Stage I Non-Hodgkin's Lymphoma Treated with Doxorubicin-containing Chemotherapy with or without Radiotherapy

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Seventy-six patients with stage I or IE intermediate-grade or immunoblastic non-Hodgkin's lymphoma were treated with a short course of doxorubicin-containing chemotherapy with (n = 58) or without (n = 18) involved field radiotherapy. Chemotherapy consisted of 3 or 4 cycles of M-BACOD or (bleo-)CHOP. Seventy-two (97%) of the 74 evaluable patients achieved a complete response. The 3-year overall survival was 89%, recurrence-free survival 94%, and lymphoma-specific survival 93%. Patients older than 60 years also had a 3-year lymphoma-specific survival rate of as high as 92%. The International Prognostic Index was associated with overall survival (p = 0.04), but not with lymphoma-specific survival (p = 0.18). We conclude that stages I and IE intermediate-grade or immunoblastic non-Hodgkin's Hodgkin's lymphoma is highly curable if treated with short doxorubicin-containing chemotherapy and involved field radiotherapy.

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In the 1970s localized intermediate-grade non-Hodgkin's lymphomas were usually treated with radiotherapy alone. The effectiveness of radiotherapy is dependent on the accuracy of staging (1). The long-term recurrence-free survival rate achieved by radiotherapy alone is about 70% when staging includes laparotomy, but in clinically staged patients the 5-year survival rates range only from 25% to 60% (2–4). These results suggest that intermediate-grade non-Hodgkin's lymphoma is often disseminated even when it appears to be local. Significantly better treatment results have been reported when up-front chemotherapy has been combined with radiotherapy, with long-term complete response rates ranging from 80 to 95% (5–8).

It has long been debated whether radiotherapy is needed after chemotherapy in the treatment of stage I or IE lymphoma (6, 8). However, if radiotherapy is given after chemotherapy, it may be possible to reduce the number of chemotherapy cycles from 6–8 to 3 or 4 cycles (9–10) even though only small radiotherapy fields are used (10). Chemotherapy regimens that contain an anthracycline are generally regarded as the most effective ones (11–12).

Because the optimal treatment of stage I or IE intermediate-grade or immunoblastic non-Hodgkin's lymphoma is not settled, we report here the results of a retrospective study on 76 patients treated at two university centres. The patients were treated with a combination of a doxorubicin-containing chemotherapy regimen with or without involved field radiotherapy. The results indicate that stage I or IE intermediate-grade or immunoblastic non-Hodgkin's lymphoma is a highly curable disease if treated in this manner.

MATERIAL AND METHODS

Patients

One hundred and six patients with stage I or IE intermediate-grade or immunoblastic non-Hodgkin's lymphoma located outside the central nervous system were treated in the Department of Oncology, Helsinki University Central Hospital, in 1988 to 1995 (n = 79) or in the Department of Oncology, Turku University Central Hospital, Finland, in 1991 to 1995 (n = 27). These time intervals were chosen because during these time periods in both hospitals most of the patients with stage I disease were treated with short doxorubicin-containing chemotherapy followed by involved field radiotherapy. Seventy-six of these patients

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were treated with a maximum of 4 cycles of M-BACOD (n = 40), CHOP (n = 29), or bleo-CHOP (n = 7) with (n = 58) or without (n = 18) involved field radiotherapy, and form the basis of the present study. The rest of the patients (n = 30) did not receive chemotherapy at all (n = 16), received some kind of chemotherapy combination other than M-BACOD, CHOP, or bleo-CHOP (n = 5, five different combinations), or received more than 4 cycles of chemotherapy (n = 9). The median follow-up time of living patients was 38 months (range, from 6 to 79 months). The patients were followed-up in an out-patient department at intervals of a few months.

Staging was carried out according to the Ann Arbor criteria (13). The staging examinations included physical examination, chest x-ray, bone-marrow aspiration and biopsy, computerized tomography of the chest and the abdomen, a complete blood count, and blood chemistry. Computerized tomography of the affected site was carried out if lymphoma was located outside the torso. Staging laparotomy was not performed.

The biopsy specimens were evaluated by a pathologist specialized in lymphoma pathology. The histologic diagnosis was made according to the modified Kiel's classification (14) and the International Working Formulation (15). The International Prognostic Index was calculated as described elsewhere (16). The patient characteristics are presented in Table 1.

Treatment

The CHOP regimen consisted of cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 given on day 1, and prednisone 50–100 mg given on days 1 to 5. The cycle was repeated at 3-week intervals. The patients who received bleo-CHOP were given 15 mg bleomycin on days 1 and 5. The M-BACOD regimen consisted of bleomycin 4 mg/m^2, doxorubicin 45 mg/m^2, vincristine 1 mg/m^2 on day 1, dexamethasone 6 mg/m^2 on days 1 to 5 and methotrexate 3 000 mg/m^2 with a leucovorin rescue on day 14. The cycle was repeated at 3-week intervals. The majority of the patients (89%) received either 3 (n = 51) or 4 cycles (n = 17) of chemotherapy, whereas chemotherapy was discontinued after 1 or 2 cycles in 8 (11%) cases. Three of these 8 patients wanted to withdraw, 1 patient died of treatment after 2 cycles, and in 4 cases the physician discontinued chemotherapy because of toxicity.

Radiotherapy was started about 4 weeks after the last cycle of chemotherapy and was applied to the clinically involved site at a median total tumour dose of 40 Gy (range, from 20 to 50 Gy, 3 patients received less than 36 Gy and 3 more than 45 Gy), with 2 Gy daily fractions 5 days a week with a linear accelerator. The radiotherapy portal included the lymph node region with clinically enlarged nodes or an extranodal tumour plus a margin of uninvolved tissue. The width of the margin was decided on by the radiotherapist in charge. Sixteen (89%) of the 18 patients who did not receive radiation therapy had lymphoma macroscopically completely removed at surgery before chemotherapy was initiated. In addition, in 9 of these 18 cases the site was considered unfavourable for radiotherapy (the intestine, n = 7; testicle, n = 2). Eighteen of the 34 patients who had all macroscopical lymphoma deposits removed at surgery received radiotherapy.

An assessment of the treatment response was made after radiotherapy. This included a physical examination, blood tests, and a computerized tomography or an ultrasound examination of the affected site. A complete response (CR)

Table 1

Characteristics of the patients

Variable	n (%)
Gender	
Male	35 (46)
Female	41 (54)
Age	
Median	60
Range	20–83
≤60	39 (51)
>60	37 (49)
B-symptoms	
Yes	7 (9)
No	69 (91)
International Prognostic Index	
0	32 (53)
1–2	28 (47)
Not available	16
Histology	
Centroblastic diffuse	28 (37)
Centrocytic/centroblastic diffuse	17 (22)
Centrocytic diffuse	6 (8)
Large cell anaplastic	6 (8)
Immunoblastic	5 (7)
Other, intermediate grade	14 (18)
Tumour bulk	
≤5 cm	40 (70)
>5 cm	17 (30)
Not available	19
Nodal disease sites	
Neck	14
Inguinal	8
Axillary	5
Submandibular	4
Other	5
Total	36 (47)
Extranodal disease sites	
Gastric	11
Skin	5
Tonsils	5
Thyroid	4
Testis	2
Other	13
Total	40 (53)

was considered to have been achieved if there was no evidence of a residual tumour.

Statistical analysis

Statistical analyses were carried out with the BMDP computer program (BMDP Statistical Software, Department of Biomathematics, University of California, Los Angeles, CA). Frequency tables were analysed with the χ^2 test or Fisher's exact test. Age distributions were compared with the Mann-Whitney test. Overall survival was measured from the time of initiation of lymphoma treatment until death or the last date of follow-up. Lymphoma-specific survival was measured from the time of initiation of treatment until death caused by lymphoma or by treatment of lymphoma, or to the last date known alive. Relapse-free survival was calculated for those patients who achieved a CR, and it was measured from the time of initiation of treatment until relapse or the last date known free of disease. Cumulative survival was estimated with the product-limit method, and comparison of survival between the groups was performed with the log-rank test. All p-values are 2-tailed.

RESULTS

Ten (13%) of the 76 patients died during follow-up. Two patients (3%) died during treatment, and were considered to have died of treatment-related infection. Three patients (4%) died from progressive lymphoma. Two of these 3 patients had diffuse centrocytic and 1 diffuse centrocytic-centroblastic lymphoma. Five patients died of an intercurrent cause.

The estimated overall 3-year and 5-year survival rates were 89% (95% confidence interval, 81%–97%) and 82% (71%–93%), respectively, and the 3- and 5-year lymphoma-specific survival rates were both 93% (87%–99%, Fig. 1). Seventy-four patients were alive at the end of treatment and were evaluable for treatment response. Seventy-two (97%) of the 74 evaluable patients achieved a complete response (CR) after therapy. The recurrence-free 3- and 5-year survival rates of these 72 patients were 94% (88%–99%) and 87% (76%–98%), respectively (Fig. 2).

The 5-year overall survival rate of the patients who were over 60 years of age at diagnosis was 73% compared with 94% among those who were 60 or younger ($p = 0.08$), but there was no difference in lymphoma-specific survival between these age groups (92% vs. 94%, respectively, $p = 0.52$), or in recurrence-free survival (91% vs. 84%, respectively, $p = 0.40$). There was no significant difference in overall and lymphoma-specific survival rates between the patients who were treated with M-BACOD and those who were treated with CHOP or bleo-CHOP, although the patients treated with CHOP or bleo-CHOP were older than the patients treated with M-BACOD (median age, 67 vs. 53.5 years, respectively, $p = 0.006$). Similarly, there was

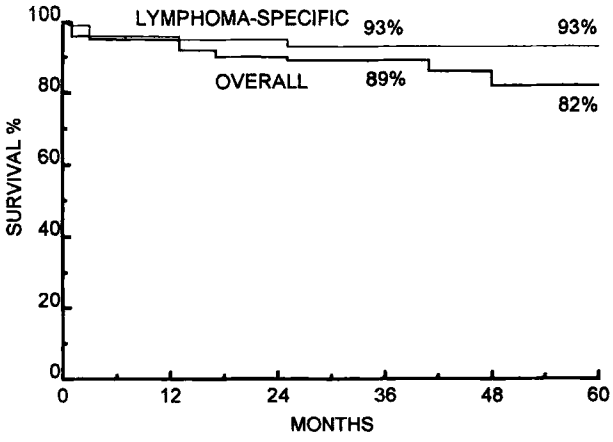

Fig. 1. Overall and lymphoma-specific survival of 76 patients with stage I intermediate-grade or immunoblastic non-Hodgkin's lymphoma treated with a short course of doxorubicin-containing chemotherapy with or without involved field radiotherapy. The 3- and 5-year survival figures are shown.

no difference in survival or lymphoma-specific survival between patients who were treated with both chemotherapy and radiotherapy and those treated with chemotherapy alone, but more patients who did not receive radiotherapy had all macroscopic lymphoma deposits completely removed by surgery before starting chemotherapy (16 out of 18 vs. 18 out of 58, $p < 0.0001$).

The patients who had the International Prognostic Index score 0 at presentation ($n = 32$) had a 3-year overall survival rate of 95% compared with 82% among those who had a score greater than 0 ($n = 28$, $p = 0.04$). However, there was no statistical difference between these two groups when lymphoma-specific survival was analysed (95% vs. 89%, respectively, $p = 0.18$). There was no statistically significant difference in overall survival by gender,

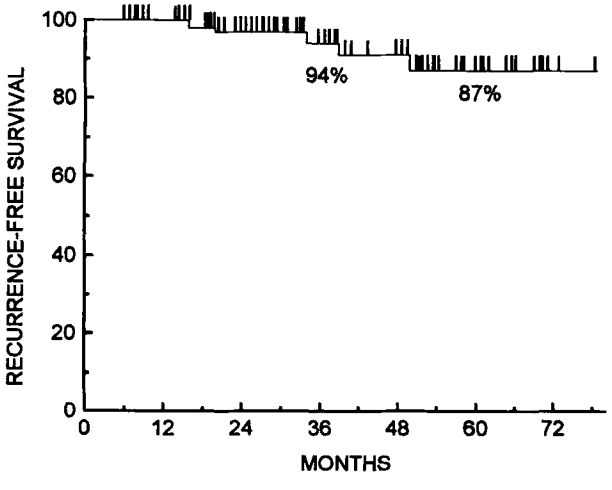

Fig. 2. Recurrence-free survival of the 72 patients who achieved a complete response to therapy and who were alive at the end of therapy. The patients without a recurrence are indicated with a bar. The 3- and 5-year survival figures are shown.

Table 2

Overall survival by nine prognostic factors

Factor	n	3-year survival (%)	p-value
International Prognostic Index Score			
0	32	95	
1–2	28	82	0.04
Age at diagnosis			
≤60	39	94	
>60	37	84	0.08
WHO performance status			
0	41	94	
1–3	23	80	0.09
Serum LDH[1] level			
Normal (<440 U/l)	60	89	
>Normal	10	80	0.30
No. of extranodal sites			
0	36	89	
1 or more	40	87	0.39
Serum thymidine kinase level			
≤ Median (5 U/l)	39	89	
>Median	15	86	0.56
B-symptoms			
No	69	89	
Yes	7	86	0.60
Gender			
Male	35	91	
Female	41	87	0.78
Chemotherapy dose reduction			
No	41	88	
Yes	34	91	0.96

[1] LDH, lactate dehydrogenase

median age, presence of B-symptoms (unexplained fever higher than 38°C, loss of more than 10% of the body weight within 6 months, or night sweats), the number of extranodal sites, WHO performance status, serum lactate dehydrogenase (LDH) or serum thymidine kinase level, or if chemotherapy doses had been reduced during treatment (n = 34) or not (n = 41; unknown, n = 1; Table 2).

Forty (53%) of the 76 patients did not experience any major toxicity. The most common toxicity causing alteration of the treatment schedule was leukopenia. M-BACOD was more toxic than (bleo-)CHOP. Twenty-nine major toxic events resulting in either chemotherapy dose reduction or interruption of the planned treatment schedule were encountered among the 40 patients treated with M-BACOD compared with 11 events among the 36 patients treated with the (bleo-)CHOP regimen (p = 0.0003, Table 3).

DISCUSSION

The present results show that stage I or IE intermediate-grade non-Hodgkin's lymphoma is a highly curable disease. The overall 5-year survival rate was 82% and the lymphoma-specific survival rate as high as 93%. These figures are comparable with those of the other studies where localized non-Hodgkin's lymphomas have been treated with chemo- and radiotherapy (5–8, 12, 17–19). However, many of these studies have included both stages I and II lymphomas, intermediate- and high-grade histologies have often been dealt together, and the median age of the patients in different series may have varied markedly, which makes comparison of the results difficult. Moreover, the type of chemotherapy, the number of cycles given, the total dose of radiotherapy, and the field sizes may have varied. The present study provides results from a more uniform series where only adult patients with stage I lymphoma with intermediate-grade or immunoblastic histology have been included.

Results reported from studies where radiotherapy alone has been given are not as favourable as those obtained with a combination of chemo- and radiotherapy. The recurrence-free 5-year survival figures have ranged from 25 to 95% and overall survival figures from 35 to 95% when localized intermediate- or high-grade non-Hodgkin's lymphoma has been treated with radiotherapy alone (4, 20–24). However, many studies where radiotherapy alone has been given are old, and therefore the staging examinations performed may have been inferior to the ones currently available, which may have resulted in more frequent inclusion of patients with disseminated disease in the radiotherapy series. In a more modern series a 70% relative survival rate was achieved in high-grade stage I non-Hodgkin's lymphoma treated with radiotherapy alone (25).

An advantage of the combination approach is that only a short course of chemotherapy (3–4 cycles) and a relatively small radiotherapy field seem to be sufficient, which may improve treatment tolerance. Several authors have suggested that chemotherapy alone might be an adequate treatment for stage I intermediate-grade non-Hodgkin's lymphoma, at least in some subsets (6, 8, 17). In the present study 18 patients did not receive radiotherapy

Table 3

Major toxicity, which resulted in dose reduction or interruption of chemotherapy

Toxicity	M-BACOD (n = 40) n (%)	(bleo-)CHOP (n = 36) n (%)
No major toxicity	14 (35)	26 (72)
Leucopenia (Gr IV)	10 (25)	3 (8)
Leucopenia + infection	8 (20)	2 (6)
Infection, other	4 (10)	0 (0)
Reduced renal function		
S-crea > 120 mmol/l	2 (5)	0 (0)
Neuropathy	2 (5)	3 (8)
Other major toxicity	3 (8)	3 (8)
Total	29[1] (73)	11[2] (31)

[1] 3 patients experienced two major toxic events
[2] 1 patient experienced two major toxic events

because lymphoma was completely removed at surgery and/or due to an unfavourable anatomical location of the tumour for radiotherapy, and no difference in survival was found between patients who received radiotherapy and those who did not These results perhaps suggest that radiotherapy may be omitted if macroscopic lymphoma is completely removed by surgery.

Anthracycline-containing chemotherapy regimens have been found to be more effective than some regimens not containing an anthracycline in the treatment of non-Hodgkin's lymphoma (11–12). Studies comparing the traditional CHOP treatment with the later generation chemotherapy regimens, such as m-BACOD or MACOP-B, have failed to show superiority of the latter ones (26–27). We found a 3-year lymphoma-specific survival of 86% among the patients treated with CHOP, which suggests that this chemotherapy regimen of only moderate toxicity is effective in most patients with stage I intermediate-grade or immunoblastic non-Hodgkin's lymphoma.

There was no difference in lymphoma-specific survival between patients who were 60 years of age or younger at the time of the diagnosis and those who were older than this. It is worth noting that 3- and 5-year lymphoma-specific survival was as high as 92% even among the patients older than 60, which underlines the importance of treating local intermediate-grade non-Hodgkin's lymphoma effectively even in elderly patients. Treatment-related mortality was no greater among the patients older than 60 (one out of 37, 2.7%) than among the patients younger than this (one out of 39, 2.6%). The elderly patients were, however, treated less often with M-BACOD than the younger ones.

Owing to the small number of deaths from lymphoma, no prognostic factors could be identified in univariate survival analyses, and for the same reason no multivariate survival analyses could be carried out. The International Prognostic Index appeared as a significant prognostic factor in a univariate survival analysis when overall survival was used as the endpoint, but it, too, lost its prognostic value when lymphoma-specific survival was analysed, suggesting that some of its prognostic value was derived from intercurrent deaths.

We conclude that stage I and IE intermediate-grade non-Hodgkin's lymphoma is a highly curable disease. Short doxorubicin-containing chemotherapy with involved field radiotherapy is an effective and usually well-tolerated treatment for this disease. A short chemotherapy with CHOP followed by involved field radiotherapy may be regarded as the standard therapy because of its good efficacy and generally low toxicity. Omission of radiotherapy may be possible in cases where all macroscopic lymphoma deposits have been removed by surgery, but this requires further study.

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