Original article

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A prospectively randomized trial carried out by the German Hodgkin Study Group (GHSG) for elderly patients with advanced Hodgkin's disease comparing BEACOPP baseline and COPP-ABVD (study $HD9_{elderly}$)

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In contrast to younger patients, the prognosis of elderly patients with advanced Hodgkin's disease (HD) has not improved substantially over the last 20 years. We thus carried out a prospectively randomized study ($HD9_{elderly}$) to compare the BEACOPP regimen in this setting against standard COPP-ABVD. Between February 1993 and 1998, 75 patients aged 66–75 years with newly diagnosed HD in advanced stages were recruited into the HD9 trial as a separate stratum ($HD9_{elderly}$). Patients were assigned to eight alternating cycles of COPP and ABVD or eight cycles of BEACOPP in baseline doses. Radiotherapy was given to initial bulky or residual disease. In total, 68 of 75 registered patients were assessable: 26 were treated with COPP-ABVD and 42 with BEACOPP baseline. There were no significant differences between COPP-ABVD and BEACOPP in terms of complete remission (76%), overall survival (50%) and freedom from treatment failure (FFTF) (46%) at 5 years. At a median follow-up of 80 months, a total of 37 patients died: 14/26 patients (54%) treated with COPP-ABVD and 23/42 patients (55%) with BEACOPP. Two patients (8%) treated with COPP-ABVD and nine patients (21%) treated with BEACOPP died of acute toxicity. Hodgkin-specific FFTF at 5 years was 55% after COPP-ABVD and 74% after BEACOPP ($P = 0.13$). Thus, there are no differences in survival between these regimens in elderly patients.

Key words: BEACOPP, chemotherapy, elderly patients, Hodgkin's lymphoma

Introduction

The age at diagnosis of Hodgkin's disease (HD) is an important clinical risk factor [1]. Several studies have shown an unfavorable outcome of elderly patients particularly in advanced stages [1–11]. The definition of 'elderly' varies between different authors and groups with the cut-off point between 50 and 65 years. Factors such as more aggressive disease, more frequent diagnosis of advanced stage [2, 12], co-morbidity [13], poor tolerance of treatment, failure to maintain dose intensity [2, 3, 8, 9, 14] and shorter survival after relapse [11, 15] contribute to the poorer outcome of elderly patients. In addition, the inclusion of deaths due to other causes obscures the prognosis in this group [16].

The number of patients aged between 60 and 65 years treated within large prospective randomized studies is generally lower than 10% [17, 18]. Prospective trials for advanced stage HD usually exclude patients older than 65 years [19–23].

With few exceptions, published data on HD elderly are of descriptive nature and generally based on retrospective analyses of study registries and population-based studies [1, 24]. Prospective studies selected for elderly patients are rare [25–27] and randomized trials are missing.

The most widely accepted regimen for HD patients with advanced stage is ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) [28]. To improve on these results, time and/or dose intensified third-line protocols were investigated. Such a protocol developed by the German Hodgkin's

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Lymphoma Study Group (GHSG), BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) [29], demonstrated considerable therapeutic improvement in younger patients with advanced HD. To assess the efficacy and toxicity of baseline and escalated BEACOPP in a large patient population, the GHSG conducted the HD9 trial comparing eight cycles of both BEACOPP variants against eight cycles of alternating COPP-ABVD [30]. As a separate stratum of the HD9 trial, patients older than 65 years were randomized between the GHSG standard, COPP-ABVD and BEACOPP baseline only ($HD9_{elderly}$), and analyzed separately from the other strata. The aim of the $HD9_{elderly}$ trial was to assess the feasibility and toxicity of BEACOPP baseline in elderly patients and to compare the efficacy of this new regimen with COPP-ABVD.

Patients and methods

Eligibility and staging

Elderly patients aged between 66 and 75 years with previously untreated biopsy-proven HD were randomized between eight cycles of alternating COPP-ABVD (arm A) and eight cycles of BEACOPP baseline (arm B) within the $HD9_{elderly}$ stratum. Radiotherapy was given to initial bulky disease (30 Gy) or residual tumor after chemotherapy (40 Gy). Patients with stage IIB and large mediastinal mass and/or extranodal involvement and/or massive spleen involvement and all patients in stage III and IV disease were eligible. Large mediastinal mass was defined as a tumor measuring one-third or more of the maximum intrathoracic diameter as determined by posterior–anterior chest radiograph. Bulky disease was defined as a single lymph node involvement or a conglomerate mass of ≥5 cm in any diameter. Stage of disease was defined according to the Ann Arbor Conference classification. Exclusion criteria included a positive human immunodeficiency (HIV) test, creatinine clearance below 60 ml/min, serum bilirubin greater than 2 mg/dl, concurrent infection, severe cardiac, pulmonary or cerebral dysfunction, white blood cell (WBC) count less than 3000/μl and platelet count less than 100 000/μl. Each patient provided written informed consent.

Pretreatment evaluation involved medical history, physical examination, complete blood count, liver and renal functional tests, erythrocyte sedimentation rate, chest radiography, abdomen ultrasound, computed tomography (CT) of chest and abdomen, bone marrow biopsy and isotopic bone scan. In addition, lung function test and echocardiography were routinely carried out before treatment.

Registration

Between February 1993 and February 1998, 75 elderly patients were enrolled into this study. Sixty-eight registered patients (91%) were eligible and assessable for this analysis, four patients did not have HD and three patients met exclusion criteria. The COPP-ABVD arm was closed prematurely in September 1996 when the second interim analysis of the HD9 study demonstrated a significantly superior freedom from treatment failure (FFTF) in both BEACOPP groups. Thereafter, elderly patients were assigned to the BEACOPP baseline arm only within the $HD9_{elderly}$ stratum.

Pathology review panel

Histological diagnosis was made initially by local pathologists who were asked to send paraffin block biopsy samples to a central pathology review panel involving six German lymphoma experts. The registration to the trial was based on the initial diagnosis. Patients with a review diagnosis other than HD were excluded from the study. In the absence of a review diagnosis, the initial diagnosis of Hodgkin's disease was considered sufficient for eligibility.

Chemotherapy

After stratification according to stage IIB/IIIA versus IIIB/IV or presence of large mediastinal mass, patients were allocated to receive eight courses of COPP alternating with ABVD (arm A) or eight courses of baseline BEACOPP (arm B) followed by radiotherapy to initial bulky or residual disease. The alternating regimen consisted of COPP monthly alternated with ABVD. COPP is identical to standard MOPP except that mechlorethamine was substituted by cyclophosphamide [31]. All cytotoxic drugs in BEACOPP baseline were given within 8 days and recycled after 21 days without routine application of granulocyte colony-stimulating factor (G-CSF). The regimens are shown in Table 1.

Radiotherapy

All sites of disease were mapped before chemotherapy was initiated. Appropriate radiotherapy was planned centrally by an expert radiation oncology review panel. Local radiotherapy was given to all regions of initial bulky disease with 30 Gy or residual disease that appeared enlarged (>2 cm) clinically or by CT with 40 Gy. Radiation fields were restricted to the extent of initial bulky tumors or persisting tumor mass. Radiotherapy was initiated 4–6 weeks after the end of chemotherapy with 1.8–2.0 Gy daily fractions.

Response assessment and follow-up

Response evaluation included physical examination, complete blood cell count, blood chemistry and CT of the chest, abdomen and pelvis. A bone

Table 1. Drug doses and schedules

	Dose (mg/m^2)	Route	Days[a]
COPP-ABVD (recycle day 57)			
Cyclophosphamide	650	i.v.	1, 8
Vincristine	1.4[b]	i.v.	1, 8
Procarbazine	100	p.o.	1–14
Prednisone	40	p.o.	1–14
Doxorubicin	25	i.v.	29, 43
Bleomycin	10	i.v.	29, 43
Vinblastine	6	i.v.	29, 43
Dacarbazine	375	i.v.	29, 43
BEACOPP (recycle day 22)			
Cyclophosphamide	650	i.v.	1
Doxorubicin	25	i.v.	1
Etoposide	100	i.v.	1–3
Procarbazine	100	p.o.	1–7
Prednisone	40	p.o.	1–14
Bleomycin	10	i.v.	8
Vincristine	1.4[b]	i.v.	8

[a]The days were counted from the beginning of the double cycle of COPP-ABVD.
[b]The absolute dose of vincristine was limited to 2.0 mg.
i.v., intravenous; p.o., oral.

marrow biopsy or isotopic bone scan was repeated if the initial examination was positive. The success of treatment was determined by restaging after four and eight cycles of chemotherapy. If radiotherapy was given, a final restaging was carried out 4–8 weeks after the end of radiation. Follow-up examination including medical history and physical examination. Complete blood cell count and blood chemistry, chest X-ray, and abdominal ultrasound were carried out within the first 2 years at 3-month intervals, at 4-month intervals during years 3 and 4, and biannually thereafter. Treatment was documented after each cycle of chemotherapy and after radiotherapy. Documentation included dose schedule, dose given and toxicity. Complete remission (CR) was defined as the disappearance of all clinical disease manifestation for at least 4 weeks; partial remission (PR) was defined as the reduction in all disease manifestation of at least 50% of maximal diameter compared with the initial involvement. Residual disease (>2 cm) with suspected active disease was allocated for radiotherapy. Residual disease after chemo- and radiotherapy was considered as CRu (CR uncertain with residual lesion) when no additional treatment was required.

Statistical methods

FFTF was defined as the time from registration to the occurrence of one of the following events: death from any cause, progressive disease, no CR at the end of protocol treatment, relapse or non-study treatment. HD-specific FFTF was defined as the time from registration to occurrence of HD-specific events including progressive disease, no CR after primary treatment, non-study treatment, relapse and death from Hodgkin's disease. Acute toxic death was not regarded as a HD-specific event. Progressive disease was defined as the occurrence of new lesions or increase of at least one already known lesion by more than 25% during or within 3 months after therapy. Overall survival (OS) was defined as the time from registration to death from any cause. FFTF and OS curves were estimated with the method of Kaplan and Meier. As randomization was closed early, separate analyses were carried out for the full analysis set and randomized patients only. The results of both analyses are comparable, thus only results of the full analysis set are reported here. Kaplan–Meier estimates were compared using the log rank test; for categorical data, Fisher's exact test was used.

Results

Patient characteristics

Of the 68 assessable patients, 26 patients were randomly assigned to receive eight alternating courses of COPP-ABVD (arm A), and 42 patients were assigned to receive eight courses of BEACOPP baseline (arm B). The flow of patients through the $HD9_{elderly}$ trial is shown in Figure 1.

The numerical differences are because randomization ceased after the COPP-ABVD arm was prematurely closed after an interim analysis of the HD9 trial showing superiority of the combined BEACOPP arms in HD9 compared with COPP-ABVD. Pretreatment clinical characteristics of the assessable patients are listed in Table 2.

Median age was 69.5 years. There were more women included in this study, with no difference between the groups. Less than one-quarter of patients had initial bulky tumor. There were more patients in the COPP-ABVD arm with B-symptoms (88%) compared with BEACOPP (60%; $P = 0.014$). Other characteristics did not differ significantly. However, patients randomized to COPP-ABVD arm were older, had a higher International Prognostic Score (IPS) according to the method of Hasenclever et al. [32] and more often presented with large mediastinal mass or extranodal involvement.

Histological review was available for 49 patients (72%). Data for the calculation of the IPS were available for 88% and 86% of patients treated with COPP-ABVD or BEACOPP, respectively.

Administration of therapy

In total, 41 patients received the full planned number of treatment cycles, 18 patients (69%) received eight alternating courses of COPP-ABVD and 23 patients (55%) received eight courses of BEACOPP baseline. At least four cycles of protocol therapy were given to 24 patients (96%) in the COPP-ABVD arm and 38 patients (90%) in the BEACOPP arm. An early termination of planned therapy during chemotherapy or before radiotherapy occurred in 13 patients (50%) in the COPP-ABVD arm and in 21 patients (50%) in the BEACOPP arm. Reasons and time of early termination are listed in Table 3.

In the BEACOPP group, considerably more patients finished the therapy prematurely due to toxicity including toxic deaths. Of 64 patients assessable for treatment and toxicity details, 60% of patients in the COPP-ABVD arm and 38% of patients in the BEACOPP baseline arm received at least 85% of the intended dose.

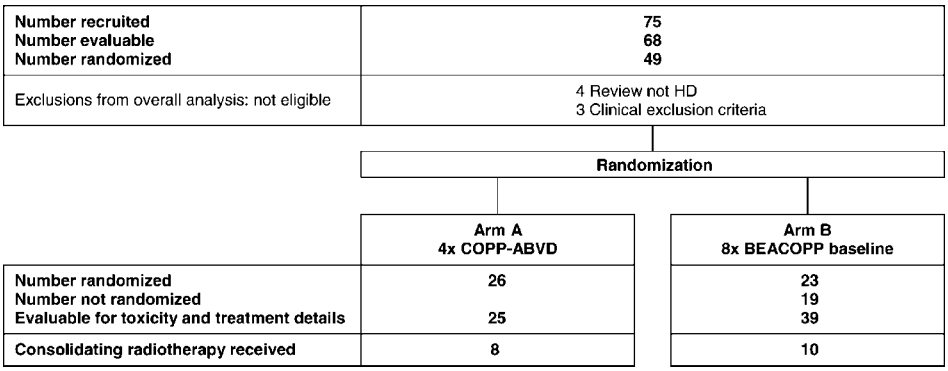

Figure 1. Flow diagram of participants through the $HD9_{elderly}$ trial. HD, Hodgkin's disease.

Table 2. Patient characteristics according to treatment arm

Characteristic	% of patients	
	COPP-ABVD ($n=26$)	BEACOPP ($n=42$)
Gender		
Male	35	26
Female	65	74
Age (years)		
Median	70 years	69 years
66–68	42	43
69–71	15	33
72–75	42	24
Stage		
IIB	11	–
III	62	67
IV	27	33
B symptoms present	88	60
Bulky tumor	23	21
Risk factors		
Large mediastinal mass	19	7
≥3 nodal areas	77	79
Extranodal involvement	31	19
ESR	85	67
Massive spleen involvement	12	10
IPS	($n=23$)	($n=36$)
0–1	9	28
2–3	48	50
4–7	43	22
Review histology	($n=16$)	($n=33$)
Lymphocyte predominant	–	3
Nodular sclerosis	50	42
Mixed cellularity	31	36
Classical HD, unspecified	19	18

ESR, erythrocyte sedimentation rate; IPS, international prognostic score; HD, Hodgkin's disease.

Table 3. Reason and time of early termination of therapy according to treatment arm

	COPP-ABVD ($n=26$)		BEACOPP baseline ($n=42$)	
	No.	%	No.	%
Total	13	50	21	50
Reason for discontinuation				
Progression	1	4	2	5
Extensive toxicity	3	12	11	26
Concomitant disease	2	8	4	9
Patient's wish	5	19	2	5
Other	4	15	6	14
Time of discontinuation				
First half of CT	2	8	6	14
Second half of CT	6	23	13	31
Before RT	5	19	2	5

CT, chemotherapy; RT, radiotherapy.

Table 4. Toxicity WHO grade III/IV in % of patients

Toxicity	% of patients	
	COPP-ABVD ($n=25$)*	BEACOPP baseline ($n=39$)*
Anemia	24	41
Thrombopenia	16	49
Leucopenia	84	92
Infection	12	23
Nausea	12	18
Mucositis	–	13
Gastrointestinal	4	3
Respiratory	–	8
Cardiac	8	15
Neurotoxicity	12	13
Alopecia	44	62
Fever	8	8

*Patients assessable for toxicity.

Radiotherapy

A total of 18 patients had consolidating radiotherapy to initial bulky or residual tumor after chemotherapy. Of these patients, 31% were in the COPP-ABVD arm and 24% in the BEACOPP arm. The mean dose given was 35.9 Gy. Four additional patients received consolidating radiotherapy after early termination of chemotherapy in CR or CRu.

Table 4 lists the frequency of acute toxicity (WHO grade III/IV) during chemotherapy in 64 patients. Leucopenia occurred in 84% and 92% of patients in the COPP-ABVD and the BEACOPP arm, respectively. There was more leucopenia WHO grade IV in BEACOPP (40% and 87%, respectively). Thrombocytopenia III/IV occurred in 16% and 49% of patients and anemia III/IV in 24% and 41%, respectively. Overall more patients treated with BEACOPP (87%) had severe toxicity (WHO grade IV) compared with COPP-ABVD (44%). A total of 11/68 toxic deaths occurred within the protocol (8% in the COPP-ABVD arm and 21% in the BEACOPP arm). The causes of toxic deaths were cardiac in three patients, pneumonia in three and sepsis in five patients (Table 5).

Of 11 toxic deaths, five occurred during or shortly after the first cycle of therapy. G-CSF was given in 10/25 patients (40%) and 15% of cycles in the COPP-ABVD arm and in 23/39 patients (59%) and 38% of cycles in the BEACOPP arm.

Table 5. Acute toxic deaths

Cause	No. of patients	
	COPP-ABVD ($n=26$)	BEACOPP ($n=42$)
Sepsis	1	4
Pneumonia	1	2
Cardiac	–	3
Total	2	9

Table 6. Treatment outcome

	COPP-ABVD ($n=26$)		BEACOPP baseline ($n=42$)	
	No.	%	No.	%
Complete remission	20	77	32	76
Partial remission	3	12	–	–
Progressive disease	2	8	3	7
Unknown (death)[a]	1	4	7	17
Relapse	6	23	5	12
Second malignancy	4	15	6	14

[a]Unknown indicates no restaging result was documented at the termination of therapy because of death during therapy from non-Hodgkin's cause.

Table 7. Causes of death

Cause of death	COPP-ABVD ($n=26$)		BEACOPP ($n=42$)	
	No.	%	No.	%
Hodgkin's disease	6	23	7	17
Acute toxicity	2	8	9	21
Secondary malignancy	2	8	4	10
Other	4	15	3	7
Total deaths	14	54	23	55

Disease control and survival

Complete responses (CR + CRu) were seen in 76% of all patients with no difference between the two treatment arms. Seven per cent of all patients developed progressive disease, 8% in the COPP-ABVD arm and 7% in the BEACOPP arm. Eight patients died before restaging with unknown effect of therapy, one patient (4%) in the COPP-ABVD arm and seven patients (17%) in the BEACOPP arm, respectively. Outcome by treatment arm is summarized in Table 6. With a median follow-up of 80 months, 11 relapses were reported, six (23%) after COPP-ABVD and five (12%) after BEACOPP. Overall, 37 patients died, 14 patients (54%) in the COPP-ABVD arm and 23 patients (55%) in the BEACOPP arm. Causes of death by treatment arm are listed in Table 7. The Kaplan–Meier plots for OS, FFTF and HD-specific FFTF are shown in Figure 2. The OS and FFTF rates at 5 years were 50% [pooled 95% confidence interval (CI 38% to 62%)] and 46% (pooled 95% CI 34% to 58%), respectively, for all patients with no difference between the treatment arms. The rate of HD-specific FFTF at 5 years was 55% (36%, 75%) and 74% (58%, 90%) (COPP-ABVD and BEACOPP, respectively). However, the Kaplan–Meier estimates were not significantly different [at 5 years −18% (−44%, 7%); $P=0.13$]. Most of the HD-related events occurred within the first 3 years in both groups.

Management at progress and relapse

A total number of 11 patients relapsed after the initial therapy, six patients (23%) after COPP-ABVD and five (12%) after BEACOPP. Relapses were observed within 4–38 months after the end of therapy. There were six early relapses (≤12 months). Eight patients received salvage therapy at relapse, five patients had chemotherapy only, one patient received radiotherapy only and two patients combined treatment. Ten patients died within 2–28 months after relapse, one patient is alive more than 5 years after relapse. Primary progressive disease occurred in five patients, two (8%) in the COPP-ABVD arm and three (7%) in the BEACOPP arm. All five patients with primary progressive disease died within 1–7 months after progressing.

Secondary malignancies

After a median follow-up of 80 months, nine patients developed secondary malignancies, three (12%) in the COPP-ABVD arm and six (14%) in the BEACOPP arm. Four patients had secondary non-Hodgkin's lymphoma (NHL), one patient acute myelogenous leukemia, three patients had solid tumors (one colon-carcinoma, one carcinoma of esophagus and one bile duct carcinoma) and one patient had both solid tumor (colon-carcinoma) and NHL. Of the patients with secondary solid tumors, three patients had no radiotherapy and one patient had the tumor outside the initially irradiated area. Six patients died within 0–35 months after the diagnosis of secondary malignancy, and three patients are still alive (23, 72 and 76 months after the diagnosis of secondary malignancy).

Discussion

The $HD9_{elderly}$ trial is the first prospectively randomized multicenter study in elderly patients with advanced stage HD comparing a standard regimen (COPP-ABVD) with a more aggressive experimental schedule (BEACOPP baseline). The following findings emerge from this trial. (i) There was no difference in terms of overall response and early progression rates between patients treated with eight alternating cycles of COPP-ABVD or eight cycles of BEACOPP baseline. In addition, there was also no difference in treatment outcome between the two arms. The 5-year OS and the 5-year FFTF were 50% and 46%, respectively. (ii) More acute toxicity and acute toxic deaths were observed in patients treated with BEACOPP baseline. (iii) Both response to treatment and tolerability were inferior when compared with younger patients in

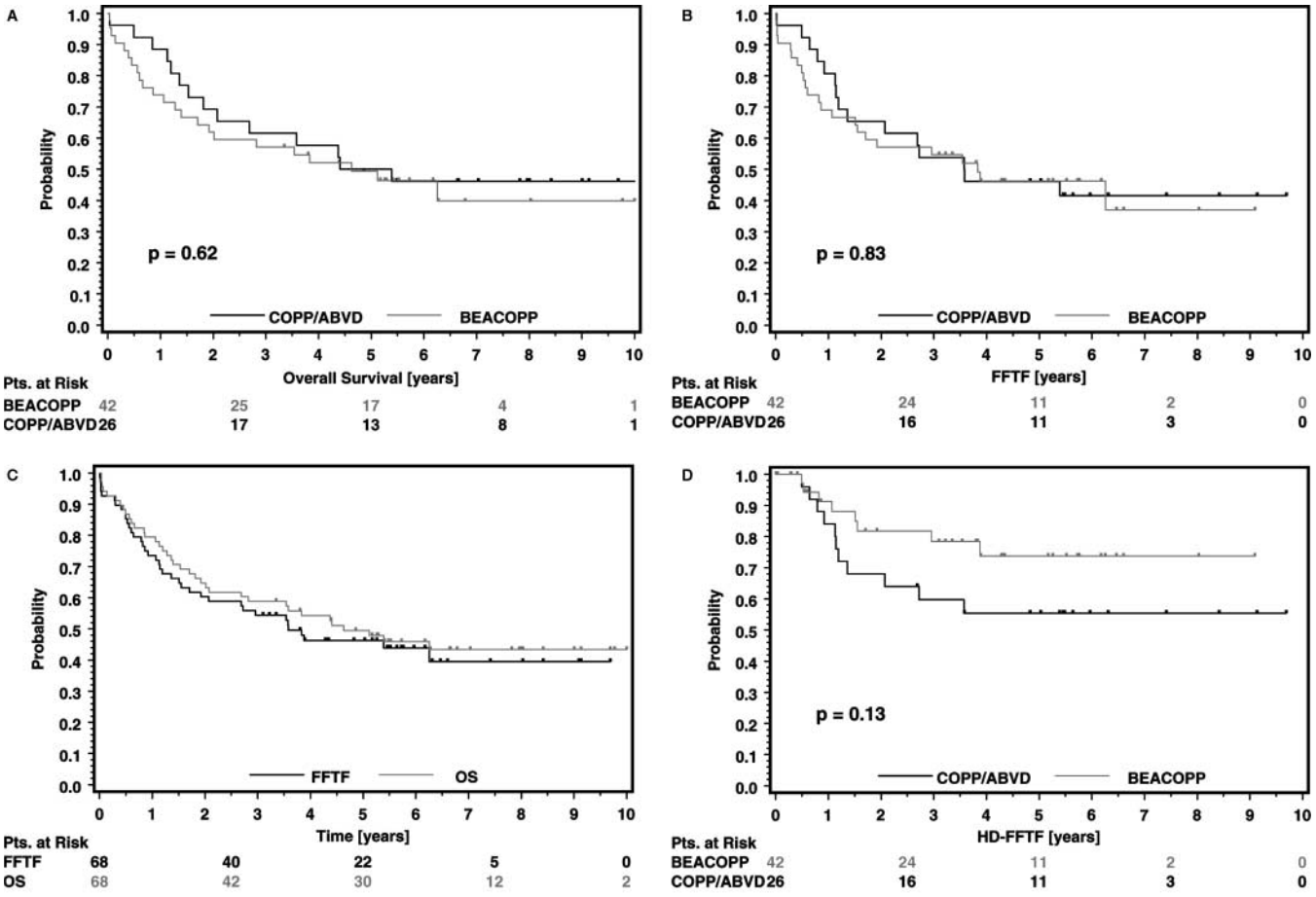

Figure 2. Kaplan–Meier analysis of overall survival (OS), freedom from treatment failure (FFTF) and Hodgkin's disease-specific FFTF (HD-FFTF) after randomization according to treatment arm. (**A**) Overall survival; (**B**) FFTF; (**C**) Comparison of OS and FFTF curves for all 68 patients; (**D**) HD-specific FFTF.

the HD9 study. (iv) The outcomes of elderly HD patients with progressive or recurrent disease are dismal.

In contrast to the HD9 study in younger patients, the $HD9_{elderly}$ study failed to identify a beneficial effect of BEACOPP baseline in patients above 65 years compared with COPP-ABVD. We detected no difference in response, FFTF or OS between the two treatment arms and observed more acute toxicity in elderly HD patients treated with BEACOPP baseline. Generally, the treatment results in this trial for elderly patients are inferior to those achieved in younger patients within the HD9 study [30]. The overall CR rate of 76%, however, compares very favorably with those reported by others ranging from 58% to 73% [25, 26]. The possible better tumor control of BEACOPP might be reflected in the lower relapse rate (12%). In contrast, 23% of patients in the COPP-ABVD arm relapsed. This results in a superior 5-year HD-specific FFTF for BEACOPP (74%) compared with COPP-ABVD (55%). This difference, however, is not significant.

In the literature, the 5-year OS in this patient group has been reported to be less than 50% [2, 4, 8, 9, 11, 12, 14, 25–27, 33–35]. With the exception of three prospective trials [25–27], these data are based on retrospective analyses using MOPP or MOPP/ABVD-like regimens. Comparisons between trials are also hampered by various definitions of 'elderly' with the lower age limit ranging from 50 to 65 years. In addition, most authors included early-stage patients in their data collection. Thus, the 5-year OS of 50% reported in our study for HD patients with advanced disease only is superior to previously reported results.

The $HD9_{elderly}$ study was a separate stratum of the HD9 trial. In contrast to the treatment of younger patients, escalated BEACOPP was considered too toxic for elderly patients. Thus, elderly patients were randomized between COPP-ABVD and BEACOPP baseline only. The small number of patients contributed to imbalances in baseline patient characteristics between the treatments groups. In particular, patients randomized to COPP-ABVD were older, more frequently had B-symptoms, large mediastinal mass or extranodal involvement, and higher IPS. However, when analyzing randomized patients only patient characteristics and results were very similar (data not shown). Thus a selection bias due to the premature closure of the COPP-ABVD arm is unlikely. Although the reported results should be interpreted with care, this is

the first prospectively collected dataset in elderly patients with advanced HD that yields important information on this high-risk group of patients.

Clinically important differences were observed in terms of toxicity between COPP-ABVD and BEACOPP baseline. In the BEACOPP group, there were more severe toxic effects compared with COPP-ABVD (WHO grade IV in 87% and 44% of patients, respectively). In addition, acute toxic death occurred in 21% of patients treated with BEACOPP. A recent analysis of toxicity of BEACOPP baseline in younger patients had demonstrated only moderate hematological toxicity which was very similar to that of COPP-ABVD [36]. In contrast, elderly patients had considerably more severe hematological toxicity with BEACOPP baseline, which led to frequent dose reductions and early termination of planned therapy. This observation is in line with those by others. Levis et al. showed that in the group of elderly patients treated with conventional hybrid MOPP/ABVD-like regimen, acute toxic death occurred in 19% of patients compared with 4% in the group treated with CVP/CEP (cyclophosphamide, vincristine, prednisone/carboplatin, etoposide and bleomycin) [25]. In patients treated with VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisolone, etoposide, mitoxantrone and bleomycin), 3% death during therapy was reported [26]. A population-based study reported 21% treatment-related deaths in patients above 60 years treated with curative intent [14].

The OS and FFTF curves of the $HD9_{elderly}$ trial are nearly superimposable. This is indicative of a poor outcome of elderly patients with progressive or recurrent disease. Salvage treatment is badly tolerated and most elderly patients receive only palliative therapy. All but one patient after relapse and all patients with progressive disease died within a median time of less than 1 year. Very similar conclusions were recently published by Kim et al., who showed that the recurrence of HD had a significant impact on survival in elderly patients [11].

Our results support the general perception that outcome of elderly HD patients is still unsatisfactory due to higher treatment-related mortality, unfavorable outcome after recurrent disease and age-related mortality. In younger patients with advanced HD, the outcome has been improved with the introduction of new intensified regimens [19, 37, 38]. The present data indicate that conventional or more intensive regimens are more difficult to apply in elderly patients. As a consequence of higher toxicity observed with strategies developed for younger patients [1, 8, 14, 25], new regimens are warranted. An Italian group evaluated the CVP/CEB regimen, which was well tolerated. However, the CR rate (73%) was offset by a high relapse rate (5-year event-free survival, 30%) [25]. An alternative regimen is VEPEMB. The recently reported encouraging results of the pilot study indicated that this regimen is effective and well tolerated, with low numbers of toxic deaths [26]. An ongoing randomized trial compares the efficacy of ABVD and VEPEMB in patients above 65 years old. The Canadian group recently reported their experience with the ODBEP regimen (vincristine, doxorubicin, bleomycin, etoposide and prednisone). Compared with historical controls treated with MOPP/ABVD-like regimen, ODBEP seems to be effective and less toxic [27]. The two new regimens currently being evaluated by our group in phase I/II trials for elderly patients are PVAG (prednisone, vinblastine, doxorubicin and gemcitabine) and BACOPP (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone).

It is obvious that new strategies are needed for elderly patients with advanced HD. In light of the increased co-morbidity and decreased functional reserve, assessment of patient frailty and ability to tolerate treatment should be introduced before treatment decision. The tool currently most often used for this evaluation is the Comprehensive Geriatric Assessment as proposed by Levis et al. [26]. The unsatisfactory high early mortality due to acute toxicity might be reduced by a better monitoring of toxicity at the onset of therapy. In addition, a short initial course of steroid therapy for patients with advanced disease might reduce the rate of early toxic deaths as shown in patients with aggressive NHL (M. Pfreundschuh, personal communication). The routine use of G-CSF remains controversial. In a recently published study from the Dutch–Belgian Hemato-Oncology Cooperative group (HOVON), prophylactic G-CSF with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in elderly patients with aggressive NHL did not lead to better response or survival. In addition, G-CSF failed to reduce serious infections and acute toxic deaths [39]. This is in line with results of a large meta-analysis investigating the impact of G-CSF on outcome and toxicity of lymphoma patients treated with standard-dose chemotherapy ± G-CSF [40].

In summary, this randomized study for elderly patients comparing COPP-ABVD with BEACOPP baseline demonstrated no difference in terms of OS and FFTF between the two regimens. Acute toxicity and number of treatment-related deaths were higher in the BEACOPP baseline group. Thus, new approaches for the treatment of elderly HD patients are warranted.

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