Will it be another 20 years before Hodgkin lymphoma patients benefit from BEACOPP therapy?

Volker Diehl and Andreas Engert

Hodgkin lymphoma (HL) has become one of the most curable malignancies in adults. Major success was achieved by vigorous improvement in radiation techniques and, more importantly, by the development of multiagent polychemotherapy. In the late 1960s, DeVita and coworkers were the first to pioneer the combination of mechlorethamine, vincristine, procarbazine and prednisone (MOPP)—one of the landmark events in modern oncology.¹ When this regimen was used in patients with advanced HL, more than 80% achieved remission, with approximately 50% alive at 5 years. In an attempt to find a non-crossresistant regimen, Bonadonna *et al.*² developed an approach using doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), which had an improved antitumor efficacy and tolerability compared with MOPP. ABVD was initially regarded as 'European' in contrast to the US-developed MOPP. Surprisingly, it took nearly 20 years before ABVD finally replaced MOPP or MOPP-like regimens for the treatment of advanced HL. This was partly because the efficacy differences between these regimens were subtle, with 5-year overall survival of around 80% and 70%, and tumor-free survival of 60% and 50%, for ABVD and MOPP, respectively. ABVD produced less short-term and long-term toxicity, and is generally considered the 'gold standard' for the treatment of advanced HL.

Experimental models and clinical practice experience has shown HL to be extremely sensitive to chemotherapy. Consequently, numerous clinical trials were designed with hybrid regimens of MOPP and ABVD or variations incorporating up to 12 different drugs. These so-called 'second generation' attempts did not result in better disease control, and showed that single-drug efficacy and drug intensity (i.e. dose over time) are more important than the number of drugs given. With this knowledge, third-generation regimens were developed based on the rationale of using the putatively most effective drugs in the shortest time possible. Reducing the dose intervals became possible with the availability of hematopoietic growth factors such as granulocyte colony-stimulating factor.

Let us hope it will not take another 20 years until all patients can benefit from this medical progress.

V Diehl is an Advisory Board member of Nature Clinical Practice Oncology and A Engert is Secretary of the GHSG and a Senior Consultant in Department I of Internal Medicine at the University Hospital Cologne, Germany.

Competing interests

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The bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) regimen, developed by the German Hodgkin Study Group (GHSG), challenged ABVD as standard therapy for patients with advanced HL. In the prospectively randomized three-arm HD9 study of the GHSG, two BEACOPP regimens (dose-escalated and standard) were compared with the cyclophosphamide, vincristine, procarbazine, and prednisone (COPP)/ABVD regimen. This trial included 1,186 patients, 466 of whom were treated with dose-escalated BEACOPP. The overall and tumor-free survival at 5 years for patients treated with dose-escalated BEACOPP were 91% and 87%, respectively.³ After a 7-year follow-up period the superiority of dose-escalated BEACOPP in terms of freedom from treatment failure (85% versus 75% versus 67%) and overall survival (90% versus 84% versus 79%) was clearly demonstrated. The overall treatment-associated mortality was also lower with this regimen. Death caused by progressive HL was considerably lower for dose-escalated BEACOPP (1.7%) compared with COPP/ABVD (8.7%). The fact that more than 400 centers contributed to this trial, including community hospitals and more than 100 private oncologists, supports the broad applicability of this regimen.

Will the initial benefit in tumor control observed with dose-escalated BEACOPP be lost by a higher rate of late side-effects with the more-aggressive drug combination? The reported 18% tumor-free survival difference at 7 years' follow-up strongly suggests otherwise. It is noteworthy that after 7 years' follow-up, the patients treated with dose-escalated BEACOPP show statistically significant improvements in overall survival compared with those receiving standard BEACOPP or ABVD. These results should influence working practices, including those of primary-care specialists. Let us hope it will not take another 20 years until all patients can benefit from this medical progress.

Supplementary information is available on the *Nature Clinical Practice Oncology* website.