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Treatment of advanced-stage Hodgkin lymphoma

Theodoros P. Vassilakopoulos[a,*], Peter W.M. Johnson[b]

[a] Department of Haematology, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece
[b] Cancer Research UK Centre, University of Southampton, Southampton General Hospital, Southampton, England

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ABSTRACT

There is now good evidence that the escalated BEACOPP regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) is more effective in controlling advanced-stage Hodgkin lymphoma (HL) than the widely used ABVD regimen (adriamycin, bleomycin, vinblastine, dacarbazine), but the extra efficacy comes at the expense of both short- and long-term toxicity, and there is debate as to whether overall survival is affected. Baseline prognostic factors have proven of limited utility for determining which patients require more intensive therapy and recent studies have sought to use interim fluoro-deoxyglucose positron emission tomography (FDG-PET) evaluation as a means to guide the modulation of treatment, both upwards and downwards in intensity. These suggest that if treatment starts with ABVD then patients remaining PET-positive after 2 months can be salvaged with escalated BEACOPP in around 65% of cases, but those becoming PET-negative may still experience recurrences in 15%–20%, an event that is more common in those with more advanced disease at presentation. There are early data to suggest that starting with escalated BEACOPP may reduce the rate of recurrence after a negative interim PET to less than 10%. This may be an attractive approach for those with very high-risk features at presentation, but risks overtreating many patients if applied nonselectively. New regimens incorporating antibody–drug conjugates may shift the balance of efficacy and toxicity once again, and further studies are underway to evaluate this.

1. Introduction

The introduction of MOPP combination chemotherapy by De Vita in the mid-1960s was the first major step towards cure of advanced-stage Hodgkin lymphoma (HL) [1–5]. ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), a regimen developed by Bonadonna in the 1970s [2,6,7] proved to be less toxic and more effective than MOPP (mechlorethamine, vincristine, procarbazine, prednisone), thus becoming the new standard of care [3–8]. Despite initial enthusiasm, several attempts to improve results over ABVD with the introduction of alternating, hybrid, or 9–10 drug regimens proved unsuccessful [9–12]. Following ABVD plus consolidation radiotherapy (RT) in selected patients, the long-term probability of tumor control is 65%–75%, depending on the definition of advanced disease.

In the 1990s, the German Hodgkin Study Group (GHSG) developed a theoretical model predicting that a time-intensified seven-drug regimen with higher drug doses compared to COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD would improve the outcome of advanced HL [13]. BEACOPP-escalated (BEACOPP = bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) was designed on this basis [14] and the HD9 trial proved that indeed this regimen, but not its "baseline" version, improved progression-free survival (PFS) and overall survival (OS) over COPP/ABVD in patients up to 65 years old with advanced HL, defined as stage III/IV or IIB with bulky mediastinal and/or extranodal disease [15]. In the 10-year report, the absolute PFS and OS benefits with BEACOPP-escalated were 18% and 10%, respectively [16]. However, these benefits, achieved by eight cycles of BEACOPP-escalated, were associated with significant treatment-related mortality (TRM) and lethal secondary myelodysplasia and leukemia (sMDS/ANLL) rates of ~2%–3% each and much higher rates of severe hematologic toxicity.

Based on these results, the GHSG focused on the improvement of BEACOPP toxicity in the HD12 and HD15 trials. By limiting the number of cycles to six and the upper age limit to 60 years, results were further improved and TRM and sMDS/ANLL were minimized to 0.8% (comparable to ABVD) and 0.3%, respectively [17]. On the other hand, investigational groups outside Germany focused on the comparison of BEACOPP-escalated versus ABVD and similar regimens [18–21].

2. Summary of trials comparing BEACOPP with ABVD or similar regimens

Based on the results of HD9 and HD15, there is good evidence that BEACOPP-escalated improves OS over alternating COPP/ABVD

* Correspondence author. Department of Haematology, National and Kapodistrian University of Athens, School of Medicine, Laikon General Hospital, Athens 11527, Greece. Tel.: +0030-213-2061699/2061906; fax: +0030-213-2061498.
E-mail address: tvassilak@med.uoa.gr (T.P. Vassilakopoulos).

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Table 1
Summary of clinical trials comparing BEACOPP-escalated with ABVD.

Treatment arm	Pts (#)	RT (%)	Toxic deaths (%)	sMDS/ANLL (%)	PFS (%)		OS (%)	
					5-yrs	10-yrs	5-yrs	10-yrs
GHSG HD9, CS IIBX/E,III,IV, 16–65 years [16]								
Besc x8	466	71	1.7	3.2*	88	82	92	86
COPP/ABVD x8	260	64	1.9	0.4*	68	64	83	75
Italian HD2000§, CS IIB,III,IV, > 16 years [12,18]								
Besc x4 + Bbase x2	98	44	2.0	~1,0	81	75¶	92	84¶
COPP/EBV/CAD x6	98	43	0.0	~1.0	78	76¶	91	86¶
ABVD x6	99	46	0.0	0.0	68	69¶	84	85¶
Italian, CS IIB,III,IV or IPS 3-7, 17–60 years [19]								
Besc x4 + Bbase x4	156	67	3.2	1.3	85** (7-yr)		89¶ (7-yr)	
ABVD x6-8	166	66	0.6	0.6	73** (7-yr)		84¶ (7-yr)	
EORTC 2012 Intergroup, CS III/IV and IPS 3–7, < 60 years [20]								
Besc x4 + Bbase x4	274	0	1.8	1.5	83 (4-yr)		90¶ (4-yr)	
ABVD x8	275	0	2.2	0.7	73 (4-yr)		87¶ (4-yr)	
LYSA H34, CS III/IV and IPS 0-2, 16–60 years [21]								
Besc x4 + Bbase x4	70	0	0.0	0.0	93	NA	99¶¶	NA
ABVD x8	80	0	0.0	0.0	75	NA	92¶¶	NA
GHSG HD15, CS IIBX/E,III,IV, 16–60 years [17]								
Besc x8	705	9	2.1	2.7	86	NA	92	NA
B14 x8	710	11	0.8	1.1	86	NA	95	NA
Besc x6	711	12	0.8	0.3	90	NA	95	NA

NOTE. The GHSG HD9 and HD15 trials are also presented for reasons of comparison.
NA = not available.

* Actuarial incidence at 10 years. All other sMDS/ANLL figures are fractions (events/total).
§ 5-year PFS and OS data of the HD2000 trial were based on the initial report [12] and are not identical to the final ones [18].
¶ Nonsignificant, ¶¶ $P = .06$. All other differences in survival rates were statistically significant.
** Freedom from second progression did not differ between BEACOPP and ABVD (88% *v* 82% at 7 years, $P = .12$)

and that six cycles are better tolerated than eight cycles in patients up to 60 years old, minimizing toxic deaths and sMDS/ANLL [15–17]. However, no direct comparison was conducted in these trials with ABVD, which is less toxic than COPP/ABVD and may be more effective, providing as it does a greater dose-intensity of doxorubicin, one of the more important drugs in HL. When BEACOPP-escalated was compared with ABVD in four subsequent trials, PFS was improved [18–21] but OS remained unaltered with the exception of a borderline benefit in low International Prognostic Score (IPS) stage III/IV patients [21] (Table 1). Furthermore, Viviani et al failed to demonstrate a benefit of BEACOPP-escalated over ABVD in terms of freedom from second progression, ie, if preplanned salvage with autologous stem cell transplantation (ASCT) was adopted, with 7-year rates of 88% versus 82% ($P = .12$). These four trials had limited power to detect small differences in OS as a result of their size and the use of a 4+4 or 4+2 design, including four cycles of BEACOPP-escalated and four (or two) cycles of BEACOPP-baseline. The 4+4 design appears equivalent to eight escalated cycles [22] but may be slightly inferior to six cycles of BEACOPP-escalated (~3%–4% absolute difference in 5-year OS), while there are no other data regarding the 4+2 design used in the HD2000 trial [12,18].

The GHSG conducted a network meta-analysis [23] aiming to compare BEACOPP-escalated with ABVD in terms of OS. In this type of analysis, not only direct comparisons within the same study, but also indirect comparisons of the two regimens through the direct comparison of each one with the same "third" regimen were performed. Based on this, the authors concluded that BEACOPP and its variants provided superior OS compared to ABVD. The estimated absolute benefit of BEACOPP-escalated x6 over ABVD for 5-year OS was suggested to be 10%, although an effect of this size should have been apparent in the direct randomized trial comparisons but was not seen. It should be noted that none of the trials included in this meta-analysis compared directly BEACOPP-escalated x6 with ABVD and that both BEACOPP-escalated x6 and BEACOPP-14 x8 were evaluated in a single trial, GHSG HD15 [17].

Even if BEACOPP-escalated x6 were associated with a ~10% OS benefit over ABVD, there are still some issues to be resolved. Approximately 70% of advanced HL patients do not need BEACOPP, because they will be cured with ABVD (Table 1), while 10%–15% of patients will not be cured with BEACOPP-escalated x6 either. Furthermore, female gonadal toxicity of BEACOPP is very high and difficult to manage, as is the marked long-term fatigue that patients report, while heavy hematologic toxicity requires close monitoring, dose reductions, and long periods of hospitalization [15,22,24]. Last but not least, the results published with BEACOPP-escalated have been achieved within the GHSG trial network with a 20-year experience with these regimens; their reproducibility in less well organized structures or the community setting has not been adequately evaluated. Thus, the crucial question is: "Which patients with advanced HL really need BEACOPP?"

3. Can baseline prognostic factors guide the selection of first-line treatment?

The standard tool for the prognostic assessment of advanced HL is the IPS [25]. In the HD9 trial, IPS was predictive for freedom from treatment failure (FFTF) and OS after either COPP/ABVD or eight cycles of BEACOPP-escalated, with differences between the two regimens being more pronounced in the intermediate- (IPS 2–3) and high-risk (IPS 4–7) groups [15]. The absolute difference between high and low-risk groups was narrower after BEACOPP-escalated than COPP/ABVD (13% *v* 25% for OS and 10% *v* 20% for FFTF) (Table 2). However, even in the worst subgroup, ie, patients with IPS 4–7, the 5-year FFTF was almost 60% under COPP/ABVD, and only a small minority of patients presented with an IPS score of 5 or more. As the delivery of chemotherapy and supportive care has improved, IPS remains predictive of the outcome in the modern era, but the level of discrimination between groups is less, with 5-year FFTF rates generally varying between 60% and 70% for the adverse group with IPS 4–7 [9,10,26–31] (Table 2).