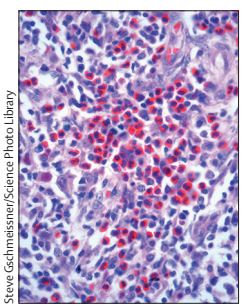
A+AVD versus eBEACOPP in advanced-stage Hodgkin lymphoma



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In *The Lancet Haematology*, 5-year updates of two of the most important studies in advanced Hodgkin lymphoma are reported: David J Straus and colleagues[1] report the 5-year update of the ECHELON-1 trial and Stefanie Kreissl and colleagues[2] report the 5-year follow-up analysis of the HD18 trial by the German Hodgkin Study Group. The controversy surrounds which treatment regimen is better: ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) or eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses). Nothing depicts this controversy more clearly than the pooled analysis, by Andre and colleagues,[3] of four randomised trials of ABVD versus eBEACOPP; 7-year progression-free survival was 71·1% (95% CI 67·1–74·6) for ABVD and 81·1% (77·5–84·2) for BEACOPP (p=0·001), but this did not translate into a significant survival advantage, with an overall survival of 84·3% (95% CI 80·8–87·2) with ABVD and 87·7% (84·5–90·2) with BEACOPP. In the pooled analysis, eight (9%) of 93 deaths with ABVD were related to secondary primary malignant neoplasms, whereas 22 (30%) of 73 deaths with eBEACOPP were related to secondary primary malignant neoplasms. The results from this pooled analysis indicate that eBEACOPP controls Hodgkin lymphoma better than ABVD but fails to improve overall survival because of the high death rates from secondary primary malignant neoplasms. The 5-year updates of the ECHELON-1 and HD18 trials published in *The Lancet Haematology* are the culmination of worldwide investigations to address these issues.

In the phase 3 ECHELON-1 trial, the investigators substituted brentuximab vedotin for bleomycin via the A+AVD (brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine) regimen, based on positive results from phase 2 studies, and compared it to standard ABVD in patients aged 18 years or older with advanced-stage, previously untreated Hodgkin lymphoma.[4,5] They did a PET scan after two cycles of therapy (PET-2), did not change planned treatment, and present the results in patients according to PET-2 status (PET-2-positive and PET-2-negative patients). Overall, 5-year progression-free survival was significantly improved with A+AVD than with ABVD in all patients (hazard ratio [HR] 0·68 [95% CI 0·53–0·87]; p=0·0017), all PET-2-negative patients (0·66 [0·50–0·88]; p=0·0035), all patients younger than 60 years (0·67 [0·51–0·88]; p=0·0034), and all PET-2-negative patients younger than 60 years (0·68 [0·49–0·93]; p=0·014). Non-significant differences in 5-year progression-free survival were reported with A+AVD versus ABVD in other groups (all PET-2-positive patients, PET-2-positive patients <60 years, PET-2-negative patients ≥60 years, and PET-2-positive patients ≥60 years).

The price to be paid for these improvements was peripheral neuropathy. Peripheral neuropathy persisted in 443 (67%) of 662 patients on A+AVD versus 286 (43%) of 659 on ABVD, and was ongoing at 5 years in 127 (19%) patients on A+AVD versus 59 (9%) on ABVD; 14 (2%) of 662 patients on A+AVD had grade 3 peripheral neuropathy versus four (<1%) of 659 on ABVD, and one (<1%) of 662 on A+AVD had grade 4 peripheral neuropathy versus none on ABVD. Taken together, these results provide a strong rationale for giving A+AVD to all patients with advanced, previously untreated stage III or IV classical Hodgkin lymphoma.

However, there are several caveats that should be taken into consideration. First, A+AVD is overall more toxic to administer than ABVD. Second, growth factor needs to be used in the A+AVD regimen. Third, for the important subgroup of patients aged 60 years and older, no significant improvement in progression-free survival was observed in this 5-year analysis (HR 0·82 [95% CI 0·49–1·36]; p=0·44). Fourth, there was no significant improvement in overall survival in any group. And, finally, the cost differential between the two regimens is substantial.[6]

In the phase 3 HD18 trial of patients with advanced-stage Hodgkin lymphoma, the trial investigators followed a response-directed treatment strategy, giving high-intensity therapy first (two cycles of eBEACOPP), then using the PET-2 results to decrease the number of cycles of eBEACOPP in PET-2-negative patients (metabolic responders). In June 1, 2011, after enrolment of 938 patients, the study was amended to reduce the overall number of eBEACOPP cycles from

eight to six, on the basis of the results of the HD15 trial, which showed that six cycles of treatment resulted in fewer secondary primary malignant neoplasms than eight cycles (2·4% *vs* 4·7%), and led to improved overall survival (95·3% [97·5% CI 93·4–97·2] *vs* 91·9% [89·4–94·4]).[7] Following this protocol amendment, patients with a positive PET-2 result received six cycles of eBEACOPP in total, and PET-2-negative patients were randomly assigned (1:1) to receive six or four cycles of eBEACOPP in total. In this 5-year follow-up analysis, Kreissl and colleagues[2] report mature data from the post-amendment cohort. In the PET-2-positive cohort, 5-year progression-free survival was 90·1% (95% CI 87·2–92·9), estimated 5-year overall survival was 96·7% (95% CI 94·9–98·4), and the cumulative incidence of secondary primary malignant neoplasms at 5 years was 4·6% (95% CI 2·6–6·7). In the PET-2-negative cohort, 5-year progression-free survival was 90·9% (95% CI 86·8–95·1), 5-year overall survival was 96·3% (95% CI 93·7–99·0), and the cumulative incidence of secondary primary malignant neoplasms at 5 years was 3·1% (95% CI 0·6–5·6) in patients who received six cycles of eBEACOPP in total, while 5-year progression-free survival was 90·9% (86·8–95·1), 5-year overall survival was 97·5% (95·0–100·0), and the cumulative incidence of secondary primary malignant neoplasms at 5 years was 2·9% (0·3–5·5) in patients who received four cycles of eBEACOPP. These data show that giving six cycles of eBEACOPP to PET-2-positive patients resulted in a comparable outcome to eight cycles and that four cycles of eBEACOPP were statistically non-inferior to six cycles in PET-2-negative patients. The incidence of secondary primary malignant neoplasms was 5% with eight cycles of eBEACOPP, 4% with six cycles of eBEACOPP, and 4% with four cycles of eBEACOPP, and the incidence of deaths from secondary primary malignant neoplasms was 3% with eight cycles of eBEACOPP, 2% with six cycles of eBEACOPP, and less than 1% with four cycles of eBEACOPP. These results provide a strong rationale for giving six cycles of eBEACOPP to PET-2-positive patients and four cycles of eBEACOPP to PET-2-negative patients.

However, there are several caveats that should be taken into consideration. First, there are no randomised data for PET-2-positive patients on eight versus six cycles. Second, all patients were younger than 60 years of age and only 13% were aged 50–60 years. Third, the incidence of secondary primary malignant neoplasms could continue to increase after this 5-year analysis, in line with the previous data showing that 21% of cases of acute myeloid leukaemia or myelodysplastic syndrome occur after 5 years.[8] Finally, PET-2 positivity was defined as a Deauville score of 3, 4, or 5. Since the Deauville score 3 PET is widely accepted as more favourable and now generally accepted as negative,[2] removing the Deauville score 3 PET from the negative group and including it in the PET-2-positive group has the effect of improving progression-free survival in both PET-2-positive and PET-2-negative cohorts.

A direct comparison between both studies is difficult, as the studies comprised different patient populations, including the age groups of patients enrolled, the disease stages included, the types of Hodgkin lymphoma included, the definitions of PET-2 positivity, and the proportion of patients with an International Prognostic Index score of 4–7 between both trials. Since there are no comparator studies of A+AVD versus reduced cycles of eBEACOPP, the differences between the two regimens come down to three issues. The first is progression-free survival. It could be argued that the difference in progression-free survival in the randomised studies between eBEACOPP and ABVD is approximately 10% and that the difference between A+AVD and ABVD is approximately 7%. The argument could be that substituting A+AVD for eBEACOPP would virtually eliminate the difference in progression-free survival, although direct comparisons between the trials are not possible. The second issue is secondary primary malignant neoplasms. In the randomised studies, 3·4% of patients on eBEACOPP died of secondary primary malignant neoplasms. If this rate was reduced to 1·7% for six cycles of eBEACOPP or 0·4% for four cycles of eBEACOPP, then overall survival might improve as a result of improved control of the disease. The third argument centres on long-term toxicity (peripheral neuropathy for A+AVD and second primary malignant neoplasms for eBEACOPP), and which regimen has the lowest risk of long-term toxic effects such as peripheral neuropathy and secondary primary malignant neoplasms. In the end, in the absence of randomised trials, it will be left to the time-honoured method of an individual physician working with an individual patient to decide what is best for that patient, with the knowledge that both of these trials improve long-term outcomes. For now, the German Hodgkin Study Group has added brentuximab

vedotin to modified eBEACOPP and the SWOG Cancer Research Network is starting a phase 3 study comparing nivolumab plus AVD with A+AVD.[9,10]

I declare no competing interests.

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Maintaining the minimal: dynamics of measurable residual disease with continuous lenalidomide therapy

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The treatment of multiple myeloma has evolved from being time-limited to a continuous strategy, made possible with the development of well tolerated drugs amenable to prolonged use. Continuous maintenance therapy improves progression-free survival and overall survival for patients either eligible or ineligible for transplantation.[1,2] The bulk of evidence for lenalidomide maintenance comes from trials in which no monitoring of disease was done beyond the detection of paraprotein in serum or urine, and in which presumably, very few patients were negative for minimal or measurable residual disease (MRD).

The therapeutic advances in multiple myeloma and the consequent achievement of deeper responses have generated the need to develop highly sensitive methods to capture residual disease. MRD became one of the most important prognostic factors, and it was shown in some instances to supersede baseline cytogenetic risk.[3,4] The international myeloma working group incorporated MRD negativity (sensitivity of at least one in 10^5 nucleated cells) as a response category in 2016.[5] MRD is being explored as a potential surrogate clinical trial endpoint on the basis of its rapid readout, consistency, and applicability in different clinical scenarios.[6]

In *The Lancet Haematology*, Benjamin Diamond and colleagues[7] present a study evaluating longitudinal changes in MRD status and their association with progression-free survival in patients with multiple myeloma. This study is novel because it prospectively and longitudinally documents MRD status in a uniformly treated cohort with a consistent methodology. A vast majority of the MRD literature to date is based on one or few points of assessment. The current study[7] further supports the importance of longitudinal assessment of MRD and pivots to an overdue approach of using MRD as a dynamic parameter necessary to understand the behaviour of multiple myeloma over time in an era in which deep responses are the norm. Patients with sustained MRD negativity have improved outcomes, and not surprisingly, the longer one stays MRD negative, the better. Prospective studies utilising MRD to inform treatment decisions have already shown feasibility and are slowly making their way into clinical practice.[8] The observations from the study by Diamond and colleagues[7] provide the framework for interventions aiming to de-escalate therapy in patients with confirmed MRD-negative status.

The most important observation from this study is that loss of MRD negativity is associated with a