DEXAMETHASONE, OXALIPLATIN AND CYTARABINE (R-DHAOX) AS SALVAGE AND STEM CELLS MOBILIZING THERAPY IN RELAPSED/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMAS.

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Abstract

Cisplatin-containing salvage regimens followed by autologous hematopoietic stem cell (HSC) transplantation are the current standard of care for relapsed or refractory (R/R) lymphomas. We retrospectively analyzed efficacy and stem cell mobilizing activity of oxaliplatin, cytarabine, dexamethasone and rituximab (R-DHAOX) in 53 R/R diffuse large B cell lymphomas (DLBCL) treated in our centre (median lines 2, range 2-5; median age 59, range 22-79). Hematological toxicity was manageable and no patients experienced renal impairment. After 2 courses the overall response rate was 60% (CR 49%, PR 11%). Median overall survival (OS) was 30.53 months (95% CI 11.5-49.55), 3-year OS 40.5%. Twenty-two eligible patients collected HSC and transplantation was performed in 21/22 patients (95%), after a median of 52 days from last cycle. Our results suggest that in DLBCL R-DHAOX has an excellent stem cell mobilizing capability, response rate comparable to cisplatin-containing regimens and good toxicity profile.

Key words: Oxaliplatin, refractory/relapsed diffuse large B cell lymphoma, salvage, stem cell mobilization

Introduction

Anthracycline-containing induction immunochemotherapy induces a high response rate in Diffuse Large B Cell Lymphomas (DLBCL) patients. 1-5 However, a significant fraction of patients is either refractory or relapses after an initial response. 6 Standard of care for younger patients with relapsed/refractory (R/R) DLBCL in good performance status is currently based on salvage chemotherapy followed by autologous stem cell transplantation (ASCT). 7 In this view, ideal, salvage chemotherapy regimen should be highly effective, tolerable and able to efficiently mobilize hemopoietic stem cells (HSC).

The most widely used salvage regimens include platinum, such as R-DHAP (rituximab, cisplatin, cytarabine, dexamethasone), R-ICE (rituximab, ifosfamide, carboplatin, etoposide), R-GDP (rituximab, cisplatin, gemcitabine, dexamethasone) or R-ESHAP (Rituximab, etoposide, methylprednisone, cytarabine, and cisplatin). 8-11

Although effective, cisplatin-containing regimens are often complicated by severe adverse events (SAEs), mainly renal impairment, but also mucositis and neuropathy. 12,13 These SAEs may lead to dose reduction and delay between courses and may also adversely impact the feasibility of subsequent ASCT, thus reducing the chance of cure. 14

Therefore, platinum-derived drug oxaliplatin was specifically designed to reduce the cisplatin-related toxicities, especially nephrotoxicity and mucositis and oxaliplatin-containing regimens were widely tested in solid tumours. 15

The experience in lymphoid malignancies is still limited 16-20 and few data are available on the anti-tumour efficacy of oxaliplatin in R/R DLBCL, whereas no data at all have been published on the feasibility of stem cell mobilization and collection in this

lymphoma subset.

After a previous experience with IEV (ifosfamide, epirubicine and etoposide) as salvage chemotherapy, 21 we adopted a modified R-DHAP regimen including oxaliplatin instead of cisplatin (R-DHAOx). 22 One hundred and three consecutive R/R lymphoma patients, including various histologies, were treated in our Centre from 2004 to 2014. In this paper we focus our analysis on efficacy, toxicity and stem cell mobilizing capacity of R-DHAOx in 53 DLBC lymphomas.

Materials and methods

Eligibility criteria and patient features

We treated 53 R/R DLBCL consecutive patients aged 18 years or older who were resistant or had relapsed after at least one anthracycline-containing regimen, (mostly R-CHOP). Inclusion criteria included eligibility for intensive chemotherapy as per Institutional guidelines, and an ECOG <3. Informed consent was obtained according to Helsinki declaration. Patients were treated from October 2004 to October 2014. The retrospective analysis was focused on toxicity, efficacy and mobilizing activity of R-DHAOx.

Forty-four patients (83%) were given R-DHAOx as second line therapy, 9 as third line or further (17%). The majority (N. 30, 56%) of patients were refractory to the previous regimen. Median duration of first CR for patients who received R-DHAOx for relapse was 11 months (range 4-32 months). Two patients had already received ASCT (4%). Patients' features are summarized in Tab. I.

Treatment Plan

R-DHAOX consisted of dexamethasone (40 mg/die on days 1-4), oxaliplatin (130 mg/sqm on day 1), cytarabine (2 g/sqm bid on day 2) with Rituximab 375 mg/sqm on day 2, repeated every 21 days. All patients received prophylactic subcutaneous G-CSF

(5µg/Kg/day) starting from day 8 until ANC >2 x 10^9/mmc. Patient attempting mobilization received G-CSF 5µg/Kg/day starting from day 8 until HSC collection. From 2013 outpatient administration of chemotherapy was planned.

Response assessment was performed after two courses. Patients achieving at least a partial remission (PR) were scheduled to receive 2 additional courses.

All patients younger than 65 years, achieving at least PR, without severe comorbidities and with 0-1 ECOG performance status were considered eligible for ASCT consolidation. HSC mobilization and collection were attempted after the third course of R-DHAOx. Monitoring of circulating HSC was started on day 10 from the beginning of chemotherapy; HSC collection was started if a minimum of 20 $CD34^+$ cells/uL was found in the peripheral blood. Plerixafor was administered if the target of circulating CD34+ count was not achieved at day 12. If an adequate amount of $CD34^+$ HSC (> 2 x10^6/Kg) was collected, ASCT with conventional BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning regimen was planned in all eligible patients achieving at least a PR. 2 Overall, patients received a median of 3 courses of R-DHAOx, with 95% of patients receiving at least 2 courses. The remaining 5% of patients showed disease progression after cycle 1 and therefore went off study.

Toxicity assessment

Renal and hepatic function were closely monitored in all patients during therapy. Toxicities and adverse events were defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

Definition of response and statistical analysis

Response to therapy was evaluated according to Lugano Classification and ESMO guidelines. 3,4

Complete Response (CR) required no residual FDG-PET uptake.

Partial Response (PR) required a decrease greater than 50% of FDG-PET uptake and of measurable lesions at CT (in the sum of the product of the perpendicular diameters).

Patients not fulfilling CR or PR criteria were defined as non-responders (NR). 3,4

Patients achieving at least PR after the previous regimen (and treated in relapse) were defined as having a chemo-sensitive disease.

Relapse free survival (RFS) was calculated from the time to documented CR to the eventual relapse.

Progression free survival (PFS) was calculated from the beginning of R-DHAOx to documented disease progression or death or last follow-up, whichever occurred first.

Overall survival (OS) was calculated from the beginning of R-DHAOx treatment until death due to any cause, or to the last follow up.

Continuous variables were compared using Student's T test or, where necessary, Wilcoxon's Rank test. Dichotomous variables were compared using the Chi-square test or, where necessary, Fisher's exact test.

Survival curves were built using the Kaplan Meier method, and univariate survival analysis was performed using the Log-rank test. For DFS evaluation in the whole cohort of patients and in the subgroup analysis for patients undergoing allogeneic bone marrow transplantation in CR1, a landmark analysis was performed at day 90, including all patients alive and achieving CR after one or two induction cycles. A Cox Proportional Hazard Model was built for multivariate survival analysis, including only the variables that respected proportional risk assumption. 23

Results

Response and Progression Free Survival

Overall response rate (ORR) after 2 courses was 60%, with 49% and 11% of patients achieving CR and PR, respectively. Notably, none of the PR patients achieved CR after the additional courses and none of the patients in CR showed loss of response during treatment. Response rate was significantly higher in patients treated for relapsed disease, compared to patients who showed resistance to the previous chemotherapy regimen (ORR 79% vs 45%, respectively, $p<0.01$, Tab. II). Disease burden at the time of R-DHAOx salvage correlated with ORR (80% for stage I/II vs 45% for stage III/IV, $p<0.05$, Tab. II). Patients with a lower IPI score had an higher ORR (93% vs 49% for patients with IPI score lower than 3 compared to 3 or higher, respectively, $p<0.03$, Tab. II). The number of previous lines of chemotherapy and patients age at time of treatment did not impact on ORR.

Multivariate regression analysis disclosed that chemosensitivity before DHAOx (i.e. relapsed vs resistant) was the only significant independent predictor of response ($p<0.05$, Tab. II).

In the whole cohort, 3-year PFS was 32.6% (Fig. 1A). If analysis was restricted only to responding patients, median PFS was not reached, three-year PFS was 59.6% (Fig. 1B). Patients receiving R-DHAOx for refractory disease had a significantly shorter PFS, if compared to patient treated for relapse after a previous CR (3-year PFS 48.9% vs 69.8%, respectively, $p<0.05$). Receiving R-DHAOx as third or further line of salvage, age at the time of treatment, IPI score and staging did not impact on PFS duration (data not shown).

Multivariate analysis showed that receiving R-DHAOx as salvage treatment after relapse from a previous CR rather than for refractory disease was the only independent predictor of longer PFS ($p<0.05$)

Toxicity

Non-hematological AEs of grade > 2 were observed in 18 patients (34%) (Table III). The most frequent were: neutropenic fever (11 patients), sepsis (1 patients), oral mucositis and other gastrointestinal events (3 patients), paraesthesia (2 patients) and atrial fibrillation in 1 patient. In 6 patients (11%) AEs required hospitalization. Seven patients (17%), treated in third or subsequent line, needed transfusion support, mainly packed red blood cell. No patients experienced renal impairment, grade III-IV neuropathy or ototoxicity of any grade. Of note, support with recombinant human erythropoiesis-stimulating factor was planned only on clinical bases.

HSC collection and ASCT

After two courses of chemotherapy, 22 patients were considered eligible for ASCT (41,5%). Thus, HSC mobilization was planned after the third R-DHAOx cycle, following G-CSF stimulation. Circulating $CD34^+$ cells peak was observed on day 14 (range: 10-16). After a median of 1 leukapheresis (range: 1-4), 22 out of 22 patients collected more than $2x10^6$ $CD34^+$ cells/kg; 18 (81%) collected more than $4x10^6$ $CD34^+$ cells/kg (median $6.4x10^6$ $CD34^+$ cells/kg). Only six patients (27%) collected less than $5x10^6$ $CD34^+$ cells/kg and only 1 patient required plerixafor administration to reach the minimum number of $CD34^+$ cells ($\geq$ 20/uL) to proceed to collection.

Among 22 patients who successfully collected HSC and were at least in PR after chemotherapy, ASCT was eventually performed in 21 (95%), after a median of 52 days

from last R-DHAOx (range 26-94). The patient who do not receive ASCT was in PR and showed disease progression before transplant.

Survival

After a median follow-up of 62 months, 26 patients died (49.1%), mostly because of disease recurrence (25/26, 96%). Median overall survival (OS) was 30.53 months (95% CI 11.5-49.55 months), and three-year OS was 40.5% (Fig. 2). Tab. IV reports factors affecting OS. Response to R-DHAOx significantly correlated with OS (3-year OS 69.7% and 9.4% for patient in CR or less than CR, respectively, $p<0.01$). Achieving a PR was correlated with longer OS if compared to SD or NR (3-year OS 22.2% and 9.4% for patient achieving PR vs SD or NR, respectively, $p<0.05$).

Higher IPI score (3-year OS 67.9% and 30.8%, for patients with IPI score lower or equal/greater than three, respectively, $p<0.03$) and advanced stage disease (3-year OS 60.9% and 28.5%, for stage I/II and III/IV, respectively, $p<0.03$) were both related to shorter survival. Neither age at the time of treatment nor chemosensitivity to previous chemotherapy regimens or number or previous lines of chemotherapy did impact on OS duration.

In multivariate analysis, achieving a CR after R-DHAOx was the strongest, independent, predictor of OS duration ($p<0.003$).

Discussion

Our retrospective study shows that R-DHAOx is a well-tolerated and effective salvage regimen for R/R DLCBL and allows optimal HSC collection. Indeed, no severe renal, neurological or GI adverse events, that are usually described with DHAP, were reported 11. This is consistent with previous studies investigating oxaliplatin administration in R/R

lymphomas. 20

In the attempt of avoiding cytarabine-related myelosuppression, the association of gemcitabine, cisplatin and dexamethasone (GDP) has been compared to DHAP in a randomized trial for patients with R/R lymphomas. 12-14 GDP +/- rituximab resulted in a similar response rate than DHAP with less myelosuppression. Progression free survival with GDP was comparable to that reported with other platinum-based regimens, such as R-ICE and R-DHAP. In our study, three-years progression-free survival (PFS) with R-DHAOx was 32.6% in the whole cohort (59.6% in responding patients) compared to 42%, 31% and 28% for R-DHAP, R-ICE and R-GDP, respectively. 24

Only a few studies are available on oxaliplatin-containing salvage regimens in NHL patients. Lacout et al. reported, in an abstract form, on R-DHAOx administration in a similar cohort of patients, with comparable efficacy and safety profile. 19

A similar regimen (Rituximab, oxaliplatin, cytosine arabinoside, dexamethasone, ROAD) but with different administration schedule was employed by Witzig et al., with similar response rate and toxicity. 18 However, the capacity of inducing HSC mobilization was not reported. Notably, in our study, the good safety profile allowed the administration of oxaliplatin-containing regimen to elderly patients (median age was 59 years and 28 were older than 65 years). Moreover, the short duration of drug infusion allowed to plan drug administration in the outpatient setting.

More recently, alternative regimens including novel drugs have been tested. lenalidomide-rituximab (ReRi) has shown very good tolerability profile and good efficacy in R/R DLBCL not originating from germinal center. 25,26 Indeed, by considering its good toxicity profile and manageability, R-DHAOx regimen could be the backbone of a novel chemotherapy incorporating lenalidomide or other novel drugs to

improve both response rate and feasibility. 27

To the best of our knowledge, no data are available on the HSC mobilizing capacity of oxaliplatin-containing regimen in R/R lymphoma patients. Indeed, in our study, all patients were able to successfully collect a sufficient amount of HSC to proceed to ASCT. Of note, the present results are at least comparable to what is observed with conventional cisplatin-based salvage regimens, 28 so that R-DHAOx can be considered an effective alternative for R/R DLBCL and HSC mobilization. Furthermore, due to the low rate of renal AEs and mucositis, almost all responding patients, who successfully collected HSC, eventually received transplantation without significant delay. This could be a major advantage if compared to cisplatin-containing regimen, where extra-hematological toxicities may limit subsequent ASCT consolidation. 28

In conclusion, with the limitations due to the small size of the cohort, the high response rate, coupled with the favourable toxicity profile and the good mobilizing capacity suggest that R-DHAOx may be an attractive option for R/R DLBCL patients.

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FB, MM designed the research.
MG and RML supervised the research.
LM, EC, FC and LG collected all data.
FG, PM and MC analyzed all data.
RM, MC, AC revised all adverse events reports.
LM, RM, MC, FG and PM wrote the manuscript.
RML, FB and MG revised the final version of the manuscript.
All authors approved the final version of the manuscript.

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1. Dunleavy K, Gross TG. Management of aggressive B-cell NHLs in the AYA population: an adult vs pediatric perspective. Blood 2018;132:369-375.
2. Caimi PF, Hill BT, Hsi ED, Smith MR. Clinical approach to diffuse large B cell lymphoma. Blood Rev 2016;30:477-491.
3. Ghielmini M, Vitolo U, Kimby E, et al. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol. 2013;24:561-76.
4. Dreyling M, Thieblemont C, Gallamini A et al. ESMO Consensus conferences: guidelines on malignantlymphoma. part 2: marginal zone lymphoma, mantle cell lymphoma, peripheral T-celllymphoma. Ann Oncol. 2013;24:857-77.
5. Feugier P, Van Hoof A, Sebban C, et al. . Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Grouped'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117-4126.
6. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. Cancer J Clin 2014;64:9-29
7. Tilly H, Dreyling M. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009;20 Suppl 4:110-112.
8. Crump M, Kuruvilla J, Couban S, et al. . Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014;32:3490-3496.
9. Hou Y, Wang HQ, Ba Y. Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma. Med Oncol 2012;29:2409-2416.
10. Ramzi M, Rezvani A, Dehghani M. GDP versus ESHAP Regimen in Relapsed and/or Refractory Hodgkin lymphoma: A Comparison Study. Int J Hematol Oncol Stem Cell Res 2015;9:10-14.
11. Schirmbeck NG, Mey UJ, Olivieri A, et al. . Salvage Chemotherapy with R-DHAP in Patients with Relapsed or Refractory Non-Hodgkin Lymphoma. Cancer Invest 2016;34:361-372.

12. Dilruba S, Kalayda GV. Platinum-based drugs: past, present and future. Cancer Chemother Pharmacol 2016;77:1103-1124.
13. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin Nephrotoxicity: A Review. Am J Med Sci.2007;334:115-124.
14. Peres LA, da Cunha AD, Jr. Acute nephrotoxicity of cisplatin: molecular mechanisms. J Bras Nefrol 2013;35:332-340.
15. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 2014;0:364-378.
16. Lisenko K, McClanahan F, Schoning T, et al. . Minimal renal toxicity after Rituximab DHAP with a modified cisplatin application scheme in patients with relapsed or refractory diffuse large B-cell lymphoma. BMC Cancer 2016;16:267.
17. Tixier F, Ranchon F, Iltis A, et al. .Comparative toxicities of 3 platinum-containing chemotherapy regimens in relapsed/refractory lymphoma patients. Hematol Oncol 2017;35:584-590.
18. Witzig TE, Johnston PB, LaPlant BR, et al. .Long-term follow-up of chemoimmunotherapy with rituximab, oxaliplatin, cytosine arabinoside, dexamethasone (ROAD) in patients with relapsed CD20+ B-cell non-Hodgkin lymphoma: Results of a study of the Mayo Clinic Cancer Center Research Consortium (MCCRC) MC0485 now known as academic and community cancer research united (ACCRU). Am J Hematol 2017;92:1004-1010.
19. Lacout C, De Vries M, Seegers-Thepot V, et al. (2015). R-DHA-Oxaliplatin Versus R-DHA-Cisplatin Regimen in B-Cell Nhl's Treatment: A Eight Years Retrospective Study. Blood, 126(23), 3959. Accessed February 21, 2019. Retrieved from http://www.bloodjournal.org/content/126/23/3959.
20. Eloit M, Iltis A, Thieblemont C, et al. Substitution of cisplatin for carboplatin or oxaliplatin in the DHAP regimen is associated with improved survival in relapsed/refractory non-Hodgkin’s lymphoma. 23th Annual Congress of the European Hematology Association; 2018 Jun 14-17, Stockholm, Sweden.
21. Clavio M, Garrone A, Pierri I, et al. Ifosfamide, epirubicin, etoposide (IEV) and autologous peripheral blood progenitor cell transplant: a feasible and effective salvage treatment for lymphoid malignancies. Oncol Rep 2005;14:933-40.
22. Rigacci L, Fabbri A, Puccini B, et al. Oxaliplatin-based chemotherapy (dexamethasone, high-dose cytarabine, and oxaliplatin) +/- rituximab is an

effective salvage regimen in patients with relapsed or refractory lymphoma. Cancer 2010;116:4573-4579.

23. Delgado J, Pereira A, Villamor N, et al. Survival analysis in hematologicmalignancies: recommendations for clinicians. Haematologica. 2014;99:1410-20.
24. Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. Br J Haematol 2018;182: 633-643.
25. Lisenko K, Cremer M, Schwarzbich MA, et al. Efficient Stem Cell Collection after Modified Cisplatin-Based Mobilization Chemotherapy in Patients with Diffuse Large B Cell Lymphoma. Biol Blood Marrow Transplant 2016;22:1397-1402.
26. Gini G, Bocci C, Sampaolo M, et al. A Combination of Lenalidomide and Rituximab (ReRi) As Salvage Therapy in Elderly Patients Affected By Diffuse Large B Cells (DLBCL) Lymphoma Relapsed and Refractory. Blood 2015;126, 5109.
27. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Leukemia 2013;27:1902-1909.
28. Chiappella A, Santambrogio E, Castellino A, Nicolosi M, Vitolo U. Integrating noveldrugs to chemoimmunotherapy in diffuse large B-celllymphoma. Expert Rev Hematol 2017;10:697-705.

Table I: Patient features

		Num.	%
DLBCL PATIENTS		**53**	-
Sex	Male	35	66
	Female	18	34
Age	Less than 65 years	39	74
	65 years or older	14	26
Number of previous lines	One	44	83
	Two	5	10
	Three or more	4	7
Setting	Relapsed	24	45
	Refractory	29	55
Stage	I or II	19	36
	III or IV	28	64
IPI score	2 or less	14	26
	3 or more	39	74

Table II: Analysis of Response

		Num.	PR (%)	CR (%)	ORR (%)	p (univ.)	p (multiv.)
ALL PATIENTS		**53**	**6 (11)**	**26 (49)**	**32 (60)**	-	-
Setting	Relapsed	24	1 (4)	18 (75)	19 (79)	0.013	0.037
	Refractory	29	5 (17)	8 (28)	13 (45)		
Number of previous lines	One	44	4 (9)	22 (50)	26 (59)	1.000	-
	Two or more	9	2 (22)	4 (44)	6 (66)		
Age	Less than 65 years	39	3 (8)	19 (49)	22 (57)	0.362	-
	65 years or older	14	3 (21)	7 (50)	10 (71)		
IPI score	2 or less	14	2 (14)	11 (79)	13 (93)	0.004	0.053
	3 or more	39	4 (10)	15 (39)	19 (49)		
Stage	I or II	19	2 (10)	14 (70)	16 (80)	0.041	0.095
	III or IV	28	4 (12)	12 (36)	16 (48)		

Table III: Reported AEs

		Num.	GI (%)	Renal (%)	FUO (%)	Unplanned Admission (%)	Anemia or PLTpenia (%)
ALL PATIENTS		**53**	**4 (8)**	**0 (0)**	**11 (21)**	**6 (11)**	**7 (13)**
Setting	Relapsed	24	2 (8)	0 (0)	5 (21)	1 (4)	3 (13)
	Refractory	29	2 (7)	0 (0)	6 (21)	5 (17)	4 (8)
Number of previous lines	One	44	3 (7)	0 (0)	8 (18)	4 (9)	5(11)
	Two or more	9	1 (11)	0 (0)	3 (33)	2 (22)	2 (22)
Age	Less than 65 years	39	3 (8)	0 (0)	7 (18)	4 (10)	5 (13)
	65 years or older	14	1 (7)	0 (0)	4 (29)	2 (14)	2 (14)

Table IV: Overall Survival

		Dead (%)	Median OS (months)	3-years OS (%)	p (univ.)	p (multiv.)
ALL PATIENTS		**26 (49)**	**30.5**	**40.5**	**-**	**-**
Setting	Relapsed	10 (47)	30.5	49.4	0.263	-
	Refractory	16 (53)	19.9	32.7		
Number of previous lines	One	20 (46)	30.5	44.0	0.485	-
	Two or more	6 (67)	20.0	27.8		
Age	Less than 65 years	18 (46)	32.8	42.4	0.458	-
	65 years or older	8 (57)	17.5	34.7		
IPI score	2 or less	3 (21)	NR	67.9	0.018	0.059
	3 or more	23 (59)	17	30.8		
Stage	I or II	5 (25)	NR	60.9	0.007	0.065
	III or IV	21 (64)	8.6	20.5		
Response	NR or SD	16 (76)	7.4	9.4	0.000	0.001
	PR	4 (67)	17.1	22.2		
	CR	6 (23)	NR	69.7		

Figure 1: Progression Free Survival (PFS)

1A: PFS in the whole cohort

1B: PFS in responding patients

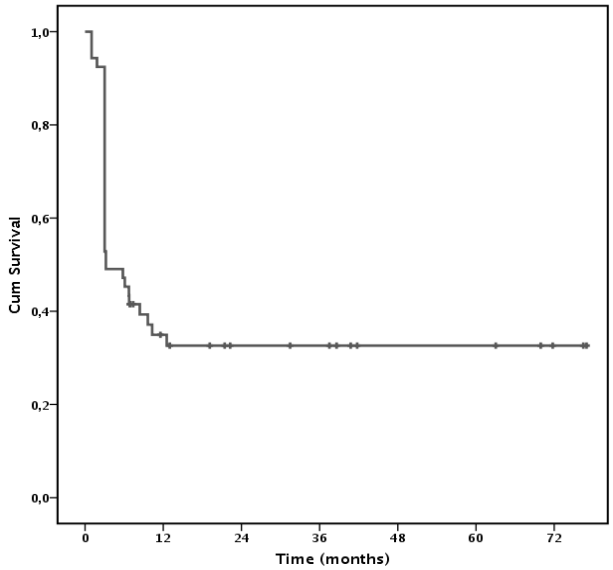

Figure 1A: PFS in all patients

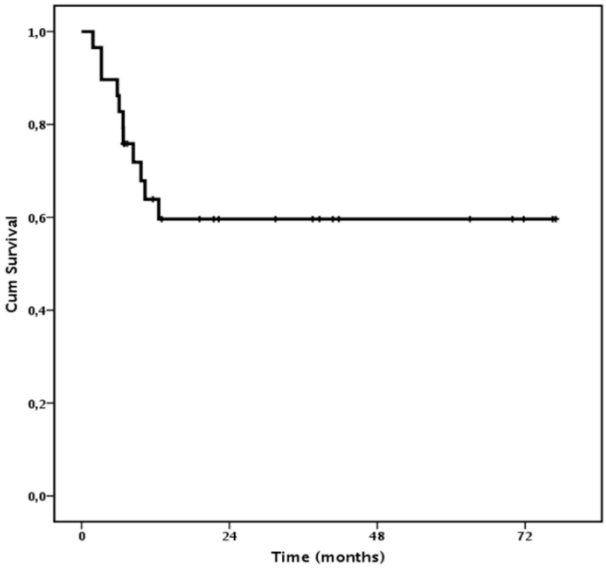

Figure 1B: PFS in responding patients

Figure 2: 3-years OS in all patients.