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Malignant Lymphomas

Etoposide, mitoxantrone and prednisone, a salvage regimen with low toxicity for refractory or relapsed non-Hodgkin's lymphoma

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ABSTRACT

Background and Objectives. **Relapsed non-Hodgkin's lymphoma (NHL) is preferably treated with high-dose therapy and stem cell support. However, not all patients qualify for intensive chemotherapy. We evaluated the efficacy and toxicity of a new salvage chemotherapy regimen designed for patients with relapsed or refractory NHL who are not appropriate candidates for high-dose therapy (HDT).**

Design and Methods. **Seventy-nine patients received a regimen consisting of etoposide (350 mg/m² i.v. day 1), mitoxantrone (14 mg/m² i.v. day 1) and prednisone (80 mg/m² p.o. days 1-5) (EMP). The majority had aggressive NHL. Twenty-one patients were elderly, i.e. >60 years of age.**

Results. **The overall response rate in the 79 patients was 38% as compared to 67% in the elderly. The progression-free survival was 54% and 30% at 12 months and 24 months, respectively. The toxicity of the regimen was relatively low. No toxic deaths have occurred. In 28 of 231 cycles (12%) a CTC-grade 2-4 infection was encountered. Twenty-one hospital admissions were necessary because of infection or fever. Other toxicity was rare. Toxicity was not greater in the elderly patients. WHO performance status 2-4 and elevated serum lactate dehydrogenase (LDH) concentrationv were adverse prognostic factors for response as well as for overall survival. Another adverse prognostic factor for response was age <60 years.**

Interpretation and Conclusions. **EMP is a new salvage regimen with a relatively low toxicity. It should be considered for patients with relapsed or refractory NHL who are not candidates for standard reinduction therapy and stem cell transplantation.**

Key words: NHL, chemotherapy, relapse, elderly

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The standard chemotherapy regimen for aggressive non-Hodgkin's lymphoma (NHL) is CHOP, consisting of cyclophosphamide, doxorubicin, vincristine and prednisone.[1-4] The complete response rate achieved with CHOP as initial treatment is 65% in young adults and 45-60% in older patients.[1,3,4] Up to 40% of these patients relapse within two years.[5] Young patients with a chemosensitive relapse may be cured by high-dose therapy (HDT), followed by stem cell transplantation (SCT).[6,7] However, for elderly patients with relapsed NHL effective salvage regimens are hampered by their toxicity.

Several salvage regimens including IMVP-16, DHAP, MIME, CAMP, MVLP and VIM, have been published.[5,8-12] The results of second-line chemotherapy regimens are, however, disappointing. Although responses may be observed in 35% to 55% of the patients, they are usually of short duration and less than 15% of patients achieve a durable complete response without SCT.

We used a new regimen in relapsed or refractory patients that is not cross-resistant with CHOP. It combines etoposide with mitoxantrone and prednisone (EMP). Etoposide is an epipodophyllotoxin derivative functioning as a topoisomerase II and protein synthesis inhibitor. It is an active drug in NHL, especially in a multidrug combination chemotherapy regimen.[13] Mitoxantrone is a synthetic anthracenedione that inhibits the nucleic acid synthesis. It is an active drug in lymphomas and is well tolerated, even by elderly patients.[3,14,15]

Here we describe the results of 79 patients with relapsed or refractory NHL who were treated with EMP.

Design and Methods

Patients

From 1994 to 1998, 79 consecutive patients with relapsed or primary refractory stage II, III or IV NHL, who were considered not to be candidates for HDT, were included in a single institution study for the evaluation of safety and efficacy of EMP treatment. All patients gave informed consent prior to their inclusion in the study.

Before EMP treatment a new biopsy was obtained from each patient and the histologic diagnosis was revised according to the REAL classification.[16]

Treatment

The EMP regimen consisted of etoposide 350 mg/m^2 combined with mitoxantrone 14 mg/m^2 intravenously (i.v.) on day 1 and prednisone 80 mg/m^2 orally on days 1 to 5. It was administered at 21-day intervals. In case of severe neutropenia or thrombocytopenia (>WHO grade 2) treatment was postponed for 1 week. Patients were scheduled to receive 3 cycles, after which restaging was performed. Responsive patients then received additional cycles of EMP to a maximum of 6 cycles. Responsive patients who achieved a complete response were allowed to be treated with intensive consolidation therapy, followed by autologous stem cell transplantation. In case of either progressive disease, unacceptable toxicity or severe adverse events, treatment was stopped. The Common Toxicity Criteria were used to classify the treatment related toxicity.[17]

Response evaluation

A complete response (CR) was defined as the disappearance of all symptoms and signs for at least 4 weeks, without the development of new lesions. A partial remission (PR) was defined as a reduction by at least 50% of all measurable lesions. Progressive disease (PD) was defined as an increase of >25% of tumor mass or appearance of a new lesion during treatment or within 4 weeks after treatment.

Statistical analysis

Overall survival (OS) was measured from the start of EMP treatment until death. Patients still alive at the time of analysis were censored at the last follow-up date. Progression-free survival (PFS) was calculated for all patients who had reached a PR or CR with EMP treatment, from the date of response until relapse, progression or death, whichever came first. The following patient characteristics at the start of EMP were included in the analysis of prognostic factors: age (up to 60 versus over 60 years), gender, best response on previous chemotherapy, histologic diagnosis (Working Formulation low versus intermediate/high grade), WHO performance status (0-1 versus 2-4) and serum LDH level at the start of EMP (normal versus elevated, i.e. above the upper limit of the normal value). Pearson's chi-squared test and Fisher's exact test, whichever appropriate, and logistic regression were used to determine an association between clinical features at the start of EMP and the response to EMP. The Kaplan-Meier method was used to estimate overall survival and progression-free survival. The logrank test and Cox regression analysis were performed to study differences in survival between subgroups. All reported p values are two-sided and a significance level ($\alpha = 0.05$) was used.

Results

The patient characteristics at the start of EMP therapy are summarized in Table 1. The international prognostic index (IPI),[18] as calculated at presentation with NHL, was low-risk in 35 patients, low-intermediate in 22, high-intermediate in 11 and high in 8 patients. In 3 patients the serum LDH level at presentation was not determined. All patients had received one or more chemotherapy regimens before inclusion in the present study (Table 2). In 61 patients CHOP had been the primary treatment. Thirty-five patients had received two or more chemotherapy regimens before EMP.

Table 1. Patient characteristics.

Characteristics	All patients	No. of patients (%) ≤ 60 years	>60 years
Number of patients	79	58	21
Age			
Median	53	50	69
Range	24-77	24-60	61-77
WHO-performance status			
0-1	56 (71)	40 (69)	16 (76)
2	15 (19)	13 (22)	2 (10)
3	7 (9)	4 (7)	3 (14)
4	1 (1)	1 (2)	-
Histopathology*			
CLL/SLL	1	1	-
LPL	1	-	1
MCL	6	3	3
FCCL grade I	5	5	-
FCCL grade II	2	2	-
FCCL grade III	5	3	2
MALT (small cell)	1	1	-
Plasmacytoma	1	1	-
DLBCL	45	31	14
MF	1	1	-
PTCL	4	3	1
ATL	1	1	-
ALCL	5	5	-
EATC	1	1	-
Transformation from low grade NHL	13	12	1
No. of extranodal sites			
0-1	65 (82)	48 (83)	17 (81)
>1	14 (18)	10 (17)	4 (19)
LDH			
Normal	37 (47)	26 (45)	11 (52)
Elevated	42 (53)	32 (55)	10 (48)

**According to the REAL classification;[16] CLL: chronic lymphocytic leukemia, SLL: small lymphocytic lymphoma, LPL: lymphoplasmacytoid lymphoma, MCL: mantle cell lymphoma, FCCL: follicular center cell lymphoma, MALT: extranodal marginal zone B-cell lymphoma, DLBCL: diffuse large B-cell lymphoma, MF: mycosis fungoides, PTCL: peripheral T-cell lymphoma, ATL: adult T-cell lymphoma, ALCL: anaplastic large cell lymphoma, EATC: enteropathy associated T-cell lymphoma.*

Of the 79 patients who started EMP, 38 patients received at least 3 cycles and 9 patients completed 6 cycles of EMP according to the planned schedule. The main reason for stopping EMP treatment prematurely was progressive disease. The overall response rate was 38%, i.e. 9% CR and 29% PR. The median follow-up of the 27 patients still alive is 14 months. The progression-free survival (PFS) of responding patients is 54% at 12 months and 35% at 24 months from the date of response (Figure 1). The overall survival at 12 and 24 months is 41% and 31%, respectively (Figure 2a). WHO performance status 2-4 (p<0.001), elevated serum LDH (p=0.001) and age below 60 years (p=0.002) were negative prognostic factors for the probability of achieving a response to EMP therapy. Although the performance status and

Table 2. Treatment before EMP.

Therapy	No. of patients								
	First line			Second line			Third line		
	All	≤60	>60	All	≤60	>60	All	≤60	>60
CHOP	61	43	18	6	4	2	5	5	–
CVP	10	9	1	2	2	–	–	–	–
DHAP	–	–	–	14	13	1	3	3	–
PSCT	–	–	–	1	1	–	1	1	–
Other	8	6	2	12	11	1	2	2	–

CHOP: cyclophosphamide, doxorubicin, vincristine and prednisone; CVP: cyclophosphamide, vincristine and prednisone; DHAP: dexamethasone, high-dose Ara-C, cisplatin; PSCT: high-dose therapy plus peripheral blood stem cell transplantation; other: fludarabine; pentostatin; leukeran; leukeran + prednisone; CEMP (cyclophosphamide, etoposide, mitoxantrone, prednisone); total body irradiation. Localized radiotherapy as a prior treatment is not included.

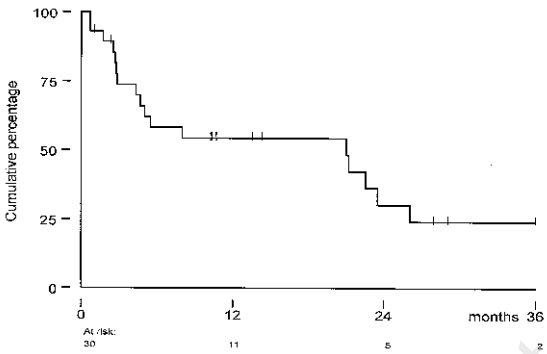

Figure 1. Kaplan-Meier curve of progression-free survival for patients who achieved a PR or CR on EMP.

serum LDH were associated with each other (p<0.01), they retained a statistical significance in multivariate logistic regression with p<0.01 and p=0.03, respectively. Univariate analysis showed that WHO performance status 2-4 and an elevated serum LDH were strong adverse prognostic factors for overall survival with p values <0.00001, and they remained statistically significant in the multivariate Cox regression with p<0.00001 and p<0.0001, respectively (Figures 3a and 3b). There was a trend towards a better survival in patients who had achieved a CR on prior treatment (median survival 17 months with CR versus 5 months without prior CR, p=0.07).

Elderly patients usually have a lower response rate and suffer more toxicity on chemotherapy regimens than younger patients. Therefore we analyzed the results in the patients >60 years as a separate group. In the 21 elderly patients the CR and PR rates were 19% and 48% (response rate = 67%) respectively. The overall survival at 24 months was 49% (Figure 2b).

The hematologic toxicity was low, as shown in Table 3. There have been 28 documented infections (Table 4). Thirty patients have been admitted to hospital, 13 because of a documented infection, 8

Table 3. White blood cell and platelet nadirs per EMP cycle.

Cycle	I	II	III	IV	V	VI
Number*	79 (5)	63 (6)	38 (6)	27 (8)	15 (6)	9 (4)
Leukocyte nadir x10^9/L						
Median	1.2	1.5	1.7	1.5	1.4	1.6
Range	0.1-145	0.1-395	0.2-14.5	0.3-6.0	0.4-16.0	0.8-4.8
Platelet nadir x10^9/L						
Median	92	108	86	111	83	128
Range	3-691	7-900	8-364	22-326	39-285	75-151

**The number of cycles administered, in brackets the number of cycles for which the nadir is unknown.*

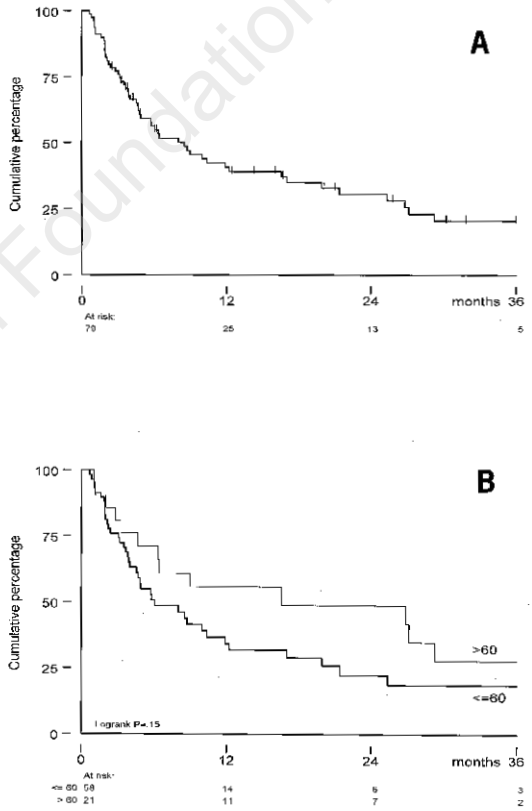

Figure 2. Kaplan-Meier curve of overall survival. A: all patients. B: by age group: ≤ 60 years and >60 years.

because of fever of unknown origin, and most others because of progressive disease. The patterns of toxicity in the elderly were not different from those in the younger patients. In 11 of the 77 cycles given to elderly patients infections of CTC grade ≥ 2 occurred. Other toxicity exceeding CTC-grade 1 was rarely observed. Gastro-intestinal toxicity was encountered after 3 cycles. One elderly patient presented with cardiac toxicity grade 3 due to heart failure in a period

Table 4. Infections.

*Infections**	*No. of cycles (%)*		
	All patients	≤ 60 years	>60 years
grade 2	17/231 (7)	12/154 (8)	5/77 (7)
grade 3	9/231 (4)	5/154 (3)	4/77 (5)
grade 4	2/231 (1)	-	2/77 (3)

**According to the Common Toxicity Criteria.[17]*

of fever. No neurologic or pulmonary toxicity has occurred. No toxic deaths were observed.

Thirty-five patients received further treatment after EMP. Sixteen patients received radiotherapy, 8 patients received another chemotherapy regimen, 3 received both of these treatments. The clinical condition of 8 responsive patients improved in such a way that it was decided to treat these individuals with HDT followed by autologous blood stem cell transplantation after 3 cycles of EMP.

Discussion

The EMP regimen consisting of etoposide, mitoxantrone and prednisone proved to be an effective schedule for refractory or relapsed non-Hodgkin's lymphoma, considering these patients did not qualify for HDT and stem cell transplantation. The overall response rate of 38% is comparable to that achieved by other salvage therapies, which have shown response rates of 40 to 60% in pretreated

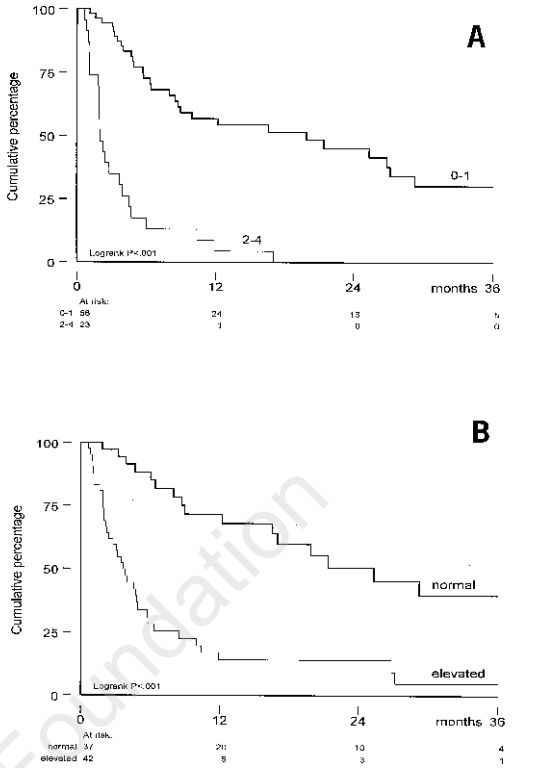

Figure 3. Kaplan-Meier curve of overall survival by prognostic features. A. WHO performance status 0-1 versus 2-4. B. LDH at start of EMP, normal versus elevated.

Table 5. Treatment results with etoposide / mitoxantrone chemotherapy regimens.

	Schedule	*No. of patients median age (range)*	*Response rate*	*Median OS (months)*	*Remarks*
EMP	E: 350 mg/m² i.v. day 1 M: 14 mg/m² i.v. day 1 P: 80 mg/m² p.o. day 1-5	79/53 (24-77)	38%	9	6 cycles @ 3 weeks, on outpatient basis, 79 pretreated patients, 71 aggressive NHL
MVP[20]	E: 150 mg/m² i.v. day 1; 200 mg/m² p.o. day 3 + 5; M: 7-9 mg/m² i.v. day 1; P: 25 mg p.o. day 1-5	54/75 (64-93)	50%	9	6 cycles @ 3-4 weeks, on outpatient basis, 14 pretreated, patients, 9 aggressive NHL
PEN[21]	E: 50 mg p.o. day 1-4; M: 8 mg/m² i.v. day 1; P: 50 mg/m² p.o. day 1-14	35/75 (67-92)	37%	4+	6 cycles @ 4 weeks, on outpatient basis, 8 pretreated, patients, 8 aggressive NHL
VMP[22]	E: 80 mg/m² p.o. day 1-5; M: 8-10 mg/m² i.v. day 1; Pm:80 mg/m² p.o. day 1-5	48/76 (71-92)	58%	17	3-9 cycles @ 3 weeks, on outpatient basis, 12 pretreated patients, 12 aggressive NHL
VIM[12]	E: 65 mg/m² i.v. day 1-3; M: 3 mg/m² i.v. day 1-3; I: 650 mg/m² i.v. day 1-3 (+ Me: 300 mg 3x/day)	55/66 (18-89)	41%	14	As many cycles as needed @ 3 weeks; 3 days in hospital; 55 pretreated, patients; 33 aggressive NHL

E: etoposide, M: mitoxantrone, P: prednisone, Pm: prednimustine, I: ifosfamide, Me: mesna.

patients.[5,8-10,12] In general, regimens that result in a better response rate also have more extensive toxicity, a significant number of toxic deaths and more hospital admissions. In the present study no toxic deaths were observed. Hematologic toxicity was moderate, while no other significant toxicity was observed, even in heavily pretreated patients.

In Table 5 we compare the results of the published trials with etoposide and mitoxantrone. The response rates are comparable between these studies. However, the overall survival of patients in the present study was longer than in the subcategory of pretreated patients in other studies.

In patients aged 50-65 years treatment-related mortality (TRM) of HDT and autologous transplantation is double that in patients <50 years.[19] Many institutions do not include patients >60 years of age in a transplant program. Therefore, we analyzed response and toxicity in the small subgroup of patients over 60 years old separately. These elderly patients responded well to EMP and no differences from younger patients were observed. It should be emphasized that the younger patients generally had received more extensive pretreatment. Indeed, 34% of the younger patients had received 2 and 19% had received 3 prior regimens. Only 19% of the elderly patients had received 2 prior regimens (Table 2).

The main reason for stopping EMP treatment prematurely was progressive disease. Within these limits, 29% of the elderly, as opposed to 5% of the younger patients, could complete all 6 cycles of EMP. The majority of these patients completed the treatment at the cost of only minor toxicity, which did not increase with age.

WHO performance status 2-4 and elevated serum LDH before the first EMP cycle were significant adverse prognostic factors for survival and response. It is well known that the LDH level is an important indication of tumor mass and turnover. Poor performance status and elevated LDH are adverse prognostic factors in the IPI.[18] In this study none of the patients with both performance status >1 and elevated LDH responded to the treatment (14 patients ≤ 60 years, 4 patients >60 years).

In conclusion, the EMP regimen is well tolerated and can easily be administered on an outpatient basis. It seems especially adequate as a salvage regimen for patients who do not qualify for HDT, because of the acceptable toxicity and relatively long median survival it produces in these patients. WHO performance status and serum LDH are valuable predictors of response and survival in order to select those patients most likely to benefit from EMP salvage therapy.

Contributions and Acknowledgments

JKD, PS, MBV and BL designed the study. PHS and JKD collected the clinical data. JKD and BH did the analyses. JKD and PHS wrote the manuscript, which was reviewed by PS and BL. LB was the review-pathologist.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

- EMP is a salvage regimen designed for patients with relapsed or refractory NHL who are not suitable candidates for intensive chemotherapy. It is easily administered on an outpatient basis. The toxicity is low, even in elderly patients.

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