Leukemia (2010) 24, 623–628

www.nature.com/leu

ORIGINAL ARTICLE

Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexaméthasone

H Avet-Loiseau[1,2,3,4], J Soulier[5], J-P Fermand[5,6], I Yakoub-Agha[7], M Attal[8], C Hulin[9], L Garderet[10], K Belhadj[11], V Dorvaux[12], S Minvielle[1,2,3,4] and P Moreau[1,3,4,13] for the IFM and MAG groups

[1]*Institut National de la Santé et de la Recherche Médicale (INSERM), Unité 892, Nantes, France;* [2]*Hematology Laboratory, University Hospital Hôtel-Dieu, Nantes, France;* [3]*Centre d'Etude et de Recherche sur le Myélome (CERM), Nantes, France;* [4]*Institut Régional du Cancer Nantes-Atlantique (IRCNA), Nantes, France;* [5]*Institut Universitaire d'Hématologie (IUH), Université Denis Diderot, Hematology Laboratory AP-HP, Hôpital St-Louis, Paris, France;* [6]*Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, Département d'Immunologie, Paris, France;* [7]*Hematology Department, University Hospital Huriez, Lille, France;* [8]*Hematology Department, Centre Hospitalier Purpan, Toulouse, France;* [9]*Hematology Department, University Hospital Brabois, Nancy, France;* [10]*Hematology Department, Hôpital Saint-Antoine, Assistance Publique-Hôpitaux de Paris, Paris, France;* [11]*Hematology Department, Hôpital Henri Mondor, Assistance Publique-Hôpitaux de Paris, Paris, France;* [12]*Hematology Department, Hôpital Notre-Dame de Bon Secours, Metz, France and* [13]*Hematology Department, University Hospital Hôtel-Dieu, Nantes, France*

This retrospective analysis investigated the prognostic value of del(13) and t(4;14) abnormalities and the impact of prior treatment on outcomes in 207 heavily pretreated patients with relapsed or refractory multiple myeloma (MM) treated with lenalidomide plus dexamethasone. Patients with relapsed or refractory MM who had either earlier received thalidomide or bortezomib, or for whom continuation of these agents was contraindicated, and who had fluorescence *in situ* hybridization data available were included in the analysis. Patients with relapsed or refractory MM who received treatment with lenalidomide plus dexamethasone in the presence of del(13) and t(4;14) chromosomal abnormalities had lower overall response rates (ORRs) and shorter median progression-free survival (PFS) and overall survival (OS) compared with those who did not have these abnormalities. The results also showed that prior treatment with bortezomib was associated with shorter median PFS and OS. Progression during thalidomide therapy was the only significant independent predictor for OS and that the presence of del(13) and hemoglobin levels <10 g per 100 ml were prognostic factors for ORR and PFS, but not OS, in these heavily pretreated relapsed or refractory MM patients treated with lenalidomide plus dexamethasone.
Leukemia (2010) **24,** 623–628; doi:10.1038/leu.2009.273; published online 14 January 2010
Keywords: myeloma; lenalidomide; cytogenetics; FISH; prognosis

Introduction

Multiple myeloma (MM) is a common hematological malignancy, which accounts for ~2% of all cancer deaths according to recent US statistics.[1] It is an incurable disease, but with the introduction of novel therapies, such as thalidomide, lenalidomide, and bortezomib, median survival has doubled to ~4–5 years and patients now have a 20% chance of surviving longer than 10 years.[2] Lenalidomide (Revlimid; Celgene Corporation, Summit, NJ, USA) in combination with dexamethasone was shown to be highly effective in the treatment of patients with relapsed or refractory MM [3,4] and has been approved in the European Union and the United States for the treatment of patients with MM who have received at least one prior therapy.

The chromosomal abnormalities of del(13), t(4;14), and del(17p) are associated with poor progression-free survival (PFS) and shorter overall survival (OS) in newly diagnosed MM patients treated with traditional chemotherapy. [5–8] It was earlier reported that newly diagnosed MM patients with an abnormal karyotype treated with lenalidomide plus dexamethasone had a lower PFS and OS compared with patients with a normal karyotype.[9] Preliminary results from a study in patients with relapsed and refractory MM treated with lenalidomide plus dexamethasone showed that this combination can overcome the poor prognosis conferred by the chromosomal abnormalities of del(13) and t(4;14), but not del(17p).[10] In contrast, a recent analysis of 100 patients treated with lenalidomide plus dexamethasone at diagnosis revealed that this combination was not able to overcome the poor prognosis of chromosomal abnormalities and high labeling index.[11] The prognostic value of these cytogenetic abnormalities and the impact of prior therapy in the relapsed and refractory setting remain to be fully defined.

We performed a retrospective analysis to investigate the prognostic values of del(13), t(4;14), and del(17p) and the impact of prior treatment on outcomes in relapsed or refractory MM patients treated with lenalidomide plus dexamethasone.

Materials and methods

The Autorisation Temporaire d'Utilisation program, or Temporary Authorization for Use, is the regulatory mechanism used by the French Health Products and Safety Agency, which allows access of non-approved drugs to patients in France, on a named-patient basis. Medical records were obtained from 49 clinical centers participating in the French Autorisation Temporaire d'Utilisation program.

Patients with relapsed or refractory MM who had earlier received alkylating agents as well as prior thalidomide and/or bortezomib and patients with available fluorescence *in situ* hybridization (FISH) data were included in the analysis. Patients

Correspondence: Professor H Avet-Loiseau, Laboratoire d'Hématologie, Institut de Biologie, 9 quai Moncouscu, Nantes 44093, France. E-mail: herve.avetloiseau@chu-nantes.fr
Received 6 May 2009; revised 29 October 2009; accepted 9 November 2009; published online 14 January 2010

received oral treatment with lenalidomide (25 mg per day on days 1–21 of every 28-day cycle) plus dexamethasone (40 mg per day on days 1–4, 9–12, and 17–20 for four cycles, then days 1–4 beginning with cycle 5).

Assessments

At enrolment, FISH cytogenetic analysis was performed by two laboratories (in Nantes and Paris). CD138-purified plasma cells were analyzed for del(13), t(4;14), and del(17p) as described earlier.[6] Response and disease progression endpoints were evaluated using the European Group for Blood and Marrow Transplantation criteria.[12,13] OS data were collected at the time of the patients' last visit.

Statistical analyses

The independent prognostic impact of the chromosomal abnormalities del(13) and t(4;14) was analyzed by comparing the outcomes (overall response rate [ORR], PFS, and OS) of patients with or without the respective abnormality. Patient response and survival according to the presence or absence of del(17p) were not evaluable because of the small number of patients with del(17p) ($n=8$). The χ^2 tests, Fisher's exact test, and logistic regression were used to compare ORR between groups. Time-to-event variables were estimated by Kaplan–Meier methods. Two-sided log-rank tests were used to compare survivorship functions between groups.

Multivariate analyses using Cox proportional-hazard regression model were performed to assess the impact of the following variables on ORR, PFS, and OS: age, sex, hemoglobin level, presence of del(13), presence of t(4;14), prior bortezomib treatment, prior thalidomide treatment, progression on thalidomide, prior stem cell transplant, and number of lines of earlier therapy. Age, hemoglobin, and number of lines of earlier therapy were continuous variables; all other variables were dichotomous. The thresholds for entry and stay were 0.25 and 0.15, respectively.

Results

Patient characteristics

Of 228 eligible patients, 207 patients enrolled in the Autorisation Temporaire d'Utilisation program between April 2006 and March 2007 were included in this analysis. The remaining 21 patients were excluded either because of early death before the end of the first cycle ($n=14$) or because of patient or physician refusal for continued participation ($n=7$).

FISH data for del(13) were available in 92% (191 of 207) of patients, for t(4;14) in 89% (184 of 207) of patients, and for del(17p) in 58% (120 of 207) of patients. Del(13) was observed in 41% of analyzed patients, t(4;14) in 14% of patients, and del(17p) in 7% of patients (Table 1), in agreement with earlier reports. Patients had received a median of three prior therapies (range, 1–10); 86% of patients had received prior thalidomide therapy and 81% had received prior bortezomib therapy. At the time of analysis (November 2007), all patients had received lenalidomide plus dexamethasone for a median of five cycles (range, 1–22) (Table 1).

Efficacy

Among the 207 patients, the ORR was achieved in 59% of patients, including complete response in 7% and very good partial response in 14%. The median PFS was 9.6 months and the median OS was 15.1 months (Table 2).

Table 1 Main characteristics of patients with relapsed or refractory MM who received lenalidomide plus dexamethasone therapy ($n=207$)

Characteristics	
Median age, years (range)	65 (37–89)
Male (%)	56
ISS stage (%)	
1	73 (35)
2	31 (15)
3	34 (16)
Missing	69 (33)
Chromosomal abnormality (%)[a]	
Del(13)	41
t(4;14)	14
Del(17p)	7
Isolated del(13)	35[b]
Median number of Len/Dex cycles (range)	5 (1–22)
Median number of prior therapies (range)	3 (1–10)
Prior therapies (%)	
High-dose melphalan	72
Bortezomib	81
Thalidomide	86
Progression on prior thalidomide (%)	39
Hemoglobin level $<$ 10 g per 100 ml (%)	39
Mild-to-moderate RI (%)	23
PN grade $\leqslant 2$ (%)	72

Abbreviations: FISH, fluorescence *in situ* hybridization; Len/Dex, lenalidomide plus dexamethasone; MM, multiple myeloma; PN, peripheral neuropathy; RI, renal impairment.
[a]Assessed using available FISH data from 191 patients for del(13), 184 patients for t(4;14), and 120 patients for del(17p).
[b]Of 92 patients with FISH data for del(13), t(4;14), and del(17p), 32 had del(13) without t(4;14) or del(17p).

Impact of chromosomal abnormalities. Among patients with del(13) compared with patients without del(13), the ORR was significantly lower, and median PFS and OS were significantly shorter, (ORR 43% vs 71%, respectively, $P<0.001$; median PFS 5.0 months vs 12.5 months, $P<0.0001$; median OS 10.4 months vs 17.4 months, $P=0.001$) (Table 2; Figures 1a and b). A similar pattern was observed among patients with t(4;14) compared with patients without t(4;14) (ORR 39% vs 62%, respectively, $P=0.04$; median PFS 5.5 months vs 10.6 months, $P<0.01$; median OS 9.4 months vs 15.4 months, $P=0.005$) (Table 2).

Patients with isolated del(13), defined as the presence of del(13) without t(4;14) or del(17p), had significantly lower ORR compared with patients without isolated del(13) (43% vs 71%, respectively; $P=0.01$) (Table 2). In contrast, the median PFS and OS were not (or marginally) shorter in patients with isolated del(13) (PFS was 8 months vs 10.4 months, $P=0.05$; OS was 10.8 months vs 15.1 months, $P=0.56$). The number of patients with del(17p) was too low for meaningful interpretation.

Impact of prior treatment. Patients who had received prior treatment with bortezomib had significantly lower ORR (55.4% vs 74.3%; $P=0.04$), shorter median PFS (8.3 months vs not reached; $P=0.0003$) and significantly shorter median OS (12.2 months vs not reached; $P<0.002$) compared with patients who did not receive prior bortezomib. In contrast, patients who received prior thalidomide therapy had comparable ORR (57.0% vs 69.2%; $P=0.24$), as well as comparable median PFS (8.5 months vs 10.6 months; $P=0.10$) and median OS

Table 2 Response, PFS, and OS in patients with relapsed or refractory MM who received treatment with lenalidomide plus dexamethasone, according to cytogenetic abnormalities

	All patients (N = 207)	*Del(13) vs no Del(13) n = 178*			*Isolated Del(13)[a] vs no Del(13) n = 92*			*t(4;14) vs no t(4;14) n = 172*		
		Del(13)	*No del(13)*	P	*Isolated Del(13)*	*No Del(13)*	P	*t(4;14)*	*No t(4;14)*	P
ORR (%)	59	43	71	<0.001[b]	43	71	0.0127	39	62	0.04[b]
Median PFS (months)	9.6	5	12.5	<0.0001[c]	8.0	10.4	0.0495	5.5	10.6	<0.01[c]
Median OS (months)	15.1	10.4	17.4	0.001[c]	10.8	15.1	0.5645	9.4	15.4	0.005[c]

Abbreviations: MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a]Defined as del(13) without t(4;14) or del(17p). On the basis of 92 patients with fluorescence *in situ* hybridization data for del(13), t(4;14), and del(17p).
[b]χ^2 test.
[c]Log-rank test.

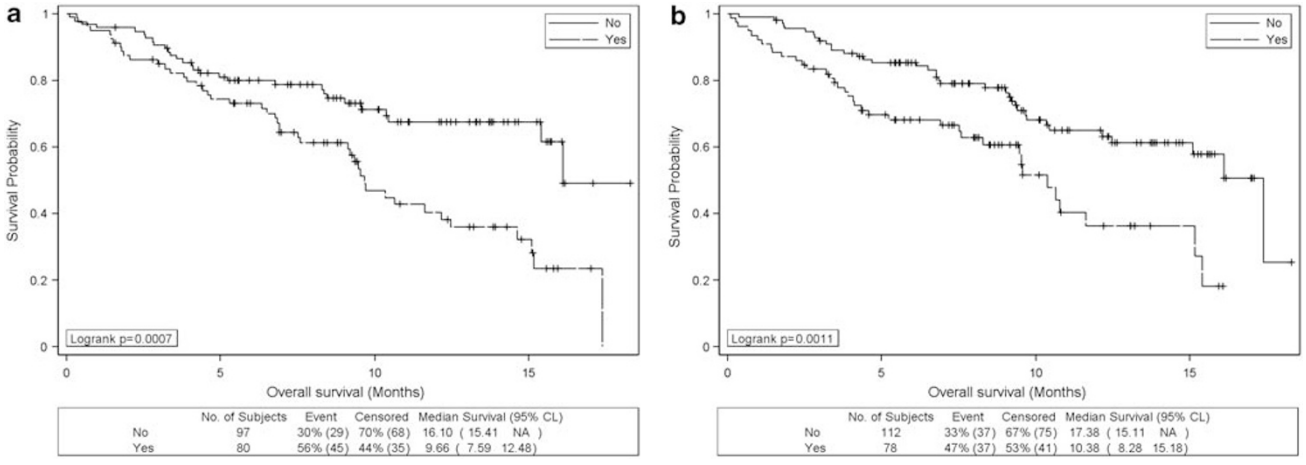

Figure 1 PFS (**a**) and OS (**b**) according to the presence of del(13).

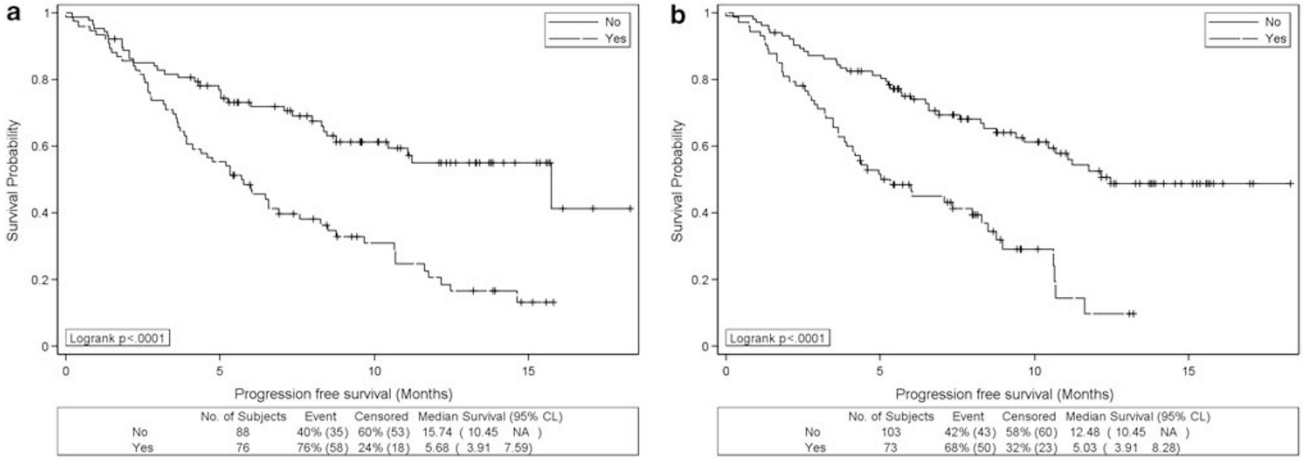

Figure 2 PFS (**a**) and OS (**b**) according to progression on thalidomide or not.

(9.4 months vs not yet reached, $P = 0.43$) compared with those who were not earlier treated with thalidomide. Patients who progressed during thalidomide therapy had a significantly shorter PFS (5.7 months vs 15.7 months; $P < 0.0001$) and OS (9.7 months vs 16.1 months; $P = 0.0007$) compared with those who did not progress during thalidomide therapy (Figures 2a and b). Patients who were thalidomide resistant had received an additional line of therapy (median, 4 vs 3) and a higher proportion had t(4;14) (16% vs 9%) compared with patients who were not thalidomide resistant.

Additional analyses were conducted to determine the combined impact of progression on thalidomide and either del(13) or prior bortezomib use on OS. For patients who did not progress on thalidomide, the median OS was 10.4 months for patients with del(13) and not reached for patients without del(13). However, for patients who progressed on thalidomide,

there was no difference in OS between patients with or without del(13) (median 9.5 months vs 9.7 months, respectively). For patients who progressed on thalidomide, the median OS was 11.6 months if they had prior bortezomib and not reached if they had no prior bortezomib. However, for patients with no prior bortezomib use, there was no difference in OS between patients with or without progression on thalidomide (median not reached for both).

Multivariate analyses

Multivariate analysis on ORR identified lower hemoglobin level <10 g 100 ml (hazard ratio (HR): 1.230; 95% confidence interval (CI): 1.000–1.511; $P=0.05$), increased number of prior therapies (HR: 0.745; 95% CI: 0.573–0.967; $P=0.03$), and del(13) (HR: 3.431; 95% CI: 1.531–7.689; $P=0.003$) as independent predictors of lower ORR (Table 3). Sex and t(4;14) met the criteria to stay in the model though they were not statistically significant. Age, sex, prior transplant, prior bortezomib use, prior thalidomide use, and progression during thalidomide did not affect ORR (Table 3).

Multivariate analysis on PFS identified progression during thalidomide (HR: 2.72; 95% CI: 1.66–4.46; $P<0.0001$), del(13) (HR: 2.35; 95% CI: 1.44–3.83; $P<0.001$), and lower hemoglobin level <10 g per 100 ml (HR: 0.81; 95% CI: 0.71–0.93; $P=0.002$) as independent predictors of reduced PFS (Table 4). There was a trend toward reduced PFS with prior bortezomib use (HR: 2.37; 95% CI: 0.91–6.16; $P=0.076$) and increased number of prior therapies (HR: 1.17. 95% CI: 0.99–1.37; $P=0.062$) (Table 4). Age, sex, prior transplant, prior thalidomide use, and t(4;14) translocation were not predictive of PFS (Table 4).

Multivariate analysis on OS identified progression on thalidomide (HR: 1.810; 95% CI: 1.081–3.030; $P<0.02$) as the only significant independent predictor of reduced OS (Table 5). There was a trend toward reduced OS with prior bortezomib use (HR: 2.611; 95% CI: 0.927–7.360; $P=0.07$) (Table 5). Del(13) and t(4;14) met the criteria to stay in the model though they were not statistically significant. Age, sex, number of lines of prior therapy, prior transplant, prior thalidomide treatment, and hemoglobin level did not affect OS (Table 5).

Discussion

In this heavily pretreated population, the combination of lenalidomide plus dexamethasone achieved an ORR of 59% and median PFS of 9.6 months. These data are consistent with the results of the pivotal phase III studies in patients with more than one prior therapy (ORR 57%; median PFS 9.5 months).[3,4] The median OS was lower in this study (15.1 months) than in the phase III studies (35.8 months). This can be explained by the higher percentage of patients with prior SCT (73% vs 53%), prior thalidomide (86% vs 52%), and prior bortezomib (81% vs 11%). In this study, multivariate analyses showed that lower hemoglobin level, increased number of prior therapies, and del(13) were independent predictors of lower ORR; that lower

Table 3 Cox proportional hazards model evaluating multi-factors on overall response rate

Variable	*Univariate analysis*		*Multivariate analysis*	
	Hazard ratio (95% CI)	P	*Hazard ratio (95% CI)*	P
Age	1.020 (0.990–1.051)	0.1965		
Sex	1.370 (0.763–2.459)	0.2917	1.820 (0.834–3.974)	0.1326
Number of prior lines of therapy	0.837 (0.700–1.001)	0.0509	0.745 (0.573–0.967)	0.0270
Prior transplant	0.936 (0.491–1.785)	0.8416		
Prior bortezomib use	2.324 (1.023–5.281)	0.0440		
Prior thalidomide use	1.699 (0.699–4.130)	0.2419		
Progression on thalidomide	1.805 (1.001–3.255)	0.0497		
Deletion of chromosome 13	3.237 (1.732–6.053)	0.0002	3.431 (1.531–7.689)	0.0027
Translocation (4;14)	2.583 (1.050–6.358)	0.0389	2.584 (0.772–8.651)	0.1236
Hemoglobin	1.296 (1.094–1.535)	0.0028	1.230 (1.000–1.511)	0.0495

Abbreviation: CI, confidence interval.

Table 4 Cox proportional hazards model evaluating multi-factors on progression-free survival

Variable	*Univariate analysis*		*Multivariate analysis*	
	Hazard ratio (95% CI)	P	*Hazard ratio (95% CI)*	P
Age	0.98 (0.96–1.00)	0.0336	Not retained	
Sex	1.02 (0.68–1.51)	0.9405	Not retained	
Number of prior lines of therapy	1.13 (1.01–1.26)	0.0281	1.17 (0.99–1.37)	0.062
Prior transplant	1.23 (0.78–1.95)	0.3733	Not retained	
Prior bortezomib use	3.31 (1.66–6.58)	0.0006	2.37 (0.91–6.16)	0.076
Prior thalidomide use	1.81 (0.88–3.72)	0.1097	Not retained	
Progression on thalidomide	2.55 (1.72–3.80)	<0.0001	2.72 (1.66–4.46)	<0.0001
Deletion of chromosome 13	2.75 (1.80–4.20)	<0.0001	2.35 (1.44–3.83)	<0.001
Translocation (4;14)	2.00 (1.17–3.40)	0.0112	Not retained	
Hemoglobin	0.79 (0.71–0.89)	<0.0001	0.81 (0.71–0.93)	0.002

Abbreviations: CI, confidence interval; PFS, progression-free survival.

Table 5 Cox proportional hazards model evaluating multi-factors on overall survival

Variable	*Univariate analysis*		*Multivariate analysis*	
	Hazard ratio (95% CI)	P	*Hazard ratio (95% CI)*	P
Age	0.984 (0.962–1.006)	0.1437	Not retained	
Sex	0.908 (0.585–1.409)	0.6658	Not retained	
Number of prior lines of therapy	1.083 (0.960–1.223)	0.1942	Not retained	
Prior transplant	1.216 (0.732–2.020)	0.4506	Not retained	
Prior bortezomib use	3.260 (1.499–7.090)	0.0029	2.611 (0.927–7.360)	0.0694
Prior thalidomide use	1.370 (0.629–2.982)	0.4282	Not retained	
Progression on thalidomide	2.158 (1.391–3.348)	0.0006	1.810 (1.081–3.030)	0.0241
Deletion of chromosome 13	2.136 (1.338–3.411)	0.0015	1.557 (0.870–2.787)	0.1357
Translocation (4;14)	2.209 (1.246–3.915)	0.0067	1.665 (0.835–3.319)	0.1478
Hemoglobin	0.878 (0.783–0.984)	0.0253	Not retained	

Abbreviation: CI, confidence interval.

hemoglobin level, progression on thalidomide, and del(13) were prognostic of reduced PFS; and that progression on thalidomide was the only significant independent predictor of OS.

The chromosomal abnormalities del(13), t(4;14), and del(17p) have been associated with a decreased OS in newly diagnosed MM treated with traditional chemotherapy.[6,7] In the presence of abnormal karyotypes, newly diagnosed MM patients treated with lenalidomide plus dexamethasone also have a shorter PFS and OS compared with patients with normal karyotypes.[9] The prognostic value of these chromosomal abnormalities has not been assessed in elderly patients with advanced heavily pretreated MM.

In this retrospective study of patients with relapsed or refractory MM who received treatment with lenalidomide plus dexamethasone, the incidence of del(13), t(4;14), and del(17p) was consistent with the incidence reported by the Intergroupe Francophone du Myélome (IFM) group. In this study of patients with relapsed or refractory MM with del(13), t(4;14), and del(17p) cytogenetic abnormalities achieved an ORR of 59%, similar to that reported (60.6%) for the overall cohort of patients in the pivotal phase III registration studies.[3,4] Patients with del(13) and t(4;14) chromosomal abnormalities had lower ORRs and shorter median PFS and OS compared with those who did not have these abnormalities. These results partly contrast the MM-016 study by Reece *et al*.,[10] which reported that relapsed and refractory MM patients treated with lenalidomide plus dexamethasone overcame poor prognosis conferred by the chromosomal abnormalities of del(13), t(4;14), but not del(17p), as evidenced by the findings that the advantage in TTP and OS conferred by the addition of lenalidomide to dexamethasone were independent of del(13) or t(4;14) abnormalities. However, the study also reported that both del(13q) and t(4;14) were associated with shorter TTP in univariate analyses, and that the ORRs in patients with del(13q), t(4;14), and del(17p13) (76.4, 78.6 and 58.3%, respectively) were lower than reported for the overall study population (83.1%). The partial contrast between these findings could be a result of differences in patient characteristics between the two studies. Patients in our study were older (median age of 65 years vs 61 years), had a higher median number of prior therapies (3 vs 2), and a higher proportion of patients with earlier thalidomide (86% vs 54%) or bortezomib (81% vs 46%) therapy. However, our results confirm those observed in newly diagnosed patients, although the definition of high-risk patients was slightly different.[11] Another finding in this study is the prognostic value of isolated del(13). In studies analyzing patients at diagnosis, isolated del(13) (that is not associated with t(4;14) or del(17p)) was not associated with a particular outcome. In other words, all the prognostic value of del(13) was related to the prognostic impact of related chromosomal abnormalities. In this study, del(13) was associated with a lower ORR and a shorter PFS. This may suggest that del(13) displays a different prognostic value at diagnosis and in later phases of the disease.

Most patients in this study had received earlier thalidomide (81%) and/or bortezomib (86%) therapy. Wang *et al*.[14] reported that efficacy of lenalidomide and dexamethasone was superior to dexamethasone alone in patients with relapsed or refractory MM treated with lenalidomide and dexamethasone regardless of prior thalidomide exposure. The efficacy results were more favorable for patients without than with prior thalidomide treatment; however, this was also observed for patients treated with dexamethasone alone and probably reflects the fact that patients with prior thalidomide exposure were more heavily pretreated (median 3 vs 2 prior therapies). In this study, we found that prior thalidomide made no difference in PFS or OS according to univariate and multivariate analyses, but that patients who progressed on thalidomide had shorter OS than patients who had not progressed on thalidomide. In addition, for patients who had not progressed on thalidomide, those without del(13) had better OS than patients with del(13); however, for patients who had progressed on thalidomide, the presence of del(13) did not have an adverse effect on OS. Patients who were resistant to thalidomide had an additional line of prior therapy (median of 4 vs 3 prior lines) and a higher incidence of t(4;14) (16% vs 9%) than patients who were not resistant to thalidomide, which may account for poorer outcomes observed in these patients. However, the main explanation is probably a cross-resistance between the two related drugs. Finally, patients who had received prior bortezomib therapy had significantly shorter median PFS and OS compared with those with no earlier bortezomib treatment. Our data show that OS is only compromised in patients who progressed on thalidomide if they received prior bortezomib, which suggests that bortezomib may induce resistance to late salvage therapy. This could be related to the adaptive mechanisms, which allow cells to develop resistance to proteasome inhibitors and establish a hyperproliferative and apoptosis-resistant phenotype.[15,16] However, we have to stress that patients who did not receive bortezomib presented a lower median number of lines of treatment (median = 2), than those who receive prior bortezomib (median = 4).

In relapsed or refractory MM patients with del(13), outcomes reported here for lenalidomide and dexamethasone are comparable with those reported for bortezomib in a consecutive patient

cohort (ORR 45%; OS 9.9 months)[17] and in a retrospective analysis of the SUMMIT (ORR 24%; OS 10.0 months) and APEX (ORR 20–53%; OS 10.0 months to not reached) trials.[18] In the consecutive patient cohort, the authors reported no significant difference in outcomes between patients with and without del(13); however, median time from initiation of first-line therapy was significantly shorter in patients with than without del(13) (26 months vs 51 months; $P=0.02$).[17] In the retrospective analysis, prognosis appeared to be poorer in patients with del(13) in both studies, but the differences were not statistically significant in the matched-pairs analyses (selected groups of patients balanced for age and ISS parameters).[18]

Our study adds new data with regard to the prognostic value of high-risk cytogenetic abnormalities in relapsed or refractory MM treated with novel therapies. The data are limited by the retrospective nature of the analysis and the relatively high rate of missing data. These results are not completely consistent with currently available data and further clarification is required, ideally by prospective studies.

In conclusion, multivariate analyses showed that an increased number of prior therapies was predictive of lower ORR; lower hemoglobin level and the presence of del(13) were prognostic of reduced ORR and lower median PFS; and progression on thalidomide was an independent predictor of both PFS and OS. This study confirms the beneficial effects of lenalidomide and dexamethasone in this heavily pretreated population and suggests that because of a better toxicity profile, lenalidomide should be proposed earlier in the patient evolution. Randomized clinical trials are needed to further evaluate these findings.

Conflict of interest

The authors declare no conflict of interest.

References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T *et al.* Cancer statistics, 2008. *CA Cancer J Clin* 2008; **58**: 71–96.
2 Sirohi B, Powles R. Epidemiology and outcomes research for MGUS, myeloma and amyloidosis. *Eur J Cancer* 2006; **42**: 1671–1683.
3 Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A *et al.* Multiple Myeloma (010) Study Investigators. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007; **357**: 2123–2132.
4 Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA *et al.* Multiple Myeloma (009) Study Investigators. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007; **357**: 2133–2142.
5 Fonseca R, Blood E, Rue M, Harrington D, Oken MM, Kyle RA *et al.* Clinical and biological implications of recurrent genomic aberrations in myeloma. *Blood* 2003; **101**: 4569–4575.
6 Avet-Loiseau H, Attal M, Moreau P, Charbonnel C, Garban F, Hulin C *et al.* Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. *Blood* 2007; **109**: 3489–3495.
7 Gertz MA, Lacy MQ, Dispenzieri A, Greipp PR, Litzow MR, Henderson KJ *et al.* Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood* 2005; **106**: 2837–2840.
8 Debes-Marun CS, Dewald GW, Bryant S, Picken E, Santana-Davila R, Gonzalez-Paz N *et al.* Chromosome abnormalities clustering and its implications for pathogenesis and prognosis in myeloma. *Leukemia* 2003; **17**: 427–436.
9 Zonder JA, Crowley JJ, Bolejack V, Hussein MA, Moore DF, Whittenberger BF *et al.* A randomized Southwest Oncology Group study comparing dexamethasone (D) to lenalidomide + dexamethasone (LD) as treatment of newly-diagnosed multiple myeloma (NDMM): impact of cytogenetic abnormalities on efficacy of LD, and updated overall study results. *J Clin Oncol* 2008; **26**. [Abstract 8521].
10 Reece D, Song KW, Fu T, Roland B, Chang H, Horsman DE *et al.* Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13. *Blood* 2009; **114**: 522–525.
11 Kapoor P, Kumar S, Fonseca R, Lacy MQ, Witzig TE, Hayman SR *et al.* Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood* 2009; **114**: 518–521.
12 Bladé J, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G *et al.* Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol* 1998; **102**: 1115–1123.
13 Stadtmauer EA, Weber DM, Niesvizky R, Belch A, Prince MH, San Miguel JF *et al.* Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. *Eur J Haematol* 2009; **82**: 426–432.
14 Wang M, Dimopoulos MA, Chen C, Cibeira MT, Attal M, Spencer A *et al.* Lenalidomide plus dexamethasone is more effective than dexamethasone alone in patients with relapsed or refractory multiple myeloma regardless of prior thalidomide exposure. *Blood* 2008; **112**: 4445–4451.
15 Naujokat C, Fuchs D, Berges C. Adaptive modification and flexibility of the proteasome system in response to proteasome inhibition. *Biochim Biophys Acta* 2007; **1773**: 1389–1397.
16 Fuchs D, Berges C, Opelz G, Daniel V, Naujokat C. Increased expression and altered subunit composition of proteasomes induced by continuous proteasome inhibition establish apoptosis resistance and hyperproliferation of Burkitt lymphoma cells. *J Cell Biochem* 2008; **103**: 270–283.
17 Sagaster V, Ludwig H, Kaufmann H, Odelga V, Zojer N, Ackermann J *et al.* Bortezomib in relapsed multiple myeloma: response rates and duration of response are independent of a chromosome 13q-deletion. *Leukemia* 2007; **21**: 164–168.
18 Jagannath S, Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA *et al.* Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials. *Leukemia* 2007; **21**: 151–157.