Early chemotherapy de-escalation strategy in patients with advanced-stage Hodgkin lymphoma with negative positron emission tomography scan after 2 escalated BEACOPP cycles

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KEY WORDS
BEACOPP, de-escalation, Hodgkin lymphoma, positron emission tomography, toxicity

ABSTRACT

INTRODUCTION Escalated BEACOPP (escBEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) significantly improves overall response rates (ORRs) and prolongs progression-free survival (PFS) in patients with advanced-stage Hodgkin lymphoma (HL). However, 6 to 8 cycles of escBEACOPP are associated with increased acute toxicity and late complications.

OBJECTIVES We aimed to determine the role of early positron emission tomography–computed tomography (PET-CT) response assessment in a de-escalation strategy.

PATIENTS AND METHODS We retrospectively analyzed 188 consecutive patients with advanced-stage HL treated at diagnosis. Patients received 2 cycles of escBEACOPP followed by an early PET-CT response assessment performed after 2 cycles of chemotherapy (PET2). Patients with an active disease continued therapy with escBEACOPP, while those with negative PET2 were de-escalated to ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine). Radiotherapy was allowed in patients with stage IIIBX.

RESULTS PET2 allowed for de-escalation of therapy in 141 patients (75%). Their ORR was 92.2%, with a complete remission (CR) rate of 91.5%; 10-year PFS and overall survival (OS) were 87.2% and 95%, respectively. In the whole cohort, ORR was 87.8% (CR, 85.6%), while the 10-year PFS and OS were 79.3% and 89.4%, respectively. Hematological and thromboembolic complications were significantly more frequent in patients treated with 6 escBEACOPP cycles, including febrile neutropenia (25 patients, [53.2%] vs 7 [5%]), serious anemia (35 [74.5%] vs 11 [7.8%]), or thrombocytopenia (16 [34%] vs 7 [5%]) ($P <0.001$ for all comparisons with de-escalation strategy) as well as pulmonary embolism (3 [6.4%] vs 0) ($P = 0.02$).

CONCLUSIONS The early de-escalation strategy allows for effective treatment of advanced HL, with a comparable efficacy to that of 6 to 8 cycles of escBEACOPP, but with significantly reduced toxicity.
INTRODUCTION  The introduction of polychemo-
therapy regimens, consolidated when required
with involved-field radiotherapy (IFRT), ren-
dered Hodgkin lymphoma (HL) a highly curable
disease. The most popular regimen used in HL
is still ABVD (doxorubicin, bleomycin, vinblas-
tine, dacarbazine), with a 5-year progression-
free survival (PFS) of 61% to 76% in patients with
advanced stage of the disease. The more
intensive regimens, such as escalated BEACOPP
(escBEACOPP: bleomycin, etoposide, doxorubi-
cin, cyclophosphamide, vincristine, procarba-
zine, and prednisone), developed by the Ger-
man Hodgkin Study Group (GHSG), improves
the outcome of younger patients with advanced
stages, allowing for a 5-year PFS of 90%. How-
ever, 6 to 8 cycles of escBEACOPP result in sig-
nificant hematological toxicity and late compli-
cations, such as secondary acute myeloid leuke-
emia (AML), myelodysplastic syndrome (MDS),
and infertility. The choice of the first-line chemother-
y regimens in HL is still a matter of controversy. It is cru-
ial to maintain the balance between disease con-
trol and treatment-related adverse events (AEs).
To avoid excess toxicity, risk-adapted strategies
have been implemented. An early response assess-
ment by 18F-fluorodeoxyglucose positron emis-
tion tomography–computed tomography (PET-
CT) performed after 2 cycles of chemotherapy
(PET2) has become an accepted prognostic tool
in classic HL. We postulated that early respond-
ers to escBEACOPP therapy (as assessed by PET2)
may be further efficiently treated with ABVD reg-
imen, with a decreased number of AEs and late
complications.

PATIENTS AND METHODS  Study cohort  In this
retrospective analysis, we collected data from
188 consecutive, previously untreated patients
with advanced HL (clinical stage III–IV or II with
large tumor burden and concomitant general
symptoms; IIBX–IV), who completed their en-
tire treatment at the Department of Hematology
at Jagiellonian University between April 2003 and
August 2012. The diagnosis, established accord-
ing to the 2001 or 2008 World Health Organiza-
tion classification, was based on histopathologi-
cal assessments of tissue samples excised before
first-line therapy. 

The clinical stage of lymphoma was assessed using the Ann Arbor classifica-
tion with Cotswolds modification. The Interna-
tional prognostic index (IPI) for HL was calcul-
ed for all patients at diagnosis.

The median age at baseline was 33 years (range,
18–59 years) with a male-to-female ratio of 1.38.
A total of 139 patients (73.9%) presented B symp-
tsoms, 119 (63.3%) had stage III or IV disease, and
69 (36.7%) had stage IIBX; 100 patients (53.2%)
had an IPI of 3 or higher. Patient characteristics
and demographic data are summarized in Table 1.

Treatment outline  Patients were referred for esc-
BEACOPP therapy based on a physician’s decision
and their informed choice. The regimen was of-
erred to all patients with stages IIBX to IV, good
performance status (0–2) according to the East-
ern Cooperative Oncology Group, and no dis-
abling comorbidities. Patients over 60 years old
were excluded, and only 16 patients (8.51%) were
over 45 years old. All patients underwent a phys-
ical examination, full blood cell count, measure-
ment of urea and electrolyte levels, liver function
tests, and PET-CT at diagnosis. The first 2 cycles
of escBEACOPP were followed by an early PET-
CT response assessment (PET2). A complete re-
sponse (CR) was initially defined as an inferior ac-
tivity of involved tissues compared with mediasti-
nal blood pool structures. In 2010, we switched to
Deauville criteria which define CR as a PET score
of 1 to 3. In responding patients, the intensity of
the therapy was decreased, and they were as-
signed to 4 cycles of ABVD regimen, while those
with an active disease continued treatment with
escBEACOPP for a total of 6 cycles. Chemother-
apy regimens were administered in accordance
with their original description. The average
relative dose intensity, calculated for all cycles of
escBEACOPP and ABVD chemotherapy, was based
on the patient’s body surface area, planned and
actually administered doses of drugs, and planned
and actual dates of chemotherapy cycles. Consi-
deration IFRT with a total of 36 Gy was allowed for
patients with stage IIBX.

The final response to first-line therapy was as-
sessed in accordance with the original Cheson cri-
teria and the results of PET-CT performed
within a month of chemotherapy completion or
3 months after consolidation IFRT. Patients with
partial remission (PR), stable disease, or pro-
gressive disease were regarded as treatment fail-
ure and, wherever possible, subjected to further
salvage therapy and autologous stem cell trans-
plantation (ASCT).

All patients received supportive treatment per
local standard, including prevention of tumor
lysis syndrome; antibacterial, antiviral, or an-
tifungal therapy, and transfusions of red blood
cells or platelets as required. Granulocyte colony-
stimulating factor was regarded mandatory dur-
ing escBEACOPP cycles as prophylaxis of neutro-
penic fever.

Follow-up visits were performed at 3-month
intervals within the first year, every 6 months
in the second year, and every 12 months until
the end of the fifth year. After that time, patients
were consulted whenever new signs or symptoms
occurred. Computed tomography scans after ther-
apy were performed at 6, 12, and 24 months; lat-	er, imaging studies were performed on individual
basis, when appropriate. The survival data were
updated in 2019, before drafting the manuscript,
in additional visits or phone conversations.

Progression-free survival was defined as the
time from onset of escBEACOPP chemother-
apy to lymphoma progression or death. Overall
survival was calculated as the time from the be-
ning of treatment to death, regardless of
Early response assessment (PET2) performed after the second cycle confirmed CR in 141 patients (75%), which allowed for a decreased intensity of chemotherapy and switch from escBEACOPP to ABVD regimen. Consolidation with IFRT was applied in 64 patients (92.8% of those with stage IIBX). After completion of the entire first-line therapy in the PET2 responder cohort, ORR was 92.2%, including 129 patients (91.5%) with CR and 1 patient (0.7%) with PR. Eleven patients (7.8%) who achieved CR on PET2 assessment progressed while on ABVD and continued with salvage high-dose therapy. The majority of them (n = 9 [81.8%]) were successfully consolidated with ASCT, while 2 patients (18.2%) did not respond to salvage therapy and died (TABLE 2). At 10-year follow-up, PFS and OS in PET2 responders were 87.2% and 95%, respectively (FIGURES 3 and 4).

Among the 47 patients with a PET2-positive scan who continued with 4 additional escBEACOPP cycles up to 6 courses, 35 (74.5%) responded to treatment with CR (32 patients [68.1%]) and PR (3 patients [6.4%]); 12 patients (25.5%) were primary refractory and subjected to high-dose therapy or ASCT, with the response observed only in 5 patients (41.7%). The inferior outcome in this group was confirmed by PFS and OS at 10 years (55.3% and 72.3%, respectively).

According to IPI stratification, in the low-risk group (IPI, 0–2; n = 88), 96.6% of patients completed the first-line treatment with CR; 1.1%, with PR; and 2.3% were primary refractory, with PFS and OS at 10 years of 93.2% and 94.3%, respectively. In the high-risk group (IPI, 3–7; n = 100), we observed CR in only 76% of patients and PR in 3%, while 21% of patients were primary refractory. In the high-risk group, PFS and OS at 10 years were 55.3% and 72.3%, respectively.

Data are presented as number (percentage) unless otherwise indicated.

Abbreviations: ECOG, Eastern Cooperative Oncology Group

### Statistical analysis

Survival analysis (PFS and OS) was performed using Kaplan–Meier statistics with the log-rank test for comparison. Response rates were compared by the Pearson $\chi^2$ test. The frequency of AEs was compared by the $\chi^2$ test (including Yates correction). Results were considered significant at a $P$ value of less than 0.05. All statistical analyses were performed using STATISTICA software (StatSoft, Kraków, Poland).

### RESULTS

In the whole cohort (n = 188), 161 patients achieved CR (85.6%) and 4 patients achieved PR (2.1%); 23 patients were regarded primary resistant (12.2%). At the median follow-up of 10.4 years (range, 1.3–18.4 years), the PFS and OS at 10 years were 79.3% and 89.4%, respectively, in the whole group (FIGURES 1 and 2). Among all analyzed patients, 21 deaths occurred (16 in high-risk patients according to IPI, 13 high-risk cases according to PET2); 20 deaths were caused by HL and 1 death resulted from a traffic accident.

Early response assessment (PET2) performed after the second cycle confirmed CR in 141 patients (75%), which allowed for a decreased intensity of chemotherapy and switch from escBEACOPP to ABVD regimen. Consolidation with IFRT was applied in 64 patients (92.8% of those with stage IIBX). After completion of the entire first-line therapy in the PET2 responder cohort, ORR was 92.2%, including 129 patients (91.5%) with CR and 1 patient (0.7%) with PR. Eleven patients (7.8%) who achieved CR on PET2 assessment progressed while on ABVD and continued with salvage high-dose therapy. The majority of them (n = 9 [81.8%]) were successfully consolidated with ASCT, while 2 patients (18.2%) did not respond to salvage therapy and died (TABLE 2). At 10-year follow-up, PFS and OS in PET2 responders were 87.2% and 95%, respectively (FIGURES 3 and 4).

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Chemotherapy dose adjustment was necessary due to neutropenia. The cumulative dose of doxorubicin was 270 mg/m² in the PET2-negative arm and 200 mg/m² in the PET2-positive arm. There were no episodes of early or late cardiotoxicity or treatment discontinuation in this group.

Adverse events of any grade occurred in 140 patients (74.5%). The most frequent AEs were neutropenia (grade 1–2, 56.9%; grade 3–4, 66%), anemia (grade 1–2, 83%; grade 3–4, 24.5%), thrombocytopenia (grade 1–2, 48.4%; grade 3–4, 12.2%), febrile neutropenia (no episodes of grade 1–2; grade 3–4, 17%). Serious AEs occurred in 26% of patients, with febrile neutropenia being the most frequent and the most common grade 3–4 events.

Response rates to treatment according to the IPI and PET2 results are presented in Table 2.

The average relative dose intensity of escBEACOPP and ABVD regimens was 84% and 96%, respectively. The average relative dose intensity of the entire treatment was 91%, which was above the recently recommended 90% in lymphoma therapy. Overall, 35 of the 188 patients (19%) required at least one dose reduction during treatment with escBEACOPP; in 29 cases, bleomycin and vincristine infusion was omitted on the eighth day of treatment because of neutropenia. In ABVD regimen, no chemotherapy dose adjustment was necessary due to neutropenia. The cumulative dose of doxorubicin was 270 mg/m² in the PET2-negative arm and 200 mg/m² in the PET2-positive arm. There were no episodes of early or late cardiotoxicity or treatment discontinuation in this group.

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We did not formally assess fertility, but it should be noted that 48 pregnancies have been reported after completion of therapy (28 women and the wives of 20 male patients). Assisted reproduction was required in 5 cases, all treated with 6 cycles of escBEACOPP, 2 of them with consolidated IFRT, and 1 after ASCT.

**DISCUSSION** There are continuous efforts to develop an effective strategy with acceptable toxicity for patients with advanced-stage HL. PET-adapted strategies provide improved control of the disease without an increase in toxicity. In frequent one. Apart from hematological toxicity, the most common complications of grade 3 or 4 were thromboembolic events (exact pulmonary embolism) in 1.6% of patients. Hematological AEs and thromboembolic complications were significantly more frequent in patients treated with 6 escBEACOPP cycles (Table 3).

During the median follow-up of 10.4 years, we did not observe MDS or AML. The only secondary cancers reported were 4 cases of basal cell skin carcinoma and 2 cases of breast cancer, all in patients treated with 6 escBEACOPP cycles. There were no deaths related to AEs.

We did not formally assess fertility, but it should be noted that 48 pregnancies have been reported after completion of therapy (28 women and the wives of 20 male patients). Assisted reproduction was required in 5 cases, all treated with 6 cycles of escBEACOPP, 2 of them with consolidated IFRT, and 1 after ASCT.

**TABLE 2** Comparison of outcome in relationship to baseline international prognostic index or positron emission tomography results and chemotherapy de-escalation strategy

<table>
<thead>
<tr>
<th>IPI for HL</th>
<th>All, n</th>
<th>CR, n (%)</th>
<th>PR, n (%)</th>
<th>SD + PD, n (%)</th>
<th>Relapse, n (%)</th>
<th>Mortality, n (%)</th>
<th>PFS at 10 years, %</th>
<th>OS at 10 years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk 0–2</td>
<td>88</td>
<td>85 (96.6)</td>
<td>1 (1.1)</td>
<td>2 (2.3)</td>
<td>4 (4.5)</td>
<td>5 (5.7)</td>
<td>93.2</td>
<td>94.3</td>
</tr>
<tr>
<td>High-risk ≥3</td>
<td>100</td>
<td>76 (76)</td>
<td>3 (3)</td>
<td>21 (21)</td>
<td>12 (12)</td>
<td>16 (16)</td>
<td>67</td>
<td>85</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.1</td>
<td>0.03</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

**Early response assessment by PET**

| PET2 negative | 141    | 129 (91.5) | 1 (0.7) | 11 (7.8) | 7 (5) | 8 (5.7) | 87.2 | 95   |
| PET2 positive | 47     | 32 (68.1)  | 3 (6.4) | 12 (25.5) | 9 (19.1) | 13 (27.7) | 55.3 | 72.3 |
| P value       | <0.001 | 0.003      | <0.001  | <0.001    | <0.001  | <0.001  |      |      |

**Complete study cohort**

| All patients | 188    | 161 (85.6) | 4 (2.1) | 23 (12.2) | 16 (8.5) | 21 (11.2) | 79.3 | 89.4 |

Abbreviations: CR, complete remission; IPI, International Prognostic Index; OS, overall survival; PD, progressive disease; PET2, positron emission tomography result after 2 cycles of chemotherapy; PFS, progression-free survival; PR, partial remission; SD, stable disease

**FIGURE 3** Progression-free survival analysis in relationship to positron emission tomography results and chemotherapy de-escalation strategy (log-rank test, \( P < 0.001 \))
patients treated with an upfront escBEACOPP regimen, the negative predictive value of PET2 for PFS was 98%. We presented a de-escalation protocol guided by early PET-CT response assessment performed after the second cycle of escBEACOPP, which allowed a de-escalation to ABVD regimen in 75% of patients. A randomized comparison (AHL2011 [PET-adapted treatment for newly diagnosed advanced Hodgkin lymphoma] study) of 6 escBEACOPP cycles, regarded as a standard arm, with PET-driven de-escalation in patients responding to the first 2 cycles (2 × escBEACOPP followed by 4 × ABVD) showed equal efficacy and decreased toxicity between approaches. Our protocol was identical to the experimental arm of the AHL2011 study; however, the median follow-up time was twice as long (10.4 vs 4.2 years). In the AHL2011 study, the projected 5-year PFS in the experimental arm was 85.7%. An increased risk of progression or relapse was associated with positive results in PET2 (5-year PFS in the PET2-negative group vs the PET2-positive group was 70.7% vs 88.9%, P < 0.0001). A multivariable analysis proved that an early PET-CT assessment had a prognostic value independent of IPI. In the AHL2011 study, the outcome of patients treated in the standard arm (6 cycles of escBEACOPP) was similar to that reported with the same regimen in the HD15 protocol of GHSG, comparing 8 and 6 cycles of escBEACOPP with 8 cycles of baseline BEACOPP 14 (PFS at 5 years was 90.3%). Progression-free survival was also similar (91.4% at 3 years) for patients treated in the escBEACOPP arm according to the HD18 protocol, allowing for a shortened therapy in PET2 responders (4 × escBEACOPP) and adding rituximab in patients with an active disease on PET2 (2 × escBEACOPP + 6 × R-BEACOPP). In our analysis, in the whole cohort, PFS and OS at 10 years were 83% and 90%, respectively. Although the PFS at 5 years was lower in our study than in the GHSG studies, a 10-year follow-up allowed us to demonstrate a durable benefit of less intensive treatment, with no relapses after 6 years. Our PET2-negative patients achieved even better results at 10 years (PFS, 87.2%; OS, 95%), without long-lasting complications.

Patients included in the analysis were treated before targeted therapies, such as anti-CD30 monoclonal antibodies (brentuximab vedotin [BV]), or checkpoint inhibitors were available. Originally approved for relapsing or refractory cases, BV has been recently tested in the first-line setting. In the ECHELON-1 study, 1334 treatment-naïve patients with advanced HL were randomized to ABVD vs BV plus AVD (ABVD without bleomycin, which was substituted by BV). At 2 years, modified PFS, the primary target of the study, in the BV-plus-AVD arm was 82.1%. Adverse events were relatively frequent: 43% of the patients experienced serious AEs, 37% had to be hospitalized, and 67% developed long-lasting peripheral neuropathy. Although a direct comparison with our results is not possible (there were more elderly patients...
A principal aim of our study was to determine if the PET2 assessment remains a predictor of good prognosis, it cannot serve as a surrogate of CR. We observed 12 primary-resistant cases (25.5%) in the PET2-positive group; further intensive therapy resulted in a 10-year PFS and OS of 55.3% and 72.3%, respectively.

In our early de-escalation strategy, IPI remained an important prognostic factor for both PFS and OS. High-risk patients according to IPI, when compared with low-risk patients, had a lower response rate (CR, 96.6% vs 76%) and higher relapse rate (4.5% vs 12%). Both low IPI and good clinical response on PET2 assessment allowed us to identify a favorable prognostic subgroup in patients with advanced HL, with an OS of 94% to 95% at 10 years. However, IPI for HL allowed us to identify only 88 cases (46%) belonging to a favorable prognostic subgroup, while an early PET assessment doubled this number to 141 patients (75%). Therefore, our data strongly suggest that PET2 is a better tool to identify low-risk patients.

In our analysis, we observed lower rates of AEs, elimination of bleomycin-related pulmonary toxicity, as well as no secondary solid tumors, MDS, or AML. Toxicity in PET2-negative patients de-escalated to ABVD in the AHLS2011 study was comparable to our results and lower than in patients treated with 4 cycles of escBEACOPP in the HD18 study.13,25 There were fewer cases of anemia (grade ≥3) (24% vs 39%) and thrombocytopenia (36% vs 57%).

Additionally, in the GHSG HD9 study,14 after the median follow-up of 9.25 years, in the arm treated with 8 cycles of escBEACOPP, an increased incidence of secondary malignancies was reported (overall, 6%, including 3% for AML and 1.9% for solid tumors).14

The identified 9% rate of thromboembolic events prompts questions as to how the optimal primary thromboprophylaxis should be defined, especially in patients treated with escBEACOPP.27 Overt cardiotoxicity was not observed in our study, which makes a significant difference in comparison with patients with non–Hodgkin lymphoma, who are older and more likely to have cardiovascular comorbidities.28

The principal aim of our study was to determine in a real-life setting whether an interim PET-CT-guided de-escalation strategy will maintain its high efficiency and reduce the number of AEs and late complications. The single-center retrospective analysis has several limitations, including the possibility of an involuntary patient selection and the lack of an independent PET-CT assessment. However, the long median follow-up duration, exceeding 10 years, relatively low
therapy-related toxicity, and the exceptionally good PFS and OS remain the meaningful value of our analysis.

In summary, the early PET-driven strategy allowed for de-escalation of upfront escBEACOPP regimen in 75% of patients with advanced-stage HL and improved tolerability of therapy without impairing its long-term results.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT  MD-D, SS, BM, AS-S, and WJ performed the study and analyzed the data. WJ designed the study. MD-D, WJ, BM, and SS had substantial contributions to conception and design of the study. MD-D, SS, PK, and WJ drafted the manuscript. MD-D, SS, PK, and WJ critically revised the manuscript for important intellectual content. MD-D, SS, WJ, AK, PK, AG, DZC, BM, AS-S, and JK contributed substantially to the acquisition, analysis, and interpretation of data for the study. The authors had full access to the data and take full responsibility for data integrity. All authors have read and agreed with the content of the manuscript.

CONFLICT OF INTEREST  None declared.

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