Treatment of Advanced-Stage Hodgkin Lymphoma

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13.1 From MOPP to MOPP/ABVD to ABVD

Before the introduction of combination chemotherapy, more than 95 % of patients with advanced HL succumbed to their disease within 5 years. Thus, remission rates in excess of 50 % achieved with MOPP (mechlorethamine, vincristine, procarbazine, and prednisone) were a major breakthrough in oncology [1, 2]. MOPP was successfully introduced almost 40 years ago and used for many years for advanced-stage disease, resulting in long-term remission of nearly 50 % [1, 3]. It was then replaced by ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), after a series of large multicenter trials had compared ABVD with alternating MOPP/ABVD or MOPP alone [3–5] (Table 13.1).

Bonadonna et al. were the first to report on the substantial relevance of anthracyclines in ABVD for the treatment of advanced-stage HL [3].

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Table 13.1 MOPP/ABVD in randomized trials

Trial (Ref.)	Publ.	Therapy regimen	# Pts.	Outcome	FU and comments
Bonadonna [3]	1986	A. MOPP/ABVD altern.	43	64.6 % (FFP); 83.9 % (OS)	FU 8 years;
		B. MOPP	45	35.9 % (FFP); 63.9 % (OS)	
Santoro [5]	1987	A. 3xMOPP-RT-3xMOPP	114	62.8 % (FFP); 77.4 % (OS)	FU 7 years; (sub)total nodal irradiation in all patients
		B. 3xABVD-RT-3xABVD	118	80.8 % (FFP); 67.9 % (OS)	
US Intergroup [4]	2003	C. ABVD (6 cycles)	433	63 % (FFS); 82 % (OS)	FU 5 years; MDS and sAML only in MOPP-treated patients
		D. MOPP/ABV hybrid (6 cycles)	419	66 % (EFS); 81 % (OS)	
Viviani [6]	1996	A. MOPP/ABVD alternating	211	67 % (FFP); 74 % (OS)	FU 10 years
		B. MOPP/ABVD hybrid	204	69 % (FFP); 72 % (OS)	
Connors [7]	1997	A. MOPP/ABVD hybrid (8 cycles)	252	71 % (FFS); 81 % (OS)	FU 5 years
		B. MOPP/ABVD altern. (8 cycles) radiotherapy after cycle 6 for PR	248	67 % (FFS); 83 % (OS)	
GHSG HD6 [8]	2003	A. COPP/ABV/IMEP (hybrid 4x)	223	54 % (FFTF); 73 % (OS)	FU 7 years
		B. COPP/ABVD (altern. 4x)	245	56 % (FFTF); 73 % (OS)	

Abbreviations: *SWOG* Southwest Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *ECOG* Eastern Cooperative Oncology 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

Patients were randomly assigned to receive either MOPP or MOPP alternated with ABVD. All 88 evaluable patients had not received prior chemotherapy, and 25 had relapsed after primary radiotherapy. The complete remission (CR) rate with MOPP/ABVD was 88.9 and 74.4 % with MOPP alone. The 8-year results showed that MOPP/ABVD was superior to MOPP in terms of freedom from progression (64.6 % vs. 35.9 %; $p<0.005$), relapse-free survival (72.6 % vs. 45.1 %; $p<0.01$), and overall survival (83.9 % vs. 63.9 %; $p<0.06$). This study impressively demonstrated the benefit of ABVD in terms of efficacy when added to MOPP.

When compared to MOPP, ABVD was more effective: Santoro et al. investigated 3xMOPP+RT+3xMOPP versus 3xABVD+RT+3xABVD. In this trial, the 7-year results indicated that ABVD was better than MOPP in terms of freedom from progression (80.8 % vs. 62.8 %; $p<0.002$), relapse-free survival (RFS, 87.7 % vs. 77.2 %; $p=0.06$), and most importantly overall survival (OS, 77.4 % vs. 67.9 %; $p=0.03$) [5]. An important US trial tested 6–8 cycles of ABVD against 6–8 cycles of MOPP or MOPP alternating with ABVD for 12 cycles [9]. Of 361 eligible patients, 123 received MOPP, 123 received MOPP alternating with ABVD, and 115 received ABVD alone. The overall response rate was 93 %, with a CR rate of 77 %: MOPP 67 %, ABVD 82 %, and MOPP-ABVD 83 % ($p=0.006$ for the comparison of MOPP with the doxorubicin-containing regimens). The rates of failure-free survival at 5 years were 50 % for MOPP, 61 % for ABVD, and 65 % for MOPP-ABVD. OS at 5 years was 66 % for MOPP, 73 % for ABVD,

and 75 % for MOPP-ABVD ($p=0.28$ for the comparison of MOPP with the doxorubicin-based regimens). MOPP was associated with more severe hematologic toxicity. Since ABVD was equally effective and less toxic than MOPP-ABVD, this trial supported the use of ABVD alone as first-line therapy for advanced-stage HL.

Finally, a large American intergroup trial ($N=856$) tested ABVD versus MOPP/ABV hybrid. The rates of complete remission (76 % vs. 80 %, $p=0.16$), failure-free survival at 5 years (63 % vs. 66 %, $p=0.42$), and OS at 5 years (82 % vs. 81 %, $p=0.82$) were similar for ABVD and MOPP/ABV, respectively [4]. However, clinically significant acute pulmonary and hematologic toxicity was more common with MOPP/ABV ($p=0.06$ and 0.001, respectively). More therapy-associated fatal outcomes were reported for the hybrid regimen (ABVD = 9, MOPP/ABV = 15, $p=0.057$). Furthermore, secondary malignancies occurred more often with MOPP/ABV, without reaching statistical significance. Out of 13 patients developing MDS or acute leukemia, 11 were initially treated with MOPP/ABV, and only 2 with ABVD. Both subsequently received MOPP-containing regimens and radiotherapy before developing leukemia ($p=0.011$) [4]. Therefore, it was concluded from this study that ABVD and MOPP/ABV hybrid are equally effective in HL, but due to significant less toxicity, ABVD should become the standard regimen for advanced-stage HL.

This conclusion is supported by the fact that the alkylating agents within the MOPP regimen lead to more severe toxicity in most studies. The comparative iatrogenic morbidity showed that irreversible gonadal dysfunction as well as acute leukemia occurred only in patients treated with MOPP [5]. Since the use of MOPP was also associated with a higher incidence of secondary acute leukemia and infertility, ABVD subsequently became standard of care.

Finally, the evaluation of rapidly alternating and non-cross-resistant regimens was not successful. Alternating MOPP/ABVD was tested against the MOPP/ABV hybrid regimen, alternating COPP/ABV/IMEP against COPP/ABVD hybrid, and alternating MOPP/ABVD against MOPP/ABVD hybrid, all without improving patient outcome [6–8].

Taken together, ABVD has become widely accepted as standard regimen for advanced-stage HL. A major advantage of this regimen is its tolerability. ABVD is a safe outpatient treatment without the need for close white blood cell monitoring and can be administered also in developing countries [10]. One has to keep in mind, though, that a long-term follow-up report of 123 patients treated with ABVD for advanced HL revealed a failure-free survival of only 47 % and an OS of 59 % after 14.1 years [11]. Since 40 % mortality among young patients suffering from a curable malignancy is unacceptably high, alternative approaches were developed to improve on these results.

13.2 Fourth-Generation Regimens

13.2.1 Hybrid and Alternating Regimens

Up-front ABVD was further tested against the Stanford V regimen (see below) and the MOPP/EBV/CAD program in an Italian cooperative study; it was also compared with alternating or hybrid multidrug regimens such as ChlVPP/PABlOE and ChlVPP/EVA in the UK [12, 13] (Table 13.2).

The Italian cooperative study was a multicenter, prospective, randomized clinical trial investigating two chemotherapy regimens (i.e., Stanford V, doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, and prednisone, and MOPPEBVCAD, mechlorethamine, vincristine, procarbazine, prednisone, epidoxorubicin, bleomycin, vinblastine, lomustine, doxorubicin, and vindesine), which were compared to ABVD [12]. Radiotherapy was limited to ≤ two sites of either previous bulky or partially remitting disease. The CR rates for ABVD, Stanford V, and MOPPEBVCAD were 89, 76, and 94 %, respectively; the 5-year failure-free survival and progression-free survival rates were 78, 54, and 81 % and 85, 73, and 94 %, respectively ($p<0.01$ for

Table 13.2 Fourth-generation trials

Trial (Ref.)	Publ.	Therapy regimen	# Pts.	Outcome	FU and comments
Intergroup Italy [12]	2005	A. ABVD (6 cycles)	98	83 % (FFS); 91 % (OS)	FU 5 years; patients in stage IIB without additional risk factors included
		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)	
UK Lymphoma Group [13]	2005	A. ABVD (6 cycles)	391	77 % (EFS); 86 % (FFP); 90 % (OS)	FU 3 years; stages I and II included; stages III and IV at FU 5 years: 65 % (EFS); 81 % (OS)
		B. ChlVPP/EVA (6 cycles)	109	77 % (EFS); 76 % (FFP); 83 % (OS)	
		C. ChlVPP/PABlOE (3x altern.)	275	74 % (EFS); 93 % (FFP); 90 % (OS)	
Intergroup GB and Italy [14]	2002	A. ChlVPP/EVA hybrid (6 cycles)	144	82 % (FFP); 78 % (EFS); 89 % (OS)	FU 5 years
		B. VAPEC-B (11 weeks) (±RT initial bulk/residual mass)	138	62 % (FFP); 58 % (EFS); 79 % (OS)	
Stanford V [15]	2002	Single-arm phase II Stanford V	142	89 % (FFP); 96 % (OS)	FU 5 years; patients with stages I or II with risk factor LMM included; 129 of 152 patients (91 %) received additional radiotherapy
		36-Gy RT to initial sites of bulky (> or =5 cm) or macroscopic splenic disease		In patients IPS ≥3: 75 % (FFP)	
UKNCRI [16]	2009	A. ABVD (6–8 cycles)	252	76 % (PFS); 90 % (OS)	FU 5 years;
		B. Stanford V 36-Gy RT to initial sites of bulky (> or =5 cm) or splenic deposits	248	74 % (PFS); 92 % (OS)	Patients in stages I and II with bulky disease included; 20 % more patients irradiated after S V (73 %)
GHSG HD9 [17]	2003	A. COPP/ABVD (4 cycles)	260	69 % (FFTF); 83 % (OS)	FU 5 years
		B. BEACOPP baseline (8 cycles)	469	76 % (FFTF); 88 % (OS)	
		C. BEACOPP escalated (8 cycles)	466	87 % (FFTF); 91 % (OS)	
GHSG HD9 [18]	2009	A. COPP/ABVD (4 cycles)	260	64 % (FFTF); 75 % (OS)	FU 10 years
		B. BEACOPP baseline (8 cycles)	469	70 % (FFTF); 80 % (OS)	
		C. BEACOPP escalated (8 cycles)	466	82 % (FFTF); 86 % (OS)	

Table 13.2 (continued)

Trial (Ref.)	Publ.	Therapy regimen	# Pts.	Outcome	FU and comments
GHSG HD12 [19]		A. 8 BEA escalated	887	A + B: 88 % (PFS); 92 % (OS)	FU 5 years
		B. 8 BEA escalated	887	C + D: 85 % (PFS); 90 % (OS)	
		C. 4 BEA esc. + 4 BEA baseline			
		D. 4 BEA esc. + 4 BEA baseline			
		(A. + C.: +RT bulk/ residual mass)			
GHSG HD15 [20]	2012	A. 8 BEA escalated	2,126	84 % (FFTF); 91.9 % (OS)	
		B. 6 BEA escalated		89 % (FFTF); 95.3 % (OS)	
		C. 8 BEA baseline-14		85 % (FFTF); 94.5 % (OS)	

Abbreviations: *SWOG* Southwest Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *ECOG* Eastern Cooperative Oncology 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

comparison of Stanford V with the other two regimens). Corresponding 5-year OS rates were 90, 82, and 89 % for ABVD, Stanford V, and MOPPEBVCAD, respectively. Stanford V was more myelotoxic than ABVD but less myelotoxic compared with MOPPEBVCAD. The authors concluded that ABVD was still the treatment choice when combined with optional limited irradiation. The reported failure-free survival for ABVD, however, was higher compared to other studies. This might in part be explained by the fact that stage IIB patients without additional risk factors were enrolled into this study, resulting in a relatively high percentage of good-prognosis patients according to the International Prognostic Score (35 %).

The UK study compared ABVD with two multidrug regimens, i.e., alternating chlorambucil, vinblastine, procarbazine, and prednisolone (ChlVPP) with prednisolone, doxorubicin, bleomycin, vincristine, and etoposide (PABIOE), or hybrid ChlVPP/etoposide, vincristine, and doxorubicin (EVA) [13]. Radiotherapy was planned for incomplete response or initial bulky disease. At 52-month median follow-up, the primary objective EFS at 3 years was 75 % (95 % CI, 71–79 %) for ABVD and 75 % (95 % CI, 70–79 %) for multidrug regimens (hazard ratio [HR] = 1.05; 95 % CI, 0.8–1.37). The 3-year OS rates were 90 % (95 % CI, 87–93 %) in patients allocated to ABVD and 88 % (95 % CI, 84–91 %) in patients allocated to multidrug regimens (HR = 1.22; 95 % CI, 0.84–1.77). Patients receiving multidrug regimen experienced more grade 3/4 side effects including infection, mucositis, and neuropathy. To conclude, in the absence of significant differences in EFS or OS between ABVD and multidrug regimen, ABVD remained the standard for treatment of advanced HL. It should be mentioned that this study reported a better EFS and OS for ABVD than other trials. This might be due to the inclusion of patients

with stage I/II disease who had systemic symptoms, multiple sites of involvement, or bulky disease. Looking at stage III and IV patients only, the 5-year EFS and OS were 65 % and 82 %, respectively.

Taken together, hybrid regimens did not show superiority over ABVD in both trials. This regimen therefore remained the treatment of choice for advanced-stage HL based on equivalent efficacy and lower toxicity in the last 40 years.

The Manchester group followed a different approach. They developed the hybrid ChlVPP/EVA to improve the outcome of MOPP [21]. Patients in the hybrid arm of this trial had a higher CR rate (68.1 % vs. 55.3 %) and a lower failure rate (2.4 % vs. 12.5 %). With a median follow-up period for survivors of 4.5 years (range 0–9), actuarial 5-year progression-free survival (PFS) for all cases was 80 % in the hybrid arm and 66 % in the MOPP arm ($p=0.005$) with a trend toward better OS. ChlVPP/EVA was therefore adopted as standard first-line therapy in this group. This regimen was then tested against VAPEC-B, an abbreviated 11-week chemotherapy program. After 5 years, event-free survival and OS were significantly better with ChlVPP/EVA than with VAPEC-B (EFS, 78 vs. 58 %; OS, 89 vs. 79 %) [14]. Thereafter, ChlVPP/EVA was tested against ABVD and did not show superiority, so that ABVD remained the gold standard [13].

13.2.2 Stanford V

Stanford V was developed as a short-duration, reduced-toxicity program and was applied weekly over 12 weeks. Consolidating radiotherapy to sites of initial disease was employed [15]. Data were initially generated in a single-center setting with a limited number of patients. One hundred forty-two patients with stage III or IV or locally extensive mediastinal stage I or II HL received Stanford V chemotherapy for 12 weeks followed by 36 Gy RT to initial sites of bulky (≥5 cm) or macroscopic splenic disease. With a median follow-up of 5.4 years, the 5-year freedom from progression (FFP) was 89 % and the OS 96 %. However, FFP was significantly worse among patients having an International Prognostic Score of 3 and higher (94 % vs. 75 %, $p=0.0001$). One hundred twenty-nine of 152 patients (91 %) received additional radiotherapy. A prospectively randomized multicenter comparison of Stanford V with MOPPEBVCAD and ABVD showed that Stanford V was inferior in terms of response rate (76 % vs. 89 % and 94 %) and PFS (73 % vs. 85 % and 94 %) in a multicenter setting [12]. These conflicting results might be partially explained by the use of less radiotherapy in the randomized setting and the better treatment quality in single-center studies. Furthermore, in a large intergroup trial including all US cooperative study groups, Stanford V was compared to ABVD ± RT [16]. In this multicenter, prospective, controlled trial, weekly alternating Stanford V was randomized against the standard twice-weekly ABVD regimen. Patients had stage IIB, III, or IV disease, or stage I to IIA disease with bulky disease or other adverse features. Radiotherapy was administered in both arms to sites of previous bulk (>5 cm) and to splenic deposits, although this was omitted in the latter part of the trial for patients achieving CR in the ABVD arm. Five hundred patients received protocol treatment, and radiotherapy was administered to 73 % in the Stanford V arm and 53 % in the ABVD arm. The overall response rate after completion of all treatment was 91 % for Stanford V and 92 % for ABVD. During a median follow-up of 4.3 years, there was no difference in the projected 5-year PFS and overall survival (OS) rates (76 and 90 %, respectively, for ABVD; 74 and 92 %, respectively, for Stanford V). Thus, in this large, randomized trial, Stanford V was not better than standard ABVD when given in combination with radiotherapy. However, 20 % more patients had to be irradiated in the Stanford V arm, and the 5-year PFS was about 15 % lower than reported in the single-center setting. This inferiority in terms of PFS is seen in this magnitude also in the Intergruppo Italiano Linfomi trial [12]. Finally, a large US intergroup (E2496) study was compared to Stanford V and ABVD. The primary endpoint was failure-free survival (FFS), defined as the time from random assignment to progression, relapse, or death.

Overall survival (OS), a secondary endpoint, was measured from random assignment to death as a result of any cause. There was no significant difference in the overall response rate between the two arms, with complete remission and clinical complete remission rates of 73 % for ABVD and 69 % for Stanford V. At a median follow-up of 6.4 years, there was no difference in FFS: 74 % for ABVD and 71 % for Stanford V at 5 years. Seventy-three percent of patients had RT after Stanford V, and 40 % of patients had RT on ABVD. Tolerability of the regimens was comparable; however, more grade 3 sensory neuropathy was observed with Stanford V (10 % vs. 3 %, $p<0.001$). Since the number of very low-risk patients with stage I or II disease was high in this trial, the authors reported the outcome for stage III and IV patients separately. In this cohort, the 5-year FFS was 66 % and OS 85 % only without differences between the treatment groups.

To summarize, the compelling single-center phase II data for Stanford V could not be confirmed in multicenter randomized trials, and this regimen has thus been abandoned in current clinical trials.

13.2.3 BEACOPP Escalated

The German Hodgkin Study Group (GHSG) developed the BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), which is characterized by an increased dose density and dose intensity compared to ABVD and hybrid regimens. Although some indications for a role of dose intensity were available in the early 1990s, no prospective randomized trial had been undertaken. Hasenclever and coworkers analyzed a set of data in which dose variations had been used and developed a novel statistical model of dose-response characteristics. The model took tumor growth and chemotherapy effects into account and was applied to correlate tumor control in relation to treatment intensity. It was fitted to the data of 706 patients who had received COPP/ABVD-like regimens and revealed considerable heterogeneity in chemosensitivity for the single drugs, but showed a positive slope for dose-response relationship. The model was used to simulate the effect of dose escalation, changes of schedule, and architecture of the COPP-ABVD regimen. On the basis of such simulations, the model predicted that shortening cycle intervals from 4 to 3 weeks should lead to small benefits (about 3 % in 5-year tumor control rates), but a moderate average-dose escalation by 30 % of a standard chemotherapy would lead to a potential benefit in the range of 10–15 % in tumor control at 5 years. Based on this model, the BEACOPP regimen was designed. G-CSF was mandatory to compensate for the myelotoxic effects. In a phase II study, the optimal dose of the BEACOPP baseline and BEACOPP escalated regimen were determined [22]. The subsequent HD9 trial of the GHSG found the predicted dose-response curve to be correct. The GHSG HD9 trial then compared COPP/ABVD, BEACOPP baseline, and BEACOPP escalated. Results from 1,195 randomized patients showed a clear superiority of BEACOPP escalated over BEACOPP baseline and COPP/ABVD at 5 years [17]. The follow-up data at 10 years confirmed these results: with a median follow-up of 112 months, the FFTF and OS rates were 64 and 75 % in the COPP/ABVD group, 70 and 80 % in the BEACOPP baseline group, and 82 and 86 % in the BEACOPP escalated group [18]. The 10-year update of the HD9 study did not only confirm a significant improvement in long-term FFTF and OS for BEACOPP escalated but also showed that this advantage is particularly evident in the subset of intermediate-prognosis patients, as defined by the International Prognostic Score (IPS 2–3). Importantly, this is the largest subset of patients (IPS 0–1, 28 %; IPS 2–3, 38 %; IPS 4–7, 13 %) [18].

However, toxicity of this more aggressive approach remained a concern. The subsequent GHSG HD12 trial thus aimed at de-escalating chemo- and radiotherapy by comparing four courses of BEACOPP escalated with four courses of escalated and four courses of baseline BEACOPP ("4+4") [19]. Furthermore, in the HD12 trial, the role of radiotherapy was tested by a second randomization between consolidating radiation to initial bulky and residual disease and

no radiotherapy. At 5 years, OS was 91 %, FFTF 85.5 %, and PFS 86.2 %. However, there was no statistical difference between 8xBEACOPP escalated and the 4+4 arm in all outcome parameters. There was also no significant difference between the RT or no-RT arms in this study, with the caveat that a number of high-risk patients received RT based on the blinded panel decision. Surprisingly, there was no relevant benefit in terms of toxicity in the 4+4 treated patients, and BEACOPP escalated remained standard for advanced-stage HL patients in the GHSG.

In the subsequent HD15 study, de-escalation of chemotherapy was investigated with a reduction in the number of escalated cycles from 8 to 6 and the introduction of a dose-dense BEACOPP baseline regimen (BEACOPP-14) [20]. The study was designed to show non-inferiority of the experimental treatment groups. In addition, PET-guided radiotherapy of residual disease ≥2.5 cm was investigated. Only PET-positive patients received consolidating radiotherapy. A total of 2,182 patients were randomized among the three study arms. Surprisingly, when comparing six cycles of BEACOPP escalated with eight cycles, both PFS (90.3 % vs. 85.6 %) and OS (95.3 % vs. 91.9 %) were significantly better with the reduced number of cycles. With regard to radiotherapy, the negative predictive value for PET at 12 months was 94.1 % (95 % CI 92.1–96.1 %) and only 11 % of all patients received additional RT without compromising the tumor control [23]. In summary, HD15 established six cycles of BEACOPP escalated as a new standard of care based on a significantly improved PFS and OS. So far, these are the best results that have been reported for advanced-stage HL patients.

13.3 What Is the Standard Treatment Today?

The academic community has intensively discussed two different strategies for the treatment of advanced-stage HL: The first strategy claimed a superior outcome when high-dose chemotherapy (HDCT) and autologous stem cell transplantation were included for patients relapsing on ABVD. With this strategy, the majority of patients could be cured with ABVD only without exposing them to the toxicity of first-line treatment with BEACOPP [4, 9]. The second strategy, followed by those using BEACOPP escalated as first-line treatment, claimed a superior outcome by curing as many patients as possible with first-line therapy accepting more toxicity for those patients who could have been cured with a less intensive therapy [18]. These opposing strategies have been discussed very intensively in the past based on indirect comparisons. This situation has changed dramatically during the last few years. Not only study results from direct comparisons have become available, but also a large meta-analysis provided evidence on this important question.

13.3.1 ABVD Versus BEACOPP in Direct Comparisons

Four studies have been conducted so far comparing these two approaches in a prospective randomized setting. The HD2000 trial enrolled 307 patients in three different treatment arms showing a significant superiority of BEACOPP over ABVD in terms of FFP but not for OS [24]. At 5 years, the freedom from progression was 68 % for ABVD and 81 % for BEACOPP (4 escalated+2 baseline, "4+2"); OS was 84 % for ABVD and 92 % for BEACOPP, respectively (Table 13.3).

In the IIL-GITIL-Michelangelo study, ABVD (6–8 courses) or BEACOPP given in 4+4 fashion plus preplanned high-dose salvage produced a comparable 3-year outcome [28]. The final analysis showed a freedom from first progression of 85 % at a median observation time of 61 months among patients who had received initial treatment with BEACOPP and 73 % among those who had received initial treatment with ABVD ($p=0.004$). A total of 65 patients (20 in the BEACOPP group, and 45 in the ABVD group) needed high-dose chemotherapy salvage treatment. However, only 15 patients (33 %) failing first-line ABVD could be rescued. After completion of the overall planned treatment includ-

Table 13.3 ABVD versus BEACOPP in direct comparisons

Study	Treatment	*n*	5-year PFS	Difference (%)	*p*	5-year OS	Difference (%)
HD 2000 [24]	ABVD	99	68	13	0.038	84	8
	BEACOPP (4 esc. +2 baseline)	98	81			92	
IIL[a] [25]	ABVD	168	73	12	0.004	84	5
	BEACOPP (4 esc. +4 baseline)	163	85			89	
IG 20012[b] [26] IPS 3–7	ABVD	275	69	15	0.0003	86.7	4
	BEACOPP (4 esc. +4 baseline)	274	84			90.3	
LYSA H34 [27] IPS 0–2	ABVD	77	75	18	0.008	92	7
	BEACOPP (4 esc. +4 baseline)	68	93			99	

Abbreviations: *SWOG* Southwest Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *GELA* Groupe d'Etude des Lymphomes de l'Adulte, *GHSG* German Hodgkin Study Group, *ECOG* Eastern Cooperative Oncology 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

[a]7-year PFS

[b]4-year PFS

ing salvage therapy, the 7-year rate of overall survival was 89 and 84 %, respectively ($p=0.39$) [25]. This trial was not powered to detect differences in OS and suffered from additional shortcomings [29]. Nonetheless, the authors concluded from the absence of evidence on the evidence of absence, although the secondary endpoint OS was well in line with the primary endpoint FFP.

The results were similar in a larger intergroup trial organized by the EORTC, which has been published so far only as abstract [26]. In this trial, ABVD was compared to BEACOPP 4+4. Only advanced-stage patients were included (Ann Arbor stage III or IV) suffering from high-risk disease as defined by an IPS ≥3. In the interim analysis, PFS was significantly different with 69 % for ABVD and 84 % for BEACOPP 4+4 with an OS of 86.7 and 90.3 %, respectively. However, there was no difference in the primary endpoint, EFS, and between ABVD and BEACOPP 4+4 so far.

Patients with low-risk advanced-stage disease (IPS 0–2) were enrolled in the H34 trial conducted by the LYSA [27]. With 150 patients randomized in this trial, the complete remission rate was 85 % for ABVD and 90 % for BEACOPP. Progression or relapse was more frequent in patients treated with ABVD than in those treated with BEACOPP (17 vs. 5 patients). With a median follow-up of 5.5 years, seven patients died: six treated with ABVD and one with BEACOPP. The EFS at 5 years was estimated at 62 % for ABVD and 77 % for BEACOPP, respectively (HR=0.6, $p=0.07$). The PFS at 5 years was 75 and 93 % (HR=0.3, $p=0.007$) and the OS 92 and 99 % (HR=0.18, $p=0.06$). Although the number of patients recruited in this trial was rather small, these results suggest that BEACOPP is more effective than ABVD in lower-risk advanced-stage patients.

13.3.2 ABVD Versus BEACOPP in a Network Meta-analysis

All trials in this analysis compared ABVD and BEACOPP directly using BEACOPP variants (4+4 or 4+2, escalated and baseline, respectively). In addition, the former standard of eight cycles BEACOPP escalated was replaced by six cycles as

established in the GHSG HD15 study. Since there was uncertainty regarding the difference in OS between ABVD and BEACOPP, a network meta-analysis was performed to indirectly compare these regimens. The analysis included more than 10,000 patients and had 47,033 patient-years of follow-up; there were 1,189 deaths, with an average median follow-up of 5.9 years. Compared to ABVD, the survival benefit for six cycles of BEACOPP escalated was 7 % (95 % CI 3–10 %). Reconstructed individual survival data indicated that BEACOPP escalated has a 10 % advantage over ABVD in terms of OS at 5 years (95 % confidence interval 3–15 %). Kaplan-Meier curves showed increasing hazard ratios over time indicating more OS differences with longer follow-up. This finding is in line with the 10-year follow-up data from the HD9 study, which also showed increasing differences over time [18]. Interestingly, event rates were too low to allow testing for second cancer or treatment-related mortality. Thus, six cycles of BEACOPP escalated offer advanced-stage HL patients the highest chance of cure.

It should be mentioned though that treatment with BEACOPP escalated is associated with more hematological toxicity. BEACOPP escalated should only be used in patients younger than 60 years; older patients should be treated with less aggressive treatment approaches. In addition, also advanced-stage patients aged >40 years have an increased treatment-related mortality when treated with BEACOPP escalated, in particular if they also suffer from a poor performance status [30].

13.4 Outcome Prediction

13.4.1 The International Prognostic Score

Overall, it would be preferable to treat each advanced-stage HL patient according to the individual risk profile in order to better balance efficacy and toxicity. In line with this, some current concepts base the treatment plan on prognostic factors by using the international prognostic score (IPS) for risk stratification [31].

The score was derived from 5,141 patients who had been treated with C(M)OPP/ABVD-like regimen with or without radiotherapy. The endpoint was freedom from progression of disease. Seven factors had similar independent prognostic effects: serum albumin of less than 4 g per deciliter, hemoglobin level of less than 10.5 g per deciliter, male sex, age of 45 years or older, stage IV disease (according to the Ann Arbor classification), leukocytosis (white cell count of at least 15,000/mm [3]), and lymphocytopenia (lymphocyte count of less than 600/mm [3], or less than 8 % of the white cell count, or both). The IPS is currently being used for a risk-adapted therapy in an Israeli phase II study (NCT00392314). Patients in lower-risk advanced stages (IPS 0–2) are treated with ABVD, and patients with an IPS ≥3 receive BEACOPP escalated induction therapy. This strategy might be questionable after the publication of the French H34 study results. However, a distinct group of patients at very high risk cannot be identified on the basis of routinely documented demographics and clinical characteristics as used in the IPS. With BEACOPP escalated, the IPS has lost most of its discriminative power since treatment failures are more rare.

13.4.2 Positron Emission Tomography (PET)

The IPS is increasingly being challenged by response-adapted risk evaluation. It has been demonstrated for HL patients that response to chemotherapy has an impact on the final treatment outcome [32, 33]. However, response as measured by computed tomography (CT) scan might occur with some delay in advanced HL. This is likely due to the fibrotic tissue infiltrating lymph nodes in this disease, which often results in residual masses remaining several months after treatment, especially in cases of bulky disease. For example, in the GHSG HD15 trial, 311 of 817 patients (38 %) showed residual disease >2.5 cm as determined by CT after the completion of chemotherapy [23]. However, 79 % ($n=245$) of these patients at the same time had a negative FDG-PET scan. These patients did not

receive any additional radiotherapy, and, with a rather short median observation time of 18 months, their outcome was not inferior compared to patients reaching a complete remission after chemotherapy. These data indicate that in this setting the biologic response determined by FDG-PET is better than the morphologic response in terms of the negative predictive value. PET is discussed in detail elsewhere in this book (see Chap. 21); nevertheless, the work by Gallamini, Hutchings, and their coworkers must be mentioned in this context. They were able to show that the early PET response (after two cycles of ABVD) overshadows the prognostic value of the IPS and thus is an important tool for planning risk-adapted treatment in advanced HL [34, 35].

Therefore, current concepts include early response evaluation, guided by FDG-PET, into treatment strategies and will hopefully help to define a new standard of care in which each patient receives as much therapy as needed.

13.5 Current Concepts: Response-Adapted Therapy

13.5.1 De-escalating BEACOPP Escalated

The HD15 trial of the GHSG was the first large trial to investigate the negative predictive value of PET in advanced HL, which was used to guide therapy after completion of chemotherapy. Patients were randomized between eight courses of BEACOPP escalated, six courses of BEACOPP escalated, or eight courses of BEACOPP-14 (a time-dense variant of BEACOPP baseline) [36]. As described above, additional radiotherapy was applied only to residual lesions >2.5 cm positive by PET, and a high negative predictive value for progression or early relapse was found (NPV = 94 %). Encouraged by these results and by reports from other studies, the GHSG decided to test a PET-guided strategy in the current HD18 trial [35, 37]. In this study, PET is used to assess the early response after two cycles of BEACOPP escalated, and, in case of negativity, therapy is reduced to a total of four cycles and compared to the standard of eight cycles. This is a de-escalating approach based on the excellent negative predictive value of PET in HL. First results from the Israeli group have recently been published and support this approach [38]. Patients with advanced-stage HL and an IPS ≥3 received two initial cycles of BEACOPP escalated and were then evaluated by PET/computed tomography scan. In case of PET negativity, they were treated with four cycles of ABVD. After a median follow-up of 48 months, progression-free survival (PFS) and overall survival at 4 years were 78 and 95 %, respectively. Though the PFS of 78 % in this trial published by Avigdor and coworkers looks a little disappointing at the first glance, this is within the expected range. In the HD9 trial, FFTF for patients in the unfavorable risk group (IPS 4–7) was 82 % at 5 years. However, looking at the PET results, the 4-year PFS for early PET-negative patients ($n = 31$) and early PET-positive patients ($n = 13$) was 87 and 53 %, respectively ($p = 0.01$).

Though the absolute patient number is small, these data suggest that a de-escalating approach in early PET-negative patients after two cycles of BEACOPP escalated might be feasible.

13.5.2 Escalating Treatment After ABVD Failure

Several groups follow the alternative approach of escalating treatment in patients not responding to two cycles of ABVD as defined by PET positivity. These patients have a very poor outcome with ABVD or ABVD-like therapy. The 2-year PFS is reported as low as 6 % [39]. So far, only very preliminary data are available from ongoing trials. First results of the GITIL (Gruppo Italiano Terapie Innovative nei Linfomi) trial were published in 2009 [40]. In this trial, PET-positive patients received two cycles of ABVD followed by eight cycles of BEACOPP (4+4). Of 164 enrolled patients, 24 (15 %) were PET-2 positive and 136 PET-2 negative, respectively. The two cohorts of patients were well matched in terms of prognostic factors, and the IPS ≥3 was equally frequent in both arms (29 and 28 %, $p = 0.95$). Of

the 24 PET-positive patients, 15 (62 %) were in continuous CR (CCR) after BEACOPP and nine progressed; the mean duration of CR for the responding patients was 18 months (11–37). 127/136 PET-negative patients (93.5 %) were in CCR after standard ABVD and nine progressed or relapsed. The 2-year PFS of PET-positive patients was 56 % only and 93 % for the PET-negative patients, respectively.

These data can be compared with those published by Dann et al. who used two cycles of BEACOPP baseline as induction and increased the dose to BEACOPP escalated in PET-positive cases. In this study, the 5-year PFS was 85 % for these high-risk patients, accounting for a difference of almost 30 % as compared to the induction with ABVD. A possible explanation for this observation is the longer duration (8 vs. 6 weeks for 2x ABVD vs. 2x BEACOPP) and lower-dose intensity in the first 2 months. The initial dose infinity might be most relevant for long-term outcome, since Hodgkin and Reed-Sternberg cells develop chemoresistance. This hypothesis developed many years ago and was termed "Kairos Principle," referring to the ancient Greek mythology. Another observation supports this hypothesis: the most relevant improvement when using BEACOPP escalated occurs in the early treatment phase with the reduction of the number of patients suffering from progressive disease compared to ABVD (difference around 8 %) [24]. There are many other study groups studying the ABVD escalation approach, and mature results are eagerly awaited.

The SWOG currently conducts a study (NCT00822120) in which treatment intensification using six cycles of BEACOPP escalated is being evaluated in PET-positive patients after two cycles of ABVD. The design of a cooperative trial including UKNCRI, Italian, and Nordic centers is very similar. In this study, PET-positive patients receive two cycles of ABVD followed by four to six cycles of dose-dense BACOPP-14 or four to six cycles of BEACOPP escalated. The FIL (Fondazione Italiana Linfomi) increased chemotherapy intensity in patients who were PET+ after two cycles of ABVD using IGEV (ifosfamide, gemcitabine, vinorelbine) followed by high-dose chemotherapy and ASCT (NCT00784537). A similar approach in the "pre-PET era" randomized patients with unfavorable HL (defined as the presence of two poor risk factors consisting of high serum LDH, large mediastinal mass, > one extranodal site, low hematocrit, or inguinal involvement) who achieved CR or PR after four courses of ABVD to either ASCT or four cycles of conventional chemotherapy [41]. ASCT was not better than conventional-dose therapy in terms of PFS or OS. However, early PET-positive patients represent a very poor-prognosis group and might benefit more from this aggressive strategy than a patient population selected by two baseline risk factors.

In summary, the early PET-guided escalation approach after ABVD induction is currently being investigated in several clinical trials. Only one of which has been presented as interim analysis so far. In this analysis, the PFS at 2 years was poor with only 56 %. Though this is better than a historical control with patients treated with ABVD only, it is much worse than the PFS for PET-positive patients after two cycles BEACOPP baseline induction [37, 40]. So far, this data supports the Kairos hypothesis, favoring an early escalation and thus a more aggressive induction therapy. However, more mature results of the ongoing trials must consolidate this hypothesis before final conclusions can be drawn.

13.5.3 Introduction of Brentuximab Vedotin into First-Line Treatment

With the approval of brentuximab vedotin (BV) for relapsed and refractory patients (see Chap. 21), a targeted drug has been introduced into the treatment of HL. This new drug has shown an outstanding balance of efficacy and tolerability. BV is therefore currently being used to improve both the ABVD and the BEACOPP regimen.

BV was initially combined with ABVD in a phase I study; however, life-threatening pulmonary toxicity in this bleomycin-containing combination was observed [42]. BV at a fixed dose (1.2 mg/kg body weight) was then added to the

bleomycin-deleted AVD variant, and 26 patients were treated. Data on safety suggest a high incidence of peripheral neuropathy with the combination of vinblastine and MMAE, two tubulin inhibitors (72 %, mainly grades 1 and 2). The outcome of this or other toxicities has not been reported so far. Concerning efficacy, response rates were very high (96 %). PFS has been reported for 12 months only, which is obviously too short to allow any conclusions. The new regimen AVD-A (Adcetris) is currently being investigated in an international phase III trial (NCT01712490). This trial aims at improving the PFS at 3 years from 75 % with ABVD to 82.5 % with AVD-A. The final analysis of this trial will show if the new regimen adds substantial efficacy to the well-established ABVD regimen without increasing toxicity. From a clinical point of view, tolerability and safety will be critically important since a better PFS has been reported for conventional chemotherapy already.

The GHSG has modified BEACOPP in order to improve tolerability while maintaining the high efficacy. The phase II targeted BEACOPP study (NCT01569204) is fully recruited. Results of 100 evaluable patients will be available in early 2015. Two BEACOPP variants have been randomized in this study. In a more conservative approach, vincristine was replaced by BV and bleomycin omitted. A more experimental regimen additionally introduced dacarbazine for procarbazine and short-term dexamethasone instead of long-term prednisone. An interim analysis showed promising results in terms of safety, feasibility, and efficacy; however, longer follow-up is needed to judge on these new regimens [43].

13.6 The Role of Radiotherapy

The role of consolidating radiotherapy for advanced HL depends on the efficacy of the prior chemotherapy. After MOPP or MOPP-like regimen, there might be a potential advantage of IFRT as detected by a meta-analysis of 16 randomized studies, whereas this advantage is not evident after ABVD or ABVD-like regimens [44, 45]. The randomized EORTC study demonstrated that consolidation with IFRT did not improve the outcome in CR patients after six to eight courses of alternating MOPP and ABV, but potentially improved the outcome of PR patients [46]. A randomized GELA trial showed that consolidation with IFRT after doxorubicin-induced CR was not superior to two additional cycles of chemotherapy [47]. The GHSG HD12 study randomized consolidating radiotherapy to residual disease versus observation only and showed a non-inferiority of the observation arm [19]. Unfortunately, the study was biased by the central review. Experts in this panel were blinded to the randomization result and recommend radiotherapy independent of the randomization status in patients deemed at very high risk of relapse. Based on this expert panel recommendation, almost 10 % of patients who had been randomized into the observation group were irradiated. This bias might have affected outcome; thus, no definite conclusions on the role of radiotherapy can be drawn from this study.

Thus, patients achieving a CR with chemotherapy might not need consolidating radiotherapy to improve the overall outcome. On the other hand, patients with residual disease or PR only might benefit from consolidating radiotherapy. However, FDG-PET scan might be more helpful to identify patients with active residual disease and the need for consolidating therapy. This has been shown to be the case after treatment with BEACOPP regimen [23]. Similar data for the less active ABVD regimen from large studies are not yet available and are eagerly warranted.

13.7 Summary

Advanced-stage HL has become a curable disease for the majority of patients. First-line treatment with six to eight cycles of ABVD is still widely being used. However, the dose-intensified BEACOPP escalated regimen induces a clinically relevant better PFS, which translated into a superior OS in a large network meta-analysis, prospectively randomized studies, and indirect comparisons to ABVD. Thus, six cycles of BEACOPP escalated meanwhile represent the

standard for the treatment of advanced-stage HL patients for many groups. Accordingly, cooperative groups such as the EORTC or LYSA have implemented BEACOPP escalated as standard arm in their ongoing prospective trials. Scientific interest is currently focusing on the questions whether (1) two cycles of the less toxic ABVD regimen should be escalated to the dose-intensified BEACOPP regimen in case of PET-2 positivity or (2) if after a more aggressive induction therapy with two cycles of BEACOPP escalated, further treatment can be de-escalated (GHSG HD18). Both approaches promise to find the best balance between toxicity and efficacy for the benefit of each individual patient. Apart from these more personalized treatment strategies, the targeted drug brentuximab vedotin is currently being used to improve both regimens, ABVD in terms of efficacy and BEACOPP in terms of tolerability. After decades of substantial but slow advances in the treatment of advanced-stage HL, personalized or targeted treatment strategies will hopefully result in better treatment options for our patients in the near future.

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