ABVD versus BEACOPP escalated in Advanced-Stage Hodgkin's Lymphoma: results from a multicenter European study

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1. Although ABVD is associated with lower disease control than BEACOPP, it is better tolerated and leads to a similar overall survival rate.
2. BEACOPP is associated with severe, early and late toxicities, which may impact survival.

Abstract

The optimal first-line treatment for advanced-stage Hodgkin's lymphoma (HL) is still a matter of debate. While ABVD is less toxic and as effective as other more intensive chemotherapy regimens, escalated BEACOPP (BEACOPPesc) is superior to ABVD for initial disease control and prolonged time-to-relapse. However, this advantage is associated with higher rate of early and late toxicities. As most of these data have been accumulated from clinical trials, a retrospective analysis was conducted in a large database of patients treated outside clinical trials to investigate the advantages and disadvantages of these regimes in a real-world setting. From October 2009 to October 2018, 397 advanced-stage HL patients treated with either ABVD or BEACOPPesc were retrospectively assessed in 7 European cancer centers (2 Austrian and 5 Italian centers). Complete metabolic remission (CMR) by PET was achieved in 76% and 85% of patients in the ABVD and BEACOPPesc groups, respectively (p=0.01). Severe adverse events occurred more frequently with BEACOPPesc than ABVD. At a median follow-up of 8 years, 9% of the patients who achieved CMR after BEACOPPesc relapsed compared to 16.6% in the ABVD group (p= 0.043). No statistical difference in progression free survival (PFS;p=0.11) was observed between the two cohorts overall, but there was a trend towards a superior PFS in high-risk patients treated with BEACOPPesc (p=0.074). Nevertheless, overall survival was similar between the two groups (p=0.94). In conclusion, we confirm that ABVD is an effective and less toxic therapeutic option for advanced-stage HL. Although BEACOPP results in better initial tumor control, the long-term outcome remains similar between the two regimens.

1 Introduction

Hodgkin's lymphoma (HL) is a rare B-cell neoplasia accounting for about 11% of all newly diagnosed lymphomas in the Western World.[1] This disease has a bimodal distribution with an increased incidence in young adults as well as in patients 55 years and older.[2] The most commonly used first line treatment is ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine).[3] This regimen achieves remission in approximately 80% of patients with a relapse rate of about 25%.[4] Approximately 50% of those who progress or relapse after first line therapy can still be cured by salvage treatments including high dose chemotherapy (HDCT) followed by autologous bone marrow transplant (ASCT).[4] In the attempt to improve cure rate with front line treatment, several groups developed novel combinations. The alternating combinations of ABVD and MOPP and more intensive chemotherapy regimens were explored; however, treatment results were similar and toxicity higher than with ABVD alone.[5–7] Subsequently, the German Hodgkin Study Group (GHSG) developed BEACOPPesc (escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone), an intensified front line regimen, which demonstrated better initial disease control and prolonged time to relapse as compared with ABVD.[8] However, this advantage was associated with higher rates of severe hematologic toxicity, treatment-related deaths, secondary neoplasms and infertility.[9,10] Four clinical trials have directly compared ABVD and BEACOPP and all demonstrated a lower relapse rate after treatment with BEACOPP, but no difference in survival rates between the two regimens in primary data analysis.[9,11–13] Therefore, which regimen should be preferred as first line for advanced-stage HL has not been established yet.

Up to now, there has been no large real-world analysis comparing the efficacy and toxicity of these two regimens in advanced Hodgkin lymphoma outside of clinical trials. This is important because patients enrolled in clinical trials are often highly selected, and consequently may not reflect results in clinical practice. To shed some light on this open question we retrospectively assessed advanced HL patients treated with either ABVD or BEACOPPesc in

seven European cancer centers outside of clinical trials and compared efficacy, safety and long-term outcome of both regimens in a real-life setting.

2 Methods

2.1 Patients

From October 2009 to October 2018, treatment results in patients with newly diagnosed HL stage III-IV who received either ABVD or BEACOPPesc outside of clinical trials were retrospectively assessed from 7 European cancer centers: 2 Austrian and 5 Italian centers. Histologic diagnosis was performed according to World Health Organization criteria by an expert pathologist at each participating center.[14] All patients were ≥ 18 years or older. The clinical stage of the disease was determined on the basis of a medical history and physical examination; complete blood count; serum biochemical profile; chest radiography; computed tomography of the chest, abdomen, and pelvis; positron-emission tomography (PET) with 18F-fluorodeoxyglucose; and core biopsy of the iliac crest. To preserve fertility, ovarian stimulation and cryopreservation of oocytes in females and sperm banking in males were performed before the initiation of treatment. All patients were followed for disease progression/relapse, re-treatment and death; all events were validated with medical records. The study was reviewed and approved by the local ethics committees, and all patients provided written informed consent before inclusion in the study. The study was conducted according to the Declaration of Helsinki.

2.2 Treatment Plan

First line treatment consisted of either six cycles of ABVD given every 4 weeks or six cycles of BEACOPPesc given every three weeks, based on the physician's choice. For historical reasons, the Austrian centers favored BEACOPPesc while the Italian ABVD. All patients underwent routine inter-cycle hematological and biochemical evaluation. Starting within 1 month from the end of chemotherapy, patients with residual metabolic active disease received high-energy

irradiation (30 Gy), with daily doses ranging between 1.5 and 1.8 Gy. The Deauville 5-point scoring system was used for assessment of treatment response. Complete metabolic response (CMR), partial metabolic response (PMR), no metabolic response (NMR) and progressive metabolic disease (PMD) determined by PET were defined according to international lymphoma consensus guidelines.[15,16] PET response was evaluated in all patients after two cycles of treatment (PET2) and at the end of treatment. Patients with an interim PET showing NMR or PMD received alternative treatment: those in the ABVD group received BEACOPPesc while those in the BEACOPPesc group underwent further salvage treatment in accordance with local protocols. After completion of the first line therapy, patients were evaluated every 3 months during the first year, every 6 months from the second year through the fifth year after the completion of treatment, and annually thereafter. All patients were evaluated for toxicity according to the National Cancer Institute's Common Toxicity Criteria (NCI-CTC).

All patients who progressed or relapsed after a CMR were treated according to a salvage chemotherapy program consisting of a reinduction regimen of multiple cycles of DHAP (cisplatin, cytosine arabinoside and dexamethasone) or ifosfamide-containing therapy followed by one high-dose course of autologous hematopoietic stem-cell–supported BEAM (carmustine, etoposide, cytarabine and melphalan).

2.3 Statistical Analysis

The χ^2 test was performed to assess the significance of differences between categorical variables. PFS and OS were defined according to Cheson[15] and plotted as curves using the Kaplan-Meier method. Statistical analyses were performed with MedCalc (version 11.0; MedCalc Software, Ostend, Belgium, http://www.medcalc.org) and GraphPad Prism (version 5.0; Graph-Pad, San Diego, CA, http://www.graphpad.com). All tests were two-sided. The limit of significance for all analyses was defined as $p < 0.05$.

3 Results

3.1 Patient Characteristics at Start of Treatment

A total of 397 consecutive patients were included in the study. One-hundred and twenty-one patients were treated with BEACOPPesc and 276 with ABVD **(Supplemental Table 1)**. The baseline characteristics of the two groups did not differ significantly **(Table 1)**. Overall, the median age at time of diagnosis was 37 years (range, 19-75). A male predominance was observed (n=269, 67.7%). Most patients had nodular sclerosing subtype (n=302, 76%), B symptoms (n=219, 55.1%) and elevated erythrocyte sedimentation rate (ESR, n=226, 56.9%). Only a minority had bulky disease (n=86, 21.6%), defined as a tumor mass of >7 cm^{17}, and a mediastinal mass (n=66, 16.6%). A lower proportion of patients with low international prognostic score (IPS 0-1) received BEACOPPesc compared with ABVD (12.4% vs 28.3% respectively; p= 0.041), while no differences were observed in the other IPS groups.

3.2 Treatment Response

After two cycles of treatment, a CMR was achieved in 69% of the ABVD group and in 78% of the BEACOPPesc group (p= 0.003), respectively. Seventy-two (25.6%) of the ABVD group achieved a PMR, 4 (1.4%) an NMR and 11 (4%) had a PMD. In contrast, 17 of the patients in the BEACOPPesc group had a PMR (14%), 6 progressed (5%) and another 4 (3%) interrupted therapy because of life-threatening toxicity. Patients with NMR or PMD at interim PET were escalated to BEACOPPesc or received salvage treatment if they were previously treated with ABVD (n=15) or BEACOPPesc (n=10), respectively. At the end of the therapy, CMR was 76% in the ABVD group and 85% in the BEACOPPesc group (p= 0.01). A total of 20% of patients in the ABVD group and 14% of patients in the BEACOPPesc group received consolidation involved field radiotherapy to residual metabolic active disease at the dose of 30Gy. After radiotherapy, the number of patients with CMR increased to 81% and 90% in the two groups, respectively (p=

0.021). All patients that failed to respond or progressed at end of treatment PET received a salvage regimen followed by HDCT with autologous hematopoietic stem-cell support.

Forty-two patients (35%) in the BEACOPPesc group required chemotherapy dose reduction due to toxicity compared to 14 patients (5%; p= <0.001) in the ABVD group. Overall, the rate of severe toxicities was higher in the BEACOPPesc group in comparison with the ABVD cohort. There was a significant increased frequency of acute grade 3-4 hematologic adverse events in the BEACOPPesc group as compared with the group treated with ABVD (neutropenia 61% vs 24%, p< 0.001; anemia 29% vs 4%, p< 0.001; thrombocytopenia 29% vs 3%, p< 0.001), febrile neutropenia (29% vs 3%, p< 0.001) and severe infections (18% vs 3%, p= 0.002). Myeloid growth factors were administered to 85% of patients in the BEACOPPesc group compared with 59% in the ABVD group (p= 0.01). **Figure 1** Blood transfusions were required in 41% of patients in the BEACOPPesc group compared with 6% in the ABVD cohort (p= < 0.001). No case of death due to acute treatment-related toxicity was registered in either group.

3.3 Follow-up

Progression during or shortly after treatment occurred in 6 patients in the BEACOPPesc group (4.9%) and in 16 patients in the ABVD group (5.8%; p= 0.71). During the median follow-up period of 8.7 years (range, 6.5-10.6 years), 10 out of 109 patients who achieved a CMR after BEACOPPesc relapsed (9%) compared to 37 of 223 patients in the ABVD group (16.6%; p= 0.043). However, no statistical difference in 8-year PFS rate was observed between the BEACOPPesc and ABVD cohorts (**Figure 2A**, 80% vs 75%; p=0.11) irrespective of PET2 status (**Supplemental Figure 1A-B,** 84% vs 80%**;** p=0.42 in PET2-negative patients and 69% vs 63.5%**;** p=0.12 in PET2-positive patients treated with BEACOPPesc and ABVD, respectively). The baseline international prognostic score (IPS <3 vs ≥ 3)[18] predicted a trend towards higher PFS for the high-risk group treated with BEACOPPesc as compared with ABVD (**Supplemental Figure 2A-B**, 81% vs 72%; p=0.074). However, there was no difference in 8-year OS rate

between the two treatment groups (**Figure 2B**; 90% vs 87%; p=0.94) irrespective of PET2 status (**Supplemental Figure 1C-D,** 93.7% vs 91%; p=0.86 in PET2-negative patients and 77% vs 78.8%; p=0.61 in PET2-positive patients treated with BEACOPPesc and ABVD, respectively) or IPS risk score (**Supplemental Figure 2C-D**, 85% vs 83%; p=0.81 in IPS <3 patients and 77% vs 79%; p=0.94 in IPS ≥3 patients in the BEACOPPesc and ABVD group, respectively). During the follow-up period, secondary malignancies were observed in 5.8% of the patients treated with BEACOPPesc compared to less than 1% of those who received ABVD. The median time from the end of treatment to diagnosis of second malignancy was 80 months (range, 3-115 months). All patients treated with BEACOPPesc who developed second malignancies were in first remission, while the ones in the ABVD cohort received second line therapy followed by autologous transplant. In particular, three patients in the BEACOPPesc group developed myelodysplasia and one acute leukemia. Second solid tumors developed in two patients in the ABVD group (one lung cancer and one breast cancer) and seven in the BEACOPPesc group (four breast cancer, one lung cancer, one melanoma and one thyroid cancer). **Table 2** Four of these 9 patients received radiotherapy as part of their initial treatment, with tumor development within or close to the irradiated field (one lung and one breast cancer in ABVD group, and one lung and one thyroid cancer in the BEACOPPesc cohort).

4 Discussion

The preferred treatment for advanced Hodgkin's lymphoma has been a matter of discussion for three decades. Four international clinical trials addressed this important question by directly comparing ABVD and BEACOPPesc.[9,11–13] All of them demonstrated the superiority of BEACOPP in achieving disease control; however, this benefit did not translate into long term advantage due to a higher rate of late major events, particularly second malignancies, which led to treatment-related patient deaths and ultimately comparable survivals to ABVD.[9,10,12,13] Hence, a balance between efficacy and toxicity should be considered in selecting the first line treatment

for these patients. Since a real-world analysis was lacking, we retrospectively assessed a large European cohort of advanced stage HL patients who underwent either ABVD or BEACOPP outside of clinical trials. This study provides real-world data confirming that ABVD is better tolerated and has similar survival rate as BEACOPPesc as previously reported in published clinical trials.

The main limitations of this study were the retrospective rather than prospective analysis and lack of central review of the diagnostic pathology and PET images. The strengths of this analysis were the relative long follow-up and the uniform treatment in a multicenter setting although patients were treated outside a clinical trial.

Patient characteristics at the time of diagnosis were comparable between both treatment groups and similar to those of other published cohorts[9,12,13,19]. As expected, a lower proportion of patients with IPS 0-1 received BEACOPPesc compared to ABVD (12.4% vs 28.3%, respectively; p= 0.041). For historical reasons, BEACOPP was the preferred first line regimen in the Austrian centers compared to the Italian ones (80.2% vs 19.2%). This different therapeutic preference among centers may actually be an advantage as a similar patient population was treated with either regimen. In the present analysis, the response rate of patients who received BEACOPPesc was superior to those who received ABVD (85% vs 76%, p= 0.01). Interestingly, the rate of patients with disease progression and interruptions for life threatening toxicity was high in the BEACOPPesc group (8%) relative to 5.4% of NMR/PMD with ABVD. Our results are in line with three prospective studies using the same treatment program, which obtained a complete response rate between 85-96% and 73-85% in the BEACOPPesc and ABVD groups, respectively.[8,9,13] However, EORTC 20012 and HD2000 failed to show a difference in CR[11,12] between the two regimens probably due to the poor tolerance of the BEACOPPesc regimen which ultimately led to dose reduction or treatment discontinuation. Indeed, the high activity of BEACOPPesc is associated with severe acute hematologic and non-hematologic toxicities. In our study 93% of patients who underwent this intensive treatment regimen experienced at least

one severe acute toxic effect, most commonly myelosuppression and febrile neutropenia. This translated into superior costs for growth factor and antibiotic use, supportive measures and hospitalization, and led to the permanent discontinuation in 4 cases. These results are comparable to those of the four prospective trials where severe hematologic toxicity was also the most frequent adverse event.[9,12,13,19] Considering the young age of patients with HL, even more important is the long-term toxicity associated with BEACOPP, which ultimately affects overall survival related to the higher incidence of second malignancies with BEACOPPesc compared with ABVD. In our study the rate of secondary malignancy was 5.8% in the patients treated with BEACOPPesc. Similarly, the GHSG H9, HD12 and HD2000 trials reported a cumulative risk for second malignancies between 4.9% and 6.5%.[8,10,20]

Previous studies showed a superior PFS at 5 years in patients treated with BEACOPP compared to ABVD[11,13]; however this advantage was lost with a longer observation time[9,10]. Similarly, we did not observe difference in long-term outcomes between the two regimens irrespective of the International Prognostic Score and PET2 status. One explanation may be the high efficacy of salvage therapies after ABVD. Another explanation might be the higher incidence of secondary malignancies in patients treated with BEACOPP, which is consistent with previous reports[10,12]. It should also be noted that despite its historical importance, IPS has lost its prognostic value in the modern era using PET-guided therapy.[29] Nevertheless, it is also possible that a larger study may have captured the difference between the two treatment groups. In addition, our study used 6 cycles of BEACOPPesc while 4 cycles has become the standard in PET2-negative patients since 2018.[21] This PET-adapted treatment led to less severe acute toxicities, and ultimately to a slightly superior 5-year OS compared with the extended treatment (97.7% vs 95.4%); however, the incidence of second malignancies did not differ between the two treatment groups (3.3% vs 3.8%; p= 0.37)[21], suggesting the need for a longer observation period for occurrence of further second malignancies to confirm the small survival advantage. It is known that the addition of radiotherapy to chemotherapy increases the

risk of secondary malignancies. However, in our study a similar number of patients in either treatment group received additional radiation therapy for residual disease. In contrast to our data, the HL9 trial demonstrated a superior 10-year OS for BEACOPPesc compared with COPP/ABVD, which has similar survival to ABVD[22]. It should be noted that this was an unplanned secondary late analysis and not the primary endpoint of the trial. It should also be noted that survival has improved with ABVD in recent retrospective analyses outside of a clinical trial setting.[23] Although a meta-analysis from the GHSG group comparing BEACOPP and ABVD showed a 10% OS benefit favoring BEACOPP[24], these results were reported after only 5 years of follow-up, and 10-year results are needed to observe long-term toxicities and consequent loss of survival advantage.

Achieving high cure rates while lowering early and late treatment-related toxicity remains a challenge for patients with advanced-stage Hodgkin's lymphoma. The use of functional imaging with PET early in the course of therapy offers a way to make treatment adjustment based on response to therapy. Recent studies have showed that excellent results can be achieved by using PET2 to modulate therapy, with escalation for those with an unsatisfactory response and de-escalation for those with chemosensitive disease.[25–28] Such an approach would spare the 70% of patients destined to be cured by ABVD from receiving the more toxic BEACOPP regimen, and avoid prolonged exposure to BEACOPP to those who do not need it. The RATHL (Response-Adapted Therapy in Advanced-Stage Hodgkin Lymphoma) trial showed that in PET2-negative patients the bleomycin-deleted AVD was as good as ABVD, hence reducing lung toxicity, with a 3-year PFS of 86%. In those who were PET2-positive after two cycles of ABVD, switching to BEACOPPesc seemed to improve outcomes, with a 3-year PFS rate of 71.1% and OS rate of 82.8%.[25] In support of the predictive power of PET in this setting, the Italian GITIL0607 study showed that PET2-negative patients treated with continued ABVD regimen reached a 3-year PFS of 87%. In this trial, the randomization of PET2-negative patients to receive or not RT did not show a PFS advantage.[30] However, in our study the outcome of

PET2-negative patients is more disappointing than the 2 larger studies with an 8-year PFS of 84% and 80% (p=0.42) in the two treatment cohorts. Our data are in line with the SWOG0816 trial which reported a 5-year PFS of only 74% for PET2-negative patients who received 6 cycles of ABVD.[31] The longer follow-up of our analysis and of the SWOG trial might be explanatory of the difference to the 2 previous studies. Indeed, toxicity related deaths occur more frequently beyond 3 years after chemotherapy. To further argue against the predictive power of PET, the HD18 trial showed that the two arms of patients with advanced Hodgkin lymphoma who were PET2-positive after 2 cycles of BEACOPPesc and continued to a total of six/eight cycles reported 5-year PFS rates of 89.7% and 88.1%, respectively. No significant differences in PFS (p= 0.30) and OS (p= 0.49) were observed between PET2-positive and PET2-negative patients.[21]

Several efforts have been made to incorporate novel molecules into the backbone of the two first line regimens to improve efficacy of ABVD and decrease toxicity of BEACOPP. Recently, Brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, has shown remarkable activity in Hodgkin lymphoma.[32] In an attempt to improve efficacy of ABVD, the ECHELON-1 phase III trial evaluated a modified variant which replaced bleomycin with BV (A-AVD) in advanced Hodgkin lymphoma patients. The 2-year modified PFS rate favored A-AVD (82.1% vs 77.2%, p= 0.004),[33] leading to the FDA approval of this new combination. However, the study has not yet showed a benefit in overall survival since the number of events has not been reached. Similarly, two modified BEACOPP variants incorporating BV were compared in a randomized phase II trial.[34] One of these variants, BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone) seems to be less toxic and highly active and is currently compared to BEACOPPesc in the GHSG phase III HD21 trial (NCT02661503). In addition, there are the promising immune checkpoint inhibitors which have demonstrated impressive activity in Hodgkin lymphoma.[35] These molecules have become

crucial in the therapeutic armament of HL and currently are evaluated as part of first line treatment (NCT03907488).

In conclusion, our study confirms that ABVD is an effective and well tolerated regimen with similar survival rate as BEACOPPesc and supports its role as first line in advanced-stage Hodgkin patients, irrespective of the IPS. However, the therapeutic horizon of Hodgkin lymphoma is likely to change in the near future with a new generation of drugs that will increasingly modify or even replace standard chemotherapies. This approach may eventually supplant both ABVD and BEACOPPesc.

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PM designed and wrote the project, analyzed the data, reviewed the literature and wrote the paper, CM, ID, JPB, FC, SF, BB, CC, DN, SDL, GM, CS, GL, SC collected the data, WD, WW, MM and DJS revised the paper, all the authors approved it.

Conflict of Interest

PM, CM, ID, J-PB, FC, BB, CC, DN, SDL, GM, WD, GL, SC and DJS have no financial disclosure. SF and MM have received honoraria from Mundipharma, WW has received honoraria and research funding from Mundipharma and Roche.

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Figure Legends

Figure 1. Severe hematologic toxicities. Bar graph showing the frequency of acute grade 3-4 hematologic adverse events that occurred in advanced-stage Hodgkin's lymphoma patients treated with either BEACOPPesc (black) or ABVD (gray). Differences between groups were calculated with the Student *t* test. ** p= 0.002; *** p< 0.001.

Figure 1

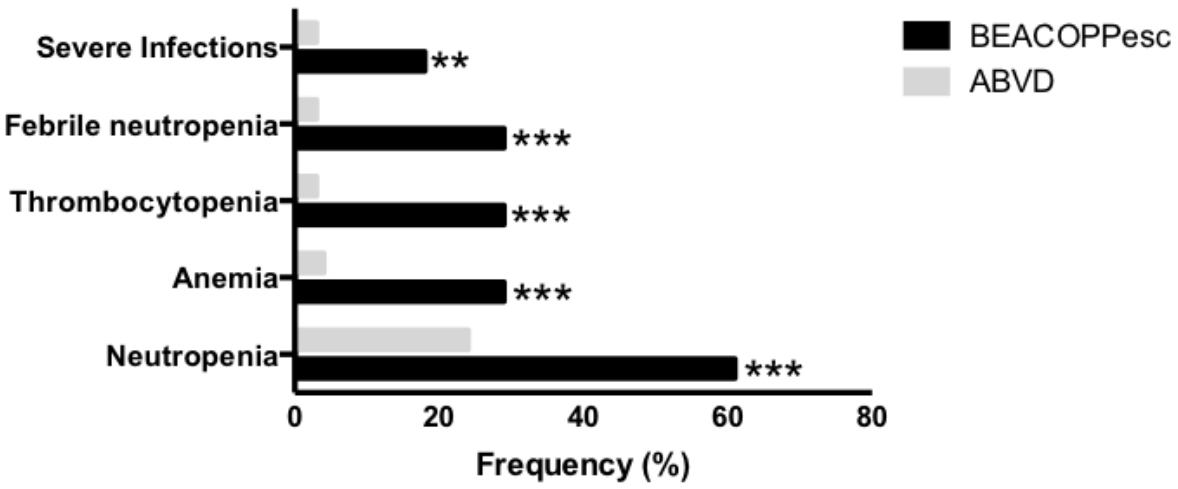
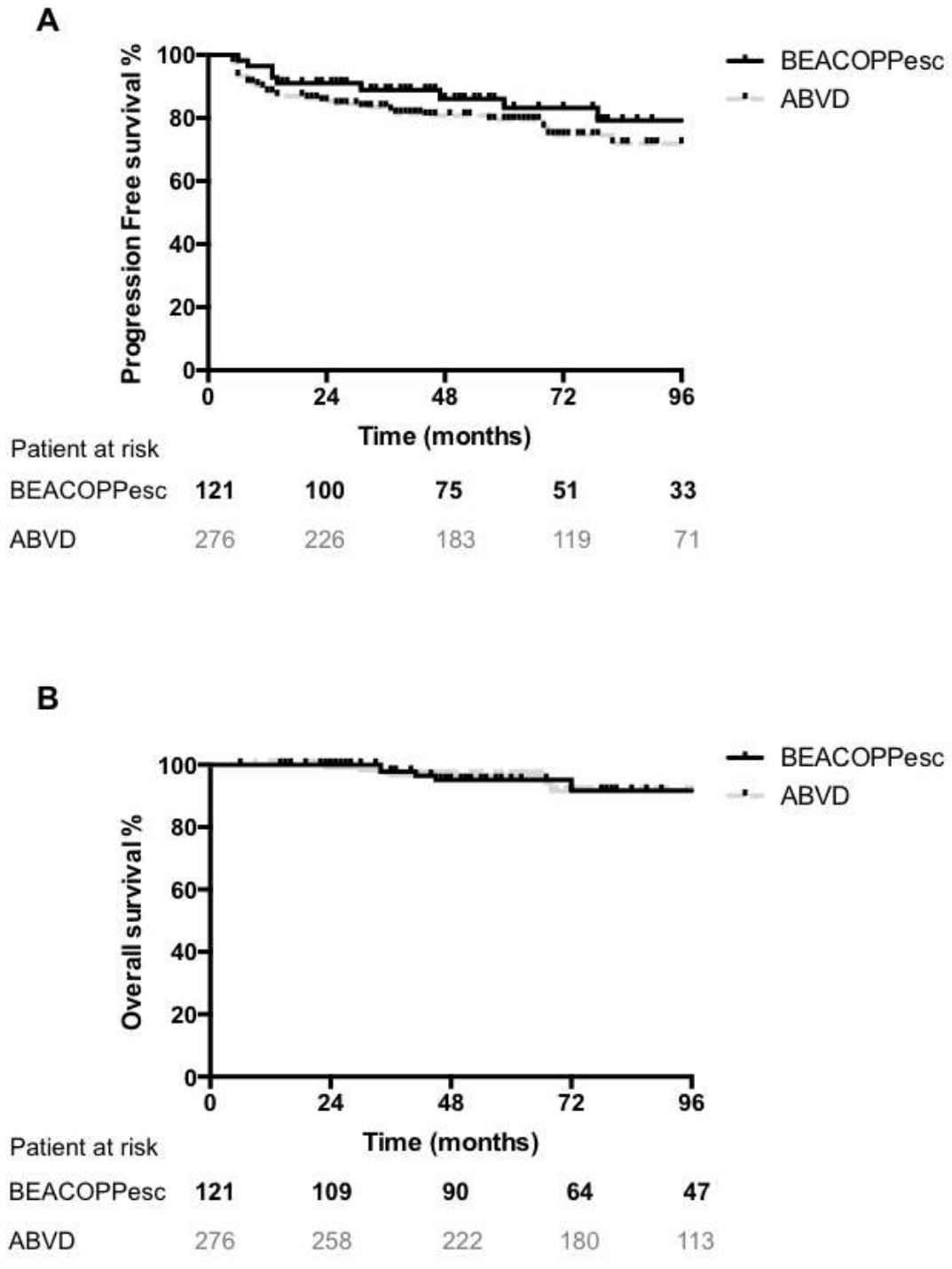


Figure 2. Kaplan-Meier analysis of progression-free survival (**A**; p=0.11) and overall survival (**B**; p=0.94) for advanced-stage Hodgkin's lymphoma patients treated with either BEACOPP escalated (black) or ABVD (gray). BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine.

Figure 2



Supplemental Figure Legends

Supplemental Figure 1. Kaplan-Meier analysis of progression-free survival and overall survival in PET2-negative (**A-C**) and PET2-positive (**B-D**) advanced-stage Hodgkin's lymphoma patients treated with either BEACOPP escalated (black) or ABVD (gray). BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine.

Supplemental Figure 2. Kaplan-Meier analysis of progression-free survival and overall survival in advanced-stage Hodgkin's lymphoma patients with International Prognostic Score <3 (**A-C**) and ≥3 (**B-D**) who were treated with either BEACOPP escalated or ABVD. BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; IPS, International Prognostic Score.

Table 1. Baseline patient characteristics

	BEACOPPesc (n=121)		ABVD (n=276)		p-value
	n	%	n	%	
Age					
Median, years	37	N.A.	36.5	N.A.	N.A
>50 years (EORTC)	24	19.8	60	21.7	0.42
>60 years	4	3.3	11	4	0.77
Sex					
Female	29	24	99	35.8	0.06
Male	92	76	177	64.1	0.08
Hodgkin subtype					
Nodular sclerosing	91	75.2	211	76.4	0.77
Mixed cellularity	20	16.5	42	15.2	0.54
Lymphocytes depleted	9	7.4	21	7.6	0.82
Lymphocytes rich	1	0.9	2	0.8	0.88
B-Symptoms	72	59.5	147	53.2	0.23
Bone marrow involvement	20	16.5	25	9.0	0.08
Bulky disease (> 7cm)	25	20.6	61	22.1	0.11
Mediastinal mass	18	14.8	48	17.4	0.37
Elevated LDH	44	36.4	97	35.1	0.83
Elevated B2M	31	25.6	60	21.7	0.28
Elevated ESR	70	57.8	156	56.5	0.77
Hb < 10.5 g/dL	28	23.1	55	19.9	0.09
WBC > 15,000/mm3	25	20.6	64	23.2	0.43
Lymphocytes <600/mm3	15	12.4	33	11.9	0.75
Monocytes >900/mm3	13	10.7	31	11.2	0.41
PLT <150,000	8	6.6	11	4.0	0.09
Albumin <4 g/dL	28	23.1	57	20.6	0.18
Stage					
III	59	48.8	139	50.3	0.11
IV	62	51.2	137	49.7	0.15
ECOG					
0-1	99	81.8	198	71.7	0.062
>1	22	18.2	78	28.2	0.065
International Prognostic Score (IPS)					
0-1	15	12.4	78	28.3	0.041
2-3	52	43	103	37.3	0.071
4-7	54	44.6	95	34.4	0.065

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; BEACOPPesc, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; LDH, lactate dehydrogenase; B2M, Beta2 microglobulin; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; WBC, white blood count; PLT, platelet.

Table 2. Secondary Malignancies by treatment group.

Secondary Malignancy	BEACOPPesc (n=121)	ABVD (n=276)
Lung cancer	1	1
Breast cancer	4	1
Thyroid cancer	1	-
Melanoma	1	-
Myelodysplasia	3	-
Acute leukemia	1	-

Abbreviations: BEACOPPesc, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine.