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ORIGINAL ARTICLE

Equitoxicity of bolus and infusional etoposide: results of a multicenter randomised trial of the German High-Grade Non-Hodgkins Lymphoma Study Group (DSHNHL) in elderly patients with refractory or relapsing aggressive non-Hodgkin lymphoma using the CEMP regimen (cisplatinum, etoposide, mitoxantrone and prednisone)

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Abstract To compare toxicity of etoposide bolus with continuous infusion and to assess the efficacy of the CEMP (cisplatinum, etoposide, mitoxantrone, prednisone) regimen, 47 patients with refractory or relapsed aggressive non-Hodgkin's lymphoma older than 60 years (n=43) or not qualifying for high-dose chemotherapy (n=4) received five four-weekly CEMP cycles. Patients were randomised to start with bolus or continuous-infusion etoposide and then received bolus and infusional etoposide in an alternating fashion. The primary objective was the comparison of differences in the course of leukocytopenia and thrombocytopenia between the two application schedules. CEMP was well tolerated with little organ and moderate haematotoxicity. There was no difference in toxicity between bolus and continuous-infusion etoposide. Complete remission rate was 44% in patients relapsing ≥1 year, 27% in patients relapsing within the first year after achieving complete remission and 5% in primary refractory patients. Median event-free and overall survivals for all patients were 3 and 10 months, respectively. The observed equitoxicity and the more challenging logistics of a 60-h infusion make bolus injection the preferred application of etoposide. As the CEMP

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regimen is well tolerated and efficacious in elderly patients with relapsed or refractory aggressive non-Hodgkin's lymphoma for whom more aggressive therapies are not feasible, a three-weekly modification of CEMP should be tested in combination with rituximab.

Keywords Aggressive lymphoma · Chemotherapy · Continuous infusion · Relapse

Introduction

High-dose chemotherapy with autologous stem cell transplantation has improved the prognosis of patients with relapsed aggressive non-Hodgkin's lymphoma [34]. However, this treatment option is often not indicated for elderly patients due to the toxicity of this approach and/or the comorbidity of the patients. Using conventional salvage regimens, the outcome for relapsed aggressive lymphoma is poor. While there is no commonly accepted salvage therapy, platinum-based therapies seem to be the most effective among the various regimens used [2, 3, 5, 7, 9, 17, 19, 26, 29, 31, 34, 37, 38, 40, 42, 45, 46].

The anti-tumor activity of anthracyclines and etoposide is clearly schedule-dependent due to the fact that the activity of topoisomerase II varies throughout the cell cycle and that these drugs are rapidly cleared from the cell after exposure, permitting DNA repair. Preclinical studies revealed that a longer exposure to a lower drug concentration induces a higher degree of cell kill than higher exposure concentrations after a short-time incubation [10, 21, 25]. Furthermore, pharmacokinetic studies performed in patients with small-cell lung cancer demonstrated that the duration of exposure to low levels of drug (>1 μg/ml) clearly correlates with response rates, whereas haematological toxicity seems to be associated with higher plasma concentrations [6, 41]. As the clinical benefit of a prolonged etoposide administration is beyond controversy, the superiority of an infusional regimen has not yet been proven. However, several studies suggested a schedule-dependent effect favouring the infusional administration of cytotoxic drugs [16, 43, 47, 48] in relapsed and refractory lymphoma, and dose-adjusted infusional EPOCH (etoposide, prednisone, vincristine, doxorubicin) has become the standard treatment for aggressive lymphomas in several centres. Because infusional and bolus etoposide have never been compared in a randomised fashion, we conducted a randomised trial comparing the continuous infusion with the bolus application of etoposide within the CEMP regimen.

CEMP consists of cytotoxic drugs with proven single-agent activity and lack of cross-resistance with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), the standard chemotherapy regimen for the primary treatment of aggressive lymphomas [14, 27]. Cisplatinum has shown considerable activity against relapsed aggressive lymphomas in several trials [39, 44, 46, 47], has reasonable haematotoxicity and is well tolerated when given in fractions of 20–30 mg/m^2 per day. Mitoxantrone was integrated into the regimen because it has a low risk of cardiotoxicity, and there is a relative lack of cross-resistance with doxorubicin [1, 22, 50]. Prednisone was included in the CEMP regimen because it adds to the cytotoxic effects of the cytotoxic drugs and relieves B-symptoms (fever, night sweats, weight loss). Finally, because the etoposide efficacy/toxicity profile had been reported to be schedule-dependent [16, 43, 47], etoposide administered as a continuous infusion was randomly compared with etoposide given as bolus. The doses of the CEMP regimen had been chosen because they had been proven safe in a small pilot study of six elderly patients with relapsed aggressive lymphoma.

Materials and methods

Patients and chemotherapy regimen

The study was conducted in accordance with the Helsinki declaration. The protocol was approved by the ethics review committee of each participating centre. All patients gave written informed consent. Eligible were patients with biopsy-proven progressive aggressive lymphoma according to WHO [20] (with an Eastern Cooperative Oncology Group performance status of 0 to 3), 61 to 75 years of age or younger if not fit for high-dose chemotherapy with stem cell support. Other inclusion criteria were first relapse after or refractoriness to primary therapy with at least four cycles of CHO(E)P [33]. Excluded were patients with congestive heart failure (NYHA III or IV), severe obstructive lung disease, renal insufficiency with serum creatinine >1.8 mg/dl, serum bilirubin >2.5 mg/dl or peripheral neuropathy.

The dosages and schedule of the CEMP regimen are shown in Table 1. G-CSF was given starting on day 6 of

Table 1 The CEMP regimen

	Dosage		Schedule
cis-Platinum	20 mg/m^2	i.v. for 1 h	Days 1–4
Etoposide	50 mg/m^2	iv. bolus or 24-h CI	Days 1–4
Mitoxantrone	3 mg/m^2	i.v.	Days 1–2
Prednisone	100 mg	p.o.	Days 1–4
Repeat			Day 29 (5 cycles)

the CEMP regimen to patients who experienced neutropenic fever or had a duration of neutropenia (neutrophils $<1.0\times10^9/mm^3$) lasting >5 days. CEMP was to be repeated on day 29 if leukocytes were $>2.5\times10^9/mm^3$ and platelets $>80\times10^9/mm^3$. If this was not the case, blood cell counts were repeated every 2 days. In case of treatment delays >7 days, the dose of the cytotoxic drugs was reduced to 75%. A total of five CEMP cycles were to be given as salvage regimen.

Staging

The stage of lymphoma was defined before the enrolment of the patient by the referring physician on the basis of the Cotswolds modification of the Ann Arbor classification [24] by means of physical examination, relevant laboratory parameters (complete blood cell count and basic blood chemistry including LDH), computed tomography of the chest and abdomen, bone marrow biopsy and other investigational procedures depending on clinical symptoms. Response was evaluated 4 weeks after the end of therapy according to the International Workshop criteria [4] and included physical examination, relevant laboratory parameters and the control of all other previously pathological findings by adequate diagnostic measures. Follow-up evaluation was performed every 3 months in the first year after treatment and every 6 months thereafter. It included physical examination, relevant laboratory parameters and computed tomography of the chest and abdomen. Complete remission (CR) and unconfirmed complete remission (CRu) are defined according to the International Workshop criteria [4]. Remissions lasting less than 2 months after the final restaging were counted as progression.

Statistical analysis

Patients were randomised after stratification for centres, age (≤60 or >60) and response to the primary therapy (refractory or relapse) to receive the first cycle of the CEMP regimen (Table 1), with etoposide given either as bolus or as continuous infusion. The etoposide application alternated in each subsequent cycle, allowing for using each patient as his/her individual control. Analyses included all patients who fulfilled the inclusion criteria and had no exclusion criterion. Primary endpoint of the study was the comparison of the duration of leukocytopenia and thrombocytopenia after CEMP with etoposide given as continuous infusion versus bolus injection. Based upon the assumption of a standard deviation of the duration of leukocytopenia ($<2.5\times10^9$/l) and of thrombocytopenia ($<80\times10^9$/l) of 4 days and that 80% of all randomised patients receive at least three cycles of chemotherapy (i.e. do not progress before the application of the third cycle), to detect a difference in the duration of leukocytopenia and thrombocytopenia, respectively, between the two modalities of etoposide application with a power of 80% at a significance level of 5%, at least 40 patients had to be included.

Secondary endpoints were the applicability of the next cycle on day 29, differences in toxicities, adherence to treatment schedule and dose response rates, event-free survival (EFS) and overall survival (OS). The median relative dose and median treatment duration were estimated according to the method by Kaplan and Meier, censoring patients withdrawn due to insufficient response. The WHO grades for haematotoxicity and non-haematotoxicity, response and progression-under-therapy rates were compared

Table 2 Patients' characteristics at baseline

	All (n=47)	Refractory (n=20)	First CR <1 year (n=11)	First CR ≥1 year (n=16)
Age: median; range (years)	68 (40–75)	65 (40–73)	69 (62–75)	70 (59–74)
Gender (male/female)	29 (62%)/18 (38%)	12 (60%)/8 (40%)	8 (73%)/3 (27%)	9 (56%)/7 (44%)
Age >60	43 (92%)	17 (85%)	11 (100%)	15 (94%)
LDH above normal[a]	18 (39%)	12 (60%)	2 (20%)	4 (25%)
Stage I	3 (6%)	2 (10%)	0 (0%)	1 (6%)
II	11 (23%)	4 (20%)	3 (27%)	4 (25%)
III	24 (51%)	10 (50%)	6 (55%)	8 (50%)
IV	9 (19%)	4 (20%)	2 (18%)	3 (19%)
ECOG >1	16 (34%)	9 (45%)	1 (9%)	6 (38%)
Extranodal involvement ≥2	4 (9%)	1 (5%)	1 (9%)	2 (13%)
B symptoms	15 (32%)	5 (25%)	3 (27%)	7 (44%)
IPI=0.1[a]	8 (17%)	2 (10%)	3 (30%)	3 (19%)
IPI=2[a]	16 (35%)	7 (35%)	3 (30%)	6 (38%)
IPI=3[a]	14 (30%)	6 (30%)	4 (40%)	4 (25%)
IPI=4.5[a]	8 (17%)	5 (25%)	0 (0%)	3 (19%)

[a] One patient without documented pretreatment LDH; elevated LDH and IPI are shown for only 46 patients.

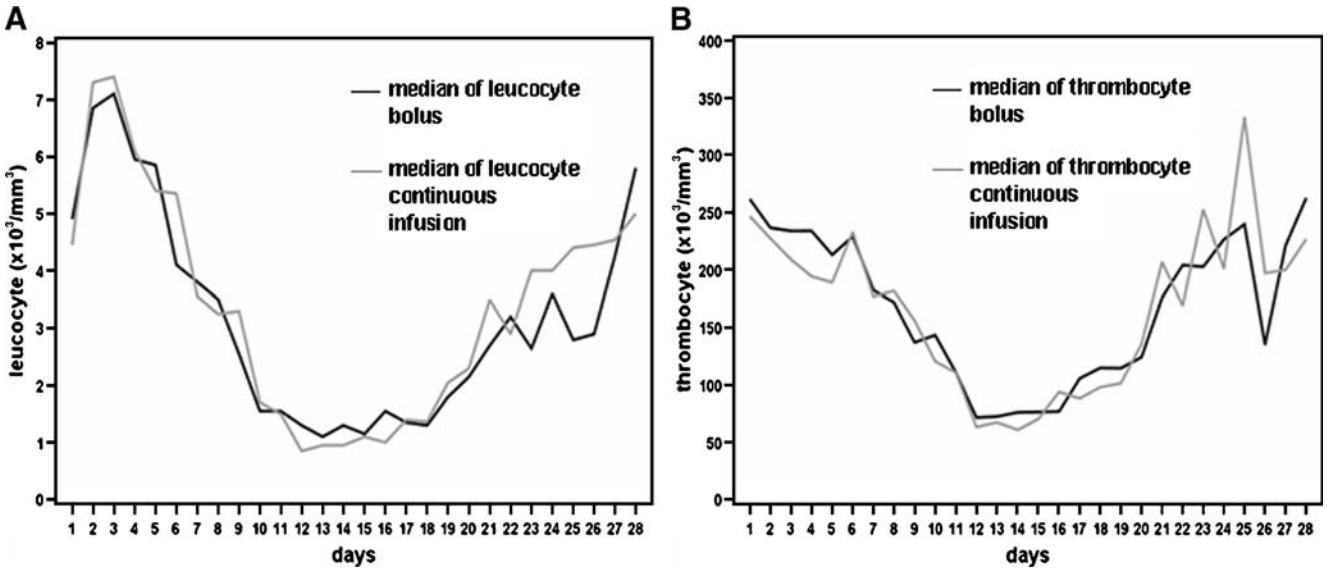

Fig. 1 Course of leukocytes (**A**) and platelets (**B**) after bolus (*black lines*) and continuous infusion (*grey lines*)

by the use χ^2 and, if required, by means of Fisher's exact test. Event-free survival was defined as time from first day of therapy to progressive disease under therapy or failure to achieve CR or CRu (i.e. no change or partial remission associated with additional therapy), additional therapy in excess of that prescribed in the protocol, relapse or death from any cause, whatever came first. Overall survival was defined as time from first day of therapy to death from any cause. Patients without an event in EFS or overall survival were censored at the last day with valid information for the respective endpoint. EFS and overall survival were estimated according to Kaplan–Meier [23] and compared by log-rank test. Nominal significance level was at 0.05, two-sided. Multivariate analyses were performed with the use of Cox proportional hazard models to estimate hazard ratios for evolving an event. Statistical analyses were performed with SPSS (version 11.5) software.

Results

Fifty-seven patients in first relapse after or refractory to at least four cycles of the CHOP or CHOEP regimens [33], respectively, were recruited from 26 institutions. Of these, 47 patients were evaluable and ten patients were excluded because they met one of the exclusion criteria (no aggressive NHL upon reference pathology, one; second or later relapse, two; other concomitant neoplasm, two; withdrawal of consent, one; death before start of treatment, one; no CRF documentation, one). The 47 patients were between 40 and 75 (median, 68) years old; only four patients were younger than 60 years. The median time of observation was 45 months for event-free and 51 months for overall survival. The characteristics of all patients and the subgroups with respect to response to primary therapy are described in Table 2.

Adherence to protocol and duration of therapy

Adherence to the protocol was excellent, and all four drugs were administered with high relative dose intensities. For cisplatinum, the median relative dose was 91%, and for etoposide, mitoxantrone and prednisone, it was 97%, 95% and 100%, respectively. The actual median duration of five cycles of CEMP was 118 days in patients who completed five cycles of CEMP compared to 116 days as per

Table 3 Response to CEMP therapy

	All (n=47)	Refractory (n=20)	First CR <1 year (n=11)	First CR ≥1 year (n=16)
Complete response	11 (23%)	1 (5%)	3 (27%)	7 (44%)
Partial response	5 (11%)	1 (5%)	1 (9%)	3 (19%)
No change/minor response	5 (11%)	1 (5%)	3 (27%)	1 (6%)
Progressive disease	22 (47%)	15 (75%)	3 (27%)	4 (25%)
Therapy-associated deaths	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	4 (9%)	2 (10%)	1 (9%)	1 (6%)

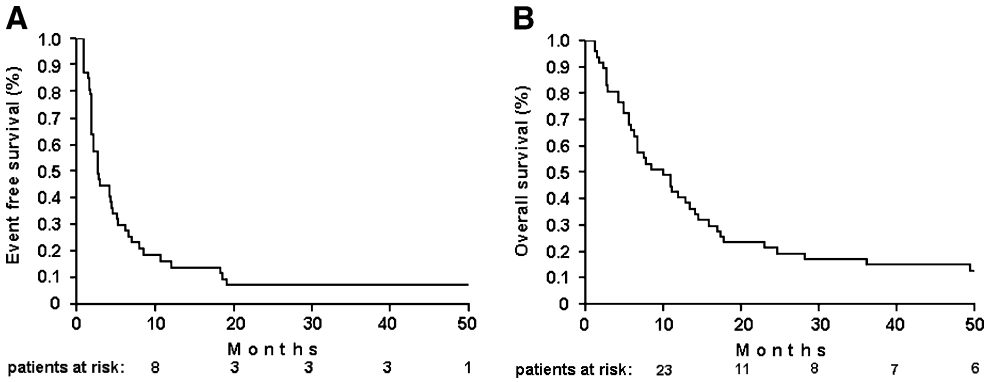

Fig. 2 Event-free (**A**) and overall survival (**B**) of 47 evaluable patients

protocol. Only 15 of 47 patients completed all five cycles of therapy as per protocol, including one patient who received an additional sixth cycle of chemotherapy for no obvious reason. The main reason for stopping therapy according to protocol was insufficient response to therapy, which was mainly due to progression under chemotherapy (see below).

Haematological toxicity

The course of leukocyte counts after continuous infusion and bolus etoposide was not different and, most importantly, with respect to the interpretation of the results, there was full recovery of leukocytes and platelets before the next scheduled cycle, with no indication of cumulative toxicity. The leukocyte nadir after CEMP occurred between days 11 and 16 (Fig. 1A). G-CSF was given in 19% of the cycles with bolus etoposide and 20% of the cycles with infusional etoposide, respectively.

Leukocytopenia of WHO grades 3 and 4 was observed in 83.8% cycles after bolus vs. 88.2% cycles after infusional etoposide (p=0.737). Median leukocyte counts ranged from 1.0 to $1.5\times10^3/mm^3$ during the nadir (days 11 to 16). By day 21, the leukocyte counts had always fully recovered (>2,500/mm^3) in all cycles and all patients.

Thrombocytopenia after CEMP was modest and occurred between days 11 and 16 of a CEMP cycle. Mean platelet counts were not different after the two forms of etoposide administration (Fig. 1B). Median thrombocyte counts during the nadir (days 11 to 16) ranged from 53 to $110\times10^3/mm^3$. Thrombocytopenia of WHO grades 3 and 4 was observed in 31.6% after bolus and 44.4% after infusional etoposide (p=0.42). Platelet transfusions were given to three (7%) patients, corresponding to a rate of thrombocyte substitution of 2% over all chemotherapy cycles. All three platelet transfusions were given after cycles with etoposide bolus injection (4% vs. 0%, p=0.27).

Both variants of the CEMP regime had little influence on haemoglobin levels. There was a trend that anaemias of WHO grades 3 and 4 occurred more often after infusional than after bolus etoposide (15.0% vs. 6.3%, p=0.092). A total of 24 packed red blood cell transfusions were given after 18% of all CEMP chemotherapy cycles to 17 (38%) of the 47 evaluable patients. The red blood cell transfusions were equally distributed between cycles with bolus and

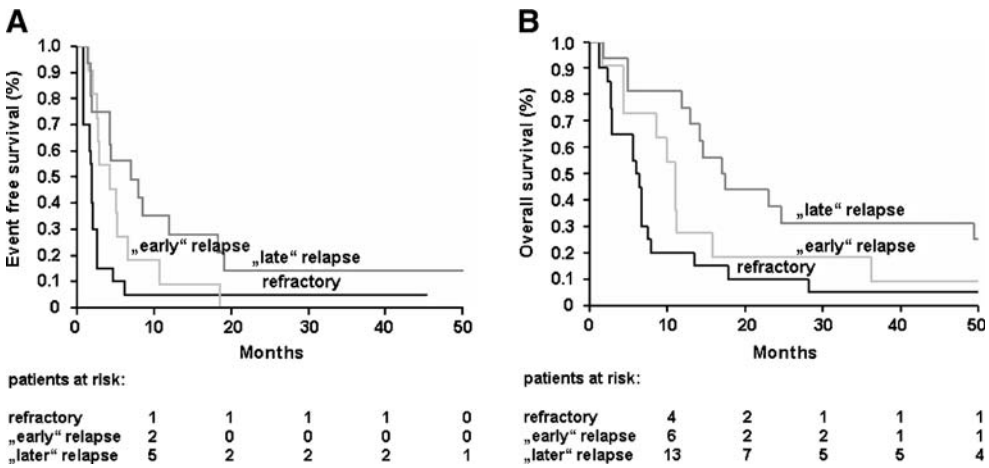

Fig. 3 Event-free (**A**) and overall survival (**B**) according to response to primary therapy

infusional etoposide (18% of all infusional and 18% of all bolus cycles).

Non-heamatological toxicity

Side effects concerning the heart, the bladder, the kidneys, the lungs, the liver, the central nervous system, the oral cavity and gastrointestinal tract were recorded according to the Bearman scale; the severity of infection was scored using the WHO scale. Grades 3 and 4 organ toxicities (other than myelosuppression) occurred in 4 of 47 patients, with no significant difference between bolus and infusional etoposide (4/84 or 5% of bolus vs. 1/54 or 2% of infusional cycles, p=0.65) and consisted of infections (pneumonias, mucositis and colitis).

Twenty-two (49%) patients received i.v. antibiotics after a total of 33 chemotherapy cycles (25%), with no significant difference between bolus and confidence interval (CI; 28% vs. 22%, p=0.43).

Response to therapy

Of 47 patients, 11 (23%, 95% confidence interval 11% to 36%) achieved a complete response and five patients (11%) a partial response, resulting in an overall response rate of 34%. Twenty-two of 47 (47%) patients had progressive disease under therapy (Table 3).

The response rates of patients with relapsing aggressive lymphomas depended on the response to the initial therapy and on the IPI risk profile as determined before CEMP. Only one of the 20 patients (5%) who were refractory to their first-line therapy achieved a complete remission, whereas 10 of 27 (37%) of the patients who had relapsed after a complete remission achieved a second complete remission with CEMP (p=0.01). Seven of 16 (44%) patients with a "late" (i.e. ≥12 months) relapse achieved a complete remission compared to 3 of 11 (27%) with a first complete remission lasting for <12 months. There was no therapy-associated death, but in three patients, therapy was stopped after cycles 1 and 2, respectively, because of excessive toxicity (pneumonia) in one and due to concomitant disease in a second patient. Results were not different if patients <60 years of age (n=4) were excluded from the analysis.

The median event-free survival was 2.7 months (Fig. 2A) and depended on the response to the primary therapy. EFS ranged from 2 months for patients with primary refractoriness, 4 months for patients with a short first CR (<12 months) and 7 months for patients with a late (≥12 months) relapse (Fig. 3A). The differences in event-free survival between primary refractory patients and patients with an early relapse (p=0.038) and between refractory patients and late relapses (p=0.003) were significant, while the difference between early and late relapses was only borderline significant (p=0.127) due to the low number of patients in each group.

The median overall survival of the evaluable patients was 10 (range, 1 to 127) months (Fig. 2B). Like the median EFS, the median OS depended on the response to the first-line treatment and the duration of this response (Fig. 3B): 6 months for primary non-responders, 11 months for patients with "early" relapse within 1 year and 17 months for patients with a "late" relapse, i.e. occurring later ≥12 months after achieving the first complete remission. The overall survival difference between refractory patients and patients with late relapse was significant (p=0.017), while the difference between early and late relapses was not (p=0.126). The respective 1-year survival rates were 20% for primary refractory patients, 27% and 75% for patients with early and late relapse, respectively; the 2-year survival rates for patients with primary progressive disease, early and late relapse were 10%, 18% and 38%, respectively, and the 3-year survival rates were 5%, 18% and 31%. After a median observation time of 51 months, 45 of 47 patients (96%) have died, 39 (83%) of them due to lymphoma progression. Two patients died of concomitant disease, and the reason of death is unknown for four patients. The 1-year, 2-year and 3-year estimates for survival rates for all patients were 40%, 21% and 17%, respectively.

Table 4 Multivariate analysis of prognostic factors

Factor	Overall survival			Event-free survival		
	Relative risk	95% CI	p value	Relative risk	95% CI	p value
LDH > UNV	1.6	0.8, 3.2	0.202	1.5	0.7, 3.4	0.283
Age >60	1.8	0.5, 7.3	0.387	2.4	0.6, 10.0	0.245
ECOG >1	1.8	0.9, 3.8	0.115	2.8	1.3, 6.2	0.010
Stage III/IV	2.1	1.0, 4.5	0.049	1.6	0.8, 3.5	0.220
Extranodal involvement >1	4.2	1.3, 13.8	0.019	2.3	0.7, 7.6	0.165
Refractory vs. late relapse	3.6	1.7, 8.0	0.001	5.8	2.3, 15.0	<0.001
Early vs. late relapse	2.2	0.9, 5.4	0.070	2.9	1.2, 7.4	0.021

Table 5 Conventionally dosed salvage regimens for relapsed and refractory aggressive lymphomas

Author	Regimen	*n*	Median age (range)	CR (%)	OR (%)	Median EFS (rate at timepoint)	Median OS
Cabanillas et al. 1982 [2]	IMVP-16	52	n.m.	37	62	12 months	15 months
Chao et al. 1990 [3]	CEPP(B)	69	1/3 >60 years	32	61	30% at 5 years	12 months
Child et al. 2002 [5]	FLUDAP	33 (24–59)	47	16	39	(including 12-SCT)	8 months
Crump et al. 2002 [8]	Topo/Eto	22 (34–76)	62	0	18	5 months	n.m.
Crump et al. 2004 [7]	CisGemDex	51 (18–84)	57	22	53	3 months	8 months
De Lord et al. 1992 [9]	IMVP-14	46	n.m.	11	37	n.m. (2%/36 months)	
El Gnaoui et al. 2003 [11]	R-GemOx	40 (43–78)	64	75	85 (20 months)	75%	
Enblad et al. 1996 [12]	MIME	75	n.m.	20	56	n.m. (13% at 2 years)	
Ezzat et al. 1995 [13]	ESHAP	26	n.m.	27	72	6 months (including 13 SCT)	6 months
Gutierrez et al. 2000 [16]	EPOCH	125 (26–85)	48	24	74	7 months	17.5 months
Girouard et al. 1997 [15]	miniBEAM	104 (18–16)	52	12	37	n.m. (incl. 38 SCT)	n.m.
Hänel et al. 2002 [18]	ASHAP	51 (17–76)	40	38	69 (21% at 3 years; including 32 SCT)	(32% at 3 years)	
Haim et al. 1997 [17]	DexEtoIfoCis	56 (21–89)	68	32	64 (9% at 2 years)	3.5 months n.m.	8 months
Haq et al. 1999 [19]	Mito-DHAP	22 (31–69)	59	23	41	5.2 months (including 2 SCT)	8 months
Mey et al. 2006 [28]	R-DHAP	53 (21–77)	62	32t	63	6.7 months	8.5 months
Moskowitz et al. 1999 [31]	ICE	163 (14–71)	46		63	n.m. (including 25 SCT)	n.m.
Nuckel et al. 2003 [32]	ASHAP	24	n.m.	50	67 (40% at 4 years)	12.5 months (60% at 4 years)	15 months
Philip et al. 1995 [34]	DHAP	107	43	25	44 (12% at 5 years)	32 at 5 years	
Press et al. 1991 [35]	DHAP	39 (16–74)	45	23	67	5 months	7 months
Reiser et al. 1999 [36]	Dexa-BEAM	16 (26–59)	44	19	25	2 months (including 3 SCT)	7 months
Rodriguez et al. 1995 [37]	MINE/ESHAP	92 (27–79)	58	48	68	8 months	24 months
Seymour et al. 2002 [40]	CisFluAra	44 (17–67)	53	7	48	4 months	20% at 2 years
Soussain et al. 1999 [42]	ESHAP+SCT	65/52 high 52 agress. NHL	52 (17–58)	26	43	n.m. including 23 SCT	10 months (28.5% at 5 years)
Sparano et al. 1993 [43]	CDE	58	54 (20–80)	17	52	4 months (10% at 2 years; including 2 SCT)	6 months
Velasquez et al. 1988 [45]	DHAP	92	55 (20–78)	31	55	n.m.	25% at 2 years
Velasquez et al. 1994 [46]	ESHAP	85 (18–78)	54	37	64 (10% at 3 years)	6 months (31% at 3 years)	14 months
Wilson et al. 1993 [47]	EPOCH	56 (21–78)	50	42	77 (28% at 1 year)	78 months (61% at 1 year; including 8 SCT)	16 months
Zelenetz et al. 2003 [51]	ICE	222 (14–71)	46	28	34 (28 at 5 years; including 146 SCT)	34 at 2 years	
This study	CEMP	47 (40–75)	68	23	34 (7% at 3 years)	2.7 months (17% at 3 years)	10 months

In a multivariate analysis (Table 4), we investigated the effect of the type of response (refractory, early and late relapse) after adjusting for the five IPI risk factors (age >60 years, elevated pretreatment LDH, ECOG performance state >1, advanced stage III/IV, >1 extranodal involvement). Remarkably, all five IPI factors had a clear trend of increasing risk (relative risks ≥1.5 for all factors), and response to primary therapy retained its independent prognostic effect with respect to event-free and overall survival.

Discussion

To our best knowledge, this is the study of a salvage regimen for aggressive lymphomas with the highest median age of patients and the longest follow-up published to date (Table 5). Despite a median age of 68 years and with only four patients under the age of 60 (who were judged not being in a condition good enough to undergo high-dose chemotherapy with stem cell support), the activity of the CEMP regimen in elderly patients with relapsed aggressive lymphoma is similar to what has been reported for other conventionally dosed cisplatinum-based regimens like DHAP or ESHAP (Table 5) [28, 29, 45, 46]. The long-term follow-up makes it very clear that event-free and overall survival rates are low in elderly patients in first relapse after or refractory to CHOP or CHOEP. Previous reports showing that the probability of achieving a second complete remission depends on the response to the primary therapy [34, 46] have been confirmed in our trial. The CEMP regimen induced a complete remission in only one patient who had been refractory to the first-line treatment. In patients with a complete response to the primary therapy and relapse after CR, a second CR was achieved in approximately 37%. In addition, patients with early relapse (within 1 year after CR) had a lower rate of second CR than patients with a late relapse (27% vs. 44%), and the same trend was observed for EFS and overall survival.

The CEMP regimen could be administered with relative dose intensities of 91% to 100% for each single drug and had a low incidence of grade 3/4 non-haematological toxicities which were observed after only 5 of 138 (3.6%) of all documented cycles given during this study. The four episodes of grade 3/4 infection and the use of i.v. antibiotics in only one fourth of the cycles compare favourably with other salvage regimens in elderly patients. There were no significant differences of grade 3/4 leukocytopenia (83.8% bolus vs. 88.2% CI, p=0,73) and thrombocytopenia (31.6% bolus vs. 44.4% CI, p=0,45) or the duration of leukocytopenia and thrombocytopenia between the two application schedules. Leukocyte and platelet counts fully recovered in all patients by day 21 so that the CEMP protocol can be given safely to elderly patients at four-weekly intervals with little organ toxicity and only moderate haematotoxicity. According to the dose intensity concept [30], a three-weekly CEMP should be more efficacious than the four-weekly schedule because the relative dose intensity of the three-weekly is 133% of the four-weekly application. Due to its low toxicity, the three-weekly CEMP in combination with rituximab may be particularly appropriate for elderly patients with relapsed aggressive lymphoma for whom more aggressive therapy is not feasible, especially for those with a late relapse.

Rituximab had not yet been approved during the recruitment of this study and therefore was not part of the used regimen. While the efficacy of salvage regimens not incorporating rituximab might be of limited interest in the era of chemoimmunotherapy, the major goal of this study, the investigation of putative differences between continuous infusion and bolus application of etoposide, is still an important issue in 2008. Based on observations in patients with refractory or relapsed DLBCL, dose-adjusted infusional DA-EPOCH [47–49] has become the standard primary chemotherapy regimen in several centers, although there has never been a randomised comparison between the infusional and bolus application. As there was complete recovery of leukocyte and platelet counts before the next scheduled chemotherapy cycle with no indication of cumulative toxicity, the design of this study with alternating cycles of CI and bolus infusions of etoposide allowed for a valid comparison of the toxicities in each cycle. In contrast to previous reports of (non-randomised) studies [16, 43, 47–49], we did not observe a qualitatively or quantitatively different toxicity profile after continuous infusion of etoposide compared to bolus injection. This suggests that the bolus application of etoposide—although presumably associated with higher peak concentrations—is not more toxic than the infusional regimen at the used dosage. Therefore, the infusional regimen should not allow for more escalated doses which might achieve an improved outcome. Based on the results of this study, we can definitely not exclude that a continuous infusion of a given dose of etoposide may still be more effective than a bolus application by exploiting the cell cycle specificity of the agent, even though a difference in efficacy of the two forms of etoposide application at the same dose is rather unlikely as long as a threshold plasma concentration is exceeded. In light of the more challenging logistics of a 60-h infusion, the bolus injection should be the preferred application for etoposide in the CEMP regimen and in other regimens designed for the treatment of aggressive lymphomas.

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