treatment of these disorders.

In medicine it is axiomatic that treatment is determined by prognosis. Indeed many different prognostic systems have been developed for patients with MDS.[1-5] These were essentially based on data from patients with primary MDS. In the early-mid 1990s the authors of the principal papers dealing with prognosis of MDS collaborated in establishing an *International Prognostic Scoring System* (IPSS). This system derived exclusively from 816 patients with primary MDS that was treated (until possible development of AML) only with transfusions or, in a small number of patients, low-dose oral chemotherapy or hematopoietic growth factors. The IPSS uses information about blood counts, cytogenetics, and percent marrow blasts to distinguish four prognostic groups, *low*, *INT-1*, *INT-2*, and *high*, with very different survival expectations.[6] The system was qualitatively if not quantitatively verified in another center, that had not participated in development of the IPSS. It is fair to say that the IPSS system is likely to become the world-wide standard.

It has been shown that the principal reason that secondary AML has a worse prognosis than primary AML is its association with chromosome abnormalities such as deletions or monosomies involving chromosomes 5 and/or 7 often with other, complex changes.[7] That is, once cytogenetics are accounted for there is only a relatively small difference in outcome between primary and secondary AML. Given the above it is reasonable to ask if the IPSS, which uses cytogenetic information, would effectively stratify patients with secondary MDS. To address this issue, we examined data from 78 patients with secondary MDS (RA, RAS, RAEB, RAEB-t, or CMML with WBC count <12,000/μL) treated at M.D. Anderson before 1991, the year when we began to systematically give patients with refractory anemia with excess blasts (RAEB) or RAEB-in transformation (RAEB-t) AML-type chemotherapy. The 78 patients were in general given hematopoietic growth factors (HGFs) ± low-dose ara-C (10-15 mg/m^2 per dose) or transfusions only, at least until development of AML. Table 1 analyzes survival in these 78 stratified by the IPSS, and compares survival in the 78 with survival in 217 patients with primary MDS also treated at M.D. Anderson before 1991 and given the same type of therapies as the secondary MDS patients. As expected given the association between secondary MDS and cytogenetic abnormalities, the secondary MDS patients are much more likely than primary MDS patients to be placed in the worse prognosis IPSS categories (especially IPSS high). There is some evidence that the IPSS effectively stratifies secondary MDS patients (Figure 1, log-rank p-value .08 with a very small number of low and INT-1 patients). There is nothing to support a difference in outcome between primary and secondary MDS patients within a given IPSS category. This is shown in Figure 2 for the INT-1 category. In addition to sample sizes, the reader must bear in mind that primary MDS patients at M.D. Anderson have lower survival probabilities than the primary MDS patients seen in hospitals contributing to the IPSS, although the reasons are unclear. Nonetheless, the M.D.

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Table 1. Application of IPSS to secondary MDS.

IPSS category	Number of patients with secondary MDS	Number of patients with primary MDS	Survival percentiles 25th Secondary	25th Primary	50th Secondary	50th Primary	75th Secondary	75th Primary
Low	5 (6%)	29 (13%)	1.3*	1.0	1.6	2.1	2.4	2.5
INT-1	14 (18%)	89 (41%)	0.4	0.6	0.7	1.2	2.0	2.8
INT-2	30 (38%)	66 (30%)	0.3	0.3	0.5	0.7	1.3	1.4
High	29 (37%)	35 (16%)	0.2	0;2	0.5	0.4	0.8	1.1

**All units are in years.*

Anderson data suggest that the IPSS is applicable to patients with secondary MDS. It should be noted that I have dealt exclusively with survival rather than transformation to AML. This reflects the fact that 70% of patients with primary MDS die of complications of their disease without transformation to AML (55% even in the IPSS high category).[6]

Treatment of secondary MDS

Better prognosis

The quotes here indicate that this definition is inherently subjective; however, for purposes of this discussion I will use it to refer to the small percent of secondary patients whose median predicted survival is in excess of two years using the IPSS (e.g. low or INT-1 categories) assuming it has been validated, or it is reasonable to expect that it could be validated, at the hospital where the patient is being treated. The principal options for these patients are transfusions only, use of erythropoietin (EPO) ± granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF), or use of other low intensity therapies (i.e. non AML-type chemotherapy) in the context of a clinical trial. An exception to the recommendation for use of low intensity therapies in these patients might be made for allogeneic transplant as discussed later. Regardless of the therapy chosen, several points about transfusions should be emphasized. First, several studies have shown that consistent use of the iron chelator desferrioxamine can remove tissue iron, lessen the likelihood of organ dam-

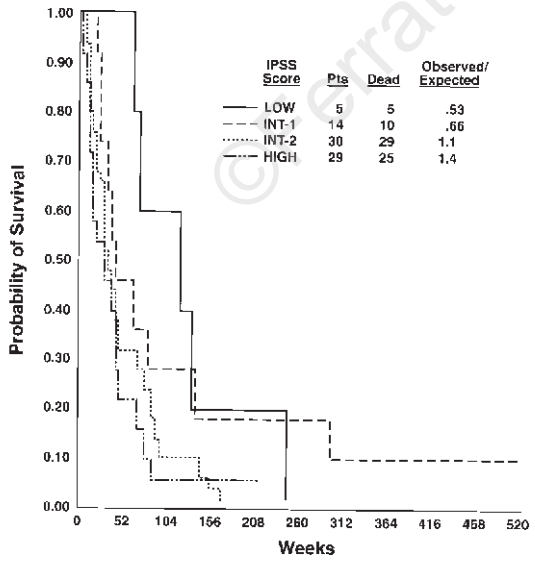

Figure 1.Survival probability by IPSS score for 78 M.D. Anderson patients with secondary MDS. The "observed expected" column refers to the number of deaths compared to the number expected given the follow-up (Log-rank statistic, p-value = .08).

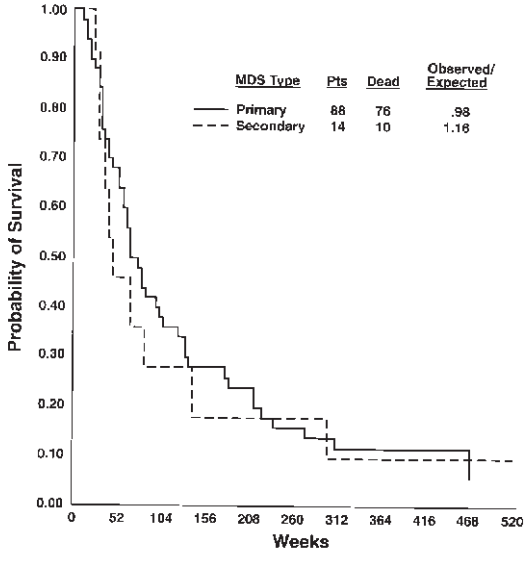

Figure 2.Survival probability for IPSS score INT-1 patients according to whether they had primary or secondary MDS. P-value = .638. Data for other IPSS categories are similar.

age, and prolong survival.[8-10] It has been recommended that chelation therapy begin after cumulative transfusion of 10-20 units of packed red cells.[11] Second, the routine use of platelet transfusions below a fixed level of 20,000/μL should be discouraged. Even in patients receiving chemotherapy for AML it has been demonstrated that routine transfusions only at lower levels are equally effective.[12-13]

At least 20 studies describing use of EPO in MDS have appeared. Hellstrom et al used a meta-analysis to summarize the results in 17 of these involving 205 patients.[14] The pre-treatment prognosis of the patients was not explicitly stated; however it seems likely that a substantial number had IPSS scores of low or INT-1 (e.g. 75% had < 5% marrow blasts) although the vast majority had a hemoglobin < 10.5 g/dL or were transfusion-dependent pre-treatment. At any rate it is not clear that IPSS score would be predictive of response to EPO. Response, defined as a stable hemoglobin without need for further transfusion, or, in patients who were not transfusion-dependent pre-treatment, a hemoglobin > 15 g/dL was seen in 16% (95% CI 12-22%) with rates varying between 0-44% in the various studies. Most of the responses were seen within the first 8 weeks of therapy. Flu symptoms were the most common side effect but occurred in < 5% of the patients. The principal predictors of response were FAB diagnosis (sideroblastic anemia vs RA or RAEB), serum EPO level (≤ 200 vs >200) and transfusion need (yes or no). Among the 8 groups formed by the various permutations of these parameters the lower boundary of the 95% confidence limit for response was >20% in patients with RA or RAEB (not RAS) who were not transfusion dependent and whose serum EPO level was < 200. Rose *et al.*'s paper[15] lent further weight to the prognostic value of diagnosis (RAS unfavorable) and serum EPO level but not transfusion requirements, although it is unclear if the Rose *et al*.'s patients' pre-treatment transfusion requirements were similar to those in the meta-analysis. Given the data I would recommend a three-month trial of EPO in RA or RAEB patients with a serum EPO level <200 provided the patients fit in IPSS low or INT-1 categories and have no need for platelet transfusions.

Another possible therapy for these patients is the combination of G-CSF+EPO. Negrin *et al.*[16] gave G-CSF beginning at 1 μg/kg/day and increasing until the neutrophil count was normal, or if normal initially, twice the starting value. G-CSF was then continued and EPO added at 300 μ/kg/day. Fifty-five patients were treated, the majority of whom appear to have been in IPSS categories low or INT-1, although 76% were transfusion dependent. Using a definition of response similar to that used in the EPO meta-analysis,[14] Negrin *et al*.[16] reported a response rate of 25% with 95% confidence interval overlapping those reported for EPO in the meta-analysis. Although this would suggest that there is little to distinguish EPO+G-CSF from EPO, it is noteworthy that Negrin *et al.* reported patients in whom response initially observed with the combination subsequently disappeared when EPO was continued by itself, only to be observed again with re-addition of G-CSF. Second, it is not clear that the Negrin et al patients were similar to those in the EPO meta-analysis. It would be interesting to do a regression analysis on the combined meta-analysis and Negrin et al groups looking at treatment (EPO vs EPO+G-CSF) as one of the potential predictors of response. GM-CSF+EPO vs GM-CSF+placebo have been compared in 66 patients (all with hemoglobin < 10 g, transfusion dependency, and RA, RAS, or RAEB) stratified by baseline EPO level.[17] 45 patients were randomized to 12 weeks of EPO (150 μ/kg 3 x weekly)+GM-CSF (0.3-1.0 μg/kg daily to maintain neutrophil count ≥ 1500) and 21 to GM-CSF alone. Results suggested that hemoglobin values were less likely to fall in the GM+EPO groups and that transfusion requirements were decreased in the GM+EPO patients with low EPO levels.

Other low-intensity options for better-prognosis patients are 5-azacytidine and amifostine. The CALGB has conducted two trials of the former.[18] CR (as in AML) rates of 10-15% have been reported with improvement in blood counts reported in another 25-30%. The CALGB is accruing patients into a randomized trial comparing subcutaneous 5-azacytidine with observation. Use of amifostine in MDS was first reported by List *et al*.[19] The great majority of patients appear to have had IPSS scores of low or INT-1. 9 of 10 patients *evaluable for hematologic response* had improvement in blood counts; specifically 6 patients had a rise in reticulocyte count(on the order of 1.3-4.1%), 3 of 7 red cell transfusion dependent patients had a >50% decrease in red cell requirements while platelet count increased (16000 to 110,000/μL) in 4 of 7 patients with thrombopenia. Obviously even the 90% confidence limits about these rates would be very wide. Hence before recommending amifostine for routine use it appears important to obtain more data in the context of clinical trials, several of which are in progress.

At M.D. Anderson about 20% of patients with secondary MDS present with marrow cellularity ≤ 20%. In the subset of these patients with better prognoses a trial of antithymocyte globulin (ATG) ± cyclosporin might be worthwhile, given the success of these regimens in patients with aplastic anemia[20] and the possibility of overlap between aplastic anemia and RA or RAS. At the 1996 meeting of the American Society of Hematology Moldrem *et al.* reported a CR (as in AML) rate of 18% (95% CI 5-40%), and a PR (≥ 50% recovery of ≥ 1 lineage) rate of 23% (95% CI 8-43%) in 22 patients of whom 19 had RA or RAS and hence were likely to be in the low or INT-1 categories of the IPSS.[21] Of note, the marrow cellularities of the patients were 30-100%. This is another treatment that, given the relative lack of data, needs further eval-

uation in formal clinical trials.

Low intensity therapies that would be difficult to recommend are G-CSF or GM-CSF, and low-dose cytosine arabinoside (ara-C). Although either CSF is virtually certain to raise the neutrophil count, neither has been reported in a manuscript to improve parameters such as infection rate or survival, although two large multicenter drug company-sponsored randomized placebo-controlled trials (1 involving GM-, the other G-CSF) were initiated over 5 years ago. Indeed Greenberg et al noted that RAEB patients had shorter survival when given G-CSF rather than placebo.[22] This may have reflected the worse prognosis of the G-CSF treated patients although no covariate-adjusted survival analysis was presented. After a meta-analysis of outcome with low-dose ara-C (LDAC), Cheson *et al.* reported a CR rate of 16% (95% CI 11-23%), finding *little evidence that achieving a CR exerted a substantial effect on survival* and concluding that until *appropriate indications can be identified LDAC should not be routinely used in clinical practice.*[23] The ECOG and SWOG randomized 140 patients to receive LDAC (10 mg/m^2 Q 12h for 21 days) or supportive care only and found no difference in survival between the two groups.[24] Furthermore, LDAC is clearly myelosuppressive,[25] and thus its classification as a *low intensity therapy* is debatable.

Worse prognosis

The majority of patients with secondary MDS would be expected to be dead within two years, e.g. have IPSS scores of INT-2 or high. Obviously the therapeutic options in these patients might be expected to differ from those in better prognosis patients. Specifically, higher intensity, hence more risk-laden, therapies, in particular AML-type chemotherapy and allogeneic transplantation, would be higher on a priority list. However, two cautions need to be expressed. First, it is not clear that these therapies improve survival compared to the therapies discussed in the previous section, except perhaps in a subset of patients, as discussed below. Second, there are clearly patients with worse prognosis secondary MDS who because they are old, have a poor performance status, or abnormal organ function are not candidates for higher intensity therapies and might benefit from some of the previously discussed lower intensity therapies.

The rationale for use of AML-type chemotherapy in secondary MDS is essentially the rationale for the use of the same in secondary AML. In fact, it has been demonstrated that after accounting for covariates such as cytogenetics, length of abnormal blood counts, age, and performance status results of AML-type chemotherapy appear independent of morphologic diagnosis (AML, RAEB-t, or RAEB), i.e. it is these other factors, not morphology, that determine response.[26] Hence, reasons for not administering AML-type chemotherapy to patients with MDS and IPSS scores of INT-2 or high might include cytogenetics, age etc., but not morphologic diagnosis *per se*. Of course, because patients with secondary MDS usually have cytogenetic abnormalities that are associated with poor response to standard AML therapy, it is difficult to argue for use of such therapy in secondary MDS, just as it is in secondary AML. However, given the natural history of secondary MDS in most patients, the likelihood that, by analogy to AML and other cancers, the treatment which is most likely to extend survival is that which eliminates all evidence of disease and restores normal hematopoiesis (i.e. a CR), it appears reasonable to offer AML-type therapy to patients with secondary MDS and unfavorable prognoses in the absence of treatment, provided the AML-type therapy is investigational and conducted within the context of a clinical trial. An exception to this guideline might be made if the patient presented with a normal karyotype (and an IPSS score of INT-2 or high). It has been reported that perhaps up to 40% of patients under age 60 with a normal karyotype can expect a CR lasting ≥ 2 years following administration of currently available AML-type chemotherapy,[27-28] particularly if high-dose ara-C based. Whether these results would obtain in secondary MDS patients with a normal karyotype is debatable and probably could be determined only after a lengthy trial given the relative rarity of a normal karyotype in secondary MDS.

As noted above however, the great majority of secondary MDS patients who are candidates for AML-type therapy should receive newer, investigational agents. Three such agents are deoxyazacytidine (DAC), topotecan, and all-trans retinoic acid (ATRA) combined with chemotherapy. DAC is a pyrimidine analogue that is of interest because of its ability to inhibit DNA methylation and hence perhaps promote differentiation. Wijermans et al reported on its use in 27 patients with MDS, the majority of whom appear to have been in IPSS categories INT-2 or high.[29] CRs occurred in 8 patients (95% CI 13-50%) including one with a t(8;21), unlikely to occur in secondary MDS. Indeed the CR rate in patients with prognostically unfavorable karyotypes (as defined in AML patients given standard chemotherapy) was 2/14 (95% CI 2-43% vs 6/13 (95% CI 19-75%) in patients with other karyotypes. Median CR duration was 40 weeks and median survival less than one year, i.e. probably no different than the natural history of the untreated diseases. DAC invariably produced 3-4 weeks severe pancytopenia, hence its classification as a *higher intensity* therapy and raising a question as to the role of methylation vs cytotoxicity in its mechanism of action. The observation that the same relation between cytogenetics and response was seen as with standard drugs suggests that DAC qualitatively resembles those drugs, although it might profitably be combined with them.

Topotecan interacts with the enzyme topoisomerase I, leading to cell death. Beran et al reported

Table 2. CR rates with topotecan-containing chemotherapy by karyotype.

	Topotecan		Topotecan+Ara-C		Total	
	Pts	CR	Pts	CR	Pts	CR
Normal karyotype	15	3	19	12	34	15 (44%)*
Chromosome 5 and/or 7 abnormality	15	5	17	12	32	17 (53%)*

**95% confidence limit for the difference [-.15,.24].*

on its use at a dose of 2 mg/m^2 daily x 5 days in 25 patients with CMML,12 with RAEB and 10 with RAEB-t.[30] Among patients who had received no chemotherapy for their disease, CR rates were 6/16 (95% CI 15-65%) for CMML, and 5/16 for RAEB or RAEB-t. Among previously treated patients the CR rate was 1/9 (95% CI 0-50%) for CMML and 1/6 (95% CI 0-64%) for RAEB or RAEB-t. Although the seemingly poor outcome in previously treated patients suggests that topotecan is qualitatively similar to more standard drugs, the CR rate in patients with a normal karyotype was 3/15 vs 9/28 in patients with abnormal karyotypes (5/15 in those with abnormalities of chromosomes 5 and/or 7). This suggests that topotecan might be a useful drug particularly in patients with cytogenetic abnormalities associated with poor response to more standard therapies. Topotecan (1.25 mg/m^2 daily days 1-5 CI) has subsequently been combined with ara-C (1 g/m^2 daily days 1-5).[31] Again the response rate appears similarly high in patients with a normal karyotype and patients with abnormalities of chromosomes 5 and/or 7 (Table 2). Considering both topotecan and topotecan + ara-C, the 95% CI for the difference in CR rate between the two cytogenetic groups is [-.15, .33]. This suggests that it is highly unlikely that topotecan will produce a CR rate in patients with abnormalities of chromosomes 5 and/or 7 that is 15% worse than that observed in patients with a normal karyotype. There are few if any other drugs about which the same could be said. Although the –5/–7 patients given topotecan may have been favorable in other ways or the normal karyotype patients unfavorable, it is clear that topotecan is an interesting drug in secondary MDS, given the association of the latter with abnormalities of chromosomes 5 and/or 7. Furthermore, although topotecan and topotecan+ara-C are highly myelosuppressive, the induction mortality rate has been <10%.

ATRA is of interest in AML, and by extension MDS, because, added to chemotherapy, it decreases recurrence rates in APL, perhaps because it decreases concentrations of proteins such as BCL-2 that interfere with chemotherapy-induced apoptosis.[32] When combined with fludarabine+ara-C+idarubicin in a small randomized trial in patients with AML, RAEB-t, or RAEB who are either over 70, have secondary disease, or a history of abnormal blood counts, ATRA has to date prolonged survival, disease-free survival from start of treatment and from time of CR compared to the same chemotherapy without ATRA, although it remains to be seen if the same will apply after accounting for factors such as cytogenetics.[33]

Allogeneic marrow transplant (allo-t) is another option for patients with secondary MDS. As with chemotherapy, results are more dependent on the patients transplanted than on the regimens used (e.g. busulfan (BU) +cyclophosphamide (CY) + total body irradiation (TBI) vs CY+TBI,[34] or BU-CY vs TBI-containing regimens)[35] and also as with chemotherapy, once ≥ 3 years have elapsed from transplant failure is unlikely.[36] Hence 3-year DFS rates are of interest. Several groups have reported an inverse relation between blast percent and DFS following allo-t.[36-37] Thus patients with RA may have DFS rates of 60% vs ≤ 30% for patients with RAEB or RAEB-t. Within the RA subset shorter disease duration (relative risk (RR) 1.13/year), younger age (RR 1.52/decade), higher neutrophil count and higher hematocrit are independent predictors of survival.[38] For example, patients treated in Seattle within one year of diagnosis (n = 40) had a 3-year actuarial survival rate of 65% vs 30% for patients (n = 10) receiving transplants ≥ 3-years after diagnosis. These data have led to the recommendation that allo-t be done early in the course of MDS. This recommendation must of course be weighed against the natural history of the disease, which of course is likely to be most favorable in the very patients who do best with allo-t, i.e. younger patients without excess blasts. In this context, it will be of interest to determine if duration of disease is an important predictor of the natural history of MDS and to determine the probability of long-term DFS following allo-t in the low, INT-1, INT-2, and high risk categories of the IPSS. This type of information would allow more informed decisions about the advisability of transplant.

Given the association of secondary MDS with cytogenetic abnormalities that are prognostically unfavorable in patients given standard AML-type chemotherapy it is of interest to determine the prognostic effect of cytogenetics in MDS patients given an allo-t as well as to examine the allo-t results in secondary MDS. With regard to the latter Anderson *et al.* reported a 3-year actuarial DFS rate of 25%[36] and O'Donnell *et al*. a 2-year actuarial survival rate of 25%.[35] However, the number of patients (8 in each series) results in exceptionally wide 95% confidence limits, e.g. 1-62% in the O'Donnell *et al.* series, and in general there is insufficient data to form even limited conclusions about allo-t in secondary MDS *per se*. The Seattle investigators found that patients with a normal karyotype had better DFS and survival than patients with abnormal karyotypes (relative risks .435 and .535 respectively following multivariate analysis).[34] While other series have not been able to

demonstrate an effect of cytogenetics, the number of patients has been small. Perhaps relevant to this issue is the finding that in AML transplanted in first remission the effect of cytogenetics is similar to that seen in AML treated exclusively with chemotherapy.[39] Furthermore, Sutton *et al.* found that MDS patients who had received, and largely failed, AML-type therapy prior to allo-t had worse outcomes than patients who had not, again suggesting the qualitative similarity of chemotherapy and allo-t in MDS.[37] In a recent letter Anderlini et al noted that the 3 year DFS probability for 84 patients with CMML, RAEB, or RAEB-t age < 60 given AML-type chemotherapy at M.D. Anderson was 24 ± 5% with a median censoring time of 1.3 years.[27] These results were essentially similar to those reported by Anderson *et al.* in patients with similar diagnoses who received an allo-t (median censoring time 1.7 years).[34] Allowing for possible differences in patient selection and characteristics, Anderlini et al emphasized that patients under age 60 with RAEB, RAEB-t, or CMML particularly those with a normal karyotype should not be considered to necessarily benefit more from allo-t than AML-type chemotherapy. The same would apply to an allo-t from a matched unrelated donor especially as results from this procedure appear worse than those following allo-t using a matched sibling donor.[40]

To a large extent the argument over whether allo-t or AML-type chemotherapy is superior for poor prognosis, e.g. secondary MDS, misses the point that neither therapy is currently satisfactory for these patients. Hence the focus should be on development of new chemotherapy and transplant strategies. Some examples of the former were discussed above. Examples of investigational transplant regimens include cyclosporin or FK507 withdrawal to stimulate the graft-vs-leukemia effect, and use of less ablative regimens followed by infusion of peripheral blood stem cells rather than bone marrow.[41] Such regimens may improve DFS by decreasing death in remission rates and thus make it possible to transplant patients over age 70 or with poor performance status in whom the primary obstacle to allo-t has been the fear of toxicity.

Disclosures

Conflict of interest: none.

Redundant publications: the author has written review on MDS before. These were also invited articles. In contrast to those papers, which were written earlier, this paper contains information about the IPSS and therapeutic options such as topotecan, amifostine etc.

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