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Supplement Article

XVII. Treatment of advanced-stage Hodgkin lymphoma

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Advanced-stage Hodgkin lymphoma (HL) usually includes all patients diagnosed in Ann Arbor stages III and IV. Many groups also include patients with stage IIB and additional risk factors such as large mediastinal mass and/or extranodal disease. Historically, less than 5% of these patients survived when left untreated or received single-agent chemotherapy. With the development of multi-agent chemotherapy such as MOPP (mechlorethamine, vincristine, procarbazine and prednisone) or ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine), the disease became curable, and a multicenter trial demonstrated that ABVD was better than MOPP in terms of freedom from progression (80.8% vs 62.8%; $p < 0.002$) and overall survival (77.4% vs 76.9%; $p = 0.03$) [1]. These findings were confirmed in different trials with longer follow-up.

The next generation of clinical trials included hybrid regimens such as MOPP/ABVD, cyclophosphamide, oncovin, procarbazine and prednisone (COPP)/ABVD or MOPP/ABV or regimens containing even more drugs in rapidly alternating sequence (Table 1). Examples were MOPP/epidoxirubicin, bleomycin, and vinblastine (EBV)/cyclophosphamide, adriamycin, dexamethason (CAD) or hybrid regimens such as chlorambucil, procarbazine, prednisolone, vinblastine, doxorubicin, vincristine, bleomycin, and etoposide (ChlVPP/PABlOE) or chlorambucil, vinblastine, procarbazine, and prednisolone/etoposide, vincristine, and doxorubicin (ChlVPP/EVA) [2]. An alternative shorter US regimen, Stanford V, gave challenging results in a phase II trial. With 142 patients treated at a single centre, the 5-year tumour control was 89% and OS 96%. Importantly, 91% of patients in this trial received additional radiotherapy. A small prospectively randomised multicenter trial compared ABVD with Stanford V and MOPP-EBV-CAD demonstrating that Stanford V was associated with poorer failure free survival (FFS) (67% vs 83% or 85%) when compared with ABVD or MOPP-EBV-CAD [3]. In addition, a larger intergroup trial compared also Stanford V with ABVD [4]. In this trial, the complete remission rates were rather similar (73% for ABVD and 69% for Stanford V), and there was no difference in FFS at 5 years (74% for ABVD and 71% for Stanford V). More patients received additional radiotherapy with Stanford V (71% vs 40%), and this regimen was more toxic. Thus, the challenging data initially reported for Stanford V in single centre phase II trials were not reproduced in the multicenter setting.

Based on statistical modelling, the German Hodgkin Study Group (GHSG) developed the BEACOPP regimen (bleomycin, etoposid, doxorubicin, cyclophosphamide, vincristin, procarbazine and prednisone). After initial dose finding studies, two variants, $BEACOPP_{baseline}$ and $BEACOPP_{escalated}$, were compared to the standard chemotherapy at that time, eight cycles of COPP alternating with ABVD. In the subsequent multicenter phase III trial, 1195 patients with advanced-stage HL were randomised. Overall, there was a clear superiority of $BEACOPP_{escalated}$ over $BEACOPP_{baseline}$ and COPP/ABVD at 5 years [5]. The results were more obvious at 10 years follow-up with significant differences between $BEACOPP_{escalated}$ and COPP/ABVD in terms of tumour control (18%) and OS (11%) [6]. Importantly, the impact of $BEACOPP_{escalated}$ was most obvious in the intermediate prognostic score (IPS 2–3) representing the largest subset of advanced-stage patients.

However, eight cycles of $BEACOPP_{escalated}$ were associated with more toxicity including leukocytopenia and thrombocytopenia, anaemia, infections, fertility and secondary leukemias. The GHSG follow-up studies Hodgkin's Disease (HD12) and HD15 consequently aimed at reducing toxicity albeit maintaining efficacy. In the HD15 trial, about 400 centres from five European countries contributed 2196 patients. At 5 years, six cycles of $BEACOPP_{escalated}$ were significantly better than the old standard of eight cycles, both in progression-free survival (90,3% vs 85,6%) and overall survival (95.3% vs 91.9%) [7]. In addition, the treatment-related mortality was only 0.8% with six cycles as compared with 2.1% with eight cycles. Also, the number of secondary leukemias was much lower (0.3% vs 2.7%). The better tolerability might in part relate to fewer patients receiving additional radiotherapy (11% in HD15 as compared with >70% in HD9). Thus, six cycles of $BEACOPP_{escalated}$

Table 1. Selected fourth generation trials for patients with advanced stage Hodgkin lymphoma*

Trial and reference	Therapy regimen	# Points	Outcome
Intergroup Italy[3]	A. ABVD (6 cycles)	98	83% (FFS); 91% (OS)
	B. Stanford V (12 weeks)	89	67% (FFS); 89% (OS)
	C. MEC hybrid (6 cycles) (+ RT initial bulk/residual mass)	88	85% (FFS); 87% (OS)
UKNCRI[4]	A. ABVD (6–8 cycles)	252	76% (PFS); 90% (OS)
	B. Stanford V 36-Gy RT to initial sites of bulky (> or =5 cm) or splenic deposits	248	74% (PFS); 92% (OS)
GHSG HD9[5]	A. COPP/ABVD (4 cycles)	260	69% (FFTF); 83% (OS)
	B. BEACOPP baseline (8 cycles)	469	76% (FFTF); 88% (OS)
	C. BEACOPP escalated (8 cycles)	466	87% (FFTF); 91% (OS)
GHSG HD15[7]	A. 8 BEA escalated	2126	84% (FFTF); 91.9% (OS)
	B. 6 BEA escalated		89% (FFTF); 95.3% (OS)
	D. 8 BEA baseline-14		85% (FFTF); 94.5% (OS)

*Follow-up was 5 years apart from HD9 (10 years)
ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; COPP, cyclophosphamide, oncovin, procarbazine and prednisone; BEACOPP, bleomycin, etoposid, doxorubicin, cyclophosphamide, vincristin, procarbazine and prednisone; GHSG, German Hodgkin Study Group; EF/IFRT, extended/involved-field radiotherapy; STNI, subtotal nodal irradiation; FFS, failure-free survival; FFP, freedom from progression; FFTF, freedom from treatment failure; EFS, event-free survival; PFS, progression-free survival; OS, overall survival; FU, follow up

are the current standard of care for HL patients in advanced stages for the GHSG.

Comparing BEACOPP with ABVD, the challenging results associated with $BEACOPP_{escalated}$ in advanced-stage HL lead to intensive discussions on the standard of care for advanced-stage HL. More patients survive after first-line treatment with $BEACOPP_{escalated}$, but there is more toxicity. In contrast, ABVD is better tolerated but cures fewer patients. Can the higher relapse rate with ABVD be compensated by effective treatment at relapse?

Another argument against $BEACOPP_{escalated}$ becoming the undisputed standard of care was the lack of direct comparisons because the GHSG trials had initially compared $BEACOPP_{escalated}$ with COPP/ABVD. A total of four smaller trials subsequently compared ABVD with BEACOPP in different versions. Taken together, a total of 1222 patients were included in these four trials. The results at 5 years indeed show significant superiority for those patients treated with BEACOPP (difference ranging from 12% to 18%). The 5-year overall survival difference ranged between 4% and 8% without significance. Because all trials were powered for differences in tumour control but not for overall survival, these data clearly support the superiority of $BEACOPP_{escalated}$ over ABVD. In addition, a more recent network analysis confirmed these findings with more than 10 000 patients and 47 033 patient years of follow-up showing a reconstructed individual survival advantage of 10% for 6 cycles of $BEACOPP_{escalated}$ over ABVD [8].

Current trials

With the advent of positron emission tomography (PET), this technique has not only improved the staging accuracy for HL patients but also indicated prognostic significance. A number of phase II trials thus currently use PET in order to identify good or poor responders early so that treatment can be adapted accordingly. Most groups start with two cycles of ABVD and continue this treatment in those who are PET negative; PET positives are then typically switched to $BEACOPP_{escalated}$. The alternative is to start with $BEACOPP_{escalated}$ and de-escalate to ABVD in PET negative cases after two cycles of chemotherapy. In the GHSG HD15 trial, PET was used to assess the activity of residual masses ≥2.5 cm after chemotherapy so that only a minority of 11% PET+ patients ($n = 191$) received additional radiotherapy. The negative predictive value was 94.1% at 12 months. At 4 years, progression-free survival for PET− was 92.6% and 86.2% for PET+ patients suggesting that this pragmatic approach is feasible, at least in those treated with $BEACOPP_{escalated}$.

Future treatment of HL patients in advanced stages will be more adapted to response and risk profile. In addition, smarter combinations of both, ABVD or BEACOPP, with new drugs such as the anti-CD30 anti-drug conjugate brentuximab vedotin are currently being evaluated in prospective randomised trials. In addition, immune checkpoint inhibitors will very likely also find a role in first line so that the treatment for HL in advanced stages will become more specific and less toxic.

Conflict of interest

Prof. Dr Andreas Engert reports Millennium/Takeda, Affimed and Bristol-Myers Squibb.

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