Annals of Oncology 9 *(Suppl. 5)*: S67–S71, 1998.

Review

BEACOPP: A new regimen for advanced Hodgkin's disease

V. Diehl, J. Franklin, D. Hasenclever, H. Tesch, M. Pfreundschuh, B. Lathan, U. Paulus, M. Sieber, J.-U. Rüffer, M. Sextro, A. Engert, J. Wolf, R. Hermann, L. Holmer, U. Stappert-Jahn, E. Winnerlein-Trump, G. Wulf, S. Krause, A. Glunz, K. von Kalle, H. Bischoff, C. Haedicke, E. Dühmke, A. Georgii & M. Loeffler for the German Hodgkin's Lymphoma Study Group

Department of Internal Medicine, University of Cologne, Germany

Summary

The BEACOPP chemotherapy regimen for advanced Hodgkin's disease employs a rearranged schedule permitting a shortened three-week cycle. With haematological growth factor support, the dosages of cyclophosphamide, etoposide and adriamycin could be moderately escalated. The 3-armed multicentre HD9 trial (recruitment 1993–1998; 1300 patients randomised) aimed to compare BEACOPP with the standard COPP/ABVD chemotherapy and to detect and measure the gain in efficacy, if any, due to moderate dose escalation of BEACOPP. Eight cycles were given, followed by local irradiation.

The most recent interim analysis, with 689 evaluable patients, circa 40% of all expected events and a median observation time of 27 months, showed significant differences in progression rate (P) and in two-year freedom from treatment failure (F) between the treatment arms, with escalated BEACOPP (P = 2%, F = 89%) better than baseline BEACOPP (P = 9%, F = 81%) better than COPP/ABVD (P = 13%, F = 72%). Survival was not significantly different. Acute toxicity was more severe due to dose escalation, but remained manageable.

These preliminary results suggest that BEACOPP improves efficacy. Moderate dose escalation is feasible with G-CSF support and appears likely to make a worthwhile improvement in the cure rate. The results must await confirmation (or otherwise) by the final analysis including all randomised patients and sufficiently mature data.

Key words: chemotheapy, dose escalation, efficacy, Hodgkin's disease, toxicity

Introduction

Treatment of advanced stage Hodgkin's disease has, since the advent of the multidrug regimen MOPP in 1964, consisted of several cycles of this regimen or the alternating regimen MOPP/ABVD (1975) or a modification of these. Chemotherapy was often followed by adjuvant radiotherapy to either local or extended fields. Compared with the previous poor results in advanced HD treated with radiotherapy alone, the success of these methods was considerable [1–3]. Nevertheless, around half of these patients continued to experience disease progression or relapse, for which the prognosis remained very poor. Addition or substitution of drugs from MOPP or MOPP/ABVD, while helping to reduce acute toxicities and the risk of secondary leukaemia in some cases, was not able to raise the cure rate appreciably [4, 5]; nor did 'hybrid' schemes, in which all drugs were given in each cycle, produce a consistent improvement [6–9].

One possible way to improve treatment results is dose escalation of cytotoxic drugs. The theoretical background of the development of a dose escalated regimen is fully described in a separate article in this supplement [10]. In experimental tumour models the response curve for several cytotoxic agents is steep in the linear phase and a positive correlation between the dose of antineoplastic drugs and tumour response has been demonstrated in retrospective analyses in humans. Prospective clinical trials which prove the role of dose escalation have not been reported yet. The German Hodgkin Study Group (GHSG) analysed the role of dose escalation in a series of clinical trials. Since a subgroup of patients with a very high risk of treatment failure could not be identified the question remained whether a moderate dose escalation applied to all patients is possible within defined and acceptable toxicities. A mathematical model of lymphoma growth and chemotherapy effects had been developed recently and fitted to the data of 705 patients of stage IIIB–IV of the GHSG. The model predicted that moderate dose escalation of 30% could lead to a potential benefit of 10%–15% in the rate of tumor control.

The GHSG initiated a phase II trial introducing the new BEACOPP scheme. BEACOPP incorporates most active drugs of COPP/ABVD i.e., cyclophosphamide, vincristine, procarbazine, prednisone, adriamycin and bleomycin. Etoposide was added since it is highly active in lymphomas and can be substantially escalated. In a

first phase II trial BEACOPP at baseline level was applied and showed high activity with low toxicities. In a second trial the maximal practicable dose of three drugs, i.e., etoposide, adriamycin and cyclophosphamide within the BEACOPP scheme was determined. This study led to the development of an escalated BEACOPP scheme in which adriamycin was escalated from 25 to 35, cyclophosphamide from 650 to 1200 and etoposide from 100 × 3 to 200 × 3 mg/m^2.

Even after eight cycles of chemotherapy, many patients still show abnormalities in CT or X-ray images, which means that the possibility of presence of active tumour cannot be excluded. Results of our previous study HD3 suggested that patients receiving consolidation after attaining CR after six cycles, either through additional cycles or through local irradiation, did better than those who refused consolidation in CR after six cycles [11].

The aim of the present trial HD9 was to test the efficacy of the new, accelerated regimen BEACOPP in comparison with our standard chemotherapy COPP/ABVD and to detect and measure the effect of moderate dose escalation within the BEACOPP regimen. The severity of acute and late toxicities was also to be evaluated.

In this report, the results of completed interim analyses, especially the most recent, third analysis in February 1998, will be presented and discussed, with particular attention to the effect of dose escalation on administration of therapy, acute toxicities and short-term treatment results. Long-term cure and survival rates will not be precisely evaluable until the final analysis in the year 2001.

Table 1. Short-term treatment results in HD9 with nominal 95% confidence intervals.

	Arm A COPP/ABVD (n = 235)	Arm B baseline BEACOPP (n = 241)	Arm C escalated BEACOPP (n = 213)
CR	83% (77%–87%)	88% (84%–92%)	95% (92%–98%)
PR	1%	2%	1%
Progression	13% (9%–18%)	9% (6%–14%)	2% (0.5%–5%)
Other death in therapy	3%	< 1%	2%
FFTF (24-month, 95% CI)	72% (67%–79%)	81% (76%–87%)	89% (84%–94%)
SV (24-month, 95% CI)	89% (85%–93%)	94% (90%–97%)	96% (93%–99%)

Abbreviations: CR – complete remission; PR – partial remission; FFTF – freedom from treatment failure; SV – survival.

The primary endpoint of the trial was Freedom From Treatment Failure (FFTF), for which the events progression, failure to reach CR after protocol therapy, relapse and death from any cause count as failure. Secondary endpoints were survival, progression rate and complete remission rate. The trial was to be monitored and analysed using a sequential plan involving four annual interim analyses (IA) and a final analysis 7.5 years after beginning recruitment, within which time 80% of events were expected to occur. For each IA the target population consisted of all patients who had been randomised at least 18 months prior to the analysis, since these patients would be expected to have completed therapy and to have undergone a three-month post-therapy examination. In order to avoid multiple comparisons as far as possible, just two arm comparisons were planned, firstly the chemotherapy comparison: BEACOPP (arms B and C pooled) *versus* COPP/ABVD (arm A) and secondly the dose comparison: BEACOPP escalated (arm C) *versus* BEACOPP baseline (arm B).

Methods

Over 250 institutions including university and municipal hospitals and oncological practices in Germany, Switzerland, Austria and the Czech Republic took part. Untreated patients with histologically proven HD aged between 16 and 65 years, with disease in stage IIB–IIIA and at least one risk factor or in stage IIIB–IV were eligible. The risk factors for stage IIB patients were large mediastinal mass (more than 1/3 of the maximum thoracic diameter), E-stage and massive splenic involvement. For stage IIIA patients two extra factors, elevated ESR level (> 50 mm/h asymptomatic, > 30 mm/h with B-symptoms) and three or more affected lymph node areas, were also recognised.

Patients were randomised into three arms as follows:

Arm A 4 × (COPP+ABVD) + RT
Arm B 8 × BEACOPP baseline + RT
Arm C 8 × BEACOPP escalated (with G-CSF) + RT

While four weeks were planned for each cycle of COPP or ABVD, the planned duration of each BEACOPP cycle was three weeks. The dosages in COPP/ABVD and of BEACOPP baseline were as previously described [12]. In escalated BEACOPP, the dosages of cyclophosphamide, etoposide and adriamycin were increased to 192%, 200% and 140% of the baseline dosage respectively. This corresponded to dose level 4 of the pilot escalation trial [13], which was carried out to determine the maximum acceptable doses of these drugs. G-CSF was administered in arm C from day 8 of each cycle until leukocyte recovery. For cases of severe acute toxicity in arm C, a stepwise reduction of the escalated dose in subsequent cycles was planned. In each arm, radiotherapy consisted of 30 Gy to areas of initial bulky disease (5 cm diameter or more) and 40Gy to residual disease following chemotherapy.

Results

During the entire recruitment period (February 1993 – February 1998) circa 1300 patients were randomised. So far three interim analyses (IA) have been performed. In each IA at least 91% of the target population were evaluable (i.e., documentation sufficiently complete to assess treatment administration and outcome). In the most recent (third) IA, in February 1998, 689 evaluable patients with a median observation time of 27 months were included.

Comparison of BEACOPP with COPP/ABVD

The first IA (September 1996) already revealed that pooled BEACOPP results were significantly superior (according to the sequential analysis plan) to those of COPP/ABVD in respect of FFTF and progression rate. Moreover, analysis of acute toxicities, given drug dose and duration of therapy showed that BEACOPP could be administered just as fully and punctually as COPP/ABVD with manageable toxicity in both baseline and escalated versions. It was therefore decided to stop recruitment into arm A. These results of the first IA were confirmed and made more precise in subsequent analyses.

Table 2. Acute haematological toxicity during BEACOPP: Maximum WHO grade experience by each patient.

WHO grade	Arm B baseline	Arm C escalated
Leukopenia		
0	2%	–
1–2	23%	–
3	37%	7%
4	37%	93%
Thrombopenia		
0	51%	5%
1–2	35%	24%
3	10%	23%
4	5%	49%
Anemia		
0	6%	–
1–2	73%	31%
3	17%	50%
4	4%	19%
Infection		
0	24%	22%
1–2	48%	55%
3	26%	16%
4	2%	6%

Table 3. Causes of death. Number of deaths and percentage of all patients.

	Arm A COPP/ ABVD (n = 235)	Arm B baseline BEACOPP (n = 241)	Arm C escalated BEACOPP (n = 213)	Total (n = 689)
Median observation time (months)	29	31	24	27
HD	11 (4.7%)	9 (3.7%)	1 (0.5%)	21 (3.0%)
Toxicity (primary)	5 (2.1%)	2 (0.8%)	4 (1.9%)	11 (1.9%)
Toxicity (salvage)	3 (1.3%)	4 (1.7%)	1 (0.5%)	8 (1.1%)
Secondary neoplasia	3 (1.3%)		2 (0.9%)	5 (0.7%)
Suicide		1 (0.4%)		1 (0.1%)
Accident	2 (0.9%)			2 (0.3%)
Cardiac	1 (0.4%)			1 (0.1%)
Lung	1 (0.4%)	1 (0.4%)		2 (0.3%)
Other illness	1 (0.4%)			1 (0.1%)
Not known	2 (0.9%)		1 (0.5%)	3 (0.4%)
Total deaths	29 (12.3%)	17 (7.1%)	9 (4.2%)	55 (8.0%)

Table 4. Secondary neoplasia: Cases reported in HD9 (as of March 1998).

	Arm A COPP/ ABVD (n = 235)	Arm B baseline BEACOPP (n = 241)	Arm C escalated BEACOPP (n = 213)
Acute leukaemia/ MDS	–	AML M2 t(10;11)	AML t(9;11) AML M2 t(9;11) AML M4 MDS
NHL	Highgrade cb Highgrade cb Highgrade cb Highgrade im-blast. B-NHL	Highgrade B-NHL Highgrade Lowgrade cutaneous Karposi sarcoma[a]	–
Solid tumour	Adeno-ca. (rectum)	Malig. melanoma	–

Abbreviations: MDS – myelodysplastic syndrome; NHL – non-Hodgkin lymphoma.
[a] Receiving continuous immunosuppressive therapy for alveolitis.

Comparison of escalated with baseline BEACOPP

(a) Toxicity

While acute haematological toxicities under baseline BEACOPP were comparable to those experienced with COPP/ABVD, they were far more severe under escalated BEACOPP despite the use of G-CSF (Table 2). All patients experienced a WHO grade 3 or 4 leukopenia in at least one cycle of escalated BEACOPP. The grade 3–4 leukopenia rate rose with BEACOPP baseline from 26% in the first cycle to 47% in the eight cycle, but with escalated BEACOPP it began and remained high at around 70%–80% in all cycles. With escalated BEACOPP, 72% of patients had at least one grade 3–4 thrombopenia. Under baseline therapy the thrombopenia rate remained under 7% in all cycles, whereas with the escalated version it climbed steadily from cycle 1 to plateau at 40%–50% at cycle 5 onwards. Anaemia also increased sharply from 5% in cycle 1 to 35% in cycles 5–8 under escalated BEACOPP (for baseline BEACOPP it remained under 8%). However, escalation did not seem to worsen the infection rate: grade 3 or 4 infections were reported in one or more of the eight cycles for 28% and 22% of patients treated with baseline and escalated BEACOPP, respectively.

The number of deaths due to acute toxicity in primary therapy was not appreciably increased by dose escalation (Table 3). Most such deaths were due to sepsis and/or pneumonia. Due to the low numbers of progressions and relapses in arm C, toxic deaths due to salvage therapy have been avoided in this arm. When interpreting this table, it must be remembered that the average follow-up was shorter in arm C due to the late start of this arm.

Late toxicities will not be evaluable for many years. So far, the only remarkable observation is the greater number of secondary acute leukaemia cases reported in arm C (Fisher's exact test: $P = 0.016$). Table 4 shows the incidence and type of secondary neoplasias per arm.

(b) Administration of therapy

The ratio of mean given to planned total dose over all cycles varied between drugs from 85% (vincristine) to 96% (prednisone), but did not differ substantially between treatment arms. Due to planned toxicity-related dose reductions and early terminations, the average given doses of escalated drugs in arm C sank steadily from over 95% of planned dose in the first cycle to 60%–70% in the last cycle. Nevertheless, actual escalations to 165% (cyclophosphamide), 170% (etoposide) and 127% (adriamycin) of planned total baseline dose were achieved. The median duration of completed chemotherapy from first to last administration of drugs was 24.6 and 24.7 weeks for baseline and escalated BEACOPP respectively, compared with a planned duration of 23 weeks. In each BEACOPP arm, 73% of patients were irradiated, compared with 62% for the COPP/

ABVD arm: this could partly be explained by the higher frequency of initial bulky disease in arms B and C. The shorter duration of BEACOPP, allowing less time for shrinking of residual abnormalities, may also have played a role.

(c) Efficacy

In the third analysis the FFTF comparison between escalated and baseline BEACOPP attained significance at the $P = 0.05$ level in favour of the escalated version. As yet, no significant differences in survival rate between the three arms have been seen.

The immediate treatment results of the third IA are shown in Table 1. The progression rate has been significantly reduced from 9% to only 2% by dose escalation. Consequently, the complete remission rate has increased from 88% with baseline BEACOPP to 95% with the escalated version.

Discussion

The third interim analysis strongly suggests that the new BEACOPP regimen improves efficacy, at least as regards short-term results. A further improvement seems likely to be attributable to dose escalation. Long-term cure rates and survival also seem to be improved, but a definitive conclusion will be possible only after further years of follow-up. Just 140 events, circa 40% of those expected on the basis of the observed FFTF rates, had been observed by this IA. The improved efficacy is achieved at a cost of increased transient haematological toxicities which remain manageable and do not appear to increase the toxic death rate. In order to optimise this therapy further, it is necessary to understand which factors are responsible for the rise in efficacy and which for the inherent acute and late toxicities.

The effectiveness of dose escalation suggested by our results must be due to a steep dose response relationship for one or more of the three escalated drugs. Further studies will be needed to determine which.

As explanations for the effectiveness of BEACOPP as such, three possible factors suggest themselves: increased dose intensity through shortening the cycle to three weeks, the addition of etoposide and the scheduling of drug dosages through the cycle (which might mobilise synergistic interactions between drugs). At least in the mathematical model [10], the shortened cycle was not predicted to produce as large an improvement as that observed so far in HD9. This could indicate that factors other than acceleration play a role. Further conclusions cannot be drawn, but must await further studies which investigate modifications of the BEACOPP regimen.

Despite widespread WHO grade 3 and 4 leukopenia in arm C, the rate of severe infections was not increased compared with baseline BEACOPP. Examination of the graphs of leukocyte levels during therapy shows that G-CSF was able to prevent prolonged leukopenia in arm C [14]. As described above, the last few cycles showed considerably more anaemia and thrombopenia, and drug doses were more often reduced. These observations suggest that by decreasing the planned administration in the last few cycles from escalated to baseline doses, a worthwhile reduction in overall toxicity, psychological burden and cost could be achieved. The efficacy of such a scheme will be tested by the GHSG in the next trial for advanced stages.

In view of the reduction in HD mortality due to escalated BEACOPP therapy, secondary leukaemia will contribute noticeably to the death rate in arm C [15, 16]. However, two considerations put this threat into perspective: firstly, the occurrence of secondary NHL appears to be lower in arm C (possibly due to efficacy of escalated BEACOPP against progression of a transformation from HD to NHL), and secondly, escalated BEACOPP treatment will reduce the foreseeable risk of secondary leukaemia which will be induced in the coming years by intensive salvage therapies for patients with progressive disease and relapse. Second cancer occurrences will be intensively monitored over the coming years.

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Correspondence to:
V. Diehl
Klinik I für Innere Medizin der Universität zu Köln
Joseph-Stelzmann-Str. 9
D-50924 Köln
Germany
E-mail: v.diehl@uni-koeln.de