Treatment with Lenalidomide does not appear to increase the risk of leukemia progression in lower risk myelodysplastic syndrome with 5q deletion. A comparative analysis by the GFM

by Lionel Ades, Fabien Lebras, Marie Sebert, Charikleia Kelaidi, Thierry Lamy, Francois Dreyfus, Virginie Eclache, Jacques Delaunay, Didier Bouscary, Sorin Visanica, Pascal Turlure, Agnes Guerci Bresler, Marie Paule Cabrol, Anne Banos, Michel Blanc, Norbert Vey, Alain Delmer, Eric Wattel, Sylvie Chevret, and Pierre Fenaux

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Treatment with lenalidomide does not appear to increase the risk of progression in lower risk myelodysplastic syndrome Leukemia with 5q deletion. A comparative analysis by the GFM

Running title: Risk of AML progression in Del 5q MDS treated with lenalidomide

Groupe Francophone des myelodysplasies

Lionel Adès, Fabien Le Bras, Marie Sebert, Charikleia Kelaidi, Thierry Lamy, François Dreyfus, Virginie Eclache, Jacques Delaunay, Didier Bouscary, Sorin Visanica, Pascal Turlure, Agnès Guerci Bresler, Marie-Paule Cabrol, Anne Banos, Michel Blanc, Norbert Vey, Alain Delmer, Eric Wattel, Sylvie Chevret, and Pierre Fenaux

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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), some concerns have been raised over the fact that it could trigger progression to acute myeloid leukemia in some patients.

Design and Methods. We treated 95 transfusion dependent lower risk myelodysplastic syndromes with del 5q by lenalidomide (10mg/d, 3 weeks every 4 weeks), of whom 6 (6.3%) progressed to acute myeloid leukemia. This cohort was compared to a historical control cohort of 99 lower risk myelodysplastic syndromes patients with del 5q who never received Lenalidomide, using a propensity score approach that allows controlling 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 that 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.
Introduction

Deletion of the long arm of chromosome 5 (del 5q) is found in 6 to 15% of myelodysplastic syndromes (MDS) (1, 2). MDS with del 5q are characterized, when belonging to the low or intermediate 1 ("lower risk") groups of the International Prognostic scoring system (IPSS) (1), by female predominance (unlike other MDS), 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, prognosis is generally favorable, with however about 20% of cases progressing to AML at 5 years, and with a median survival of 60 to 65 months (1, 2, 3, 4, 5). In case of cytogenetic abnormalities associated with 5q deletion (especially if more than one) and/or 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 erythroblastic stimulating agents (ESAs) than other lower risk MDS (6). On the other hand, lenalidomide led to RBC transfusion independence in two thirds of lower risk MDS with del 5q in MDS 003 trial (7). Those results led the Food and Drug Administration (FDA) to approve 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 Medicines Agency (EMEA) did not approve the drug in this indication, raising the concern, from MDS 003 trial results, that lenalidomide may trigger progression to AML in some MDS with del 5q.

Those findings led us to compare the outcome of a cohort of RBC transfusion dependent lower risk MDS with del 5q treated with lenalidomide to that of a similar historical cohort that never received lenalidomide. To perform such an observational study, we used a propensity score-based approach that allows controlling for potentially confounding bias.
Design and Methods

**Lenalidomide cohort**

Between January and September 2007, the French health agency (AFSSAPS) conducted, in cooperation with the Groupe Francophone des Myélodysplasies (G.F.M.), a patient named compassionate program (autorisation temporaire d’utilisation or A.T.U.) of lenalidomide (Revlimid, Celgene Corp, NJ, USA) in IPSS Low and Int-1 risk MDS with del 5q and transfusion-dependent anemia (defined by having received at least 2 RBC concentrates every 8 weeks over the previous 16 weeks). All applications were reviewed by AFSSAPS for approval, and patient informed consent was required prior to inclusion. A case report form (CRF) was sent to the treating physician after inclusion. A total of 115 MDS patients from 35 centers were enrolled in the program. Twenty of them were excluded, due to diagnosis error in 14 cases (8 AML and 6 MDS with high or int-2 IPSS), and because they did not receive treatment in 6 cases. The remaining 95 patients, who fit inclusion criteria and had all received at least 3 days of treatment, were analyzed. Information was collected after patient informed consent. The study was conducted according to the Declaration of Helsinki. Median time from diagnosis to lenalidomide treatment was 29 months (IQR, 11-53).

Results of lenalidomide treatment in those patients have been reported in detail elsewhere. Briefly, patients were treated with 10 mg of lenalidomide daily, 21 days every 28 days. Responders continued 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, Sixty-two of the 95 patients (65%) achieved erythroid response (HI-E) according to IWG 2006 criteria, including 60 patients (63%) who achieved transfusion independence (TI). All but two responders continued lenalidomide until relapse. Median follow up from diagnosis was 4 years. Six patients had progressed to AML, including 2 patients who had achieved TI. Four of them had RAEB 1 at inclusion with 1 (n=2) or
2 (n=2) cytopenias and had an IPSS of 1, one had RA with 2 cytopenias and an IPSS of 0.5 and one RCMD with 3 cytopenias and an IPSS of 0.5. Among them 2 had isolated del 5q, 3 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 lower risk MDS with del 5q treated without lenalidomide consisted of 99 patients treated in GFM centers (before lenalidomide was available) by ESAs 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 ESA (with or without G-CSF) in 3 prospective GFM clinical trials or according to guidelines of the GFM and the French Society of Haematology for the use of ESAs 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 overall 120 patients were included) (9, 10) (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. Treatment results, in part of that comparative cohort, have been previously reported (6, 9, 10). Sixty five percent of those patients were RBC transfusion dependent at inclusion. 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 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, for comparison of outcomes between patients treated and untreated by lenalidomide,
a propensity score based approach. The objective of this approach is to control for potential selection bias in estimating treatment effect 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); moreover, we also adjusted for time from diagnosis to treatment decision (or censoring). The resulting so-called propensity score (PS), 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 neighbours in PS with calipers at 0.2 times the standard deviation of the PS, as previously recommended (11, 12, 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 in estimating the treatment effect on outcome, ie 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, 12, 13). However, since the treatment decision was not made at diagnosis, the delayed issue should be taken into account. We thus consider this issue as a delayed entry problem, though restricted to the treated. Indeed, the sample of treated could be considered as left truncated because subjects were treated conditionally on the fact that they have not died nor developed acute transformation before. This was handled by secondly defining survival of treated from date of treatment onset (while that of untreated was still accounted from diagnosis). Then, a treated subject participates to the “at risk set” from the date of treatment in the cohort to the date of censoring or date of outcome. This is further denoted “survival after treatment onset”.

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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 statistical significance.
Results

Baseline characteristics of the 2 patient cohorts
Baseline characteristics of the two patient cohorts, at inclusion in the ATU program for patients treated with lenalidomide, and in ESA trials, thalidomide trials or at diagnosis for patients treated without lenalidomide are shown in table 1. Baseline characteristics of the 2 cohorts were generally similar, except that patients in the lenalidomide group were somewhat younger (median age: 70.4) than the control group (73 years, p= 0.03), and had more frequently RARS or RCMD-RS (14% vs. 4%, p= 0.05). Median transfusion requirement was similar in the two groups (4 RBC units/2 months).

Propensity score derivation and matching
The PS was estimated for each patient, incorporating age, gender, WHO diagnosis, cytogenetics (isolated 5q versus del 5q + 1 additional abnormality, versus del 5q + at least 2 additional abnormalities), and IPSS.

The probability of having received lenalidomide was lower in older patients, in males and in patients with RAEB 1, compared to 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) compared to 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 (IQR : 50.3-69.2) and a WHO classification of 5q- syndrome in 4 cases, RARS in 10 cases, RA in 2 cases, RAEB-1 in 1 case , and RCMD in 2 cases, representing 11% (4/36), 77% (10/13), 15% (2/13), 4%, (2/23) and 22% of the patients treated with 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. 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 more found after matching.
Progression to AML 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 that did not receive lenalidomide (HR= 0.87, 95%CI: 0.27-2.82; p=0.82) (figure 1B). 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 (figure 1D; p= 0.15).

Of note, in the group treated with lenalidomide, 2 of the 62 (3%) responders progressed to AML, compared to 4 of the 33 (12%) non responders.

Discussion

The relatively high incidence of progression to AML observed in lower risk MDS treated with lenalidomide in MDS 003 trial lead EMEA to consider that triggering of AML progression by lenalidomide could not be excluded in some cases, and to rejection of this drug indication in the European Union. The relatively high incidence of progression to AML in that trial was attributed by some authors to the fact that the interval between diagnosis of MDS and onset of lenalidomide was particularly long, and that patients had on average a longer history of RBC transfusions, an expected finding the first multicenter trial using lenalidomide in this situation.

Those findings suggest that further analyses on the long term effects of lenalidomide in lower risk MDS with del 5q are required. However, no prospective randomized trial comparing the long term outcome of lower risk MDS with del 5q treated with and without lenalidomide has been performed. Such trial may now be difficult to conduct by the hematological community given the dramatic effect of lenalidomide on anemia in this MDS subset (where other drugs like ESAs have limited efficacy) and its approval in this indication in many
countries. This situation prompted several groups of investigators to perform historical controls in 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, a 2 year and 5 year AML progression rate of 7% and 18%, respectively, in 300 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 published (15). However, it was also higher in RBC transfusion dependent patients, who represent candidates for lenalidomide. In the last patient subgroup, no obvious difference in progression to AML was seen with patients included in 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 (PS) defined as a subject’s probability to receive lenalidomide conditionally on his (her) observed covariates. For this purpose, we modelled through multivariate logistic regression, 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 1:1 patients with similar propensity to receive lenalidomide. Using this method, we found the incidence of progression to AML, in the cohort treated with lenalidomide, not to be greater than that of a comparable historical cohort of lower risk MDS with del 5q treated without lenalidomide. Likewise, no significant survival difference was found between the 2 groups. It could be argued that all but 4 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 from that of untreated – though overestimated given accounted from diagnosis.

The specific methodology used for the present comparison lead to exclusion, in the cohort treated with lenalidomide, of a certain number of patients for matching due to the absence of controls. However, those excluded patients were mostly relatively younger females, and included 10 RARS patients, who may not be representative of lower risk MDS with del 5q, where RARS/RCMD-RS is rare and median age generally higher (1, 2, 3, 4, 5). In addition, it is unlikely that exclusion of those patients could have biased the comparison in favour of the treated cohort for studied endpoints (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 published reports (14).

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

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

Our conclusions may also not apply to some subgroups of 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 TP 53 gene. Both groups respond poorly to
lenalidomide, which has even been suspected to trigger disease progression in the case of TP 53 mutation (16). On the other hand, complex karyotype is rare in lower risk MDS with del 5q (as complex karyotype is generally associated to IPSS int 2 or high) (7). Regarding TP 53 gene mutations, they are known to carry a very poor prognosis in MDS in general, that may be independent of karyotype. It has not been demonstrated in that situation if treatment with Lenalidomide can worsen an already unfavorable outcome by accelerating progression to AML, through possible “selection “ of TP 53 mutated clones (15, 16, 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 the 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 more careful follow up.

**Authorship and Disclosures**

LA and PF analyzed data and wrote the manuscript; LA PF and FD designed study; FLB and MS collected the data; CK, TL, FD, JD, DB, SV, PT, AG, M-P C, AB, MB, NV, VE, AD, ChB, CaB, JPP, BdR, EW, PM provided clinical care to patients, assisted in the analysis of data and co-authored the paper. SC did the statistical analysis.
References


Table 1. Main patient baseline characteristics according to treatment, before and after matching on a propensity score to receive or not Lenalidomide

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Figure legend

Figure 1. (A) Comparison of the “propensity” of being treated by Lenalidomide, based on patient age, gender, WHO diagnosis, IPSS score, and cytogenetic features, in treated and untreated original 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.
A

B

C

D

Control cohort
Lenalidomide cohort

Cum Incidence of AML

Control cohort
Lenalidomide cohort

Overall survival

Control cohort
Lenalidomide cohort

Overall survival

Control cohort
Lenalidomide cohort

Time from diagnosis, Years

Time from diagnosis, Years

Time from treatment onset, Years

Time from treatment onset, Years

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