Lenalidomide combined with intensive chemotherapy in acute myeloid leukemia and higher-risk myelodysplastic syndrome with 5q deletion. Results of a phase II study by the *Groupe Francophone Des Myélodysplasies*

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ABSTRACT

Patients with acute myeloblastic leukemia or higher risk myelodysplastic syndromes with 5q deletion (generally within a complex karyotype) respond poorly to intensive chemotherapy and have very poor survival. In this population, we evaluated escalating doses of lenalidomide combined with intensive chemotherapy in a phase II study. Treatment consisted of daunorubicin (45 mg/m^2/day, days 1-3 in cohort 1, escalated to 60 mg/m^2/day, days 1-3 in cohorts 2 and 3) combined with cytosine arabinoside (200 mg/m^2/day, days 1-7) and lenalidomide (10 mg/day, days 1-21 in cohorts 1 and 2, escalated to 25 mg/day, days 1-21 in cohort 3). Eighty-two patients with 5q deletion were enrolled, including 62 with acute myeloblastic leukemia, 62/79 (78%) of whom had a complex karyotype (median 7 cytogenetic abnormalities, all but 2 of them monosomal) and three had unknown karyotypes. Thirty-eight patients (46%) achieved complete remission and the overall response rate was 58.5%. Among the 62 patients with a complex karyotype, 27 achieved complete remission (44%) and 21 had cytogenetic responses. A lower response rate was observed in patients with acute myeloblastic leukemia but other pretreatment factors, including cytogenetic complexity and treatment cohort, did not significantly influence response. Fifteen patients underwent allogeneic stem cell transplantation, including 11 patients in first remission. The 1-year cumulative incidence of relapse was 64.6% and the median overall survival was 8.2 months. By comparison with conventional intensive chemotherapy, the treatment protocol we used appeared to produce higher hematologic and cytogenetic complete remission rates in patients with very poor cytogenetics, but response duration was short in this very poor risk population, highlighting the need for better post-induction strategies. *Clinical trial registry number: NCT00885508*

Introduction

Deletion 5q [del(5q)] is the most common cytogenetic abnormality in myelodysplastic syndromes (MDS).[1] It can occur as a single abnormality, especially in MDS without excess of bone marrow blasts and is associated in that case with a relatively favorable prognosis. On the other hand, the prognosis of MDS with del(5q) and increased bone marrow blast percentage and/or additional cytogenetic abnormalities, and of acute myeloblastic leukemia (AML) with del(5q) (isolated or complex) is poor.[2] Furthermore, del(5q) is found in 40–50% of higher-risk MDS and AML with complex karyotypes (sometimes detectable only using fluorescence *in situ* hybridization techniques).[3,4] Such patients respond poorly to intensive anthracycline-cytosine arabinoside chemotherapy with only 20–30% obtaining a complete remission, of short duration.[5–8] In these patients, azacytidine may possibly produce a somewhat higher response rate, but responses are of very short duration.[9] Most complex karyotypes that include del(5q) are monosomal karyotypes, and at least 50% have a *TP53* mutation,[10] which is also associated with a very low complete response (CR) rate; long-term survival with conventional intensive chemotherapy is very rare and there is a high relapse rate after allogeneic stem cell transplantation.[11]

In patients with MDS with del (5q) who had low- or intermediate-1-risk disease according to the International Prognostic Scoring System (IPSS) lenalidomide produced an erythroid response in 65% to 70% of patients, and cytogenetic partial or complete response in 50% to 75% of responders.[12,13] More recently, lenalidomide was tested in IPSS intermediate-2- and high-risk MDS with del(5q), with a lower 28% overall response in our experience, and 36% in the Nordic MDS group's experience.[14,15] On the other hand, six of the nine patients with isolated del(5q) in our series reached hematologic complete remission, compared to one of the 38 patients with additional cytogenetic abnormalities. This suggests a specific effect of lenalidomide on the del(5q) clone, which was possibly sufficient to induce a response in the case of isolated del(5q), but not if other chromosomal abnormalities were present.[14]

Those results prompted us to combine intensive chemotherapy and lenalidomide in higher risk MDS and AML with del(5q), generally as part of a complex monosomal karyotype.

Methods

Trial design

This was a phase II clinical trial (NCT00885508) using the combination of anthracycline-cytosine arabinoside (AraC) chemotherapy and lenalidomide in IPSS high- and intermediate-2 ("higher")-risk MDS and AML with 5q(del).

We used the Simon two-stage phase II design in order to assess whether the response rate to lenalidomide combined with escalating dose chemotherapy, compared to that observed with chemotherapy alone or lenalidomide alone, was particularly promising (at least 50% responses) or not promising (less than 30% responses), controlling for type I and II error rates of 0.025 and 0.10, respectively. A first cohort of 31 patients was included at the first dose level (daunorubicin 45 mg/m^2/day for 3 days), combined with lenalidomide 10 mg/day for 21 days, in order to estimate the dose-limiting toxicity, defined by more than three of ten patients recovering from aplasia after more than 40 days, or the occurrence of unexpected grade III-IV non-hematologic toxicity. Efficacy was defined as a response rate, including CR, CR with incomplete recovery (CRi) or marrow CR, of at least 50%. An interim analysis was planned following inclusion of the first 31 patients, in order to implement a reduction of the anthracycline dose in the subsequent cohort in the case of dose-limiting toxicity, or on the contrary an increase in the anthracycline dose if toxicity was considered acceptable.

After review of the first cohort by the Data Safety Monitoring Board, toxicity was considered acceptable and the dose of daunorubicin increased to 60 mg/m^2/day for 3 days in the second cohort, keeping the same daily dose of lenalidomide. Finally, the protocol was extended in August 2011 to allow a dose escalation of lenalidomide to 25 mg/day in 20 additional patients, but the final dose escalation (to lenalidomide 50 mg/day) was denied due to dose-limiting toxicity.

Patients

Inclusion criteria were as follows: (i) age 18 years or older; (ii) documented diagnosis of MDS or AML according to the French-American-British classification[16] and World Health Organization (WHO) 2008 criteria,[17] with IPSS intermediate-2- or high-risk MDS,[18] including cases of chronic myelomonocytic leukemia with a white blood cell count less than 13x10^9/L and refractory anemia with excess blasts in transformation (AML/RAEB-t); (iii) del(5q) by conventional cytogenetics or by fluorescence *in situ* hybridization in the case of cytogenetic failure, with or without additional chromosomal changes. Conventional cytogenetic analysis was performed by analyzing G- and R-banded metaphase chromosomes in at least 20 mitoses, and results were interpreted using International System Cytogenetic Nomenclature; (iv) no contraindication to anthracycline-based intensive chemotherapy; (v) written informed consent; and (vi) negative serum or urine pregnancy test in women of childbearing potential.

The trial was approved by the *Comité de Protection des Personnes Paris—Ile de France* (ethical committee whose approval is valid for all participating French institutions). The *Groupe Francophone des Myélodysplasies* sponsored the trial, and Celgene (Paris, France) provided lenalidomide and a scientific grant, but was not involved in analyzing the results of the study or writing the manuscript.

Treatment

Patients in the first cohort received induction treatment with daunorubicin (45 mg/m^2/day, days 1-3, by IV push) + AraC (200 mg/m^2/day, days 1-7, continuous infusion) and lenalidomide (10 mg/day, days 1-21, orally) and granulocyte colony-stimulating factor (from day 8 to the end of aplasia). The dosing and schedule of lenalidomide was similar to the dosing used in our previous phase II trial evaluating lenalidomide as a single agent in the same population.[14] Responders [patients who achieved CR, CRi or marrow CR according to the International Working Group (IWG) AML criteria[19] for AML, and IWG 2006 criteria for MDS[20]] received six consolidation courses of daunorubicin (45 mg/m^2, day 1), AraC (120 mg/m^2/day, days 1-5, subcutaneously) and lenalidomide 10 mg/day, days 1-15, followed by maintenance lenalidomide 10 mg/day as a continuous schedule until progression or toxicity.

After daunorubicin at a dose of 45 mg/m^2/day had proven safe in the first cohort (n=31), escalation to daunorubicin 60 mg/m^2/day during induction (3 days) and consolidation (1 day) was made in an additional cohort of 33 patients. Finally, after this dose had also been proven safe in the second cohort, a third cohort of patients was given 25 mg/day of lenalidomide while the daunorubicin dose remained unchanged at 60 mg/m^2/day.

Endpoints

The primary trial endpoint was hematologic response to induction treatment (including CR, CRi and marrow CR), according to IWG AML criteria[19] for AML, and IWG 2006 criteria for MDS.[20] Secondary endpoints included cumulative incidence of relapse, event-free survival, overall survival and safety.

All patients who, after induction treatment, achieved a CR, CRi or marrow CR were considered responders and were to continue treatment until relapse. In agreement with MDS and AML response criteria, complete cytogenetic response was defined by the disappearance of all chromosomal abnormalities, including del(5q) and other additional abnormalities, without appearance of new ones. A partial cytogenetic response was defined by at least a 50% reduction of the number of mitoses with any chromosomal abnormality. In agreement with IWG 2006 recommendations, the response of patients with 20% to 30% marrow blasts (AML/RAEB-t patients) was evaluated according to criteria that apply to MDS.

Statistical analysis

The statistical analysis was performed on a modified intent-to-treat principle, excluding diagnostic errors and consent withdrawals. Medians with interquartile ranges (IQR) and numbers with percentages are given as summary statistics for quantitative and qualitative variables, respectively.

Exact 95% confidence intervals (95% CI) were computed for response rates. Censored endpoints (overall survival and event-free survival) were estimated by the non-parametric Kaplan-Meier method, and compared between randomized groups by the log-rank test. Analyses were stratified on treatment cohorts. Prognostic factors for achieving CR were assessed by the Wilcoxon rank sum test or Fisher exact test. Multivariable logistic regression modeling was used to summarize prognostic information. All statistical tests were two-sided, with P values of 0.05 or less denoting statistical significance.

Statistical computations were performed on SAS 9.3 (SAS Inc., Cary, NC; USA) and R 2.13.0 (http://www.R-project.org/), at the reference date of 1 January, 2015.

Results

Patients' baseline characteristics

Figure 1 shows the flow chart for the trial. Between February 2009 and May 2012, 85 patients from 13 centers were included, of whom 82 were evaluable [2 patients withdrew consent and did not receive treatment, and 1 was excluded because of the absence of del(5q)]. Among the 82 evaluable patients, who constituted the modified intent-to-treat population, 31 patients were included in the first cohort, 32 in the second cohort and 19 in the third cohort. Table 1 summarizes the patients' main characteristics at inclusion, showing no obvious difference between the three treatment cohorts.

The 82 patients included 42 males, with a median age of 66 years (IQR: 58–72; range, 30–79). At inclusion, according to the WHO 2008 classification, 20 patients had RAEB-2, and 62 had AML (including 22 AML/RAEB-t, with 20%-30% marrow blasts). Among the 20 RAEB-2 patients, 16 had IPSS high-risk disease and four had IPSS intermediate-2-risk. Among the 79 available karyotypes [conventional cytogenetic analysis failed in the other 3 patients and del(5q) was only identified by fluorescence *in situ* hybridization analysis], del(5q) was isolated in eight (10%) patients, associated with one additional abnormality in nine (11%) patients and associated with more than one additional abnormality (complex karyotype) in 62 (78%) patients. In patients with a complex karyotype, the median number of cytogenetic abnormalities, in addition to del(5q), was seven (range, 3–17): 28 had chromosome 17p deletion (generally associated with *TP53* mutation in MDS and AML) and all but two of the patients with additional abnormalities had a monosomal karyotype. Median baseline white blood cell count, platelet count and hemoglobin level were $2.6x10^9$/L (IQR: 1.7-5.2), $46.5x10^9$/L (IQR: 28–93) and 8.8 g/dL (IQR: 8.2-9.6), respectively.

During induction treatment, 80% of the patients received the planned schedule of lenalidomide (21 days), whereas 20% received lenalidomide for only 5 to 20 days.

Treatment outcomes

Forty-eight (58.5%) of the 82 patients responded, including 38 (46%) who achieved a CR, four (4.8%) a CRi, and six (7%) a marrow CR according to IWG 2006/AML criteria, while 34 had progression or induction failure. The response rate did not differ between the three cohorts (58%, 59%, 58% in the first, second and third cohorts, respectively; P=1.00, by the Fisher exact test). Overall, 28 of the 38 patients who achieved a CR also achieved a

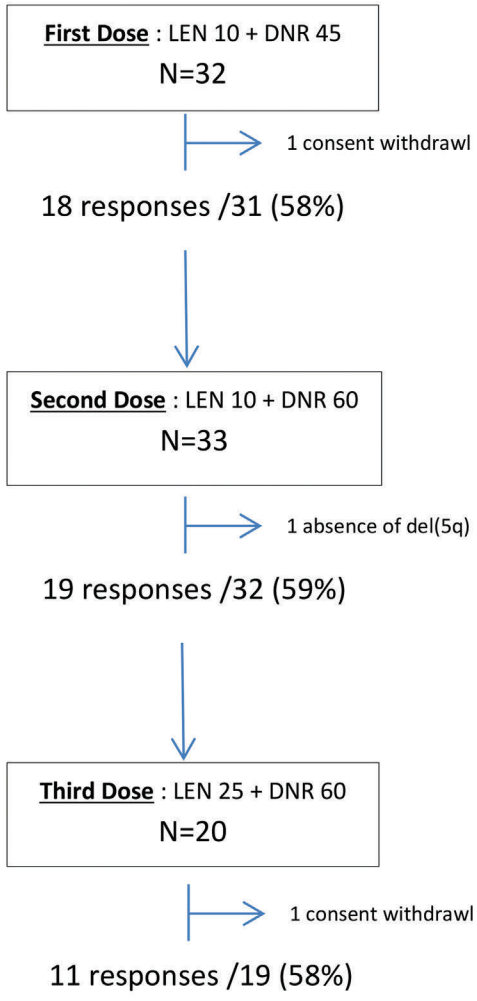

Figure 1. Flow chart of the study. LEN: lenalidomide (dose in mg/day); DNR: daunorubicin (dose in mg/m^2/day).

cytogenetic response, comprising 18 complete cytogenetic responses and ten partial cytogenetic responses.

Overall, 130 consolidation courses were administered to 41 of the patients who achieved a hematologic response after induction treatment. The seven other responders did not receive the planned consolidation courses, as two underwent allogeneic stem cell transplantation, two relapsed before consolidation and three received alternative consolidation treatment [azacitidine (n=2) and clofarabine (n=1)].

Fifteen patients, corresponding to 29% of the patients aged less than 70 years, defined by age as eligible for transplantation, underwent allogeneic stem cell transplantation, 11 in first remission (9 in complete remission, 2 in partial remission), and four after induction failure.

Thirty-five of the 48 responders subsequently relapsed, including 29 of the 38 patients who had achieved a CR, with a 1-year cumulative incidence of relapse of 64.6% (95% CI: 50.7-78.4). The median duration of response was 6 months, while that of CR was 6.2 months. Among the 11 patients allografted in first remission, six relapsed, three had an early death and two were alive in complete remission after 12 and 14 months. Three of the four patients allografted after induction failure died, two from relapse and one from graft-*versus*-host disease, and one was still alive after 8 months.

Seventy-seven patients died, 16 of them within 90 days of treatment onset (early death) leading to an early death rate of 20.8% (95% CI: 12.4-31.5%). The median overall survival was 8.2 months (95% CI: 7.15-10.5), and 1- and 2-

Table 1. Main baseline characteristics of the patients in the three cohorts.

Variables	Overall N=82		Cohort 1 LEN 10/DNR 45 N=31		Cohort 2 LEN 10/DNR 60 N=32		Cohort 3 LEN 25/DNR 60 N=19	
	n.	%	n.	%	n.	%	n.	%
Age [IQR]	66.1 [58.2;71.8]		65.2 [59.4;73.0]		66.7 [54.6;71.9]		66.1 [61;68.8]	
Gender								
Female	40	49%	15	48%	17	53%	8	42%
Male	42	51%	16	52%	15	47%	11	58%
WHO 2008 diagnosis								
RAEB-2	21	26%	11	35%	6	19%	4	21%
AML	61	74%	20	65%	26	81%	15	79%
FAB diagnosis								
RAEB	20	24%	11	35%	6	19%	3	16%
RAEB-t	22	27%	7	23%	5	16%	10	53%
AML	40	49%	13	42%	21	65%	6	31%
Performance Status								
0	20	30%	13	45%	5	21%	2	14%
1	36	55%	11	38%	16	67%	9	64%
2	10	15%	5	17%	3	12%	3	22%
Cytogenetics								
Failure (5q by FISH)	3	4%	2	6%	1	3%	0	0%
Isolated del(5q)	8	10%	2	6%	2	6%	4	21%
del(5q) +1 abnormality	9	11%	2	6%	5	16%	2	10%
Complex	62	75%	25	82%	24	75%	13	69%

LEN: lenalidomide (dose in mg/day); DNR: daunorubicin (dose in mg/m²/day); WHO: World Health Organization; RAEB: refractory anemia with excess blasts; FAB: French American British; RAEB-t: refractory anemia with excess blasts in transformation; AML: acute myeloid leukemia; FISH: fluorescence *in situ* hybridization.

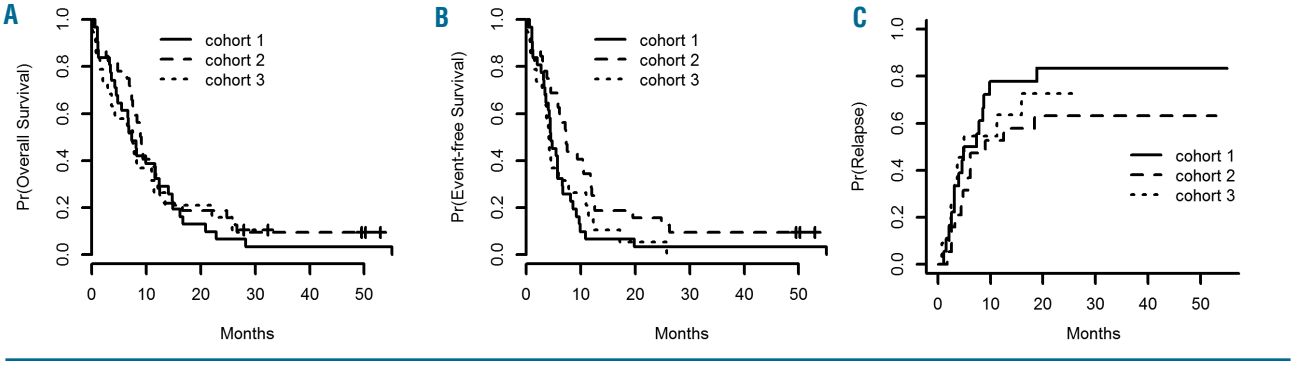

Figure 2. Outcome in the different treatment cohorts. (A) Overall survival, (B) event-free survival, (C) cumulative incidence of relapse.

year overall survival rates were 30.5% (95% CI: 22–42.3) and 13.4% (95% CI: 7.7-23.2), respectively. The median event-free survival was 5.7 months (95% CI: 4.4-7.2). No difference in outcome was observed between treatment cohorts for cumulative incidence of relapse, event-free survival or overall survival (Figure 2).

When patients were censored at the time of transplantation, the median overall survival was 7.8 months (95% CI: 6.7-9.4), and 1- and 2-year overall survival rates were 27.6% (95% CI: 18.6-41) and 8.6% (95% CI: 3.8-19.7), respectively. The median event-free survival was 4.8 months (95% CI: 4.3-6.6) (Figure 3).

Among patients who did not receive an allograft, only 16 were alive at 1 year, and five at 2 years.

Table 2. Prognostic factors for complete response to induction treatment (univariate analysis)

Variables	Complete remission (n.) and % or median [IQR]	*P*-value
Age, years	66.6 [58.9 ;71.2]	0.57
Gender		
Female	(18/40) 45%	0.83
Male	(20/42) 48%	
WHO diagnosis		
RAEB	(14/21) 68%	**0.037**
AML	(24/61) 40%	
FAB diagnosis		
RAEB	(13/20) 65%	0.46
RAEB-t	(9/22) 41%	
AML	(16/40) 40%	
Karyotype		
Complex	(27/62) 44%	0.99
Isolated del5q	(2/8) 25%	
Del5q+1 abnormality	(6/9) 67%	
WBC count (10^9/L)	2.5 [1.9;3.9]	0.72
Hemoglobin level (g/dL)	8.95 [8.5;10]	**0.003**
Platelet count (10^9/L)	49.5 [31;92]	0.39
% circulating blasts	5 [0.75;15.5]	**0.017**
% bone marrow blasts	14 [10;30]	**0.03**
Serum albumin level	39 [32;41]	**0.003**
Treatment cohort		
DNR 45, LEN 10	(14/31) 45%	0.88
DNR 60, LEN 10	(16/32) 50%	
DNR 60, LEN 25	(8/19) 42%	

IQR: interquartile range; WHO: World Health Organization; RAEB: refractory anemia with excess blasts; AML: acute myeloid leukemia; FAB: French American British; RAEB-t: refractory anemia with excess blasts in transformation; WBC: white blood cell; DNR: daunorubicin (dose in mg/m²/day); LEN: lenalidomide (dose in mg/day).

Prognostic factors for response and overall survival

Tables 2 and 3 summarize prognostic factors for CR and overall survival, respectively. The CR rate was significantly lower among AML patients (including those with AML/RAEB-t) (40%) than among those with MDS (68%; *P*=0.037), with higher blast percentage (*P*=0.03), higher circulating blast percentage (*P*=0.017) and lower hemoglobin level (*P*=0.003). Among the eight patients with isolated del(5q), two achieved a CR (25%) and both of these patients also achieved a complete cytogenetic response. Among the nine patients with del(5q) in association with one other abnormality, six (88%) achieved a CR, five of whom also had a cytogenetic response (3 complete and 2 partial). Finally, among the 62 patients with a complex karyotype, 27 achieved a CR (44%) and 21 (34%) had a cytogenetic response (13 complete and 8 partial). The CR rate was 25%, 67% and 44% in patients with isolated del(5q), del(5q) with one additional abnormality, and del(5q) in a complex karyotype, respectively (*P*=0.24); the presence of chromosome 17p abnormalities did not have a significant influence on achievement of CR. Likewise, other factors, including the revised IPSS classification, cytogenetic complexity and treatment cohort, did not influence response achievement.

By multivariate analysis, WHO 2008 diagnosis [odds ratio (OR)=0.3 (0.1;0.9); *P*=0.03)], percentage of circulating blasts [OR=0.95 (0.94-1), *P*=0.035] and baseline hemoglobin level [OR=1.73 (1.14;2.62); *P*=0.01] retained prognostic significance for achievement of CR.

Prognostic factors associated with a shorter overall survival were a higher white blood cell count (*P*=0.003), higher percentage of circulating blasts (*P*=0.009), and higher platelet count (*P*=0.009), while cytogenetic complexity (HR= 1.45, 95% CI: 0.82-2.58; *P*=0.21) and treatment cohort had no significant influence. In a multivariate Cox model, only platelet count remained of prognostic value for survival.

Finally, among responders, achieving a cytogenetic

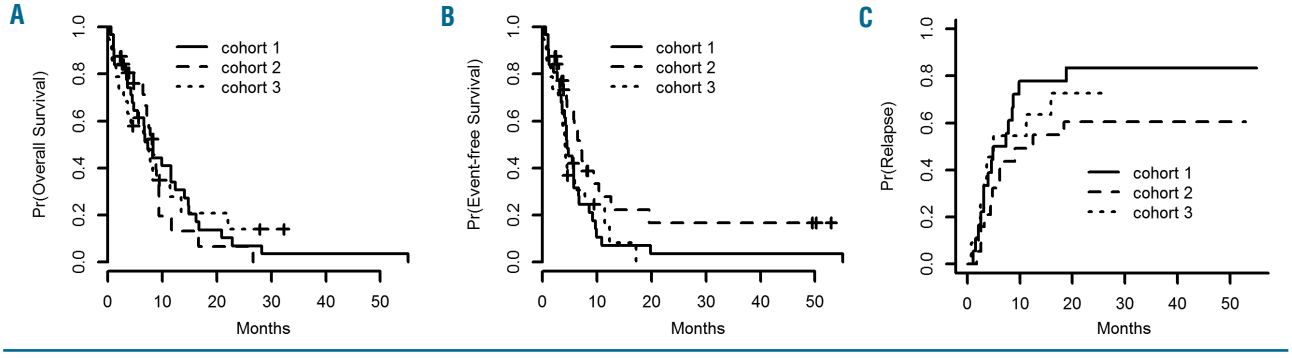

Figure 3. Outcome in the different treatment cohorts with transplanted patients censored. (A) Overall survival, (B) event-free survival, (C) cumulative incidence of relapse.

response was not associated with a survival advantage (median survival: 11.6 *versus* 11.6 months, *P*=0.46, log-rank test).

Toxicity

The median duration of hospitalization during induction treatment was 30 days (IQR: 26–35; range, 7–70). In the 48 responders, the median time to an absolute neutrophil count >1x10^9/L and a platelet count >50x10^9/L was 23 days (IQR: 17–28) and 21 days (IQR: 16–26) respectively. The median number of red blood cell and platelet units transfused during induction treatment was ten (IQR: 8–12) and seven (IQR: 6–11), respectively. No obvious differences were observed between the treatment cohorts.

Grade III-IV non-hematologic toxicities (Table 4) included transient liver toxicity with an increase in transaminases (n=7), increase in creatinine level (n=2), and lung disease (n=17) related mainly to sepsis. No other clinically relevant toxicities were observed during the induction course. Of note, the grade III-IV increases in transaminases were mainly observed in the 25 mg/day lenalidomide cohort: 6/19 (31%) compared to 1/63 (2%) in patients who received 10 mg/day (*P*=0.0004), suggesting that dose-limiting toxicity was reached at this dose level. Due to this hepatic dose-limiting toxicity, the escalating dose process planned (to lenalidomide 50 mg/day) was stopped, and the trial closed for inclusion. During consolidation cycles, 11 patients had to be hospitalized, in all cases due to sepsis, including ten (91%) who were admitted during the first consolidation course.

Table 3. Prognostic factors for overall survival (univariate analysis).

Variable	HR	95% CI	*P* value
Age	1.01	(0.98-1.03)	0.61
Gender			
Female	1.00		0.22
Male	0.75	(0.48-1.18)	
WHO diagnosis			
AML	1.00		
RAEB	0.57	(0.33-1.01)	0.053
FAB diagnosis			
RAEB	1.00		
RAEB-t	1.66	(0.88-3.14)	0.12
AML	1.57	(0.88-2.79)	0.12
Karyotype			
Complex	1.00		
Isolated del(5q)	0.89	(0.42-1.89)	0.77
Del(5q) + 1 abnormality	0.54	(0.25-1.21)	0.14
Complex karyotype	1.45	(0.82-2.58)	0.21
WBC count	**1.02**	**(1.01-1.04)**	**0.003**
Platelets count	0.99	(0.99-1)	0.009
% circulating blasts	**1.01**	**(1.00-1.04)**	**0.009**
Treatment cohort			
DNR 45, LEN 10	1.00		
DNR 60, LEN 10	0.81	(0.48-1.35)	0.41
DNR 60, LEN 25	0.95	(0.52-1.73)	0.87

Statistically significant variables are shown in bold. HR: hazard ratio; 95% confidence interval; LEN: lenalidomide (dose in mg/day); DNR: daunorubicin (dose in mg/m^2/day); WHO: World Health Organization; RAEB: refractory anemia with excess blasts; FAB: French American British; RAEB-t: refractory anemia with excess blasts in transformation; AML: acute myeloid leukemia; FISH: fluorescence *in situ* hybridization.

Discussion

The higher-risk MDS and AML population treated in the present study was characterized by a highly complex karyotype in most cases, monosomal in 73% of the patients, with 17p deletion (generally associated with *TP53* mutation) in 34% of the patients. Using a combination of classical daunorubicin-AraC chemotherapy and lenalidomide, we report a response rate of 58.5% (CR rate, 46%). A cytogenetic CR was obtained in 18/38 (47%) of the patients who achieved a CR, including 80% of those with a complex karyotype.

In AML, the 3+7 regimen (with either daunorubicin 60–90 mg/m^2 or idarubicin 10–12 mg/m^2), remains the standard induction therapy, yielding CR rates of 60% to 80% in younger adults and 50% to 60% in older patients.[7,21] However, in patients with a complex karyotype, CR rates ranging from 25% to 30% have been reported. Patients with a monosomal karyotype and/or *TP53* mutations (which are generally associated with a complex karyotype) have even lower CR rates, usually below 20%.[22–24] Karyotype also influences long-term survival and in elderly patients with high-risk karyotype, the overall survival after intensive chemotherapy has been reported to be 4 months. Thus the hematologic and cytogenetic response rate observed in our patients, most of whom had had a complex and monosomal karyotype, with conventional doses of anthracyclines and AraC plus lenalidomide, appears encouraging. In particular, 34% of our patients had 17p deletion, generally associated with a complex karyotype. Moreover, the cytogenetic response rate in patients with unfavorable karyotype achieving hematologic CR with intensive chemotherapy is reportedly low (28%),[25] whereas in our series the cytogenetic response rate in the patients with a complex karyotype who achieved hematologic CR was 77%.

The CR rate in the present study was nevertheless significantly lower in patients with AML than in those with MDS (40% *versus* 68%, *P*=0.037) while karyotype (complex or not) had no influence. This is an unexpected finding because the prognosis of these patients is usually correlated with a complex karyotype rather than with the WHO 2008 classification.

Lenalidomide, in lower-risk MDS with del(5q), appears to act largely by targeting the malignant del(5q) clone, leading to a high incidence of complete cytogenetic response.[12,13] It was recently reported that the mechanism of action of lenalidomide is mediated by the degradation

Table 4. Grade III-IV non-hematologic toxicities during induction treatment.

	Lenalidomide 10 mg cohorts		Lenalidomide 25 mg cohort	
	n.	%	n.	%
Patients	63	-	19	-
Cardiovascular	2	3%	4	21%
Lung toxicity	10	16%	7	37%
Transaminases	1	2%	6	32%
Gut toxicity	2	3%	2	11%
Creatinine level	2	3%	0	-
Neurological	2	3%	1	5%

of casein kinase 1A1 (CK1α), and that the heterozygous deletion of *CSNK1A1* in del(5q) MDS allowed lenalidomide to target the malignant clone selectively.[26] In higher-risk MDS and AML with del(5q), however, three phase 2 studies and two reports on using lenalidomide as a single agent showed response rates of only 25% to 35%.[14,15,27–29] This lower efficacy could result from cytogenetic complexity and/or to the fact that deleted segments on chromosome 5 are often different in higher-risk MDS or AML with del(5q) and lower-risk MDS with del(5q).[30] In our series of higher-risk MDS and AML patients with del(5q), however, six of the nine patients with isolated del(5q) achieved CR, compared to only 1/38 of patients with additional cytogenetic abnormalities, pointing to cytogenetic complexity as a major factor of resistance. This prompted us to add conventional 3+7 chemotherapy to lenalidomide in those patients, with higher response rates than using either chemotherapy or lenalidomide alone. The fact that 80% of hematologic responders also achieved a cytogenetic response may suggest an additive effect of lenalidomide and chemotherapy on del(5q) cells. Given that the del(5q) in MDS and AML appears to be an early genetic event, even in the case of complex karyotype, such an effect on early clonal cells may be particularly important. In a recent report on lenalidomide monotherapy, followed by lenalidomide (10 mg/day for 10 days) combined with intensive chemotherapy (cytarabine: 200 mg/m^2 for 10 days, daunorubicin: 50 mg/m^2 for 3 days and etoposide (100 mg/m^2 for 5 days) in nine patients with higher-risk MDS or AML with chromosome 5 abnormalities, four achieved a response, including two CR.[31] Lenalidomide may also have different mechanisms of action in AML and MDS, which we cannot exclude in the present case. Indeed, in AML patients without del(5q), a CR/CRi rate of 30% was obtained with lenalidomide as a single agent (50 mg/day).[32,33] Similarly, in MDS patients without del(5q), lenalidomide induced an erythroid response with transfusion independence in 25% to 30% of the cases, suggesting a different mechanism of action than that in patients with del(5q).

Despite these results, most of our patients relapsed within a few months, and the median overall survival was only 8.2 months. In AML patients aged less than 60 years with del(5q) treated with intensive chemotherapy, the 4-year overall survival rate was reported to be limited (23%) and even lower (2%) when associated with a monosomal karyotype.[23] Similarly, in patients with higher-risk MDS and monosomal karyotype treated with a hypomethylating agent, the CR rate was low (17%) and overall survival remained short (7 months).[34] The fact that lenalidomide does not act on stem cells but only on progenitors may provide a possible explanation for the early relapses observed despite the achievement of a CR.[35] The post-remission strategy with low-intensity chemotherapy combined with lenalidomide that we used was possibly suboptimal in this situation, suggesting that a high or intermediate dose of AraC combined with lenalidomide should be tested. It has also been suggested, based on a recent report that haploinsufficiency of Rps14 is associated with activation of S100A8-S100A9, that inhibition of S100A8-S100A9 with pharmaceutical agents could be of potential clinical interest in this situation.[36,37]

In terms of toxicity, our strategy was well tolerated, without any additional hematologic toxicities compared to those following similar dose intensive chemotherapy. The dose-limiting toxicity was reached with a daily dose of 25 mg of lenalidomide with transient grade III–IV increases in transaminases in 31% of the patients, preventing an increase of the lenalidomide dose to 50 mg/day. In a UK experience with a 10 mg/day dose of lenalidomide, two of the nine patients treated had a grade III increase in transaminases.[31]

In conclusion, in patients with a very unfavorable karyotype including del(5q), we report a hematologic response rate of 58.5% after induction treatment combining 3+7 chemotherapy and lenalidomide. This outcome is of potential clinical interest if consolidation strategies and pre-emptive therapy after transplantation can be found to avoid the very high relapse rate still observed in this very poor-risk population.

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