

Improved Survival in Patients with Myelodysplastic Syndrome Receiving Iron Chelation Therapy

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Abstract

Purpose: Patients with myelodysplastic syndrome (MDS) and iron overload (IOL) often receive iron chelation therapy (ICT); however, data on clinical outcomes are limited. We reviewed 178 patients with MDS to determine the effect of ICT on survival. **Patients and Methods:** Data were collected by chart review and survival analysis performed. A subgroup analysis compared control patients with clinical features similar to patients who received ICT. **Results:** French-American-British MDS subtypes for patients were as follows: refractory anemia (RA), n = 36; RA with ringed sideroblasts, n = 42; RA with excess blasts (RAEB), n = 28; RAEB in transformation or acute myeloid leukemia (AML), n = 16; chronic myelomonocytic leukemia, n = 25; other, n = 31. International Prognostic Scoring System (IPSS) scores were as follows: low risk, n = 44; intermediate-1 risk, n = 55; intermediate-2 risk, n = 17; high risk, n = 17. Eighteen patients received ICT; median duration was 21.6 months (range, 1.3-151 months). In univariate analysis (UVA), factors significant for overall survival (OS) were IPSS score; MDS subtype; number of red blood cell (RBC) units transfused; MDS treatment; elevated ferritin; clinical IOL; receiving ICT ($P < .05$ for all); and age ($P = .01$). In multivariate analysis (MVA), significant factors included IPSS score ($P = .008$; hazard ratio [HR], 2.2 [95% CI, 1.3-3.7]) receiving ICT ($P = .02$; HR, 0.2 [95% CI, 0.01-1.0]). For low/intermediate-1 risk IPSS score, 4-year OS was 64% for patients receiving ICT and 43% for patients not receiving ICT ($P = .003$). An MVA was performed, including number of cytopenias; blast count; karyotype; AML transformation; ≥ 1 serious infection ($P < .05$ in UVA for all) with MDS treatment; number of RBC units transfused; and clinical IO; receipt of iron chelation therapy determined that factors significant for OS were infection ($P = .05$; HR, 3.2 [95% CI, 0.97-10.4]) and ICT ($P = .02$). Improved OS was maintained in the subgroup analysis ($P = .01$; HR, 0.29 [95% CI, 0.1-0.79]). **Conclusion:** Patients with MDS and IOL receiving ICT had improved survival compared with patients not receiving ICT, suggesting a possible beneficial effect on clinical outcome. Prospective studies of ICT in MDS are warranted.

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Introduction

The myelodysplastic syndromes (MDS) are a group of bone marrow disorders that occur more commonly in the older population and are characterized by ineffective hematopoiesis, cytopenias, and risk of progression to acute myeloid leukemia (AML).¹⁻⁴ The International Prognostic Scoring System (IPSS)⁵ and World Health Organization (WHO) Prognostic Scoring System separate⁶ patients into risk groups that predict survival.

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An allogeneic hematopoietic stem cell transplantation is currently the only potentially curative therapy for MDS, but this is a treatment option only for younger patients.⁷ Although several investigational approaches to treatment have shown promise,⁸⁻¹¹ many patients with lower-risk MDS require ongoing transfusion support. Over time, red blood cell (RBC) transfusion-dependent patients accumulate iron. In addition, increased absorption of iron via the gastrointestinal tract is observed in anemia^{12,13} and contributes to iron overload (IOL).

The effects of iron from RBC transfusions in thalassemia are well documented.¹⁴ Clinical evidence of IOL can occur after 10-20 units of RBC and, without iron chelation therapy (ICT),¹⁵ results in progressive dysfunction in the heart, liver, and endocrine system.^{14,16} Patients with MDS can be at increased risk of the toxic effects of IOL because of the presence of comorbidities associated with aging.^{17,18} Although it is well established that ICT extends the survival of patients with thalassemia by mitigating iron toxicity,^{14,16} there is currently little data to guide ICT in patients with MDS, although some reports suggest benefit.¹⁸ Iron chelation therapy is usually offered to patients with lower-risk MDS because their expected survival might be sufficient for ICT to confer benefit.^{17,19-21}

To evaluate the effects of ICT on clinical outcomes in patients with MDS, we performed a retrospective review and examined the effect of ICT on survival. To control for possible bias favoring patients who received ICT, we performed a subgroup analysis comparing the patients with control patients matched for baseline features.

Patients and Methods

Patients seen at St. Paul's Hospital in Vancouver, Canada, between 1981 and 2006 with MDS confirmed by bone marrow (BM) aspirate and biopsy were identified from the database of the hematology practice and the Provincial Home Hemosiderosis Program of British Columbia. A chart review was performed, and clinical and laboratory features were collected.

Criteria for initiating ICT were low or intermediate-1 IPSS score with an estimated life expectancy of 5 years at MDS diagnosis and ≥ 1 of the following: ferritin level $> 2000 \mu\text{g/L}$, transfusion of ≥ 20 units of RBCs, or clinical evidence of IOL. Before the availability of the IPSS, patients received ICT if they had a diagnosis of refractory anemia (RA) or RA with ringed sideroblasts (RARS) and fulfilled the remainder of the criteria stated earlier. Patients who received ICT received desferrioxamine 0.5-3 g by subcutaneous infusion over 12 hours, adjusted to ferritin level, 5 days weekly. All assessment for suitability for ICT using desferrioxamine, initiation, and monitoring of desferrioxamine therapy for all patients requiring ICT in the province of British Columbia is and has been performed by a single hematologist. Clinical evidence of IOL was defined retrospectively as end-organ toxicity in the absence of other etiology, demonstrated as follows: cardiac (left ventricular enlargement or decreased left ventricular ejection fraction [LVEF] on echocardiogram or other imaging, or clinical signs of systolic or diastolic cardiac dysfunction, or congestive heart failure/cardiac arrhythmia); hepatic (liver iron concentration of $\geq 7 \text{ mg Fe/g}$ liver dry weight on liver biopsy, clinical signs of chronic liver disease or portal hypertension, alanine aminotransferase or aspartate aminotransferase > 1.5 times the upper limit of normal [ULN]);

endocrine (glucose intolerance or diabetes, thyroid-stimulating hormone level above the ULN, sexual dysfunction); arthropathy or skin hyperpigmentation; documented or undocumented elevated ferritin level. Serious infection was defined retrospectively as ≥ 1 episode of infection requiring hospital admission.

For the subgroup analysis, 1 control patient was selected for each patient who received ICT. Selection was made by first eliminating all non-ICT patients with an intermediate-2 or high-risk IPSS score or a French-American-British (FAB) diagnosis of RA with excess blasts, then selecting 1 patient from the remaining non-ICT patients most closely matched to each of the patients who received ICT for Eastern Cooperative Oncology Group (ECOG) performance status (PS)²²; FAB MDS subtype; neutrophil, hemoglobin, and platelet counts at diagnosis; number of cytopenias at diagnosis; karyotype risk group (as defined by the IPSS)⁵; and total number of RBC units received over their course. Because there was no more than 1 control patient in this series who was a sufficiently close match as to be meaningful (for example, who fell into the same IPSS category or for number of cytopenias or karyotype risk group at diagnosis or for total number of RBC transfusions received) for some patients who received ICT, only 1 control patient was selected for each ICT patient.

Overall survival (OS) was defined as the time from diagnosis of MDS to the time of death from any cause. Overall survival was determined by the Kaplan-Meier method and the significance of differences in actuarial survival by the log-rank method using SPSS for Windows, version 13.0. Patients still alive were censored at the last known date of follow-up. Acute myeloid leukemia transformation was defined as a change in clinical behavior of the MDS associated with a new appearance of circulating blasts in the peripheral blood and/or $\geq 20\%$ blasts in the BM.⁴ Overall survival was compared in subgroups, and patient outcomes were compared according to baseline features. Univariate analysis (UVA) was performed using the Kaplan-Meier method. Cox regression analysis was also performed using SPSS.

Baseline clinical characteristics, initial and follow-up ferritin levels, number of AML transformations, and total deaths were compared between groups using the Student *t* test using SPSS. This study was performed in accordance with the requirements of St. Paul's Hospital Research Ethics Board.

Results

Patient Characteristics

A total of 178 patients with a BM aspirate and biopsy confirming a diagnosis of MDS by FAB² or WHO⁴ criteria were identified. Baseline clinical and laboratory features are summarized in Table 1. The median age at diagnosis was 69 years (range, 18-94 years), and 59% were men. Eighty-nine percent of patients had an ECOG PS²² of 0/1. Blast count in the marrow was documented in 165 patients, and the median was 1% (0-31%). Fifty-nine patients had a ferritin level measurement documented within 3 years of diagnosis, and the median ferritin level was $358 \mu\text{g/L}$ (range, 12-6447 $\mu\text{g/L}$). Twenty-seven patients (15%) were RBC transfusion-independent, and 84 (47%) received > 20 RBC units. The majority of patients ($n = 127$; 71%) received supportive care as primary MDS therapy. Eighteen patients received ICT for a median of 21.6 months (range, 1.3-151 months). Median time from MDS diagnosis to initiation of ICT was 36.4 months (range, 0-186 months).

Table 1A Clinical and Laboratory Features of 178 Patients with Myelodysplastic Syndromes

Characteristic	N (%)
Age at Diagnosis, Years	
≤ 65	57 (32)
> 65	121 (68)
Sex	
Female	73 (41)
Male	105 (59)
ECOG Performance Score	
0	25 (14)
1	133 (75)
2	14 (8)
3	2 (1)
4	1 (1)
MDS Subtype	
RA	36 (20)
RARS	42 (24)
RAEB	28 (16)
RAEB-t/AML	16 (9)
CMML	25 (14)
Other*	31 (17)
Neutrophil Count at Diagnosis	
< 1.5 × 10 ⁹ /L	80 (45)
≥ 1.5 × 10 ⁹ /L	86 (48)
Hemoglobin at Diagnosis	
< 100 g/L	111 (62)
≥ 100 g/L	64 (36)
Platelet Count at Diagnosis	
< 100 × 10 ⁹ /L	73 (41)
≥ 100 × 10 ⁹ /L	97 (54)
Number of Cytopenias at Diagnosis	
0/1	92 (53)
2/3	80 (45)
Blast Count in Marrow	
< 5%	118 (66)
≥ 5%	47 (26)

*Other: MDS NOS, n = 18; hypoplastic MDS, n = 7; deletion 5q, n = 4; refractory cytopenia with multilineage dysplasia, n = 2.

Abbreviations: CMML = chronic myelomonocytic leukemia; RAEB = refractory anemia with excess blasts; RAEB-t = RAEB in transformation

Survival

At a median follow-up of 17 months (range, 0.1-226 months), median OS for all patients was 37.8 months (range, 0.2-255.9 months). In a UVA, factors significant for OS included the FAB MDS subtype, IPSS score, number of RBC units transfused, primary MDS-directed treatment, elevated ferritin level, clinical IOL, and ICT ($P < .05$ for all); age showed a trend ($P = .1$) and was

Table 1B Clinical and Laboratory Features of 178 Patients with Myelodysplastic Syndromes

Characteristic	N (%)
Karyotype*	
Good	107 (60)
Intermediate	22 (12)
Poor	21 (8)
IPSS Risk Group	
Low	44 (25)
Intermediate-1	55 (31)
Intermediate-2	17 (10)
High	17 (10)
Initial Ferritin Level (µg/L)†	
≤ 400	31 (40)
401-1000	12 (7)
1001-2000	8 (4)
> 2000	8 (4)
Number of RBC Units Transfused	
0	27 (15)
1-20	36 (20)
21-50	28 (16)
> 50	56 (31)
MDS Treatment	
Low-dose chemotherapy	14 (8)
AML chemotherapy ± SCT	8 (4)
Immunomodulatory‡	20 (11)
EPO ± G-CSF	11 (6)
Supportive§	127 (71)

*As defined for the IPSS: good = normal, deletion 5q, deletion 20q, -Y; poor = complex (≥ 3 karyotypic abnormalities), chromosome 7 anomalies; intermediate = other anomalies.

†Within 3 years of MDS diagnosis.

‡Including steroids, n = 13; cyclosporine with or without other therapy, n = 5; thalidomide, n = 1; lenalidomide, n = 1.

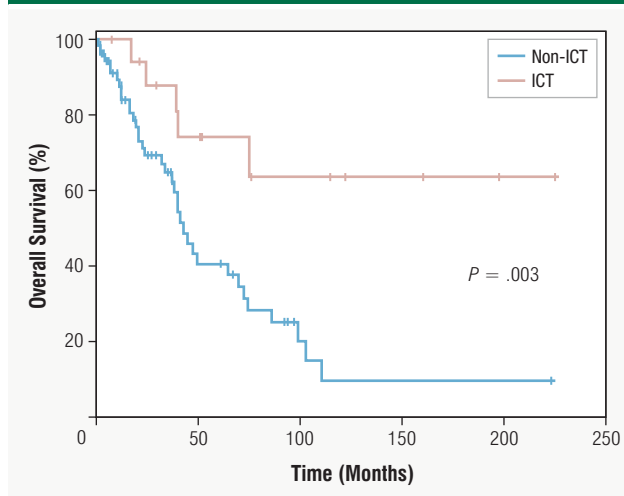
§Including transfusions only.

Abbreviations: EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; SCT = stem cell transplantation

included in the multivariate analysis (MVA). In an MVA, factors that remained significant for OS were IPSS score ($P = .008$; hazard ratio [HR] for intermediate-2- or high-risk IPSS vs. low- or intermediate-1-risk, 2.2 [95% CI, 1.3-3.7]) and ICT ($P = .02$; HR, 0.1 [95% CI, 0.01-1.0]). For patients with low- or intermediate-1-risk IPSS, the median OS for patients who received ICT was not reached at 226 months compared with a median OS of 40 months (range, 0.5-224 months; $P = .003$) for non-ICT patients. Sixty-four percent of patients receiving ICT were alive at 4 years compared with 43% of patients not receiving ICT ($P = .003$; Figure 1).

Because some patients were diagnosed with MDS before the advent of the IPSS, an additional analysis was performed. In a UVA, further features significant for OS included neutrophil count at MDS diagnosis, platelet count at MDS diagnosis, number of cytopenias (as defined by the IPSS), blast count, karyotype risk

Figure 1 Overall Survival in Patients with Low or Intermediate-1 MDS According to Receipt of Iron Chelation Therapy



group (as defined by the IPSS), AML transformation, and ≥ 1 serious infection ($P < .05$ for all). Because the number of factors that can be entered into an MVA is limited in a series this size, the following factors were selected: number of cytopenias; blast count; karyotype; AML transformation; serious infection; and patients entered along with primary MDS treatment, clinical IOL, and receipt of ICT. French-American-British MDS diagnosis was excluded because it correlates well with blast count, and increased ferritin was excluded because it is included in the clinical determination of IOL. Significant factors for OS in this analysis were serious infection ($P = .05$; HR, 3.2 [95% CI, 0.97-10.4]) and receipt of ICT ($P = .02$). Finally, an MVA was performed that was restricted to patients of low- and intermediate-1-risk IPSS only. In this analysis, IPSS score (low vs. intermediate-1 risk) lost significance, but ICT remained significant for OS ($P = .01$; HR, 0.05 [95% CI, 0.003-0.68]). In a second analysis in low- and intermediate-1-risk IPSS patients using number of cytopenias, blast count, etc, as listed earlier, only ICT remained significant for OS ($P = .0002$; HR, 0.01 [95% CI, 0.003-0.68]).

Ferritin Levels

The initial/pre-ICT ferritin level in ICT patients was a median of 4215 $\mu\text{g/L}$ (range, 1500-8400 $\mu\text{g/L}$) compared with 1647 $\mu\text{g/L}$ (range, 265-5009 $\mu\text{g/L}$) in non-ICT patients ($P = .07$). The most recent follow-up ferritin level in ICT patients was a median of 2659 $\mu\text{g/L}$ (range, 567-5228 $\mu\text{g/L}$) compared with 3188 $\mu\text{g/L}$ (range, 763-12,723 $\mu\text{g/L}$) in non-ICT patients ($P = .003$ for ICT compared with non-ICT patients and $P = .001$ for initial ferritin compared with follow-up in patients undergoing ICT).

Subgroup Analysis

Clinical features of the 18 patients who received ICT and 18 controls used in the subgroup analysis are shown in Table 2. The median age at MDS diagnosis was 64 years (range, 32-70 years) for patients who received ICT and 73 years (range, 39-81 years) for

Table 2A Clinical and Laboratory Features of 36 Patients with MDS Undergoing Iron Chelation Therapy: Characteristics and Controls

Characteristic	ICT (%) (n = 18)	Non-ICT (%) (n = 18)	P Value
Age at Diagnosis, Years			
≤ 65	11 (61)	4 (22)	.04
> 65	7 (39)	14 (78)	
Sex			
Female	9 (50)	6 (33)	NS
Male	9 (50)	12 (67)	
ECOG PS			
0	3 (17)	2 (11)	NS
1	13 (72)	15 (83)	
2	1 (6)	0	
3	1 (6)	0	
4	0	0	
FAB MDS Subtype			
RA	7 (39)	6 (33)	NS
RARS	8 (44)	7 (39)	
Deletion 5q	1 (6)	0	
Hypoplastic MDS	1 (6)	1 (6)	
MDS-NOS	1 (6)	4 (22)	
Neutrophil Count at Diagnosis			
$< 1.8 \times 10^9/\text{L}$	10 (56)	9 (50)	NS
$\geq 1.8 \times 10^9/\text{L}$	8 (44)	8 (44)	
Hemoglobin at Diagnosis			
$< 100 \text{ g/L}$	9 (50)	6 (33)	NS
$\geq 100 \text{ g/L}$	8 (44)	12 (67)	
Platelet Count at Diagnosis			
$< 100 \times 10^9/\text{L}$	3 (17)	13 (72)	NS
$\geq 100 \times 10^9/\text{L}$	15 (83)	5 (28)	

Abbreviation: NS = not significant

controls ($P = .04$). International Prognostic Scoring System score was low or intermediate-1 risk in all patients. Two patients in the ICT group had an initial ferritin level $> 1000 \mu\text{g/L}$ compared with none in the control group ($P = .03$). All patients received ≥ 50 RBC units in transfusion over their period of follow-up.

Follow-up was 51.1 months (range, 12.8-225.8 months) for all patients, 51.4 months (range, 7.1-226 months) for patients who received ICT, and 44.8 months (range, 10.1-224 months) for controls. The median OS for patients who received ICT was not reached at 225 months versus a median of 40.5 months for controls, and 4-year OS was 64% and 49%, respectively ($P = .01$; HR, 0.29 [95% CI, 0.10-0.79]; Figure 2).

Acute Myeloid Leukemia Transformation and Causes of Death.

One patient who received ICT developed AML at 15 months from MDS diagnosis as did 4 patients not receiving ICT at a median of

Table 2B Clinical and Laboratory Features of 36 Patients with Myelodysplastic Syndrome: Iron Chelation Therapy Patients and Controls

Characteristic	ICT (%) (n = 18)	Non-ICT (%) (n = 18)	P Value
Number of Cytopenias at Diagnosis			
0/1	13 (72)	11 (61)	NS
2/3	5 (28)	7 (39)	
Karyotype*			
Good	9 (50)	11 (61)	NS
Intermediate	4 (22)	3 (44)	
IPSS Risk Group			
Low	6 (33)	5 (28)	NS
Intermediate-1	6 (33)	8 (44)	
Initial Ferritin Level (µg/L)			
≤ 400	5 (28)	5 (28)	.03
401-1000	1 (6)	1 (6)	
1001-2000	2 (11)	0	
> 2000	5 (28)	0	
Number of RBC Units Transfused			
< 50	0	0	NS
> 50	18 (100)	18 (100)	
Primary MDS Treatment			
Low-dose chemotherapy	0	1 (6)	NS
AML chemotherapy ± SCT	0	1 (6)	
Immunomodulatory†	0	1 (6)	
EPO ± G-CSF	1 (6)	0	
Supportive care‡	17 (94)	15 (83)	

*As defined for the IPSS: good = normal, deletion 5q, deletion 20q, -Y; poor = complex (≥ 3 karyotypic abnormalities), chromosome 7 anomalies; intermediate = other anomalies.

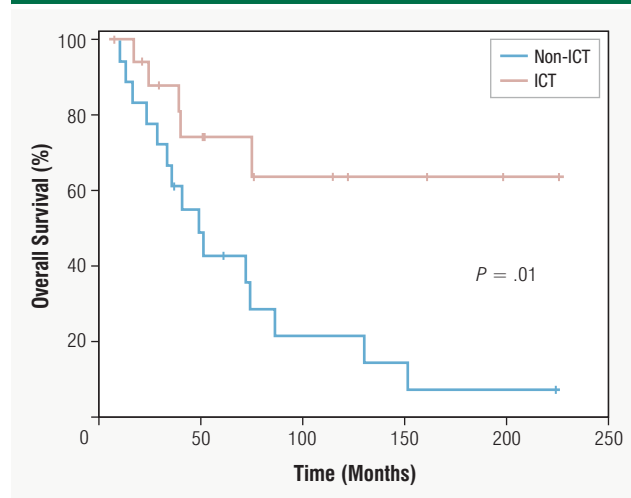
†Including prednisone.

‡Including transfusions with or without ICT.

Abbreviations: EPO = erythropoietin; G-CSF = granulocyte colony-stimulating factor; NS = not significant; SCT = stem cell transplantation

35 months (range, 19-71 months). The patient who received ICT and 1 control patient each received AML chemotherapy, and the remaining 3 patients received supportive care. All 5 patients died of progressive AML within weeks of AML transformation. There were 5 deaths (28%) in the ICT group and 15 (83%) in controls. Causes of death for the ICT group were as follows: cardiac toxicity, n = 2 (1 congestive heart failure and 1 arrhythmia); AML, n = 1; infection, n = 1; and MDS not otherwise specified (NOS), n = 1. Causes of death for control patients were as follows: MDS-NOS, n = 6; AML, n = 4; infection, n = 2; bleeding, n = 2; and MDS unrelated (chronic obstructive pulmonary disease), n = 1.

Ferritin Levels. There was a trend toward higher initial/pre-ICT ferritin level in patients who received ICT (n = 13 vs. n = 4; $P = .09$), and ferritin in patients who received ICT trended lower at follow-up (n = 16; $P = .09$) but did not change significantly in patients not receiving ICT (n = 8; $P =$ not significant).

Figure 2 Overall Survival in Patients with MDS According to Receipt of Iron Chelation Therapy in a Subgroup Analysis

Control patients with similar clinical features to those undergoing ICT were selected.

Discussion

It is well established that ICT extends the survival of transfusion-dependent patients with thalassemia by mitigating iron toxicity²³⁻²⁷; however, there is comparatively little data on clinical outcomes in patients with MDS receiving ICT. Gonzalez et al demonstrated that ICT with desferrioxamine is effective in preventing IOL in transfusion-dependent patients with MDS,²⁸ and it has also been shown that desferrioxamine can reduce cytopenias in MDS.²⁹ We performed a retrospective review of patients with MDS and showed in an MVA of patients of all IPSS scores that patients receiving ICT had improved OS compared with non-ICT patients. In this analysis, lower IPSS score was also significant for improved OS. Because ICT is generally restricted to patients with low- or intermediate-1-risk IPSS score, we compared the OS of patients with low- or intermediate-1-risk IPSS scores according to whether they received ICT and found that the OS at 4 years was significantly improved in patients with low- or intermediate-1-risk IPSS score receiving ICT ($P = .003$). Because some patients were diagnosed with MDS before the IPSS and IPSS scores for some patients were missing, further analysis was performed, including number of cytopenias, blast count, and karyotype risk along with AML transformation, serious infection, primary MDS treatment, number of RBC units transfused, ≥ 1 serious infection, clinical IOL, and ICT. This analysis showed that serious infection ($P = .05$) and ICT ($P = .02$) were significant for OS. Although FAB MDS diagnosis and elevated ferritin level were excluded from this analysis, these factors are influenced by blast count and clinical IOL, respectively.

The improvement in OS in patients receiving ICT was sustained in a subgroup analysis ($P = .01$; HR, 0.29), which was performed to minimize the possibility that improved outcomes in patients who received ICT might be a result of selection or referral bias. For example, the possibility that only patients who were clinically well and expected to live longer than others were referred and/or selected

to receive ICT must be considered. Fewer patients in the ICT group underwent AML transformation (1 vs. 4; $P = .06$), and there were fewer deaths (5 vs. 15; $P = .0001$). Although the median age in non-ICT control patients was 9 years older than in patients who received ICT (median, 73 years vs. 64 years), only 1 death appeared to be age-related (chronic lung disease), and all other deaths were from complications of MDS, suggesting that age was not a major factor in determining outcome. In addition, in the UVA, age showed a trend toward significance only for OS ($P = .1$) and was not significant in the MVA. Thus, the difference in age in these 2 groups might not have significantly affected the findings. However, to verify these results, another MVA restricted to patients with low- or intermediate-1-risk IPSS score was performed, and receipt of ICT remained significant for OS ($P = .01$; HR, 0.05).

The decrease in leukemic transformation and improvement in survival observed in patients who received ICT is encouraging; however, there are limitations to this analysis, which is retrospective and must be interpreted with caution. However, the majority of patients (92%) had a good PS and were treated with supportive care (71%) as their primary MDS-directed treatment, resulting in a relatively homogeneous group of patients in which to follow the effect of ICT. In this analysis, although the median interval to ICT was 36.4 months (range, 0-186 months), the median and range of follow-up duration between ICT (51.4 months [range, 7.1-226 months]) and non-ICT subgroup control patients (44.8 months [range, 10.7-224 months]) were comparable, and OS was determined from the date of MDS diagnosis, making lead time bias in favor of patients who received ICT unlikely. Similarly, although clinical evidence of IOL and life expectancy were determined in many cases by clinical impression rather than biopsy or imaging or by predetermined criteria, respectively, because ICT with desferrioxamine in British Columbia was initiated and managed by a single hematologist, gross inconsistencies in clinical impression are unlikely. Also, although this analysis was planned retrospectively and data regarding ferritin levels and other parameters were incomplete and recorded at irregular intervals, gross inconsistencies in management from patient to patient are unlikely for the same reason.

Iron chelation therapy could have improved survival by decreasing the body iron burden. In the whole group of 178 patients, ferritin levels in patients who received ICT decreased significantly over the period of follow-up, rose significantly in non-ICT patients, and was significantly higher at most recent follow-up in non-ICT patients than in patients who received ICT. In the subgroup analysis, the changes and differences in ferritin levels did not reach statistical significance, which is likely a result of insufficient numbers for comparison. Although the ferritin level is a suboptimal marker of total body iron, it has been shown that maintenance of a serum ferritin below 2500 $\mu\text{g/L}$ improves survival in iron-overloaded patients with thalassemia treated with desferrioxamine.¹⁴ It was difficult to determine with certainty whether individual deaths in this study might have been related indirectly to IOL; for example, an increased predisposition to infection in IOL has been postulated,^{30,31} an effect that might be difficult to separate from a susceptibility to infection from neutropenia. In most patients, an assessment of IOL was made by clinical impression, and death could be definitely attributed to IOL in only 1 case.

These findings are in keeping, however, with the results of other analyses. In a recent study of 467 patients with MDS, IOL was an adverse prognostic factor for survival, and transfusion-dependent patients died more frequently of a cardiac event than patients who were transfusion-independent.¹⁸ In another study, > 40% of patients with MDS showed signs of congestive heart failure, 24% had hepatic dysfunction, and 10% developed diabetes mellitus.³² Organ toxicity as a result of iron is likely to be under-recognized in clinical practice, and the potential to mitigate this toxicity through treatment is likely underutilized. Recent guidelines suggest a ferritin level be obtained at MDS diagnosis and at regular intervals^{19-21,33} in addition to an evaluation of cardiac status by imaging,³⁴ electrocardiogram (ECG), evaluation of LVEF,³⁵ and imaging or biopsy of the liver; these studies were not regularly documented in this retrospective series. As an example of the probable under-recognition of iron-mediated toxicity, one of our patients with IOL did not undergo ICT because of the presence of cardiac arrhythmias and congestive heart failure, which were judged to be the limiting factor for survival. However, in retrospect, it is possible that these problems might have been a result of cardiac toxicity from iron,^{18,36,37} and recent studies suggest that ICT will at least partially reverse these complications.^{25,38} In addition, a recent report confirms an improvement in OS in patients with MDS receiving ICT and suggests that survival was superior in patients who were well chelated compared with those who were poorly chelated.³⁹ However, another recent study suggests that, in patients with the FAB MDS subgroup diagnosis RARS, no improvement in survival was observed in patients receiving ICT⁴⁰; thus, the survival benefit of ICT in this setting remains controversial.

Iron might have its toxic effects not only by direct deposition into tissues but also by the formation of reactive oxygen species (ROS), which could damage lipids, proteins, and nucleic acids.⁴¹⁻⁴⁵ One study suggests that cytopenias in MDS could be mitigated by ICT through a decrease in ROS-mediated damage to hematopoietic cells.²⁹ We examined neutrophil and platelet counts and RBC transfusion requirements and found no significant difference between groups (data not shown). However, the median duration of ICT was only 21.6 months, and the number of patients was small, so an effect of ICT on cytopenias cannot be ruled out. This potential effect as well as the effect on survival should be further analyzed in prospective studies in which parameters such as transferrin saturation, non-transferrin-bound iron (NTBI), and labile plasma iron (LPI) and even ROS can be regularly monitored.

Conclusion

This study is retrospective and therefore subject to the biases of any analysis not randomized and controlled. Drawbacks of the retrospective design include the fact that life expectancy and clinical evidence of IOL were determined largely by clinical impression and not by a predetermined set of criteria. Despite these limitations, however, important points were raised that warrant further study. To further clarify the role of ICT in MDS, it is important to verify these findings in prospective trials. Such trials would ideally use objective measurements of iron load such as NTBI, LPI, T2-weighted magnetic resonance imaging, and measurements of iron indices and organ function, such as liver tests, glucose, hor-

mone levels, ECG, Holter monitor, and determination of LVEF, at standardized intervals. Finally, further studies are needed to evaluate the effect of ICT on patient quality of life⁴⁶ as well as its cost/benefit ratio.⁴⁷ Because of the suggested survival benefit and other potential benefits of ICT²³⁻³⁰ and particularly now that oral iron chelators are available in many countries, further study of this intervention in patients with MDS is warranted.

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