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ABVD versus BEACOPP for Hodgkin's Lymphoma When High-Dose Salvage Is Planned

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ABSTRACT

BACKGROUND

BEACOPP, an intensified regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, has been advocated as the new standard of treatment for advanced Hodgkin's lymphoma, in place of the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).

METHODS

We randomly assigned 331 patients with previously untreated and unfavorable Hodgkin's lymphoma (stage IIB, III, or IV, or an international prognostic score of ≥ 3 on a scale of 0 to 7, with higher scores indicating increased risk), to receive either BEACOPP or ABVD, each followed by local radiotherapy when indicated. Patients with residual or progressive disease after the initial therapy were to be treated according to a state-of-the-art high-dose salvage program. The median follow-up period was 61 months.

RESULTS

The 7-year rate of freedom from first progression was 85% among patients who had received initial treatment with BEACOPP and 73% among those who had received initial treatment with ABVD ($P=0.004$), and the 7-year rate of event-free survival was 78% and 71%, respectively ($P=0.15$). A total of 65 patients (20 in the BEACOPP group, and 45 in the ABVD group) went on to receive the intended high-dose salvage regimen. As of the cutoff date, 3 of the 20 patients in the BEACOPP group and 15 of the 45 in the ABVD group who had had progressive disease or relapse after the initial therapy were alive and free of disease. After completion of the overall planned treatment, including salvage therapy, the 7-year rate of freedom from a second progression was 88% in the BEACOPP group and 82% in the ABVD group ($P=0.12$), and the 7-year rate of overall survival was 89% and 84%, respectively ($P=0.39$). Severe adverse events occurred more frequently in the BEACOPP group than in the ABVD group.

CONCLUSIONS

Treatment with BEACOPP, as compared with ABVD, resulted in better initial tumor control, but the long-term clinical outcome did not differ significantly between the two regimens. (Funded by Fondazione Michelangelo; ClinicalTrials.gov number, NCT01251107.)

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THE REGIMEN OF DOXORUBICIN, BLEOMYCIN, VINBLASTINE, and DACARBAZINE (ABVD) was introduced in the mid-1970s as treatment for advanced Hodgkin's lymphoma¹ and became the standard of treatment for this disease after trials showed that ABVD was as effective as, or more effective than, the regimen of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), with fewer toxic effects.² More recently, the German Hodgkin Lymphoma Study Group (GHSG) has developed a front-line intensified regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated BEACOPP regimen, which includes higher-than-standard doses of etoposide, doxorubicin, and cyclophosphamide). This regimen, as compared with COPP-ABVD, has been shown to lead to better tumor control and to an 11% increase in overall survival at 10 years, and the GHSG has advocated BEACOPP as the new standard of treatment for patients with high-risk, advanced-stage Hodgkin's lymphoma.³⁻⁵

The choice of a preferred first-line treatment requires balancing the control of the disease with the occurrence of early and late treatment-related effects. To fully assess this balance, the treatment decision process should ideally take into account the outcome after a consistent second-line therapy, particularly when widely applicable and effective salvage regimens exist.

In this study, we assessed the long-term clinical outcome after initial therapy with BEACOPP as compared with ABVD in patients with advanced-stage Hodgkin's lymphoma. All patients with residual or progressing disease after the initial treatment went on to receive a salvage regimen consisting of reinduction standard-dose chemotherapy (usually ifosfamide-based) followed by a high-dose consolidation therapy with carmustine, etoposide, cytarabine, and melphalan (BEAM),⁶ with autologous hematopoietic stem-cell support. We report on the 7-year results of this trial.

METHODS

PATIENTS

Eligible patients were 17 to 60 years of age and had untreated Hodgkin's lymphoma in clinical stage IIB, III, or IV with any international prognostic score or in any clinical stage with a prognostic score of 3 or higher (see the Supplementary Appendix, available with the full text of this article

at NEJM.org). The international prognostic score ranges from 0 to 7, with higher scores indicating increased risk. Patients with clinically relevant cardiovascular or respiratory diseases and patients who were positive for hepatitis B virus, hepatitis C virus, or the human immunodeficiency virus were excluded. The pathological diagnosis that was used in the study was determined at the institution at which the patient was treated.

Before the initiation of treatment, the clinical stage of the disease was determined on the basis of a medical history and physical examination; complete blood count; serum biochemical profile; chest radiography; computed tomography of the chest, abdomen, and pelvis; total-body scintigraphy with gallium-67 citrate or (after 2003) positron-emission tomography with ¹⁸F-fluorodeoxyglucose; and bilateral core biopsy of the iliac crest.

STUDY OVERSIGHT

The study was approved by the ethics committee at each participating center. All patients provided written informed consent. The study was designed by the investigators, and the coordination of the study, the collection and quality control of the data, and the statistical analyses were performed at the operations office of Fondazione Michelangelo (the sponsoring organization). No commercial support was provided. The study was conducted in accordance with the protocol; both the protocol and the statistical analysis plan are available at NEJM.org.

STUDY DESIGN

A total of 331 patients were enrolled at three Italian cooperative groups of medical centers. Randomization was stratified according to the participating research group and the international prognostic score⁷ (3, 4, or ≥ 5) if the score was 3 or higher or the disease stage (IIB or III vs. IV) if the prognostic score was less than 3. All the data were updated on November 30, 2009. The median follow-up period was 61 months (maximum, 110 months). Patients were randomly assigned to receive ABVD in either six cycles (if they had a complete response after four cycles) or eight cycles or BEACOPP in eight cycles (four courses of the escalated regimen followed by four standard courses). The BEACOPP regimen was determined on the basis of early reports from the HD12 trial suggesting that there was a better side-effect profile and similar efficacy with the regimen of four escalated courses followed by four standard courses.

es as with the regimen of eight escalated courses.⁸ The doses and schedules of the chemotherapy combinations are listed in Table S2 in the Supplementary Appendix. Starting within 1 month after the end of chemotherapy, patients with a complete response or a very good ($\geq 80\%$) partial response received high-energy irradiation to nodal sites of initial bulky lymphoma (25.2 Gy), areas of residual disease (30.6 Gy), or both, with daily doses ranging between 1.5 and 1.8 Gy.

Complete remission, unconfirmed complete remission ($>75\%$ decrease in nodal masses with residual stable abnormality), partial remission, partial remission of more than 80%, stable disease, and progressive disease were defined according to the criteria of the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas.⁹ All patients were to be followed during the period in which they were receiving chemotherapy, after they received radiotherapy, every 3 months during the first year after the completion of treatment, every 6 months from the second year through the fifth year after the completion of treatment, and annually thereafter. Toxic effects were recorded at each cycle during the treatment period on the basis of the World Health Organization (WHO) Toxicity Grading Scale.¹⁰

All patients who had less than a complete response after the initial therapy or who had a relapse after a complete response were to be treated according to a salvage chemotherapy program that included, as recommended but not mandated, a reinduction regimen of multiple cycles of ifosfamide-containing therapy (up to maximum response, as assessed clinically), followed by one high-dose course of autologous hematopoietic stem-cell-supported BEAM. One of three ifosfamide-containing regimens, described in detail in Table S3 in the Supplementary Appendix (ifosfamide, vinorelbine, and prednisone [Ifo-Vinorelbine]¹¹; ifosfamide, gemcitabine, vinorelbine, and prednisolone [IGeV]¹²; and ifosfamide, epirubicin, and etoposide [IEV]¹³), was used as the preferred reinduction therapy in 83% of the salvage treatments, and the three regimens were balanced across the two groups of the study. Toxic effects and response to second-line therapy were defined as described above for first-line therapy.

STATISTICAL ANALYSIS

The primary end point of the trial was the rate of freedom from first progression. The trial was de-

signed to have 80% power to detect at least a 15% difference between the two groups in the rate of freedom from first progression, at a two-sided significance level of 5%. Secondary end points were the rates of freedom from second progression, event-free survival after the initial therapy, and overall survival. All events were calculated from the day of randomization. No statistical calculations with respect to power, between-group differences, and significance level were performed for the secondary end points.

The probabilities of event-free survival, freedom from progression, and overall survival were estimated with the use of the Kaplan-Meier method and were compared with the use of the log-rank test. Cox proportional-hazards regression analysis was used to estimate hazard ratios and 95% confidence intervals. Outcomes were compared with the use of the chi-square test. The primary and secondary efficacy variables were analyzed on data from the full analysis set (intention-to-treat population). The safety population comprised all patients who underwent randomization and received at least one dose of a study medication. All tests were two-sided. SAS statistical software, version 8, was used to analyze the data.

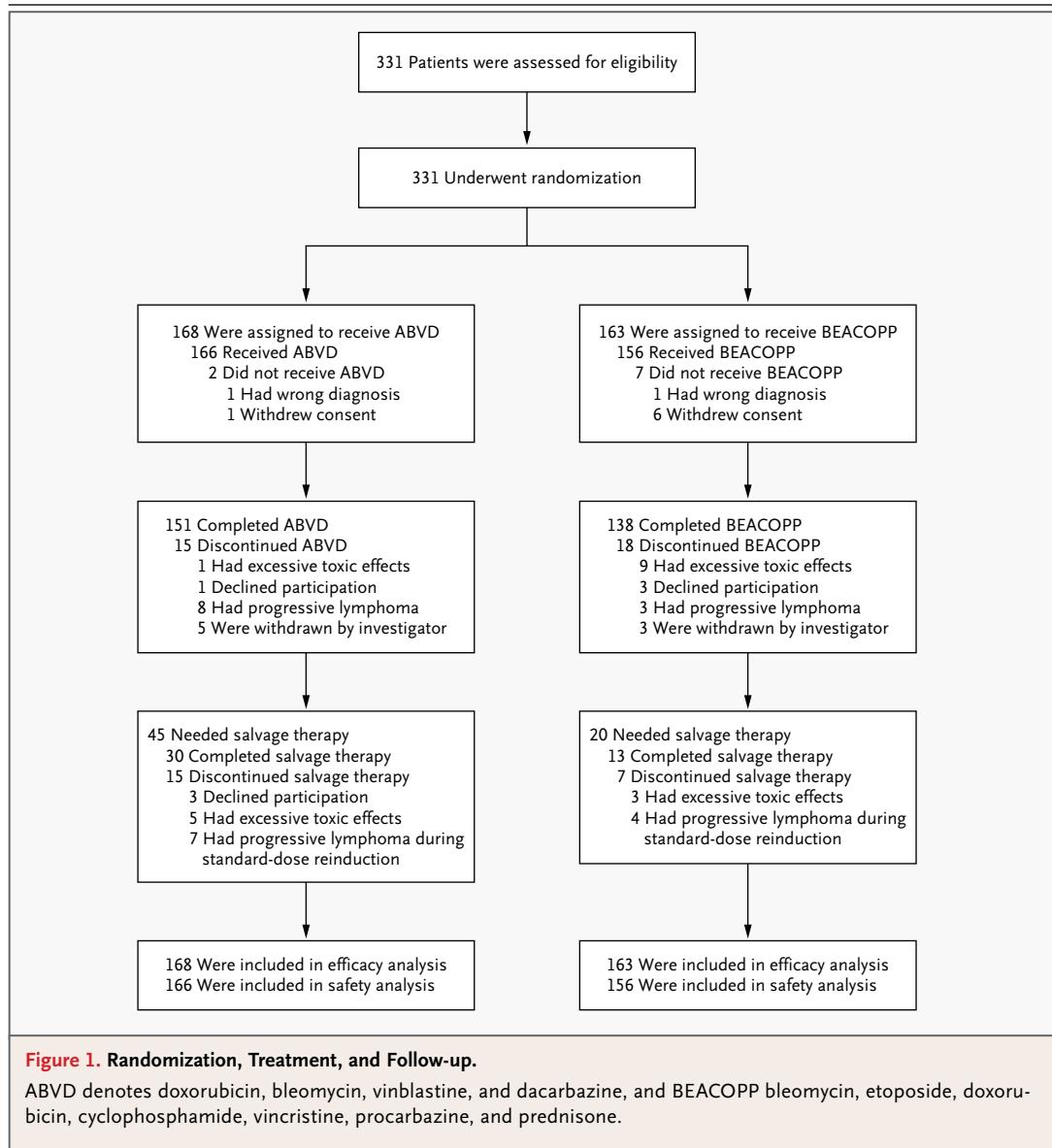
RESULTS

PATIENTS

From March 2000 through March 2007, a total of 331 patients were recruited (Fig. 1); 168 patients were assigned to receive ABVD and 163 to receive BEACOPP. Two patients were subsequently found to be ineligible because of a wrong diagnosis, and 7 withdrew consent before starting chemotherapy. Thus, 166 patients were initiated on ABVD chemotherapy and 156 on BEACOPP chemotherapy (safety population), whereas all 331 patients who underwent randomization were assessed for efficacy (intention-to-treat population). The baseline characteristics of the two groups did not differ significantly (Table S1 in the Supplementary Appendix).

INITIAL THERAPY

The rate of adherence to the protocol was high in both treatment groups (Table S1 in the Supplementary Appendix). The median duration of chemotherapy was 34 weeks in the ABVD group (the planned duration was 32 weeks) and 26 weeks in the BEACOPP group (planned duration, 24 weeks); approximately 90% of the patients completed the



assigned treatment, with 48% of the patients in the ABVD group undergoing six cycles of treatment. The main reason for discontinuation of treatment reported in the ABVD group was progressive lymphoma and the main reason reported in the BEACOPP group was life-threatening toxic effects (Table S1 in the Supplementary Appendix).

The proportion of patients who had at least one episode of severe toxic effects, either hematologic or nonhematologic, in any cycle was lower in the ABVD group than in the BEACOPP group (43% vs. 81% with hematologic toxic ef-

fects, $P < 0.001$; and 7% vs. 19% with nonhematologic toxic effects, $P = 0.001$); in particular, there was an increased frequency of acute hematologic adverse events, severe infections, and mucositis in the BEACOPP group (Table 1). During the treatment period, there were five deaths unrelated to the progression of lymphoma among patients assigned to BEACOPP therapy, as compared with one death among the patients assigned to ABVD therapy (Table 1).

Overall, 107 patients assigned to ABVD therapy (64%) and 114 patients assigned to BEACOPP therapy (70%) had a complete response by the

Table 1. Outcomes and Important Adverse Events Associated with Initial Treatment, According to Regimen.*

Outcome or Adverse Event	ABVD (N=168)	BEACOPP (N=163)
Outcome of initial treatment†		
Complete remission at the end of chemotherapy — no. (%)	107 (64)	114 (70)
Response at the end of chemotherapy and radiotherapy — no. (%)		
Complete remission	128 (76)	132 (81)
Partial remission >80%	12 (7)	11 (7)
Progression	19 (11)	8 (5)
No response	7 (4)	5 (3)
Response could not be evaluated	2 (1)	7 (4)
Relapse — no. (%)	19 (11)	7 (4)
Severe adverse events — no. (%)	2 (1)	10 (6)
Fatal toxic events during therapy‡	1 (1)	4 (2)
Secondary leukemia during follow-up§	1 (1)	2 (1)
Severe events during therapy leading to permanent discontinuation¶	0	4 (2)¶
Death from any cause — no. (%)	22 (13)	15 (9)
Severe adverse events during administration of initial chemotherapy 		
At least one grade 3 or 4 acute hematologic adverse event — no./total no. (%)**	72/166 (43)	127/156 (81)
At least one grade 3 or 4 acute nonhematologic adverse event — no./total no. (%)††	12/166 (7)	30/156 (19)
Death from toxic effects — no./total no. (%)	1/166 (1)	5/156 (3)

* ABVD denotes doxorubicin, bleomycin, vinblastine, and dacarbazine, and BEACOPP bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone.

† The outcomes of the initial treatment were analyzed in the intention-to-treat population, comprising all patients who underwent randomization.

‡ The fatal events were the result of cardiorespiratory disease (one patient in the ABVD group and two patients in the BEACOPP group), hepatic failure (one patient in the BEACOPP group), and sepsis (one patient in the BEACOPP group).

§ The secondary leukemia in all three cases (one in the ABVD group and two in the BEACOPP group) was acute myeloid leukemia.

¶ In the case of all four patients, the permanent discontinuation of the treatment was the result of severe infection.

|| Adverse events associated with chemotherapy were assessed in the safety population, which comprised all patients who underwent randomization and received at least one dose of a study medication. Acute hematologic adverse events and acute nonhematologic adverse events were graded according to the World Health Organization Toxicity Grading Scale.

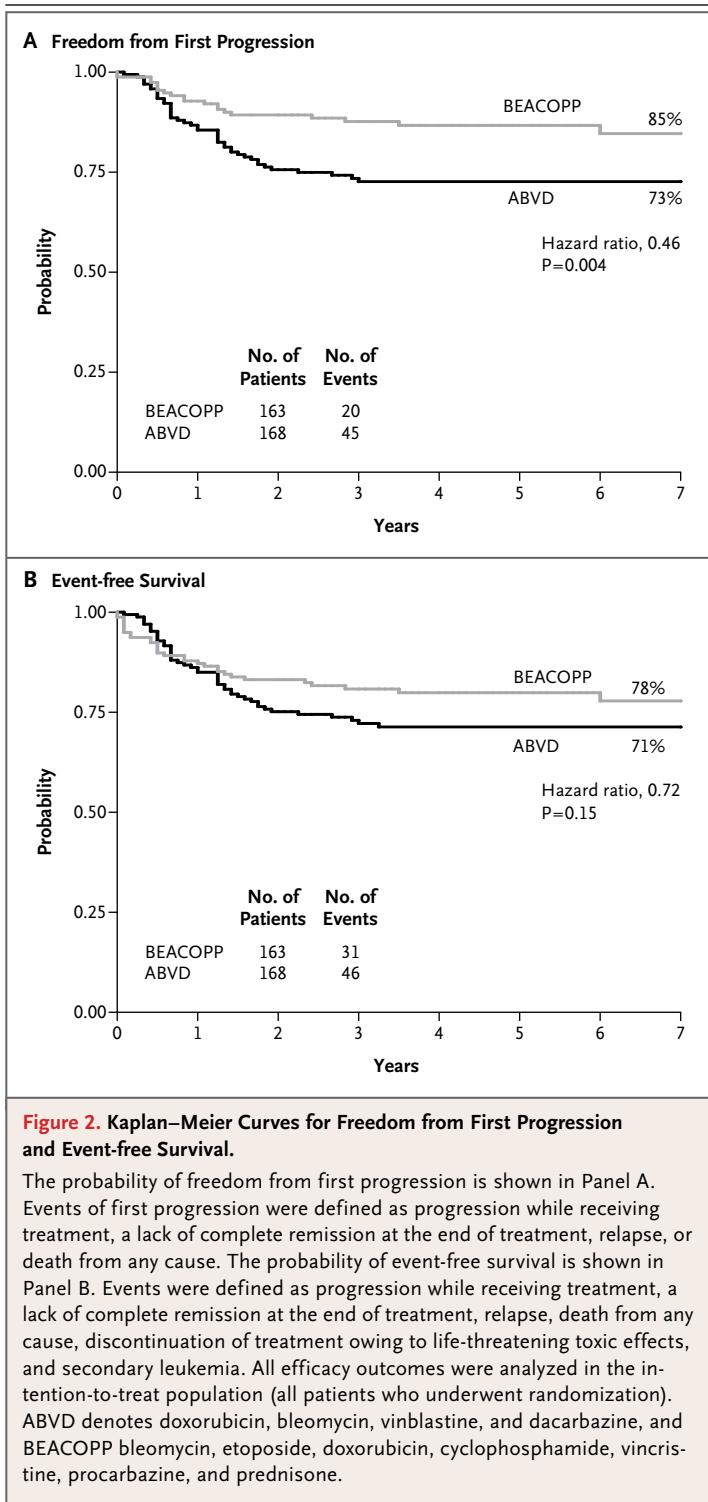
** Full blood counts were assessed only on days 1 and 15 of each ABVD cycle, and on days 1 and 8 of each BEACOPP cycle. Events of asymptomatic grade 3 or 4 hematologic toxic effects might have escaped detection. P<0.001 for the comparison between groups.

†† P=0.001 for the comparison between groups.

end of the initial chemotherapy phase (Table 1). A total of 66% of the patients in the ABVD group and 67% in the BEACOPP group underwent radiotherapy. After radiotherapy, the number of patients with a complete response increased to 128 patients (76%) and 132 patients (81%) in the two groups, respectively. Progression during or shortly after treatment occurred in 25 patients in the ABVD group (15%) and in 12 patients in the BEACOPP group (7%). Among the 128 patients who had a complete remission after ABVD therapy and radiotherapy, 20 had a relapse (16%), whereas there were fewer relapses in the BEACOPP group (8 of

132 patients with a complete response [6%]). After completion of the initial treatment, there were 22 deaths due to disease progression or toxic effects in the ABVD group (13%), as compared with 15 in the BEACOPP group (9%).

The estimated 7-year rate of freedom from first progression in the intention-to-treat population was 85% in the BEACOPP group, as compared with 73% in the ABVD group, a difference of 12 percentage points (P=0.004) (Fig. 2A and Table 2). The baseline international prognostic score⁷ (<3 vs. ≥3) did not significantly influence the outcome of treatment. However, when discon-



tinuation of treatment owing to life-threatening toxic effects or secondary leukemia was taken into account, the between-group difference of 7 percentage points in the 7-year rate of event-

free survival (78% in the BEACOPP group vs. 71% in the ABVD group) failed to reach significance ($P=0.15$) (Fig. 2B and Table 2).

SALVAGE THERAPY

A total of 65 patients did not meet the criteria for a complete response to the initial therapy or had a relapse — 45 after ABVD therapy and 20 after BEACOPP therapy. As part of the intended treatment, all 65 patients were recommended for a standard-dose salvage chemotherapy regimen containing ifosfamide, followed by high-dose BEAM consolidation with autologous hematopoietic stem-cell rescue. Of these 65 patients, two thirds in both groups could complete high-dose consolidation therapy as planned (Table 2), whereas 15 of those originally assigned to ABVD and 7 of those originally assigned to BEACOPP were either unable to start on salvage therapy or could not finish the salvage program because of poor clinical status, progressive disease, or both, while receiving standard-dose reinduction therapy.

During the course of salvage therapy, there were 3 deaths from toxic effects in the ABVD group (7%) and 3 in the BEACOPP group (15%) (Table 2). The rate of complete response at the end of salvage therapy was higher among those who had initially received ABVD than among those who had initially received BEACOPP (51% vs. 35%). As of the cutoff date, 15 patients in the ABVD group (33%) and 3 in the BEACOPP group (15%) were alive and free of disease (Table 2).

OVERALL RESULTS

After completion of the assigned treatment, including salvage therapy, the estimated 7-year rate of freedom from second progression in the intention-to-treat population was 88% in the BEACOPP group, as compared with 82% in the ABVD group ($P=0.12$), a difference of 6 percentage points (Fig. 3A and Table 2). The difference of 5 percentage points in the estimated 7-year rate of overall survival (89% in the BEACOPP group as compared with 84% in the ABVD group) was also not significant ($P=0.39$) (Fig. 3B and Table 2). During the follow-up period, acute leukemia developed in two patients in the BEACOPP group and in one patient in the ABVD group. In the patient from the ABVD group, a non-Hodgkin's lymphoma developed before the acute leukemia. Second solid tumors developed in four additional patients (three in the ABVD group and one in the

Table 2. Salvage Therapy and Outcome of Overall Intended Treatment.*

Variable	ABVD	BEACOPP
Salvage therapy		
Characteristics of patients		
No. undergoing salvage therapy	45	20
Induction failure, less than complete remission, or complete remission <12 mo — no. (%)	26 (58)	14 (70)
Complete remission ≥12 mo — no. (%)	19 (42)	6 (30)
Stage III or IV disease — no. (%)	24 (53)	13 (65)
Feasibility of salvage regimen — no. (%)		
Unable to start on protocol salvage therapy	6 (13)	5 (25)
Started on protocol salvage therapy	39 (87)	15 (75)
Induction therapy completed	39 (87)	15 (75)
Consolidation therapy completed	30 (67)	13 (65)
Complete response at end of salvage therapy — no. (%) [95% CI]	23 (51 [26–66])	7 (35 [15–59])
Deaths — no. (%)		
Hodgkin's lymphoma	0	1 (5)
Acute toxic effects	3 (7)	3 (15)
In continuous complete response as of cutoff date — no. (%) [95% CI]	15 (33 [20–49])	3 (15 [3–38])
7-Year outcome of overall intended treatment after initial therapy, with or without salvage therapy†		
Freedom from first progression — % (95% CI)‡	73 (66–80)	85 (78–91)
Event-free survival — % (95% CI)§	71 (64–78)	78 (70–85)
Freedom from second progression — % (95% CI)¶	82 (76–88)	88 (82–94)
Overall survival — % (95% CI)‖	84 (77–91)	89 (84–95)

* ABVD denotes doxorubicin, bleomycin, vinblastine, and dacarbazine, BEACOPP bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, and CI confidence interval.

† The analysis of overall intended treatment and 7-year survival were performed on the intention-to-treat population comprising all patients who underwent randomization — 168 patients in the ABVD group and 163 in the BEACOPP group.

‡ The hazard ratio for freedom from first progression with BEACOPP was 0.46 (95% CI, 0.27 to 0.78), P=0.004.

§ The hazard ratio for event-free survival with BEACOPP was 0.72 (95% CI, 0.46 to 1.13), P=0.15.

¶ The hazard ratio for freedom from second progression with BEACOPP was 0.60 (95% CI, 0.32 to 1.14), P=0.12.

‖ The hazard ratio for 7-year overall survival with BEACOPP was 0.75 (95% CI, 0.39 to 1.45), P=0.39.

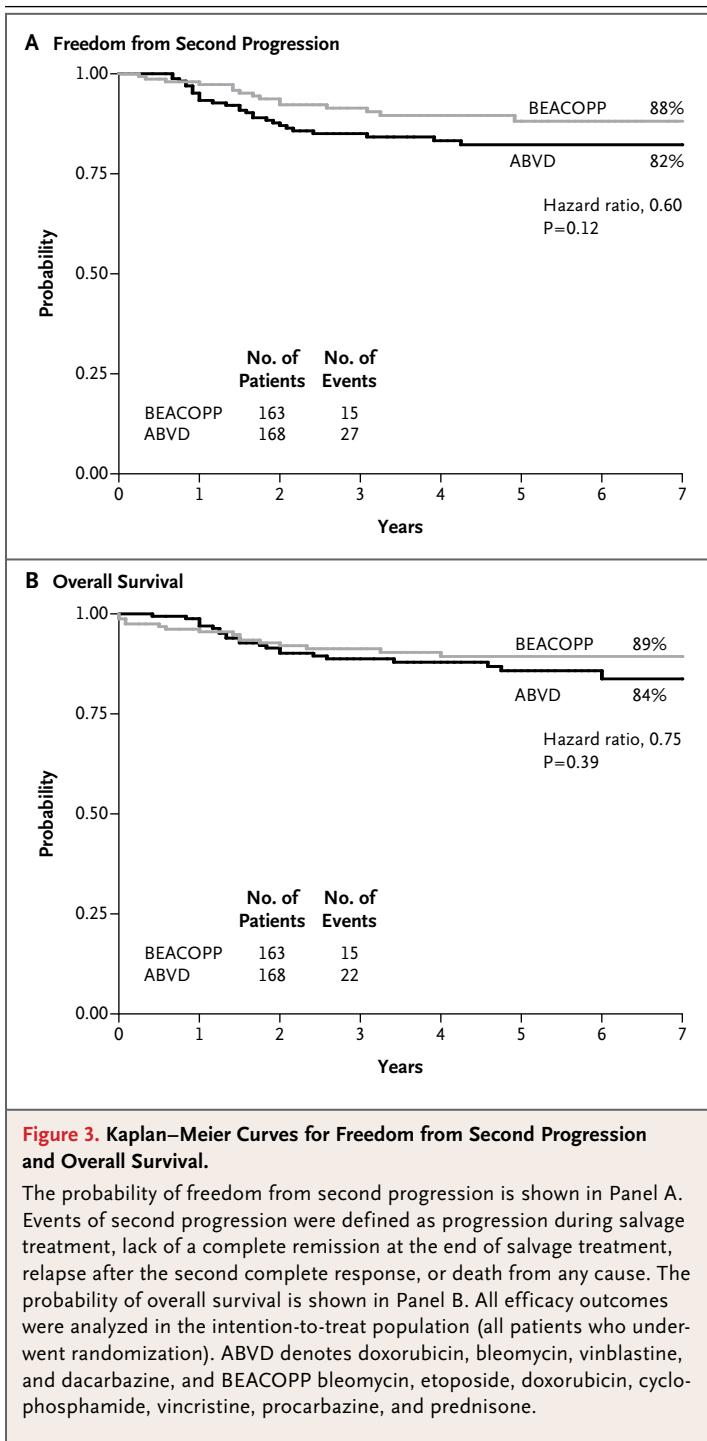
BEACOPP group), and all these patients were alive as of the cutoff date for the current analysis.

DISCUSSION

The objective of this study was to confirm previous reports that showed the superiority of BEACOPP therapy in patients with advanced Hodgkin's lymphoma,³ and to determine, as a secondary end point, whether this advantage would translate into a higher rate of overall survival when a state-of-the-art salvage treatment was planned for all patients who required additional therapy. The results of our trial showed that the choice of the initial treatment did not significantly influence long-term survival, and adds to the ongoing debate about

which regimen should be considered the standard of care for the initial treatment of advanced Hodgkin's lymphoma.^{14,15}

In making a decision about a regimen for initial therapy, physicians should consider not only the activity of the initial treatment, but also the toxic effects of the treatment and the results of salvage programs in the event of treatment failure. As previously reported by the GHSG,⁸ patients with advanced-stage Hodgkin's lymphoma who received four cycles of BEACOPP in the escalated regimen, followed by four cycles of BEACOPP in the standard regimen, had a rate of freedom from treatment failure at 5 years of 85.5%. In the current study, in a similar patient population receiving the same program of an escalated regimen followed



by a standard regimen, the corresponding figure (defined here as the rate of freedom from first progression) was 85%, a rate that is significantly higher than the rate of 73% in the ABVD group. The higher activity of BEACOPP is known to be associated with severe acute hematologic and non-

hematologic toxic effects, infertility, and secondary neoplasias. In the final analysis of the HD12 trial,⁸ at least one event of severe acute toxic effects was observed in 97% of the patients, with severe anemia or thrombocytopenia documented in 51% of the cases. The rate of death due to acute toxic effects was 3%, and the rate of secondary cancers was 4.9%.⁸ Published data on reproductive function after BEACOPP therapy are less detailed. However, after only three cycles of the escalated BEACOPP regimen, more than 50% of the women are expected to become infertile,¹⁶ and even the standard BEACOPP regimen caused azoospermia in close to 90% of male patients.¹⁷ Conversely, after ABVD, severe myelosuppression requiring treatment with growth factor or transfusion support, death from acute toxic effects, secondary leukemias, and infertility are rare events.¹⁸ In the current study, patients receiving BEACOPP required growth-factor support, had a significantly higher number of severe toxic effects that led in seven instances to the permanent discontinuation of the intended treatment, and had a higher number of fatal acute toxic effects (five, as compared with one in the ABVD group); in addition, secondary acute leukemias developed in two patients. Considering both efficacy and safety data, the BEACOPP and ABVD groups did not differ significantly with respect to the outcome of the 7-year rate of event-free survival (78% and 71%, respectively).

At the end of first-line treatment, 65 patients had disease progression or a relapse. The treatment for progressive disease was a program in which, after a number of standard-dose reinduction courses to produce a maximum response, all patients had to receive a consolidation course of stem-cell-supported myeloablative chemotherapy. Since there are no randomized studies comparing various pretransplantation or preparative salvage regimens,¹⁹ a choice was permitted among similarly effective therapies that included an alkylating agent to allow the majority of patients to safely receive the most familiar salvage program applicable locally. Nevertheless, the vast majority of the patients (83%) completed a consistent regimen comprising an ifosfamide-containing combination for reinduction and high-dose BEAM for consolidation. Although statistical comparisons were limited given the small number of patients with progressive disease, the larger proportion of patients in the ABVD group than in the BEACOPP group

who had a continuous complete response to salvage therapy (33% vs. 15%) reduced the difference in the estimated 7-year rate of freedom from second progression to 6 percentage points and the difference in the rate of overall survival to 5 percentage points — both nonsignificant differences ($P=0.12$ and $P=0.39$, respectively).

These results differ from those reported by the GHSG in the HD9 study, which showed a significant improvement in long-term freedom from treatment failure as well as in overall survival among patients receiving BEACOPP escalated therapy as compared with those receiving COPP-ABVD.⁴ It appears that this inconsistency cannot be explained by differences in the patient populations, the intensity of treatment delivery, the duration of follow-up, or a reduced efficacy of BEACOPP administered as an escalated regimen followed by a standard regimen in the current study. In fact, our results are similar to those reported by the GHSG among patients who underwent eight cycles of BEACOPP escalated therapy, both in freedom from treatment failure (85% in our study and 82% in the GHSG study) and in overall survival (89% and 86%, respectively).⁴ The inconsistency between the results of the two trials might conversely relate to the lower efficacy of the COPP-ABVD regimen that was being compared with BEACOPP in the GHSG study. The rate of freedom from treatment failure with the COPP-ABVD regimen was 64% and the rate of overall survival was 75%; the corresponding figures with ABVD therapy in our study were 73% and 84%, which were in line with the results of other randomized trials.²⁰⁻²² The same explanation might also apply to the 5-year results of the HD2000

randomized study, which showed a rate of failure-free survival of 65% after six cycles of ABVD.²³

In conclusion, in this study, the 7-year rate of freedom from first progression was 12 percentage points higher in patients with advanced Hodgkin's lymphoma who received four courses of escalated BEACOPP therapy followed by four courses of standard BEACOPP therapy than in those who received six to eight cycles of ABVD; however, after state-of-the-art salvage therapy, the rate of overall survival among the patients who had initially received BEACOPP therapy was not significantly higher than the rate among patients who had initially received ABVD therapy, and the BEACOPP therapy represented an overtreatment in the case of 73% of the patients (the proportion already cured by ABVD). Patients should be informed of the trade-off involved in choosing between two initial therapies — one an intensified regimen (BEACOPP) that, in the absence of a significant survival benefit, exposes seven of eight patients to an unnecessarily high risk of severe toxic effects and the other (ABVD), a therapy that results in one of eight patients requiring a subsequent salvage program involving severe early and late toxic effects that are not dissimilar from those with BEACOPP — that is, death from acute toxic effects in approximately 3% of patients,²⁴ sterility, and secondary cancers in approximately 9% of patients.²⁵

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REFERENCES

- Bonadonna G, Zucali R, Monfardini S, De Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer* 1975;36:252-9.
- Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *N Engl J Med* 1992;327:1478-84.
- Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. *N Engl J Med* 2003;348:2386-95. [Erratum, *N Engl J Med* 2005;353:744.]
- Engert A, Diehl V, Franklin J, et al. Escalated-dose BEACOPP in the treatment of patients with advanced-stage Hodgkin's lymphoma: 10 years of follow-up of the GHSG HD9 study. *J Clin Oncol* 2009;27:4548-54.
- Diehl V, Fuchs M. Will BEACOPP be the standard for high risk Hodgkin lymphoma patients in advanced stages? *Transfus Apher Sci* 2007;37:37-41.
- Mills W, Chopra R, McMillan A, Pearce R, Linch DC, Goldstone AH. BEAM chemotherapy and autologous bone marrow transplantation for patients with relapsed or refractory non-Hodgkin's lymphoma. *J Clin Oncol* 1995;13:588-95.
- Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease. *N Engl J Med* 1998;339:1506-14.
- Diehl V, Haverkamp H, Mueller R, et al. Eight cycles of BEACOPP escalated compared with 4 cycles of BEACOPP escalated followed by 4 cycles of BEACOPP baseline with or without radiotherapy in patients in advanced stage Hodgkin lymphoma (HL): final analysis of the HD12 trial of the German Hodgkin Study Group (GHSG). In: 2009 American Society of Clinical Oncology Annual Meeting Proceedings. *J Clin Oncol* 2009;27:Suppl:8544. abstract.
- Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. *J Clin Oncol* 1999;17:1244-53. [Erratum, *J Clin Oncol* 2000;18:2351.]

10. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207-14.
11. Bonfante V, Viviani S, Santoro A, et al. Ifosfamide and vinorelbine: an active regimen for patients with relapsed or refractory Hodgkin's disease. *Br J Haematol* 1998;103:533-5.
12. Santoro A, Magagnoli M, Spina M, et al. Ifosfamide, gemcitabine, and vinorelbine: a new induction regimen for refractory and relapsed Hodgkin's lymphoma. *Haematologica* 2007;92:35-41.
13. Clavio M, Garrone A, Pierrri I, et al. Ifosfamide, epirubicin, etoposide (IEV) and autologous peripheral blood progenitor cell transplant: a feasible and effective salvage treatment for lymphoid malignancies. *Oncol Rep* 2005;14:933-40.
14. Horning SJ. Risk, cure and complications in advanced Hodgkin disease. *Hematology Am Soc Hematol Educ Program* 2007:197-203.
15. Cheson BD. Is BEACOPP better than ABVD? *Curr Hematol Malig Rep* 2007;2:161-6.
16. Jurczak W, Krochmalczyk D, Pabian W, et al. Quality of life and fertility in Hodgkin disease patients treated with escalated BEACOPP. *Haematologica* 2009;94:Suppl 2:35. abstract.
17. Sieniawski M, Reineke T, Nogova L, et al. Fertility in male patients with advanced Hodgkin lymphoma treated with BEACOPP: a report of the German Hodgkin Study Group (GHSG). *Blood* 2008;111:71-6.
18. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *J Clin Oncol* 1987;5:27-37.
19. Bartlett NL. Therapies for relapsed Hodgkin lymphoma: transplant and non-transplant approaches including immunotherapy. *Hematology Am Soc Hematol Educ Program* 2005:245-51.
20. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: report of an intergroup trial. *J Clin Oncol* 2003;21:607-14.
21. Johnson PW, Radford JA, Cullen MH, et al. Comparison of ABVD and alternating or hybrid multidrug regimens for the treatment of advanced Hodgkin's lymphoma: results of the United Kingdom Lymphoma Group LY09 Trial (ISRCTN97144519). *J Clin Oncol* 2005;23:9208-18.
22. Hoskin PJ, Lowry L, Horwich A, et al. Randomized comparison of the Stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National Cancer Research Institute Lymphoma Group Study ISRCTN 64141244. *J Clin Oncol* 2009;27:5390-6.
23. Federico M, Luminari S, Iannitto E, et al. 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. *J Clin Oncol* 2009;27:805-11.
24. Jantunen E, Itälä M, Lehtinen T, et al. Early treatment-related mortality in adult autologous stem cell transplant recipients: a nation-wide survey of 1482 transplanted patients. *Eur J Haematol* 2006;76:245-50.
25. Forrest DL, Hogge DE, Nevill TJ, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation does not increase the risk of second neoplasms for patients with Hodgkin's lymphoma: a comparison of conventional therapy alone versus conventional therapy followed by autologous hematopoietic stem-cell transplantation. *J Clin Oncol* 2005;23:7994-8002.

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