Two cycles of escalated BEACOPP followed by four cycles of ABVD utilizing early-interim PET/CT scan is an effective regimen for advanced high-risk Hodgkin’s lymphoma

A. Avigdor1*, S. Bulvik2, I. Levi2, E. J. Dann4, N. Shemtov1, G. Perez-Avraham3, A. Shimon1, A. Nagler1, I. Ben-Bassat1 & A. Polliack5

1Department of Hematology and Bone Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine, Tel Aviv University, Tel Aviv; 2Department of Hematology, Laniado Hospital, Netanya; 3Department of Hematology, Soroka Medical Center, Beer-Sheva; 4Department of Hematology and Bone Marrow Transplantation, Rambam Medical Center, Haifa and 5Department of Hematology, Hadassah University Hospital, Jerusalem, Israel

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Background: Escalated combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone (escBEACOPP) regimen is superior to cyclophosphamide, vincristine, procarbazine and prednisone alternating with doxorubicin, bleomycin, vinblastine and dacarbazine (COPP–ABVD) for advanced-stage Hodgkin’s lymphoma (HL) patients. However, the original schedule of eight cycles of escBEACOPP was associated with significant toxicity. This study was conducted in an attempt to reduce the toxicity of the original schedule, while attempting to preserve improved initial tumor control.

Patients and methods: Forty-five newly diagnosed patients with advanced-stage HL and International Prognostic Score (IPS) ≥ 3 received two initial cycles of escBEACOPP and then were evaluated by positron emission tomography (PET)/computed tomography scan. If a good imaging response was obtained, they were treated by four cycles of ABVD.

Results: Following the first two cycles of escBEACOPP, the overall response was 100% and at the end of all therapy, 40 (89%) patients were in complete response (disappearance of all clinical evidence of disease and PET negativity), three (7%) in partial response (PET-positive residual lesions and a size reduction of the majority of large masses by >50%), while two (4%) had progressive disease. After a median follow-up of 48 months, progression-free survival (PFS) and overall survival at 4 years were 78% and 95%, respectively. The 4-year PFS for early PET-negative patients (n = 31) and early PET-positive patients (n = 13) were 87% and 53%, respectively (P = 0.01).

Conclusions: These data indicate that combined escBEACOPP–ABVD may improve the outcome in patients with high-risk advanced HL. The potential benefit of early-interim PET activity as a guide to continuing therapy in these patients merits further study in the future.

Key words: chemotherapy, Hodgkin’s lymphoma, PET/CT scan
These newer therapeutic schedules, supported by hematopoietic growth factors, were designed to deliver higher doses of cytotoxic drugs in an attempt to improve tumor control and increase the cure rate in patients with advanced HL.

The first complete analysis of the HD99 trial of the German Hodgkin Lymphoma Study Group (GHSG) highlighted the superiority of escBEACOPP over baseline BEACOPP and COPP/ABVD in terms of tumor control and OS after a median follow-up of 5 years [6]. Subsequently, an updated analysis showed that escBEACOPP significantly maintained the improved survival rates after a median follow-up of 7 years. Freedom from treatment failure (FTF) for COPP/ABVD, baseline BEACOPP and escBEACOPP were 64%, 70% and 82%, while OS were 75%, 80% and 86% at 10 years, respectively [10]. In the latter study, patients received eight cycles of chemotherapy followed by 36 Gy radiotherapy to sites of bulky or residual tumor. However, eight cycles of escBEACOPP were associated with considerably more acute grade 3–4 hematologic toxic effects as well as infections, which were more apparent during the last four cycles of therapy [6].

The late adverse effects of this schedule included an increased incidence of secondary acute myeloid leukemia (AML) (3.2% at 10 years) [10] and infertility in most male and female patients [11, 12].

In subsequent GHSG studies, the BEACOPP regimens were modified in an attempt to decrease the incidence of adverse effects while still maintaining the high cure rates obtained in the earlier reports. Preliminary analyses of these studies showed that less cumulative doses used in regimens such as four cycles of escBEACOPP followed by four cycles of baseline BEACOPP (HD12 trial) [13] or eight courses of BEACOPP-14 [7] resulted in similar survival rates and a reduced incidence of acute and late toxic effects compared with the earlier study using eight cycles of escBEACOPP.

The major goal of most of the current and planned studies in advanced HL is to attempt to individualize treatment so as to optimize survivorship while reducing the risk for late complications. These studies use risk- and/or response-adapted strategies, based on the IPS and early response to therapy according to 2-[fluorine-18]fluoro-2-deoxy-D-glucose (FDG)–positron emission tomography (PET)/computed tomography (CT) findings, utilizing them as a guide for escalating or de-escalating subsequent treatment.

Here, we report the results of a phase II study conducted in an attempt to reduce the toxicity of the original GHSG schedule (eight cycles of escBEACOPP), while attempting to preserve the improved initial tumor control obtained in patients with poor-risk (IPS ≥ 3) advanced HL. In this study, we employed the combination of two initial cycles of escBEACOPP followed by four cycles of ABVD, which was only given after a good imaging response was obtained, using the results of early PET/CT findings as a guide. The findings of early FDG–PET, carried out after the first two cycles of escBEACOPP, were evaluated retrospectively and then related to treatment failure and long-term outcome.

patients and methods

patients

During the period of January 2001 to May 2007, 45 newly diagnosed HL patients with Ann Arbor clinical stages bulky IIB or III–IV and an IPS ≥ 3 were included in this phase II study. Patients were eligible for this study if they were 18–65 years old. Inclusion criteria included Eastern Cooperative Oncology Group performance status of zero to one and adequate pulmonary, renal and hepatic function. Patients were excluded if they had infection with human immunodeficiency virus, concomitant severe infection, cardiovascular disease or if pregnant. All patients signed an informed consent in accordance with the institutional review boards.

study design

At diagnosis, all patients were staged with complete blood count, biochemistry, bone marrow trephine biopsy and by a baseline FDG–PET/CT scan. Patients received only two cycles of escBEACOPP as described [6], followed by reevaluation of their disease status clinically and by FDG–PET/CT scan. Early-interim PET–CT scan was carried out during the week after completion of the oral prednisone of the second escBEACOPP cycle and not earlier than 14 days after the last chemotherapy. We defined a ‘good response’ to the first two cycles of escBEACOPP as the conversion of early-interim PET activity to negative. Patients were also considered good responders in the presence of residual FDG uptake in previously involved sites, provided that the CT scan results were compatible with at least a partial response (PR), defined according to the international working group response criteria adopted in 1999 [14].

Good response patients continued to receive four cycles of ABVD, while those who did not achieve this response status were removed from the study and considered for salvage therapy followed by high-dose chemotherapy and autologous peripheral blood stem-cell transplantation (APBSCT).

All patients who continued to receive ABVD were then restaged by FDG–PET/CT 3–4 weeks after completion of all therapy. Patients who did not achieve complete response (CR) after completion of all therapy received cis-platinum-based salvage chemotherapy followed by APBSCT. At this stage, CR was defined as the disappearance of all clinical evidence of disease and PET negativity with or without a residual mass of any size. PR was defined as the presence of one or more PET-positive residual lesions at previously involved sites and a size reduction of the majority of large masses by >50%. Progressive disease (PD) was considered as a >50% increase in the largest diameter of any residual PET-positive lesion identified in the early-interim PET/CT or when any new PET-positive findings developed.

After completion of chemotherapy, patients were allowed to receive involved-field radiotherapy with 30 Gy to any initial site of bulky disease (≥20 cm maximal diameter) or mediastinum (one-third or more of the maximal thoracic diameter in the chest X-ray), according to the discretion of the treating physician. Patients continued to be followed with a chest radiograph and routine laboratory data carried out every 3 months during the first 2 years, every 6 months during years 3–5 and annually thereafter. FDG–PET/CT scans were carried out every 6 months during the first 2 years of follow-up.

The FDG–PET/CT scans were independently reviewed by three separate experienced nuclear medicine and radiology senior physicians with expertise in the field of PET/CT. FDG–PET scans were scored as positive or negative for disease activity based on visual assessment. Semiquantitative analyses were not used. PET results were defined as positive in the presence of focal or diffuse FDG uptake greater than that of the background, outside the physiological areas. A study was considered negative in the absence of pathologic FDG uptake at any site, including all sites of previously increased pathologic uptake.

statistical analysis

The primary end points in this study were progression-free survival (PFS) and OS. PFS was defined as the time from the initial onset of treatment until progression or relapse of HL or death from any cause. PR at the end of therapy was also considered as event for progression analysis. OS was measured from the onset of treatment until death from any cause. Survival curves were calculated by the methods of Kaplan and Meier [15]. The correlation between early-interim PET results and the PFS was assessed by the log-rank test.
results

patients

Forty-five consecutive patients who met the criteria outlined earlier were included in the study. The clinical characteristics of these patients are listed in Table 1. The median age was 27 years (range 18–59), with 32 males and 13 females. There were three (7%) patients with stage IIB, nine (20%) with stage III and 33 (73%) with stage IV disease. Thirty-six (80%) had B symptoms and the majority had extranodal involvement (33 patients), including bone marrow (15), bone (22), lung (nine) and liver (five). Bulky mediastinum was evident in 15 (33%) patients. Forty-four of the 45 patients had PET-positive scans pretreatment, while one had non-FDG-avid disease at the time of diagnosis.

response to the first two cycles of escBEACOPP and outcome after completion of all therapy

All 45 patients completed the treatment and all received the intended full dose of the first cycle of escBEACOPP. In two patients, the dose of cyclophosphamide and etoposide was reduced by 20% in the second cycle of escBEACOPP due to grade 4 infection and delayed recovery of blood counts, respectively. All 45 patients completed the subsequent four cycles of ABVD, receiving >85% of the planned full dosage. There were no treatment interruptions because of toxicity or toxic death. Five patients received involved-field radiotherapy (30 Gy to the initial site of bulky mediastinum) after completion of chemotherapy and all of these were in CR. Three of these five patients had negative early-interim PET scans and two had positive interim scans. Only one of these five patients who had a positive early-interim PET scan relapsed 5 months after completion of radiotherapy.

outcome according to early-interim PET activity

Early-interim PET was negative in 31 patients and of these, only one progressed during further therapy. Three of the 31 patients relapsed after completion of all therapy. Early-interim PET was positive in 13 patients and of these, nine patients converted to negative and achieved CR after completion of ABVD, three remained PET positive in PR and one progressed at the end of chemotherapy, and four of the five relapsed patients subsequently received one to two cycles of etoposide, solu-medrol, high-dose cytosine arabinoside and cis-platin salvage chemotherapy followed by high-dose carmustine (BCNU), etoposide, cytosine arabinoside and melphalan and APBSCT. One patient had minimal and localized relapse in the mediastinum and received involved-field radiation alone. Two patients with disease progression after APBSCT received reduced intensity conditioning followed by allogeneic stem-cell transplantation.

After a median follow-up of 48 months (range 18–82), 43 of the 45 patients are alive and two have died with PD. In all, PFS and OS at 4 years were 78% [95% confidence interval (CI) 65% to 90%; Figure 1A] and 95% (95% CI 88% to 100%; Figure 1B), respectively.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Total</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>27 (18–59)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>32 (71)</td>
</tr>
<tr>
<td>Histology, n (%)</td>
<td></td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>34 (75)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Stages, n (%)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>3 (7)</td>
</tr>
<tr>
<td>III</td>
<td>9 (20)</td>
</tr>
<tr>
<td>IV</td>
<td>33 (73)</td>
</tr>
<tr>
<td>Bulky mediastinum, n (%)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Extranodal involvement, n (%)</td>
<td>33 (73)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>15</td>
</tr>
<tr>
<td>Bone</td>
<td>22</td>
</tr>
<tr>
<td>Lung</td>
<td>9</td>
</tr>
<tr>
<td>Liver</td>
<td>5</td>
</tr>
<tr>
<td>International Prognostic Score, n (%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31 (69)</td>
</tr>
<tr>
<td>4–5</td>
<td>13 (29)</td>
</tr>
<tr>
<td>6–7</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Table 2. Response after completing all therapy according to early-interim PET results

<table>
<thead>
<tr>
<th>Early-interim PET results</th>
<th>Negative, n = 31 (21%)</th>
<th>Positive, n = 13 (29%)</th>
<th>Total*, n = 44 (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>30</td>
<td>9</td>
<td>39 (89%)</td>
</tr>
<tr>
<td>PR</td>
<td>–</td>
<td>3</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>PD</td>
<td>1</td>
<td>1</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

*One patient had non-FDG-avid disease at the time of diagnosis. This patient achieved CR based on the CT scan results alone after two cycles of escalated combination therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone and remained in CR at the end of therapy.

PET, positron emission tomography; CR, complete response; PR, partial response; PD, progressive disease; CT, computed tomography.
specificity for predicting 4-year PFS were 60% and 79%, respectively. The negative predictive value (NPV) was 87%, while the positive predictive value (PPV) was only 45%.

toxicity
As expected, the incidence of acute hematologic toxic effects was more frequently encountered in patients during the two cycles of escBEACOPP than in the ABVD phase of their therapy. Acute toxic effects evident during the escBEACOPP phase included grade 3/4 neutropenia in 83% of patients, grade 3/4 thrombocytopenia in 23% and grade 4 infections in only one patient. During this phase, 44% of the patients required hospitalization for febrile neutropenia. One patient developed cognitive impairment after completion of all therapy and one patient had avascular necrosis of the head of femur, diagnosed during the ABVD phase. There was no treatment-related mortality and until now, no cases of secondary AML or MDS have been encountered.

discussion
The results of this study indicate that two initial cycles of escBEACOPP followed by four cycles of ABVD is effective treatment of newly diagnosed advanced HL patients with IPS ≥3. We observed PFS of 78% and OS of 95% at 4 years after a median follow-up of 48 months. Despite the fact that our patient group is small and direct comparison difficult, the outcome of our patients is comparable with the estimated long-term survival rates (FFTF and OS of 82%, each at 5 years), obtained in the poor prognosis subgroup of patients who received eight cycles of escBEACOPP as reported in the HD9 trial [6].

The introduction of eight cycles of escBEACOPP in the GHSG HD9 trial [6] led to promising progress in the treatment of advanced-stage HL patients and undoubtedly, the improvement of long-term survival seen after this regimen was due to prolonged exposure to high concentrations of cytotoxic drugs. However, this schedule resulted in a marked increase in both short-term and long-term toxic effects, including severe hematologic adverse effects, infectious complication and infertility [6, 11, 12]. The cumulative incidence of secondary
malignancy, including AML/MDS, in that study was a matter of concern—6.8% at 10 years [10]. Consequently, further efforts have been made to develop new drug combinations utilizing a smaller total dose of chemotherapy attempting to achieve similar good results while minimizing toxicity as much as possible. Indeed, in the GHSG HD12 trial, it was evident that there was no statistical difference in patient outcome between the group receiving eight cycles of escBEACOPP and those treated with four cycles of escBEACOPP followed by four cycles of baseline BEACOPP [13]. Since then, Sieber et al. [7] have also reported comparable long-term survival rates and lower acute hematologic toxicity using the BEACOPP-14 regimen compared with the original escBEACOPP regimen.

In the light of the results of some of these earlier reports, we conducted our study in an attempt to further reduce the toxicity while still trying to maintain the improved initial control of disease by escBEACOPP. Taking into consideration the important role of achieving rapid tumor control as soon as possible after the beginning of treatment, particularly in this poor-risk subgroup of HL patients, we changed our policy of therapy. We decided to start with two cycles of escBEACOPP and then to de-escalate the treatment to four cycles of ABVD in those achieving a good clinical and imaging (FDG-PET/CT) response after the first two cycles of escBEACOPP. Furthermore, as the benefit of escBEACOPP was most pronounced in patients with high IPS [6], we limited the use of this regimen only to the poor-risk group (IPS ≥ 3), while those patients with an IPS of 0–2 received the standard ABVD therapy alone.

In our study, the incidence of severe hematologic toxic effects and the need for hospitalization during the first two cycles of escBEACOPP was not different from that reported in the GHSG HD9 trial [6]. However, as expected, these toxic effects were limited to the relatively short period of two escBEACOPP, while toxic effects were indeed only minimal during the ABVD phase of therapy. The data on the risk of infertility in our cohort of patients is not available yet, but we predict it to be lower than that reported for the patients who received the different BEACOPP regimens in the GHSG trials [11, 12]. Importantly, no cases of secondary malignancy, including AML/MDS, have been encountered in our cohort of patients until now, but median follow-up is currently only 48 months.

Although our data imply that combined escBEACOPP–ABVD may provide better results than ABVD alone in patients with advanced HL and a high IPS, this still needs to be confirmed in a larger prospective randomized study. Our results must still contend with the recently published data from the randomized HD2000 trial of the Italian Study Group, which showed that although the BEACOPP regimen used there (four cycles escBEACOPP followed by two courses of standard BEACOPP) was associated with a significantly better PFS than ABVD alone in patients with advanced HL, this difference did not translate into a superior OS rate [16]. In addition, the interim analysis of the randomized HD11 and HD14 trials for early-stage HL also showed comparable survival rates between BEACOPP regimens and ABVD, when combined with radiotherapy [13].

It should also be noted that our study only included patients <65 years because we anticipated unacceptable acute toxic effects in elderly patients during the initial escBEACOPP cycles and accordingly excluded them from the study. Indeed, the administration of BEACOPP variants in the HD9 and HD9elderly trials resulted in more dose reductions and early withdrawals in elderly patients due to excessive toxicity [6, 17]. The lower dose-intensity delivery in this subgroup of elderly patients may explain the results of the HD9 and HD9elderly trials, which showed no benefit of BEACOPP variants over COPP/ABVD in the 60- to 65-year-old subgroup and in patients >65 years [18].

In our study, all patients met the criteria for a good response after the first two cycles of escBEACOPP, which subsequently enabled us to de-escalate treatment and continue with the less toxic ABVD regimen in all patients. Since 29% of these patients also had positive PET scans at this stage, we were able to examine the prognostic value of early-interim PET activity. It should be noted, however, that the outcome of our patients and the predictive values of the early-interim PET in this study may possibly have been affected by the fact that a small number of patients also received consolidation with radiotherapy after completing their chemotherapy. This group included five patients in CR (three with negative and two with positive early-interim PET) and the only patient in this group who relapsed indeed had a positive early PET.

Recently, the prognostic significance of interim PET has been widely appreciated in advanced HL patients treated with ABVD. In the studies reported until now, most have shown that the results of PET carried out after two to three cycles of ABVD strongly predicted long-term outcome, with a NPV of 94%–100% and a PPV of 60%–100% [19–23]. In the prospective study reported by Gallamini et al. [20], there was a striking divergence in the outcome, with a 2-year PFS of 13% for early PET-positive patients versus 95% for early PET-negative patients. After multivariate analysis was carried out only, the early PET findings and the existence of stage IV disease were of independent prognostic value, while the value of the IPS variable was lost.

Until now, the role of early-interim PET activity as a prognostic tool in the context of escBEACOPP/BEACOPP regimens in advanced HL patients has not been established. In our study, the PET carried out after two cycles of escBEACOPP before de-escalation of therapy to ABVD had a relatively high NPV (87%) but a much lower PPV (45%). These findings were indeed different from those reported until now for early-interim PET results during ABVD treatment of advanced HL patients [19–23]. Nevertheless, the results of early PET still maintained a significant long-term prognostic role in terms of PFS presumably due to the relatively high NPV. Preliminary data presented by Gallamini et al. [24] appear to support the results of our study. The results of their study showed that PET carried out after two cycles of escBEACOPP retained its long-term prognostic role despite a PPV of 60%, which was also much lower than expected. Interestingly, PET carried out after completion of chemotherapy, for restaging and tailoring the need for further radiation in the BEACOPP-based HD15 trial, also had a very low PPV and a high NPV, which still proved to be prognostically significant in terms of long-term progression rates [25].

Collectively, it appears that PET activity has the potential to predict long-term outcome in advanced HL patients. However, it is still unclear whether alterations in treatment policy based
on the PET findings will result in improved survival. In this respect, the prospective study of Dann et al. [26] showed that subsequent escalation or de-escalation of therapy in HL patients, based on the results of cycle 2 FDG–PET or gallium scans, resulted in lower progression and relapse rates than expected. The ongoing HD18 trial of the GHSG is also currently evaluating the role of PET scan carried out after two cycles of escBEACOPP in patients with advanced HL. In this study, depending on the results of the early-interim PET scan, patients either receive intensified therapy (another six cycles of escBEACOPP combined with rituximab) or a reduced program of only two additional cycles of escBEACOPP. These two experimental arms are being compared with the control arm utilizing a total of eight cycles of escBEACOPP. Furthermore, in respect to the use of radiotherapy in these patients, the BEACOPP-based HD15 trial has already shown that consolidation radiotherapy can be omitted in PET-negative patients who still have a residual mass, without increasing the risk for disease progression or early relapse compared with patients in CR [25].

These and other ongoing and planned future studies, incorporating risk-adapted strategies based on PET activity in patients with advanced HL, will hopefully provide important information and an answer to the appropriate therapy to be given to patients with a positive interim or postchemotherapy PET scan. Given the significantly low PFS rate in the early PET-positive patients compared with the good outcome of early PET-negative patients evident in our study, we think it reasonable to explore the possibility of adding at least one additional cycle of escBEACOPP (total of at least three cycles) for good responders who still have residual FDG-avid disease after receiving the initial two cycles of escBEACOPP. The decision for de-escalation of escBEACOPP to ABVD in these patients would then be postponed and only be taken after another PET/CT carried out after the completion of the additional escBEACOPP cycles.

In conclusion, the current study shows that combined escBEACOPP–ABVD therapy is well tolerated and may improve the outcome in patients with advanced HL with high IPS. Based on our results and the existing data from other studies, it appears that eight cycles of escBEACOPP is an unreasonable choice for advanced HL patients, even for those with a high IPS, because of the noted toxicity encountered with this regimen. Our results provide a basis for planning future phase III studies, which combine initial escBEACOPP and sequential ABVD administration for advanced HL patients. The potential benefit of using early-interim PET activity as a guide to continuing therapy in patients with advanced-stage HL certainly merits further consideration in larger randomized studies in the future.

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**disclosures**

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**references**

20. Gallamini A, Hutchings M, Rigacci L et al. Early interim 1(18F)fluorodeoxy-D-glucose positron emission tomography is prognostically superior to international