ABVD or BEACOPP for Advanced Hodgkin Lymphoma

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The development of multiagent chemotherapy dramatically changed the prognosis of patients with advanced-stage Hodgkin lymphoma (HL). Although almost all of these patients died when treated with radiotherapy or single-agent chemotherapy, the four-drug regimen MOPP (mustargen, oncovin, procarbazine, and prednisone) led to remission rates of more than 50% and an overall survival (OS) rate of more than 60%.1 Shortly thereafter, ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as an alternative anthracycline-containing regimen was introduced in the treatment of HL.2 It took 20 years before ABVD was accepted as better than MOPP or MOPP-based hybrid variants.3 In the meantime, multiagent regimens such as CHVP (chlorambucil, vinblastine, procarbazine, and prednisolone) plus EVA (etoposide, vinblastine, and doxorubicin) and Stanford V were evaluated but failed to improve outcomes of patients with advanced-stage HL.4,5

The quest for a more effective regimen in HL was the rationale for the German Hodgkin Study Group (GHSG) to design BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) more than 20 years ago. This regimen was developed using baseline (BEACOPPbaseline) or escalated doses (BEACOPPescalated) and subsequently compared with the GHSG standard at that time, COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) – ABVD, in the HD9 trial.6 With a total of 1,195 randomly assigned patients and 5 years of follow-up, BEACOPPescalated was found to be significantly better than BEACOPPbaseline and COPP-ABVD. The 10-year update confirmed and extended the initial findings, demonstrating an improvement of 18% in tumor control between BEACOPPescalated and COPP-ABVD as well as an OS difference of 11%.7 Because BEACOPPescalated was also associated with more hematologic toxicity, infections, infertility, and secondary leukemia, there has been some controversy about this regimen since the initial publication. The majority of patients treated with BEACOPPescalated in HD9 developed grade 3 to 4 leukopenia and thrombocytopenia, and 22% had infectious complications. However, this did not translate into higher treatment-associated mortality with BEACOPPescalated as compared with the other two arms of the HD9 trial, BEACOPPbaseline and COPP-ABVD. In the 10-year update,7 the higher response rates in patients treated with BEACOPPescalated resulted in significantly lower overall mortality (12%) as compared with those in patients treated with BEACOPPbaseline (19%) or COPP-ABVD (24%). With this clear improvement in efficacy, the GHSG HD12 follow-up trial for advanced-stage HL8 aimed at reducing overall toxicity of BEACOPP by employing four cycles of BEACOPPescalated followed by four cycles of BEACOPPbaseline (ie, 4 + 4). However, this approach failed. It was the next-generation trial in advanced-stage HL, HD15, in which more than 2,100 patients were randomly assigned, that demonstrated the reduction to six cycles of BEACOPPescalated followed by radiation administered to residual positron emission tomography (PET) – positive disease ≥ 2.5 cm led to a significantly improved and less toxic regimen.9

With the disappearance of potential alternatives such as Stanford V,5 the choice of the best treatment for advanced-stage HL increasingly focused on the question of ABVD or BEACOPP. Subsequently, collaborative groups directly compared ABVD with BEACOPPescalated in four prospective trials.10-13 Instead of using eight cycles of BEACOPPescalated, as in HD9, three of these trials used 4 + 4, similar to the experimental arms of the HD12 trial; the Italian HD2000 instead used four cycles of BEACOPPescalated followed by two cycles of BEACOPPbaseline (4 + 2). In these four trials, a total of 1,227 patients were randomly assigned to 4 + 4 or 4 + 2 BEACOPP variants and ABVD. All four trials reported significant improvements in tumor control, with 5-year progression-free survival (PFS) gains ranging between 12% and 18% and OS differences of 4% to 8% favoring BEACOPP.

In the article accompanying this editorial, Merli et al14 report an update of their 2009 publication of the Italian HD2000 trial. This three-arm randomized trial registered 307 patients with HL, of whom 12 were subsequently excluded. The initial article, with a median follow-up of 42 months, also published in Journal of Clinical Oncology, had shown a significantly better PFS with BEACOPP 4 + 2 as compared with ABVD (81% v 68% P = .038).10 In the 10-year update, with a median follow-up of 120 months, PFS with ABVD, BEACOPP 4 + 2, and the 10-drug COPP-EBV-CAD (cyclophosphamide, lomustine, vindesine, melphalan, prednisone, epidoxorubicin, vincristine, procarbazine, vinblastine, and bleomycin) regimen was 69%, 75%, and 76%, respectively, with corresponding OS rates of 85%, 84%, and 86%. A total of 13 secondary neoplasias were reported, one after treatment with ABVD, six after BEACOPP, and six after COPP-EBV-CAD. The authors concluded that with longer follow-up, they were no longer able to confirm the superiority of BEACOPP 4 + 2 over ABVD in terms of PFS and that this was mainly because of higher mortality from secondary malignancies. However, with fewer
than 100 patients treated in each arm and a total of 80 events, this trial could identify only large differences; the power to detect a 10% difference in 10-year PFS was only 50%. Importantly, the trial also had not been designed to detect differences in OS. Nonetheless, we should congratulate Merli et al. for their stringency in observing their patients; long-term follow-up is particularly important in HL because most patients are young and at risk for late adverse effects.

There are other recent examples of smaller clinical trials in HL and controversial follow-up reports. The Canadian HD.6 study randomly assigned 405 patients with stage IIA or IIA nonbulky HL to either four to six cycles of ABVD alone or a strategy that included subtotal nodal irradiation. With an initial follow-up of 4.2 years, the major finding was poorer PFS for patients treated without radiotherapy. However, in the consecutive report, at 11.3 years of follow-up, OS in the no-radiotherapy arm was better. This was mainly because more patients in the combined-modality arm of the HD.6 trial died as a result of reasons that were unlikely related to the radiotherapy received. Nonetheless, the borderline difference in OS became the main message of this study. Thus, one of the main lessons to be learned from HD2000, HD.6, and similar trials is that larger trials are needed to balance random events to create reliable evidence.

Where do we go from here? What do we know regarding patients’ preferences in terms of tumor control and late events? From their perspective, successful tumor control with primary treatment is the highest priority. A more recent survey among GHSG patients clearly confirmed the desire to be cured with single-line treatment. In addition to examining well-known adverse effects, more emphasis clearly needs to be placed on patient-oriented outcomes such as fatigue. Here, more recent data suggest that up to 30% to 40% of patients with HL in remission experience severe or extreme fatigue, with devastating effects on their lives. Thus, fatigue should become a co–end point in future trials.

Can PET be used to decide if a given patient would be better treated with ABVD or BEACOPP? A number of smaller non–randomized trials have addressed this question by switching to BEACOPP if PET positivity is seen after two cycles of ABVD or, conversely, switching to ABVD if PET negativity is seen after two cycles of BEACOPPescalated. However, nonrandomized trials, unfortunately, cannot provide the final answer. Some clues might be taken from the recently reported United Kingdom RATHL (Response-Adapted Therapy in Advanced-Stage Hodgkin Lymphoma) trial. In this prospectively randomized PET-driven phase III trial, a total of 1,200 patients with advanced-stage HL were randomly assigned. In PET-negative patients, the bleomycin-deleted arm of the HD.6 trial died as a result of reasons that were unlikely related to the radiotherapy received. Nonetheless, the borderline difference in OS became the main message of this study. Thus, one of the main lessons to be learned from HD2000, HD.6, and similar trials is that larger trials are needed to balance random events to create reliable evidence.

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES


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