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ORIGINAL ARTICLE

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Long-term results of dose density therapy in patients with aggressive lymphoma

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Abstract To evaluate the long-term outcome of dose density chemotherapy in the treatment of aggressive lymphoma, we analyzed 142 patients with untreated aggressive lymphoma. Chemotherapy was an eight-drug regimen given in weekly intervals in two prospective trials. The median observation period was 8 years; the longest follow-up was 13 years. Overall survival at 8 years was 0.583. The 8-year survival of patients ≤60 years was significantly better than that of older patients, namely 0.713 vs 0.304 (p=0.000000697). This excellent survival of patients aged ≤60 years was identical for high-risk and high-intermediate-risk patients compared with low-risk and low-intermediate-risk patients in the age-adjusted international prognostic index (IPI). The excellent long-term results of the CEOP/IMVP-Dexa regimen (cyclophosphamide, epirubicin, vincristine, and prednisone/ifosfamide with systemic mesna, methotrexate, etoposide, and dexamethasone) for patients aged ≤60 years suggest that this regimen might be superior to the standard CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone) and needs to be tested in comparison to high-dose regimens and novel approaches including antibody treatment.

Keywords Lymphoma · Large-cell lymphoma · Drug therapy · Antineoplastic combined chemotherapy protocols

Conflict of interest: there are no conflicts of interest.

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Introduction

Aggressive non-Hodgkin's lymphoma (NHL) is a fatal disease. Survival depends on the histological subgroup [20] and the international prognostic index (IPI) [19]. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is the current standard in first-line treatment of aggressive lymphoma. Despite a high remission rate, more than 50% relapse and will eventually die.

So far it has not been possible to show that more intensive standard dose regimens achieve better survival than CHOP [12]. CEOP/IMVP-Dexa (cyclophosphamide, epirubicin, vincristine, and prednisone/ifosfamide with systemic mesna, methotrexate, etoposide, and dexamethasone) is a multidrug dose density regimen with weekly chemotherapy. It is a hybrid of a CHOP-like regimen fused with IMVP-16. In order to maintain a high-dose density, the doses were not reduced as long as neutrophil counts were higher than 1.0 G/l. With this regimen we were able to achieve a high remission rate, a long time to treatment failure (TTF), and a long time to relapse (TTR) [13]. These

are excellent surrogate markers for the outcome of treatment in aggressive lymphoma. However, overall survival is the most important endpoint. Another concern is long-term toxicity in terms of secondary cancer, which can occur up to 25 years after therapy [17].

Our trials were based on the hypothesis that dose density is an important factor in curing aggressive lymphoma. We started our trials in 1988 and followed this concept over three consecutive trials. After a median observation period of 8 years, the results of the first two trials seem to be stable with no further decrease in the outcome.

Materials and methods

One hundred forty-two patients from two consecutive trials were pooled for this analysis. In the first study, a phase 2 trial from October 1988 to March 1991, we assessed the feasibility, toxicity, and efficacy of this new dose-dense regimen in a multicenter setting [13]. From this study two patients were excluded because of human immunodeficiency virus (HIV)-positive serology. The patients of the second trial (July 1991 to November 1995) were randomized to receive CEOP/IMVP-Dexa with and without filgrastim [14]. The patient population was comparable with inclusion and exclusion criteria identical to the first trial. The endpoint was febrile neutropenia. There was no difference between the two randomized groups in respect of remission rates, TTR, TTF, and survival. Inclusion and exclusion criteria, staging modalities, toxicity, and details of the chemotherapy regimen have been published elsewhere [13, 14]. Both studies were done according to the Helsinki Declaration; the local Ethics Committees of the participating centers approved them. All patients signed a confirmed consent. All patients had a previously untreated aggressive lymphoma. The chemotherapy regimen is outlined in Table 1; no intrathecal prophylaxis was given. Irradiation to residual lymphoma or to regions with bulky disease at diagnosis was allowed and was given on discretion of the treating physician. The longest observation is 13 years; the median observation time for living patients is 8 years.

The median age of the patients was 52 years (range: 19–72 years). Forty-eight patients (33.8%) were >60 years. The number of patients in the low-risk, low-intermediate-risk, high-intermediate-risk, and high-risk groups according to the IPI were 71 (50%), 34 (24%), 25 (18%), and 12 (8%), respectively. Of the 142 patients, 22 (15.5%), 51 (35.9%), 24 (16.9%), and 45 (31.7%) had stage 1, 2, 3, and 4 disease, respectively. Histologies were centrally reviewed. Diffuse large-cell lymphoma was found in 116 patients (81.46%), lymphoblastic B in 5, Burkitt-like in 1, and anaplastic large cell 0-cell primary systemic type in 3 patients. Seventeen (12%) patients had a lymphoma of the T-cell phenotype, two lymphoblastic T, nine peripheral T-cell, and six anaplastic large cell T-cell primary systemic type.

Biostatistics

All eligible patients were included in the analysis. Survival estimates were calculated by the Kaplan–Meier method. Comparison of survival between the different risk groups was done by the log-rank test, between remission rates or other events by the κ^2-test.

The TTR and the TTF were defined as proposed by Dixon et al. [9]. Briefly, survival included all eligible patients and counted all deaths as events. TTF was the time from registration until relapse, progression, toxic death, withdrawal, or the date the patient was last known to be alive, excluding deaths from unrelated causes. TTR was the time from registration until relapse or the date the patient was last known to be alive, including only complete responses (CRs) and counting only relapses as events.

For comparison of the occurrence of second primaries in the study with the expected rate of malignancies in a normal population, an age-adjusted and sex-adjusted sample was used.

Results

One hundred nine patients (76.8%) achieved a complete (CR) and 22 (15.5%) a partial response (PR). Stable disease (SD), and progression (PD) during therapy, was observed in three patients each. Five patients were not evaluable for response, four because of early death and one patient because of loss to follow-up. The mean dose intensity was 74% of the planned dose.

Fifty-four patients (38%) have relapsed to date. Twenty-five (46.3%) relapsed within an originally involved site,

Table 1 Chemotherapy regimen CEOP/IMVP-Dexa

Cyclophosphamide	750 mg/m^2	i.v. 30 min	Day 1
Epirubicin	70 mg/m^2	i.v. 2 h	Day 1
Vincristine	1.4 mg/m^2	i.v. push	Days 1+8
Prednisolone	100 mg	p.o.	Days 1–5
Ifosfamide	2000 mg/m^2	i.v. 30 min.	Days 15–17
Uromitexan	400 mg/m^2	i.v. push at 0, 4, and 8 h after ifosfamide	Days 15–17
VP-16	100 mg/m^2	i.v. 2 h	Days 15–17
Dexamethasone	40 mg	p.o.	Days 15–19
Methotrexate	800 mg/m^2	i.v. 4 h	Day 22
Ca folinate	15 mg/m^2	p.o. every 6 h	Days 23–25

Table 2 Toxic deaths

Age (years)	Histology	IPI	No. of risk factors	No. of days after entry	Cause of death
69	DLBCL	Low	1	11	Pneumonia
59	DLBCL	High	4	12	Neutropenic fever
66	DLBCL	Low-intermediate	2	14	Pulmonary embolism
72	DLBCL	High	4	22	Cardiopulmonary failure
63	DLBCL	Low	1	29	Neutropenic fever
64	Peripheral T-cell	High	3	30	Urosepsis
63	DLBCL	Low	1	51	Colitis, pneumonia
62	DLBCL	High-intermediate	3	63	Pneumonia
52	DLBCL	Low	0	121	Pneumonia
68	DLBCL	Low-intermediate	2	133	Pneumonia

12 (22.2%) within an originally involved site and within an originally uninvolved site, and 11 (20.4%) within an originally uninvolved site. For six patients the site of relapse was unknown. Only two patients had a relapse in the central nervous system (CNS). Of the relapsing patients, 27 (50%), 13 (24%), 6 (11%), 3 (5.6%), and 4 (4.7%) relapsed in the 1st, 2nd, 3rd, 4th, and 5th to 8th year, respectively. The only relapse after 8 years occurred as late as 12 years after study entry. Biopsy results of relapses were not systematically collected. All relapses from which we know that they had a biopsy were of the same histological subtype as the first manifestation.

Fifty-five patients have died: 39 (70.9%) of lymphoma, 10 (18.2%) of toxicity, and 6 (10.9%) due to unrelated causes. The treatment-related death rate was 7%. Eight of ten toxic deaths occurred in patients >60 years (p=0.01667), most of them in the first cycle. IPI score at diagnosis had no influence on toxic deaths (Table 2). Acute toxicity has been reported elsewhere [13, 14].

In 980 patient years, six second primaries occurred. One carcinoma of the bile duct occurred 20 months after entry to the study and the patient died 3 months later. One esophageal carcinoma occurred 42 months after entry and the patient died 52 months later of the tumor. One patient developed a melanoma 6 years after entry into the study, but was lost to follow-up thereafter. One patient was nephrectomized because of a right-sided renal cell carcinoma 90 months after entry to the study. He was free of disease 50 months after the nephrectomy. In one single patient two cancers developed. First, a papillary thyroid cancer 92 months after study entry developed. A thyroidectomy and therapy with radiolabeled iodine were done. The patient was cured from this disease. Consecutively, chronic myeloid leukemia developed 140 months after entry to the study. He was treated with imatinib and hydroxyurea thereafter, never achieved a hematological remission, and died 37 months after the diagnosis of chronic myeloid leukemia. No other long-term toxicities were observed.

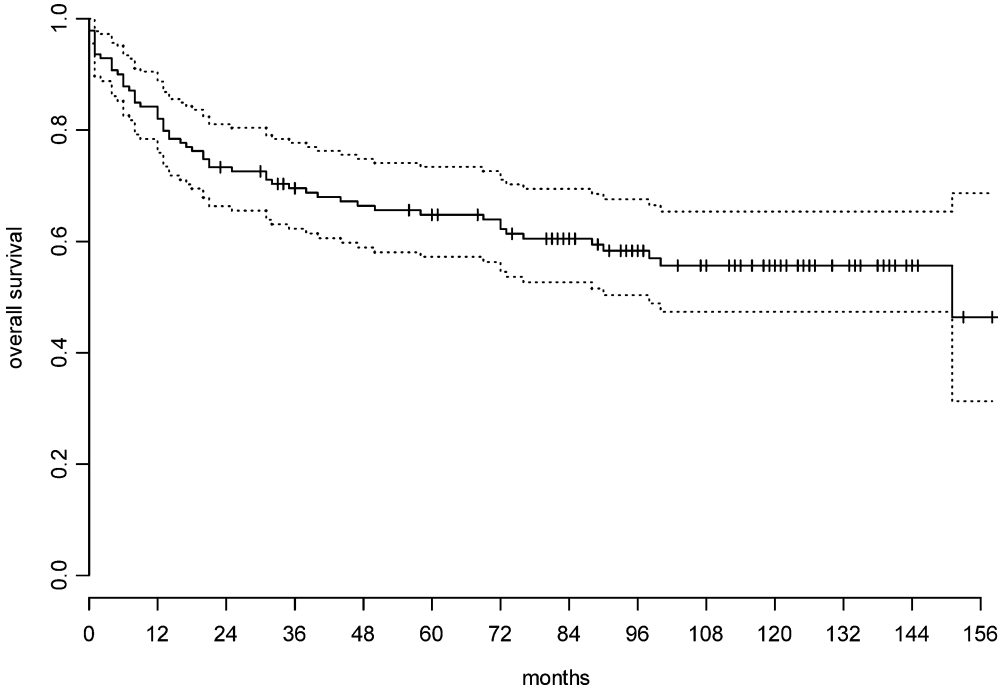

Fig. 1 Overall survival in months. *Dotted lines* 95% CI

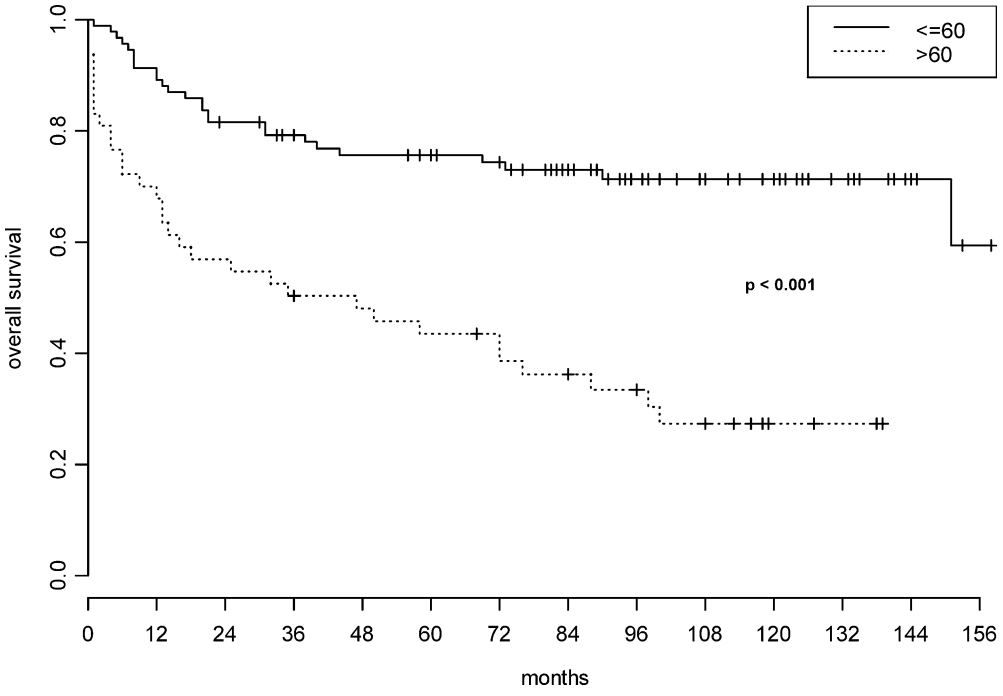

Fig. 2 Overall survival in months according to age

TTR at 8 years for patients with CR was 0.619 [95% confidence interval (CI): 0.53–0.72]. The TTF at 8 years was 0.536 (95% CI: 0.457–0.63). Overall survival at 3, 5, and 8 years was 0.695 (95% CI: 0.623–0.777), 0.648 (95% CI: 0.572–0.7340), and 0.583 (95% CI: 0.503 – 0.665), respectively (Fig. 1).

CR rates for patients ≤60 years were not significantly higher than those for patients >60 years (81.9 vs 66.7%, p=0.25). Overall survival at 8 years for patients ≤60 years was 0.713 (95% CI: 0.662–0.816). In patients >60 years the overall survival was only 0.304 (95% CI: 0.192–0.453). This difference was highly significant (p=0.000000697) (Fig. 2). This difference may be due to several reasons. Only 4 of 16 patients dying of causes other than lymphoma were >60 years. Remissions in elderly patients are not as stable as in younger patients [19]. Salvage regimens are more effective in younger patients; especially high-dose therapy is preferably used in patients ≤60 years of age. Patients in the high-risk IPI group had a significantly worse survival than patients in the other groups. However, there was no difference in overall survival in patients ≤60 years with 0 or 1 point vs 2

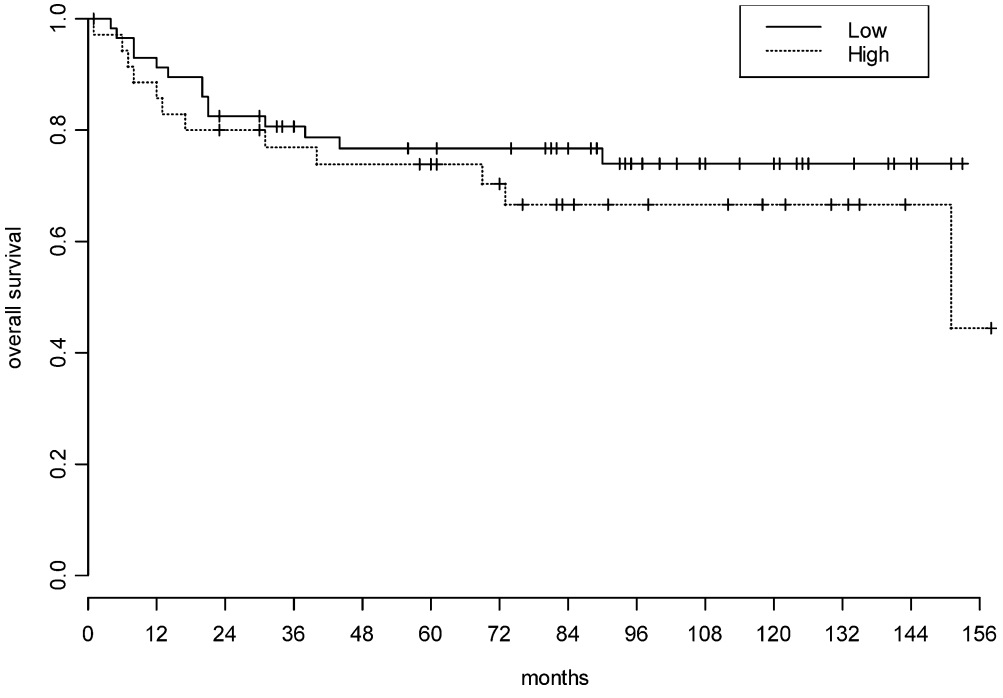

Fig. 3 Overall survival in months according to the age-adjusted IPI for patients ≤60 years [19]. Low=IPI low and low-intermediate (0 or 1 risk factor), high=high and high-intermediate (2 or 3 risk factors)

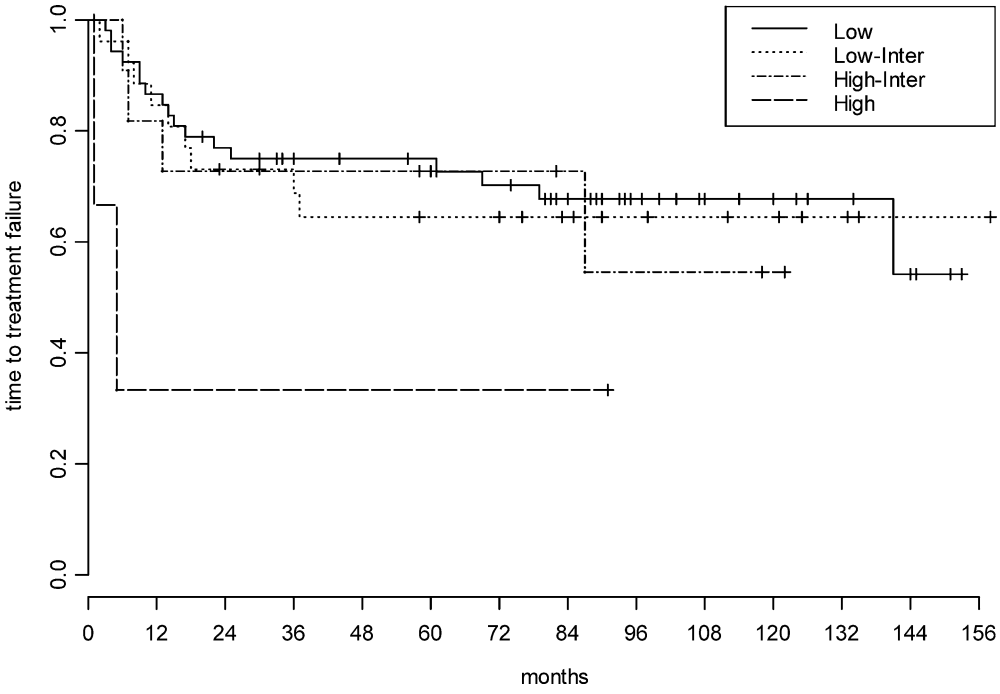

Fig. 4 Time to treatment failure for patients ≤60 years according to age-adjusted IPI (low=0, low-intermediate=1, high-intermediate=2, and high=3 risk factors)

or 3 points according to the age-adjusted IPI (Fig. 3). In terms of TTF for younger patients the IPI did not make a difference (Fig. 4). For older patients there seems to be a difference, but the patient numbers in the different groups was too low to reach statistical difference (Fig. 5). There was no statistically significant overall survival difference between the different histological subgroups (data not shown).

Discussion

A long follow-up is necessary to assess the final value of a treatment regimen in aggressive lymphoma. The results are mature and the final value of this dose density therapy can be assessed. In our analyses 15% of relapses occurred after 3 years of follow-up. This compares well with the outcome of other dose-intense regimens [10, 16].

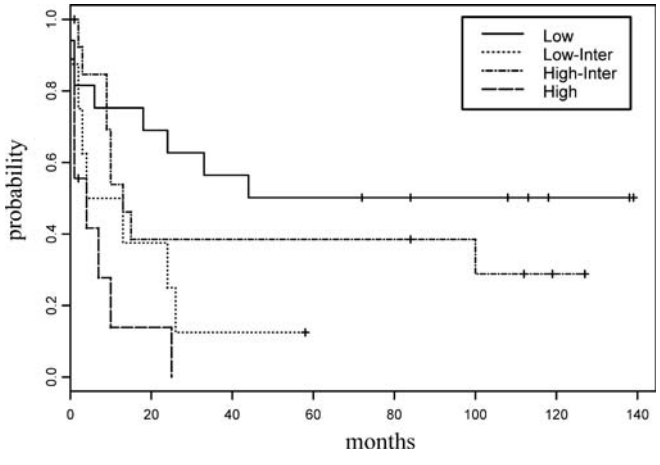

Fig. 5 Time to treatment failure for patients ≤60 years according to IPI (low=0–1, low-intermediate=2, high-intermediate=3, and high=4–5 risk factors)

Patients >60 years had an unacceptably high toxic death rate and did not seem to benefit from this regimen (Fig. 2). Treatment options other than dose density should be used for older patients. Targeted therapy may be one of these strategies [6].

CNS recurrence is common in advanced aggressive NHL. The treatment recommendations for CNS disease are radiotherapy, intrathecal therapy, or intravenous high-dose methotrexate [11]. Usually a methotrexate dose higher than 800 mg/m^2 is necessary to reach adequate levels in the CNS. However, only two CNS relapses occurred in our patients although no intrathecal prophylaxis was given. This is remarkable because 79 patients had stage 3 or 4 and were, therefore, at risk for a CNS relapse. High-dose dexamethasone may have played a role in the low CNS relapse rate. Recently, a lower CNS relapse rate could be found for dexamethasone over prednisone in a randomized trial in children with lymphoblastic leukemia [4].

Second malignancies are a serious concern for all antineoplastic therapies [17]. According to estimates, a cohort of normal persons comparable to the patients treated in our studies would experience 8.8 second malignancies. However, in the present study we encountered six second malignancies. Although the rate of second malignancies is lower than expected for a normal population, even lower incidence rates of 2.75% are described for other dose intensive regimens such as the ACVBP of the GELA Group [1]. It was surprising that we had no patient with myelodysplastic syndrome or acute myeloid leukemia. This may be just by chance because of the low number of patients in comparison to other reports [1].

Although comparisons of different trials are prone to several biases, CEOP/IMVP-Dexa with an overall survival of 58% may be better than the long-term results of the CHOP regimen [12, 8, 2]. An even better survival was observed for patients aged ≤60 years, including those in the high-risk and high-intermediate-risk groups of the age-adjusted IPI [19] [(Figs. 2, 3)]. For these patients, high-dose chemotherapy with stem cell support has proven to be without any benefit in the majority of the trials [7]. Similarly, dose intensification after incomplete chemotherapy could not improve the results [15]. The same is true for dose intensification in slowly responding patients [21]. However, several lines of evidence point to a role of early dose intensification [3, 5]. The German Non-Hodgkin's Lymphoma Study Group reported a significant improvement of the CR rate and the 5-year event-free survival but not for overall survival by adding etoposide to the CHOP regimen for patients ≤60 years of age with a normal lactic dehydrogenase (LDH) level [18]. These studies are supported by our data, where patients ≤60 years in the high-risk and intermediate-high-risk groups according to the age-adjusted IPI [19] achieved a long-term survival rate as good as that of the low-risk patients receiving dose density therapy (Fig. 3).

Several biases can influence comparisons between different trials. To prove the superiority of CEOP/IMVP-Dexa, we recently finished accrual to a randomized trial with standard CHOP. Final results are pending.

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