Lenalidomide and low-dose dexamethasone (Rd) versus bortezomib, melphalan, prednisone (VMP) in elderly newly diagnosed multiple myeloma patients: A comparison of two prospective trials

Lenalidomide and low-dose dexamethasone (Rd) versus bortezomib, melphalan, prednisone (VMP) in elderly newly diagnosed multiple myeloma patients: A comparison of two prospective trials

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Abstract

There are currently no direct head-to-head clinical trials evaluating bortezomib-melphalan-prednisone (VMP) versus lenalidomide and low-dose dexamethasone (Rd). VMP (257 cases) and Rd (222 cases) arms of two randomized phase III trials were employed to assess the treatment influence on outcome in untreated elderly MM patients.

Progression free survival (PFS) and overall survival (OS) were the primary and secondary end-points, respectively, and were investigated according to treatments administered over a 60-months follow-up period.

While VMP significantly reduced the disease progression rate between enrolment and 12 months of follow-up, no difference between the two schedules was found between 12 and 32 months. After 32 months, Rd-treated patients had a lower incidence of disease progression. A statistically significant higher OS rate was seen in the VMP arm, which was maintained after data adjustment for potential confounders. Both approaches showed acceptable toxicity profiles.

The profound tumor reduction by VMP over Rd justifies the initial higher PFS rate in favor of the bortezomib schedule, while the Rd regimen overcomes this evident initial drawback in reducing the tumor burden by long-term drug administration, gaining a subsequent improved disease control. VMP is associated with a significant reduced risk of death. This study may help physicians make a more informed therapy choice.

1 Introduction

Currently, the combinations of bortezomib, melphalan (M), and prednisone (P) (VMP) or MP and thalidomide (T) (MPT) represent the standard of care for untreated multiple myeloma (MM) patients over 65 years of age.[1] The VISTA trial showed that VMP was superior to MP, with risk reductions in progression (52%) and in death (31%).[2-4] Other large randomized trials confirmed the efficacy and safety of this schedule in this setting of patients.[5-8] Moreover, a reduced intensity schedule (once-weekly) of bortezomib[7, 8] and its subcutaneous administration[9] allowed a reduction in the incidence of peripheral neuropathy without any negative impact on efficacy. Recently, our group showed the superiority of VMP on MPT through a case-matched study in elderly untreated MM patients enrolled in six randomized trials.[10]

More recently, three phase III randomized trials have shown the safety and efficacy of the combination of lenalidomide and low-dose dexamethasone (Rd) as first line therapy for elderly MM patients.[11-13] Based on the results of one of these trials (FIRST MM-020)[11] the American Food and Drug Administration and the European Medicines Agency (EMA) have expanded the existing indication for lenalidomide in combination with dexamethasone to include newly diagnosed MM patients who are not eligible for transplant. Thus, the Rd combination represents a suitable alternative to VMP for the first line treatment of elderly MM patients.

No randomized trial comparing VMP versus Rd has been performed to date. In this analysis, we compared patient data, over a 60-month follow-up period, from two randomized phase III trials with the aim of assessing the impact of treatment on outcome as well as the effect modification by time on the treatment-outcome relationship in elderly untreated MM patients receiving VMP or Rd.

2 Methods

2.1 Patient selection

Patients >65 years of age with untreated MM, ineligible for autologous transplantation, enrolled in the VMP arm of the GIMEMA-MM0305 trial or in the Rd arm of the European Myeloma Network-01 (EMN-01) trial were evaluated.[5, 6, 13] From May 2006 to January 2009 a total of 511 patients were enrolled in the GIMEMA-MM0305 trial; 257 patients were randomized to receive nine 6-week cycles of VMP (oral melphalan 9 mg/m2 on days 1 to 4; oral prednisone 60 mg/m2 on days 1 to 4; intravenous bortezomib 1.3 mg/m2 on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5–9; after the inclusion of the first 139 patients, the schedule was changed to nine 5-week cycles and bortezomib dose was modified to 1.3 mg/m2 on days 1, 8, 15, and 22 during cycles 1–9).[5, 6] While, between August 2009 and September 2012, a total of 662 patients were enrolled in the EMN-01 trial; 222 of these patients were randomly allocated to receive Rd (lenalidomide 25 mg/day for 21 days; dexamethasone 40 mg on days 1, 8, 15, 22 in patients 65–75 years old and 20 mg in those >75 years; after induction, patients were randomized to receive maintenance treatment with lenalidomide alone at 10 mg on days 1–21 every 28 days, or in combination with prednisone at 25 mg every other day continuously).[13] Overall, 257 patients received VMP and 222 Rd. More specifically, 191/257 cases received bortezomib once-weekly, and 66 received twice-weekly doses for the first few cycles (range 1–4 cycles) and were then

subsequently switched to once-weekly doses. Patients were treated between 2006 and 2012 with median follow-up of 40 months (range 1–101) for the entire cohort, 39 (1–61) for the Rd group, and 51 (1–101) for the VMP group. Primary and secondary endpoints were progression free survival (PFS) and overall survival (OS), respectively. The response to treatment was defined by using the International Uniform Response Criteria.[14] The institutional review board at each participating center approved trials, which were performed in accordance with the Declaration of Helsinki. All patients provided written informed consent. Trials were registered at ClinicalTrials.gov or controlled-trials.com, NCT01063179[5, 6] and NCT01093196,[13] respectively.

2.2 Assessment

The following data were collected at each participating center, sent to a centralized coordinating center, reviewed for consistency and completeness, and entered into a new database: age, sex, creatinine value, ISS score, ECOG performance status, cytogenetic abnormalities determined by FISH analysis, serum calcium and Ig isotype; date of progression or date of last follow-up; date of death or of last follow-up; best response achievement, grade of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for AEs, v3.0. Responses were assessed using IMWG criteria.[14]

2.3 Statistical analysis

Patients were analyzed on an intention-to-treat basis for all time-to-event end points. OS was defined as the time from study entry to death due to any cause, PFS as the time from study entry until progression or death due to myeloma; in both cases, patients still alive were censored at the date of last contact.

PFS and OS rates were estimated using the method of Kaplan-Meier.[15] PFS and OS survival curves for VMP and Rd arms were compared using the log-rank test. Univariate and multiple Cox regression models were used to assess the effect of covariates on PFS and OS.[16] The proportionally assumption (i.e., the homogeneity across time of the hazard ratio (HR) of VMP versus RD on PFS was tested by visual inspection of the survival curves and a violation of this assumption was found at 32 months (Figure 1-bottom panel). The effect modification by time on the efficacy of VMP versus Rd of PFS was investigated by considering a predefined time interval (from enrolment to 12 months) as well as the time spanning from 12 to 32 months and from 32 months onwards, 32 months being the point in time in which the two survival curves crossed (Figure 1-bottom panel). In Cox models evaluating PFS we introduced treatment (VMP vs. RD), the above-mentioned time intervals and the treatment × time intervals interaction term, as well as a series of potential confounders (i.e., all variables that resulted to be significantly related to study outcomes with $P < .05$ at univariate Cox analyses). The time-specific HRs (VMP vs. RD) and the corresponding 95% Confidence Interval (CI) were calculated by the linear combination method. No time by treatment interaction was found for all-cause mortality. The choice of a 60-month follow-up for both cohorts was dictated by the fact that, although a longer (about 100 months) follow-up period was available for the VMP cohort,[6] the comparison of the effects of the two treatments on study outcomes according to time (treatment × time interaction) demands to be investigated over a similar time period. Because the RD cohort had a 60-month follow-up, the follow-up of the VMP cohort was thus similarly evaluated at this time. In multiple Cox models for OS, the allocation arm (VMP vs. RD) was adjusted for all univariate

correlates of all-cause mortality. Given the fact that cytogenetic risk data were available for only 369 patients, the potential confounding effect of this variable on the study results was tested in the subgroup of patients having available data for this variable. Data were expressed as HR, 95% CI and P-value. Response rates and safety were analyzed in patients who received at least one dose of study drugs. Patient characteristics were compared using the Pearson $\chi 2$ test for categorical variables and the Mann-Whitney test for continuous variables. All reported P-values were two-sided, at the conventional 5% significance level. Data were analyzed by IBM SPSS (v20.0.0, IBM Corporation, New York).

3 Results

Baseline characteristics were well-balanced between the two groups, although a significantly higher percentage of cases with worse ECOG performance status and with elevated creatinine value were present in the VMP group, while a significantly higher rate of elderly patients (age ≥75 years) were observed in the Rd group (Table 1).

3.1 Response rate

Four patients in the VMP (2 for physician choice, 1 for withdrawal of consent, and 1 for progressive disease) and ten in the Rd (5 for screening failure, 2 for death, 2 for withdrawal of consent and 1 for second primary malignancy) did not receive any chemotherapy and were excluded from the response and safety analyses.

After induction therapy the overall response rate (at least partial response, PR) was higher, although still not statistically significant, in the VMP arm: 81% with VMP and 74% with Rd (P = 0.074). While a statistically greater proportion of patients in the VMP group had a CR (VMP vs. Rd: 24% vs. 3%; P < .0001; Table 2). The rate of VGPR was similar in the two arms (VMP vs. Rd: 26 vs. 31%; P = .25; Table 2).

3.2 Survival analysis

During the follow-up period (median 32 months, interquartile range 10–32 months), 306 patients of 479 experienced disease progression or died. The total number of deaths was 111. In PFS analysis, a violation of the proportionality assumption was found at 32 months after enrollment (Figure 1, bottom panel) and for this reason time specific HRs needed to be calculated. Indeed, on both crude and adjusted Cox analyses (Figure 1, upper panel and Supporting Information Table S1a), time significantly modified the effect of VMP versus Rd on the PFS. In fact, VMP significantly reduced the incidence rate of disease progression as compared to Rd between enrolment and 12 months of follow-up (Figure 1, upper panel), whereas no difference between the two drugs was found between 12 and 32 months (Figure 1, upper panel). Of note, after 32 months of follow-up, patients treated with VMP had a shorter PFS than those on Rd (Figure 1, upper panel) indicating that time plays a crucial role in the interpretation of the effect of VMP versus Rd on the incidence rate of study outcome. A Cox analysis performed in the subgroup of patients with available cytogenetic risk data (n = 369) showed that the effect modification by time on the effect of VMP remained

significant (P = .039) also following adjustment for cytogenetic risk. A stratified analysis by treatment of the effect of cytogenetic risk on PFS showed that in the Rd arm patients with high cytogenetic risk had a HR of PFS, which was about two times higher (HR: 2.06, 95% CI: 1.36–3.12, P = .001) than those with standard cytogenetic risk (Supporting Information Figure S1, left panel). Vice-versa, in the VMP arm the cumulative PFS in patients with high cytogenetic risk overlapped with that of patients with standard cytogenetic risk (HR: 0.97, 95% CI: 0.64–1.48, P = 0.90) indicating that VMP treatment abrogated the risk excess predicted by the high cytogenetic risk variable (Supporting Information Figure 1, right panel) in our study population. A formal statistical test of the effect modification by treatment on the cytogenetic risk-PFS link showed that the two HRs (2.06 vs. 0.97) were statistically different (P = .005).

The analysis of the effect of study drugs on OS showed that the HR of VMP versus RD for OS was quite homogenous throughout time (Figure 2; no time by treatment interaction was found) and the higher efficacy of VMP as compared to Rd was maintained also after data adjustment for potential confounders (Supporting Information Table S1b). Again, a Cox analysis performed in the subgroup of patients with available cytogenetic risk data (n = 369) showed that the effect of VMP versus Rd remained significant (HR: 0.64, 95% CI: 0.41–1.00, P = .05) also by adjusting for cytogenetic risk.

3.3 Frequency of AEs

Rates of treatment-related death were similar between the VMP and Rd group: 7 patients (3%) died in the VMP group and 10 (4%) in the Rd. Likewise, the two groups did not differ significantly in the discontinuation rates due to AEs: 42/257 (17%) in the VMP group and 30/212 (14%) in the Rd. Supporting Information Table S2 lists the grade 3–4 AEs during induction. The incidence of any grade 3–4 hematologic AEs was significantly higher in the VMP arm (41 vs. 29%; P = .009). Severe anemia (10 vs. 4%; P = .031) and severe thrombocytopenia (20 vs. 7%; P < .0001) were more frequent with treatment by VMP. While, the rate of severe neutropenia was similar in the two groups (28% in the VMP group and 25% in the Rd). The rate of non-hematologic AEs was 33% in VMP and 30% in Rd patients. A significantly higher rate of grade 3–4 sensory neuropathy and/or neuralgia was reported in VMP cases (12 vs. 2%; P < .0001). While, the distribution of other nonhematological grade 3–4 AEs was similar in the two groups. The incidence of severe infections was 9% in both arms.

4 Discussion

In the absence of available randomized clinical trials directly comparing MPT versus VMP, our group performed a case-matched study on elderly untreated MM patients enrolled in six randomized trials, demonstrating the superiority of VMP over MPT.[10] Similarly, there are currently no direct head-to-head clinical trials evaluating Rd versus VMP. In this study, we compared patient data from VMP and Rd arms of two randomized phase III trials with the aim of assessing the impact of the specific treatment on outcome in elderly untreated MM patients.

In this retrospective analysis data, 479 patients (257 receiving VMP and 222 Rd) were analyzed. Over a pre-defined 60-months follow-up period, VMP was associated with a significantly higher CR rate and with a trend toward significance for ORR. VMP was also associated with a significant reduced risk of progression for the first 12 months after therapy start. After this period and up to 32 months follow-up no statistically significant differences in terms of PFS were observed between the two schedules; vice versa, after 32 months, Rd showed a statistically significant benefit in PFS. These results are likely related to the ability for deeper tumor shrinkage (higher CR rate) by VMP than Rd approach allowing a longer PFS initially, while the Rd schedule, overcomes this evident initial hitch in reducing the tumor burden, through long term drug administration (continuous therapy), thus obtaining a subsequent better disease control. Nevertheless, although a late advantage in terms of PFS has been observed for Rd, VMP was associated with a significant longer OS. In order to interpret these data we should consider that most patients treated with VMP in first line received lenalidomide-containing regimens in second line and vice-versa. Thus, we can speculate that, in light of available data regarding clonal evolution in MM, the V-R sequence seems to be more effective in controlling the emergence of resistant clones compared with R-V. Moreover, we must also consider that the Rd group consisted of a significantly higher number of elderly patients, although this is offset by the fact that the VMP group is characterized by a significantly higher number of cases with worse ECOG performance status and impaired renal function.

Furthermore, despite evident limitations due to missing data, the VMP schedule allowed to overcome the negative impact of high cytogenetic risk on PFS.

Both the toxicity profiles of VMP and Rd and treatment-related deaths were quite similar in the two groups. The overall incidence of grade 3–4 hematologic AEs was significantly higher in VMP patients, especially the incidence of thrombocytopenia. The incidence of grade 3–4 sensory neuropathy and/or neuralgia was significantly higher in the VMP group. Subcutaneous bortezomib could further improve the drug toxicity profile.[9]

As alluded to above, to date there have been no direct head-to-head randomized clinical trials comparing the effect of Rd versus VMP on improvement of PFS and reducing mortality in patients with MM. Recently, a network meta-analysis (i.e., a relatively new statistical technique to simultaneously evaluate the comparative efficacy of multiple treatment options through the use of direct and indirect comparisons) reported the superiority of Rd versus VMP; Rd being associated with a significant PFS and survival advantage versus other first-line treatments (VMP, MPT, MP).[17] The results of our study are only partially in line with those reported in Weisel's network meta-analysis because we found, using an effect-modification analysis having time as an effect modifier, that Rd is superior to VMP only after 32 months of follow-up. However, an effect modification promoted by a potential effect-modifier can only be studied when individual data is available, and for this reason, it is not testable on aggregated data such as those used in a network meta-analysis, which assumes, by definition, no interaction with time. Furthermore, despite the growing use of network meta-analysis in many fields of medicine, several issues need to be addressed to avoid conclusions that are inaccurate, invalid, or not clearly justified. Transitivity is the main basic assumption underlying a network meta-analysis. For the transitivity criterion to hold, studies making different direct comparisons must be sufficiently similar in all aspects except for the treatments being

compared, an assumption, which is largely unlikely to be verified in Weisel's network meta-analysis. In other words, randomization “within studies” included in the network meta-analysis does not imply randomization “among studies.” Thus, heterogeneity in baseline characteristics (i.e., the presence of confounding factors) among studies included in Weisel's network meta-analysis could explain the superiority of Rd versus VMP for OS, a result that contrasts with that emerging from our study, in which we found an advantage of VMP compared with Rd for OS. In our study, we adequately controlled for potential confounders while comparing the effect of Rd and VMP on OS whereas this is impossible to do in the setting of a network meta-analysis.

VMP could theoretically be preferred to Rd considering that most of the emerging second-line three-drug protocols contain Rd as backbone, foreseeing a potential reduced efficacy for patients already exposed to an IMID. However, the treatment effect, as evaluated by HRs, is generally consistent regardless of prior treatment with a proteasome inhibitor, which is quite expected, or IMID across all recent protocols, in which new proteasome inhibitors[18, 19] or monoclonal antibodies[20, 21] were combined with Rd. In the light of our results, we can speculate that an induction with a bortezomib-containing regimen followed by maintenance with an IMiD may provide the best long-term outcome.

Finally, the use of the VMP schedule in clinical practice should be considered mainly for patients with a significant tumor mass who need a relatively rapid reduction, as well as for those patients with renal impairment and at high cytogenetic risk. Conversely, Rd also finds wide therapeutic application especially in the remaining patients or in cases where patients may face difficulties in reaching the hospital for treatment.

In conclusion, given the limits of this analysis, such as heterogeneity in the patient population and the lack of relevant data (postrelapse treatment and comorbidity) this is the first direct comparison between the two schedules. In light of our results, Rd seems to be associated to better PFS in the long term, while VMP seems to be linked to a longer OS. Both therapeutic approaches show an acceptable toxicity profile. Nonetheless, this head-to-head retrospective study of the two schedules may help physicians make a more informed therapy choice.

Conflicts of interest

Authors disclosures of potential conflicts of interest Employment or Leadership Position: Antonio Palumbo, Takeda

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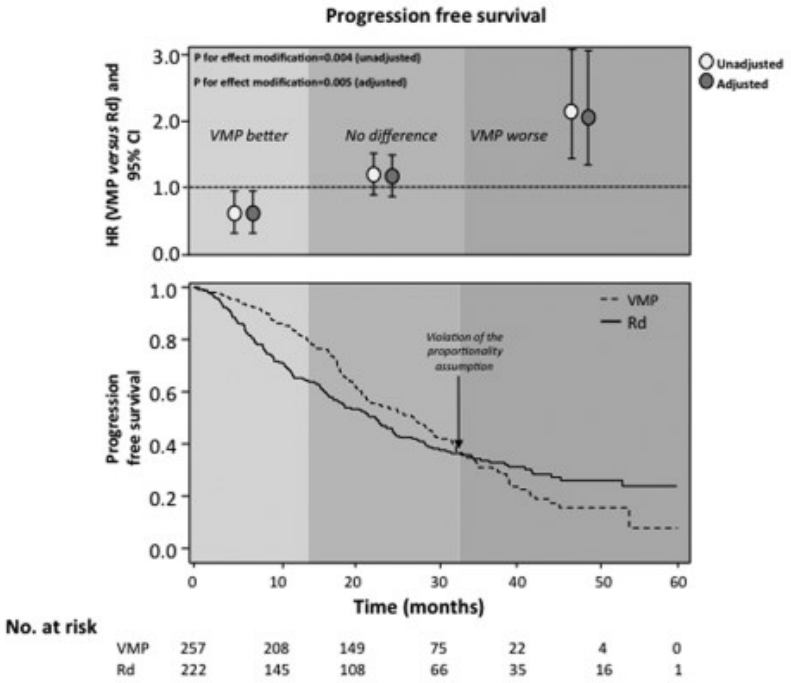

Figure 1. Bottom panel: Kaplan-Meier survival curves for PFS in VMP and Rd treated patients. The arrow indicates the point in time (32 months) at which a violation of the proportionality assumption clearly occurs. Upper panel: HR (and 95% CI) of the effect of VMP versus Rd at predefined points in time (≤12 months; 12.1–32 months; >32 months; see Methods – Statistical Analysis). White circles are unadjusted and gray circles are adjusted HRs (see Supporting Information Table S1b and text for more details)

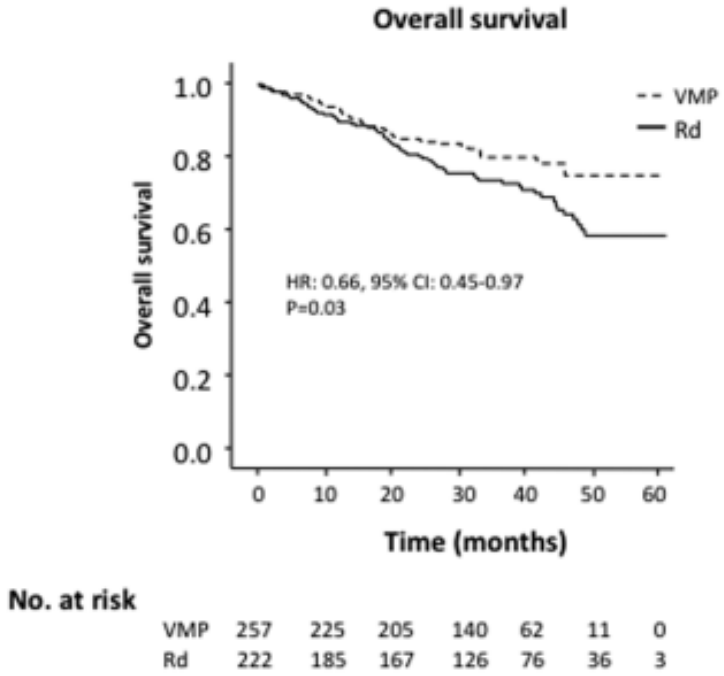

Figure 2. Kaplan-Meier survival analysis of OS in VMP and Rd-treated patients. Data are HR, 95% CI and P value

Table 1. Baseline characteristics of patients

	VMP (*n* = 257)		Rd (*n* = 222)		
Variable	***n***	**%**	***n***	**%**	***P*** [a]
Age (years)					
Median	71		73		
IQR	68–75		70–77		
≥75	69	27	83	37	0.014
Male (sex)	122	47	108	49	0.85
Isotype					
IgG	147	59	141	66	
IgA	67	27	51	24	0.12
Light chain	37	15	19	9	
IgE	0	0	1	0.5	
Data missing	6	2	0	0	
International Staging System stage					
I	56	28	62	28	
II	88	44	99	45	0.85
III	57	28	60	27	
Missing data	56	22	1	0.004	
ECOG Performance Status[a]					

	VMP (*n* = 257)		Rd (*n* = 222)		
Variable	***n***	**%**	***n***	**%**	***P*** [a]
0–1	156	61	190	90	<0.0001
2–3	101	39	22	10	
Creatinine					
Median	1.01		0.95		
≥ 1.2 mg/dL	79	31	41	19	0.008
Missing data	0		6	3	
Albumin					
Median	3.75		3.7		
≤3.5 (mg/dL)	83	37	80	36	0.88
Missing data	34	13	1	0.5	
ß2-microglobulin					
Median	4.0		3.86		
≥3.5 (mg/L)	125	60	131	59	0.9
Missing Data	48	19	1	0.5	
Cytogenetic abnormalities (FISH)					
High risk[b]	55	30	47	25	0.85
Missing data	73	28	37	14	

a *P* vaues have been calculated using cases with available data for each characteristic.

b At least one among deletion17p (del17) or translocation (4;14) [t(4;14)] or translocation (14;16) [t(14;16)].

IQR, interquartile range; ISS, International Staging System; ECOG, Eastern Cooperative Oncology Group; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone.

Table 2. Response rate

Response	**VMP (*n* = 253)**	**Rd (*n* = 212)**	***P*-value**
	***n* (%)**	***n* (%)**	
VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone.			
Best response according to International Uniform Response Criteria			
Complete, very good partial or partial response	205 (81)	157 (74.0)	0.074
Complete response	61 (24)	6 (3)	<0.0001
Very good partial response	65 (26)	65 (31)	
Partial response	79 (31)	86 (41)	
Stable disease	43 (17)	49 (23)	
Progressive disease	2 (1)	1 (0.5)	
Not available	3 (1)	5 (2)	