

New Strategies in Advanced-Stage Hodgkin's Lymphoma: The BEACOPP Regimen

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ABSTRACT

Despite modifications of standard chemotherapy regimens, long-term survival of patients with advanced Hodgkin's lymphoma has remained disappointing, with survival rates of only 50% to 60%. In an attempt to improve the prognosis of these patients, the German Hodgkin's Lymphoma Study Group (GHSG) has developed the BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen in a baseline and a dose-escalated version. The main principles of BEACOPP are (1) increase of total dose, (2) acceleration of administration schedule, and (3) addition of etoposide. Both BEACOPP variants have been compared with the standard regimen COPP (cyclophosphamide, vincristine, procarbazine, and prednisone)/ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in the randomized HD9 trial for advanced Hodgkin's lymphoma. Interim analysis in February 1999 showed significant superiority of the BEACOPP regimen with regard to induction of complete remission, reduction of progressive disease, and freedom from treatment failure. Despite increased transient hematologic toxicity, the regimen is manageable, showing no increase in the rate of toxic deaths during primary chemotherapy.

INTRODUCTION

The treatment of adult Hodgkin's lymphoma is strictly dependent on stage. In early- and intermediate-stage Hodgkin's lymphoma (ie, Ann Arbor stage I/II, without or with clinical risk factors), the strategy of radiotherapy alone or in combination with polychemotherapy has led to excellent long-term survival rates of ~90%. In contrast, only ~60% of patients with advanced-stage Hodgkin's lymphoma (ie, stages IIB with particular risk factors, III, and IV) can be cured. Standard treatment in advanced Hodgkin's lymphoma has been the administration of 6–8 cycles of polychemotherapy (MOPP [mechlorethamine, vincristine, procarbazine, and prednisone], COPP, ABVD). Commonly, radiotherapy is used only as

an adjuvant for initial bulky tumor sites and residual lymphomas after chemotherapy. Several modifications of the standard polychemotherapy regimens have been evaluated, eg, MOPP alternating with ABVD, MOPP/ABV hybrid, and others. None of these modifications, however, has improved survival of patients with advanced-stage Hodgkin's lymphoma.¹⁻³

Based on a mathematical model of tumor growth and chemotherapy sensitivity, the GHSG has developed the BEACOPP regimen. The BEACOPP regimen contains the main agents in COPP/ABVD (without vinblastine and dacarbazine) and, as an addition, etoposide. Compared with the BEACOPP baseline regimen, cyclophosphamide, doxorubicin, and etoposide are dose-escalated in the BEACOPP escalated version, with mandatory use of granulocyte colony-stimulating factor (G-CSF). Efficacy and feasibility of BEACOPP in patients with advanced-stage Hodgkin's disease were confirmed in an initial phase 2 study followed by a dose-finding study with G-CSF-supported dose escalation of cyclophosphamide, doxorubicin, and etoposide.⁴

PATIENTS AND METHODS

In 1993, the GHSG started a randomized trial (HD9) in which the standard treatment (4 cycles of COPP/ABVD, arm A) was compared with baseline BEACOPP (arm B) and escalated BEACOPP (arm C). Radiotherapy was administered to initial bulky sites and residual lymphomas in all 3 arms. The first interim analyses with 321 evaluable patients in September 1996 showed significant inferiority of the COPP/ABVD arm in terms of progression rate and freedom from treatment failure (FFTF), compared with the pooled results of both BEACOPP variants. Accordingly, arm A of the HD9 study had to be closed, and further patients were randomized between arms B and C. When the fourth interim analysis in February 1999 was performed, 1128 patients were randomized in the HD9 trial before November 1, 1997. One thousand seventy patients (94%) were evaluable. The median observation time was 28 months. Two hundred sixty-two patients were randomized in arm A, 405 in arm B, and 403 in arm C. In this analysis, all patients were analyzed in the arm to which they were originally randomized—strictly intent-to-treat. Fourteen arm C patients and 3 arm B patients were switched to COPP/ABVD, and 1 arm A patient was switched to BEACOPP (escalated) due to progression. Only negligible differences were observed in patient characteristics.

RESULTS

There was significant superiority of the BEACOPP regimen compared with COPP/ABVD in terms of complete remission, progressive disease, and FFTF. Complete remission at the end of the treatment was achieved by 83% of the patients

in arm A, 88% in arm B, and 96% in arm C. In parallel, a significant reduction of the rate of patients with progressive disease could be observed: 12% progressive disease in arm A, 8% in arm B, and 2% in arm C. FFTF at 24 months was 74% in arm A, 81% in arm B, and 90% in arm C. Also, the Hodgkin's-specific FFTF reflected significant superiority of the BEACOPP regimen compared with COPP/ABVD and, in addition, of escalated BEACOPP compared with baseline BEACOPP. Analysis of overall survival (OS) at 24 months yielded OS in arm A, 89%; arm B, 93%; and arm C, 96% (due to the short observation period, no significant differences could be observed).

Despite the higher transient hematologic toxicity of the BEACOPP regimen, there was no increase in the toxic death rate during primary chemotherapy (1.9% arm A, 1.2% arm B, 1.5% arm C). Five cases of leukemia/myelodysplastic syndrome (MDS) (1 MDS, 4 acute myeloid leukemia [AML]) occurred in arm C and 1 (AML) in arm B. Eleven NHL and 4 solid tumors were equally distributed between arms A and B. In arm C, there was 1 NHL and no solid tumors. However, the median observation period is still too short to draw any conclusions on the impact of the new regimen on the induction of secondary neoplasias.

CONCLUSIONS

With regard to induction of complete remission, reduction of the rate of progressive disease, and freedom from treatment failure, the new BEACOPP regimen for treatment of advanced Hodgkin's lymphoma shows significantly improved efficacy compared with the COPP/ABVD regimen. The regimen is manageable and does not increase the toxic death rate. Although the final analysis of the HD9 study was not performed before 2001, the results obtained so far support the strategy of a moderate dose escalation for the total population of patients with advanced Hodgkin's lymphoma. Thus, the GHSG has replaced COPP/ABVD with BEACOPP as standard treatment for patients with advanced Hodgkin's lymphoma. Questions as to the optimal dose (escalated or baseline) and the role of adjuvant radiotherapy are addressed in the current HD12 trial of the GHSG. In this protocol, 8 cycles of escalated BEACOPP are being compared with 4 cycles of escalated BEACOPP followed by 4 cycles of baseline BEACOPP. A factorial design allows for a comparison of the effect of adjuvant radiotherapy on residual disease and initial tumor bulk.

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