Treatment with lenalidomide does not appear to increase the risk of progression in lower risk myelodysplastic syndromes with 5q deletion. A comparative analysis by the *Groupe Francophone des Myelodysplasies*

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ABSTRACT

Background
Although lenalidomide is very effective in the treatment of anemia of lower risk myelodysplastic syndromes with 5q deletion (del 5q), concerns have been raised over the fact that this drug could trigger progression to acute myeloid leukemia in some patients.

Design and Methods
Ninety-five transfusion-dependent patients with lower risk myelodysplastic syndromes with del 5q were treated with lenalidomide (10 mg/day, for 3 weeks every 4 weeks); six (6.3%) of the patients progressed to acute myeloid leukemia. This cohort of 95 lenalidomide-treated patients was compared to a historical control cohort of 99 patients with lower risk myelodysplastic syndromes with del 5q who never received lenalidomide, using a propensity score approach that can control for potential confounders in non-randomized comparisons.

Results
The 4-year estimated cumulative incidence of leukemia was 9% in patients treated with lenalidomide and 15.8% in controls who did not receive lenalidomide (P=0.16).

Conclusions
Using a propensity score approach, we found no significant difference in acute myeloid leukemia progression and survival from diagnosis between the cohort treated with lenalidomide and the control cohort.

Key words: lenalidomide, myelodysplastic syndrome, 5q deletion, acute myeloid leukemia, progression.

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Introduction

Deletion of the long arm of chromosome 5 (del 5q) is found in 6 to 15% of patients with myelodysplastic syndromes (MDS).[1,2] MDS with del 5q, when belonging to the low or intermediate 1 ("lower risk") groups of the International Prognostic Scoring System (IPSS),[1] occur more frequently in females (unlike other MDS) and are characterized by severe anemia, normal or elevated platelet counts, abnormal monolobulated megakaryocytes with eccentric nucleus, and generally isolated del 5q. When del 5q is the only cytogenetic abnormality and there is no increase in marrow blasts, the prognosis is generally favorable, although about 20% of cases progress to acute myeloid leukemia (AML) by 5 years; the median survival is 60 to 65 months.[1-5] In the case of 5q deletion in association with other cytogenetic abnormalities (especially if more than one) and/or an excess of marrow blasts, the risk of AML evolution is higher and survival shorter.[2]

Anemia, in lower risk MDS with del 5q, responds less often and with shorter responses to erythropoiesis-stimulating agents than does anemia in other lower risk MDS.[6] On the other hand, lenalidomide led to independence from red blood cell transfusion in two-thirds of patients with lower risk MDS with del 5q in the MDS 003 trial.[7] These results led the Food and Drug Administration in the USA to approve the use of lenalidomide for the treatment of red blood cell transfusion-dependent anemia due to lower risk MDS with del 5q, with or without additional cytogenetic abnormalities. However, the European Medicine Agency (EMEA) did not approve the drug for this indication, raising the concern, based on the results of the MDS 003 trial, that lenalidomide may trigger progression to AML in some patients with MDS with del 5q.

These findings led us to compare the outcome of a cohort of transfusion-dependent lower risk MDS patients with del 5q treated with lenalidomide to that of a similar historical cohort of patients who never received lenalidomide. In order to perform this observational study, we used a propensity score-based approach that can control for potentially confounding biases.

Design and Methods

Lenalidomide cohort

Between January and September 2007, the French health agency conducted, in cooperation with the *Groupe Francophone des Myélodysplasies* (GFM), a named-patient program of compassionate use of lenalidomide (Revlimid, Celgene Corp, NJ, USA) in patients with IPSS low and int-1 risk MDS with del 5q and transfusion-dependent anemia (defined by having received at least 2 red blood cell concentrates every 8 weeks over the previous 16 weeks). All applications were reviewed by the French health agency for approval, and informed consent was required from the patient prior to his or her inclusion in the study. A case report form was sent to the treating physician after the patient's inclusion in the study. A total of 115 MDS patients from 35 centers were enrolled in the program. Twenty of them were subsequently excluded, because of diagnostic error in 14 cases (8 AML and 6 MDS with high or int-2 IPSS) or because they did not receive treatment in six cases. The remaining 95 patients, who met the inclusion criteria and had all received at least 3 days of treatment, were analyzed. Information was collected after informed consent from the patients. The study was conducted according to the Declaration of Helsinki. The median time from diagnosis to lenalidomide treatment was 29 months (interquartile range, 11 - 53).

The results of lenalidomide treatment in these patients have been reported in detail elsewhere. Briefly, patients were treated with 10 mg of lenalidomide daily, for 21 days every 28 days. Responders continued to receive lenalidomide at the same dose until disease progression, treatment failure or treatment-limiting toxicity. With a median follow-up of 24 months from the onset of lenalidomide therapy, 62 of the 95 patients (65%) had an erythroid response according to the International Working Group 2006 criteria, including 60 patients (63%) who achieved transfusion independence. All but two responders continued to take lenalidomide until relapse. The median follow up from diagnosis was 4 years. Six patients progressed to AML, including two patients who had achieved transfusion independence. Four of them had refractory anemia with excess blasts 1 (RAEB 1) at inclusion with one (n=2) or two (n=2) cytopenias and had an IPSS score of 1, one had refractory anemia (RA) with two cytopenias and an IPSS score of 0.5 and one had refractory cytopenia with multilineage dysplasia (RCMD) with three cytopenias and an IPSS score of 0.5. Of the six patients who developed AML, two had isolated del 5q, three had one additional abnormality and the last patient had a predominant t(1;3) clone and only a minor clone with del 5q.

Control cohort

The control cohort of patients with lower risk MDS with del 5q treated without lenalidomide consisted of 99 patients treated in GFM centers (before lenalidomide was available) by erythropoiesis-stimulating agents or thalidomide. Briefly, this cohort included: (i) 48 patients diagnosed between 1998 and May 2006, and part of a series of 403 low or int-1 risk MDS treated with an erythropoiesis-stimulating agent (with or without granulocyte colony-stimulating factor) in three prospective GFM clinical trials or according to guidelines of the GFM and the French Society of Hematology for the use of erythropoiesis-stimulating agents in MDS with anemia (hemoglobin <10 g/dL, with or without transfusion requirement);[8] (ii) 24 patients included during the same period in two consecutive prospective clinical trials of the GFM using thalidomide (in which 120 patients were included overall);[9,10] and (iii) 27 other lower risk MDS patients with 5q deletion who never received lenalidomide and were included at diagnosis between 2003 and 2006 in the prospective French registry of MDS. The results of treatment of part of that comparative cohort have already been reported.[6,9,10] Sixty-five percent of those patients were dependent on red blood cell transfusions at inclusion into the study. The median follow up from diagnosis was 6.5 years.

Statistical analysis

The main outcomes were cumulative incidence of AML and overall survival, both computed from diagnosis. As bone marrow examination was not systematically performed in the absence of loss of response to lenalidomide or occurrence of cytopenias, assessment of progression to a more advanced disease stage without AML progression was not taken into account in this study. Since treatment with lenalidomide was not allocated through randomization we used a propensity score-based approach for the comparison of outcomes between patients treated and untreated by lenalidomide.

The objective of this approach was to control for potential selection bias in estimating treatment effects from observational data, by matching treated and untreated patients on their "propensity" to having been treated.[11]

The study was conducted in three main steps: First, multivariate logistic regression was used to estimate the probability of having been treated by lenalidomide conditionally on baseline prognostic characteristics (including age, gender, WHO diagnosis, IP, presence or not of cytogenetic abnormalities in addition to del 5q, IPSS score); moreover, we also adjusted for time from diagnosis to treatment decision (or censoring). The resulting so-called propensity score, computed for each of the 194 patients enrolled in the study, was then used to match each treated patient with one control, on the basis of their "similar" propensity to have been treated, that is, on the basis of the nearest neighbors in the propensity score with calipers at 0.2 times the standard deviation of the propensity score, as previously recommended.[11-13] To assess the extent to which confounding was controlled by matching, baseline mean imbalances across matched groups were compared by paired t-tests.[12] The third step consisted of estimating the treatment effect on outcome, i.e. overall survival since diagnosis, using a frailty model to account for the matched nature of the data. As previously reported, no adjustment was performed on this matched data set.[11-13] However, since the treatment decision was not made at diagnosis, the issue of delay had to be taken into account. We thus considered this issue as a delayed entry problem, though restricted to the treated patients. Indeed, the sample of treated patients could be considered as left truncated because subjects were treated conditionally on the fact that they had not died or developed acute transformation before. This was handled by secondly defining survival of treated patients from the date of treatment onset (while that of untreated patients was still counted from diagnosis). Thus, a treated subject participates in the "at risk set" from the date of treatment in the cohort to the date of censoring or date of outcome. This is subsequently denoted "survival after treatment onset".

Statistical analyses were performed using R 2.10.1 (*http ://www.R-project.org*). All tests were two-sided, with *P* values of 0.05 or less denoting statistically significant differences.

Results

Baseline characteristics of the two cohorts of patients

The baseline characteristics of the two cohorts of patients, at inclusion in the compassionate use program for patients treated with lenalidomide and in the trials on erythropoiesis-stimulating agents or thalidomide or at diagnosis for patients treated without lenalidomide, are shown in Table 1. The baseline characteristics of the two cohorts were generally similar, except that patients in the lenalidomide group were somewhat younger (median age: 70.4 years) than those in the control group (73 years, *P*=0.03), and more frequently had refractory anemia with ring sideroblasts (RARS) or RCMD with ring sideroblasts (RCMD-RS) (14% *versus* 4%, *P*=0.05). Median transfusion requirements were similar in the two groups (4 red blood cell units/2 months).

Propensity score derivation and matching

The propensity score was estimated for each patient, incorporating age, gender, WHO diagnosis, cytogenetics (isolated 5q *versus* del 5q and one additional abnormality, *versus* del 5q and at least two additional abnormalities), and IPSS score.

The probability of having received lenalidomide was lower in older patients, in males and in patients with RAEB 1 compared with that in other patients. When including such baseline characteristics as well as time from diagnosis to treatment decision or censoring, the propensity to be treated was still somewhat higher in patients actually treated (median: 0.52, IQR: 0.42-0.60) than in untreated patients (median: 0.45, IQR: 0.37-0.53) (Figure 1), illustrating the potential selection bias when comparing the original cohorts. Notably, the score ranged from 0.29 to 0.89 in treated patients while it ranged from 0.15 to 0.78 in untreated patients. Thus, only 71 treated patients could be matched to a control. The 24 unmatched treated patients were mostly females (79%) with a median age of 65 years (IQR: 50.3-69.2) and a WHO classification of 5q- syndrome in four cases, RARS in ten cases, RA in two cases, RAEB-1 in one case and RCMD in two cases, representing 11% (4/36), 77% (10/13), 15% (2/13), 4%, (2/23) and 22% of the patients treated with an initial diagnosis of 5q- syndrome, RARS, RA, RAEB-1, and RCMD, respectively. Of note, none of the unmatched patients progressed to AML or died during follow up.

Table 1. The patients' main baseline characteristics according to treatment with or without lenalidomide, before and after matching on a propensity score.

N. % Median [Q1-Q3] Before matching	Control cohort N=99	Lenalidomide cohort N=95	*P* value Unpaired tests
Median age at diagnosis, (range)	73 [64.9-81.2]	70.4 [42-92]	**0.03**
Male gender	33 (33%)	25 (26%)	0.36
Cytogenetics			
Isolated del 5q	73 (74%)	75 (80%)	0.41
Del 5q + 1 abnormality	17 (17%)	13 (14%)	0.66
Del 5q+2 or more abnormalities	9 (9%)	6 (6%)	0.66
WHO classification			
5q- syndrome	38 (38%)	36 (38%)	0.70
RA	14(14%)	13 (14%)	0.90
RAEB-1	25 (26%)	23 (24%)	0.73
RARS/RCMD-RS	4 (4%)	13 (14%)	**0.05**
RCMD	9 (9%)	10 (10%)	0.88
CMML	1 (1%)	1(1%)	1.00
IPSS score			
0	43 (46%)	29 (31%)	0.33
0.5	28 (30%)	47 (50%)	
1	23 (25%)	19 (20%)	
After matching	**N=71 (72%)**	**N=71 (76%)**	**Paired tests**
Median age, (range)	69.8	71.3	0.85
Male gender	21 (30%)	20 (28%)	1.00
Cytogenetics			
Isolated del 5q	58 (82%)	56 (79%)	0.84
Del 5q + 1 abnormality	8 (11%)	11 (15%)	0.65
Del 5q+2 or more abnormalities	5 (7%)	4 (6%)	1.00
WHO classification			
5q- syndrome	26 (37%)	29 (41%)	0.71
RA	10 (14%)	9 (13%)	1.00
RAEB-1	23 (32%)	22 (31%)	1.00
RARS	4 (6%)	3 (4%)	1.00
RCMD	8 (11%)	7 (11%)	1.00
CMML	0	0	-
IPSS score			
0	26 (37%)	23 (32%)	
0.5	27 (38%)	32 (45%)	0.92
1	18 (25%)	16 (22%)	

The baseline characteristics of the matched samples according to treatment are summarized in Table 1. As expected, previous differences in mean values of covariates between the two treatment groups were no longer found after matching.

Progression to acute myeloid leukemia and survival according to treatment

The 4-year estimated cumulative incidence of AML from diagnosis was 9.0% in the 71 matched patients treated with lenalidomide and 15.7% in the 71 matched controls who did not receive lenalidomide (HR= 0.87, 95%CI: 0.27-2.82; *P*=0.82) (Figure 1B). The median survival after diagnosis (Figure 1C) was 150 months in the 71 patients treated with lenalidomide compared to 78 months in the 71 matched controls (HR= 0.47, 95%CI: 0.23-1.01; *P*=0.06). The 4-year survival after treatment onset was 67% in patients treated with lenalidomide, as compared to 73% in untreated patients (Figure 1D; *P*=0.15).

Of note, in the group treated with lenalidomide, two of the 62 (3%) responders progressed to AML, compared to four of the 33 (12%) non-responders.

Discussion

The relatively high incidence of progression to AML observed in patients with lower risk MDS treated with lenalidomide in the MDS 003 trial led the EMEA to consider that it could not be excluded that lenalidomide had triggered the progression to AML and, therefore, to reject the use of the this drug for the proposed indication in the European Union. The relatively high incidence of progression to AML in the MDS 003 trial was attributed by some authors to the fact that the interval between the diagnosis of MDS and the onset of lenalidomide treatment was particularly long and that patients had, on average, a longer history of red blood cell transfusions, an expected finding in the first multicenter trial using lenalidomide in this situation.

These findings suggest that further analyses on the long-term effects of lenalidomide in patients with lower risk MDS with del 5q are required. However, no prospective randomized trial comparing the long-term outcome of patients with lower risk MDS with del 5q treated or not treated with lenalidomide has been performed. Such a trial

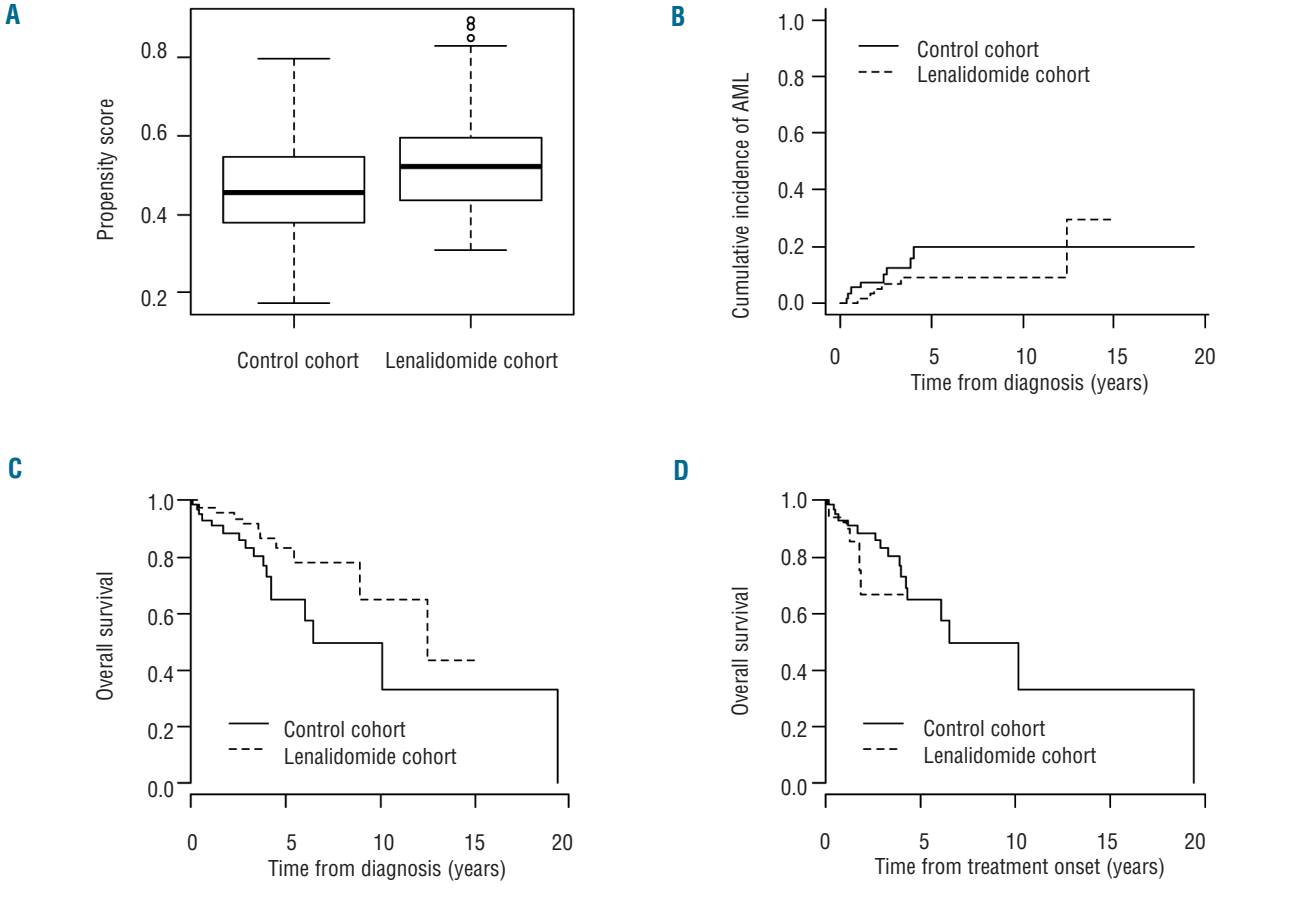

Figure 1. (A) Comparison of the "propensity" of being treated with lenalidomide, based on patients' age, gender, WHO diagnosis, IPSS score, and cytogenetic features, in the original treated and untreated cohorts. (B) Cumulative incidence of AML after diagnosis according to treatment in the matched cohorts. (C) Overall survival after diagnosis, according to treatment in the matched cohorts. (D) Overall survival after treatment onset, according to treatment in the matched cohorts.

may now be difficult to conduct by the hematology community given the dramatic effect of lenalidomide on anemia in this MDS subset (in which other drugs such as erythropoiesis-stimulating agents have limited efficacy) and the drug's approval for this indication in many countries.

This situation prompted several groups of investigators to perform historical comparisons of the rate of progression to AML of lower risk del 5q MDS patients, between patients treated before the lenalidomide era and patients who, more recently, received lenalidomide in clinical trials or other therapeutic programs. The Dusseldorf group recently reported, so far only in abstract form, 2-year and 5-year AML progression rates of 7% and 18%, respectively, in 300 patients with lower risk MDS with del 5q treated without lenalidomide.[14] The rate was higher in patients with an excess of marrow blasts, and in patients with cytogenetic abnormalities in addition to del 5q, as previously reported.[15] However, it was also higher in patients dependent on red blood cell transfusions, who represent candidates for lenalidomide. In the last patient subgroup, no obvious difference in progression to AML was seen with patients included in the MDS 003 trial, who had received lenalidomide.

For a more precise, although still historical, comparison, we used the propensity score method,[13] a method which can estimate unbiased treatment effects from observational studies by re-creating the exchangeability between two treatments groups, as when randomized allocation is made. We determined a propensity score defined as a subject's probability of receiving lenalidomide conditionally on his (her) observed covariates. For this purpose, through multivariate logistic regression we modeled, in patients with lower risk MDS with del 5q, the probability of receiving lenalidomide conditionally on a set of baseline characteristics (including age, gender, WHO diagnosis, presence or not of cytogenetic abnormalities in addition to del 5q and IPSS score). The estimated propensity was then used to match patients 1:1 with a similar propensity to receive lenalidomide. Using this method, we found that the incidence of progression to AML in the cohort treated with lenalidomide was not greater than that of a comparable historical cohort of patients with lower risk MDS with del 5q treated without lenalidomide. Likewise, no significant survival difference was found between the two groups. It could be argued that all but four patients treated with lenalidomide did not receive this treatment at diagnosis but several months thereafter. This was handled by secondly defining survival from date of treatment onset with no significant difference in survival of treated patients from untreated patients – despite the overestimate given by counting from diagnosis.

The specific methodology used for the present comparison led to the exclusion of a certain number of patients from the cohort treated with lenalidomide because they could not be matched with controls. The excluded patients were, however, mostly relatively young females, and included ten patients with RARS, who may not be representative of patients with lower risk MDS with del 5q, among whom RARS/RCMD-RS is rare and who generally have a higher median age.[1-5] In addition, it is unlikely that exclusion of those patients could have biased the comparison in favor of the treated cohort for the studied end-points (progression to AML and survival), as none of them progressed to AML or died during the follow-up period. In addition, the incidence of progression to AML in the cohort that did not receive lenalidomide was similar to that observed in previously reported studies.[14]

Another potential issue with the propensity score approach used is that it allowed the two groups of patients (treated and untreated) to be similar on average at the time of diagnosis but not at the time of treatment onset, since the onset of lenalidomide treatment was delayed in many cases. To handle the issue of delayed time to treatment in the treated group, we first considered time to treatment or censoring as an additional covariate in the propensity score model; we then considered a Cox model allowing delayed entry. Whatever the approach, survival curves remained not significantly different from each another.

Since lenalidomide treatment was only given to transfusion-dependent patients, the onset of transfusion dependency could have been taken as the starting point for the follow-up, but this parameter was not recorded in this study, preventing us from performing this analysis.

Our conclusions may not apply to some subgroups of patients with lower risk MDS with del 5q, including patients with several cytogenetic abnormalities in addition to del 5q, and patients with isolated del 5q but mutation of the *TP53* gene. Both groups respond poorly to lenalidomide, which has even been suspected to trigger disease progression in the case of patients harboring the *TP53* mutation.[16] On the other hand, a complex karyotype is rare in patients with lower risk MDS with del 5q (as complex karyotypes are generally associated with IPSS int 2 or high).[7] As far as concerns *TP53* gene mutations, these are known to confer a very poor prognosis in MDS in general, which may be independent of karyotype. It has not been demonstrated in that situation whether treatment with lenalidomide can worsen an already unfavorable outcome by accelerating progression to AML, through possible "selection" of *TP53* mutated clones.[15-17]

Finally, some of our patients treated without lenalidomide had received thalidomide. However thalidomide, contrary to lenalidomide, yields similar erythroid response rates in lower risk MDS with and without del 5q[6,9,10] and appears to have no obvious impact on progression to AML and survival in those patients

In summary, we found no evidence of a higher cumulative incidence of progression to AML in the cohort treated with lenalidomide, compared with a control cohort. However, continued follow up remains necessary, as progression to AML might occur after a more prolonged exposure to lenalidomide. The recent report of a possible increase of secondary malignancies, including myeloid and lymphoid malignancies, in myeloma patients treated with lenalidomide represents one more reason for careful follow up.

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