Eleventh Biannual Report of the Cochrane Haematological Malignancies Group: Focus on Hodgkin Lymphoma

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The 11th biannual report of the Cochrane Haematological Malignancies Group highlights recently published randomized controlled trials in the field of hemato-oncology that were identified through the continuous systematic search of MEDLINE. For this electronic search, a broad search filter covering all topics in hemato-oncology was combined with a highly sensitive search filter for randomized studies. This report covers publications from February 1, 2009, through August 31, 2009 (including electronic publications). For this 7-month period, 6344 potentially interesting articles were screened to identify 121 controlled clinical trials (randomized controlled trials or quasi-randomized clinical trials) of therapeutic interventions in hematologic malignancies.

In this summary of key features of recent randomized controlled trials, we focus on Hodgkin lymphoma. Two recently published trials in patients with Hodgkin lymphoma are presented in detail. They examine different therapeutic regimens for first-line therapy of patients with
advanced Hodgkin lymphoma. In less detail, we present the results of three other interesting hematological trials whose results were published during the 7-month period from February 1, 2009, through August 31, 2009. After a short overview of the clinical relevance and the selection of patients for the Hodgkin lymphoma trials, we discuss important methodological aspects of each trial (eg, randomization, dropout rate, and statistical analysis). We also discuss the results of the primary efficacy endpoints and overall survival. In addition, we will present a short summary of newly published Cochrane reviews and protocols from our group. The main objective of this report was to provide the information in a way that busy practitioners can easily interpret it.

Published Trials in Patients With Hodgkin Lymphoma From February 1, 2009, Through August 31, 2009 (1)

Hodgkin lymphoma is a malignant disease of the lymphatic system. With an annual incidence of two to three diagnoses per 100,000 in Western countries, Hodgkin lymphoma is a comparatively rare disease. But it is one of the most common malignancies in young adults (2,3). Staging of Hodgkin lymphoma is based on the Ann Arbor system (4), B symptoms, and risk factors (eg, large mediastinal mass, three or more involved lymph node areas, high erythrocyte sedimentation rate, extranodal lesion, and advanced age). Generally, Hodgkin lymphoma is classified into early favorable, early unfavorable, and advanced stage (5,6). The standard treatment for patients with early-stage Hodgkin lymphoma is two to six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy with or without involved field radiation therapy (7,8). For the treatment of early unfavorable and advanced-stage Hodgkin lymphoma, there are two different international standards: chemotherapy with an ABVD regimen and chemotherapy with an escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen (8). The trials that we discuss in this commentary present results of different BEACOPP regimens compared with ABVD or ABVD-including regimens for treatment of patients with advanced Hodgkin lymphoma.

Trial 1: Escalated-Dose BEACOPP in the Treatment of Patients With Advanced-Stage Hodgkin’s Lymphoma: 10 Years of Follow-up of the GHSG HD9 Study (9)


Clinical Background.
The German Hodgkin Study Group (GHSG) developed and examined a regimen for the treatment of advanced-stage Hodgkin lymphoma consisting of BEACOPP. The escalated BEACOPP schedule combined a time (shorter cycle) and dose (increased single dose) increased scheme (Table 1).

**Contribution.**

The GHSG HD9 trial enrolled 1282 previously untreated patients with advanced Hodgkin lymphoma. The trial compared eight cycles of BEACOPP escalated with eight cycles of the baseline dose variant of BEACOPP and eight cycles of cyclophosphamide, vincristine, procarbazine, and prednisone (COPP) plus ABVD. Because of the statistically significant superior freedom from treatment failure rates in both BEACOPP arms compared with the COPP plus ABVD arm, assignment to the COPP plus ABVD arm was stopped by the safety board after the first interim analysis.

A previous publication (10) presented outcome data of this trial after 5 years of follow-up. This article (9) presents the long-term results after 10 years of follow-up, which show that advantages in terms of overall survival and freedom from treatment failure become more pronounced with follow-up. The absolute difference in overall survival between COPP plus ABVD and escalated BEACOPP was 11% at 10 years compared with 9% at 5 years of follow-up. The study also presents data regarding secondary malignancies, which were not statistically significantly different between the three treatment arms.

**Implication for Practice.**

The 10-year follow-up of the HD9 trial demonstrates that eight courses of escalated BEACOPP were more effective for patients with advanced-stage Hodgkin lymphoma than eight courses of BEACOPP baseline and that both are more effective than eight courses of COPP plus ABVD.

**Most Interesting Feature.**

This trial reports long-term results in terms of overall survival and secondary malignancies. Key study features are shown in Table 2.

**Trial 2: ABVD Compared With BEACOPP Compared With CEC for the Initial Treatment of Patients With Advanced Hodgkin’s Lymphoma: Results From the HD2000 Gruppo Italiano per lo Studio dei Linfomi Trial (11)**

**Clinical Background.**

The HD2000 trial compared ABVD, BEACOPP, and cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin (CEC).

**Contribution.**

The study enrolled 307 previously untreated patients with advanced Hodgkin lymphoma. They were randomly assigned to six courses of ABVD, to four escalated plus two standard courses of BEACOPP, or to six courses of CEC. After a median follow-up time of 41 months, patients treated with BEACOPP showed statistically significant better failure-free survival and progression-free survival than patients treated with ABVD. However, this better outcome of failure-free survival or progression-free survival by BEACOPP did not lead to improved overall survival for these patients. The survival curves of all three arms were similar. In addition, patients treated with BEACOPP showed lower risk of disease progression or relapse, but they also had more frequent severe treatment-related adverse events.

**Implication for Practice.**

Fewer cycles of BEACOPP escalated were used in this trial than in the BEACOPP trial discussed above. Although four escalated plus two standard courses of BEACOPP led to an improved progression-free survival, it is too early to determine whether there will be an improvement in overall survival.

**Most Interesting Feature.**

This is another trial that demonstrated superiority of BEACOPP escalated. Key study features are shown in Table 3.

**Other Interesting Trials**


This randomized controlled trial examined the effectiveness of azacitidine compared with the three most common conventional care regimens (best supportive care, low-dose cytarabine, or intensive chemotherapy). Patients older than 17 years of age with higher-risk myelodysplastic syndromes (international prognostic scoring system rating of intermediate-2 or high risk) were enrolled. They were randomly assigned to either six cycles of azacitidine (n = 179) or a predefined conventional care regimen (n = 179). Conventional care regimen was selected by the investigators before randomization (in the best supportive care regimen, 117 patients were randomly assigned to the azacitidine arm and 105 to the control arm; in the low-dose cytarabine regimen, 45 patients to the azacitidine arm and 49 to the control arm; for the intensive chemotherapy regimen, 17 patients to the azacitidine arm and 25 to the control arm). After a median follow-up of 21.1 months (range = 15.1–26.9 months), the overall survival was improved in patients who received azacitidine compared with those who received conventional care regimens (hazard ratio [HR] for overall survival = 0.58, 95% confidence interval [CI] = 0.43 to 0.77, *P* = .001). Additionally, the median time to acute myeloid leukemia transformation in the azacitidine group was also statistically significantly increased (17.8 months compared with 11.5 months in the conventional care group, HR = 0.50, 95% CI = 0.35 to 0.70, *P* < .001). A methodological issue of this interesting trial is the unclearness of the criteria for assigning a patient to one of the three conventional care regimens, which may cause bias (13). Different centers and investigators might have different principles for treatment decisions that may lead to unequal patient characteristics in the experimental and control groups. Further trials with more rigid treatment decisions would be welcome.

**Trial 4: Phase III Randomized Study of Bendamustine Compared With Chlorambucil in Previously Untreated Patients With Chronic Lymphocytic Leukemia (14)**


This randomized controlled trial was initiated to compare the efficacy and tolerability of bendamustine with those of chlorambucil in previously untreated patients with chronic
lymphocytic leukemia. Patients who were aged up to 75 years with a Binet stage of B or C and World Health Organization performance status of 0–2 were included. They were randomly assigned to up to a maximum of six courses of bendamustine \((n = 162)\) or to six courses of chlorambucil \((n = 157)\). Overall response rate, which was defined as the sum of complete and partial responses, was the primary endpoint. After a median follow-up time of 35 months \((\text{range} = 1–68 \text{ months})\), the overall response rate was statistically significantly higher in the bendamustine-treated patients \((68\%)\) than in the chlorambucil-treated patients \((31\%)\) \((P < .001)\). The progression-free survival was also statistically significantly improved in the bendamustine group \((21.6 \text{ months})\) than in the chlorambucil group \((8.3 \text{ months})\) \((P < .001)\). However, after 3 years of follow-up, the observed overall survival tended to be better for the bendamustine group, but it was not statistically significant. Further trials with longer follow-up and more patients are needed to determine whether bendamustine improves overall survival compared with chlorambucil when used as a first-line treatment of chronic lymphocytic leukemia.

**Trial 5: Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients (15)**


This randomized controlled trial examined the effects of exercise training in patients, older than 17 years of age, with Hodgkin or non-Hodgkin lymphoma, who were receiving chemotherapy or no treatment. Baseline exercise was not a reason for exclusion, but patients were asked not to improve the training level during the time of study. Among the 122 patients \((\text{who are 9\% of the 1306 screened and 26\% of the 476 eligible patients})\), 60 were randomly assigned to supervised aerobic exercise training and 62 were randomly assigned to usual care. The primary endpoint was patient-rated physical functioning assessed by the Trial Outcome Index–Anemia. At the end of the 12 weeks of the training program, the exercise group was statistically significantly superior to usual care in terms of patient-rated physical functioning \((\text{mean group difference} = 9.0, 95\% \text{ CI} = 2.0 \text{ to } 16.0, P = .012)\), overall quality of life \((P = .021)\), fatigue \((P = .013)\), happiness \((P = .004)\), depression \((P = .005)\), general health \((P = .001)\), cardiovascular fitness \((P = .001)\), and lean body mass \((P = .008)\). However, 6 months after the intervention ended, 63.6\% of the exercise group and 40.0\% of the usual care group reported self-managed regular exercise. At that time, exercise group was still statistically significantly superior to usual care for overall quality of
life \((P = .054)\), happiness \((P = .034)\), and depression \((P = .009)\). Interpretation of this study was challenging. The effect on quality of life was not mediated by the improvement in physical fitness. Therefore, other factors may have influenced the improvement in quality of life. Suggestions given by the authors included increased social interaction and distraction from cancer and its treatments. Even if it is unclear which effects improve outcomes, an aerobic exercise program may have a positive influence on quality of life for lymphoma patients.

**New Reviews of the Cochrane Haematological Malignancies Group in the Cochrane Library**


*Contribution.*

Erythropoiesis-stimulating agents reduce anemia in cancer patients and may improve quality of life, but there are concerns that erythropoiesis-stimulating agents might increase mortality. Earlier reviews (17–20) of the research showed that erythropoiesis-stimulating agent treatment reduces the need for transfusion, but, in recent years, several studies (21–23) have shown that erythropoiesis-stimulating agents themselves cause harm. The drug may, for example, stimulate tumor growth and cause potentially fatal blood clots. In 2007, studies (23–25) reported that erythropoiesis-stimulating agents shortens survival in people with breast, non–small cell lung, head and neck, lymphoid, and cervical cancers.

It was concluded that a new systematic review was needed to evaluate the old and the new evidence together and to determine the impact of erythropoiesis-stimulating agents on survival in cancer patients to see whether there are groups of patients who are at higher or lower risk than the average patient. To complete this study, the authors of this meta-analysis conducted an in-depth assessment of the individual patient data that was generated by the care of approximately 14,000 patients from 53 trials that were conducted worldwide. Data on each of these patients were provided by three companies that make erythropoiesis-stimulating agents (ie, Amgen, Johnson & Johnson, and Roche) and by several independent researchers (24–28). (The drug companies, however, had no role in conducting the meta-analysis.) The trials investigated one of the two types of erythropoiesis-stimulating agents (erythropoietin or darbepoetin) and compared the use of one of these drugs plus red blood cell transfusion (as needed) with red blood cell transfusion alone (as needed). Most patients were given their treatment while undergoing anticancer therapy.
(chemotherapy and/or radiation therapy), but other patients received treatment with an erythropoiesis-stimulating agent after they had completed their anticancer therapy. Some patients already had anemia; others were treated to prevent it. The patients had many different forms of cancer and had received many different anticancer treatments. The review showed that erythropoiesis-stimulating agents increased the on-study mortality (HR = 1.17, 95% CI = 1.06 to 1.30) and worsened overall survival (HR = 1.06, 95% CI = 1.00 to 1.12). The authors concluded that treatment with an erythropoiesis-stimulating agent shortened survival. They could not, however, identify with certainty any subgroup of patients at either increased or decreased risk of dying when taking erythropoiesis-stimulating agents.

**Implications for Practice.**

For patients undergoing chemotherapy, the increased mortality and worsened overall survival was less pronounced, but an adverse effect of erythropoiesis-stimulating agent could not be excluded. With the help of their doctors, cancer patients should consider the risks of taking erythropoiesis-stimulating agent against the risks of a blood transfusion. Be aware, however, that uncertainties remain about the magnitude of each treatment option.

**New Protocols of the Cochrane Haematological Malignancies Group in the Cochrane Library**


Herbst C, Naumann F, Bohlius J, Skoetz N, Monsef I, Engert A. Antibiotics plus colony stimulating factors versus antibiotics alone for the prevention of infections in cancer patients


**Funding**

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**References**


27. Moebus V, Lueck H, Thomssen C, et al. The impact of epoetin-alpha on anemia, red blood cell (RBC) transfusions, and survival in breast cancer patients (pts) treated with dose-dense


**Table 1.** The escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen*  

<table>
<thead>
<tr>
<th>Drug</th>
<th>Single dose, mg/m²</th>
<th>Route</th>
<th>Days given†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>10</td>
<td>iv</td>
<td>8</td>
</tr>
<tr>
<td>Etoposide</td>
<td>200</td>
<td>iv</td>
<td>1–3</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>35</td>
<td>iv</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>1200</td>
<td>iv</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4</td>
<td>iv</td>
<td>8</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100</td>
<td>po</td>
<td>1–7</td>
</tr>
<tr>
<td>Prednisone</td>
<td>40</td>
<td>po</td>
<td>1–14</td>
</tr>
<tr>
<td>G-CSF</td>
<td>sc</td>
<td>From day 8 onward</td>
<td></td>
</tr>
</tbody>
</table>

*G-CSF = granulocyte colony-stimulating factor; iv = intravenously; po = orally; sc = subcutaneous.

†The regimen has to be repeated on day 22.

**Table 2.** Key study features for Engert et al. (9)*  

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size calculation</td>
<td>80% power for the detection for the absolute difference terms of FFTF of 10%</td>
</tr>
<tr>
<td>Randomization</td>
<td>Generation of allocation sequences was by computer, and allocation was by telephone call to the trial coordination center</td>
</tr>
<tr>
<td>Blinding</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Setting</td>
<td>Centers included 370 hospitals and practices in Germany, Switzerland, Austria, and the Czech Republic</td>
</tr>
<tr>
<td>Patients</td>
<td>Newly diagnosed patients aged 16–65 years, with histologically proven Hodgkin lymphoma of stage IIB or IIIA plus risk factors or of stage IIB or IV and Karnofsky performance status of &gt;70%</td>
</tr>
<tr>
<td>Study drug regimen</td>
<td>Study arm 1 = eight courses of BEACOPP escalated</td>
</tr>
<tr>
<td>Study arm 2</td>
<td>Study arm 2 = eight courses of BEACOPP baseline</td>
</tr>
<tr>
<td>Study arm 3</td>
<td>Study arm 3 = eight courses of COPP plus ABVD</td>
</tr>
</tbody>
</table>
**Feature** | **Details**
---|---
**Patient flow** | No. of patients randomly assigned to treatment = 1282
Total No. of patients analyzed = 1196

- No. of patients per arm = 466 in BEACOPP escalated arm, 469 in BEACOPP baseline arm, 261 in COPP plus ABVD arm
- No. of dropouts = not reported
- No. of protocol violations = not reported

**Duration of follow-up** | Median follow-up = 111 months (range = 3–167 months)

**Analysis** | Authors stated that all analyses were conducted according to the intention-to-treat principle, but 86 patients were excluded from analysis after randomization. Details about these patients were given.

**Outcomes** | Primary outcome = FFTF, defined as progression during treatment, lack of complete response at the end of treatment, relapse, or death from any cause

- Secondary outcomes = OS, response, or toxicity

**Results** | FFTF at 10 years: Statistically significant differences were found among the BEACOPP escalated arm (82%, 95% CI = 78% to 86%), the BEACOPP baseline arm (70%, 95% CI = 66% to 75%), and the COPP plus ABVD arm (64%, 95% CI = 58% to 70%) ($P < .001$). In the subgroup of patients aged >60 years, no FFTF differences were found in terms of FFTF between COPP plus ABVD and BEACOPP escalated.

- Overall survival at 10 years: Statistically significant differences were found among the BEACOPP escalated arm (86%, 95% CI = 83% to 90%), the BEACOPP baseline arm (80%, 95% CI = 75% to 84%), and the COPP plus ABVD arm (75%, 95% CI = 70% to 81%) ($P < .001$).

- Complete response rate = 96% (95% CI = 93% to 97%) in the BEACOPP escalated arm, 88% (95% CI = 85% to 91%) in the BEACOPP baseline arm, and 85% (95% CI = 80% to 89%) in the COPP plus ABVD arm.

- Total secondary malignancy rate = 6.5% in the BEACOPP escalated arm, 7.9% in the BEACOPP baseline arm, and 5.3% in the COPP plus ABVD arm ($P = .82$).
Table 3. Key study features for Federico et al. (11)*

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size calculation</strong></td>
<td>80% power to detect a hazard ratio of 0.4 for failure between the BEAC OPP and CEC arms</td>
</tr>
<tr>
<td>Randomization</td>
<td>Generation of allocation sequences and allocation = not reported</td>
</tr>
<tr>
<td>Blinding</td>
<td>Not blinded</td>
</tr>
<tr>
<td>Setting</td>
<td>Centers = not reported</td>
</tr>
<tr>
<td>Patients</td>
<td>Previously untreated patients aged &gt;16 years, with histologically confirmed diagnosis of Hodgkin lymphoma, clinical stage IIB, III, or IV, and Eastern Cooperative Oncology Group performance status = 0–3</td>
</tr>
<tr>
<td>Study drug regimen</td>
<td>Study arm 1 = six courses of ABVD</td>
</tr>
<tr>
<td></td>
<td>Study arm 2 = four escalated plus two standard courses of BEAC OPP</td>
</tr>
<tr>
<td></td>
<td>Study arm 3 = six courses of CEC</td>
</tr>
<tr>
<td>Patient flow</td>
<td>Total No. of patients randomly assigned to treatment = 307</td>
</tr>
<tr>
<td></td>
<td>No. of patients per arm = 103 in the ABVD arm, 102 in the BEAC OPP arm, and 102 in the CEC arm</td>
</tr>
<tr>
<td></td>
<td>No. of patients analyzed per arm = 99 in the ABVD arm, 98 in the BEAC OPP arm, and 98 in the CEC arm</td>
</tr>
<tr>
<td></td>
<td>No. of dropouts = not reported</td>
</tr>
<tr>
<td></td>
<td>No. of protocol violations = not reported</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td>Median follow-up = 41 months (range = 4–91 months)</td>
</tr>
<tr>
<td>Analysis</td>
<td>Authors stated that all analyses were conducted according to the intention-to-treat principle; however, 12 patients (four in the ABVD arm, four in the BEAC OPP arm, and four in the CEC arm) were excluded from analysis after randomization. Detailed reasons for exclusion were presented</td>
</tr>
</tbody>
</table>
**Feature** | **Details**
--- | ---
**Outcomes** | Primary outcome = FFS was defined from the date of study entry to the last follow-up or to one of the following events: any response other than complete remission at the end of therapy, progression, relapse, or death from any cause. Secondary outcomes = OS, PFS, complete response rate, relapse-free survival, and toxicity.

**Results** | BEACOPP showed statistically significant improved FFS vs ABVD ($P = .036$). Estimated 5-year FFS = 65% (95% CI = 53% to 74%) in the ABVD arm, 78% (95% CI = 67% to 86%) in the BEACOPP arm, and 71% (95% CI = 60% to 79%) in the CEC arm. BEACOPP showed statistically significant improved PFS vs ABVD ($P = .038$). Estimated 5-year PFS = 68% (95% CI = 56% to 78%) in the ABVD arm, 81% (95% CI = 70% to 89%) in the BEACOPP arm, and 78% (95% CI = 68% to 86%) in the CEC arm. Survival curves of the three arms were similar ($P$ value not reported). Estimated 5-year OS = 84% (95% CI = 69% to 92%) in the ABVD arm, 92% (95% CI = 84% to 96%) in the BEACOPP arm, and 91% (95% CI = 81% to 96%) in the CEC arm. Complete response rates were similar in the three arms ($P = .207$): 84% (95% CI = 76% to 91%) in the ABVD arm, 91% (95% CI = 85% to 97%) in the BEACOPP arm, and 83% (95% CI = 75% to 90%) in the CEC arm.

**Safety** | Acute toxicity grade 3 or 4:

- Anemia (5% in the ABVD arm, 16% in the BEACOPP escalated arm, and 15% in the CEC arm) ($P = .038$)
- Leukopenia (22% in the ABVD arm, 57% in the BEACOPP escalated arm, and 47% in the CEC arm) ($P < .001$)
- Neutropenia (34% in the ABVD arm, 54% in the BEACOPP escalated arm, and 48% in the CEC arm) ($P = .016$)
- Thrombocytopenia (3% in the ABVD arm, 22% in the BEACOPP escalated arm, and 17% in the CEC arm) ($P < .001$)
- Infections of grade 3 or 4 (2% in the ABVD arm, 14% in the BEACOPP escalated arm, and 4% in the CEC arm) ($P = .003$)
<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary malignancies:</td>
<td>four second malignancies (one in the ABVD arm, one in the BEACOPP arm,</td>
</tr>
<tr>
<td></td>
<td>two in the CEC arm)</td>
</tr>
<tr>
<td>Potential conflict of interest</td>
<td>Author(s) indicated none</td>
</tr>
</tbody>
</table>

*ABVD = doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP = bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; CEC = cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxirubicin, vincristine, procarbazine, vinblastine, and bleomycin; CI = confidence interval; FFS = failure-free survival; OS = overall survival; PFS = progression-free survival.