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Recent Advances in Myelodysplastic Syndromes
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A patient-oriented approach to treatment of myelodysplastic syndromes

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Abstract

Background and Objective. **There are several therapeutic options for patients with myelodysplastic syndrome (MDS) but most of them are poorly effective and the potentially curative ones are available only for a minority of individuals. The aim of this article is to define a rational basis for a patient-oriented approach to treatment of MDS.**

Evidence and Information Sources. **All four authors have done clinical studies of treatment of MDS, including stem cell transplantation, intensive and low-dose chemotherapy, and use of hematopoietic growth factors. They also participated in the Fourth International Symposium on MDS (Barcelona, 24-27 April 1997). In addition, the present review critically examines relevant articles and abstracts published in journals covered by the Science Citation Index® and Medline®.**

State of the Art and Perspectives. **At present, the only two treatments that can prolong survival are allogeneic stem cell transplantation (SCT) and intensive chemotherapy, but only a minority of MDS patients can really benefit from them. The heterogeneity of MDS patients, the wide variety of patient inclusion criteria and transplant procedures used, and relatively small numbers of patients in the individual reports of allogeneic SCT make it difficult to draw many definitive conclusions. However, approximately 40% of patients with MDS who are eligible for allogeneic SCT are likely to be cured by this treatment. Intensive chemotherapy with a combination of cytosine arabinoside and an anthracycline should be offered to all patients with an increase in bone marrow blasts who are not eligible for allogeneic SCT, especially those patients up to 65 years of age. Complete remission rates are similar to those obtained in patients with acute myelogenous leukemia, but probability of long-term survival is low. The remaining treatments validated in clinical trials (erythropoietin and / or granulocyte colony-stimulating factor, low-dose cytosine arabinoside) can improve the efficiency of hematopoiesis in subsets of patients. Responsive individuals might experience an improvement in quality of life but very few studies have addressed this question so far. The majority of MDS patients still rely upon supportive therapy. A clinical decision path based on findings of clinical trials and the patient's expectations can help physicians in decision making. Because of the inadequacies of all current treatment modalities, participiation in clinical trials should always be encouraged.**

Key words: myelodysplastic syndromes, therapy

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Recent papers in this journal have analyzed the pathogenesis and clinical features of myelodysplastic syndromes (MDS).[1-5] For the purpose of this article on the therapy of MDS, the following two points need to be recollected:

a) MDS are clonal disorders of hematopoiesis in which peripheral blood cell production is inefficiently sustained by hematopoietic progenitors belonging to the abnormal clone(s).[1] A few observations indicate that the normal hematopoietic stem cell reservoir may be preserved early after diagnosis,[6] but undergoes decline with time, so that most patients with long-lasting, advanced disease would have very few normal residual stem cells left;

b) Although the disease progression is highly variable from patient to patient, the International Prognostic Scoring System (IPSS)[7] provides an improved method for evaluating prognosis in individual MDS patients, as long as they remain untreated.

The list of therapeutic options available for MDS patients is as long as the list of names previously used for defining these conditions.[8] Unfortunately most of these therapeutic tools are poorly effective, especially when given to unselected patient populations, while the potentially curative ones (see later) are available only for a minority of individuals. Facing an individual patient with MDS and bearing the above considerations in mind, as clinicians we first have to define treatment objectives. We basically have three choices:

1) to avoid any manipulation of hematopoiesis

and just rely upon supportive therapy;

2) to stimulate normal residual hematopoietic progenitors and/or improve the efficiency of the myelodysplastic hematopoiesis;

3) to eradicate the myelodysplastic clone and restore a normal (autologous or allogeneic) polyclonal hematopoiesis.

We will first consider the single therapeutic options within each of the above categories and then shall propose a patient-oriented approach to MDS therapy.

Therapeutic options for MDS patients

Before making therapeutic decisions we recommend that the diagnostic process be carefully reviewed in order to be sure that the individual patient has MDS. This diagnosis is often difficult and diagnostic errors are possible, some being quite common while others more rare. Among the former must be included megaloblastic anemia and anemia associated with other disorders. With respect to more subtle misdiagnoses, Cotter *et al.*[9] reported a previously unaffected 77-year-old male who developed severe anemia: the initial diagnosis was sideroblastic anemia with ring sideroblasts. This patient responded dramatically to pyridoxine with normalization of hemoglobin values. Since anemia was microcytic, he was studied for point mutations in the erythroid-specific delta-aminolevulinate synthase gene (ALAS2) and found to have an A to C transversion in exon 7. This patient therefore had a late-onset form of X-linked sideroblastic anemia,[10] which can be distinguished from refractory anemia with ringed sideroblasts (RARS) by microcytosis, pyridoxine-responsiveness, and ALAS2 mutations.

Watchful-waiting strategy

The approach to a patient with MDS should begin with a period of observation, with sequential peripheral blood counts – and sometimes bone marrow examinations – to assess the rate of progression, if any. Not all patients need be treated. A considerable portion of MDS patients have Hb levels > 9-10 g/dL, neutrophil count > 0.5×10^9/L and platelet count > 50×10^9/L. In elderly patients such Hb levels may be compatible with a reasonably good quality of life, and the above degrees of granulocytopenia and thrombocytopenia are generally not troublesome and can just be followed regularly. In addition, occasional patients may have spontaneous improvement in blood counts.

Responses of anemia to androgens,[11,12] of granulocytopenia to corticosteroids,[13] and of thrombocytopenia to danazol[14] have been reported but they do represent the exception rather than the rule, and anecdotal positive evolution in a few patients cannot be formally ascribed to a drug. For instance, a careful study did not support a positive effect of danazol in MDS patients during long term follow-up.[15] Therefore, we do not recommend the regular use of androgens and/or corticosteroids in MDS patients. If the clinical condition is stable and a curative treatment is not feasible, close follow-up with no treatment may be the best choice.

Table 1. Criteria for supportive therapy in MDS patients.

Anemia

Red cell transfusions should be given when anemia is symptomatic.

Any low or intermediate-1 risk patient (with an average life expectancy > 4 years according to the IPSS[7]) who has received at least 30 blood transfusions or whose serum ferritin is ≥ 1,000 µg/L should be regularly treated with subcutaneous desferrioxamine, 30-40 mg/kg daily for 5 days a week.

Granulocytopenia

Since there is no clear evidence that regular administration of G-CSF can prevent infective episodes and/or prolong survival in neutropenic MDS patients, this use is not recommended. However, individual patients may benefit from short-term treatment with G-CSF during an infective episode.

Thrombocytopenia

Platelet transfusions should be given when the platelet count drops below 10×10^9/L, or with higher platelet counts during hemorrhagic episodes.

Supportive treatment

Once a cytopenia becomes symptomatic, supportive therapy with blood products and conservative measures are still the mainstay of therapy (Table 1).

Symptomatic anemia requires regular transfusions of red cells, and transfusional iron overload is inevitable. One unit of blood (400 mL) contains about 200 mg of iron, so that the annual burden may be 2-4 g on average. Although transfusional iron is primarily taken up by the reticuloendothelial cells, it is later redistributed to parenchymal cells, with the redistribution rate being proportional to erythroid proliferation and plasma iron turnover. When the body iron load exceeds 100-200 mg/kg, secondary hemochromatosis develops and liver disease, diabetes mellitus, hypogonadotropic hypogonadism, and eventually heart failure may occur.[16]

We believe that any low or intermediate-1 risk patient (with an average life expectancy > 4 years according to the IPSS[7]) who has received at least 30 blood transfusions or whose serum ferritin is ≥ 1,000 µg/L should be regularly treated with subcutaneous desferrioxamine, 30-40 mg/kg daily for 5 days a week. Long-term desferrioxamine iron chelation therapy has been proven to be effective not only in retarding but even reversing organ damage caused by transfusional iron overload.[17] Individuals with poor compliance to a conventional subcutaneous pump, may benefit from subcutaneous bolus injections (1 g twice dai-

ly).[18] In most instances, this latter posology may represent the most practical way of desferrioxamine administration. Regular iron chelation therapy with desferrioxamine may reduce red blood transfusion requirements and improve the degree of cytopenia in MDS patients.[18,19] However, the mechanism underlying these effects is unclear and these findings require confirmation in prospective clinical trials. The use of deferiprone (L1) as an oral iron chelator must be considered strictly experimental for several reasons, including the risk of agranulocytosis.[20,21]

Treatment of infections should follow standard criteria. There is no clear evidence that the regular use of granulocyte colony-stimulating factor (G-CSF) can prevent infective episodes and/or prolong survival in neutropenic MDS patients, so that we do not recommend its routine use.[22-25] However, individual patients may benefit from a short-term treatment with G-CSF during an infective episode, particularly in the case of fungal infections.

Severe thrombocytopenia can be a major clinical problem in some MDS patients. A recent study in leukemic patients[25] has clearly shown that the risk of major bleeding during induction chemotherapy is similar with platelet-transfusion thresholds of 20×10^9/L and 10×10^9/L. Therefore, we recommend using the lower threshold in MDS patients as well.

Differentiating agents

The rationale for differentiation therapy in MDS is to overcome the phenotypic differentiation arrest and to induce a normalization of differentiation with normally functioning mature cells. Based on the findings with leukemic cell lines, clinical trials have been performed with retinoic acids, vitamin D3, interferons, hematopoietic growth factors, certain chemical differentiation inducers, e.g. hexamethylene bisacetamide (HBMA), and combinations of these.[27]

13-cis-retinoic acid (13-cis-RA) was the first retinoid to be studied in the treatment of MDS (Table 2).[28-38] Treatment had to be given for prolonged periods. The response rates were small with no prolongation of survival. Two randomized trials have been reported. In the trial by Clark *et al.*[33] in 98 patients, the treatment group received 20 mg/m^2/day 13-cis-RA while control patients received only supportive care; in patients with more than 5% blasts in the marrow, low-dose cytosine arabinoside (ara-C) was initially given, and 13-cis-RA was added after 12 weeks. There was no difference in overall survival after 25 months, except in a selected group of 39 patients with no ring sideroblasts and <5% bone marrow blasts treated with 13-cis-RA. Koeffler *et al.*[35] conducted a randomized double-blind trial in which 68 patients received either 13-cis-RA at a dose of 100 mg/m^2/day or placebo for 6 months. There was no difference between the two arms with regard to hematologic response, leukemic progression, or overall survival. The dose of 13-cis-RA was relatively high and not well tolerated. Dose limiting factors are hepatotoxicity with an elevation of liver enzymes and hyperbilirubinemia. Addition of α-tocopherol seems to improve the tolerability,[37] although not improving the response rate.

Based on the impressive results in acute promyelocytic leukemia (APL), all-trans-retinoic acid (ATRA) was studied in patients with MDS (Table 3).[39-46] Used as a single agent the results have been disappointing. An exception might be the use of ATRA in patients with chronic myelomonocytic leukemia (CMML) where it might reduce pancytopenia;[44] however, this suggestion stems from a pilot study and consequently needs to be confirmed by a prospective randomized trial.

The role of vitamin D3 analogues has been studied in several trials (Table 4).[47-50] No sustained hematologic effects were observed. At higher dosages, hypercalcemia and increases in the serum creatinine levels are the dose-limiting adverse events. However, vitamin D3 derivatives might reduce the rate of leukemic transformation either when used alone[50] and in combination with low-dose ara-C and 13-cis retinoic acid.[51] Further trials combined vitamin D3 with 13-cis retinoic acid and – in the case of increased bone marrow blast cells – with 6-thioguanine.[52]

Both α- and γ-interferon have been studied in several clinical trials (Table 5).[53-62] In general, the

Table 2. 13-cis-retinoic acid in the treatment of myelodysplastic syndromes.

Authors	*No. of patients*	*Dose per day*	*Duration of therapy*	*Response (%)*
Gold et al, 1983[28]	15	20-125 mg/m^2	7-30 weeks	33
Greenberg et al, 1985[29]	18	1-2 mg/kg	> 2 weeks	17
Swanson et al, 1986[30]	10	2.5-4 mg/kg	8 weeks	30
Picozzi et al, 1986[31]	15	2.5-4 mg/kg	4 weeks	33
Kerndrup et al, 1987[32]	8	20-100 mg/m^2	> 6 weeks	12
Clark et al, 1987[33]	18	20 mg/m^2 (±ara-C)	52 weeks	17
	16	control		25
Leoni et al, 1988[34]	20	50-100 mg m^2	> 4 weeks	60
Koeffler et al, 1988[35]	35	100 mg/m^2	6 weeks	3
	33	control		6
Hast et al, 1989[36]	8	1 mg/kg	4 weeks	38
	10	25 mg	12 weeks	0
Besa et al, 1990[37]	66	100 mg/m^2 (+ tocopherol)	24 weeks	23
Bourantas et al, 1995[38]	34	10-60 mg/m^2 (+ tocopherol)	12-250 weeks	12

Table 3. All-trans retinoic acid in the treatment of myelodysplastic syndromes.

Authors	*No. of patients*	*Dose (mg/m²/day)*	*Duration of therapy (weeks)*	*Response (%)*
Visani et al, 1992[39]	2	45	8-10	2/2
Ohno et al, 1993[40]	23	45	> 4	3/23
Aul et al, 1993[41]	14	30-90	12	0
Kurzrock et al, 1993[42]	29	10-250	8	1/29
Baldus et al, 1994[43]	5	45	3-9	0
Cambier et al, 1996[44]	10	45 (± hydroxyurea)	> 8	4/10
Ganser et al, 1994[45]	15	45 (+ G-CSF)	12	3/15
Ganser et al, 1996[46]	17	25 (+ G-CSF/EPO/tocopherol)	8-16	6/17

Table 4. Vitamin D3 in the treatment of myelodysplastic syndromes.

Authors	*No. of patients*	*Dosage*	*Effects*
Metha et al, 1984[47]	6	1 µg /day for > 12 weeks	None
Koeffler et al, 1985[48]	18	up to 2 µg/day for 12 weeks	Transient hematopoietic in 8 patients
Richard et al, 1986[49]	7	2.5 µg/d for at least 8 weeks	None
Motomura et al, 1991[50]	15	4-6 µg/day for a median of 17 months	Hematopoietic improvement in one patient;
	15	none (control)	Prolonged transformation-free survival in treated group

response rates have been low, and only a few sustained responses, including complete remissions, have been reported. The major adverse effect is myelosuppression.

Hematopoietic growth factors which can also act through differentiation-inducing mechanisms are dealt with separately below (see below *Hematopoietic growth factors* section).

While low-dose cytosine arabinoside was initially thought to act by inducing differentiation, it is now generally accepted that its main mode of action is suppression of the leukemic clone (see *Low dose ara-C in combination with growth factors*). Based on *in vitro* findings, the polar-planar solvent hexamethylene bisacetamide (HMBA) was studied in two clinical trials[63,64] (Table 6). Several remissions were obtained, although the overall response rate was low.

Table 5. Interferons in the treatment of myelodysplastic syndromes.

Authors	*No. of patients*	*Dose (mg/m²/day)*	*Duration of therapy (weeks)*	*HR (%)*
IFN-α				
Elias et al, 1987[53]	14	2×10^6 U, 3×/week, 2 wks/month	8	0/14
Catalano et al, 1989[55]	10	3×10^6 U/day	12	4/10
Gisslinger et al, 1990[56]	10	$2\text{-}35\times10^6$ U/week	6-144	3/10
Petti et al, 1996[58]	17	$0.5\text{-}3\times10^6$ U, 3×/week	8-120	8/17
Hellström et al, 1988[59]	18	3×10^6 U/day (+13-cis-RA, vit D_3)	16	9/18
IFN-γ				
Schwarzinger et al, 1990[60]	8	0.1 mg/m²/day, 2 wks/month	12	3/8
Maiolo et al, 1990[61]	30	0.01 or 0.1 mg/m², 3×/week	up to 148	13/30
Stone et al, 1993[62]	2	1-10 mg/m²/day	2	0/2

Legends: HR = hematologic response.

A higher response rate was obtained with 5-azacytidine which intracellularly reduces the DNA methyltransferase activity and thereby leads to hypomethylation. An overall response rate of 47%, including 11% complete remissions, was found among 44 patients receiving a dosage of 75 mg/m²/day,[65] whereas less impressive results were obtained with lower dosages (Table 6).[66,67] Another analog, 5-aza-2'-deoxycytidine, induced a complete remission in four out of ten patients.[68] Newer approaches, which according to the authors exert their action partially by differentiation induction, use homoharringtonine.[69]

Trials combining various agents aim to take advantage of additive or synergistic actions to induce differentiation. The results of combining various hematopoietic growth factors, e.g. erythropoietin with either G-CSF or GM-CSF, will be presented separately. The combination of low-dose ara-C with 13 cis-retinoic acid in 14 MDS patients was disappointing with only one partial remission.[70] Better results were seen after a combined treatment with IFN-α, 13-cis-retinoic acid and vitamin D3 with a partial response in 9 of 18 MDS patients.[59] The combination of ATRA with G-CSF in 15 MDS patients resulted in a combined transient increase of platelets and neutrophils in 3 patients, while neutrophils increased in nearly all.[45] The addition of erythropoietin and tocopherol to ATRA/G-CSF led to a trilineage hematopoietic response in 6 out of 17 MDS patients.[46] Patients with an increase in hematocrit also had an increase in their

Table 6. Chemical inducers in the treatment of myelodysplastic syndromes.

Authors	*No. of patients*	*Dose (mg/m²/day)*	*Duration of therapy (wks)*	*Resp. (%)*
Rowinsky et al, 1992[63]	16	HMBA* 24 g/m²/day x 5 every 28 days	8-10 weeks	0/16
Andreeff et al, 1992[64]	24	HMBA 24 g/m²/day	10 days	5/24
Chitambar et al, 1991[66]	15	azacytidin (10-35 mg/m²/day)	14 days	3/15
Silverman et al, 1993[67]	44	azacytidin (75 mg/m²/day)	7 days	21/44
Wijermans et al, 1997[68]	29	azacytidin (40-75 mg/m²/day)	3 days	15/29
Zagonel et al, 1993[68]	10	decitabin (45-50 mg/m²/day)	3 days every 6 wks	4/10
Feldman et al, 1996[69]	28	homoharringtonine (5 mg/m²/day)	9 days	8/28
Omoto et al, 1996[132]	21	melphalan (2 mg/day)	continuously	8/21
List et al, 1997[72]	18	amifostine	3 times weekly for 3 weeks	15/18

Legends: wks = weeks; HMBA = hexamethylene bisacetamide.

BFU-E numbers.[71]

Aminothiol amifostine, which in vitro can promote the formation and survival of primitive hematopoietic progenitors derived from MDS patients, has been evaluated in a phase I/II trial.[72] This study showed that amifostine administered intravenously at doses ≤ 200 mg/m² three times a week was well tolerated and produced single- or multi-lineage hematologic responses in 15 out of 18 MDS patients.

Although leading to some encouraging results *in vivo*, the ways by which the differentiation-inducing agents actually work, have remained largely unresolved. Further clinical trials are necessary and should concentrate on the low-risk groups of MDS, i.e. refractory anemia (RA) and RARS. Further patient populations are the elderly not qualifying for the intensive chemotherapy and stem cell transplantation.

Hematopoietic growth factors

Recombinant human erythropoietin (rHuEpo)

Anemia is a major clinical problem in MDS with many patients being adversely affected by transfusion-dependency and secondary hemochromatosis. The phase I-II studies on the use of rHuEpo in MDS have been previously reviewed.[73] Overall 15 to 20% of patients with myelodysplastic syndrome respond to rHuEpo treatment but the vast majority of responders are not transfusion-dependent and the doses required to achieve response are > 450 IU/kg per week.[74-76] Factors predicting response include serum erythropoietin levels < 100 mU/mL, female gender, no or mild transfusion requirement and normal karyotype. MDS are stem cell disorders, so that the typical anemic MDS patient is expected to have a high serum Epo level, i.e. an appropriately increased endogenous Epo production. It is therefore unclear why some individuals show inappropriately low Epo levels, although it is now established that serum Epo reflects a balance between renal production and erythroid consumption.[77]

Recognizing potential responders to rHuEpo can be extremely important in individual cases of MDS.[78] In general, we favor a patient-oriented approach to the use of rHuEpo where the physician carefully evaluates the individual patient's needs and likelihood of reponse:[73] such approach can also be applied to MDS patients.

G-CSF, GM-CSF, IL-3 and IL-6

GM-CSF increases neutrophil counts in 64 to 100% of treated patients.[79-83] Other types of white blood cells, particularly eosinophils and monocytes, also increase in response to treatment. Interestingly, similar response rates were found in studies using high doses (60-500 µg/m²/day) and in those using low-doses (0.2-0.5 µg/kg/day). One randomized study on GM-CSF versus observation has been performed.[84,85] As expected, neutrophil counts significantly increased; hemoglobin levels and incidence of leukemic transformation were not influenced while there was a clear decrease in platelet count in the GM-CSF treated patients. The first preliminary report showed a tendency towards fewer infections in the actively treated group, but the study has not been reported in final form. A positive effect of GM-CSF on the frequency of infections has also been suggested, however, this was not proven in another study.[86]

G-CSF has been used in a similar way as GM-CSF. A couple of phase I-II pilot studies showed significant effects on neutrophil counts in the majority of patients.[23,87] Long-term results showed that neutrophilic response could be maintained for up to 30 months.[24] A randomized study between G-CSF and observation showed a significant G-CSF induced increase in neutrophil counts but no difference in hemoglobin levels and, as for GM-CSF, a significant reduction of platelet counts.[25] Overall survival and evolution to acute myeloid leukemia (AML) were not influenced by treatment. The finding of a poorer survival in patients with refractory anemia with excess of blasts (RAEB) treated with G-CSF was probably related to a higher proportion of high-risk patients in this group. Comparing GM-CSF with G-CSF, side effects were milder during G-CSF treatment. GM-CSF tended to give more general side effects such as flu-like symptoms, capillary leak symptoms and local reactions at injection sites.

With the aim of inducing trilineage responses in MDS, interleukin-3 (IL3) was used in two phase I-II trials.[88,89] Granulocyte counts increased in 40-78% of the

patients while hemoglobin values were unchanged. Some single patients had a significant increase in platelet counts, while worsened thrombocytopenia was observed in others. Treatment-induced fever was frequently observed. The combination of GM-CSF and IL 3 was used in a small phase I study with essentially negative results.[90]

Interleukin 6 was used in a phase II study of 22 patients with MDS and thrombocytopenia.[91] About one third of the patients showed increased platelet counts, but reduced hemoglobin levels were observed in almost all patients and the significant toxicity of the drug was dose-limiting and prevented in most cases long-term treatment.

rHuEpo combined with G-CSF or GM-CSF

Based upon the hypothesis that the addition of other cytokines might improve the response to rHuEpo, several clinical trials have studied the combination of rHuEpo with G-CSF, GM-CSF or IL 3 (Table 7).

The hitherto largest experience is with the combination of G-CSF and rHuEpo. The first two phase I-II pilot studies showed response rates of 38 and 42%, respectively, suggesting that the response rate to this treatment was better than that with rHuEpo alone.[92,93] Both study groups then proceeded with enlarged studies. Additional data from the American study, showed that around 50% of the patients with a response to the combination lost their response when G-CSF was withdrawn and regained it when G-CSF was reintroduced.[94]

In a phase II study 56 MDS patients were randomized to treatment with G-CSF plus rHuEpo according to one of two alternatives: arm A staring with G-CSF for 4 weeks followed by the combination for 12 weeks, and arm B starting with rHuEpo for 8 weeks followed by the combination for 10 weeks.[95] The overall response rate to G-CSF plus rHuEpo was 38% and there was no difference between the two arms. Twenty patients entered long-term maintenance treatment and showed a median duration of response of 24 months. These findings provide evidence of an *in vivo* synergy between the two drugs.

Four additional studies have examined the effects of G-CSF plus rHuEpo.[96-99] In two of these, results were comparable with the larger studies while two failed to show a good response to treatment. The reason for this might have been the lower rHuEpo dose used in these *negative* studies. Data from the Scandinavian and American studies have recently been put together in a joint multivariate analysis, showing that serum erythropoietin (< 100 mU/mL, 500-1000 mU/mL or > 500 mU/mL) and the level of pre-treatment transfusion needed (< or ≥ 2 units per month) are good predictors of erythroid response to treatment and may be combined in a predictive model.[100] The response rates in the good, intermediate and poor groups were 74%, 23% and 7%, respectively.

GM-CSF and rHuEpo have been combined in four smaller phase II studies (Table 7).[101,104] In these studies, 5 out of 23 patients with a documented lack of response to rHuEpo alone responded to the combination. In a preliminary reported randomized phase II study a synergistic effect of the two drugs was suggested in patients with serum Epo values < 500 mU/L.

Interleukin 3 and rHuEpo show synergistic effects *in vitro* but have not met with the expectations in two reported preliminary clinical studies.[106,107] Only minor hematologic improvements have been observed along with substantial adverse reactions including eosinophils and induction of TNF-α.

Table 7. Recombinant human erythropoietin in combination with other growth factors in the treatment of myelodysplastic syndromes.

Authors	*No of patients*	*Treatment*	*Erythroid response*
Negrin et al, 1993[92]	24	rHuEpo+G-CSF	42%
Hellström-Lindberg et al, 1993[93]	21	rHuEpo+G-CSF	38%
Bessho et al, 1994[96]	7	rHuEpo+G-CSF	57%
Imamura et al, 1994[97]	10	rHuEpo+G-CSF	10%
Musto et al, 1994[98]	12*	rHuEpo+G-CSF	0%
Ganser et al, 1996[99]	17	rHuEpo+G-CSF+ ATRA	35%
Negrin et al, 1996[94]	44*	rHuEpo + G-CSF	48%
Hellström-Lindberg et al, 1998[95]	56	rHuEpo+G-CSF	38%
Hansen et al, 1993[101]	11	rHuEpoO+GM-CSF	27%
Runde et al, 1995[102]	8	rHuEpo+GM-CSF	25%
Bernell et al, 1995[103]	13°	rHuEpo+GM-CSF	23%
Musto et al, 1996[104]	10	rHuEpo+GM-CSF	20%
List et al, 1994[106]	16	rHuEpo+IL-3	14%
Verhoef et al, 1994[107]	8	rHuEpo+IL-3	13%

Number of patients refers to number of evaluable patients. Response rates use criteria in each article. The difference in response rates between the studies by Negrin and Hellström-Lindberg is explained by different response criteria (50% and 100% reduction in RBC transfusion needed respectively).
**Whereof 24 reported in 1993.*
°All non-respondent to erythropoietin alone.

Low-dose chemotherapy

The first studies on treatment of preleukemia with low doses of chemotherapeutic agents were published almost twenty years ago.[108,109] The reasons for initiating these studies included the extremely poor results of high-dose chemotherapy in MDS patients at that time, and the hypothesis that low-dose chemotherapy might act via different mechanisms than the higher doses and induce differentiation of the malignant cells.

Table 8. Selected studies with low-dose chemotherapy in MDS.

References	*Study*	*No. of pts**	*Treatment*	*Response°*
Castaigne et al, 1983[113]	phase II	21	ara-C	71%
Tricot et al, 1984[115]	phase II	26	ara-C	46%
Powell et al, 1988[116]	phase II	38	ara-C	35%
Aul et al, 1989	phase II	51	ara-C	26%
Cheson & Simon, 1987[119]	review	266	ara-C	25%
Hellström et al, 1992[120]	phase II	102	ara-C	29%
Miller et al, 1992[121]	phase III	53	ara-C	32%
Gerhartz et al, 1994[124]	phase II	108	ara-C+GM	24%
Gerhartz et al, 1996[125]	phase III	37 46 47	ara-C ara-C+GM ara-C+IL3	49% 28% 45%
Im et al, 1994[126]	phase II	21	ara-C+G	33%
Harada et al, 1993[128]	phase II	18	aclarubicin	44%
Johnson et al, 1987[129]	phase II	13	idarubicin[#]	54%
Greenberg et al, 1993[131]	phase II	42	idarubicin[#]	2%
Omoto et al, 1996[132]	phase II	21	melphalan	38%
Wattel et al, 1996[134]	phase III	53[@] 52[@]	hydroxyurea etoposide	60% 36%

**Number of patients refers to number of evaluable patients, actively treated with the drug. Studies include patients with MDS and MDS-AML.*
°Response rates; CR and PR as defined by each article. Minor responses excluded.
[#]Johnson used a dose of 50 mg/m², d 14-21 and Greenberg a dose of 2 mg/day for 21 days.
[@]Only patients with chronic myelomonocytic leukemia.

Low-dose ara-C

Low-dose ara-C has been extensively used in MDS (Table 8) and its mechanisms of action have been widely discussed. A predominant cytotoxic effect was proposed by some authors,[110] while others suggested the possibility of both cytotoxic and differentiating effects.[111] As suggested by recent studies, induction of apoptosis is probably an important mechanism in this setting.[112] In the first clinical studies, response rates up to 71% were reported.[113] This gave rise to a series of smaller and larger phase II studies, which, however, never could repeated the initial results. In these studies, the response rates varied between 26-46%.[114-116] Low-dose ara-C has mostly been given subcutaneously, 10-30 mg/m²/day, divided into two daily doses for 2-8 weeks, but some of the earlier studies used the intravenous route with comparable results.[117] Very low doses, down to 6 mg/m²/day, have also been tried with some effect.[118]

In 1987, Cheson and Simon[119] reviewed the experience of low-dose ara-C in MDS and AML. In patients with primary MDS, complete and partial remission rates were 17% and 19%, respectively, and in secondary AML (including MDS-AML), 16% and 14%.

In a series of 102 Scandinavian patients with MDS or MDS-AML, the overall response rate was 29% with a median duration of response of 8 months (range 2-58 months).[120] The response criteria were thougher in this study, since changes in only blast or neutrophil counts were not defined as a response to treatment. Multivariate analysis identified platelet counts, bone marrow cellularity, chromosomal aberrations and ring sideroblasts as significant predictive variables for a response to treatment. Patients with platelet counts $> 150\times10^9$/L had a response rate of 55% compared to 23.5% in patients with subnormal platelet counts. Logistic regression identified low bone marrow cellularity, absence of ring sideroblasts and < 2 chromosomal aberrations as predictors of a favorable response in patients with platelet counts $< 150\times10^9$/L. All these variables were combined in a predictive model for the use of low-dose ara-C in MDS and MDS-AML. The model identified three groups of patients with 3%, 24% and >50 % response rate. This model is at present being used in a prospective trial.

Aul *et al.*[114] compared survival of patients who had been treated with low dose ara-C with another group treated with supportive care only, and found no difference between the two groups. A randomized phase III trial comparing low-dose ara-C with supportive care showed a response rate for ara-C of 32% with a median duration of response of 5.9 months.[121] There was no difference in survival between the two alternatives, but patients with active treatment showed a tendency to a lower progression rate. The authors concluded that a cytoreductive effect seemed to be required for a favorable effect.

Although if this treatment is often initiated on an outpatient basis and doesn't show side effects like nausea and alopecia, hematologic toxicity in terms of bone marrow hypoplasia and pancytopenia may be pronounced. Therapy-related death ranges from 15 to 20%.[115,119] There is, however, a considerable interpatient variation with regard to toxicity and the Scandinavian studies showed a fatal toxicity of 7%.[120]

Low-dose ara-C in combination with growth factors

Low-dose ara-C has been combined with growth factors in a number of studies (Table 8). The rationale for this was not only the treatment-induced cytopenia caused by ara-C alone, but also the ability of growth factors to recruit more progenitors into the cell cycle, thus making them more susceptible to ara-C.[122] Ara-C and GM-CSF were combined in a couple of phase II studies showing that the treatment was feasible and that it possibly reduced neutropenia due to ara-C.[123] The EORTC Leukemia Group then compared two alternative treatment schedules in high risk MDS, one with ara-C and GM-CSF given sequentially and one in which the drugs were partly given simultaneously.[124] The total response rate in 108 patients was 24%, there were 16% treatment-related deaths and no difference between the two randomization arms. EORTC then continued with a

randomized phase III trial comparing low-dose ara-C alone vs ara-C + GM-CSF vs ara-C + IL3.[125] No statistically significant differences between the three alternatives were observed, response rates varied between 28 and 49% (highest for ara-C alone) and survival varied between 10.5 to 24 months (lowest in the GM-CSF group). The combination of G-CSF and ara-C has only been used in one small phase II trial in which seven out of 21 patients with MDS or MDS-AML responded to treatment.[126]

Other chemotherapeutic agents given in low-doses

Other chemotherapeutic agents have been employed in low doses in MDS patients (Table 8).

Low doses of an anthracycline, aclarubicin (ACR) were given to 15 patients with MDS and MDS-AML, of whom 33% responded to treatment.[127] The same researches then continued with a small randomized phase II trial comparing the effect of low-dose ACR with very low-dose ara-C.[128] No significant differences were observed between the two groups. The response rates in the ara-C and ACR groups were 32% and 44% and the survival times 24 and 12 months, respectively.

Another anthracycline, idarubicin, has been orally given in several phase II trials. The first study[129] used a relatively high dose, 50 mg/m^2, given with 14-21 days intervals, and showed a response rate in 7/13 patients (54%). In another study, the dose was 30-50 mg/m^2, and the response rate 14%. [130] Lastly, Greenberg *et al.*[131] used a very low dose, 2 mg/day for 21 days, but failed to show a response in any except one of the 42 patients. These studies suggest that oral idarubicin has a limited effect in MDS, unless given in clearly myelosuppressive doses.

Studies on the use of 5-azacytidine and homoharringtonine have been mentioned before (Table 6). More interesting is a recently published study on low-dose melphalan (2 mg/day until progression/toxicity or response) for patients with high-risk MDS.[132] Eight of 21 patients with RAEB or RAEB in transformation (RAEB-t) (38%) achieved a complete (7) or partial (1) response with a median survival of 27 months for CR patients and 6.5 months for the rest. No severe side effects were observed in any patient.

Chronic myelomonocytic leukemia is a proliferative entity of MDS in which the proliferative symptoms have often been treated with hydroxyurea. A positive report on the use of low dose etoposide in this subgroup[133] preceded a large randomized phase III trial on hydroxyurea versus etoposide in 105 patients with CMML.[134] The results from this trial were surprisingly clear-cut in that hydroxyurea in all aspects was better than etoposide. A response to treatment was observed in 60% of the hydroxyurea patients versus 36% in those treated with etoposide, and survival was significantly better in the former group. However, the median survival in the hydroxyurea group was only 20 months, which is comparable to the survival observed in most prognostic studies.[4] Real treatment advances in CMML have thus not yet been achieved.

In summary, low doses of chemotherapeutic agents may be used to reduce bone marrow blast counts and improve the pancytopenia in MDS and MDS-AML. Hematologic complete remissions are observed, but patients are not cured and there are no data showing a beneficial effect on survival in unselected groups of patients. The larger studies show that the response rate is around 30% for most of the agents but even if the median duration of response is often less than one year, there are undoubtedly patients with long-lasting and stable responses. Studies of low-dose ara-C show that it is possible to define both patients with a higher probability of responding to treatment and those who should not be treated. Such tools may prove useful in the therapeutic decision for individual patients. Based on the present experience, there is no evidence that routine addition of various growth factors either enhances or reduces the effect of low-dose chemotherapy.

Intensive chemotherapy

Intensive chemotherapy is aimed at eradicating or suppressing the myelodysplastic clone and thereby to induce long-term complete remission. The first reports on successful treatment of MDS patients with intensive chemotherapy appeared in the early 1980s and have now been confirmed by many other groups (for a comprehensive review see Cheson[135] and Gassmann *et al*.[136]) (Table 9).[137-144] Apart from combinations of daunorubicin with either conventional or high-dose ara-C, combinations of ara-C with idarubicin, idarubicin plus etoposide, mitoxantrone plus etoposide, fludarabine plus ara-C, fludarabine plus ara-C, as well as hematopoietic growth factors such as G-CSF, GM-CSF or IL-3, have been tested in more recent trials (Table 10 and 11).[145-160] Although reporting better results, the newer regimens have not yet been shown in randomized trials to be superior to standard AML-type regimens. The same is true for the CSFs, used either after chemotherapy or as priming agent together with induction therapy. Similarly, the value of immunotherapy with interleukin-2 as maintenance has still to be proven.[155]

While it was long assumed that CR rates are considerably lower in MDS than in *de novo* AML, using an identical chemotherapy regimen, De Witte *et al*.[144] achieved an identical CR rate in patients younger than 45 years irrespective of whether the patients had *de novo* AML or MDS (75% versus 71%). More recent reports also indicate that in patients above age 60 CR rates in the range of 50% to 60% can be achieved (Table 10). The large variation of complete remission rates, ranging from 15% to 74% is probably related not only to the type of chemotherapy and the dose intensity used, but also to differences in the median age of the patients (due to better responses in the

Table 9. Intensive chemotherapy for treatment of MDS and AML evolving from MDS (older trials).

Authors	*Patients*	*Chemotherapy*	*CR (%)*	*Survival*
Mertelsmann et al, 1980[137]	MDS: 45 AML/MDS: 16	thioguanine, ara-C, +/- daunorubicin	51% 31%	OS: 8% (4 yr) MDR: 7 mo
Keating et al, 1981[138]	AML/MDS: 32	rubidazone, vincristine, ara-C, prednisone	22%	
Fenaux et al, 1988[139]	RAEB-T: 16 AML/MDS: 9	rubidazone	56% 44%	MDR: 8.5 mo
Martiat et al, 1988[140]	AML/MDS: 25	daunorubicin, ara-C	24%	MDR: 7 mo
Michels et al, 1989[141]	RAEB-T: 31	AML-type	61%	
Gajewski et al, 1989[142]	AML/MDS: 44	thioguanine, ara-C, daunorubicin	41%	DFS: 17% (3 yr); MDR: 8 mo
Hoyle et al, 1989[143]	AML/MDS: 36	thioguanine, ara-C, daunorubicin	42%	MDR: 8 mo
De Witte et al, 1989[144]	MDS: 14 AML/MDS: 22	ara-C+daunorubicin or doxorubicin	64% 32%	OS: 7 mo MDR: 6-7 mo

OS: overall survival; MDR: median duration of remission.

Table 10. Intensive chemotherapy for treatment of MDS and AML evolving from MDS (recent trials).

Authors	*Patients*	*Chemotherapy*	*CR (%)*	*Survival*
Fenaux et al, 1991[145]	MDS: 31 AML/MDS: 16	rubidazone, ara-C	55% 31%	DFS: 11 mo OS: 14 mo
Knauf et al, 1994[146]	AML/MDS: 21	mitoxantrone, etoposide	57%	MDR: 7 mo
Wattel et al, 1995[147]	MDS/sMDS: 38 AML/MDS, sec. AML:58	high-dose ara-C, mitoxantrone	41%	MDR: 10 mo OS: 8 m
De Witte et al, 1995[148]	MDS + AML/MDS: 50	idarubicin, ara-C	54%	DFS: 11 mo OS: 14 mo
De Witte et al, 1995[149]	MDS + AML/MDS: 87	idarubicin, etoposide, ara-C	60%	OS: 40% (1.5 yr)
Aul et al, 1995[150]	MDS + AML/MDS: 76	thioguanine, ara-C, daunorubicin	63%	DFS: 23% (5 yr)
Invernizzi et al, 1997[159]	RAEB/RAEB-t: 25	idarubicin, ara-C	48%	OS: 10% at 3 yr
Ruutu et al, 1997[160]	MDS: 14 AML/MDS: 21	idarubicin, ara-C	58% 48%	DFS: 8 mo OS: 12 mo

OS: overall survival; MDR: median duration of remission.

younger patients) and to selection bias. The recent study by Estey *et al*.[158] clearly indicates that patients with RAEB and RAEB-t have the same chances of responding to chemotherapy regimens as AML patients with similar prognostic factors.

Factors responsible for the lower CR rates in MDS patients include drug resistance of the neoplastic cell clone[161] and, more generally a higher incidence of poor prognostic characteristics.[158] While achievement of CR usually results in the restoration of a polyclonal hematopoiesis,[162] the median duration of complete remission is usually short-lived and less than 12 months. Relapse-free survival rates above 10% at 3 to 4 years are rare.

Factors influencing CR rate, overall survival and relapse-free survival in some but not all treatment series include patient age, presence or absence of cytogenetic aberrations, and the diagnosis of *de novo* MDS or MDS after prior exposure to leukemogenic chemotherapy. The presence of karyotypic abnormalities which are frequently observed in MDS, including monosomy 7 and 5q-, is associated with lower CR rates (31% versus 57%) and significantly shorter remission duration (0% versus 25% at 3

Table 11. Intensive chemotherapy combined with hematopoietic growth factors for treatment of MDS and AML evolving from MDS (recent trials).

Authors	*Patients*	*Chemotherapy*	*CR (%)*	*Survival*
Bernasconi et al, 1998[151]	MDS + AML/MDS: 53	idarubicin, etoposide ± G-CSF	74%	DFS: 4.5 mo
Estey et al, 1995[152]	RAEB: 27 RAEB-T: 58	FLA ± G-CSF	63% 67%	DFS: 31% (2 yr) OS: 15% (2 yr)
Gore et al, 1995[153]	MDS: 9 AML/MDS: 39	DAV, DAAm ± IL-3, GM-CSF	35%	OS: 13 mo
Ossenkoppele et al, 1995[154]	non-RAEB-T: 22 RAEB-T: 38	DA ± G-CSF	55%	OS: 22% (2 yr)
Ganser et al, 1995[155]	MDS + AML/MDS: 104	idarubicin, etoposide, ara-C + G-CSF	49%	MRD: 11 mo DFS: 10 mo
Steinmetz et al, 1996[156]	AML/MDS: 27	FLA + G-CSF	74%	MRD: 4 mo
Gardin et al, 1997[157]	sec MDS: 25 sec AML: 9	idarubicin/ara-C (standard or high-dose) + G-CSF	56% 56%	MRD: 3 mo OS: 9 mo
Estey et al, 1997[158]	RAEB: 52 RAEB-t: 106 AML: 372	idarubicin/ara-C or FLA ± G-CSF	62% 66% 66%	

OS: overall survival; MDR: median duration of remission.

years).[139,145] Comparable data on the influence of an abnormal karyotype have been reported by others.[158]

In conclusion, the available evidence indicates that intensive chemotherapy based on a combination of ara-C and an anthracycline should be proposed to all patients with excess blasts, especially in those below 65 years of age. Deterrents to standard chemotherapy in these patients could include age and abnormal cytogenetics.

Stem cell transplantation

While MDS is hard to cure with conventional therapies, cures have been achieved with complete eradication of the marrow and replacement using stem cells from a normal donor. Although restrictions based on patient age and donor availability limit the use of allogeneic stem cell transplantation (SCT) to a small number of MDS patients, the potential for cure has encouraged extensive investigation of this therapeutic option.

Stem cell transplantation: overview of large published series

Between 1990 and 1997 twelve publications have described series of greater than 20 patients with MDS undergoing allogeneic SCT (Table 12).[163-174] A total of 516 patients were reported in these 12 publications, including 64 whose disease had progressed into AML before or at time of transplantation. Although there was a wide variety of patient characteristics and transplantation procedures used, the major endpoints of relapse and death were relatively similar between these studies. There were 209 patients (41%) reported to be alive and disease-free, with a median follow-up ranging from 11 months[164] to 6 years,[168] while 115 (22%) patients had relapsed and 192 (37%) had died of transplant-related causes. A major conclusion from these data is that durable cures, lasting up to 12 years, can be achieved in a significant fraction of patients with an otherwise incurable hematologic disorder.[168,170] A representative example of disease-free survival (DFS) and relapse for the largest published single-center study is shown in Figure 1.

Two of the largest series reported results of multivariable analyses.[168] Anderson *et al.*[170] found that both older age and longer disease duration were independently associated with lower DFS, due to significantly higher non-relapse mortality (NRM). More advanced disease morphology (beyond the phase of refractory anemia) was associated with increased risk of relapse. In a follow-up study with a larger number of patients, advanced disease morphology was also significantly associated with lower DFS.[175] Sutton *et al.* reported that increased marrow blast count was associated with lower DFS because of both increased risk of relapse and NRM and that older age was associated with lower DFS because of increase risk of relapse.[168] In addition, the use of cytoreductive therapy before transplant (in 17 of 71 patients) was associated with a higher risk of relapse, probably because such treatment was used mostly in patients with RAEB-t. The association of age and survival has been reported in several other series.[165,169]

Table 12. Published reports on allogeneic SC for MDS (series consisting of > 20 patients).

Authors	*No. of pts, median age, median disease duration*	*Morphology at SCT, number of patients*	*Preparative regimen, number of patients*	*Donor, number of patients*	*Median follow-up*	*Actuarial DFS (actual number of patients)*	*Actuarial relapse (actual number of patients)*	*Actuarial NRM (actual number of patients)*
Anderson et al, 1993[170]	93 30 yrs 10 mos	RA, 40 RAEB, 31 RAEB-T, 14 CMML, 2 Other, 6	CY-TBI, 88 BU-CY, 5	HLA-id sib, 64 Syngeneic, 3 Other family, 20 Unrelated, 6	4 yrs	41%	28% (n=17)	43% (n=36)
DeWitte et al, 1990a[173]	78 32 yrs 7 mos	RA, 9 RAEB, 16 RAEB-T, 20 sAML, 32 CMML, 1	Chemotherapy +TBI, 69 –TBI, 9	HLA-id sib, 74 Syngeneic, 3 Other family, 1	2.3 yrs	not stated (n=35)	not stated (n=18)	not stated (n=25)
Sutton et al, 1996[168]	71 37 yrs 201 days	RA, 11 RAEB, 21 RAEB-T, 21 sAML, 11 CR, 7	CY-TBI, 26 BU-CY, 17 Other, 28	HLA-id sib, 70 Syngeneic, 1	6 yrs	32%	48% (n=24)	39% (n=24)
Locatelli et al, 1997[164]	43 2 yrs 7 mos	CMML, 43	Chemotherapy +TBI, 22 –TBI, 21	Related, 29 Unrelated, 14	11 mos	31%	58% (n=22)	20% (n=7)
O'Donnell et al, 1995[169]	38 35 yrs 7 mos	Blasts <10%, 20 Blasts ≥10%, 18	BU-CY, 38	HLA-id sib, 38	approx 2 yrs	38%	24% (n=5)	not stated (n=19)
Mattijssen et al, 1997[163]	35 41 yrs 9 mos	RAEB-T, 11 RAEB, 7 RA, 13 CMML, 1 AML 3	CY-TBI, 9 CY-Ida-TBI, 22 Other, 4	HLA-id sib, 32 Other family, 1 Unrelated, 2	1.7 yrs	39%	34% (n=7)	not stated (n=14)
Anderson et al, 1996a[166]	31 41 yrs 5 mos	RAEB, 15 RAEB-T, 8 CMML, 8	BU-CY-TBI, 31	HLA-id sib, 22 Other family, 3 Unrelated, 6	1.7 yrs	23%	28% (n=6)	68% (n=17)
Anderson et al, 1996b[165]	30 29 yrs 8 mos	RA, 30	BU-CY, 30	HLA-id sib, 16 Other family, 1 Unrelated, 13	2.1 yrs	63%	0% (n=0)	37% (n=11)
Ratanatharathorn et al, 1993[171]	27 33 yrs 5.6 mos	RA, 9 RAEB, 8 RAEB-T, 3 sAML, 6 Other, 1	BU-CY, 1 BU-AraC-CY, 24 BU-TLI, 2	HLA-id sib, 18 Other family, 6 Unrelated, 3	1.7 yrs	56%	not stated (n=1)	not stated (n=9)
Demuynck et al, 1996[167]	24 30 yrs 5 mos	RA, 4 RAEB, 4 RAEB-T, 9 CMML, 1 sAML, 6	CY-TBI ± chemotherapy, 24	HLA-id sib, 16 Other family, 5 Unrelated, 3	3.3 yrs	35%	25% (n=6)	50% (n=11)
Nevill et al, 1992[172]	23 35 yrs	RA, 2 RAEB, 2	BU-CY, 23	HLA-id sib, 22	2.3 yrs	35%	not stated (n=5)	not stated

Abbreviations: SCT, stem cell transplantation; DFS, disease-free survival; NRM, nonrelapse mortality; RA, refractory anemia; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia; sAML, secondary AML; CR, complete remission; CY, cyclophosphamide; TBI, total body irradiation; BU, busulfan; Ida, idarubicin; AraC, cytosine arabinoside; TLI, total lymphoid irradiation; HLA-id sib, human leukocyte antigen identical sibling.

Stem cell transplantation: outcome by disease morphology and cytogenetics

According to the French-American-British (FAB) classification, patients with RA have fewer than 5% blasts in the marrow and 1% or fewer blasts in the peripheral blood; whereas patients with RAEB or RAEB-t have increased blasts in the marrow and/or peripheral blood.[176] As outlined above, many studies of allogeneic SCT for MDS have demonstrated that with increasing blast percentage or advanced disease morphology (i.e., RAEB or RAEB-t compared with RA) there is a higher risk of relapse post-transplantation, and, in some studies, a lower DFS.[177] A representative example of the difference in actuarial relapse rate and DFS based on the FAB classification is shown in Figure 2.

In this study the 5-year actuarial estimates of relapse and DFS were 49% and 31%, respectively, for 47 patients with MDS with excess blasts (i.e., RAEB or RAEB-t) compared with 4% and 54%, respectively, for 40 patients with MDS without excess blasts (i.e., RA).[177]

Approximately 40% of patients with MDS at diagnosis have a clonal cytogenetic abnormality, with complex abnormalities and chromosome 7 abnormalities being associated with the shortest survival in the non-transplant setting.[178,179] Following allogeneic SCT, however, the prognostic significance of karyotype has not been as clearly established as it has for morphology. In an initial multivariable analysis of

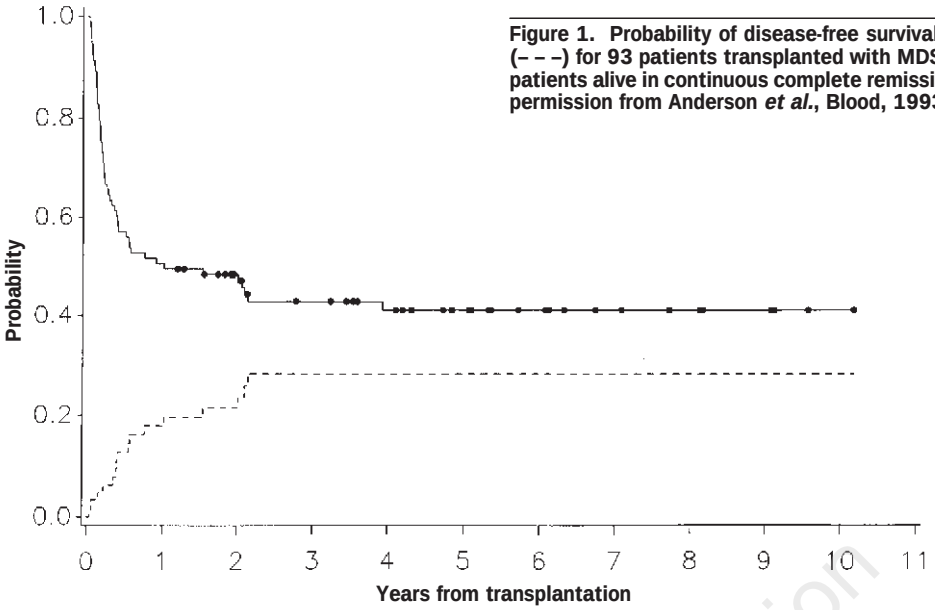

Figure 1. Probability of disease-free survival (—) and relapse (– – –) for 93 patients transplanted with MDS. Dots represent patients alive in continuous complete remission (reprinted with permission from Anderson *et al.*, Blood, 1993).

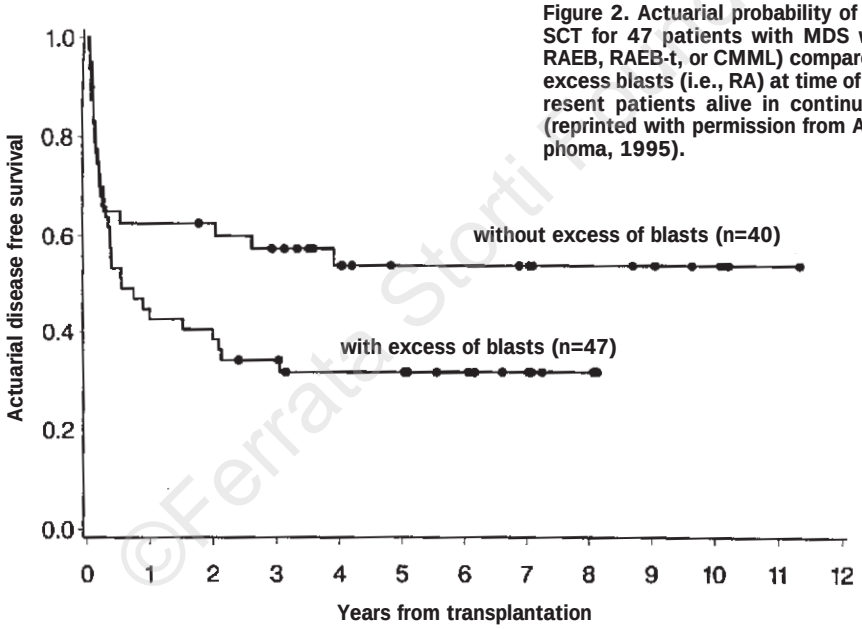

Figure 2. Actuarial probability of DFS following allogeneic SCT for 47 patients with MDS with excess blasts (i.e., RAEB, RAEB-t, or CMML) compared to 40 patients without excess blasts (i.e., RA) at time of SCT (p = 0.07). Dots represent patients alive in continuous complete remission (reprinted with permission from Anderson *et al*, Leuk Lymphoma, 1995).

data from 59 patients from Seattle, the presence of an abnormal karyotype was associated with improved DFS and lower NRM.[180] However, this association of karyotype was not upheld in a subsequent multivariable analysis of these 59 patients and an additional 34.[170] In univariable analysis of 40 patients (data was not available on the remaining 31 patients in the study) from the *French Bone Marrow Registry*, patients with a single cytogenetic abnormality had a statistically significantly lower risk of relapse and higher DFS compared with patients with either normal karyotype or complex abnormalities.[168] However, this association did not emerge as a significant finding in the multivariable analysis in that study. In a univariable analysis from the *European Bone Marrow Transplantation Group*, in which cytogenetic data were available from 54 patients, there was a lower relapse rate among patients with a normal karyotype.[181] More recent and larger multivariable analyses of patients with MDS (excluding those who progressed into secondary AML) have been reported in abstract form.[175,182] One study of 251 patients reported that

patients with complex cytogenetic abnormalities had a significantly higher risk of relapse and lower DFS[175] and the other study of 338 patients reported that a normal karyotype was associated with improved DFS.[182] Therefore, it is likely that cytogenetic features that are associated with a poor survival in absence of transplantation[178,179] are also independent predictors of worse outcome following allogeneic transplantation.

The association of poor risk cytogenetic features and relapse after allogeneic SCT does not, however, appear to extend to patients transplanted with RA who never progressed to a more advanced FAB morphologic classification. Only 1 of 70 patients with RA (of whom 39 had cytogenetic abnormalities) relapsed, with a median follow-up of approximately 3.5 years post-transplant.[165] Similarly, Sutton *et al.*[168] reported no relapses among 11 patients transplanted with RA. In these 2 studies, the long-term DFS rates among patients receiving human leukocyte antigen (HLA)-identical related donor SCT were 74 and 73%, respectively. Other studies have also corroborated the low risk of relapse among patients transplanted for RA, despite the presence of cytogenetic abnormalities (Table 12).

Stem cell transplantation: choice of stem cell donor

Most patients transplanted for MDS have received marrow from HLA-matched related individuals, but suitable related donors are only available to a minority of patients who are otherwise eligible for allogeneic SCT. With increasing size of the worldwide registries of HLA typed volunteer donors, the potential use of unrelated donor transplantation is expanding. Results published from Seattle on 52 patients with MDS or MDS-related AML transplanted from unrelated donors show a 2-year actuarial DFS, risk of relapse, and risk of NRM of 38%, 28%, and 48%, respectively.[183] The risk of relapse was significantly higher among patients with RAEB-t or MDS-related AML compared to RA, RAEB, or CMML. The risk of NRM was significantly higher among older patients and those with longer disease duration. At time of publication, 16 of the 19 survivors had a performance status of 90-100%. Registry reports on the use of unrelated donor SCT in MDS patients have described a higher NRM and lower DFS than the Seattle group,[182,184,185] but because of lack of detail it is not possible to explore these differences.

Another study among patients with advanced disease morphology found that there was a significantly lower risk of relapse among recipients of unrelated or partially matched related donor marrow compared with recipients of HLA-matched related donor marrow.[166] Two smaller studies which included a total of 19 children with MDS undergoing unrelated donor SCT reported 10 disease-free survivors.[186,187] These data suggest that the use of alternative donors is feasible, but further study is necessary to determine whether the long-term DFS is significantly different from that of HLA-matched related donors.

Stem cell transplantation: preparative regimens

The type of myeloablative preparative regimens used has varied between the different series reported (Table 12). Because prospective, randomized studies comparing different preparative regimens have not been reported, only tentative conclusions can be drawn from existing data. The two most frequently used regimens are cyclophosphamide and total body irradiation (CY-TBI) and busulfan and CY (BU-CY). In a prospective, single-arm study of BU-CY in patients with RA, the 3-year DFS rate was 63% and was similar to a group of historical controls treated with CY-TBI.[165] Other single-arm studies[169,172] using BU-CY in patients with both RA and more advanced disease morphology have found similar results to other published series in which predominantly CY-TBI regimens were used. Two studies[164,171] which included patients receiving regimens containing BU-CY and additional chemotherapy found higher DFS than for patients receiving CY-TBI or BU-CY alone, but small patient numbers and short median follow-up (< 2 years) make definitive conclusions hazardous. Because of the high risk of relapse among patients with advanced disease morphology, regimens consisting of TBI and intensified chemotherapy have been studied, and have showed greater toxicity with no benefit in DFS.[166,168]

Stem cell transplantation: therapy-related MDS

Although the etiology of MDS is unknown in the majority of cases, an increasing proportion of patients diagnosed with MDS have developed their disease following treatment with chemotherapy or ionizing radiation or the combination of both. Alkylating agents used for Hodgkin's and non-Hodgkin's lymphoma are the most common drugs associated with development of therapy-related MDS (t-MDS). t-MDS typically develops 4-5 years following exposure to the inciting agent, and in 90% of cases is associated with chromosome abnormalities, most commonly involving chromosomes 5 and 7.[188] With increasing intensity of chemotherapy for malignancies, such as autologous SCT for lymphoma, there appears to be an increasing incidence of t-MDS.[189]

A number of reports on SCT for MDS and secondary AML have included patients with t-MDS and therapy-related AML (t-AML)(Table 13).[165-167,169-172,174,190-195] Table 13 outlines some of the available statistics from these reports. With complete survival data on 135 of the 147 reported patients with t-MDS or t-AML, 45 patients (33%) were disease-free survivors, 29 (22%) relapsed and 61 (45%) died of transplant-related causes. These data suggest that allogeneic SCT is a

feasible treatment option for therapy-related myeloid malignancies, but do not address the question of whether results are different from results for patients with *de novo* MDS. In Seattle, 251 patients with MDS underwent allogeneic SCT through 1996, 36 of whom had t-MDS.[175] In multivariable analysis, there was a significantly higher incidence of NRM among patients with t-MDS compared with the remaining patients (relative risk 1.9, p-value 0.014), but no difference in relapse rate or DFS (unpublished data, Anderson, 1997). This finding of greater NRM, after adjustment for other factors known to influence NRM, is not surprising and may be due to the cumulative toxicity associated with treatment for the prior malignancy.

Stem cell transplantation: timing of allogeneic SCT

The most appropriate timing for allogeneic SCT for MDS is not well defined. Multivariable analysis from a Seattle study including all morphologic subtypes found DFS to be better among patients with shorter rather than longer disease duration due to lower NRM.[170] However, in the multivariable analysis of the French series there was no association between disease duration and outcome.[168] It is possible that the effect of disease duration on DFS and NRM is more important among patients with RA, since the association was found in the multivariable analysis of 70 patients with RA,[165] but not in the analysis of 75

Table 13. Published reports on allogeneic SCT for therapy-related MDS and AML.

Authors	*No. of patients*	*No. of disease-free survivors*	*No. of relapses*	*No. of transplant-related deaths*	*Duration of follow-up of survivors, years (median)*
Anderson et al, 1997[190]	29 t-AML	4	10	15	2.4-6.1 (4.1)
Le Maignan et al, 1990[192]	25 (morphology not detailed)	9	5	11	0.25-7.2
DeWitte et al, 1990b[194]	20 9 t-MDS 11 t-AML	8	3	9	0.13-7.6 (4.4)
Ballen et al,* 1995[191]	18 t-MDS	Not stated (actuarial DFS 24%)	4	Not reported	(3 years median)
Bandini et al, 1990[193]	17 t-AML	8	2	7	1.0-4.6
O'Donnell et al, 1995[169]	8 5 t-MDS 3 t-AML	4	1	3	Not stated (lead survivor 3 years)
Anderson et al, 1993[170]	8 t-MDS	2	2	4	Not stated
Ratanatharathorn et al, 1993[171]	8 t-MDS	4	1	3	0.36-4.1 (0.83)
Longmore et al, 1990[174]	11 6 t-MDS 5 t-AML	3	3	5	3-9 (5)
Demuynck et al, 1996[167]	3 1 t-MDS 2 t-AML	1	1	1	1.6
Anderson et al, 1996b[166]	3 t-MDS	1	0	2	3.8
Anderson et al, 1996a[165]	2 t-MDS	1	0	1	2.0
Nevill et al,1992[172]	1 t-MDS	0	1	0	---
Bunin et al, 1988[195]	3 2 t-MDS 1 t-AML	2	0	1	0.65, 1.1

**Six patients in this report with are also presumably included in Longmore 1990. Abbreviations: t-MDS, therapy-related MDS; t-AML, therapy-related AML; DFS, disease-free survival.*

patients with advanced disease morphology.[166] As discussed above, patients with fewer blasts and patients without poor risk cytogenetic features have an improved DFS due to a lower risk of relapse. Therefore, we have generally recommended consideration of SCT early after diagnosis of MDS, before complications from cytopenias develop, and, if possible, before the blast percentage increases or karyotype evolves. However, there may be some patients with MDS who have a particularly indolent course, in whom early SCT might be ill advised. Patients ≤ 60 years of age with a low risk International Prognostic Score have a median survival of 11.8 years without transplantation.[179] Therefore, because of the early mortality associated with allogeneic SCT, some patients with low risk MDS should probably not be advised to undergo early SCT.

Stem cell transplantation: current challenges in allogeneic SCT for MDS

Innovative approaches to reduce the high risk of relapse after SCT among patients with excess blasts with or without poor risk cytogenetic features are needed. Current approaches include the use of intensive chemotherapy before the preparative regimen in an attempt to induce a morphologic and cytogenetic remission, the development of more effective preparative regimens, and the use of donor lymphocyte infusions after relapse. Retrospective comparisons of patients transplanted without attempt at remission induction therapy or after such treatment have resulted in contradictory results.[168,173,190,196] Patients who fail to obtain a complete remission after such chemotherapy, generally do poorly with SCT. Patients transplanted after obtaining a complete remission were reported to have a 60% 2-year DFS (n=16) in one study[173] and a 43% 7-year DFS (n=7) in another.[168] However, in the latter study, the improved outcome after SCT among complete responders was due to a lower NRM, not a lower relapse rate. Furthermore, as discussed earlier, no more than 60% of patients achieve a complete response with remission induction chemotherapy. Analysis of 46 patients with MDS-AML and t-AML who underwent SCT without an attempt at induction chemotherapy showed a 24% 5-year DFS, which was not significantly different from the 15% 5-year DFS of 20 patients who underwent SCT after induction chemotherapy.[190] Only prospective studies or large retrospective studies that account for all patients receiving remission induction chemotherapy (including those who die during such treatment or become ineligible for SCT) will be able to address the use of such pre-transplant therapy definitively.

Evaluation of preparative regimens to reduce the risk of relapse is ongoing in Seattle and elsewhere and includes the use of BU instead of CY along with TBI and the addition of radionuclides conjugated to monoclonal antibodies directed against hematopoietic cells. The use of donor lymphocyte infusions after relapse (designed to induce a graft-versus-*leukemia* effect) has been reported in 15 MDS patients, 7 of whom achieved a complete hematologic response with 6 in remission between 2 and 18 months after infusion.[198-203]

The reason for the high NRM rate (approximately 40%) seen in patients with MDS treated with allogeneic SCT is not well understood, but may be due to the prolonged period of marrow failure preceding SCT. A reduction in the risk of NRM is needed to improve outcome of currently eligible patients and, perhaps, to expand eligibility of allogeneic transplantation to older patients and to those without currently suitable donors. Encouraging results using T-cell depleted (10^3-10^4 reduction) marrow in 11 patients with RA have been reported. However, results using marrow depleted of T cells by counterflow centrifugation (10^2 reduction) in a heterogeneous group of 35 patients, including 11 with RA, do not appear to be better than those from series using non-T-depleted grafts.[163] Alternative methods to reduce severity of graft-versus-host disease and toxicity of the preparative regimen need to be investigated.

Table 14. Published reports on autologous SCT for MDS or secondary AML.

Authors	*Source of cells*	*No. of pts.*	*No. of disease free survivors*	*Duration of follow-up of survivors (months)*
De Witte et al, 1997[208]	Marrow	79	32	Median 10 Range 0-89
Wattel et al, 1997[210]	Marrow (n=17) Peripheral blood (n=6)	23	13	2 – 13
Oberg et al, 1989[211]	Marrow	17	1	Not reported
Laporte et al, 1993[212]	Marrow	7	2	10, 28
Demuynck et al, 1996[168]	Peripheral blood	5	4	4–14
Carella et al, 1996[207]	Peripheral blood	3	2	1, 6

Stem cell transplantation: autologous SCT for MDS

The use of autologous stem cells in transplantation for MDS is dependent on the ability to collect non-clonal hematopoietic stem cells. The finding that some MDS patients treated with remission induction chemotherapy can achieve a complete morphologic and cytogenetic remission[148] suggests polyclonal hematopoiesis can be achieved. X-linked clonality studies in females with MDS have shown residual polyclonal hematopoietic cells either at steady state[205] or after chemotherapy.[206] Peripheral blood

stem cell collections following chemotherapy have been shown in some patients to be polyclonal based on X-chromosome inactivation patterns[6] or to be cytogenetically normal.[207]

A small number of patients have undergone autologous SCT for MDS or MDS-AML (Table 14)[168,207-211] and it appears that patients can reliably engraft. Duration of follow-up in these studies is too short to make meaningful conclusions about incidence of relapse, although NRM appears to be relatively low. An important issue in the successful use of autologous stem cells from MDS patients following chemotherapy or other purging techniques is the difficulty in detecting residual tumor contamination. It is not yet known whether loss of a previous cytogenetic abnormality or demonstration of polyclonality correlates with complete suppression of the neoplastic clonal stem cell compartment. Further studies of autologous stem cell collection and transplantation, including *in vivo* and *ex vivo* purging and detection of minimum residual disease,[212,213] are ongoing.

Stem cell transplantation for MDS: conclusions

The heterogeneity of patients with MDS, the wide variety of patient inclusion criteria and transplant procedures used, and relatively small numbers of patients in the individual reports of allogeneic SCT described in this chapter make it difficult to draw many definitive conclusions. However, approximately 40% of patients with MDS who are eligible for allogeneic SCT are likely to be cured by this treatment. The most fortunate subgroup of patients appears to be formed of those with RA who have an HLA-matched related donor, in whom long-term DFS rates of approximately 75% have been achieved. Currently, the major limitations in applying this treatment option to the majority of patients are the advanced age of most patients with MDS and the lack of an HLA-compatible related or unrelated donor. In addition, the major limitations to a greater success rate following allogeneic SCT are the increased relapse rate among patients with increased blasts and poor risk cytogenetic features and the increased NRM rate among patients with longer disease duration, patients with t-MDS, and patients receiving mismatched or unrelated grafts. The use of allogeneic SCT early in the disease course, if possible, before increase in blast percentage, karyotypic evolution, or complications of cytopenias develop may help improve outcome. Although a subset of patients may benefit from the use of remission induction chemotherapy before the start of the preparative regimen, such pretransplant treatment has not been conclusively shown to benefit the majority of patients who are at high risk of relapse. In addition, no specific preparative regimen has been conclusively shown to be preferable over others. The preliminary data on the use of autologous SCT suggest this approach may be a feasible option for a minority of patients, but the appropriate type of patient has not yet been defined.

In our opinion, some general recommendations for the use of allogeneic SCT for patients with MDS can be made given the available data. Patients up to 55 years of age should be evaluated at diagnosis for potential SCT, and those with intermediate to high risk should be considered for transplantation early after diagnosis while those with a low risk score should probably be observed until evidence of disease progression. Patients between 55 and 65 years of age should be considered in the context of clinical trials.

Immunosuppressive therapy

In a recent study[214] 25 transfusion-dependent MDS patients (with < 20% blasts) were treated in a phase II study with antithymocyte globulin (ATG) at 40 mg/kg/d for four doses. Eleven subjects responded and became transfusion-independent after ATG; median response duration was 10 months (range 3-38 months). Biesma *et al*.[215] reported similar response in two patients with hypoplastic MDS treated with ATG and cyclosporin A.

Randomized studies are required to establish whether ATG can be effective in restoring hematopoiesis in some MDS patients. Since aplastic anemia and hypoplastic MDS show many similarities, it is possible that the latter also respond to immunosuppressive therapy.

Treatment of the individual patient with MDS: decision making by patient and physician

Clinicians facing an individual patient with MDS should be aware of the fact that the therapeutic choice is difficult and partly dependent on the patient's expectations. Treatments proven to be effective in clinical trials are summarized in Table 15.

We believe that any MDS patient should be given the following information:

a) the natural history of MDS is highly variable, ranging from a few months to more than ten years, but most patients die because of disease-related causes (complications of cytopenia, evolution into AML);

b) by using prognostic systems, e.g., the International Scoring System,[7] it is possible to establish the individual's life expectancy with good approximation;

c) the only known curative treatment at present is allogeneic stem cell transplantation. Transplant-related mortality depends on the patient's age and, perhaps, on the stem cell source (related versus unrelated donor) and disease duration; in no case, at present, can it be considered negligible;

d) aggressive AML-like chemotherapy can restore normal polyclonal hematopoiesis[216] and may cure a small portion of MDS patients with relatively good prognostic factors (in terms of age and cytogenetics);

e) some treatments (supportive therapy in all individuals, rHuEpo±G-CSF and low-dose ara-C in subsets

Table 15. Treatments of proven efficacy in MDS. Only treatments validated in clinical trials are herein reported.

Treatment	*Positive effects*	*Adverse effects and/or disadvantages*
Curative (or potentially curative) treatments (i.e., capable of eradicating the myelodysplastic clone and restoring a normal - allogeneic or autologous - polyclonal hematopoiesis)		
Allogeneic stem cell transplantation	Curative therapy for about 40% of eligible patients	High transplant-related mortality
Intensive chemotherapy (anthracycline + ara-C)	Potentially curative for a subset of patients	Complications of cytopenia, short-lasting remissions
Treatments potentially capable of stimulating residual normal hematopoiesis and/or of improving the efficiency of myelodysplastic hematopoiesis		
G-CSF	Improvement in neutrophil count but with no impact on overall survival. Probably useful in individual patients with febrile neutropenia	High cost. Potentially capable of inducing/worsening thrombocytopenia
rHuEpo	Amelioration of anemia in patients with serum Epo levels < 100 mU/mL and no or low transfusion requirement	High cost
rHuEpo + G-CSF	Amelioration of anemia and elimination of transfusion requirements in patients with serum Epo levels < 500 mU/mL and transfusion need < 2 units/month	High cost
Low-dose ara-C	Achievement of complete or partial remission in patients with normal platelet count but no impact on overall survival	Hematologic toxicity in terms of pancytopenia may be pronounced; therapy-related death ranges from 7 to 20%

of MDS patients) may improve the patient's quality of life. Theoretically, some patients who benefit from these treatments in terms of quality of life might also have prolongation of survival, but this is unproven.

The fully informed individual patient will then be asked to participate in the therapeutic decision. The approach we consider most appropriate based on the evidence provided by clinical trials is that reported in Figure 3. We are fully aware of the fact that many physicians will disagree with us, but still feel that this approach may represent a useful starting base. Because of the inadequacies of all current treatment modalities, participation in clinical trials is encouraged.

Since cytogenetic information is not available from at least 40% of MDS patients, the IPSS[7] cannot be used in these individuals. Alternative prognostic scoring systems[4] that are not based on cytogenetics should be used in these cases to define the patient's risk. More generally each clinician should use a prognostic scoring system[217-220] that he or she is familiar with, and classify the patient's risk as low, intermediate or high.

Patients up to 55 years of age should be evaluated at diagnosis for allogeneic SCT, the major potentially curative treatment.

Patients likely to experience a short-term unfavorable evolution (those with an intermediate-1, intermediate-2, or high risk IPSS which will include patients with either increased blasts or intermediate or poor risk cytogenetic features) should be considered for transplantation (from an HLA-identical family donor or from a compatible unrelated donor) early after diagnosis. The use of single HLA antigen mismatched related or HLA-matched unrelated donor grafts should be considered at institutions with favorable experience of using such alternative donors. If no donor is available, AML-like chemotherapy should be given. Such patients could also be considered for a clinical trial with autologous SCT, if available. Those refusing aggressive chemotherapy can be considered for low-dose chemotherapy or just supportive therapy.

Patients up to 55 years of age with a low risk score should be observed until evidence of disease progression, except, perhaps, in the case of a single life-threatening cytopenia or a particularly young individual with an HLA-matched related donor. In any case, the patient's expectations prevail: he or she should decide whether to undergo SCT with a risk of transplant-related mortality in the order of 25-50% and a probability of cure of 50 to 75%. Patients up to 55 years who do not have a donor or decide not to undergo SCT can be offered a *watchful-waiting* strategy, or rHuEpo if Hb is below 10 g/dL and serum Epo is below 100 mU/mL, or participation in trials on the use of differentiating agents, or supportive therapy. When there is evidence of disease progression, the patient should be offered SCT or AML-like chemotherapy.

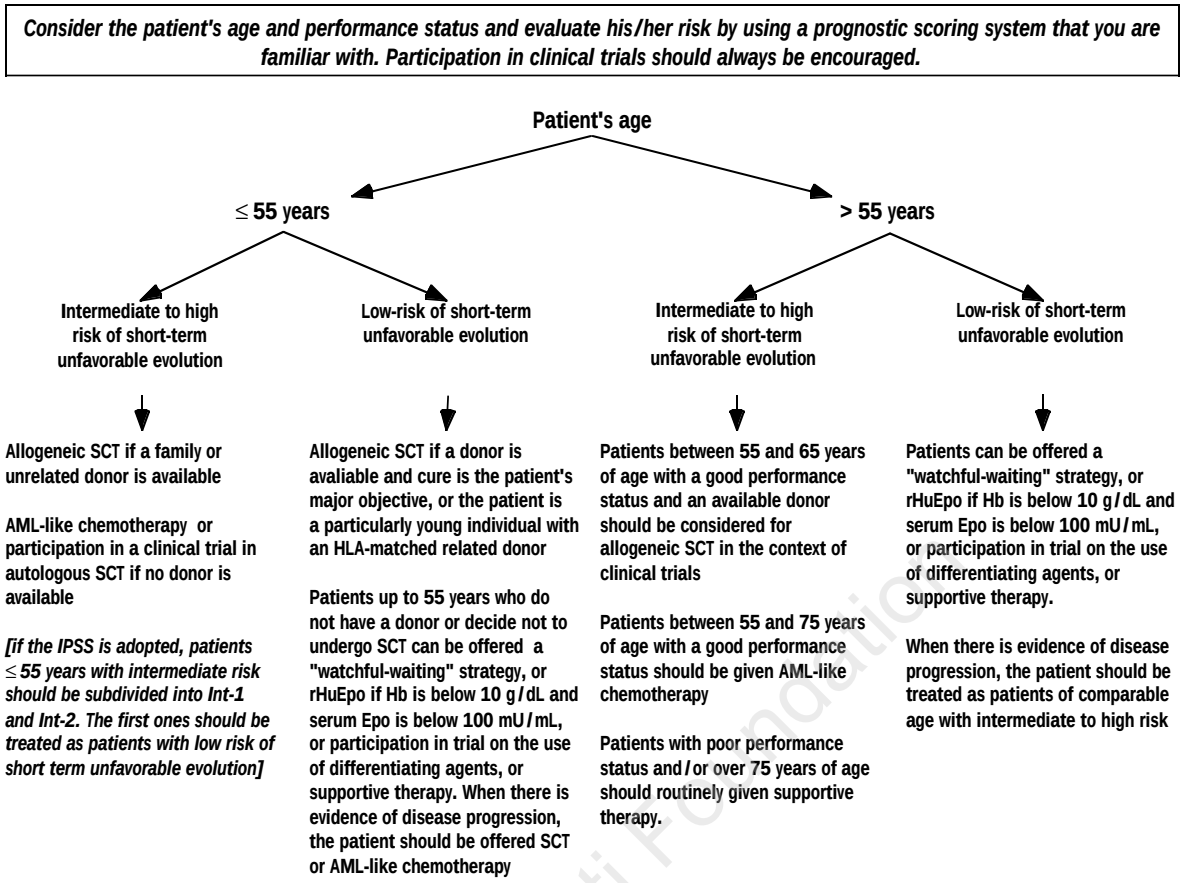

Figure 3. Proposed approach to treatment of the individual patient with MDS.
Since at least 40% of the MDS patients do not have cytogenetic information, the IPSS[7] cannot be used in these individuals. Alternative prognostic scoring systems that are not based on cytogenetics, e.g. the Sanz's one[218] should be used in these cases to define the patient's risk. More generally each clinician should use a prognostic scoring system that he or she is familiar with, and classify the patient's risk as low, intermediate or high.
Age limits should be considered very flexible due to the high biologic variability.

For patients over 55 years of age, risk of unfavorable evolution and performance status represent the major factors for decision making. Patients between 55 and 65 years of age with an intermediate or high risk, a good performance status and an HLA-identical family donor should be considered for allogeneic SCT in the context of clinical trials. If no donor is available, participation in a clinical trial of autologous SCT should be considered. Patients between 55 and 75 years of age with a good performance status should be given AML-like chemotherapy.

Patients with poor performance status and/or over 75 years of age should routinely be given supportive therapy.

Patients over 55 years of age with a low risk score can be offered a *watchful-waiting* strategy, or rHuEpo if Hb is below 10 g/dL and serum Epo is below 100 mU/mL, or participation in clinical trial on the use of differentiating agents, or supportive therapy. When there is evidence of disease progression, the patient should be treated as patients of comparable age with intermediate to high risk.

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The four authors contributed equally to this paper. In particular, JEA was primarily responsible for chapters on stem cell transplantation; MC was responsible for the chapters on supportive therapy, rHuEpo and rational approach to treatment of the individual patient with MDS; AG was responsible for the chapters on differentiation induction and intensive chemotherapy; and EH-L was responsible for chapters on hematopoietic growth factors and low-dose chemotherapy.

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