Is BEACOPP Better than ABVD?

Bruce D. Cheson, MD

Corresponding author
Bruce D. Cheson, MD
Georgetown University Hospital, 3800 Reservoir Road, N.W.,
Washington, DC 20007, USA.
E-mail: bdc4@georgetown.edu

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The majority of patients with advanced Hodgkin's lymphoma are cured with currently available therapy, such as ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine). However, almost 20% of patients fail to achieve a complete remission and almost 40% relapse with prolonged follow-up. BEACOPP (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) was developed by the German Hodgkin's Study Group to improve on standard therapy by intensifying treatment and substituting the active agent etoposide for vinblastine and dacarbazine. Promising results led to the HD9 trial, in which escalated BEACOPP was superior to COPP/ABVD (cyclophosphamide, vincristine, prednisone, procarbazine/ABVD). Nevertheless, escalated BEACOPP is myelosuppressive and is associated with an increased risk of secondary malignancies. Modifications of BEACOPP have been developed in an attempt to increase efficacy and reduce the adverse effects. Whether BEACOPP should be selected in preference to ABVD may be determined by clinical stage, patient age, and other risk factors. The answer to whether escalated BEACOPP is superior to ABVD will require the results of an ongoing randomized trial.

Introduction

The treatment of patients with Hodgkin's lymphoma is one of the great successes of modern hematology/oncology. The first major advance was the introduction of MOPP, the combination of mechlorethamine mustard, vincristine, prednisone, and procarbazine, by DeVita et al. [1,2], which was curative for about half of the treated patients with advanced disease (stage III or IV). However, more than 20% of patients failed to enter a complete remission and another third relapsed. Moreover, MOPP is associated with an unacceptable rate of infertility and secondary malignancies. Santoro et al. [3] demonstrated that the ABVD regimen (Adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine) was successful in salvaging MOPP failures, and several studies confirmed that it was highly effective as front-line therapy, with about 90% of patients attaining a complete remission and two thirds still free from progression with prolonged follow-up [4–6]. Encouraging data were also published about MOPP alternating with ABVD [7] and an MOPP/ABV hybrid [8,9]. However, data from a series of randomized trials comparing ABVD with MOPP and MOPP alternating with ABVD [6] and comparing ABVD with the MOPP/ABV hybrid demonstrated that ABVD had superior efficacy compared with MOPP and it was at least comparable to MOPP/ABVD or the MOPP/ABV hybrid. Moreover, ABVD was associated with less toxicity and fewer secondary neoplasms [10]. Based on its efficacy and favorable toxicity profile, ABVD has become the standard chemotherapy for patients with early or advanced-stage disease [6,10]. Nevertheless, in a multicenter trial, almost 20% of patients did not achieve a complete remission with ABVD, and almost 40% failed therapy with prolonged follow-up [6].

Development of the BEACOPP Regimens

Attempting to improve patient outcome, Diehl et al. [11] modified their standard regimen of cyclophosphamide, vincristine, prednisone, procarbazine/ABVD (COPP/ABVD) by increasing the dose intensity, shortening the duration of therapy, and substituting another active agent, etoposide, for vinblastine and dacarbazine. The myelotoxic drugs were delivered on days 1 to 3 to allow for the administration of filgrastim from day 8 forward. These changes resulted in a series of highly effective BEACOPP regimens (bleomycin, etoposide, Adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone). In their first report of 30 patients with stage IIB to stage IV disease, 29 received the intended eight cycles of therapy with one of two BEACOPP regimens, differing in their dose of doxorubicin and etoposide [11]. The overall complete remission rate was 93% and the rate of freedom from treatment failure (FFTF) was 89% at a median follow-up of 40 months. The mean delivered dose intensity of drugs on both regimens was in the range of 90%, except for about 70% for vincristine because of its neurotoxicity. Grade IV leukopenia was reported in 34% and 21% for the two regimens, with no other significant toxicities. In a subsequent study, the German Hodgkin's

Table 1. BEACOPP clinical trials

Trial	Risk group	Design
HD11 [35,36]	Early stage, unfavorable	4 ABVD/IF vs 4 BEACOPP/IF
HD14	Early stage, unfavorable	4 ABVD/IF vs 2 eBEACOPP–2 ABVD/IF
HD9 [13]	Advanced	8 COPP/ABVD vs 8 BEACOPP vs 8 eBEACOPP
HD12 [21]	Advanced	4 eBEACOPP + 4 BEACOPP/IF
BEACOPP-14 [19,20]	Advanced	BEACOPP every 14 d
HD15 [36]	Stage IIB + risk factors; stage III/IV	8 eBEACOPP vs 6 eBEACOPP vs 8 BEACOPP-14
EORTC #20012 [36]	Advanced	8 eBEACOPP vs 8 ABVD

ABVD—Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine; BEACOPP—bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, vincristine, procarbazine, prednisone; eBEACOPP—escalated BEACOPP; EORTC—European Organisation for Research and Treatment of Cancer; HD—trials of the German Hodgkin's Study Group; IF—involved-field radiation.

Study Group (GHSG) further intensified the BEACOPP regimen using filgrastim support in 60 patients; this escalated BEACOPP resulted in a complete remission rate of 93% with a projected FFTF rate of 91% with a median follow-up of 32 months [12]. These impressive results, however, were accompanied by considerable toxicity. Grade III to IV neutropenia occurred in more than 70% of cycles but was rarely accompanied by infections (2%). Finally, in 2003, the GHSG published the results of Trial HD9, a randomized, phase III comparison of standard-dose BEACOPP, escalated BEACOPP, and COPP/ABVD in 1201 patients aged 15 to 65 years with stage IIB to stage IV disease (Table 1) [13]. The FFTF rate at 5 years favored the escalated BEACOPP arm (87%) over both standard BEACOPP (76%) and COPP/ABVD (69%). Five-year overall survival was 91% for escalated BEACOPP, 88% for standard BEACOPP, and 83% for COPP/ABVD. Early progression was least common with the escalated regimen. In a retrospective analysis, BEACOPP was also superior to COPP/ABVD in salvaging patients who relapsed following extended-field irradiation [14].

Experience with BEACOPP outside of Germany has thus far been limited. Dann et al. [15] reported on 108 patients with Hodgkin's lymphoma and adverse clinical features: stage I or II with bulky disease or disease-related symptoms, four or more sites of disease, an elevated erythrocyte sedimentation rate, age over 50 years, lymphocyte-depleted histology, "E" site, or stage III or IV disease. Patients were treated on the basis of a risk-adapted approach. Low-risk patients with early, unfavorable disease and those with standard risk but an International Prognostic Score (IPS) of 2 or less received two cycles of baseline BEACOPP. Patients considered at high risk because of an IPS of 3 or greater received two cycles of escalated BEACOPP; response was assessed by scanning with gallium or fluorodeoxyglucose positron emission tomography (FDG-PET). Those patients with a negative scan received four additional cycles of baseline BEACOPP, whereas those with residual disease received four cycles of escalated BEACOPP. The complete remission rate was 97% with 5-year event-free survival of 85% and overall survival of 90%. These values were similar between treatment groups. PET scan predicted outcome, with progression occurring in 27% of those with a positive scan, compared with only 2.3% with a negative study. The authors concluded that six cycles of treatment provide excellent results, and that PET scans could identify patients who would benefit from more intensive therapy. The latter conclusion requires confirmation by a prospectively randomized study.

Despite their impressive activity, the BEACOPP regimens are associated with substantial toxicities. Two thirds of women who receive escalated BEACOPP develop prolonged amenorrhea [16•], compared with one third receiving the baseline BEACOPP regimen and one half with COPP/ABVD. BEACOPP is also very myelosuppressive. In the HD9 trial, 70% of patients developed grade IV thrombocytopenia, with grade 4 leukopenia in 90% and grade 3 or 4 infections in 22% [13]. There were 1.8% fatal acute toxicities, primarily sepsis. Of greater concern is the 2.5% risk of secondary acute myeloid leukemia/myelodysplastic syndrome (AML/MDS), which is associated with an extremely poor outcome, 8% survival at 24 months [13,17]. In addition, the published rate of 1.2% of patients who developed a solid tumor would be expected to increase with longer follow-up [18].

The GHSG has produced a series of derivations of BEACOPP designed to improve on the BEACOPP results or to reduce the toxicity of the program. A more dose-dense BEACOPP-14 regimen, also using filgrastim or peg-filgrastim support, was used to treat 41 patients with high-risk disease [19,20]. Patients received up to eight cycles of therapy, resulting in a complete remission rate of 85%. Importantly, 90% of cycles were delivered, and 81% of cycles were given at full dose and on schedule. How the long-term results of this regimen will compare with the earlier BEACOPP programs remains to be determined by a randomized trial. In the current HD15 trial, patients are randomized to eight courses of escalated BEACOPP, six courses of escalated BEACOPP, or eight courses of baseline BEACOPP-14.

In the HD12 trial, GHSG investigators randomized patients with advanced-stage Hodgkin's lymphoma to either eight cycles of escalated BEACOPP or four cycles of

escalated BEACOPP followed by four cycles of the baseline regimen [21]. To date there is no difference in FFTF or overall survival by treatment regimen. The rate of secondary AML and MDS was reduced by half compared with the HD9 trial, perhaps in part because fewer patients in the new trial received radiation therapy.

Which Regimen is Superior?

Is BEACOPP superior to ABVD? The answer clearly will depend on the patient population being treated, the clinical setting, and the BEACOPP regimen being used. The benefit may differ for patients with different prognoses. In 1998, Hasenclever and Diehl [22] published the International Prognostic Score (IPS) for Hodgkin's lymphoma. The data were based on analyses of 5141 patients treated with combination chemotherapy with or without radiation therapy at 25 international centers and lymphoma study groups. Using freedom from progressive disease as the major endpoint of interest, seven adverse factors with independent prognostic effect were identified: serum albumin less than 4 g/dL, hemoglobin level less than 10.5 g/dL, male sex, age 45 years or older, stage IV disease, leukocytosis of at least 15,000/mm^3, and lymphopenia with a lymphocyte count below 600/mm^3 or 8% of the white blood cell count (or both). Based on the number of adverse factors, patients could be distinguished into risk groups that correlated with outcome, as shown on Table 2. This scheme permits a risk-benefit assessment of various regimens.

For example, patients with low-risk Hodgkin's lymphoma (0 or 1 IPS factors) have a long-term survival rate with ABVD therapy that is greater than 90%. Because the rate of treatment-related death with escalated BEACOPP is almost 2% and the risk of AML/MDS is 2.5%, it would be difficult to justify BEACOPP in that patient population. For patients with intermediate-risk disease, the GHSG conducted protocol HD11 including those patients with clinical stage I or IIA with any risk factors, as well as those with stage IIB with an elevated erythrocyte sedimentation rate and/or at least three nodal areas involved. The study addressed questions of both chemotherapy and radiation therapy. Patients were randomized to four cycles of either ABVD or baseline BEACOPP plus either 20 or 30 Gy of involved-field radiation therapy. There was no difference among the arms, with a 2-year overall survival of 97.4% and FFTF of 89.9%. Thus, ABVD appears to be adequate for this group; there is little justification for standard BEACOPP or the escalated regimen. The HD13 trial is comparing ABVD with AVD, ABV, and AV in an attempt to maintain the efficacy of ABVD while reducing its toxicities in patients with stage I or II disease and without either a large mediastinal mass, extranodal disease, an elevated sedimentation rate, or three or more involved lymph node areas. For patients with early-stage unfavorable disease, the GHSG is conducting trial HD14, comparing four cycles of ABVD with two cycles of escalated BEACOPP followed by two cycles of ABVD, both followed by 30 Gy of involved-field irradiation.

Table 2. International Prognostic Score for Hodgkin's lymphoma

Adverse prognostic factors*, *n*	Freedom from progression of disease, %	Patients, %
0	84	7
1	77	22
2	77	29
3	60	23
4	51	12
5+	42	7

*Factors are serum albumin less than 4 g/dL, hemoglobin level less than 10.5 g/dL, male sex, age 45 years or older, stage IV disease, leukocytosis of at least 15,000/mm^3, and lymphopenia with a lymphocyte count below 600/mm^3 or 8% of the white blood cell count (or both).
(*Data from* Hasenclever and Diehl [22].)

The question of the superior regimen becomes most relevant for patients with advanced-stage disease. Based on the HD9 study already described, escalated BEACOPP is superior to baseline BEACOPP and COPP/ABVD for patients with stage IIB, III, or IV disease based on a prolongation of survival and FFTF [13]. However the comparator, the COPP/ABVD regimen, is not widely used and is itself associated with about a 2% risk of secondary solid tumors [18]. Escalated BEACOPP was associated with an increased risk of malignancies compared with COPP/ABVD, and both are most likely associated with a higher risk of malignancies than ABVD by itself [10]. BEACOPP is also more expensive than regimens such as ABVD, and whether it is cost-effective with regard to the cost of the drugs as well as the consequences of the therapy remains to be determined. Decision making about the optimal regimen for initial therapy for high-risk patients should also consider the options in the event of relapse. Given the number of drugs used in escalated BEACOPP and the intensity of that regimen, it is quite unlikely that salvage therapy will be as successful following BEACOPP or COPP/ABVD as it would be after ABVD. However, this possibility must be weighed against the fact that fewer patients are likely to relapse following escalated BEACOPP. Clearly, a direct comparison of escalated BEACOPP with ABVD, such as is currently being conducted in Europe as EORTC 20012, is an important question (Table 1). BEACOPP also includes two agents that we are trying to eliminate from future treatment strategies: bleomycin, which has questionable activity and considerable toxicity, and dacarbazine, which is highly emetogenic. Towards this end, the Cancer and Acute Leukemia Group B (CALGB) cooperative group has recently completed a study of a novel regimen including Adriamycin, vinblas-

tine, and gemcitabine in previously untreated patients with early-stage Hodgkin's lymphoma. If the results are promising, this regimen could be the basis for the next generation of clinical trials.

In the HD9 study, a large proportion of patients received radiation therapy. One could argue about whether the radiation is actually needed, especially in patients with advanced-stage disease. Moreover, the administration of radiation may hinder subsequent stem cell harvest at the time of relapse.

Thus, given the risks of BEACOPP but considering its impressive activity, we need to identify those patients who are most likely to benefit from this regimen. Performing a subset analysis of the HD9 results, the rate of early progression and FFTF favored escalated BEACOPP over COPP/ABVD regardless of the risk group. The survival benefit for escalated BEACOPP compared with COPP/ABVD was of greatest significance in the high-risk patients (IPS 4 to 7), who represented 13% to 16% of patients in this study by arm, or 19% in the IPS cases [22]. There was no apparent difference in survival between escalated BEACOPP (82%) and baseline BEACOPP (81%) in this group of patients.

The standard BEACOPP regimen has been evaluated in patients aged 66 to 75 years, who accounted for 13% to 16% of patients on the HD9 trial. Patients were randomized to either BEACOPP baseline or COPP/ABVD [23]. There was no difference between the two regimens in rate of complete remission (76%), overall survival (50%) or FFTF (46%). Unfortunately, there were 8% treatment-related deaths with COPP-ABVD and 21% with BEACOPP.

BEACOPP also has been used in a small number of patients with HIV-associated Hodgkin's lymphoma. One third of these patients were unable to complete the full courses of therapy and two died of opportunistic infections while receiving treatment [24].

Future Directions

Whereas the outcome for the majority of patients with Hodgkin's lymphoma is excellent as a result of regimens such as ABVD and the BEACOPPs, there is considerable room for improvement in efficacy for high-risk patients and for reduction of acute and long-term toxicities for all patients. For example, one goal of therapy should be to eliminate those drugs with the poorest risk-to-benefit ratio, and possibly to substitute other effective agents. Bleomycin is an agent with only modest activity in Hodgkin's lymphoma but with considerable toxicity [25,26]. Martin et al. [26] have provided data to suggest that bleomycin pulmonary toxicity is associated with a poor outcome in Hodgkin's lymphoma. They treated 141 patients with bleomycin-containing chemotherapy as their initial therapy; bleomycin toxicity was identified in 18%, defined by the presence of pulmonary symptoms with interstitial infiltrates on chest x-ray or CT in the absence of infection. This adverse event correlated with increasing age, use of the ABVD regimen, and the administration of granulocyte colony-stimulating factor (G-CSF). For those patients with bleomycin toxicity, 5-year survival was 63%, compared with 90% for those who were not affected. In addition, there was a 4.2% mortality rate from bleomycin pulmonary toxicity in the group as a whole, and 24% in patients who developed the syndrome. Importantly, omitting the bleomycin once toxicity developed did not change patient outcome.

Gemcitabine is a highly active agent with response rates as high as 50% in patients with relapsed and refractory Hodgkin's lymphoma [27,28]. As a result, the GHSG treated 27 patients with stage IIB disease and risk factors or stage III or IV disease using a modified escalated BEACOPP regimen in which gemcitabine was substituted for the etoposide and vinblastine (BAGCOPP) [29•]. The dose of gemcitabine was 800 mg/m^2 on days 1 and 4 of each cycle. After 14 patients were treated, the hematologic toxicity was considered excessive and the regimen was modified to eliminate the dose of gemcitabine on day 4. In addition, eight patients developed pulmonary toxicity, terminating the study. The authors concluded that this adverse event was related to the concomitant administration of gemcitabine and bleomycin. This report confirmed the previous observations of added toxicity from these two agents previously reported by Friedberg et al. [30]. Although 24 patients treated with BAGCOPP received all eight of the planned cycles, only 54 of the 212 cycles were delivered as planned. Nevertheless, 25 patients remained in continuous complete remission at a median follow-up of 27 months. In contrast, CALGB investigators have combined gemcitabine with liposomal doxorubicin and vinorelbine to form an effective regimen (DVG) for patients with relapsed or refractory disease [31]. Other new agents of potential interest include the monoclonal antibodies directed against the CD30 antigen. Thus, the successor CALGB study has built on the DVG regimen by adding an anti-CD30 monoclonal antibody, SGN-30.

Clearly, the treatment of Hodgkin's lymphoma is becoming more risk-adapted. Risk is defined by the IPS score before treatment begins. However, it would be more valuable to have additional measures that predict which patients will require a standard regimen and which might require more intensive treatment. One means is use of mid-treatment FDG-PET scans [32,33••]. For example, trials in Great Britain and within the CALGB in the United States are exploring whether a PET scan can identify those patients with early-stage Hodgkin's disease who might require less therapy. A PET-based question in patients with bulky stage I or II disease is whether radiation therapy is necessary. Appropriate clinical questions for patients with stage III or IV disease and an IPS score of 0 to 3 include whether the number of cycles of chemotherapy can be reduced based on PET findings. For those patients with stage III or IV disease, PET should be evalu-

ated as a measure to determine whether therapy should be modified after several cycles of treatment. In the future, other technologies, such as gene expression profiling, may provide additional information to direct therapy [34].

Conclusions

Given the information currently available, the answer to the question "Is BEACOPP better than ABVD?" is unknown. To date, we have only indirect evidence. In the HD9 trial, the overall results with escalated BEACOPP were superior to COPP/ABVD [13]. Nevertheless, the impact was most pronounced in patients with higher-risk disease. Because there was no difference among treatment arms for the 64 patients between the ages of 60 and 64 years in that trial, and because the regimen is poorly tolerated in patients over the age of 65 years [23], escalated BEACOPP appears to be of greatest benefit for those patients with higher-risk disease who are under the age of 60 years and who are HIV-negative [24]. However, the true answer to the question will be resolved, in part, by the ongoing international trial led by the European Organisation for Research and Treatment of Cancer (EORTC #20012), which is a direct comparison of the two regimens. We eagerly await the results of that study, but we still will not know how ABVD will compare to the next generation of equally effective but less toxic BEACOPP programs.

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