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ORIGINAL ARTICLE

Treatment of patients with relapsed/refractory multiple myeloma with lenalidomide and dexamethasone with or without bortezomib: prospective evaluation of the impact of cytogenetic abnormalities and of previous therapies

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We prospectively studied the impact of several cytogenetic abnormalities (CAs) in patients with relapsed/refractory myeloma who received lenalidomide and dexamethasone (RD) with or without the addition of bortezomib (V). On the basis of the presence of previous neuropathy, 50 patients were treated with RD and 49, without preexisting neuropathy, with VRD. The overall response rate was 63%, similar for RD and VRD. Poor risk cytogenetics were associated with lower response rates in RD ($P=0.01$), but not in VRD ($P=0.219$). The median progression-free survival (PFS) was similar for RD (9 months) and VRD (7 months). The median overall survival (OS) for all patients was 16 months, with no differences between RD or VRD regimens. Poor risk cytogenetics, especially del17p, resistance to previous thalidomide, elevated lactate dehydrogenase (LDH) and presence of extramedullary disease were associated with inferior response to therapy and shorter PFS and OS. The impact of other CAs on OS was more pronounced in RD. In conclusion, the presence of CAs is an important adverse prognostic factor for patients with relapsed/refractory myeloma, but resistance to previous thalidomide, elevated LDH and presence of extramedullary disease remain of major prognostic importance. The outcome of patients with del17p remains extremely poor even with VRD combination.
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Introduction

Lenalidomide combined with dexamethasone is an effective treatment for patients with relapsed/refractory multiple myeloma and is associated with an overall response rate of 60% including a complete response rate of 15%.[1,2] Bortezomib as a single agent may induce objective responses in up to 43% of patients with refractory/relapsed myeloma.[3–5] *In vitro* studies have shown that thalidomide and lenalidomide may enhance the activity of bortezomib and dexamethasone.[6,7] Furthermore, clinical data indicated that the combination of lenalidomide and bortezomib (RD) has significant activity in patients with relapsed/refractory myeloma several of whom had failed to previous treatment with bortezomib or with an immunomodulatory agent. In a phase 1 study, the combination of lenalidomide, bortezomib and dexamethasone (VRD) produced a minimal response or better to 61% of patients with relapsed/refractory myeloma,[8] whereas in the following phase 2 study this combination produced an overall response rate of 68%.[9]

Although novel agent-based treatments have improved the outcome of patients with relapsed/refractory myeloma, they produce significant toxicity in a subset of those. Peripheral neuropathy occurs in approximately 35% of patients with relapsed/refractory myeloma treated with bortezomib.[10] Furthermore, it is not clear whether these treatments may overcome the adverse impact of several cytogenetic abnormalities (CAs). Abnormalities such as deletion 17p13, t(4;14) as detected by fluorescent *in situ* hybridization (FISH) and deletion 13q as detected by metaphase cytogenetics retain their poor prognosis despite the use of high dose therapy and autologous stem cell transplantation and thalidomide maintenance.[11–14] Preliminary data have recently shown that bortezomib may overcome the negative prognostic impact of del13p[15] and of t(4;14).[16]

Therefore, we treated consecutive patients with relapsed or refractory multiple myeloma (MM) either with lenalidomide and dexamethasone or with bortezomib, lenalidomide and dexamethasone based on the presence of peripheral neuropathy and we, prospectively evaluated whether these treatments may overcome the adverse prognosis of several cytogenetic abnormalities detected by metaphase karyotype and by FISH.

Patients and methods

Study design

Patients with relapsed or refractory myeloma, after one or more previous therapies, were included in this treatment plan. Patients were considered refractory if they had progressive disease, while on previous therapy or within 60 days of treatment completion.[17] Patients were treated regardless of their performance status, renal function, previous peripheral neuropathy and treatment with high dose dexamethasone, thalidomide or bortezomib. However, patients who were previously treated with lenalidomide were not included in this analysis.

Selection of treatment was based on the presence or absence of peripheral neuropathy: patients with previous neuropathy $\geqslant$grade 2 received RD, whereas patients with previous neuropathy $<$grade 2 received VRD. Patients who were treated with RD received the standard dose of lenalidomide 25 mg p.o. daily, on days 1–21 of a 28–day cycle, if the baseline creatinine clearance (CrCl) was >50 ml/min. For patients with lower CrCl the following adjustments were made: for CrCl $\geqslant 30$ ml/min and <50 ml/min, lenalidomide was given at 10 mg/day; for CrCl <30 ml/min without need for dialysis, lenalidomide was given

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at 15 mg every other day; and for patients on dialysis, lenalidomide was given 15 mg, three times a week, on the day after dialysis. Dexamethasone was administered at a dose of 40 mg p.o. on days 1–4 and 15–18 for the first four cycles, and only on days 1–4 for the cycles, thereafter. RD was repeated every 28 days until disease progression or unacceptable toxicity. The doses of VRD were chosen on the basis of the maximum tolerated dose reported by Richardson *et al*.[8] Bortezomib was given at 1 mg/m^2 i.v. on days 1, 4, 8 and 11, lenalidomide was given at a dose 15 mg p.o. daily on days 2–14 (or at a lower dose if creatinine clearance was <30 ml/min) and dexamethasone was administered at a dose of 40 mg p.o. on days 1–4. VRD treatment was repeated every 21 days for eight courses and patients without progression continued treatment with lenalidomide, dosed according to CrCl, for 21 days and dexamethasone 40 mg p.o. days 1–4 every 28 days. This treatment was repeated until disease progression or unacceptable toxicity.

In case of toxicity, the dose of bortezomib could be reduced to 0.7 mg/m^2 for 4 days on each cycle or to 0.7 mg/m^2 weekly. Lenalidomide could be reduced to 15–10 mg/day or less and dexamethasone could be reduced to 20–10 mg/day.

Patients received supportive treatment with zoledronic acid, erythropoietin or darbepoietin and granulocyte colony-stimulating factor, as clinically indicated. All patients received prophylaxis with valacyclovir and trimpethoprine-sulfamethoxazole. Thromboprophylaxis was mandatory and consisted of low dose aspirin (100 mg p.o. daily), unless the patient was already on low-molecular-weight heparin or coumadin for another indication.

Adverse events were followed prospectively and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3). Response to treatment was determined by using the International Myeloma Working Group Criteria.[17]

Approval from the hospital's ethics committee was obtained for the collection, analysis and report of the data. All patients signed an informed consent for treatment, collection and analysis of data.

Laboratory examination

Before treatment initiation, all patients underwent complete staging with routine biochemical profile, complete blood count, serum and urine electrophoresis and immunofixation, serum free light chain measurement, bone marrow aspiration and trephine bone marrow biopsy. Marrow samples were obtained for metaphase karyotype and FISH analysis for del13q, del17p, t(4;14), t(14;16) amp1q21 after CD138-positive selection. All cytogenetic studies were performed in a single laboratory, using standard methodology, before treatment with RD or VRD.

Poor risk cytogenetics were defined by the presence of at least one of the following: nonhyperdipoid metaphase karyotype, del13q by metaphase karyotype, del17p or amp 1q21 or t(4;14) or t(14;16) by FISH.

Statistical analysis

Comparisons among different groups were made with the χ^2-test, using Fisher's exact test when appropriate. Logistic regression was used for multivariate analysis of factors associated with response to treatment. Progression-free survival (PFS) was measured from the time of treatment initiation to progressive disease or death from any cause and overall survival (OS) was measured from the time of treatment initiation to death from any cause. Time to event curves was plotted by the Kaplan–Meier method and comparisons among groups was performed with the log-rank test. For multivariate analysis, factors associated with time to event were introduced to a Cox proportional hazards model.

Results

Patients

Between February 2007 and October 2009, 99 consecutive patients were treated either with RD (50 patients) or with VRD (49 patients). Patients and disease features are shown in Table 1. The median time from initial treatment to the current treatment was 35 months, and was similar for those treated with RD or RVD. The median number of previous treatments was two, similar for RD and VRD treated patients; however, 48% of the patients had received three or more lines of treatment. Patients with thalidomide resistance had a median of 3 vs 2 previous therapies for thalidomide-sensitive or thalidomide-naïve patients ($P=0.1$). Similarly, patients with bortezomib resistance had a median of three previous therapies compared with bortezomib-naïve or -sensitive patients who had a median of two previous therapies ($P=0.056$). All demographic characteristics of patients and disease features were comparable between the two groups except for elevated serum lactate dehydrogenase (LDH), which was significantly more common in the VRD-treated patients.

In all, 22 patients (12 in RD and 10 in VRD) received lenalidomide at a dose adjusted to their renal function. The median number of RD cycles in RD-treated patients were 7 (range 1–29), the median number of VRD cycles were 8 (range 1–8), the median number of bortezomib infusions in VRD treated patients was 23 (range 2–32), whereas 12 patients (25%) continued RD maintenance after VRD for a median of 5 (range 1–15) cycles.

Table 2 shows the distribution of cytogenetic abnormalities among patients treated with RD or VRD. Presence of del13q was strongly associated with the concomitant presence of other cytogenetic abnormalities ($P<0.001$ for correlation with the presence of del17p, t(4;14) and amp1q21). Similarly, all patients with del13q by metaphase karyotype had at least one additional high-risk cytogenetic abnormality. Patients who were resistant to thalidomide had similar rates of high-risk CAs with thalidomide-sensitive or thalidomide-naïve patients. Similarly, there was no difference in the frequency of CAs in patients with bortezomib resistance compared with bortezomib-sensitive or -naïve patients. There was no correlation among the frequency of CAs and the number of previous lines of therapy.

Response to treatment

Response rates and quality of responses after treatment were similar for RD and VRD (Table 3). Poor risk cytogenetics were associated with lower response rates, but that was significant in RD ($P=0.01$) and not in VRD-treated patients ($P=0.219$) (Table 4a). The adverse effect of del13q, amp1q21 and t(4;14) were more pronounced mainly for the RD-treated patients. Nevertheless, del17p was associated with an inferior response after either RD or VRD.

Patients who had not received thalidomide (thalidomide naïve) had similar outcome to thalidomide-sensitive patients (objective response rate ($\geqslant$partial response (PR)) 84 vs 82%, $P=0.9$). Resistance to previous thalidomide treatment was associated with lower response rates after either RD or VRD (Table 4a). Patients with resistance to bortezomib had similar response rates after RD or VRD. The quality of response was also affected by previous thalidomide resistance, with $\geqslant$very good

Table 1 Patients and disease features

	All patients	*RD*	*VRD*	P-*value*
Age >70 years	46%	57%	70%	0.113
Male	53%	52%	55%	0.841
ISS at treatment				
1	44%	46%	45%	
2	24%	24%	23%	0.875
3	28%	27%	32%	
ECOG performance status ⩽1	68%	66%	71%	0.666
Platelet counts $<100\,000/mm^3$	6%	4%	8%	0.436
CrCl <50 ml/min	25%	24%	27%	0.820
LDH (IU/l) ⩾300 U/l	20%	12%	29%	0.048
Extramedullary disease	10%	8%	12%	0.525
Time from diagnosis (range) in months	35 (1–217)	34 (5–118)	36 (1–217)	
Median number of previous lines of therapy	2 (1–8)	2 (1–6)	2 (1–8)	
1		22%	22%	
2		30%	30%	0.670
3		28%	20%	
>3		20%	26%	
Refractory relapse	58%	60%	57%	0.773
Relapse off treatment	41%	40%	43%	
Previous thalidomide	78%	76%	80%	0.810
Thalidomide refractory	47%	50%	43%	0.547
Previous bortezomib	82%	76%	88%	0.192
Bortezomib therapy	49%	42%	55%	0.230
Thalidomide resistant only	18%			
Bortezomib resistant only	21%			
Both thalidomide and bortezomib resistant	27%			
No resistance to novel drugs	32%			

Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology group; ISS, International Staging System; LDH, lactate dehydrogenase; RD, lenalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone.

Table 2 Cytogenetic studies

	All patients N *(%)*	*RD* N *(%)*	*VRD* N *(%)*	P-*value for RD* vs *VRD*
Hyperdiploid	8 (35%)	3 (27%)	5 (42%)	0.667
Nonhyperdiploid	15 (65%)	8 (73%)	7 (58%)	
t(14;16)	1 (1%)	0	1 (2%)	0.495
del13q	25 (27%)	10 (20%)	15 (31%)	0.240
del17p	10 (11%)	3 (6%)	7 (14%)	0.188
amp1q21	24 (27%)	10 (20%)	14 (29%)	0.343
t(4;14)	10 (11%)	6 (12%)	4 (8%)	0.740
del13 by karyotype	7 (8%)	1 (2%)	6 (12%)	0.055
Poor risk cytogenetics	36 (37%)	16 (32%)	20 (41%)	0.512

Abbreviations: RD, lenalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone.

Table 3 Response after RD or VRD

	All patients N *(%)*	*RD* N *(%)*	*VRD* N *(%)*
sCR	1 (1%)	0	1 (2%)
CR	9 (9%)	7 (14%)	2 (4%)
VGPR	14 (14%)	7 (14%)	7 (14%)
PR	37 (37%)	16 (33%)	21 (43%)

Abbreviations: CR, complete response; PR, partial response; RD, lenalidomide and dexamethasone; sCR, serum creatinine; VGPR, very good partial response; VRD, bortezomib, lenalidomide and dexamethasone.

partial response (VGPR) in 7 vs 40% in nonresistant patients ($P<0.001$). Similar results were observed in bortezomib-resistant patients (⩾VGPR in 8%) vs nonresistant (⩾VGPR in 40%, $P<0.001$). Table 4a depicts factors that were analyzed for association with response to RD or VRD.

In a multivariate model that included del13q, t(4;14), del17p, amp1q21, resistance to thalidomide, resistance to bortezomib, type of treatment (RD or VRD), extramedullary disease and elevated LDH, only del17p, thalidomide resistance (vs thalidomide-sensitive or thalidomide-naïve patients), extramedullary disease and elevated LDH were independently associated with inferior response (Table 4b). The presence of t(4;14) was of borderline significance ($P=0.055$), probably due to the small number of patients with this specific CA.

PFS and OS data

So far, 66 (67%) patients have progressed; the median PFS is 8 months, similar for RD (9 months) and for VRD-treated patients

Table 4a Impact of disease features and cytogenetic abnormalities on response after RD or VRD

	All patients	P-*value*	*RD*	P-*value*	*VRD*	P-*value*
del13q	52%	0.230	30%	0.066	66%	0.990
No del13q	67%		67%		67%	
del17p	20%	0.005	0%	0.06	29%	0.036
No del17p	68%		63%		73%	
amp1q21	50%	0.219	20%	0.009	71%	0.738
No amp1q21	67%		69%		63%	
t(4;14)	40%	0.172	17%	0.033	75%	0.990
No t(4;14)	65%		66%		63%	
Any cytogenetic abnormality	50%	0.046				
No cytogenetic abnormality	72%					
Poor risk cytogenetics	44%	0.007	31%	0.01	55%	0.219
Standard risk cytogenetics	74%		74%		74%	
Thalidomide resistant	37%	<0.001	40%	0.009	33%	0.001
Thalidomide naïve or sensitive	83%		80%		86%	
Bortezomib resistant	56%	0.309	55%	0.560	48%	0.019
Bortezomib naïve or sensitive	67%		67%		82%	
Previous HDT	59%	0.679	61%	0.990	56%	0.390
No previous HDT	64%		59%		69%	
Resistant relapse	44%	<0.001	53%	0.377	39%	0.001
Sensitive relapse	83%		70%		95%	
Extramedullary disease	20%	0.006	25%	0.289	17%	0.20
No extrameduallary disease	66%		63%		70%	
Hyperdiploid karyotype	75%	0.023	67%	0.491	80%	0.72
Nonhyperdiploid karyotype	20%		25%		14%	
LDH ⩾300 IU/l	35%	0.009	17%	0.32	43%	0.1
LDH<300 IU/l	68%		66%		71%	
⩾3 previous treatments	57%	0.535	58%	0.990	57%	0.390
⩽2 previous treatments	65%		61%		69%	
Thalidomide + bortezomib resistant	33%	<0.001	50%	0.287	20%	0.001
Sensitive or resistant only to thalidomide or bortezomib	77%		71%		82%	
CrCl <30 ml/min			60%	0.990	50%	0.656
CrCl ⩾30 ml/min			60%		65%	
Age ⩾70 years			57%	0.779	70%	0.550
Age <70 years			63%		59%	

Abbreviations: CrCl, creatinine clearance; HDT, high dose therapy; LDH, lactate dehydrogenase; RD, lenalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone.

Table 4b Multivariate analysis for factors associated with response to therapy

	P-*value*	*Odds ratio*	*95.0% CI for OR*
del13q	0.158	3.86	0.59–25
t(4:14)	0.055	8.41	0.95–74.15
del17p	0.002	43.91	3.92–490.96
amp1q21	0.610	1.47	0.26–8.13
Thalidomide resistance	0.000	23.87	5.31–107.12
Bortezomib resistance	0.599	2.68	0.38–8.13
RD (vs VRD)	0.126	0.37	0.10–1.31
Extramedullary disease	0.006	34.37	2.78–424.80
LDH⩾300 IU/l	0.006	13.15	2.11–83.33

Abbreviations: CI, confidence interval; LDH, lactate dehydrogenase; OR, odds ratio; RD, lenalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone.

(7 months, $P=0.787$). Patients with poor risk cytogenetics had shorter PFS than patients with standard risk cytogenetics ($P=0.003$) (Table 5a). This difference was found both in patients treated with RD and those treated with VRD (Table 5b). Among patients who had informative metaphase karyotypes ($n=23$), those with a hyperdiploid karyotype had longer PFS than those with a nonhyperdiploid karyotype ($P=0.018$). Patients with del17p had a short PFS of just 2 months, compared with 9 months for patients without del17p ($P<0.001$). The presence of del13q by FISH (6.4 vs 10 months, $P=0.008$), of t(4;14) translocation (6.4 vs 9 months, $P=0.088$) and of amp1q21 (5 months vs 10 months, $P=0.016$) were also associated with shorter median PFS. However, the impact of amp1q21 was more pronounced in patients treated with RD ($P=0.034$) than in those treated with VRD ($P=0.231$). Although the numbers are small, the negative impact of del17p was evident in both RD- ($P=0.005$) and VRD-treated ($P=0.002$) patients. When patients with del13q by FISH as their single abnormality ($n=5$) were compared with patients with no other cytogenetic abnormalities ($n=53$), there was no difference in PFS (14.2 vs 10 months, $P=0.835$). Figure 1 shows the impact of individual CAs abnormalities on PFS.

We subsequently evaluated other variables for their possible impact on PFS. Resistance to previous thalidomide ($P<0.001$), or bortezomib ($P=0.047$) were associated with shorter PFS. Thalidomide resistance was associated with shorter PFS both in patients who had previous bortezomib (10 vs 4 months $P=0.003$) and in those who did not had previous bortezomib treatment (15 vs 7 months, $P=0.223$). Elevated LDH ($P<0.001$), the presence of extramedullary disease ($P<0.001$) and low platelet counts ($P=0.036$) were also associated with shorter PFS. We then constructed a multivariate model that included specific CAs, International Staging System, thalidomide resistance, bortezomib resistance, elevated LDH and the presence of extrameduallary disease. In this model, del17p, t(4;14), thalidomide resistance, elevated LDH and extramedullary disease were independently associated with shorter PFS (Table 5a).

Table 5a Factors associated with PFS

	Univariate analysis		*Multivariate analysis*	
	Median months (CI 95%)	P-*value*	*HR (95% CI)*	P-*value*
RD	9.4 (5.6–13.1)	0.737	1.06 (0.57–1.98)	0.841
VRD	7.7 (4.3–11.2)			
Thalidomide refractory	5.1 (3–7.2)	0.001	3 (1.6–5.6)	0.001
Thalidomide sensitive or never exposed	11.4 (9.4–13.4)			
Resistant or refractory relapse	5.7 (2.8–8.6)	0.003		
Nonresistant relapse	11.4 (9.6–13.2)			
Previous HDT	7.5 (4.5–10.4)	0.301		
No previous HDT	10.1 (5.2–15)			
LDH $\geqslant$300 IU/l	2 (1.6–2.5)	$<$0.001	10.3 (4.1–25.8)	$<$0.001
LDH $<$300 IU/l	10.1 (7.5–12.7)			
Previous bortezomib	7.7 (1.3–5.2)	0.167		
No previous bortezomib	15.1 (4.5–26)			
Bortezomib resistant	5.9 (2.9–9)	0.047	1.25 (0.65–2.4)	0.502
Bortezomib sensitive or naïve	10.1 (7.4–12.8)			
ISS I	10 (7.3–12.8)	0.196	0.9 (0.44–1.85)	0.770
II	6.4 (1.5–11.4)		1.3 (0.55–2.9)	0.568
III	5.9 (3–8.8)			0.668
Poor risk cytogenetics	5.6 (3.6–7.6)	0.003		
Standard risk cytogenetics	10.1 (6.6–13.5)			
del17p	2.3 (0.2–4.4)	$<$0.001	6.6 (2.4–18.0)	$<$0.001
No del17p	9.9 (6.9–12.9)			
amp1q21	5.9 (4.7–7.1)	0.04	1.31 (0.6–2.8)	0.474
No amp1q21	9.9 (8.5–11.3)			
t(4;14)	6.4 (3.1–9.7)	0.088	3.1 (1.2–7.9)	0.018
No t(4;14)	9 (6–12)			
del13q	6.4 (4–8.8)	0.008	1.03 (0.52–2.0)	0.934
No del13q	10 (7.3–12.8)			
Extramedullary disease	1.8 (0.3–2.5)	$<$0.001	6.5 (1.9–21.7)	0.002
No extramedullary disease	9 (6.6–11.3)			
Age $\geqslant$70 years	8.9 (3.8–14)	0.973		
Age $<$70 years	8.1 (5.6–10.6)			
CrCl $\geqslant$50 ml/min	7.7 (5.3–10.1)	0.461		
CrCl $<$50 ml/min	9.9 (4.6–15.2)			
Hb $<$11.5 g/100ml	7 (3.7–10.2)	0.400		
Hb $\geqslant$11.5 g/100ml	9.4 (6.7–12)			
PLT $<100\times10^3$/ml	8.9 (6.6–11.2)	0.036		
PLT $\geqslant100\times10^3$/ml	1.8 (0.3–3.2)			

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; Hb, hemoglobin; HDT, high dose therapy; HR, hazards ratio; ISS, International Staging System; LDH, lactate dehydrogenase; PFS, progression free survival; PLT, platelet; RD, lenalidomide and dexamethasone, VRD, bortezomib, lenalidomide and dexamethasone.

Table 5b Impact of cytogenetics on PFS (median–range) according to treatment

	RD	*VRD*	P-*value*
Poor risk cytogenetics	5 (0–10.2)	5 (2.7–7.2)	0.570
del13	5 (0–11.2)	6 (3.2–8.8)	0.724
del17	2 (0.4–3.6)	3 (0–8.1)	0.980
t(4;14)	6 (0–14)	5 (0–11.8)	0.339
amp1q21	5 (0.4–9.6)	6 (3.6–8.4)	0.603

Abbreviations: RD, lenalidomide and dexamethasone; PFS, progression-free survival; VRD, bortezomib, lenalidomide and dexamethasone.

After a median follow-up of 11 months (range 0.4–36 months), 45 (45%) patients have died and the median OS for all patients is 16 (95% CI: 10–22) months. There is no difference in the OS among patients treated with RD or VRD. Poor risk cytogenetics are prognostic for inferior survival ($P=0.017$). The presence of del17p ($P=0.003$), amp1q21 ($P=0.009$) were associated with inferior OS. Presence of del13q by FISH ($P=0.01$) was also associated with shorter OS. For patients with informative karyotypes, nonhyperdiploidy was associated with shorter, but non statistically significant, OS ($P=0.11$). The presence of a t(4;14) translocation was not associated with shorter OS ($P=0.555$) neither in RD- nor in VRD-treated patients. The adverse impact of del13q by FISH was more pronounced in RD-treated ($P=0.03$) than in VRD-treated patients ($P=0.112$). Similarly, amp1q21 was significant for OS in RD ($P=0.032$), but not in VRD-treated patients ($P=0.121$). Despite small numbers, del17p offered a dismal prognosis in both RD ($P=0.052$) and VRD ($P=0.095$) treated patients. Figure 2 shows the impact of individual CAs abnormalities on OS.

Resistance to previous thalidomide treatment was also significantly associated with poor OS ($P<0.001$), both for RD-treated ($P=0.002$) or VRD-treated ($P=0.003$) patients. We then constructed a multivariate model that included specific CAs, International Staging System, thalidomide resistance, bortezomib resistance, elevated LDH and the presence of extrameduallary disease. In this model, thalidomide resistance, del17p, elevated LDH and extramedullary disease were independently associated with shorter OS (Table 6).

In order to assess the impact of response to the OS, we analyzed patients who survived at least 3 months according to response: patients who achieved an objective response ($\geqslant$PR)

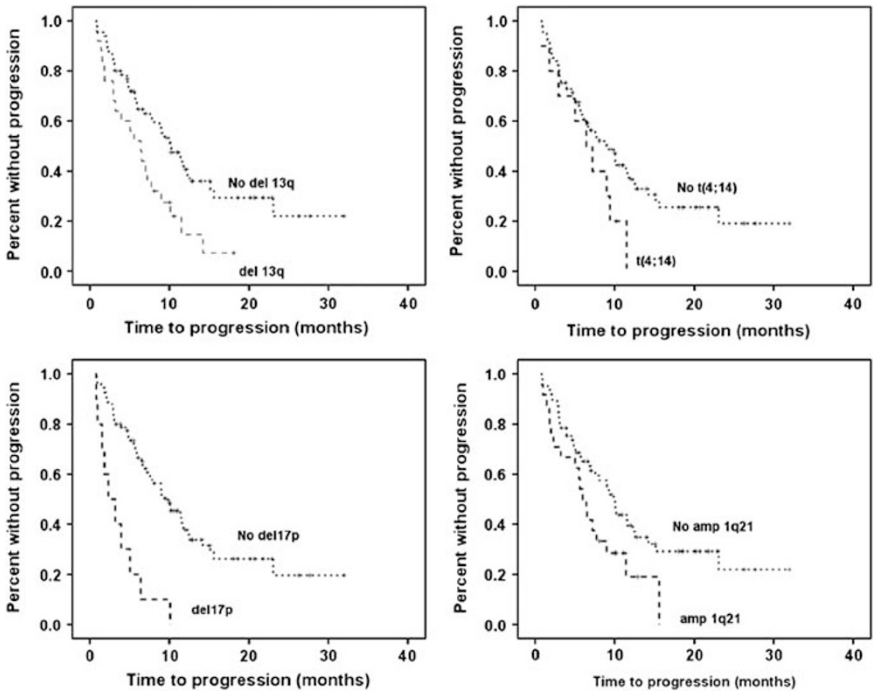

Figure 1 Impact of specific cytogenetic abnormalities on PFS.

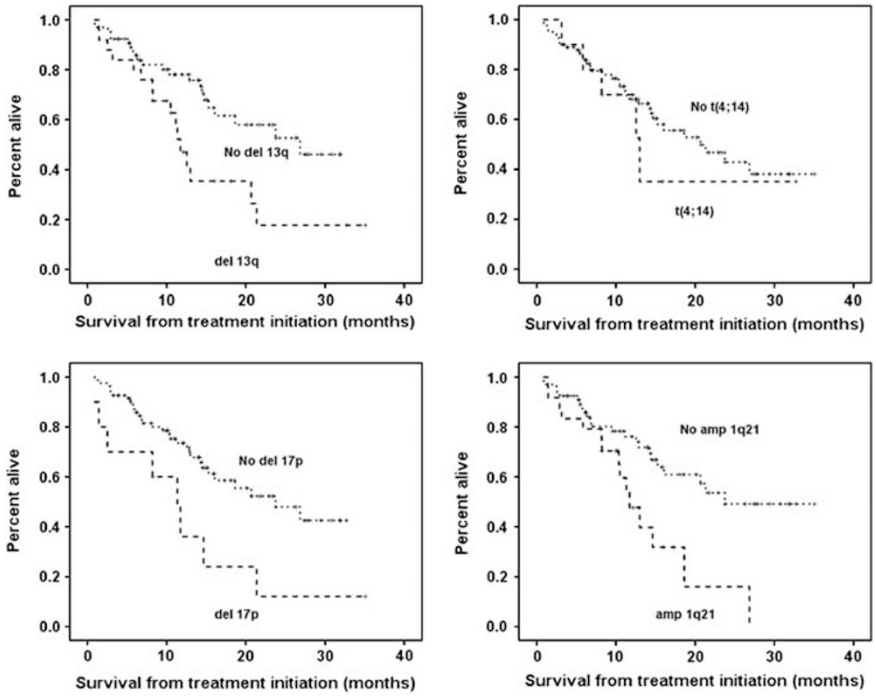

Figure 2 Impact of specific cytogenetic abnormalities on OS.

had significantly better survival than patient who did not respond to treatment (Figure 3). Furthermore, patients who achieved ⩾VGPR had a better outcome (median OS: not reached) than those who achieved a PR (median OS: 23 months; 95% CI: 14-31; $P<0.001$), and those who did not achieve an objective response; (median OS: 7 months; 95% CI: 4–10 months; $P<0.001$; Figure 3b).

Safety data

Table 7 depicts toxicities recorded during treatment with RD or VRD. Thromboprophylaxis with aspirin was given in 84%, coumadin in 7% and low-molecular-weight heparin in 8% of patients. Dose reduction of lenalidomide was required in 36 (36%) of patients, in 24 (48%) in RD and 12 (24%) in VRD-treated patients. The dose of dexamethasone was reduced

Table 6 Parameters associated with OS

	Univariate analysis		*Multivariate analysis*	
	Median months (CI 95%)	P-*value*	*HR (95% CI)*	P-*value*
RD	16 (11–21)	0.729	1.8 (0.78–4.2)	0.170
VRD	20.7 (11.7–29.6)			
Thalidomide refractory	11.3 (9.6–13.1)	<0.001	3.8 (1.8–7.8)	<0.001
Thalidomide sensitive or never exposed	NR			
Resistant or refractory relapse	11 (9.2–12.8)	0.001		
Nonresistant relapse	NR			
Previous HDT	14.6 (NE)	0.922		
No previous HDT	18.6 (11.5–25.7)			
Previous bortezomib	16 (10.4–21.7)	0.298		
No previous bortezomib	NR			
ISS I	NR	0.003	1.5 (0.96–2.5)	0.072
ISS II	11 (8.5–13.5)			
ISS III	11 (4–18)			
Bortezomib resistant	14.6 (9.1–20)	0.090	1.02 (0.4–2.4)	0.927
Bortezomib sensitive or naïve	20.6 (NE)			
del17p	9 (6.3–11.7)	0.003	3.8 (1.2–12.3)	0.027
No del17p	23 (13.2–32.7)			
t(4;14)	12 (7–16.9)	0.555	1.7 (0.5–5.6)	0.409
No t(4;14)	20 (10.3–29.7)			
del13q	11 (9.7–23.3)	0.003	1.23 (0.47–3.2)	0.672
No del13q	NR			
amp1q21	12 (9.5–14.5)	0.009	1.4 (0.62–3)	0.424
No amp1q21	NR			
Hyperdiploid[a]	24 (NE)	0.11		
Nonhyperdiploid	9.4 (3.2–15.6)			
Poor risk cytogenetics	12.5 (10.2–15)	0.017		
Standard risk cytogenetics	24 (NE)			
Extramedullary disease	6 (3.2–8.7)	0.001	8 (2–32)	0.003
No extramedullary disease	20(10.6–29.4)			
Age $\geqslant$70 years	16 (8.9–23)	0.522		
Age <70 years	26 (7.9–44)			
CrCl $\geqslant$50 ml/min	16 (5.9–26.1)	0.916		
CrCl<50 ml/min	20 (11.3–28.6)			
Hb <11.5 g/100ml	12.8 (8.8–16.8)	0.026		
Hb $\geqslant$11.5 g/100ml	26.8 (14–39.6)			
LDH $\geqslant$300 IU/l	6 (2.2–9.8)	<0.001		
LDH <300 IU/l	26 (NE)		6.9 (2.3–20.8)	0.001
PLT $<100\times10^3$/ml	8.9 (6.6–11.2)	0.001		
PLT $\geqslant100\times10^3$/ml	1.8 (0.3–3.2)			
Previous treatments $\leqslant$2	20.65	0.503		
Previous treatment >2	15.3 (9.2–21.3)			

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; Hb, hemoglobin; HDT, high dose therapy; HR, hazards ratio; ISS, International Staging System; LDH, lactate dehydrogenase; NR, not reached; NE, nonevaluated; OS, overall survival; PFS, progression-free survival; PLT, platelet; RD, lenalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone.
[a]$N=23$ patients.

in 26 (26%) patients—in 15 (30%) in RD and 11 (22%) in VRD. Bortezomib dose was reduced in 17 (34%) patients. Neuropathy developed in 33 (66%) of patients treated with VRD. It was of grade 2 in 10 (20%) and of grade 3 in 7 (14%) patients; no patient developed grade 4 peripheral neuropathy. Thirty percent of RD patients (according to inclusion criteria all had at least grade 2 peripheral neuropathy) deteriorated their neuropathy during therapy.

Discussion

In our study, the presence of CAs remains an important prognostic factor in patients with relapsed or refractory MM treated with RD or VRD; however, resistance to previous therapy, especially thalidomide, the presence of high LDH and of extramedullary disease were also major determinants of outcome.

The presence of del17p is probably the most important of the CAs that we studied, and is associated with significantly lower response rates, short PFS and OS. This detrimental effect of del17p has also been shown in previously treated patients who were treated with RD,[18] RD plus doxorubicin,[19] or in newly diagnosed patients treated with RD[20] or with bortezomib plus dexamethasone.[21] However, it is disappointing the fact that even combinations of the most active novel agents cannot overcome this effect, which is present in about 10% of patients, suggesting that new treatments and innovative approaches are urgently needed.

The combination of bortezomib with RD, may, however, overcome to some extent the adverse impact other CAs, such as del13q, amp1q21 and t(4;14), while RD alone may not. We would like to mention that the dosage of lenalidomide in VRD

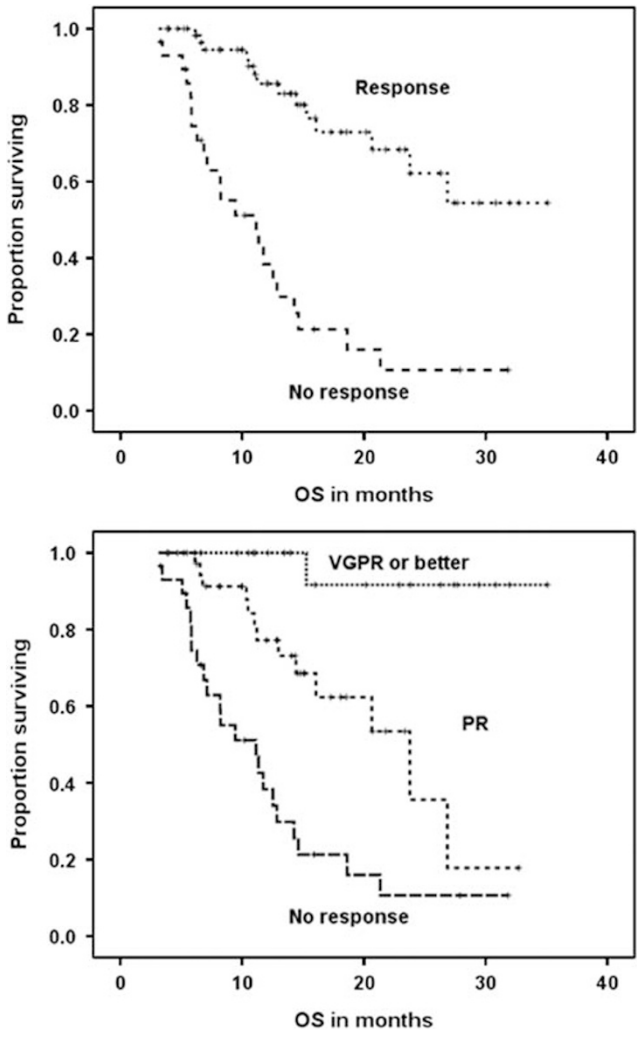

Figure 3 Impact of response to RD or VRD (**a**) and quality of response (**b**) on overall survival (3 month landmark).

Table 7 Toxicities after VRD or RD

	Any grade	*Grade 3/4*	*RD grade 3/4*	*VRD grade 3/4*
Constipation	20 (20%)	0	0	0
Diarrhea	12 (12%)	1 (1%)	1 (2%)	0
Tremor	2 (2%)	0	0	0
Thrombosis	3 (3%)	3 (3%)	1 (2%)	2 (4%)
Rash	8 (8%)	1 (1%)	1 (3%)	0
Hyponatremia	6 (6%)	0	0	0
Fever	13 (13%)	0	0	0
Anemia	37 (37%)	16 (16%)	6 (12%)	10 (20%)
Thrombocytopenia	38 (38%)	12 (12%)	5 (10%)	7 (14%)
Neutropenia	49 (49%)	27 (27%)	14 (28%)	13 (26%)
Infection	35 (35%)	16 (16%)	8 (16%)	8 (16%)
Elevation of serum creatinine	11 (11%)	6 (6%)	2 (4%)	4 (8%)
Liver toxicity	7 (7%)	0	0	0
Hypotension	5 (5%)	0	0	0
Nausea	3 (3%)	1 (1%)	0	1 (2%)
Fatigue	61 (62%)	19 (19%)	8 (16%)	11 (22%)
Myalgias	3 (3%)	1 (1%)	1 (2%)	0
Arrhythmia	6 (6%)	4 (4%)	0	4 (8%)

Abbreviations: RD, lenalidomide and dexamethasone; VRD, bortezomib, lenalidomide and dexamethasone.
Peripheral neuropathy data are described into the text (results/safety data).

was lower than that of the RD arm of the study, supporting a possible combination effect of bortezomib with RD in overriding some adverse prognostic features in myeloma. It has been suggested that bortezomib may be able to overcome the adverse impact of del13q (by FISH) in patients with relapsed or refractory MM in a retrospective analysis of the APEX/SUMMIT trials,[15] whereas bortezomib with dexamethasone could partly overcome the negative impact of t(4;14) in newly diagnosed, autologous stem cell transplantation-eligible patients.[21] Two recent reports suggested that t(4;14) may not be as important in patients with relapsed or refractory MM treated with RD. However, these reports had quite different conclusions about the importance of del13q: Reece *et al*.[18] suggested that RD overcomes the effect of del13q, whereas in the report of Avet-Loiseau *et al*. del13q (by FISH) was an independent poor prognostic factor. The differences between these studies and our data can be explained by several factors: (a) differences in the characteristics of the patients that were included, (b) the inclusion of additional CAs (amp1q, del17p) in our multivariate models, (c) the relatively low numbers of patients with t(4;14) or del17p in our analysis; (d) a trend to imbalance in the number of patients with del13q detected by karyotype between RD and VRD (1 vs 6 patients, respectively); (e) the different dosage of dexamethasone used in our VRD regimen compared with the original RVD[8] and (f) the major prognostic impact of resistance to previous therapy, high LDH and extramedullary disease, which may mitigate the impact of CAs in the analysis. Thus, in our analysis, del13q was strongly associated with the concomitant presence of other high risk CAs, such as amp1q21. Indeed, chromosome 1 abnormalities have been associated with del13q.[22] The incidence of 1q21 appears to be increased with more advanced disease[23] and altered transcriptional regulation of genes mapping to chromosome 1 is common in high-risk disease.[24] The importance of amp1q21 has been investigated in newly diagnosed patients treated with intensive therapies, with or without novel agents,[23,25] but this is the first report on the impact of amp1q21 in relapsed or refractory myeloma treated with RD or VRD.

The PFS of our VRD-treated patients (7 months) is similar to that reported by Richardson *et al*.[8] (6.9 months) for the phase 1 study of the lenalidomide with bortezomib combination. RD-treated patients had a median PFS of 9 months, which is shorter that the PFS in the phase 3 trials (11 months), but almost all our patients (97%) had been previously treated with thalidomide or bortezomib or both, and most of them were resistant to at least one, whereas 25% were resistant to both. Indeed, our results in thalidomide-resistant patients are similar to that of thalidomide-resistant patients treated in phase 2 or 3 trials. The median PFS of thalidomide refractory patients in MM009 and MM010 trials was 7 months (95% CI: 4.9–16.9),[26] the median PFS for thalidomide refractory patients in the report by Avet-Loiseau *et al*.[27] was 5.7 months, whereas the median time to progression in immunomodulatory drug refractory patients in the MMY-3001 study was 6 months for patients treated with bortezomib and pegylated liposomal doxorubicin and 5.5 months for those treated with bortezomib alone.[28] It is also interesting that the addition of bortezomib to RD could not overcome the major detrimental effect of previous thalidomide resistance. Although the hypothesis that there may be a cross-resistance for lenalidomide and thalidomide could explain to some extent the impact of thalidomide resistance to response after RD, it is difficult to support cross-resistance for thalidomide and bortezomib. Rather, thalidomide-resistance may indicate either selection of a resistant clone or may be an epiphenomenon due

to an inherently resistant clone. However, we did not find a significant impact of bortezomib resistance. In the report by Avet-Loiseau *et al*.[27] although earlier bortezomib use was associated with inferior PFS and OS in univariate, was not significant in multivariate analysis. The authors suggested that the OS of patients who had progressed on thalidomide was affected negatively, only if they also had received previous bortezomib. In our patients, thalidomide resistance was detrimental both in those who had and in those who did not have previous bortezomib. Thus, our data do not indicate that bortezomib treatment induces more resistant clones that may compromise outcome after subsequent therapies.

In our analysis, high LDH and the presence of extramedullary disease were independent prognostic factors for inferior response to therapy, shorter PFS and shorter OS. It is well-known that high LDH is present to approximately 10% of myeloma patients at diagnosis and predicts for poor survival in several studies.[29,30] Furthermore, in a recent analysis reported by the Greek Myeloma Study Group, LDH was found to be of prognostic value even in the era of novel agents. The median OS of high and normal LDH groups among 598 patients who received novel agents was 21 vs 51 months, respectively ($P<0.001$).[31] These data along with our results in the relapsed/refractory setting support the notion that serum LDH should be included in future phase 2/3 studies to evaluate its impact on the management of myeloma patients, as LDH prognostic value appears to be as important as that of more expensive and not so easily available parameters.

Extramedullary disease was also an independent prognostic factor in this analysis. Recently, the incidence of extramedullary disease, its relationship with previous exposure to high-dose therapy or novel agents, and its prognostic impact were analyzed in 1003 myeloma patients. In that study, the risk of extramedullary spread was not significantly increased after high-dose therapy, bortezomib or immunomodulatory drug-based therapies, but the presence of extramedullary disease was associated with shorter OS (Hazards ratio 3.26; $P<0.0001$) and PFS (Hazards ratio 1.46; $P=0.04$),[32] supporting the results of previous studies.[33] These data suggest that the presence of extramedullary disease has to be taken into consideration in the results of large phase 3 trials in order to reveal the best treatment options for these patients.

It was also very interesting that patients with low platelet counts had a shorter OS in our multivariate model. This result has also been described in studies that included patients who were treated with immunomodulatory drugs or bortezomib,[31,34] and supports the adverse prognostic impact of thrombocytopenia on survival in myeloma.

Patients who responded to therapy (PR or better) had a superior survival compared with nonresponders, whereas patients who achieved at least VGPR had better survival compared with patients who achieved PR. This result confirms data from the two major phase 3 studies on RD combination in relapsed/refractory myeloma, where OS was longer in patients with complete response/VGPR vs PR (median OS: not reached vs 44.2 months, $P=0.021$, respectively). Furthermore, the effect of at least VGPR on OS was irrespective of the time that it was achieved.[35] In bortezomib-based regimens, the response to therapy was also associated with longer survival.[36] These data suggest that VGPR/complete response may be a logical goal of therapy in patients with relapsed/refractory myeloma.

One of the limitations of our treatment strategy is the clinical randomization on the basis of peripheral neuropathy. The treatment plan was scheduled in this way because peripheral neuropathy is a very common problem when physicians have to decide for the management of their patients. In the phase 3 registration studies, patients with significant previous neuropathy were not included. However, our data suggest that even for patients with preexisting neuropathy, RD can still be a safe and effective treatment, with appropriate dose adjustments. In the VRD arm of our strategy, in which patients with no previous neuropathy were included, the presence of grade 3 peripheral neuropathy was 14% and no grade 4 peripheral neuropathy was observed. Although we used 1.0 mg/m^2 of bortezomib in our VRD regimen, the incidence of grade 3/4 peripheral neuropathy was similar with that observed with the dose of 1.3 mg/m^2 of bortezomib in other studies with bortezomib-based regimens[10,37] and higher than that observed with the same dosage of bortezomib-1.0 mg/m^2 in CREST trial (the incidence of peripheral neuropathy was 8%).[37] This may be due to the difference in study population and/or due to the presence of lenalidomide, which can produce severe peripheral neuropathy in 3% of MM patients when it is given as monotherapy[38] and in $<1\%$ when it is given in combination with dexamethasone[1] in the relapsed/refractory setting.

Our treatment also included patients with renal impairment: 25% had moderate or severe renal impairment with a CrCl of <50 ml/min, including 11% who had a CrCl of <30 ml/min. RD and VRD can be safely administered and are active in patients with poor renal function, provided that appropriate dose adjustments are made, as previously shown with RD.[39] Similarly, we also treated patients with impaired performance status (32% were PS 2 or 3) and elderly patients (46% of our patients were older than 70 years), and both RD and VRD were active and safe.

In conclusion, the presence of CAs is an important adverse prognostic factor for patients with relapsed or refractory myeloma, but resistance to previous therapy with novel agents, high LDH and extramedullary disease remain also of major prognostic importance. RD with or without bortezomib is active in heavily pretreated patients, but certain adverse features remain associated with poorer outcome; the addition of bortezomib perhaps overdrives the deleterious effect of these adverse features in some patients. However, the outcome of patients with del17p remains extremely poor. The optimal sequence or the concomitant administration of novel agents should be investigated through rationally designed randomized trials. Until then novel drugs and innovative treatment approaches are needed for very poor risk patients.

Conflict of interest

The authors declare no conflict of interest.

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