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Original article

Acute hematologic toxicity and practicability of dose-intensified BEACOPP chemotherapy for advanced stage Hodgkin's disease

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Summary

Background: Evidence is recently accumulating that the novel BEACOPP (bleomycin (B), etoposide (E), adriamycin (A), cyclophosphamide (C), vincristine (O), procarbazine (P), prednisone (P)) chemotherapy is a highly effective treatment for advanced stage Hodgkin's disease. Two dose variants of BEACOPP are currently tested in a phase III randomized multicenter trial of the GHSG. To enable more extensive testing of BEACOPP we characterized its practicability regarding schedule adherence, acute hematotoxicity and need for supportive treatment.

Patients and methods: Data of 858 patients (6592 therapy cycles) from 184 participating institutions were evaluated. Planned total drug doses of the baseline variant (arm 1) were 80, 2400, 200, 5200, 11.2, 5600 and 4480 mg/m^2 for B, E, A, C, O, P and P, respectively. Compared to arm 1, the doses of E, A and C in the dose-intensified variant (arm 2) were escalated by factor 2.0, 1.4, 1.92, respectively, using G-CSF assistance. Stepwise dose reductions were specified in case of dose-limiting toxicities. Both variants are given in eight three-weekly courses.

Results: Median dose adherence (dose actually given relative to planned arm 1 dose) in arm 1 was 1.0 for all drugs. Relative dose escalation of E, A, and C actually maintained in arm 2 was 1.83, 1.37 and 1.77 (medians), respectively, and 70% of patients maintained elevated dose levels throughout the entire treatment. Dose-limiting toxicities occurred in 25% of cycles in arm 2, most frequently due to leukocytopenia and thrombocytopenia. Time courses of leukocytes in arm 2 showed more severe but not more prolonged leukocytopenia compared with arm 1. WHO grades 3–4 infections were documented in 2.1% (arm 1) and 3.1% (arm 2) of all cycles. Erythrocytes were transfused in 6% (arm 1) and 28% (arm 2), platelets in <1% (arm 1) and 6% (arm 2) of all cycles.

Conclusions: Both BEACOPP schemes are practicable in a large multicenter setting. Despite increased hematotoxicity, moderate dose escalation is safe for the majority of the patients with G-CSF assistance and standard supportive treatment.

Key words: BEACOPP, chemotherapy, dose intensification, hematotoxicity, Hodgkin's disease, practicability

Introduction

In search of new strategies for first-line treatment of advanced adult Hodgkin's disease the question has been raised whether a moderate dose intensification of established conventional chemotherapies would be able to substantially improve the treatment outcome [1–10]. A statistical model of tumor growth and chemotherapy effects designed on the basis of clinical data on tumor control rates of patients receiving COPP/ABVD-like regimens predicted that shortening of the cycle interval to three weeks would improve five-year tumor control rates by 3% and that an additional moderate dose escalation by 30% on average should result in 10%–15% improvement [11, 12]. This prediction is currently subject of a large three-arm randomized multicenter trial (HD9) of the German Hodgkin's Lymphoma Study Group comparing four double cycles of four-weekly standard COPP/ABVD (cyclophosphamide, vincristine, procarbazine, prednisone and adriamycin, bleomycin, vinblastine, dacarbazine) with two variants of the new three-weekly BEACOPP regimen (8 cycles of bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) [13, 17].

The first variant of BEACOPP, further on referred to as the BEACOPP-baseline scheme, was intensified compared to COPP/ABVD by shortening of the cycle duration from four to three weeks. In this scheme vinblastine and dacarbazine have been replaced by etoposide. To achieve sufficient hematopoietic recovery within three weeks without regular administration of granulocyte colony-stimulating factor (G-CSF), the major myelotoxic drugs cyclophosphamide, adriamycin and etoposide were scheduled for the first three days of the cycle. A phase II study with 30 patients confirmed the feasibility and efficacy of BEACOPP-baseline at moderate hematologic toxicities [14]. This regimen was subsequently intensified by escalating the doses of cyclophosphamide,

Table 1. Planned dosage and schedule of the BEACOPP regimen.

Drug	Route	Day	Dose per cycle[a] (mg/m^2/day)				
			BEACOPP-escalated[b]				BEACOPP-baseline
			Level 4	Level 3	Level 2	Level 1	
(B) Bleomycin	i.v.	8	10	10	10	10	10
(E) Etoposide	i.v.	1–3	200	175	150	125	100
(A) Adriamycin	i.v.	1	35	35	35	35	25
(C) Cyclophosphamide[c]	i.v.	1	1250	1100	950	800	650
(O) Vincristine	i.v.	8	1.4[d]	1.4[d]	1.4[d]	1.4[d]	1.4[d]
(P) Procarbazine	p.o.	1–7	100	100	100	100	100
(P) Prednisone	p.o.	1–14	40	40	40	40	40
G-CSF[e]	s.c.	8–[f]	Yes	Yes	Yes	Yes	No[g]

[a] Planned total number of cycles was 8, planned cycle duration was 21 days.
[b] Level 4 is the initial dose level. Levels 1–3 are applied in case of dose reductions. See text for detailed description of the dose reduction scheme.
[c] Plus Mesna i.v. on hours 0, 4 and 8 (20% of cyclophosphamide dose).
[d] Maximum 2 mg.
[e] 300 and 480 µg per day at body weight less and greater than 75 kg, respectively.
[f] Until leukocyte recovery (3 days greater than 1,000/µl).
[g] Yes, if required from the clinician's point of view.

adriamycin and etoposide. G-CSF was included to overcome dose-limiting neutropenia. Using an adaptive dose-finding strategy the maximum practicable dose escalation resulting in a predefined rate of hematologic and nonhematologic toxicities was then identified in a second phase II study [15]. This escalation study led to the definition of the BEACOPP-escalated scheme with the doses of cyclophosphamide, adriamycin and etoposide being increased to 192%, 140%, and 200%, respectively, relative to baseline dosage.

The HD9 trial started in 1993 and recruitment was closed in 1998. The 1999 interim analysis of the HD9 trial with 1070 evaluable patients and a median follow-up of 28 months showed significant differences between COPP/ABVD, BEACOPP-baseline and BEACOPP-escalated in progression during therapy (12%, 8%, and 2%, respectively) as well as failure free survival (69%, 79%, and 88%, respectively, at 36 months) [19].

It is the objective of this presentation to describe in detail the practicability of BEACOPP by analyzing how well the intended schedule could actually be applied, to which extent dose erosion occurred and what spectrum of dose-limiting toxicities was observed. As the HD9 trial was conducted in a multicenter setting with a broad spectrum of participating institutions this analysis should provide important information for wider use of this new protocol.

Patients and methods

Data were obtained from the HD9 trial of the German Hodgkin's Lymphoma Study Group. This three-arm, randomized multicenter trial (phase III) compares standard COPP/ABVD chemotherapy with BEACOPP-baseline and BEACOPP-escalated. The 184 participating centers which contributed patients to this analysis comprised a broad spectrum of university hospitals, general hospitals of different sizes and private practices, mainly in Germany but also in Switzerland, Austria and the Czech Republic. A list of the major participating centers is included in the appendix. The HD9 trial was performed after approval by the ethics commitee. Patient accrual lasted from February 1993 until March 1998. By April 1999, 442 and 416 patients had complete documentation of BEACOPP-baseline and BEACOPP-escalated chemotherapy, respectively, and were considered evaluable for this analysis. Of these, 26 (5.9%) and 21 (5.0%) patients, respectively, discontinued chemotherapy due to progression of disease, excessive toxicity or on their own request.

Patients

Eligibility criteria for the trial were (1) histologically proven untreated Hodgkin's disease, (2) age between 16 and 65 years, and (3) either (a) Ann Arbor stage IIB with at least one of the following risk factors: large mediastinal mass (more than one-third of the thoracic diameter), extranodal disease or massive splenic involvement, or (b) stage IIIA with at least one of the above risk factors and/or elevated erythrocyte sedimentation rate (=50 mm/h) and/or three or more affected lymph node areas, or (c) stages IIIB or IV. Lack of written informed consent, malignant disease within the last five years, or severe impairment of heart, lung or liver function were criteria for exclusion.

Chemotherapy

Schedules and planned dosages of both BEACOPP variants are summarized in Table 1. BEACOPP consisted of 8 cycles with a planned duration of 21 days per cycle. Each cycle was initiated in due time if sufficient hematopoietic recovery had been achieved and if G-CSF administration had been ceased at least 48 hours previously. Sufficient hematopoietic recovery was defined as leukocyte and thrombocyte counts after 21 days being at least 2,500/µl and 80,000/µl, respectively, after the nadirs have been passed. If this was not the case therapy was postponed until these conditions were fulfilled. If the postponement amounted to more than two weeks, the protocol for BEACOPP-baseline requested a dose reduction of cyclophosphamide, adriamycin, etoposide and procarbazine to 75% of the planned dose ('reduced baseline') for the remaining cycles. BEACOPP-escalated commenced at dose level 4 (Table 1). Dose reductions were only permitted in case of severe toxicities (dose-limiting toxicities), which were defined as follows: (1) leukocytopenia $<1000/\mu l$ for more than four days, (2) thrombocytopenia $<25{,}000/\mu l$, (3) severe infection of WHO grade 4, (4) any other toxicity of WHO grade 4 (e.g., mucositis) or (5) postponement of therapy for more than two weeks due to insufficient hematopoietic recovery. At each occurrence of a dose-limiting toxicity during one cycle the current dose level was reduced by one level in the remaining cycles. The dose level was reduced to the baseline level in the remaining cycles if dose-limiting toxicities emerged during two consecutive cycles. If the baseline dose level was reached, further dose reductions followed the scheme for BEACOPP-baseline. The protocol did not provide an option to increase the doses again once they had been reduced. Thus, a dose escalation of 192% (cyclophosphamide), 140% (adriamycin) and 200% (etoposide) in total could only be achieved if no dose-limiting toxicity occured during therapy at all.

Data acquisition and preparation

For each treatment cycle information was gathered about administered drug doses, cycle durations, G-CSF usage, packed red cell and platelet transfusions, and dose-limiting hematologic and nonhematologic toxicities. Unless otherwise reported, missing information was below 5% for each item. Valid information on the doses administered was given in at least 97.6% of all therapy cycles. The doses and dose-intensities actually delivered were calculated relative to the intended doses and dose-intensities of the baseline scheme, respectively (abbreviated as RD and RDI). Dose-intensity of total therapy was defined as the ratio of total dose given to the total duration of therapy (the

duration of the last cycle was three weeks by definition). The information whether G-CSF was given was available in 92% of all cycles for BEACOPP-baseline. The duration of G-CSF treatment (i.e., the number of days on which a G-CSF injection was given) was not documented in 10% (BEACOPP-baseline) and 21% (BEACOPP-escalated) of all cycles. Each type of the above mentioned dose-limiting toxicities was recorded separately as being either present or absent (about 8% missing information for each type). Infections during therapy were documented according to the recommendations of the World Health Organization (WHO) for the assessment of acute und subacute toxicities (grades 0–4: no, minor, moderate, major and major infection with hypotension, respectively) [16]. In 48% (BEACOPP-baseline) and 31% (BEACOPP-escalated) of the cycles no information about infections was available. The number of transfused units was not documented in 15% and 11% for packed erythrocyte and 16% and 15% for packed platelets (baseline and escalated variant, respectively). Leukocyte counts (WBC), platelet counts (PLT) and hemoglobin concentrations (Hb) were also gathered during therapy. The numbers and intervals of blood samples within the cycle period could freely be chosen by the treating physician. The median number of documented values per cycle was three (quartiles Q1–Q3: 2–5) and five (Q1–Q3: 4–7) for the baseline and escalated regimen, respectively. A total number of 12459 (BEACOPP-baseline) and 16844 (BEACOPP-escalated) values was documented for all patients. By pooling data from all cycles of all patients, several values were available on each day within the three-week cycle period, thus allowing to characterize an average time course of blood hematology during chemotherapy.

Results

Patient characteristics

A total of 858 patients (6592 cycles) was considered evaluable for this analysis. They were treated in 184 different institutions of whom 35 were university centers (324 patients), 131 general hospitals (497 patients) and 18 private practitioners (37 patients).

Table 2 outlines the basic patient characteristics. No marked imbalances could be noticed between the two groups. Initial hematopoiesis was characterized by leukocytosis and anemia.

Table 2. Patient characteristics.

	BEACOPP-baseline (n = 442) (%)	BEACOPP-escalated (n = 416) (%)
Gender		
Male	62	62
Female	38	38
Age		
16–29	43	46
30–39	26	25
40–49	13	18
50–59	12	9
60–65	6	3
Stage		
IIB	15	16
IIIA	22	20
IIIB	26	29
IVA	10	10
IVB	27	25
Risk factors		
Large mediastinal tumor	29	29
Extranodal disease (stage II–III only)	34	33
Massive spleen involvement	18	23
$\geqslant$ 3 lymph node areas	84	85
Elevated erythrocyte sedimentation rate ($\geqslant$ 30 mm/h with B- and $\geqslant$ 50 mm/h without B-symptoms)	69	71
Bone marrow involvement	6	5
	Median (Q1–Q3)	Median (Q1–Q3)
Blood hematology		
Leukocytes 1000/µl	10.6 (7.6–14.1)	10.1 (7.4–13.4)
Platelets 1000/µl	369 (279–478)	362 (278–448)
Hemoglobin g/dl		
Male	12.8 (11.3–14.0)	12.8 (11.2–14.0)
Female	11.4 (10.3–12.4)	11.8 (10.9–12.9)
Karnofsky performance status	9 (9–10)	9 (8–10)

Adherence to planned dosing and timing of chemotherapy

Figure 1 gives a comprehensive view of the adherence to the planned dose and timing of the BEACOPP regimens. Panel a shows the cumulative distribution of the total therapy duration observed in the study population. Median therapy duration was 178 and 180 days for BEACOPP-baseline and BEACOPP-escalated, respectively. This was somewhat longer than the planned therapy duration (8 cycles of 21 days, i.e., a total of 168 days). Therapies shorter than the planned duration occurred in patients who prematurely discontinued treatment, e.g., due to progression of disease, excessive toxicity or on their own request. Panels b–h show the cumulative distribution of the relative total dose (RD) and relative total dose-intensity (RDI) actually delivered in the study population (compared to the planned total dose and dose-intensity of the BEACOPP-baseline scheme). Due to the deviations from planned therapy duration RDIs were generally lower than the corresponding RDs. Little dose erosion was observed under BEACOPP-baseline. The median RD was 100% for all drugs of this scheme. Regarding the drugs C, A, and E a clear escalation of the RDs and RDIs was actually achieved under the escalated scheme (Panels b–d). The median RD was 177% (= 9211 mg/m^2) for C, 137% (= 274 mg/m^2) for A, and 183% (= 4381 mg/m^2) for E. The median RDI was 158% (= 347 mg/m^2/week) for C, 124% (= 10.4 mg/m^2/week) for A, and 163% (= 165 mg/m^2/week) for E. However, heterogeneity and dose erosion of RDs and RDIs was clearly larger than under BEACOPP-baseline. With respect to the initial dose level 4 (i.e., planned RDs and RDIs of 192% for C, 140% for A, and 200% for E) the percentage of patients who received at least 90% of the initial doses was 55% for C, 77% for A, and 53% for E. The cumulative distributions of the RD and RDI of bleomycin, vincristine, procarbazine and prednisone (the planned doses

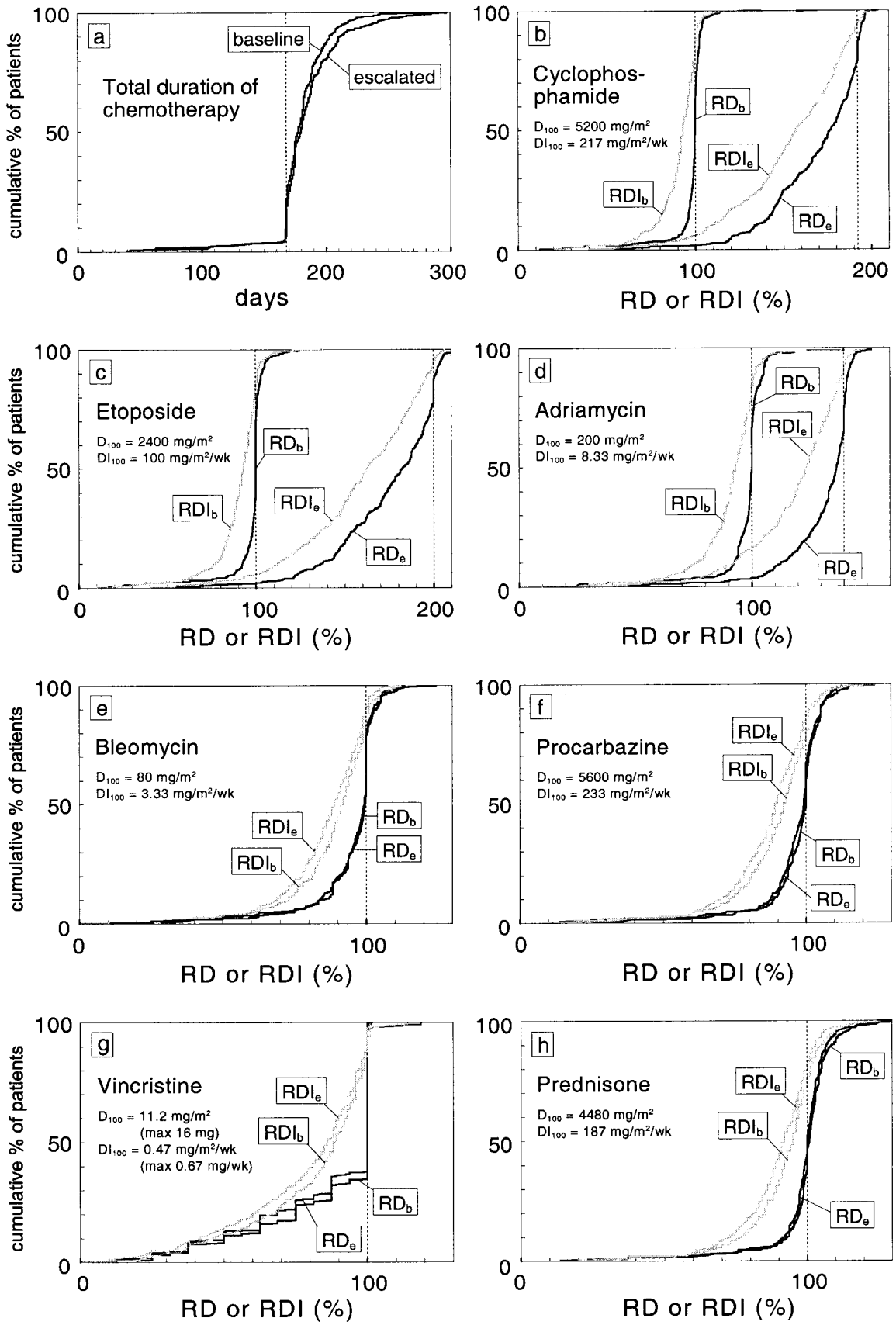

Figure 1. Adherence to planned total doses and therapy duration. Panel a shows the cumulative distributions of the actual total therapy durations. Panels b–h show the cumulative distributions of the actual relative doses (RD_x, black curves) and dose-intensities (RDI_x, grey curves) totally been given (indexed with 'b' and 'e' for the baseline and escalated scheme, respectively). RDs and RDIs are given as percentages of the planned BEACOPP-baseline doses and dose-intensities, respectively. D_{100} and DI_{100} values denote the absolute planned doses and dose-intensities of BEACOPP-baseline, respectively. RD and RDI values on the X-axis can be transformed to absolute doses (mg/m^2) and absolute dose-intensities (mg/m^2/week) by $RD/100 \times D_{100}$ and $RDI/100 \times DI_{100}$, respectively.

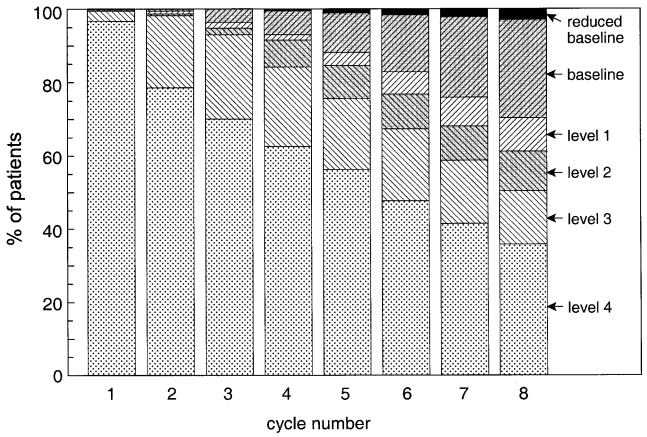

Figure 2. Deescalation of BEACOPP-escalated over the successive therapy cycles. Stacked bars show the percentages of patients being treated at the specified dose levels.

of which were identical in the baseline and escalated variant) were almost identical for the baseline and escalated scheme (Panels e–h). Deviations from the planned doses of these drugs were primarily due to their specific toxicities, such as pulmonary toxicities due to bleomycin, polyneuropathia due to vincristine and allergic reactions due to procarbazine.

Figure 2 provides more detailed insight into dose erosion during BEACOPP-escalated therapy by showing the actual given dose levels for each of the successive therapy cycles. Of all patients, 97% started therapy at dose level 4, 63% adhered to this level during the first four cycles and 36% during all eight cycles. Seventy percent of the patients adhered to a dose level 1 or larger during all cycles.

Dose-limiting toxicities during BEACOPP-escalated

The study protocol specified a dose-reduction strategy for the BEACOPP-escalated regimen if dose-limiting toxicities emerged during therapy (see material and methods). Dose-limiting toxicities emerged in 25% of all therapy cycles during BEACOPP-escalated. Dose-limiting leukocytopenia was observed in 15%, thrombocytopenia in 14% and postponement of more than two weeks in 2.8% of all cycles. Of all dose-limiting toxicities 35% were exclusively due to neutropenia, 29% exclusively due to thrombocytopenia, 19% due to both concurrently and 6% exclusively due to postponement of therapy. Dose-limiting infections and other toxicities were present in 5.3% and 1.7% of all observed dose-limiting toxicities, respectively. The frequency of dose-limiting toxicities tended to increase with cycle number (except from cycle 1 to cycle 2), which could chiefly be ascribed to the increasing frequencies of thrombocytopenia (Figure 3).

In 49% of all cycles with a dose-limiting toxicity the immediately preceding cycle also showed a dose-limiting toxicity (in this case the study protocol specified an immediate dose reduction to the baseline level). An analysis of the adherence to the prescribed dose-reduction scheme revealed that in 94% of the cycles with documented absence of a dose-limiting toxicity the current dose-level was actually maintained in the following cycle as specified in the study protocol. Conversely, however, in 33% of cycles in which a dose-limiting toxicity was present no dose reductions were performed in the next cycle.

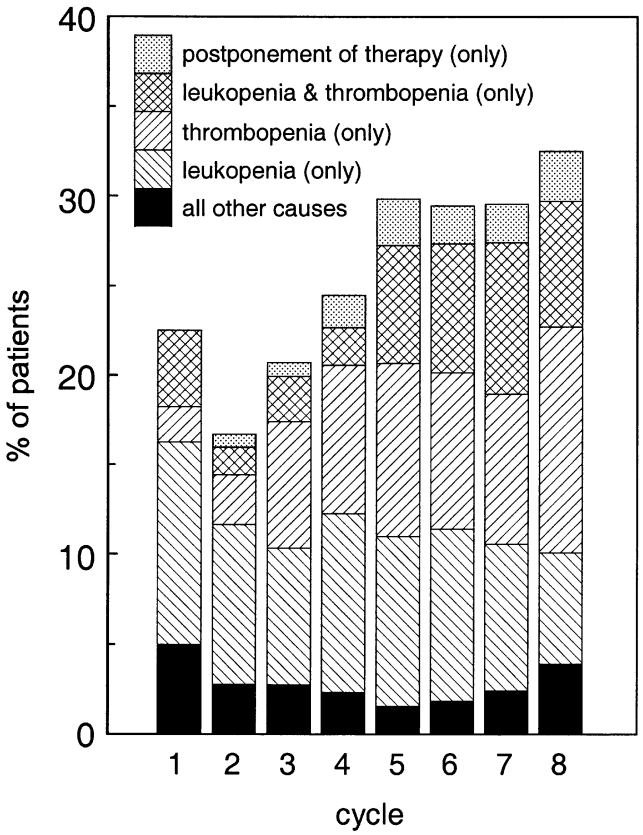

Figure 3. Frequencies of dose-limiting toxicities under BEACOPP-escalated therapy. See text for definition of toxicities.

Peripheral blood hematology

Figure 4 depicts the average time courses of leukocyte and platelet numbers in the peripheral blood and the frequencies of WHO grade 4 toxicities, respectively, that were observed during the three-weeks of a BEACOPP treatment cycle. The nadir of leukocytopenia was found on days 11 and 12 in both variants, however, being more profound under the escalated regimen despite the more frequent use of G-CSF. Accordingly, the percentage of WBC counts that were lower than 1000/μl (WHO grade 4 leukocytopenia) was considerably different between the baseline and escalated regimen. The occurrence of a WHO grade 4 leukocytopenia was documented in 11% (BEACOPP-baseline) and 52% (BEACOPP-escalated) of the therapy cycles, but in 38% (BEACOPP-baseline) and 92% (BEACOPP-escalated) of the patients. Nevertheless, leukopenia resolved very quickly under BEACOPP-escalated after passing the nadir, showing a pronounced temporary overshoot to leukocyte levels above the normal range about four days after the nadir.

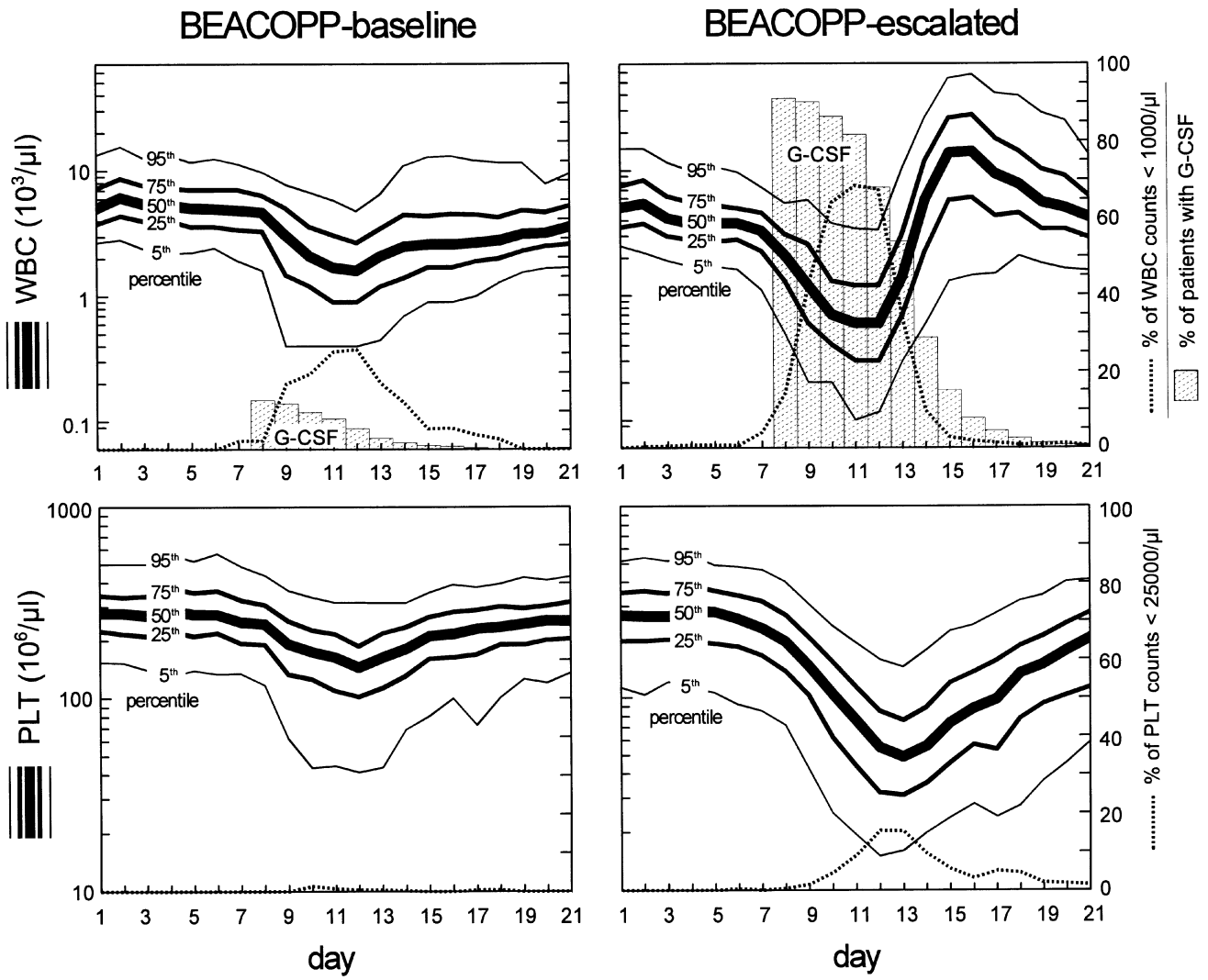

Figure 4. Average time course of leukocyte and platelet counts (left Y-axis) during the cycle period (all therapy cycles pooled). Variation is quantified by different percentiles (5th, 25th, 50th, 75th, and 95th). The dotted lines show the percentage of observations (right Y-axis) fulfilling WHO grade 4 criteria. The bars in the upper panels indicate the percentage of patients (right Y-axis) who reveived G-CSF at the specified day.

Platelets were found to reach their lowest level on days 11–13 (baseline) and 12–14 (escalated). As for leukopenia, severity of thrombocytopenia was considerably higher under BEACOPP-escalated. In 0.3% of the baseline cycles and in 13% of the escalated cycles a WHO grade 4 thrombocytopenia was recorded (in 2.3% and 48% of the patients, respectively). The average hemoglobin concentration did not exhibit systematic fluctuations within the course of a cycle period (not shown).

Figure 5 shows the time courses of leukocytes, platelets, and hemoglobin over all eight cycles of chemotherapy. Regarding the depth of the leukocyte nadir, a cumulative myelosuppression was observed over successive cycles of BEACOPP-baseline treatment, but not of BEACOPP-escalated. However, peak leukocyte counts (i.e., the maximum count after each recovery phase) tended to decrease also under BEACOPP-escalated. Thrombocytopoiesis showed cumulative myelosuppression during either regimen with successively decreasing nadir and peak counts. Interestingly, during the first two cycles of BEACOPP-escalated the platelet counts recovered to higher peak values in comparison with those during the baseline regimen despite a much lower nadir. Hemoglobin levels did not change considerably during the baseline treatment, in contrast to the escalated variant, during which a rapid decrease within the first four cycles was observed.

Infections and toxicity related deaths

Infections during both regimens were recorded according to the WHO grading system of toxicities and are summarized in Table 3. Considering only documented cycles, the relative risk (RR) for the occurrence severe infections of WHO grade 3 or 4 under BEACOPP-escalated was 1.1 (95% confidence interval (95% CI): 0.8–1.4) compared to BEACOPP-baseline. However, this information is potentially biased as in 48% of the cycles for BEACOPP-baseline but only 31% for BEACOPP-escalated no information about infections was given at all. Under the assumption that during all cycles with missing information no severe infections

Table 3. Infections by WHO grade. Values indicate percentages of cycles in which an infection was documented.

WHO grade	BEACOPP-baseline (n = 3408)	BEACOPP-escalated (n = 3184)
0	38.7	51.7
1	7.4	8.8
2	4.1	5.5
3	1.9	2.1
4	0.2	1.0

were observed, the RR can be estimated as 1.4 (95% CI: 1.1–1.9). Six patients died from acute toxicity during BEACOPP-baseline therapy and four patients during BEACOPP-escalated, respectively.

G-CSF usage and transfusions

Figure 5 also gives information about the extent of lineage-specific hematologic support during therapy. G-CSF administration was performed in 15% of all BEACOPP-baseline cycles and 91% of all BEACOPP-escalated cycles. The mean number of G-CSF injections per cycle was 0.7 (baseline scheme) and 6.3 (escalated scheme). A small increase of G-CSF usage was noticed over successive cycles of BEACOPP-baseline, whereas the number of injections slightly decreased under BEACOPP-escalated. Platelet transfusions were reported in 0.3% (baseline scheme) and 6% (escalated scheme) of all therapy cycles, showing the highest frequencies in the later cycles. In 5.5% (baseline scheme) and 28% (escalated scheme) of all cycles erythrocyte transfusions were documented. With regard to patients, 1.8% (baseline scheme) and 28% (escalated scheme) received platelets and 21% (baseline scheme) and 69% (escalated scheme) received erythrocytes at least once during therapy.

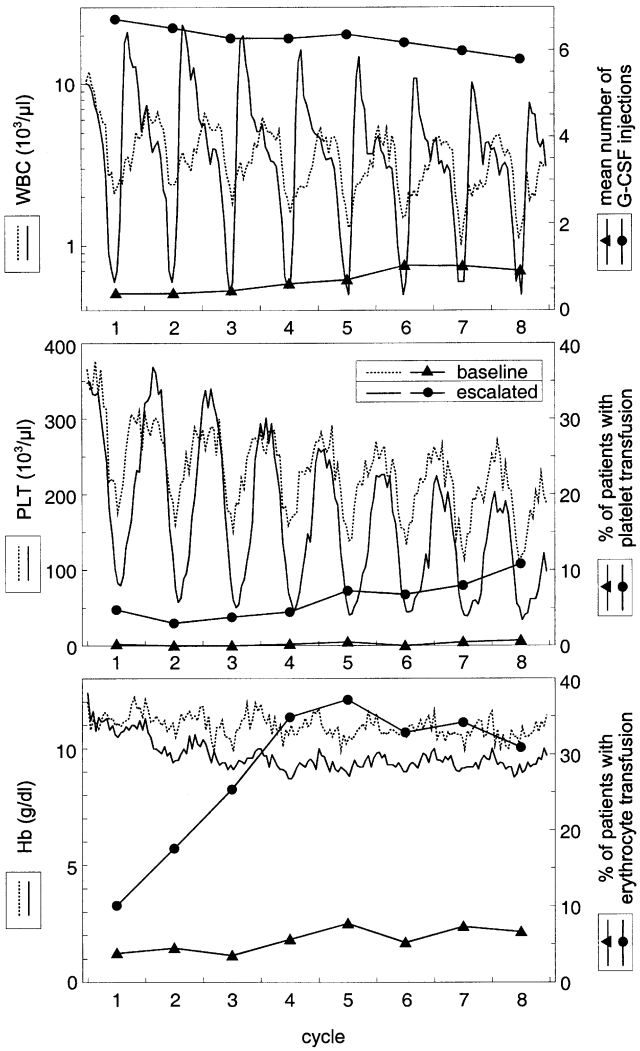

Figure 5. Hematologic toxicity over the successive therapy cycles, showing the median time course of leukocytes, platelets and hemoglobin (left Y-axis) and lineage specific support (G-CSF, platelet and erythrocyte transfusions) during each cycle (right Y-axis).

Discussion

As recent interim analyses of the HD9 trial of the GHSG have indicated, both variants of the new BEACOPP regimens are highly effective chemotherapies for advanced stage Hodgkin's disease [14, 17, 19, 20]. In particular the moderately dose escalated variant bears the potential of being superior to present standard schemes like COPP/ABVD, MOPP/ABVD or ABVD. In order to permit more widespread examination of the potential benefits of BEACOPP it was our objective to provide detailed information on the practicability of the new BEACOPP regimens with regard to acute hematologic toxicities, adherence to the intended dosing, complications (severe infections and deaths) and required supportive care (G-CSF, transfusions).

The BEACOPP-baseline regimen was characterized by a moderate degree of hematopoietic toxicities and could be applied very closely to the intended dose and time schedule. Leukocytopenia of WHO grade 4 emerged in only 11% of all cycles and most therapy cycles (85%) were performed without administration of G-CSF. Severe thrombocytopenia (WHO grade 4) and platelet transfusions were very rare events (both 0.3% of all cycles). The time course of leukocytes and platelets during the therapy cycles showed that within three weeks sufficient recovery was achieved on average. However, over eight consecutive therapy cycles some exhaustion of the hematopoietic recovery dynamics could be noticed, which was reflected in a decreasing trend of the average cell counts at the time points of maximum depression and recovery.

The BEACOPP-escalated regimen pursued the goal of a moderate dose escalation of cyclophosphamide (C), adriamycin (A) and etoposide (E) compared to BEACOPP-baseline, however, under the clinical constraint of maintaining multicenter practicability as in any other conventional multicycle chemotherapy. The present analysis showed myelosuppression as the most important factor limiting the extent of dose escalation. To maintain as much overall dose and dose intensity in

the population as possible but simultaneously to assure individual safety, the protocol specified a defined scheme of individual stepwise dose reductions in case of clinically undesired toxicities (referred to as dose-limiting toxicities). In a dose-finding study an initial dose level was chosen such that in not more than one-third of all therapy cycles a dose-limiting toxicity should occur [15]. The present analysis showed that this threshold was not exceeded during the HD9 trial (25% of cycles with dose-limiting toxicities), which confirms the reliability of the dose-finding strategy. However, our data also showed that most patients (65%) underwent stepwise dose-reductions from the initial dose level 4 due to the occurrence of dose-limiting toxicities. The interindividual heterogeneity in the number of dose-limiting toxicities (and thus the number of dose-reductions) caused a pronounced interindividual heterogeneity in the dose escalation achieved. Despite this heterogenous dose erosion, considerable overall escalation of dose and dose intensity was achieved compared to BEACOPP-baseline (median relative-dose escalation for C, A and E by factor 1.77, 1.37 and 1.83, respectively). An important finding was that the escalation of C, A and E did not compromise the dose adherence of the other drugs of the regimen compared to BEACOPP-baseline. Hence, any treatment differences in treatment outcomes between the two BEACOPP variants are solely related to the different doses of cyclophosphamide, etoposide and adriamycin.

As expected, the dose intensification achieved in the BEACOPP-escalated regimen led to considerably more severe hematologic toxicities compared to BEACOPP-baseline. This was reflected in the time courses of leukocytes and platelets during the cycles and over total therapy, showing more pronounced depression and cumulative toxicity. Despite regular G-CSF administration most patients experienced WHO grade 4 leukocytopenia during treatment but the period of severe leukopenia was confined to four days. The use of G-CSF apparently permitted a rapid and safe recovery such that treatment could regularly be continued on time.

An important aspect of the practicability of myelosuppressive chemotherapy regimens are infections due to neutropenia, since they are potentially life-threatening. The present data on the incidences of infections during both regimens and their comparison were not fully conclusive due to incomplete documentation. Considering only cycles with complete information, the relative risk to develop a severe infection (WHO grade 3 or 4) under BEACOPP-escalated was not significantly increased compared to BEACOPP-baseline. Under the assumption that no severe infections were present in those cycles with missing information, the estimated relative risk was 1.4 (95% CI: 1.1–1.9). As a whole, however, dose-limiting infections (which were documented separately) were reported in only 1.4% of all cycles. We therefore conclude that BEACOPP-escalated was as feasible as BEACOPP-baseline regarding the risk to develop severe infections during therapy. Whether the lack of difference in the rate of severe infections could solely be ascribed to the preventive use of G-CSF or whether further factors might have contributed to this (e.g., differences in prophylactic antibiotics usage or hospitalization rates) remains unclear. A more comprehensive assessment of the medical care required during treatment is currently under way within the framework of a cost-effectiveness analysis of the BEACOPP regimen.

As a consequence of the increased hematotoxicity, clearly more hematosupportive treatment (G-CSF and packed blood-cell transfusions) was required during BEACOPP-escalated. A median number of six G-CSF injections per cycle was given in the escalated regimen, thus being a considerable cost factor of this regimen. At present, it is not clear whether the currently applied G-CSF schedule is optimal regarding cost-effectiveness. The number of G-CSF injections might be able to be reduced without jeopardizing its role in permitting dose-intensification or its role in possibly preventing neutropenic infections. Efforts to identify G-CSF administration schedules that potentially are more cost-effective have been initiated using computer-based modelling of granulopoiesis [18]. Moreover, the highly increased rate of erythrocyte transfusions due to chemotherapy-induced anemia was clearly a problem. Erythropoietin might be a candidate to mitigate anemia and thus to reduce the rate of erythrocyte transfusions, the medical benefits and costs of which, however, have to be carefully weighed against transfusions. A prospective study of the GHSG addressing this issue has been initiated. Finally, since a large part of the dose-limiting toxicities during BEACOPP-escalated was exclusively due to severe thrombocytopenia (in particular in the later cycles of therapy), the administration of thrombopoietic growth factors might be considered for subsets of patients. However, this will require more detailed knowledge on prognostic factors for hematotoxicity to identify patients at risk.

The forthcoming analyses of the HD9 trial will provide further clarification about whether the BEACOPP-escalated regimen is superior to other treatment regimens with regard to tumor control and long-term outcome. In view of the increased aggressiveness of BEACOPP therapy late sequelae such as the rate of secondary leukemias or myelodysplastic syndromes need to be carefully monitored. However, due to short follow-up the data presently being available are too immature and incomplete to allow an appropriate weighting of all favorable and unfavorable effects of BEACOPP therapy. The final analysis is planned for 2001.

In summary we conclude that both variants of the new BEACOPP regimen are safe and feasible within a broad multicenter setting regarding acute hematotoxicity, supportive treatment required and rate of infections.

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*Appendix

Participating study centers

List of Study Participants: Hospitals and practitioners that contributed at least three patients to this analysis (listed according to number of patients recruited). The institutions are located in Germany unless otherwise specified.

Swiss Institute for Applied Cancer Research, Bern, Switzerland; Westfaelische Wilhelms-Universitaet Muenster; Klinikum Chemnitz gGmbH; Medizinische Fakultaet Charité der Humboldt-Universitaet zu Berlin (Campus Berlin-Buch); Medizinische Einrichtungen der Universitaet zu Koeln; Fakultní nemocnice Královské Vinohrady, Praha, Czechia; Georg-August-Universitaet Goettingen; Klinikum Nuernberg; Universitaetskliniken des Saarlandes, Homburg; Justus-Liebig-Universitaet Giessen; Otto-von-Guericke-Universitaet Magdeburg; Staedtisches Krankenhaus Kiel; Medizinische Fakultaet Charité der Humboldt-Universitaet zu Berlin (Campus Charité Mitte); Robert-Bosch-Krankenhaus Cannstadt, Stuttgart; Staedtisches Klinikum Karlsruhe; Albert-Ludwigs-Universitaet Freiburg; Ruprecht-Karls-Universitaet Heidelberg; Universitaet Regensburg; Bayerische Julius-Maximilians-Universitaet Wuerzburg; Rehabilitationsklinik Koenigstuhl der LVA Baden, Heidelberg; Universitaet Gesamthochschule Essen; Evangelisches Krankenhaus Essen-Werden gGmbH; Philipps-Universitaet Marburg; Staedtisches Klinikum Braunschweig; Staedtisches Krankenhaus Sued, Luebeck; Friedrich-Alexander-Universitaet Erlangen-Nuernberg; Friedrich-Schiller-Universitaet Jena; Klinik Dr. Hancken GmbH, Stade; Klinikum Carl Gustav Carus der Technischen Universitaet Dresden; Klinikum Minden (Westf); Klinikum rechts der Isar der Technischen Universitaet Muenchen; Staedtisches Krankenhaus Muenchen-Schwabing; Universitaets-Krankenhaus Eppendorf, Hamburg; Buergerhospital Stuttgart; Dr.-Horst-Schmidt-Kliniken, Wiesbaden; Evangelisches Krankenhaus Hamm (Westf); Gemeinschaftspraxis Innere Medizin Dr. med. S. Hahnfeld, Jena; Gemeinschaftspraxis Innere Medizin und Haematologie Drs. Wysk/Gaede/Mao, Hannover; Kreiskrankenhaus Offenburg; Medizinische Universitaet Luebeck; St. Vincentius Krankenhaeuser Karlsruhe; Bernwardkrankenhaus Hildesheim; Caritasklinik St. Theresia, Saarbruecken; Klinikum Mannheim gGmbH; Krankenhaus der Barmherzigen Brueder, Regensburg; Krankenhaus Neukoelln, Berlin; Krankenhaeuser Klinikum Bayreuth; Mutterhaus der Borromaeerinnen Krankenanstalt, Trier; Rheinische Friedrich-Wilhelms-Universitaet Bonn; St. Antonius-Hospital, Eschweiler; Staedtische Kliniken Kassel gGmbH; Eberhard-Karls-Universitaet Tuebingen; Klinikum Darmstadt; Klinikum Krefeld; Klinikum Lahr (Schwarzwald); Marienhospital Hagen (Westf); Martin-Luther-Universitaet Halle-Wittenberg; St. Johannes-Hospital Dortmund; Diakonissenkrankenhaus Stuttgart; Klinikum Frankfurt (Oder); Klinikum Muenchen-Grosshadern; Krankenhaus Leopoldina, Schweinfurt; Krankenhaus Maria Hilf GmbH, Moenchengladbach; Krankenhaus Merheim, Koeln; Krankenhaus Nordwest, Frankfurt (am Main); Krankenhaus St. Elisabeth und St. Nikolaus, Ravensburg; Kreiskrankenhaus Guenzburg; Kreiskrankenhaus Aurich; St. Johannes-Hospital Duisburg; Staedtisches Krankenhaus Sindelfingen; Staedtisches Krankenhaus Heilbronn; Universitaet Rostock Klinikum; Allgemeinkrankenhaus Barmbeck, Hamburg; Caritas-Krankenhaus Lebach; Evangelisches Diakoniekrankenhaus Freiburg (im Breisgau); Evangelisches Krankenhaus Oldenburg (Oldb); Evangelisches Krankenhaus und Augenklinik Muelheim (an der Ruhr); Gemeinschaftspraxis fuer Innere Medizin und Haematologie Verpoort/Zeller, Hamburg; Gemeinschaftspraxis Haematologie/Internistische Onkologie O. Burkhard/B. Reimann, Worms; K. Becker/U.R. Kleeberg, Hamburg; Klinikum der Stadt Ludwigshafen; Krankenhaus Barmherzige Brueder, Trier; Krankenhaus St. Vincenz, Limburg; Kreiskrankenhaus Hameln; Medizinische Hochschule Hannover; Moabit Krankenhaus GbR, Berlin; Ostalb-Klinikum, Aalen; Staedtische Kliniken Oldenburg (Oldb); Staedtisches Klinikum Dresden; Staedtisches Krankenhaus Pforzheim; Staedtisches Krankenhaus Guetersloh.

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