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Salvage therapy in first relapse: a retrospective study in a large patient population with Multiple Myeloma

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Running title

Retrospective analysis of treatment of multiple myeloma patients in first relapse

Summary

OBJECTIVE: There is no strong evidence to guide therapeutic approach to multiple myeloma (MM) patients who experience first relapse. The treatment choice can be difficult since currently all patients are exposed to novel agents as thalidomide, bortezomib and lenalidomide.

METHODS: In this retrospective analysis, we evaluated the best therapeutic sequence, the role of retreatment, and the most beneficial cutoff of first remission in order to choose retreatment, analyzing 476 patients relapsed after first-line therapy.

RESULTS: Bortezomib-based regimens upfront followed by lenalidomide-based regimens at first relapse resulted in significantly better second progression-free survival (2ndPFS), PFS2, and overall survival (OS) compared to the opposite sequence. Changing therapy resulted in significantly better 2ndPFS in the whole population, whereas PFS2 was significantly longer only in patients who underwent maintenance therapy. Moreover, until PFS1 was shorter than 27 months, changing therapy at first relapse significantly extended 2ndPFS and PFS2 compared to retreatment, whereas similar outcomes were observed between the two strategies, when PFS1 was longer than 27 months.

CONCLUSION: Lacking randomized trials, our study could help to choose the most appropriate therapy algorithm in patients with MM.

Key words: bortezomib; first relapse; lenalidomide; multiple myeloma

Introduction

In the last few years, progression-free survival (PFS) and overall survival (OS) have significantly improved in patients with newly diagnosed Multiple Myeloma (MM) due to the availability of new effective drugs, such as thalidomide, bortezomib and lenalidomide, and the improved supportive care (Brenner *et al*, 2008; Kumar *et al*, 2008). Yet, the vast majority of MM patients eventually relapse. Outcome of relapsed-refractory MM has improved after the introduction of novel combinations such as lenalidomide-dexamethasone (Rd) (Dimopoulos *et al*, 2007; Weber *et al*, 2007), bortezomib-dexamethasone (VD) (Jagannath *et al*, 2004; Jagannath *et al*, 2006; Mikhael *et al*, 2008; Dimopoulos *et al*, 2015a) and bortezomib-doxorubicin (V-doxo) (Orlowski *et al*, 2007). However, there are no clear recommendations about the choice of salvage therapy and one randomized study conducted in the relapse setting demonstrated the superiority of the triplet bortezomib-thalidomide-dexamethasone (VTD) over the doublet thalidomide-dexamethasone (TD) (Garderet *et al*, 2012). Moreover, most of the patients enrolled in the registrational studies above (Richardson *et al*, 2005; Dimopoulos *et al*, 2007; Weber *et al*, 2007; Orlowski *et al*, 2007) had received old drugs upfront, while currently all patients are exposed to novel agents thalidomide, lenalidomide and bortezomib. Recently, phase II studies evaluating three-drug combinations containing bendamustine have reported interesting results, particularly in less advanced disease stages (Offidani *et al*, 2013; Ludwig *et al*, 2014; Rodon *et al*, 2015). However, whether two- or three-drug combinations should be preferred at relapse remains an open question.

The therapeutic approach to first relapse is of outstanding importance. Indeed. at this stage, therapy can still have a substantial impact on outcome.

Nevertheless, the selection of therapy in this setting is mainly empirical. To date, the toxicity and the efficacy of upfront therapies are considered the key factors to decide whether to treat patients with the same drug used at diagnosis or to change class of drug. To better evaluate the impact of first- and second-line therapies on outcome, the European Medicines Agency (European Medicines Agency, 2012) recommended to include PFS2, defined as the time from random assignment until the second disease progression or death, as endpoint in clinical trials. Since it is unlikely that randomized clinical trials will be performed to establish the best strategy in first relapse, a thorough analysis of recent salvage therapies used in clinical practice in patients previously exposed to new drugs will provide a valid guide to physicians.

In this retrospective study, we compared the results obtained with several combinations in a large population of patients with relapsed MM. We aimed to address some burning questions such as the best sequence of therapy, re-challenge with previous therapy vs. changing strategies, and the most appropriate number of drugs to be administered in first relapse.

Patients and Methods

Patient population

Patients with MM enrolled in two phase III prospective trials [bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide (VMPT-VT) vs. bortezomib-melphalan-prednisone (VMP) (NCT01063179); and melphalan-prednisone-lenalidomide (MPR) vs. high-dose melphalan (Mel-200) and transplantation (NCT00551928)] relapsed after first-line therapy and who underwent first salvage therapy were analyzed.

Study design

This is a retrospective study. Data about salvage therapies at first relapse for patients enrolled in the VMPT-VT vs. VMP and in the MPR vs. Mel-200 studies were collected. The aims were to describe and compare salvage therapies at first relapse, to analyze the best sequence of first/second-line therapy, to assess re-challenge with previous therapy vs. change of treatment, and to evaluate two- vs. three-drug approaches in terms of second PFS, PFS2 and OS.

Definitions

Second PFS (2ndPFS) was defined as the time from start of first salvage therapy to confirmed progressive disease (PD) or death from any cause.

PSF2 was defined as the time from start of first line therapy to confirmed PD or death from any cause after second-line therapy.

OS was defined as the time from diagnosis to death from any cause and post-relapse OS was defined as the time from start of second-line therapy to death from any cause.

Statistical analysis

Continuous and categorical data were summarized using descriptive statistics. Comparison between groups was performed by Chi-square test for contingency table for categorical variables and by Mann-Whitney test for continuous variables. The Kaplan-Meier product limit method was used to estimate survivorship functions for time-to-event endpoints (2ndPFS, PFS2 and OS). Log-rank test was used to compare outcomes between the two treatment groups. Per i due gruppi si intende “the two sequences of first/second-line therapy, namely lenalidomide upfront/bortezomib at first-relapse (L-B group) vs bortezomib upfront/lenalidomide at first-relapse (B-L group)”, giusto? Se sì, si potrebbe modificare come messo tra virgolette per evitare equivoci

SPSS System Version 20 was used for all statistical analyses.

Results

All population

We analyzed 476 patients who relapsed after first-line therapy and underwent salvage therapies including bortezomib (n = 136), lenalidomide (n = 142), thalidomide (n = 36), chemotherapy (n = 63), autologous stem-cell transplant (ASCT) (n = 92) and allogeneic transplant (n = 7). After a median follow-up of 51 months (range 0.7-81.5), median 2ndPFS, PFS2 and OS were 14 (95%CI = 11.8-16.1), 39.8 (95%CI = 36.8-42.9) and 71 (95%CI = 57-NR) months, respectively.

Subgroup analysis according to salvage therapies

Of 257 patients not eligible for transplantation, 15% received bortezomib (2ndPFS = 8.8 months), 50% lenalidomide (2ndPFS = 16.6 months), 12% thalidomide (2ndPFS = 8.6 months), and 21% chemotherapy (2ndPFS = 6.6 months) as salvage therapy at first relapse.

Of 219 younger patients eligible for transplantation, 44% received salvage therapy with bortezomib (2ndPFS = 7.2 months), 7% immunomodulatory drugs (IMiDs) (2ndPFS = 14.3 months), 41.5% bortezomib followed by ASCT (2ndPFS = 21.5 months), and 3% allogeneic transplant (2ndPFS = 35.7 months).

Subgroup analysis according to sequence of therapy

Fifty-six patients received lenalidomide-based induction followed by ASCT as frontline therapy and bortezomib-based regimen at first relapse (L-B group) whereas 130 patients received the opposite sequence, i.e. bortezomib-based front-line therapy followed by lenalidomide-based regimen at first relapse (B-L group). Patients who underwent ASCT as salvage therapy were excluded from the analysis. The two groups of patients were matched for the main characteristics as shown in the Table I.

The median 2ndPFS was 7.2 months in the L-B group vs. 16.6 months in the B-L group ($p<0.0001$) whereas the respective median PFS2 was 36.6 months vs. 51.7 months ($p<0.0001$) (Fig. 1A). The median OS was 45 months in the L-B group and 62.3 months in B-L group, with a 5-year OS of 50% vs. 65% ($p=0.015$) (Fig. 1B).

Subgroup analysis according to re-challenge vs. change of therapy

Out of 476 patients, 311 could be included in the analysis of re-challenge with previous therapy (group R) vs. change of therapy (group C), and patients received bortezomib- or lenalidomide-based treatment without transplantation at first relapse. Group R included 52 patients (17%) (37 patients received bortezomib-based and 15 lenalidomide-based treatments) whereas group C included 259 patients (83%) (162 patients treated with lenalidomide-based and 97 with bortezomib-based regimens). The 2 groups of patients were comparable for the main prognostic factors (Table II) and for follow-up (median: 57.3 *vs* 56.2 months). Group R received salvage therapy at a median time of

30.4 months from diagnosis/start of first-line treatment..?(4.2-64.4 months; <12 months = 4 patients; 12-24 months = 12 patients; > 24 months = 36 patients) while group C after a median time of 25.1 months (1.2-63.9 months; p = 0.001). In the whole population, the median 2ndPFS and PFS2 were 23.1 and 39.0 months, respectively. The median 2ndPFS was 8.8 months in group R compared with 12.7 months in group C (p=0.038) (Fig 2 A). The median PFS2 was 39.9 months in group R compared with 38.8 months in group C (p = 0.584) (Fig. 2 B). By considering the duration of PFS1 (≤ 27 months and > 27 months), in patients with PFS1 up to 27 months (xx patients in group C and yy patients in group R), 2ndPFS (10.2 months *vs.* 5.3 months; p=0.006) and PFS2 (29 *vs.* 24 months, p=0.080) were significantly longer for patients in group C compared with patients in group R . Among patients with PFS1 longer than 27 months (95 patients in group C and 31 patients in group R), 2ndPFS (16.6 months *vs* 16.3 months, p=0.614) and PFS2 (38.6 months *vs* 39.8 months; p = 0.584) were similar between the two therapeutic options (Fig. 3 A, B, C, D).

Subgroup analysis according to two- vs. three-drug combinations

One hundred and sixty-nine patients received two-drug combinations (TD: n = 17, Rd: n = 90, VD: n = 51LA SOMMA è 158 NON 169; è CORRETTO?), whereas 67 patients were treated with three-drug combinations (T-based: n = 7, L-based: n = 9, V-based: n = 51) as first salvage therapy without transplantation. The two groups of patients were comparable for the main prognostic factors except for age, since a higher proportion of older patients received two-drug combinations (Table III).

The median 2ndPFS was 12.2 months in patients who were treated with two-drug combinations compared with 8.1 months in patients who received three-drug combinations (p = 0.068). The median PFS2 was 40.5 and 41.5 months (p = 0.717) (Fig. 4 A), while the median OS was 71 months *vs* NR (p = 0.828), with two-drug and three-drug regimens respectively (Fig 4 B). By splitting the population into 3 groups, the median PFS2 was 35.7 months with VD, 41.5 months with three-drug combinations (p = 0.634) and 43.2 months with Rd (Rd *vs* VD, p = 0.045, Rd *vs* three-drug combinations, p = 0.261).

Discussion

Although many newer second-generation anti-myeloma agents have been evaluated for relapsed-refractory MM, in many European countries, nowadays, only thalidomide-, lenalidomide- and bortezomib-based therapies are available for clinical use in first relapse (Laubach *et al*, 2016). No treatment can be currently considered standard of care in relapsed MM and the choice of appropriate therapy is based on several factors, particularly outcome and toxicity of first-line treatment. When a patients relapses, the very first step is to decide whether re-treatment with the same agents, and in which combination, can be a valid therapeutic option.

Our study showed that, in first relapse, physicians prefer to change the class of new drugs. Indeed, less than 20% of patients received the same compound administered upfront. Moreover, although guidelines suggest using re-treatment with previous agents when remission duration is longer than 6 months, this strategy is mainly adopted with remission lasting more than 24 months. Changing therapy seems to be the preferable strategy as it significantly prolonged 2ndPFS and PFS2 in patients with PFS1 duration up to 27 months, whereas in patients with PFS1 longer than 27 months the two strategies (re-challenge with previous agents or changing therapy) were equivalent. Although confirmation from randomized studies is needed, our results support the concept that, in first relapse, re-challenge with previous agents is a sensible choice when PFS1 is longer than expected, and not based on *a priori* established PFS1 duration. Moreover, sequential strategies with new drugs used in the earlier phases of the disease showed to be more effective, because

drug resistance is unlikely to emerge in these stages. Some studies evaluated re-treatment with bortezomib or lenalidomide in relapsed/refractory MM. The prospective phase 2 RETRIEVE study (Petrucci *et al,* 2013) demonstrated the efficacy of re-challenging with bortezomib (± dexamethasone) in patients who had previously responded to, and relapsed ≥ 6 months after, prior bortezomib therapy. The median time from prior bortezomib was 13.9 months and the median TTP was not affected by the number of prior lines of therapy (8.4 months in patients who had received one prior therapy). Similar results were reported in a meta-analysis in relapsed and not refractory patients, where re-treatment with bortezomib induced a median TTP of 8.5 months (Knop *et al*, 2014). Our results are comparable to those reported in the previous studies (median 2PFS: 8.8 months). Re-challenge with lenalidomide is a possible option as well, as shown by a post-hoc analysis of relapsed patients enrolled in the MM-015 trial (Dimopoulos *et al*, 2015b).

Recent biological studies (Egan *et al*, 2012; Walker *et al*, 2012; Bianchi *et al*, 2014) on MM demonstrated a complex clonal heterogeneity at diagnosis and an unpredictable clonal evolution at relapse due to clonal competition in the marrow niche that may be strongly affected by prior therapies. Because of this unpredictable complexity, the choice of therapy at relapse is quite empirical. By definition, empirical therapy should be a broad-spectrum therapy and this consideration suggests that triplets may work better than doublets. Only one randomized study compared two-drug (TD) *vs* three-drug regimens (VTD) in first relapse (Garderet *et al*, 2012) and it demonstrated a significantly longer PFS in patients treated with triplet combination. However, 80% of patients enrolled in that study had never received new drugs and the remaining 20%

had received thalidomide. Therefore, such results are poorly informative in clinical practice, since nowadays all patients are exposed to bortezomib- or lenalidomide-based therapies. Our results showed that PFS was similar between two- or three-drug combinations. However, Rd was superior to VD and also to three-drug combinations. This suggests that changing drug at first relapse can be more effective than increasing the number of agents and also leads to better results compared with re-treating with previous agents. Nevertheless, adding a third agent such as bendamustine (Offidani *et al*, 2013; Ludwig *et al*, 2014; Rodon *et al*, 2015), panobinostat (Richardson *et al*, 2013; San-Miguel *et al*, 2014) or pomalidomide (Richardson *et al*, 2014) to VD seems to partially overcome the resistance to previous treatment with bortezomib.

Carfilzomib in combination with dexamethasone is approved in the Unites States and other countries for the treatment of relapsed/refractory MM. In the phase 3 ENDEAVOR study, carfilzomib-dexamethasone significantly improved PFS compared to VD (18.7 *vs* 9.4 months; HR = 0.53; p<0.0001) in patients with relapsed but not refractory MM (Dimopoulos *et al*, 2016). A recent subgroup analysis showed a median PFS of 22.2 months in patients who had received one prior therapy compared to 14.9 months in those with ≥ 2 prior lines and a PFS benefit with carfilzomib regardless of prior therapy (Moreau *et al*, 2015a). In a “real word” setting in which patients had received a median of 3 prior lines of therapy and nearly all patients had been exposed to bortezomib and lenalidomide and 66% were refractory to both agents, carfilzomib as part of two- or three-drug combinations (dexamethasone ± cyclophosphamide) induced a median PFS and OS of 4.9 and 12.2 months, respectively (Muchtar *et al*, 2015). Moreover, resistance to bortezomib and lenalidomide was found to

be a negative predictor of response (Muchtar *et al*, 2015), suggesting that novel second-in-class myeloma agents such as carfilzomib may not lead to excellent results when used in later lines. Triplet combinations including two novel agents such as carfilzomib, pomalidomide and dexamethasone (CPD) (Shah *et al*, 2015) could be able to overcome resistance to proteasome inhibitors and IMiDs. Carfilzomib and ixazomib, the first oral proteasome inhibitor to be evaluated in MM, combined with lenalidomide and dexamethasone led to a significant improvement in PFS if compared with Rd. This benefit was observed also in patients previously exposed to bortezomib and lenalidomide (Stewart *et al*, 2015; Moreau *et al*, 2015b). Similar findings were reported with the addition of elotuzumab to Rd. Elotuzumab was the first monoclonal antibody showing a PFS benefit in relapsed/refractory MM (Dimopoulos *et al*, 2015c).

The first two lines of therapy are considered of paramount importance for final outcome of MM since generally, at this stage, the disease is still sensitive to therapy, leading to longer remission duration. Nonetheless, the sequence of therapy could significantly affect PFS2, which considers the outcome of first- and second-line therapy. Our study demonstrated that bortezomib-based therapies in first-line followed by lenalidomide-based therapies in second-line significantly prolonged PFS2 and OS compared with the opposite sequence. This finding applies to either elderly or younger patients who underwent transplant upfront. In light of the last biological discoveries about clonal evolution in MM, it seems that B-L sequence is able to better control emergence of resistant clones compared with the L-B one.

In conclusion, our post-hoc analysis suggests that bortezomib-based therapy upfront followed by lenalidomide-based salvage therapy at first relapse is the

best approach both in elderly and in younger patients with MM. Re-treatment with previous agents should be considered when PFS1 is longer than what was expected with the regimen used. Using more than two drugs in first relapse does not seem to improve outcome compared with two agents only, although this may depend on the type of drug used in triplet combinations. However, it is likely that triplet combinations including second-generation new drugs will be more effective compared with those currently available. Since it is unlikely that randomized studies will be performed to answer the above questions, our results can be a valid help in everyday clinical practice to choose the most appropriate therapy in first relapse.

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Table I Main characteristics of patients according to the two sequences of therapy

Patient Characteristics	L-B (*n* = 56)	B-L (*n* = 130)	p
Myeloma subtype IgA heavy chain, *n* (%)	14 (25)	32 (24.5)	0.956
International Staging System III, *n* (%)	18 (32)	21 (21)	0.115
High-risk cytogenetics*, *n* (%)	13 (33)	24 (26)	0.400
Karnofsky score ≤ 70%, *n* (%)	13 (23)	41 (31.5)	0.251
Renal failure, *n* (%)	1 (2)	3 (2)	0.829
Extramedullary disease, *n* (%)	9 (16)	9 (13)	0.632
Maintenance therapy, *n* (%)	25 (45)	60 (46)	0.849
Follow-up, median (months)	48	54.5	

L, Lenalidomide; B, Bortezomib

* defined by the presence of t(4;14) and/or del(17p)

Table II Main characteristics of patients who were re-treated with previous agents or changed therapy at first relapse

Patient Characteristics	Group R (*n* = 52)	Group C (*n* = 259)	p
Myeloma subtype IgA heavy chain, *n* (%)	12 (23)	64 (25)	0.830
Age (older than 65 years), *n* (%)	37 (71)	156 (60)	0.139
International Staging System III, *n* (%)	11 (24)	60 (27)	0.687
High-risk cytogenetics*, *n* (%)	17 (37)	57 (31)	0.286
Renal failure, *n* (%)	2 (4)	6 (2.5)	0.156
Extramedullary disease, *n* (%)	7 (19)	27 (15)	0.486
Maintenance therapy, *n* (%)	15 (29)	102 (39)	0.152
Follow-up, median (months)	57.3	56.2	

R, patients re-treated with the same agent used at induction; C, patients who changed therapy

* defined by the presence of t(4;14) and/or del(17p)

Table III Main characteristics of patients who received 2- or 3-drug combinations at first relapse

Patient Characteristics	2-drug combinations (*n* = 169)	3-drug combinations (*n* = 67)	P
Myeloma subtype IgA heavy chain, *n* (%)	47 (28)	16 (24)	0.736
Age (older than 65 years), *n* (%)	117 (69)	34 (51)	0.003
International Staging System III, *n* (%)	34 (24)	17 825)	0.289
High-risk cytogenetics*, *n* (%)	37 (33)	17 (33)	0.970
Renal failure, *n* (%)	4 (2.5)	3 (4.5)	0.388
Extramedullary disease, *n* (%)	14 (13)	10 (18)	0.349
Maintenance therapy, *n* (%)	64 (38)	27 (39)	0.831
Follow-up, median (months)	50.4	49.2	

* defined by the presence of t(4;14) and/or del(17p)

FIGURE 1

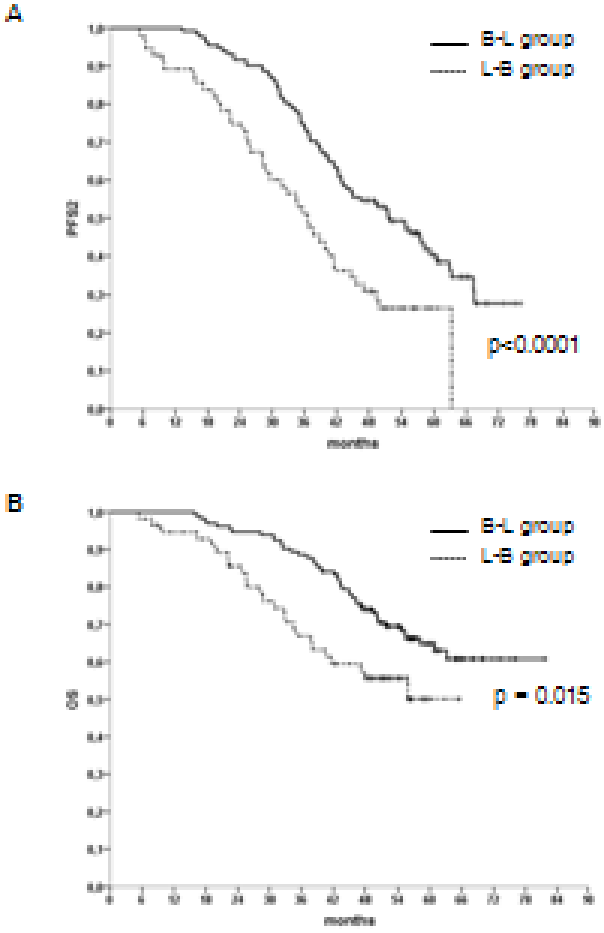

Fig. 1 PFS 2 (A) and OS (B) in patients receiving lenalidomide-based induction followed by regimens containing bortezomib at first relapse (L-B) and in those receiving the opposite sequence (B-L)

FIGURE 2

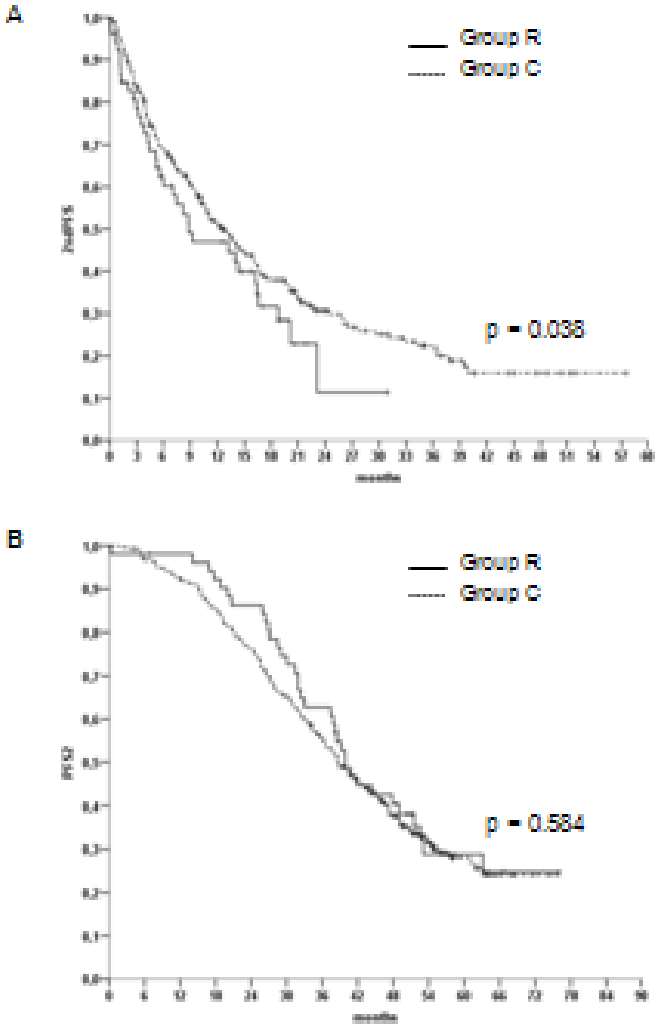

Fig. 2 2ndPFS (A) and PFS2 (B) in patients who received the same agent administerd upfront (group R) and in those who changed therapy (group C)

FIGURE 3

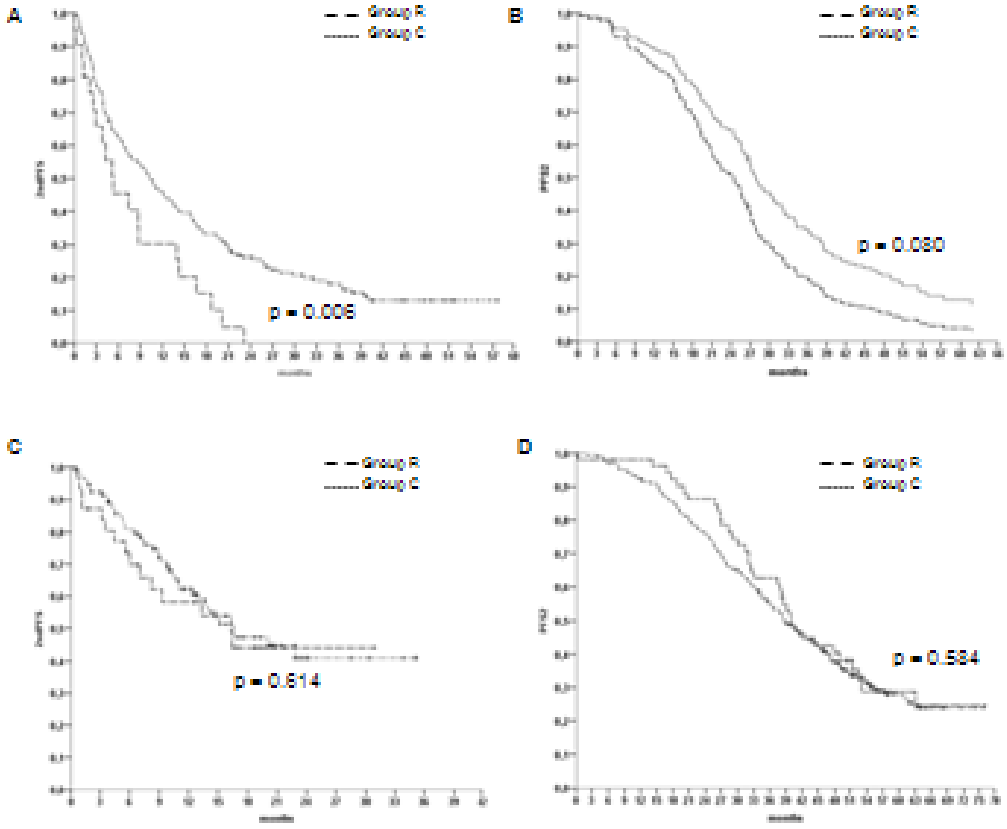

Fig. 3 2ndPFS and PFS2 in patients who received the same agent used upfront or were re-treated according to the duration of PFS1 up to 27 months (A) and (B) or longer than 27 months (C) and (D)

FIGURE 4

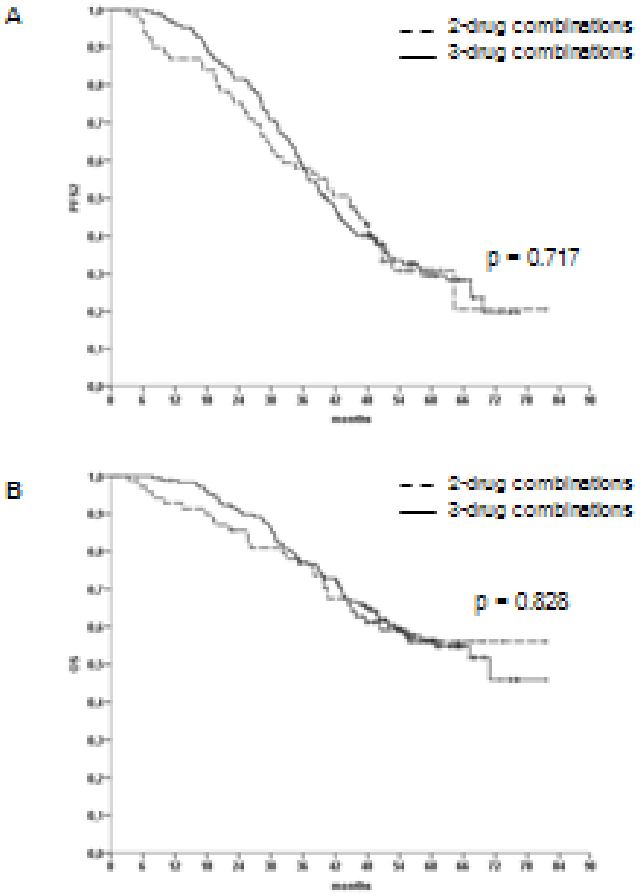

Fig. 4 PFS 2 (A) and OS (B) in patients receiving 2- or 3-drug combinations