

# Treatment of advanced Hodgkin's disease with COPP/ABV/IMEP versus COPP/ABVD and consolidating radiotherapy: final results of the German Hodgkin's Lymphoma Study Group HD6 trial

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Received 14 March 2003; revised 25 July 2003; accepted 4 September 2003

**Background:** The purpose of this study was to compare the efficacy of the hybrid chemotherapeutic regimen COPP/ABV/IMEP (cyclophosphamide–vincristine–procarbazine–prednisone–doxorubicin–bleomycin–vinblastine–ifosfamide–methotrexate–etoposide) (CAI) with that of the standard regimen COPP/ABVD (COPP/ABV, dacarbazine) (CA) in the treatment of advanced-stage Hodgkin's disease (HD).

**Patients and methods:** Between January 1988 and January 1993, 588 eligible patients with HD in stages IIIB and IV were randomly assigned to a treatment or control group. The treatment group received four cycles of CAI over a complete cycle duration of 43 days. The control group received four cycles of CA over 57 days. Both groups then received consolidating radiotherapy.

**Results:** Five hundred and eighty-four patients were suitable for arm comparison. Patients in each group were similar in age, sex, histological subtype and clinical risk factors. Complete remission rates, overall survival and freedom from treatment failure at 7 years were similar for the two groups: 77% versus 78%, 73% versus 73% and 54% versus 56% for CAI and CA, respectively. Differences in acute chemotherapy-related toxicity were significant, however. Prognostic factor analysis confirmed the relevance of the International Prognostic Index and revealed that stage IVB, low hemoglobin, low lymphocyte count, high age and male gender were associated with a poor prognosis

**Conclusion:** The rapidly alternating hybrid CAI did not give superior results when compared with the standard regimen CA in advanced-stage HD.

**Key words:** advanced stage, chemotherapy, COPP/ABV/IMEP, Hodgkin's disease, randomized clinical trial

## Introduction

Unlike most other malignancies, Hodgkin's disease (HD) can be cured with polychemotherapy, even in advanced stages. The first highly successful chemotherapy regimen used in HD was MOPP (mustargen–vincristine–procarbazine–prednisone) introduced by DeVita and Serpick in 1967 [1]. In 1974, the Milan group introduced a treatment strategy of alternating cycles of MOPP and ABVD (doxorubicin–bleomycin–vinblastine–dacarbazine) [2]. This was based on the efficacy of ABVD in certain patients refractory to MOPP as well as the therapeutic limitations of MOPP in others. The results of this trial were striking and statistically signifi-

cant. Subsequently, several large cooperative group trials were carried out confirming the Milan group's findings and establishing the superiority of MOPP/ABVD over MOPP and MOPP derivatives in the treatment of advanced-stage HD [3–5].

Goldie and Coldman [6] proposed a mathematical model describing the relationship between tumor drug sensitivity and spontaneous mutation rates. This model was the basis for the development of hybrid chemotherapeutic regimens. Groups in Vancouver and Milan independently developed a MOPP/ABV hybrid scheme in which all cytostatic agents were given within 8 days. The MOPP/ABV hybrid regimen did not, however, show better remission or relapse-free survival rates when compared with standard ABVD or MOPP/ABVD and, in fact, was shown to be more toxic [7–9].

The purpose of this trial was to compare the efficacy of a new rapid alternating hybrid scheme COPP/ABV/IMEP (cyclophosphamide–vincristine–procarbazine–prednisone–doxorubicin–

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bleomycin–vinblastine–ifosfamide–methotrexate–etoposide) or CAI with that of the standard COPP/ABVD (cyclophosphamide–vincristine–procarbazine–prednisone–doxorubicine–bleomycin–vinblastine–dacarbazine) or CA in the treatment of advanced-stage HD. The rationale for the new CAI scheme is as follows. It contains the most active substances of the standard CA regimen with the exception of dacarbazine, which is highly emetic and whose activity in HD is thus far not proven. Ifosfamide, methotrexate and etoposide were added based on their activity in relapsed lymphomas [10, 11]. Methotrexate was also a component of MOMP, a MOPP derivative proposed by DeVita and Serpick [1].

In 1989, the German Hodgkin's Lymphoma Study Group began two multicenter trials to evaluate the COPP/ABV/IMEP scheme in comparison with COPP/ABVD: the HD5 trial for patients with intermediate stage HD and the HD6 trial for advanced stages. This paper presents the final results of the HD6 trial. The results of the HD5 trial were reported by Sieber et al. [12].

## Patients and methods

### Patient eligibility

Between January 1988 and January 1993, 622 patients with advanced-stage HD were recruited from 92 participating centers in Germany, Switzerland and Austria (see Acknowledgements for a list of participating centers). Previously untreated patients between 15 and 75 years of age with biopsy-proven HD in stages IIIB and IV were eligible. Exclusion criteria included a positive HIV test, previous malignant disease, pregnancy, creatinine clearance <60 ml/min, leukocyte count <3000/μl, platelet count <100 000/μl, serum bilirubin >2 mg/dl, concurrent infections and severe cardiac, pulmonary or cerebral dysfunction.

### Staging

Disease staging was determined according to the Ann Arbor classification. Pretreatment evaluation included medical history, physical examination, complete blood count, liver and renal function tests, erythrocyte sedimentation rate, chest X-ray, abdominal ultrasound, thoracic, abdominal and pelvic computed tomography (CT) and bone marrow biopsy. In 86 patients a staging laparotomy was carried out. A liver biopsy was required if staging laparotomy was not carried out.

### Patient characteristics

Of 622 patients who were registered, 588 were eligible and randomly assigned; 17 patients were ineligible due to concurrent disease, 11 due the review diagnosis as non-Hodgkin's lymphoma and six due to staging errors or previous treatment. In addition, four patients were ineligible for arm comparison: two terminated before starting therapy, one received another treatment. Another was lost before starting therapy and was therefore not included in the overall results. Patients characteristics for those 584 informative patients are given in Table 1. Age, sex, histological subtype, stage and clinical risk factors were evenly balanced in both arms. More than 80% of patients had B symptoms and >50% were in stage IV. Patients in stage IV had diffuse infiltrations of non-lymphoid organs such as liver (97 patients), lung (96 patients) and/or bone (62 patients). Localized extra-nodal disease was detected in 325 patients (56%).

A pathology review of the biopsies taken before treatment was also requested. Biopsy materials were reviewed by four expert pathologists who examined 439 out of 584 cases (75%) and revealed predominance of nodular sclerosis (59% of reviewed cases), followed by mixed cellularity (18%),

**Table 1.** Patient characteristics

	COPP/ABVD (n = 291)	COPP/ABV/IMEP (n = 293)
Age (years)		
Median	34	35
Range	15–73	15–74
Male sex	171 (59%)	165 (56%)
Stage (CS/PS)		
IIIB	143 (49%)	147 (50%)
IVA	40 (14%)	54 (18%)
IVB	108 (37%)	92 (31%)
B symptoms	251 (86%)	239 (82%)
Bulky disease	155 (53%)	164 (56%)
Staging laparotomy	41 (14%)	45 (15%)
Histological subtype (reviewed) <sup>a</sup>		
Lymphocyte predominance	3 (1%)	6 (3%)
Nodular sclerosis	139 (63%)	118 (54%)
Mixed cellularity	34 (15%)	46 (21%)
Lymphocyte depletion	5 (2%)	5 (2%)
Unclassified	22 (10%)	25 (11%)
Hodgkin's disease uncertain	16 (7%)	20 (9%)
Risk factors		
Large mediastinal mass	67 (23%)	80 (27%)
Extra-nodal involvement	165 (57%)	160 (55%)
High ESR	224 (77%)	228 (78%)
International Prognostic Index <sup>b</sup>		
0–3	161 (55%)	180 (61%)
4–7	55 (19%)	58 (20%)
Missing	75 (26%)	55 (19%)

<sup>a</sup>The histological subtype was reviewed in 75% cases for each arm; the percentages given refer to reviewed cases only.

<sup>b</sup>See [13].

CS/PS, clinical stage/pathological stage; ESR, erythrocyte sedimentation rate.

lymphocyte depletion (2%) and lymphocyte predominance (2%). In 47 specimens (11%) the subtype could not be classified by the review panel and in 36 cases (8%) HD was not certain.

### Treatment protocol

The study design is shown in Figure 1. After informed consent was obtained, the eligible patients were randomly assigned to receive four treatment cycles with either CA or CAI. The doses and schedules are given as shown in Table 2.

Patients treated in centers in Switzerland received mustargen instead of cyclophosphamide (MOPP instead of COPP). They were included in the analysis of treatment results but not in those of drug delivery and toxicity. In eight patients, the therapy was switched mid-treatment because of either excessive toxicity or for unknown reasons: two patients randomly assigned to CA were switched to CAI and six patients from CAI to CA. These patients are retained in the assigned treatment group for data analysis purposes (intention-to-treat).

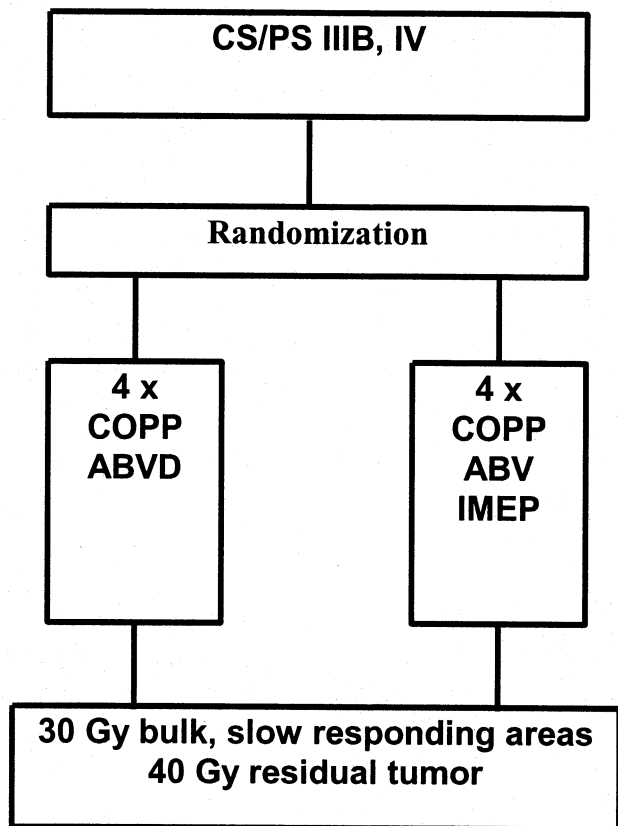


Figure 1. Flow diagram for the HD6 trial.

All drugs were given in full doses if the leukocyte count was  $>2500/\mu\text{l}$  and the platelet count  $>80\,000/\mu\text{l}$ . If the leukocyte or platelet counts following a treatment cycle were below these values, subsequent cycles were delayed by 2 weeks and doses of cyclophosphamide, doxorubicin, vinblastine, ifosfamide, methotrexate and etoposide were adjusted. If myelosuppression caused a delay between 1 and 2 weeks, the doses were reduced by 25%. If the delay was  $>2$  weeks, the doses were reduced by 50%.

### Consolidating radiotherapy

Bulky disease areas (initially  $>5$  cm measured by CT scan) and slow-responding lymph node sites which appeared enlarged ( $>2$  cm) after two cycles of CA or CAI were irradiated locally with 30 Gy; residual disease that appeared enlarged ( $>2$  cm) clinically or by CT scan after eight cycles of chemotherapy was treated locally with 40 Gy.

### Response assessment and follow-up

Patient data were collected following each cycle of chemotherapy and after radiotherapy. Data collected included dose schedule, actual doses given and toxicity. Toxicity data included hematological toxicities (leukocytopenia, thrombocytopenia and anemia), alopecia, nausea and vomiting, neuropathy, infections, fever, allergic reactions, gastrointestinal, skin, renal and pulmonary toxicities and secondary malignancies. The data were checked by two data managers and a physician.

Response was assessed by physical examination, complete blood cell count, blood chemistries and CT scans following the fourth and eighth cycles of chemotherapy and following radiotherapy. Restaging consisted of an analysis and documentation of all initial disease manifestations by adequate clinical and

histological methods. Complete remission (CR) was defined as the absence of all clinical disease manifestations 3 months following the completion of treatment. Partial remission (PR) was defined as an at least 50% reduction in all disease sites (measured by the products of perpendicular diameters). Residual disease was defined as suspected active disease  $>2$  cm after the completion of eight cycles of chemotherapy. Patients with residual disease after radiotherapy were considered to be in CR with residual lesions and were observed but not treated further. Follow-up examinations were then carried out every 3 months during the first 2 years following treatment, every 4 months during the subsequent 2 years and every 6 months beginning with the 5th year.

### Statistical analysis

Randomization was carried out centrally by computer. Five hundred and eight-four patients were evaluable for arm comparison analyses. All analyses are based on intention-to-treat. The major end point was freedom from treatment failure (FFTF), which was defined as the time from the start of randomization to the first of the following events: death, progressive disease, non-CR status at the end of the protocol treatment or relapse. Overall survival (OS) analysis included all deaths whether disease-related or not. Kaplan–Meier estimates are given for the probabilities of survival beyond a given time. The significance of comparisons of survival were calculated with the log-rank test.

For the comparison of treatment delivery the analysis was restricted to patients who had received the intended treatment. Drug delivery was assessed by comparing given dose intensity and full protocol dose without reduction. Dose intensity ( $\text{mg}/\text{m}^2/\text{week}$ ) was defined as the total dose given divided by the product of the body surface area and the number of weeks of treatment (number of weeks from the first day of treatment to the last day of drug delivery).

The International Prognostic Index was calculated as described by Hasenclever and Diehl [13].

## Results

### Chemotherapy delivery

Four cycles of the CA treatment scheme were administered over a median time of 34 weeks (113% of the intended time). Four cycles of CAI were administered over 28 weeks (121% of the intended time). Vincristine was applied at 75% and 80% of the intended doses in the CA and CAI regimens, respectively. All other drugs were applied on average  $>92\%$  of the intended doses. The median dose intensity for vincristine was 67% of the intended intensity. All other drugs had a median dose intensity  $>78\%$ . The median dose intensities of most drugs (cyclophosphamide, vincristine, prednisone, procarbazine, doxorubicin, bleomycin, vinblastine) were slightly, but not significantly, lower in the CAI group.

### Radiotherapy

Three hundred and twenty-three patients received consolidating radiotherapy, 156 patients (79%) in the CA arm and 167 (78%) in the CAI arm. Patients with bulky disease areas (52% of CA and 53% of CAI patients) received 30 Gy in these areas. Slow-responding areas received also 30 Gy (59% of CA and 61% of CAI patients). Patients with residual disease (disease  $>2$  cm following chemotherapy, 38% of each group) received 40 Gy. Eighteen patients in CR (11 of CA and seven of CAI) who did not meet any of the above criteria also received radiation without an obvious reason.

**Table 2.** Planned dosage and schedule of the COPP/ABVD and COPP/ABV/IMEP regimens

	COPP/ABVD			COPP/ABV/IMEP		
	Dose (mg/m <sup>2</sup> )	Route	Days	Dose (mg/m <sup>2</sup> )	Route	Days
Cyclophosphamide	650	i.v.	1, 8	800	i.v.	1
Vincristine	1.4 <sup>a</sup>	i.v.	1, 8	1.4 <sup>a</sup>	i.v.	1
Procarbazine	100	p.o.	1–14	100	p.o.	1–10
Prednisone	40	p.o.	1–14	40	p.o.	1–15
Doxorubicin	25	i.v.	29, 43	40	i.v.	15
Bleomycin	10	i.v.	29, 43	10	i.v.	15
Vinblastine	6	i.v.	29, 43	6	i.v.	15
Dacarbazine	375	i.v.	29, 43	–	–	–
Ifosfamide	–	–	–	1000	i.v.	29–33
Methotrexate	–	–	–	30	i.v.	31
Etoposide	–	–	–	100	i.v.	29–31
Prednisone	–	–	–	40	p.o.	29–35
Recycle	–	–	57	–	–	43

<sup>a</sup>Maximal 2 mg.

**Table 3.** Percentage of patients with acute toxicity (WHO grade 3/4) during chemotherapy

Toxicity	COPP/ABVD (n = 223)	COPP/ABV/IMEP (n = 245)	P
Leucocytopenia	63	71	
Neurotoxicity	3	3	
Thrombocytopenia	1	5	0.011
Anemia	2	4	
Infection	4	3	
Gastrointestinal	1	2	
Cardiac	1	1	
Pulmonary	0	0.5	
Emesis	34	19	<0.001
Alopecia	33	51	<0.001

WHO, World Health Organization.

### Toxicity

The World Health Organization (WHO) grade of acute toxicity was documented in 223 patients in the CA group and in 245 patients in the CAI group. Patients treated in Switzerland were excluded from this comparison because of the switch from COPP to MOPP. WHO grade 3/4 toxicity is compared in Table 3 for the two groups. Leukocytopenia grade 3/4 (<1000/μl) occurred in 63% of patients treated with CA and 71% of those treated with CAI (not statistically significant). Thrombocytopenia grade 3/4 (<25 000/μl) was also more frequent with CAI (5%) than CA (1%)

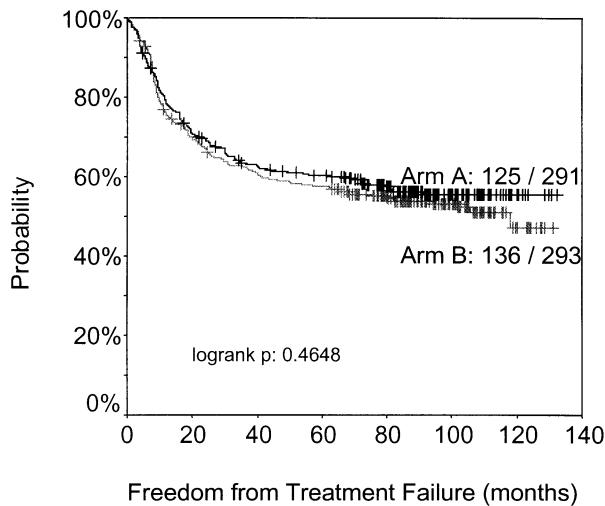
( $P = 0.01$ ). Alopecia occurred in 51% of the CAI group compared with 33% of the CA group ( $P < 0.001$ ). Emesis was more pronounced in the CA group with an incidence of 34% versus 19% ( $P < 0.001$ ). Neuropathy, anemia, infections, pain, gastrointestinal toxicity, fever, allergic reactions, skin toxicity, renal toxicity, cardiac toxicity and pulmonary toxicity all occurred in <5% of patients without significant differences between the two treatment arms.

A total of 29 secondary malignancies were documented, including eight acute myelogenous leukemias (AMLs), 11 non-Hodgkin's lymphomas, four lung cancers and six other solid tumors. AML occurred more frequently in the CA group (six versus two patients) and solid tumors more frequently in CAI group (seven versus three patients), but both differences are not significant due to small numbers.

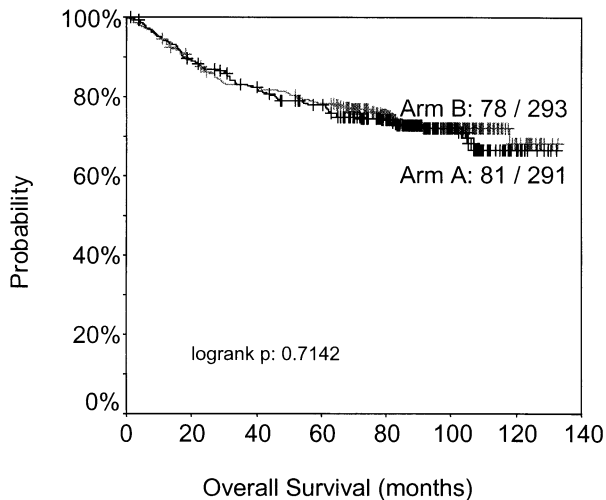
### Treatment results

CR was reached by 78% of CA patients and 77% of CAI patients. PR was achieved by 3% of patients with CA and 5% of patients with CAI. Progressive disease was seen in 17% of those in the CA group and 15% of those in the CAI group. Relapses occurred in 18% of CA patients and 19% of CAI patients.

Kaplan–Meier estimates of FFTF and OS are compared in Figures 2 and 3. At a median observation time of 7 years, OS was  $73\% \pm 5\%$  [95% confidence interval (CI)] in both groups and FFTF was  $56\% \pm 6\%$  (95% CI) for CA group and  $54\% \pm 6\%$  (95% CI) for the CAI group. There was no significant difference between the two groups with regard to OS or FFTF.



**Figure 2.** Freedom from treatment failure for COPP/ABVD (Arm A) versus COPP/ABV/IMEP (Arm B).



**Figure 3.** Overall survival for COPP/ABVD (Arm A) versus COPP/ABV/IMEP (Arm B).

### Causes of death

One hundred and fifty-nine patients (27%) have died at the time of this analysis (median observation time 7 years). HD was the most frequent cause accounting for 95 deaths (60%). This was followed by acute toxicity during primary chemotherapy or salvage chemotherapy (13%), secondary neoplasias (12%) and cardiac failure (7%). Seventeen patients died during therapy, eight receiving CA and nine receiving CAI. There was no statistically significant difference between the CA and CAI groups with regard to any category of cause of death.

### Discussion

The primary goal of this clinical trial was to compare the efficacy of the time-abbreviated, rapidly alternating CAI hybrid scheme with that of the standard alternating CA regimen in patients with

advanced-stage HD. In this trial, CAI did not yield superior results. The CR rates, FFTF and OS rates at 7 years were similar for the two groups. In general, toxicity was moderate with both schemes and thrombocytopenia and alopecia were more pronounced in the CAI group, while emesis was more pronounced in the CA group.

What can we conclude from this trial? Both regimens have a similar backbone of chemotherapeutic drugs with some important differences. Dacarbazine was included in the CA regimen and excluded from the CAI scheme. In CAI, three new drugs were introduced: methotrexate, etoposide and ifosfamide. Another important difference is the time frame: one cycle of CAI was applied over 6 weeks and one cycle of CA over 8 weeks. It is difficult to distinguish between the effects of these changes.

The results of this trial agree with those from other groups comparing hybrid regimens with conventional ones in HD. Groups in Vancouver and Milan independently developed a MOPP/ABV hybrid which was compared by the National Cancer Institute with alternating MOPP/ABVD in patients with stages IIIB and IV HD. At 5 years, there was no significant difference in the OS rates between the two groups; however, the hybrid scheme was associated with greater hematological and non-hematological toxicity [9]. The Milan group comparing MOPP/ABV with MOPP/ABVD also showed no significant difference in OS rates at 10 years [7]. A large USA intergroup trial comparing MOPP/ABV with ABVD in patients with advanced-stage or recurrent HD was prematurely stopped by the Data and Safety Monitoring Board when excessive treatment-related deaths and secondary malignancies were observed in the hybrid regimen group [14]. At 3 years, both regimens had shown similar failure-free survival rates. The potential relevance of dose and scheduling was shown in a British National Lymphoma Investigation trial comparing the LOPP/EVA hybrid scheme with alternating LOPP/EVA. Both regimens contained identical doses. There was a significantly lower CR rate in the hybrid group and this trial was also stopped prematurely [15].

In summary, the Goldie–Coldman hypothesis predicting that multidrug chemotherapeutic regimens utilizing larger number of drugs in rapid alternation would yield superior results has not been validated by randomized clinical trials in advanced-stage HD. ABVD has been considered the standard regimen against which all new regimens are compared. ABVD-based regimens have been shown to yield a 60–70% FFTF rate at 5 years. Compared with the hybrid schemes tested thus far, ABVD is equally effective and appears to cause less myelotoxicity, acute leukemias and sterility. However, this could be due to the fact that the optimal hybrid regimen has not yet been identified.

Although ABVD is considered the standard regimen for advanced-stage HD, the treatment results are not satisfactory, especially in comparison with the results in limited stages. Primary treatment fails in more than one-third of patients and these patients have a dismal prognosis. Furthermore, the pulmonary toxicity of bleomycin, which is more pronounced in children and in combination with mediastinal radiation, remains a concern with ABVD.

Two new promising regimens are currently under study. At Stanford University, a new regimen was developed including

doxorubicin–vinblastine–mustargen–bleomycin–vincristine–etoposide–prednisone [16]. The drug regimen, known as Stanford V, was applied weekly over a total of 12 weeks. Consolidating radiotherapy to initial bulky disease sites was essential. In a single-center trial which included 142 patients, the estimated freedom from progression at 5 years was 89% and the OS 96% years of observation [17]. Lower toxicity and preserved fertility were major goals of this regimen and were achieved in both men and women.

The German Hodgkin's Lymphoma Study Group developed the BEACOPP regimen (bleomycin–etoposide–doxorubicin–cyclophosphamide–procarbazine–prednisone) [18]. In the three-arm HD9 trial, BEACOPP in standard and escalated doses were compared with standard COPP/ABVD in patients with advanced-stage HD [19]. At the time of a planned interim analysis, the COPP/ABVD arm was closed to accrual due to observed superior outcomes in the BEACOPP arms.

The role of consolidating radiotherapy in advanced-stage HD remains highly controversial [20]. Although the contribution of radiotherapy is unclear, many large clinical trials include radiotherapy as an integral part of their protocols. In this study, no significant difference in outcome was observed between patients who received radiotherapy and those who did not (data not shown). This is in agreement with results from other groups and a meta-analysis of 14 studies including over 1700 patients [20, 21]. It seems likely, therefore, that radiotherapy is not essential in patients with advanced-stage HD after a sufficient amount of anthracycline-containing chemotherapy is applied.

In conclusion, the hybrid regimen CAI did not give superior results when compared with the standard regimen CA. ABVD should still be considered the standard treatment protocol in patients with advanced-stage HD against which promising new regimens like BEACOPP and the Stanford V should be compared. The role of adjuvant radiotherapy after chemotherapy remains unproven and is currently being analyzed in the HD12 trial of the German Hodgkin's Lymphoma Study Group.

## Acknowledgements

This clinical trial was supported by a grant from the Federal Minister of Science and Technology, Bundesministerium für Forschung und Technologie, Germany. Writing committee: H. Tesch, M. Sieber, B. Pfister; biometry: B. Pfister, U. Paulus, D. Hasenclever, M. Loeffler, O. Brosteanu; radiotherapy panel: E. Duehmke, R. P. Mueller, N. Willich; pathology panel: A. Georgii, R. Fischer, M. L. Hansmann, H. Stein; data management: T. Schober, B. Koch.

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Klinikum Lippe-Lemgo, Medizinische Klinik II, Lemgo (U. Weiß)

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