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Brentuximab Vedotin for recurrent Hodgkin lymphoma after allogeneic hematopoietic cell transplantation: a report from the EBMT Lymphoma Working Party

Running tittle: Brentuximab Vedotin post AlloSCT for HL

Ali Bazarbachi MD PhD [1]MD, Ariane Boumendil MD [2], Hervé Finel MD [2], Mohamad Mohty MD [3], Luca Castagna MD [4], Didier Blaise MD [5], Karl S Peggs MD [6], Boris Afanasyev MD [7], J.L. Diez-Martin MD [8], Paolo Corradini MD [9], David Michonneau MD [10], Stephen Robinson MD [11], Gonzalo Gutiérrez García MD [12], Francesca Bonifazi MD [13], Ibrahim Yakoub-Agha MD [14], Zafer Gülbas MD [15], Adrian Bloor MD [16], Jeremy Delage MD [17], Albert Esquirol MD [18], Ram Malladi MD [19], Christof Scheid MD [20], Jean El-Cheikh MD [1], Hervé Ghesquières MD [21], Silvia Montoto MD [22], Peter Dreger MD [23], Anna Sureda MD [24].

[1]Department of Internal Medicine/ American University of Beirut, Beirut, Lebanon.

[2]EBMT LWP Paris Office/ Hôpital Saint-Antoine, Paris, France.

[3]Service d'Hématologie et Thérapie Cellulaire/ Hôpital Saint Antoine, Sorbonne University, Paris, France.

[4] Istituto Clinico Humanitas, Rozzano Milano, Italy.

[5] Institut Paoli Calmettes, Marseille, France.

[6] University College London Hospital, London United Kingdom.

[7] First State Pavlov Medical University of St. Petersburg/ St. Petersburg ,Russia.

[8] Hospital Gregorio Marañón, Madrid, Spain.

[9] IRCCS Istituto Nazionale dei Tumori/ University of Milano, Milano, Italy.

[10] Hopital St. Louis, Paris, France.

[11]University Hospital Bristol, United Kingdom.

[12] Hospital Clinic, Barcelona, Spain.

[13] Hematology Department "Seràgnoli", S. Orsola-Malpighi University Hospital, Bologna, Italy

[14] CHU de Lille, LIRIC INSERM U995, Université Lille2, France.

[15] Anadolu Medical Center Hospital, Kocaeli, Turkey.

[16] Christie NHS Foundation Trust, Manchester, United Kingdom.

[17] CHU Lapeyronie, Montpellier, France.

[18] Hospital Santa Creu i Sant Pau, Barcelona, Spain.

[19] Queen Elizabeth Hospital, Birmingham, United Kingdom.

[20] Department of Internal Medicine/ University of Cologne, Cologne, Germany.

[21] Centre Hospitalier Lyon Sud, France.

[22] Department of Haemato-oncology/ St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom.

[23] Dept Medicine V/ University of Heidelberg, Heidelberg, Germany

[24] Department of Haematology/ Institut Catala d'Oncologia, Barcelona, Spain.

Running head: Brentuximab after allogeneic transplant in Hodgkin lymphoma

Correspondence:
Prof Ali Bazarbachi, MD, PhD
Department of Internal Medicine
American University of Beirut, Medical Center
P.O. Box 113-6044 Beirut, Lebanon
Tel: +961-361-2434
Fax: +961-134-5325
Email: bazarbac@aub.edu.lb

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Table of contents: BV is safe and effective salvage therapy for HL patients after allo-SCT even after prior exposure to BV. Post-transplant BV may synergize with immune interventions.

Key words: Hodgkin lymphoma, Brentuximab vedotin, allogeneic stem cell transplantation, relapse, donor lymphocyte infusion.

Abstract

Background: Treatment of patients with Hodgkin lymphoma (HL) progressing after allogeneic stem cell transplantation (allo-SCT) remains challenging.

Methods: We assessed outcomes in 184 adult patients with HL who relapsed or progressed after a matched related or unrelated allo-SCT at EBMT-participating centers between 2010 and 2014.

Results: Eighty patients who received Brentuximab Vedotin (BV) salvage (BV group) were compared with 104 patients who did not. Patients in the BV group were younger (median age: 30 versus 34 years) and more likely to receive pre-transplant BV (65% versus 46%) or post-transplant donor lymphocyte infusion (66% versus 33%). The two groups were otherwise comparable. Patients in the BV group received a median of 6 doses of post-transplant BV resulting in 29% complete remission, 45% partial response and 26% stable disease. Response to BV post allo-SCT was not affected by pre-transplant BV. Despite a longer median follow up for alive patients in the BV group (33 versus 23 months; $p<0{\cdot}001$), 34% of the original BV cohort were alive and in CR at last follow up versus 18% only in the no-BV group ($p=0{\cdot}003$). The use of BV before donor lymphocyte infusion was associated with the highest probability of being alive in CR (40%) at last follow-up. Salvage BV had no effect on chronic graft-versus-host-disease or 1-year overall survival from relapse post allo-SCT (76% versus 67%).

Conclusion: In conclusion, BV is a safe and effective salvage therapy for patients with HL relapsing or progressing after allo-SCT even after prior exposure to BV.

INTRODUCTION

Salvage chemotherapy and autologous stem cell transplantation (auto-SCT) results in the cure of around 50% of patients with Hodgkin lymphoma (HL) failing first line therapy.[1-4] However, patients who progress after auto-SCT have a poor outcome, with a median overall survival (OS) of around 1-2 years.[5-8] The use of brentuximab vedotin (BV) [9-11] or check point inhibitors [12-14] in this setting is associated with a high rate of response; however, most of the responses are not durable, with a median progression free survival (PFS) of less than one year. Therefore, allogeneic SCT (allo-SCT) is still considered as a potentially curative and widely used treatment modality for patients with HL who progress after auto-SCT [15-19]. Unfortunately, only about 25-40% of patients allografted after prior autograft achieve long-term disease control.

For patients who relapse or progress after allo-SCT, prognosis is dismal, and treatment is challenging, because most of them are heavily pretreated and often refractory to chemotherapy [16, 17, 20-23]. Check point inhibitors are increasingly used in this setting, and appear to be highly efficacious, although with conflicting safety results, as they may be complicated by the rapid onset of severe and treatment-refractory graft versus host disease (GVHD) [24, 25]. Anecdotal reports and a few small series suggest that BV, either alone [26, 27] or combined with donor lymphocyte infusion (DLI) [28] may be efficacious in the post allograft setting.

The purpose of this study was to assess the safety and efficacy of BV when given as salvage treatment for HL recurrence after allo-SCT, by comparing the outcome of patients who received BV salvage with that of patients who did not receive BV salvage, using a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

PATIENTS AND METHODS

Study design and data collection

This was a retrospective registry-based multicenter analysis. Data were provided and approved for this study by the Lymphoma Working Party (LWP) of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centers that are required to report all consecutive SCT and follow-up once a year. Audits are routinely performed to determine the accuracy of the data. Since January 1, 2003, all transplant centres have been required to obtain written informed consent prior to data registration with the EBMT, following the Helsinki Declaration of 1975.

Eligibility criteria for this analysis included adult patients (age >18 years) with classical HL who relapsed or progressed after a first allo-SCT performed between 2010 and 2014 from an HLA-matched related or unrelated donor with bone marrow (BM) or peripheral blood (PB) stem cells. Patients who received cord blood, mismatched or haploidentical stem cells and tandem transplants were excluded.

Variables collected included recipient and donor age and gender, date of diagnosis, lines and detailed type of therapy prior to allo-SCT, response to each individual treatment line, previous auto-SCT, date, duration and number of doses of pre-transplant BV, disease status at transplant (complete remission [CR], partial remission [PR] or active disease), performance status and comorbidity index, transplant related-factors including conditioning regimen, immunosuppression (*in vivo* T-cell depletion vs. none), GVHD prophylaxis, stem cell source (BM or PB) and donor type. Active disease was defined as not being in CR or PR including stable disease (SD), primary induction failure, primary refractory, or disease progression. Finally, we collected the date of relapse or progression after allo-SCT, the date of BV administration after allo-

SCT, the duration and number of BV doses, the response to BV, and additional cellular therapy such as DLI, acute and chronic GVHD, and disease status at last follow up.

Definitions

The histological diagnosis was based on local review, and patients were staged according to the Ann Arbor system. Disease status at transplantation was classified as CR, PR, or active disease. Disease status was assessed by each investigator according to the Revised Response Criteria [29] for Malignant Lymphoma and to the institutional standard of care. The intensity of conditioning regimens was defined as previously published [17].

Statistical analysis

Endpoints included response to BV, acute and chronic GVHD, and OS measured from the time of relapse post-allo-SCT. OS was defined as death from any cause. The probability of OS was calculated by using the Kaplan-Meier estimator. Comparison of OS for patients who received BV within 60 days from relapse and control patients was performed using a landmark curve starting at day 60 after relapse. For all prognostic analyses, continuous variables were categorized and the median used as the cut-off point. Univariate comparisons were performed using the log-rank test for OS. Use of BV post-transplant was analyzed as a time-dependent variable. A Cox proportional hazards model was used for multivariate regression. Factors known to influence the outcome and factors associated with a p value less than 0·10 with any endpoint by univariate analysis were included in the model. Results are expressed as hazard ratio (HR) with 95% confidence interval (CI). All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time to event outcomes.

All analyses were performed using R version 3·1·1 with the R packages survival version 2·38, cmprsk version 2·2-7 and Hmisc version 3·16-0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient and transplant characteristics

A total of 184 patients met the eligibility criteria for this study. The median age at diagnosis and at allo-SCT was 27 (IQR 21-37) and 31 years (IQR 25-40), respectively. Median age at SCT according to donor type was 30 years (IQR 24-38) and 30 years (IQR 22-39) for related and unrelated donors, respectively. Patients were heavily pretreated with a median of 4 lines (1-9) of therapy before allo-SCT. One hundred and forty-two patients (77%) received a prior auto-SCT. Disease status prior to auto-SCT was CR in 25%, PR in 27% and active disease in 29% of patients. One hundred patients (54%) received BV prior to allo-SCT. Ninety-one patients (50%) had active disease at allo-SCT. Forty-three patients (24%) had a Karnofsky score $\leq$ 80. The median time from allo-SCT to relapse was 7 months (range 3-13). Eighty patients received BV as salvage therapy for relapse/progression after allo-SCT (BV group), at a median time of 67 days (IQR 29-300) after relapse. These patients were compared with the remaining 104 who did not receive BV salvage after allo-SCT (no-BV group). The median follow-up after relapse of alive patients was 29 months (range 14-38). Comparison of patients and transplant characteristics between the two groups are listed on Table 1 and Table 2, respectively.

Effect of salvage BV after allo-SCT

Patients in the BV group received a median of 6 doses of BV for relapse after allo-SCT (range 1-16). Out of 58 patients with available data on response in the BV group, 17 (29%) achieved CR, 26 (45%) achieved PR and 15 (26%) had SD (Figure 1). Response to BV post allo-SCT was not affected by whether patients had received BV (CR 26%; PR 48%; SD 26%) or not (CR 37%; PR 37%; SD 25%) pre-transplant (Figure 1). Response to BV was highly predictive of disease status at last follow up (Figure 2). Indeed, out of 17 patients who achieved CR after BV salvage, 12 patients (71%) remained in CR at last follow up (Figure 2). For these CR patients, median BV duration was 6 months and median follow up after BV was 30 months (Figure 2). Conversely, in the 26 who achieved PR after BV salvage, only 5 patients (19%) were in CR at last follow up (Figure 2). For these PR patients, median BV duration was 5 months and median follow up after BV was 25 months (Figure 2). Finally, out of 15 patients who achieved SD after BV salvage, only 1 patient (7%) was in CR at last follow up (Figure 2). Median BV duration was 2 months only for these SD patients and median follow up after BV was 16 months (Figure 2). Overall survival from relapse was also highly influenced by response to BV with a significantly better OS for responders ($p=0{\cdot}007$) (Figure 3). The outcome of the 22 patients with missing response data to BV does not look quite different from the rest of the group (8 patients in CR; 12 patients alive) (Figures 2 and 3). Despite a longer median follow up for alive patients in the BV group (33 versus 23 months; $p<0{\cdot}001$), 34% of BV-treated patients were alive and in CR at last follow up versus 18% in the no-BV group ($p=0{\cdot}003$).

Among 62 patients in the BV group with no evidence of chronic GVHD before relapse, 22 (35%) developed chronic GVHD after relapse. In the no-BV group, 23 patients (28%) out of 82 with no evidence of chronic GVHD before relapse, developed chronic

GVHD after relapse. In univariate analysis, salvage BV had no effect on chronic GVHD.

Donor lymphocyte infusion

In our cohort, DLI was administered to 66% of patients in the BV group compared to 33% of patients in the no BV group. In 25 patients receiving BV before DLI, median time from relapse to BV is 32 days (IQR 14-60) and median time between BV and DLI is 98 days (IQR 50-203). In 25 patients receiving DLI before BV, median time from relapse to DLI is 18 days (IQR 0-65 days) and median time between DLI and BV is 302 days (IQR 215-674). In 34 patients receiving only DLI, the median time from relapse to DLI is 1·34 months (IQR 0·61-2·70). In 29 patients receiving only BV, the median time from relapse to BV is 1·74 months (IQR 0·89-6·32). In alive patients with no BV or DLI registered (N=20), the median follow-up is 13.52 months after relapse (IQR 7·74-23·9). The probability of being alive and in CR at last follow up was 11% for 70 patients who did not receive BV nor DLI, 24% for 34 patients who received DLI without BV, 21% for 29 patients who received BV without DLI, 24% for 25 patients who received DLI followed by BV and 40% for 25 patients who received BV followed by DLI (p=0.003).

Overall survival and multivariate analysis

The one-year OS with a landmark curve starting at day 60 from relapse post allo-SCT was 76% for patients who received BV within 60 days from relapse versus 67% in the no-BV group (p=0·13). In multivariate analysis, BV salvage had no effect on OS for all

patients, nor for the subgroups who received or not BV prior to allo-SCT. Older age and poor performance status at the time of allo-HCT adversely affected OS whereas DLI significantly improved OS (Table 3).

Discussion

In this study, we compared the outcomes of 80 patients with heavily pretreated HL who relapsed or progressed after allo-SCT and received BV as salvage therapy, to those of 104 similar patients who did not receive BV salvage. In this challenging setting, BV treatment resulted in an overall response rate (CR+PR) of 74% and a CR rate of 29%. Interestingly, the overall response rate to BV was not influenced by whether patients received or not BV prior to allo-SCT, suggesting that re-challenge with BV can be advantageous in HL patients who relapse after allo-SCT, even if they had received it before transplant. The one-year OS with landmark from Day 60 after relapse post allo-SCT was encouraging (76%), even though not significantly different from the 67% OS observed in 104 HL patients who relapsed after allo-SCT but did not receive salvage BV. Nevertheless, 34% of patients in the BV group were alive and in CR at last follow up compared to 18% only in the no-BV group ($p=0{\cdot}003$), despite a longer median follow up for alive patients in the BV group (33 vs 23 months; $p<0{\cdot}001$). These results strongly suggest that BV allowed better disease control than the alternative salvage modalities used in the no-BV group. However, the disease status at last follow up also includes the effect of all salvage therapies received. In 25 patients, BV was followed by DLI, which may have contributed to response. Indeed, the use of BV before DLI was associated with the highest probability of being alive in CR at last follow-up.

In our cohort, DLI was administered to 66% of patients in the BV group compared to 33% of patients in the no BV group indicating that two dominant strategies were used for salvage post allo-SCT: combination of BV+DLI or chemotherapy alone. The reason for this higher frequency of DLI in the BV group remains unknown but one can speculate that DLI is mostly used in responding patients after debulking. Tsirigotis et al. reported 16 patients with advanced HL who received BV after allo-SCT for active disease (13 patients) or as consolidation (3 patients) [28]. Ten of these patients also received DLI resulting in GVHD in 7 patients. Among the 13 patients treated for active disease, CR and PR were observed in 7 and 2 patients, respectively, and the median PFS was 6 months. DLI may add to BV to achieve sustained disease control. We did not observe any increase in *de novo* GVHD in our BV group, despite a significantly higher rate of DLI in this group. Indeed, BV may reduce GVHD by targeting CD30-positive T-lymphocytes [30]. In that sense, we recently reported that BV treatment prior to allo-SCT significantly decreased chronic GVHD in multivariate analysis (Bazarbachi et al., 2018).

Treatment of patients with HL who relapse or progress after allo-SCT remains a real challenge and an unmet medical need [16, 17, 20-23]. Single agents or combination chemotherapy are rarely effective, because most of these patients are heavily pretreated and are often resistant to chemotherapy, although encouraging results were reported with the use of bendamustine in patients who have not received it before [31, 32]. DLI with or without prior chemotherapy resulted in 43-56% response rate at the expense of 32-38% grade II-IV GVHD [15, 18, 33]. Currently, the most attractive treatment options for patients with HL failing allo-SCT are BV with or without DLI or check-point inhibitors.

Our results are in agreement with those of Gopal et al. who reported a small cohort of 25 patients with heavily pretreated HL who received BV salvage for relapse after allo-SCT [26]. Half of their evaluable patients achieved an objective response, and 38% attained a CR. The median PFS was 7·8 months and the median OS was not reached. Similarly, Carlo-Stella et al. reported a small series of 16 patients with HL who received BV salvage for relapse after allo-SCT [27]. Five patients (31%) had CR, and 6 (37%) had PR. After a median follow-up of 26 months, median PFS, OS, and duration of response were 7, 25, and 5 months, respectively. In addition to the larger number of patients in our study, one major difference from these two other series is that 64% of our 80 patients in the BV group had received BV before allo-SCT, whereas all patients in the Gopal and Carlo-Stella series were BV naive. Our results are in agreement with reported data on efficacy of BV re-treatment in patients who have received it earlier [34]. Another difference is that in the Gopal study, patients were excluded if they were within 100 days of allo-SCT or if they had active GVHD, potentially eliminating the highest-risk patients.

Given the limited treatment options for HL patients relapsing after allo-SCT, and the promising clinical and preclinical studies with check-point inhibitors, many clinicians are considering their off-label use in this setting. Indeed, both nivolumab and pembrolizumab appear to be highly efficacious, but with conflicting results on whether their use is frequently complicated by rapid onset of severe and treatment-refractory GVHD and on the influence of time from allo-SCT. Herbaux et al. reported 95% overall response with single agent nivolumab in 20 HL patients relapsing after allo-SCT. De novo GVHD occurred in 6 patients (30%) resulting in 2 deaths (10%) [24]. In this study, nivolumab-induced GVHD was strongly associated with early initiation of nivolumab after allo-SCT. In another multicenter retrospective analysis, Haverkos et al. reported

an overall response rate of 77% including 50% CR in 31 lymphoma (29 HL) patients receiving nivolumab (28 patients) or pembrolizumab (3 patients) for relapse after allo-SCT [25]. Unfortunately, 17 (55%) patients developed treatment-emergent GVHD, including grade III-IV acute or severe chronic GVHD in 9 patients. Finally, 8 (26%) deaths related to new onset GVHD were reported in this study. Based on these results, more data are needed on the use of check-point inhibitors after allo-SCT, and these agents cannot be recommended for routine use outside of a clinical trial.

One important limitation of our retrospective registry study is the risk of selection bias. Ideally, this question should be answered by a prospective randomized trial comparing BV and DLI to investigator choice in patients with HL recurring after allogeneic SCT. A stratification is needed for whether patients were or not exposed to BV prior to allo-SCT. However, this type of study is ethically questionable because of the limited alternative options in these often chemoresistant patients, particularly with the potential fatal toxicities after checkpoint inhibitors.

In conclusion, BV is a safe and highly effective salvage therapy for patients with HL relapsing or progressing after allo-SCT, even after prior exposure to BV. Post-transplant BV may synergize with immune interventions such as DLI to achieve sustained control of HL recurring after allo-SCT. Finally, these results also provide rationale for the upcoming French and German studies testing BV maintenance therapy after allo-SCT in high-risk patients[35].

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FIGURE LEGENDS

Figure 1: Response to brentuximab-vedotin post-allogeneic stem cell transplantation. Abbreviation: SD= stable disease; PR= partial response; CR= complete remission; BV= brentuximab-vedotin.

Figure 2: Disease status at last follow up according to response to brentuximab-vedotin post-allogeneic stem cell transplantation

Figure 3: Overall survival according to response to brentuximab-vedotin post-allogeneic stem cell transplantation.

Table1: Patient Characteristics

	No Brentuximab N (%)	Brentuximab N (%)	P
Patients	104	80	
Age at SCT median (range)	**34 (18-71)**	**30 (19-59)**	**0·03**
Female	39 (38%)	31 (39%)	0·98
Lines before SCT median (range)	4 (1-9)	4 (1-7)	0·91
4 or more treatment lines	46 (53%)	38 (60%)	0·46
BV before SCT	**48 (46%)**	**52 (65%)**	**0·02**
Median months from BV pre-SCT	6 (4-11)	5 (4-7)	0·14
Median doses of BV pre (range)	5 (1-16)	5 (1-12)	0·88
Prior autologous SCT	79 (76%)	63 (79%)	0·79
Karnofsky score 90-100 at SCT	74 (73%)	62 (80%)	0·29
Disease status at allo-SCT			0·31
Active disease	58 (56%)	33 (41%)	
CR	27 (26%)	30 (37%)	
PR	18 (18%)	17 (21%)	

Abbreviation: SCT= Stem cell transplantation; BV= brentuximab vedotin; CR= complete remission; PR= partial response.

Table 2: Transplant characteristics

	No Brentuximab N (%)	**Brentuximab N (%)**	**P**
Patients	104	80	
Non myeloablative conditioning	75 (72%)	62 (77%)	0·72
No TBI	77 (74%)	68 (85%)	0·10
Donor type			0·59
MRD	66 (63%)	53 (66%)	
MUD	38 (37%)	27 (34%)	
Stem cell source			**0·01**
BM	**30 (29%)**	**10 (12%)**	
PB	**74 (71%)**	**70 (87%)**	
Engraftment	97 (98%)	78 (99%)	0·33
Best response at D100 CR	40 (39%)	43 (53%)	0·15
Median months from SCT to relapse	6 (3-12)	10 (5-16)	0·08
DLI	**34 (33%)**	**51 (66%)**	**<0·001**
Median days from relapse to DLI	41 (19-83)	71 (16-84)	0·053
Median months of follow up after relapse for live patients (range)	**23 (9-32)**	**32 (22-45)**	**<0·001**
Cause of death Relapse/progression	51 (82%)	25 (74%)	0·4

Abbreviations: TBI= total body irradiation; MRD= matched related donor; MUD= matched unrelated donor; BM= bone marrow; PB= peripheral blood; D100= day 100; CR= complete remission; SCT= Stem cell transplantation; DLI= donor lymphocytes infusion.

Table 3: Multivariate analysis for OS

	HR (95%CI) p-value
Brentuximab before SCT vs no	0·96 (0·57-1·61) p=0·88
Age over 40 vs below	**2·17 (1·24-3·82) p=0·007**
Male vs female	1·32 (0·8-2·17) p=0·28
Karnofsky score 90,100 vs less	**0·53 (0·33-0·84) p=0·007**
Active disease vs CR,PR	1·45 (0·9-2·34) p=0·13
Time from Diagnosis to SCT ≥24 m vs under	0·79 (0·45-1·38) p=0·4
Radiotherapy before SCT vs no RT	1·49 (0·94-2·35) p=0·09
DLI vs no DLI	**0·51 (0·32-0·83) p=0·007**
Brentuximab post SCT vs no	1·26 (0·8-2) p=0·32

Abbreviation: CR= complete remission; PR= partial response; SCT= Stem cell transplant; RT= radiotherapy; DLI= donor lymphocyte infusion.

Figure 1:

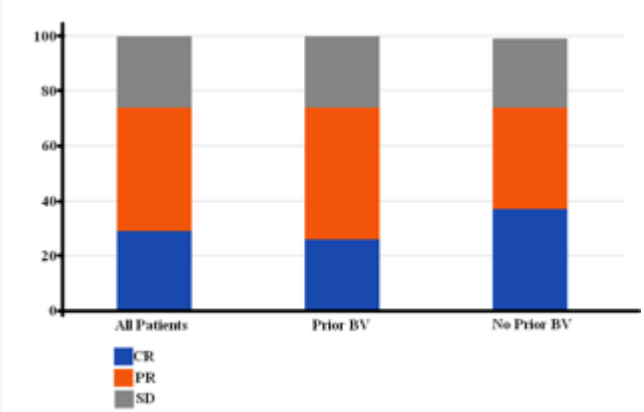

Figure 2:

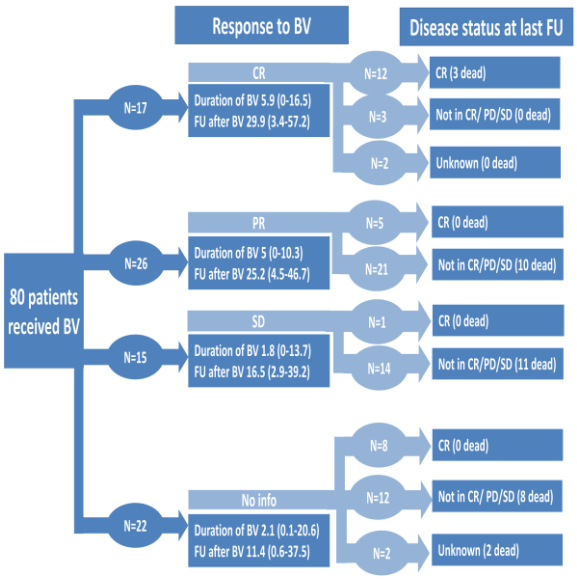
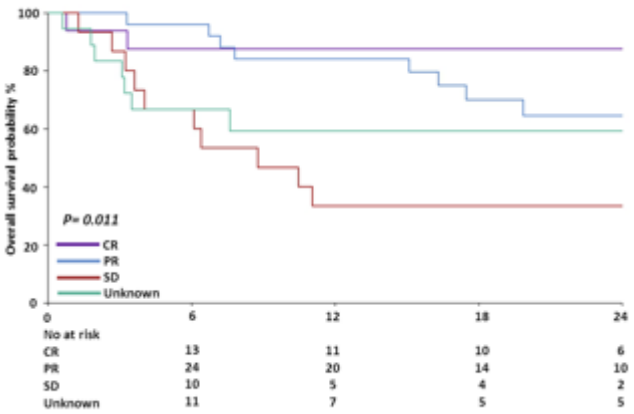
Figure 3