Daily practice management of myelodysplastic syndromes in France: data from 907 patients in a one-week cross-sectional study by the *Groupe Francophone des Myélodysplasies*

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ABSTRACT

Background
There is little published information on the everyday clinical management of myelodysplastic syndromes in real world practice.

Design and Methods
We conducted a cross-sectional study of all patients with myelodysplastic syndromes attending 74 French centers in a 1-week period for inpatient admission, day-hospital care or outpatient visits.

Results
Nine hundred and seven patients were included; 67.3% had lower-risk myelodysplastic syndromes (International Prognostic Scoring System: low or intermediate-1). Karyotype had been analyzed in 82.5% of the cases and was more often of intermediate or poor risk in patients under 65 years old compared with those who were older. Red blood cell transfusions accounted for as many as 31.4% of the admissions. Endogenous erythropoietin level was less than 500 IU/L in 88% of the patients tested. Erythroid stimulating agents had been or were being used in 36.8% of the lower risk patients, iron chelation in 31% of lower risk patients requiring red blood cell transfusions and lenalidomide in 41% of lower risk patients with del 5q. High-dose chemotherapy, hypomethylating agents, low dose cytarabine and allogeneic stem cell transplantation had been or were being used in 14.8%, 31.1%, 8.8% and 5.1%, respectively, of higher-risk patients.

Conclusions
Karyotype is now assessed in most patients with myelodysplastic syndromes, and patients under 65 years old may have more aggressive disease. Apart from erythroid-stimulating agents and, in higher-risk myelodysplastic syndromes, hypomethylating agents, specific treatments are used in a minority of patients with myelodysplastic syndromes and red blood cell transfusions still represent the major reason for hospital admission.

Key words: MDS, cross-sectional study, outpatient visit, erythropoietin, erythropoiesis stimulating agents.

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Introduction

Myelodysplastic syndromes (MDS) are clonal bone marrow disorders occurring predominantly in the elderly and characterized by ineffective hematopoiesis leading to blood cytopenias and by frequent transformation to acute myeloid leukemia (AML).[1] The overall incidence of this syndrome is about 3-5 cases per 100,000 persons per year. Although some epidemiological data have been generated in MDS from registries covering large periods of time,[2-6] case control studies[7,8] and, to a lesser degree, clinical trials, the use of different treatments in MDS in real world practice and the burden of MDS patients on health care systems, in terms of transfusion needs and admission rate, have rarely been studied in large MDS cohorts. Such an analysis may be particularly important now that more effective drug treatments have become available for MDS.

We performed a cross-sectional study in France. We recorded epidemiological characteristics and treatments received during the previous 6 months in all MDS patients who attended a large number of hematology centers in a 1-week period in 2008.

Design and Methods

Patients

Data were collected by the *Groupe Francophone des Myélodysplasies* (GFM) through a questionnaire administered between 28th January and 3rd February, 2008. This study was approved by a central ethics committee and by the *Commission Nationale Informatique et Liberté*, and all patients gave their informed consent to participation. The International Prognostic Scoring System (IPSS) score was calculated at inclusion, except for patients whose MDS had improved as a result of response to treatment such as intensive chemotherapy, allogeneic stem cell transplantation (SCT), hypomethylating agents, erythroid-stimulating agents (ESA) and lenalidomide. In those patients, the IPSS score was calculated at the onset of the treatment that led to the improvement. A unique identifying number was attributed to each patient and data were cross-checked with date of birth, gender and date of diagnosis to avoid duplication. All data were subsequently anonymized.

The participating physicians worked in 71 public and 3 private hospitals from all French regions in hematology departments, hematology-oncology departments and blood transfusion centers (belonging to the French National Blood Service). In France, the vast majority of patients with hematologic malignancies, including elderly patients, are followed by hospital-based hematology departments, so our study population was representative of the French situation. The physicians involved were GFM members in charge of MDS in their specific center. Physicians had to report on every MDS patient accessing their hematology unit during the 1-week period of the study. Accesses included: full hospitalization (admission for >24 h in a hospital ward), day hospital care (hospital admission for < 24 h without an overnight stay; essentially for intravenous or subcutaneous admission of chemotherapy or transfusions) and outpatient visits (consultation for diagnosis or follow-up). Of note, in France, ESA and low-dose chemotherapy (especially low-dose cytarabine) are systematically administered at home, while most azacytidine cycles are also administered at home by specialized nurses, through a specific program, with the patients being regularly followed-up during outpatient consultations. Physicians, or clinical research personnel under the supervision of physicians, personally filled in the questionnaire during the observation period.

The questionnaire was developed by the GFM and consisted of 171 items on the characteristics of the MDS both at diagnosis and at the time of the study, on concomitant diseases (past and present), particularly immunological disorders, treatment modalities and supportive care. More specifically, the questionnaire items included: (i) center, demographic data (age, gender) and type of access to care; (ii) reason(s) for admission; (iii) disease status with regard to active treatment or supportive care; (iv) disease characteristics at diagnosis; (v) disease characteristics at time of completing the questionnaire; (vi) treatment(s) received during the preceding 6 months; (vii) treatment for anemia during the preceding 6 months; (viii) treatment of neutropenia; and (ix) treatment of thrombocytopenia. Enrollment in clinical trials was not documented in the questionnaire.

Statistical methods

Comparisons were tested using Pearson's χ^2 test for qualitative variables and with Wilcoxon's test for quantitative variables. Odds' ratios (OR) were calculated with 95% confidence intervals (CI). Calculations were performed with JMP6 software. All comparisons were two-sided and *P* values less than 0.05 were considered statistically significant.

Results

Clinical and hematologic characteristics of the cohort

Overall, 907 MDS patients were included in this cross-sectional study by 74 centers belonging to the GFM. The characteristics of the patients at inclusion are shown in Table 1. Their median age was 74 years, with only two patients being aged less than 18 years at diagnosis, and one of them at inclusion; 22.4% and 26.6% of the patients were aged less than 65 and more than 80 years, respectively. Karyotype had been analyzed at least once in 749 (82.5%) of the total cohort. Patients in whom cytogenetic analysis had not been performed were significantly older than patients for whom karyotype information was available (median age 80 years *versus* 73 years; $P<0.0001$). The majority of patients (67.3%) had lower-risk MDS (IPSS score: low and intermediate-1). As regards MDS subtype, 18.7% and 16.9% of patients had refractory anemia with excess blasts (RAEB)-1 and RAEB-2, respectively. Multilineage dysplasia was present in 17.3% of the cases. The MDS was secondary to chemotherapy or radiotherapy in 13% of the patients. Past or present concomitant immunological disorders were present in 20 patients (2.2%). These disorders were autoimmune thyroiditis (n=4), rheumatoid arthritis or not specified inflammatory rheumatic disease (n=4), polymyalgia rheumatica (n=2), psoriasis (n=2), relapsing polychondritis (n=1), Sjögren's syndrome (n=1); Wegener's granulomatosis (n=1), polymyositis (n=1), and Evans' syndrome (n=1); details were not available for three of the 20 patients. The distribution of patients according to the French-American-British and World Health Organization classifications and cytogenetic abnormalities is shown in Table 1.

The reasons for access to the participating centers during the week of the study are summarized in Table 2. Most (86.5%) patients were seen as outpatients (day hospital care, or outpatient visits), but 41% of the patients had had a full admission to hospital at least once during the preceding 6 months. Transfusions [31.4% for red blood cell (RBC) transfusions and 7.1% for platelet transfusions] and follow-

Table 1. Characteristics of the 907 MDS patients at inclusion in the study.

Total	N=907
Age	
Median	74 years
Q1-Q3	[66-80]
Range	[14, 95]
Gender	
Male	57%
ECOG Performance Status	
0-1	28.3%
2-4	71.6%
Time from diagnosis	
Median	1.25 years
Quartiles¶	[0.41-3]¶
Range	[0-20]
Therapy-related MDS ¶¶	13%
Prior chemotherapy	9.1%
Prior irradiation	5.6%
Prior autologous SCT	0.6%
Association with an immune disorder	2.2%
Marrow blasts (%)	
Median	4%
Quartiles¶	[2-10]¶
Range	[0-30]
French-American-British classification	
Refractory anemia (RA)	31.3%
RA with ringed sideroblasts	17.6%
RA with excess blasts	32.7%
RA with excess of blasts in transformation	9.6%
Chronic myelomonocytic leukemia	8.5%
World-Health-Organization classification	
Refractory anemia	18.6%
RA with ringed sideroblasts	13.3%
Refractory cytopenia with multilineage dysplasia (RCMD)	15.4%
RCMD with ringed sideroblasts	3.8%
5q- syndrome	4.8%
RA with excess blasts-1	20.7%
RA with excess blasts-2	18.3%
Unclassified MDS	4.9%
Karyotype (749 patients)	
Normal	55.1%
Abnormal¶¶¶¶	44.8%
Del 5q	13.6%
Isolated del 5q	8.8%
Del 5q +1 abnormality	2.6%
Del 5q + >1 abnormalities	2.1%
Trisomy 8	6.4%
-7 or del 7q	5.6%
-Y	4.5%
Del 20q	5.3%
Del 12p	1.7%
≥ 3 abnormalities	9.3% (including 1.2% patients with -7 or del 7q)
Good	72.2%
Intermediate	14%
Poor	13.7%
IPSS (749 patients)	
Low	34.8%
Int-1	32.5%
Int-2	16.3%
High	16.3%
IPSS grouped (811 patients)¶¶¶	
Lower-risk	67.3%
Higher-risk	32.7%

up visits (36.4% of admissions) were the leading reasons for accesses. The reasons for full hospital admission were initial work-up, intensive treatment, transfusion, infection and hemorrhage in 13%, 27%, 31%, 25% and 4% of cases, respectively. Transfusion, treatment with a hypomethylating agent and chemotherapy were the reasons for 76%, 6% and 2%, respectively, of day-hospital accesses, while regular follow-up was managed at outpatient visits. Among the patients with lower-risk MDS, 10%, 42.3% and 47.7% were fully hospitalized, managed in a day-hospital or seen in outpatient clinics, compared to 21.3%, 54.7% and 23.9% of cases, respectively, in patients with higher-risk MDS (IPSS intermediate-2/high) (P<0.0001).

In 115 (13%) of the patients, the diagnosis of MDS had been made recently (i.e. within the preceding 2 months). These patients differed from the others in that they were seen more often in outpatient visits (52% *versus* 39%, P=0.0083) and had significantly higher hemoglobin and platelets values (P=0.0023); they did not, however, differ significantly with regard to age and IPSS category.

Treatments received

During the preceding 6 months, 41.7% of the patients had received no treatment other than supportive care; the remaining patients had received some form of "active" treatment, including ESA in 40%, high-dose chemotherapy (5.8% of all patients; 14.8% of those with higher-risk MDS), allogeneic stem cell transplantation (2.3% of all patients; 5.1% of those with higher-risk MDS), mostly with reduced intensity conditioning regimens, and a hypomethylating agent in 10.4% of all patients (azacytidine and decitabine in 9.2% and 1.2%, respectively) and in 31.1% of those with higher-risk MDS (Table 3). Lenalidomide had been or was being used in 44 (4.8%) of the patients: of these 44 patients, 30 (68.1%) had lower-risk MDS with del 5q, 4 (9%) had lower-risk MDS without del 5q and 10 (22.7%) had higher-risk MDS. The 30 patients with lower-risk MDS with del 5q who were receiving or had received lenalidomide in the preceding 6 months accounted for 41% of the 73 patients with this condition in the whole cohort. Low-dose chemotherapy (which consisted of low-dose cytarabine, except for patients with chronic myelomonoctyic leukema who were given hydroxyurea and/or 6-mercaptopurine) had been used in 5.1% of all cases (in 8.8% of those with higher-risk MDS). Androgens had been prescribed to 3% of the patients (for thrombocytopenia), whereas thalidomide and immunosuppressive

Table 1. *continued.*

Total	N=907		
Endogenous erythropoietin level (IU/L) (N=409)		Lower-risk	Higher-risk
Median	59	60	43
Quartiles¶	[27-200]¶	[27-200]	[17-101]
Range	[1-7,500]	[2-7,500]	[4-1,030]
<200	75%	75.2%	72%
<500	88%	87.6%	87.3%

¶Quartiles [25%-75%]; ¶¶ Total >100% because patients received several treatments; ¶¶¶ In 62 patients without karyotype, the number of cytopenias and the percentage of bone marrow blasts were sufficient to classify as lower- or higher-risk MDS, as karyotype would not have changed this classification; ¶¶¶¶ Total of abnormal karyotypes >100% because total frequencies of abnormalities are reported (not accounting for combined abnormalities).

treatment (anti-thymocyte globulin, cyclosporine or both) had been used in 1% and 0.5% of the cases, respectively. Treatment modalities according to IPSS category are represented in Figure 1A.

Treatment of anemia and of iron overload

The median hemoglobin level at the time of the survey was 9.3 g/dL and 62% of the patients had a hemoglobin concentration of less than 10 g/dL at this time. During the preceding 6 months, 61% of the patients had received RBC concentrates, with a median number of two RBC concentrates per month (range, 1-13). In accordance with French health authorities (AFSSAPS) and GFM recommendations (*www.gfmgroup.org*), RBC transfusions were administered to patients with a hemoglobin below 8 g/dL although a higher transfusion trigger threshold was used in the case of severe symptoms or limited cardiopulmonary capacity. The percentages of lower-risk and higher-risk MDS patients transfused during the preceding 6 months were 56.8% and 75.8%, respectively (P<0.0001).

During the same period, 39.5% of all patients and 41.3% of those with lower-risk MDS and anemia were treated with an ESA (Tables 3 and 4). Granulocyte colony-stimulating factor (G-CSF) was combined with the ESA in 19.4% of these patients. Among higher-risk patients who were given an ESA, 51.3% received a hypomethylating agent, high-dose chemotherapy or low-dose cytarabine during the same period. Interestingly, 19.4% of the patients with anemia had received both transfusions and an ESA during the preceding 6 months; the questionaire was not able to show the proportion of those patients still receiving ESA, although this treatment had failed and they were being chronically transfused.

Levels of endogenous serum erythropoietin were measured at least once in 45% of the patients, including 43.5% of those with lower-risk MDS and 39.7% of those with higher-risk MDS; in 88% of the cases, the values were below 500 IU/L. Serum erythropoietin level did not differ according to IPSS category (mean 233 IU/L in lower-risk *versus* 262 IU/L in higher-risk MDS, P=0.74) but was significantly higher in MDS with isolated del 5q (n=37) (mean, 1,075 IU/L; range, 1-7,500) than in other types of MDS (n=318) (mean, 199 IU/L; range 1-5,788, P<0.0001).

The erythroid reponse was evaluated by the individual reporting physicians (based on International Working Group 2006 criteria). The overall erythroid response rate to ESA was 51.2%, and 60% in lower-risk MDS. In univariate analysis, response was correlated with the lack of RBC transfusion requirement (OR 7.81, 95% CI 4.38-13.91; P<0.0001), IPSS low/intermediate-1 (OR 2.86, 95% CI 1.55-5.29; P=0.0005) and serum erythropoietin level less than or equal to 100 IU/L (OR 6.85, 95% CI 2.46-19.02; P=0.0001). In multivariate analysis, lack of RBC transfusion requirement and serum erythropoietin level less than or equal to 100 IU/L were associated with better response to ESA.

Iron chelation was administered to 24.9% of the patients requiring RBC transfusions (including 31% and 16% of those with lower and higher-risk MDS, respectively); the chelator used was desferrioxamine, deferasirox and deferiprone in 33.1%, 65.5% and 2% of the chelated cases, respectively.

Treatment of thrombocytopenia and neutropenia

The median platelet count was 104×10^9/L. Platelet counts were below 100×10^9/L, 50×10^9/L and 20×10^9/L in 46%, 25% and 10% of the patients, respectively. Of the patients with a platelet count less than 50×10^9/L, 61.7% had received platelet transfusions during the preceding 6 months, including 53.3% and 68.8% of the patients with lower-risk and higher-risk MDS, respectively; the median number of platelet concentrates transfused during the preceding 6 months was eight (range, 1-51). Androgens and AMG531 (romiplostim) were used for thrombocytopenia in 27 (6.6%) and 9 (1.5%) of patients, with mean baseline platelet counts of 50×10^9/L and 59×10^9/L, respectively.

The absolute neutrophil count was less than or equal to 1.8×10^9/L, 1×10^9/L and 0.5×10^9/L in 46.9%, 26.7% and 11.8% of the patients, respectively. Overall, 30.4% of the patients had experienced at least one infectious event dur-

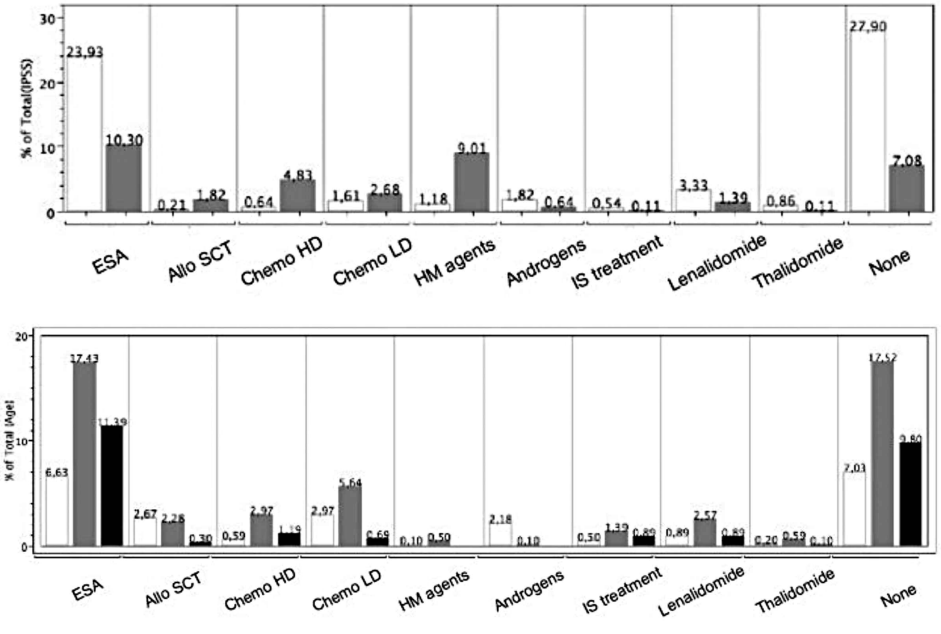

Figure 1. (**A**). **Treatment modalities according to IPSS (% of all treatments used during the preceding 6 months) in patients with IPSS low/int-1 (white columns) and IPSS int-2/high (gray columns). (B) Treatment modalities according to age (% of all treatments used during the preceding 6 months) in patients aged <65 years (white columns), 65-80 years (gray columns) and > 80 years (black columns). ESA: erythropoiesis-stimulating Agents; Allo SCT: allogeneic stem cell transplantation; Chemo HD: intensive anthracycline-cytarabine chemotherapy; Chemo LD, low-dose chemotherapy (including low-dose cytarabine, or less often hydroxyurea or 6-mercaptopurine); HM agents, hypomethylating agents; IS treatment, immunosuppressive treatment.**

ing the preceding 6 months. Infections occurred at least once in 26.4% and 37.3% of patients with absolute neutrophil counts greater than 1.8×10^9/L and less than or equal to 1.8×10^9/L, respectively (P=0.002). G-CSF had been used in 9.9% of all patients for neutropenia (after chemotherapy, in association with a hypomethylating agent or lenalidomide, or for severe infection in 27.7%, 13.3%, 12.2% and 28.8%, respectively) and in 7.7% of all patients for anemia, in combination with an ESA.

Table 2. Types and reasons of accesses, and transfusion requirements.

Total	N=907
Type of access	
Inpatient	13.3%
Outpatient – Day-hospital care	45.5%
Outpatient visit (consultation)	40.9%
Reason for access (% of all)	
Initial workup	10.2%
Follow-up	36.4%
Chemotherapy or hypomethylating agents	8.1%
Transfusion	38.6%
Red blood cells	31.4%
Platelets	7.1%
Infectious event	3.6%
Severe bleeding event (requiring hospitalization)	0.5%
Treatment (% of all)	
Not yet treated	22.1%
On treatment	39.5%
Off treatment	32.8%
Stable disease without transfusion	4.6%
Transfusion only (RBC and/or platelets)	28.1%
During the last 6 months	
Hospitalization	
Yes	41.0%
No	58.9%
Median number of days spent in hospital (calculated on patients who had been hospitalized)	10
Day hospital care	
Yes	67.1%
No	32.8%
Number of stays in day-hospital care	
Median	7
Infectious events	
0	69.6%
1	16.9%
≥2	13.4%
Bleeding events	
0	84.2%
1-2	11.1%
>2	4.5%
Patients requiring RBC concentrates (%)	61%
Number of RBC concentrates	
Median	12
Quartiles[¶]	[6-20]
Range	[1-78]
Patients requiring platelet transfusions (%)	24.5%
Number of transfusions	
Median	6
Quartiles[¶]	[3-15]
Range	[1-51]

[¶]Quartiles [25%-75%]

Correlations with age

Patients less than 65 years old (corresponding to patients often proposed some form of intensive treatment, including allogeneic SCT and intensive chemotherapy, in the case of higher risk features) significantly more often had intermediate and poor risk karyotypes (40.7% *versus* 23.5% in patients over 65 years old; P<0.0001) and -7/del 7q (12.5% *versus* 3.3%; P<0.0001) than older patients. These differences persisted when patients aged over 80 years (i.e. those under-represented among patients for whom karyotype information was available) were excluded from the analysis. A trend for younger age was observed for trisomy 8 (mean age 68.2 *versus* 71.4 years, P=0.06).

IPSS category differed significantly according to age (IPSS low/intermediate-1 in 58% of patients <65 years *versus* 70.1% in patients >65 years, P=0.0017). The mean percentage of bone marrow blasts was 5% *versus* 7% in patients aged more and less than 65 years, respectively (P=0.0197). Multilineage dysplasia was more frequent in patients aged less than 65 years (21.2% *versus* 12.1% in patients over 65 years, P=0.0073) while chronic myelomonocytic leukemia was more common in patients aged more than 65 years (6% *versus* 9.8% in patients less than and over 65 years old, respectively, P=0.035). During the preceding 6 months, patients less than 65 years old had more often required platelet transfusions (40.1% *versus* 22.3% of the patients; P<0.0001) and less often RBC transfusions (54.8% *versus*

Table 3. Treatment during the preceding 6 months.[¶¶]

	% of all[¶]	% of the higher-risk patients	% of the lower-risk patients
Erythroid-stimulating agent	39.5%	37.7%	40%
Allogeneic SCT[¶¶]	2.3%	5.1%	0.3%
Standard	0.5%		
Reduced intensity conditioning	1.8%		
Chemotherapy	11.1%	23.4%	5.6%
High dose	5.8%	14.8%	2.1%
Low dose	5.2%	8.8%	3.5%
Low dose cytarabine	1.5%		
Hydroxyurea / 6 MP	3.6%		
Hypomethylating agent	10.4%	31.1%	2%
5'-azacytidine	9.2%		
Decitabine	1.2%		
Androgens	3.0%	1.8%	2.8%
Immunosuppressive treatment	0.5%	0.3%	0.8%
ATG	0.1%		
ATG + cyclosporine	0.1%		
Cyclosporine	0.3%		
Lenalidomide			
All patients	4.8%	4.8%	5.5%
Patients with del 5q	4.4%	4%	5.2%
Isolated del 5q	77.5%	2.2%	4.5%
Del 5q + 1 abnormality	15%	1.2%	0.5%
Del 5q + >1 abnormality	7.5%	0.8%	0.1%
Patients without del 5q	0.4%	0.7%	0.3%
Thalidomide	0.9%	0.3%	1.3%

[¶]Including patients without known IPSS; [¶¶]Allogeneic SCT was performed earlier than in the 6 months preceding the survey in 10 out of 23 cases. Abbreviations: ATG, anti-thymocyte globulin; 6MP, 6-mercapto purine.

64.7% of the patients; *P*=0.0147) than patients over 65 years old. These differences were probably related to differences in treatment modalities between the two age groups as myelosuppressive treatments were administered more often to younger patients. Treatment modalities across age groups are shown in Figure 1B.

Discussion

This nationwide cross-sectional study included a large cohort of patients, i.e. all MDS patients seen during a given week in 74 centers of the GFM for diagnosis, follow-up visits or treatment. Due to this mode of accrual, the present cohort had an overrepresentation of patients in need of treatment and may not have precisely reflected the prevalence of different MDS characteristics in one country. This overrepresentation would have particularly concerned patients receiving RBC transfusions, or hospitalized for intensive chemotherapy or allogeneic SCT. On the other hand, treatment with ESA and low-dose chemotherapy (especially low-dose cytarabine) is almost exclusively administered at home in France, along with a large proportion of azacytidine cycles; patients only attend hospital for their regular out-patient visits. One could also argue that the study method restricted the inclusion to patients followed in hematology units. However, given that private practice in hematology is very limited in France, the vast majority of patients with chronic hematologic malignancies are referred to specialized hematology centers (in university hospitals or general hospitals), even when the patients are quite old.

Some of the patients' characteristics in this study are noteworthy. First, the fact that a majority of patients had low-risk MDS confirmed previous findings, such as those of the large Dusseldorf registry in which 63% of patients had lower-risk MDS.[2] More interestingly, karyotyping had been performed at least once in more than 80% of the patients (and in 89% of the patients under 80 years old), showing that this test is now widely recognized as necessary for the management of MDS patients.

In comparison with data on incident MDS cases collected during the period 2001-2004 in the Surveillance, Epidemiology and End Results (SEER) Program and the North American Association of Central Cancer Registries (NAACCR) covering almost the entire US population, gender and age distribution in the present study were similar, including the proportion of patients aged under 65 years, although patients aged more than 80 years were somewhat underrepresented (26.6% *versus* 37.3% in the combined SEER-NAACCR databases).[5,6] However, there were more cases of refractory anemia with excess blasts, refractory anemia with excess blasts in trasformation, and refractory cytopenia with multilineage dysplasia and treatment-related MDS in the present study than in the combined SEER+NAACCR databases (32.7%, 9.6%, 13.9% and 13%, respectively, in our study, *versus* 26%, 3.5%, 5.5% and 5.5% of specified MDS in SEER+NAACCR) although different classification systems and the frequency of *not specified* MDS in the US registries (56%) render comparisons difficult.

It had not been previously reported that serum erythropoietin levels are below 500 IU/L in as many as 85% of the tested patients (and in 86.5% of those with lower-risk MDS). This observation could possibly be explained by the earlier diagnosis of MDS and/or earlier assessment of serum erythropoietin values in our patients than in older studies.[9] This high prevalence of low erythropoietin levels suggests that a perhaps larger than usually considered proportion of patients with MDS may benefit from ESA. It is worth noting the much higher median serum erythropoietin level in patients with del 5q, compared to that in other patients, a finding that may be related to the poorer response to ESA among patients with the deletion.[10]

In the present cohort, as in previously published series of MDS patients, anemia remained the major clinical problem, and RBC transfusions were the most frequent reason for hospital access (31.4%). Furthemore, 40% of the patients were receiving or had received an ESA during the 6 months preceding the analysis, an interesting figure given the fact that these agents are not formally approved in the European Union for the treatment of anemia of MDS. Response rates to ESA and the prognostic factors for response were similar to those previously published.[11,12] The median weekly doses of erythropoietin α/β and darbepoetin, 40,000 IU and 250 μg, respectively, were in the range of those recommended by most groups including the GFM (40,000-60,000 IU and 150-300 μg, respectively).[13] Darbepoetin was the most frequently used ESA in this study, probably because of its longer half-life, allowing less frequent administration. In a previous study, we had found that 300 μg of darbepoetin every 2 weeks was the most common maintenance dose in patients with lower-risk MDS responding to this drug.[14] Interestingly G-CSF, generally not associated upfront with ESA in France, was added in only 19% of patients treated with ESA. In a large cross-sectional study in MDS patients performed in the USA, the percentage of MDS patients having ever received a RBC transfusion was lower than in the present series, especially in lower-risk MDS (25% of lower-risk MDS patients in the USA *versus* 57% in our series).[15] Different modes of accrual, i.e. hospital-based accrual in the present study as opposed to office-based accrual in the study in the USA, could have accounted for these differences. The proportions of patients receiving an ESA were, however, similar in

Table 4. Treatment of anemia during the preceding 6 months.

Patients with Hb<10 g/dL at diagnosis or upon inclusion	N=694 (76.5% of all patients)
Erythropoiesis-stimulating agent	51.8%
RBC transfusions only	48.1%
% of patients transfused during the last 6 months	75.4%
Median number of RBC transfused during the last 6 months in those patients	12
Type of erythropoiesis-stimulating agent	
Epoietin α	15.4%
Epoietin β	16%
Darbepoetin α	68.5%
Weekly dose of darbepoetin μg	
Median	250
Weekly dose of epoietin α/β UI	
Median	40,000
Addition of G-CSF	19.4% of pts treated with ESA
Erythroid response	
Yes	51.1%
No	48.8%

the two studies.

There are only few published data on the frequency of platelet transfusions in MDS.[16] In our series, patients dependent on platelet transfusions had received a median of eight platelet transfusions during the preceding 6 months; among the patients who had not received myelosuppressive treatments, the median was one platelet transfusion every 6 weeks. Of note, severe bleeding occurred in 38.5% of patients with a platelet count below 50×10^9/L in our series.

The hypomethylating agents azacytidine and decitabine, widely available through a compassionate program in France in February 2008, were used (or had been used in the preceding 6 months) in 10.4% of the patients. This percentage is likely to increase with the approval of azacytidine for the treatment of higher-risk MDS in December 2008. Azacytidine and decitabine had been used more frequently in the USA experience (18% and 2%, respectively), probably because they were already approved drugs in that country at the time of the US survey.[15] Our study showed, by contrast, a decline in the use of chemotherapy (intensive or low-dose cytarabine), administered to only 14.8% and 7.5%, respectively, of patients with higher-risk MDS. Five percent of the patients with higher-risk MDS (including 20% and 23% of those aged less than 55 and 65 years, respectively) had undergone allogeneic SCT, confirming that this procedure, although it remains the only curative treatment in MDS, can only be used in a minority of patients.[17] Eighty percent of the transplants were performed using non-myeloablative conditioning, confirming the increasing use of this strategy, especially in MDS, given the median age of such patients. The percentage of patients treated with allogeneic SCT in the US study was similar to that in our cohort, although myeloablative regimens were used more commonly (in more than half of the procedures).[15]

Lenalidomide had been used mainly in patients with lower-risk MDS with del 5q, 41% of whom had received the drug through a compassionate program existing in France at the time of the survey. The response rate was 61.5%. In the US experience, 8% of patients had received lenalidomide (the proportion of those without del 5q was not specified).[15] The wider use in the USA probably also resulted from the fact that this drug was approved in that country at the time of the US survey. By contrast thalidomide, probably due to its side effects, was seldom used (1% of patients, including 1.3% of lower-risk patients). Antithymocyte globulin was also very rarely prescribed (to only two patients, both with lower-risk MDS, aged 48 and 71 years). These findings place antithymocyte globulin, at least in France, as a rarely applied treatment. However, the percentage of patients treated with antithymocyte globulin in the large Düsseldorf MDS registry was similar, i.e. 0.5%.[18] Danazol had been used in 3% of the patients, generally for thrombocytopenia in lower-risk cases, following some results observed with this drug in two GFM studies.[19,20]

Finally, chelating agents were used in 31% of the lower-risk patients with transfusion requirements, including 35% of those who needed two or more RBC/month for 1 year or longer, in whom chelating agents are advocated.[21] Data on ferritin levels were not collected in this study. Interestingly, although it was approved only in 2006 for the treatment of MDS in Europe (and only in the case of inefficacy of or intolerance to desferroxamine), deferasirox was already the most widely used chelating agent, probably because of its oral route of administration. Another interesting finding was that 16% of higher-risk patients received iron chelation, although chelating agents are generally recommended only in lower-risk MDS. However, 51% of these patients were receiving or had received during the preceding 6 months some treatment potentially able to improve their survival (high-dose chemotherapy, hypomethylating agents and allogeneic SCT in 1, 13 and 3 cases, respectively). In addition, recent results suggest that iron overload prior to allogeneic SCT has a negative impact on post-transplant survival, prompting clinicians to administer chelation prior to transplant in regularly transfused patients with MDS.[22] Poor-risk karyotype, del 7q or -7, multilineage dysplasia and, as a trend, trisomy 8, were more often found in patients under 65 years old. Several other investigators also found an increased frequency of del 7q or monosomy 7 but not of complex karyotype in patients aged under 65 years old as well as in patients aged under 50 years.[23-26] An increased frequency of trisomy 8 in younger patients had not been reported so far, to our knowledge.[28] The prevalences of del 5q/-5 and -7/del 7q in patients aged less than 65 years appeared similar to those reported for patients with AML (excluding acute promyelocytic leukemia) in two studies.[29-30] In contrast, the frequency of -7/del 7q in our MDS patients aged more than 65 years seemed lower than that in AML patients of the same age.[29-30]

In conclusion, anemia and requirement for RBC transfusions represent important burdens for health care and quality of life in MDS patients in France. Apart from ESA, active treatments are still only considered for a minority of patients, except hypomethylating agents for those with higher-risk MDS. The higher frequency of unfavorable karyotypes in patients under 65 years old supports wider use of agents that can be active with those karyotypes, especially hypomethylating agents, and broader use of allogeneic SCT. The fact that in lower-risk MDS, especially at diagnosis, endogenous serum erythropoietin levels are generally below 500 IU/L may justify the expanding use of ESA in that population.

Authorship and Disclosures

CK provided patients, analyzed the data and wrote the paper; AS, OBR, ER, BQ, AG, and FD provided patients and were members of the steering committee; SB, CB, TP, YH, MH, JD, MPG, JMC, HZ, ALT, LL, and BC provided patients; PF provided patients, had the original idea, designed the study and wrote the paper. All other contributing authors are listed in the appendix, with the number of patients they included in the study.

ER: board membership, reimbursements from Cephalon; BQ: reimbursements and grants from Celgene and Amgen; PF: received honoraria from Celgene, Johnson and Johnson, Cephalon, Roche, GSK, Amgen and Novartis and grants from Celgene, Roche and Johnson and Johnson. The other authors reported no potential conflicts of interest.

Appendix

Fenaux P (Bobigny, n=47), Berthou C (Brest, n=31), Stamatoullas A (Rouen, n=27), Prebet T (Marseille, n=26), Beyne-Rauzy O (Toulouse, n=24), Quesnel B (Lille-Claude Huriez, n=24), Guerci A (Nancy, n=23), Hicheri Y (Creteil, n=23),

Delaunay J (Nantes, n=21), Dreyfus F (Paris-Cochin, n=21), Gourin MP (Limoges, n=21), Hacini M (Chambery, n=21), Camo JM (Perpignan, n=20), Zerazhi H (Avignon, n=20), Taksin AL (n=19), Lafon I (Dijon, n=17), Legros L (Nice, n=19), Bons JM (Montluçon, n=16), Dine G (Troyes, n=16), Raffoux E (Paris-Saint-Louis, n=14), Cheze S (Caen, n=13), Ghomari K (Beauvais, n=13), De Renzis B (Clermont-Ferrand, n=12), Plantier I (Roubaix, n=12), Stalnikiewicz L (Lens, n=12), Bouabdallah KK (Pessac, n=11), Wattel E (Lyon, n=11), Amé S (Strasbourg, n=10), Arkam Y (Mulhouse, n=10), Atmani S (Creil, n=10), Abossallue I (Charleville-Mezieres, n=9), Gyan E (Tours, n=9), Sebillot M (Rennes, n=9), Quittet P (Montpellier, n=9), Jelassi Z (Angers, n=8), Etienne G (Bordeaux, n=8), Klepping D (Chalons-sur-Saone, n=8), Vekhoff A (Paris-Hotel-Dieu, n=8), Damaj G (Amiens, n=7), Garidi R (Saint-Quentin, n=7), Jourdan E (Nimes, n=7), Sanhes L (Perpignan, n=7), Vives L (Saint-Gaudens, n=7), Allangba O (Saint-Brieuc, n=6), Cluet S (Compiegne, n=6), Frenkiel N (Poissy, n=6), Giron C (Strasbourg, n=6), Lenoble M (Montfermeil, n=6), Rose C (Lille-Saint-Vincent de Paul, n=6), Rumilly F (Metz, n=6), Tertian G (Paris-Kremlin-Bicetre, n=6), Beaumont M (Dunkerque, n=5), Boumalassa A (Draguignan, n=5), Courby S (Grenoble, n=5), Isnard F (Paris-Saint-Antoine, n=5), Leyronnas C (Grenoble, n=5), Malou M (Morlaix, n=5), Agape P (Saint-Denis, n=4), Boisseau M (Toulouse, n=4), Debourdeau P (Lyon-Hôpital des Armées, n=4), Gutnecht J (Frejus, n=4), Minard P (Vichy, n=4), Bijou FD (Bordeaux-EFS, n=3), Cony-Makhoul P (Annecy, n=3), Dagada C (Pau, n=3), Grange MJ (Paris-Bichat, n=3), Kitschke B (Sete, n=3), Pouaty C (Dieppe, n=3), Brunel V (Marseille, n=2), Devesa Mansour D (Gueret, n=2), Fezoui H (Toulon, n=2), Maigre M (Le Coudray, n=2), Re D (Antibes, n=2), Villemagne B (La Roche-sur-Yon, n=2), Fontaine C (Montpelier-Saint-Eloi, n=1).

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