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Original article

Combined modality treatment with a weekly brief chemotherapy (ACOP-B) followed by locoregional radiotherapy in localized-stage intermediate- to high-grade non-Hodgkin's lymphoma

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Summary

Background: A cooperative study was undertaken to evaluate the efficacy and toxicity of a very brief course of chemotherapy followed by locoregional radiotherapy in patients with localized-stage intermediate- to high-grade non-Hodgkin's lymphoma (NHL).

Patients and method: From January 1988 to November 1994, 84 patients with localized stages IA and IIA intermediate- to high-grade NHL underwent a combined modality treatment. All patients underwent a six-week chemotherapy regimen, ACOP-B (doxorubicin 50 mg/sqm and cyclophosphamide 350 mg/sqm on weeks 1, 3, 5; vincristine 1.4 mg/sqm and bleomycin 10 mg/sqm on weeks 2, 4, 6; prednisone 50 mg p.o. daily throughout the first two weeks and thereafter every other day), followed by locoregional radiotherapy (36 Gy).

Results: The median age was 58 years, with 35% older than 65 years; 52 patients had stage I and 32 stage II; 39 patients had extranodal ± nodal involvement, and 4 had testicular involvement. Treatment was well tolerated, with only 38% suffering from mild mucositis and no toxic deaths. Seventy-nine patients achieved CR after ACOP-B and 83 at the end of the program. With a median follow-up of four years, relapse-free survival was 79% with 15 relapses (93% disseminated). Two patients with testis lymphoma had CNS relapses. Overall survival was 90% at four years.

Conclusion: This combined program is effective and probably curative in localized stage intermediate- to high-grade NHL, with low toxicity, also in elderly people. Patients with NHL of the testis, as primary site, require CNS prophylaxis due to the high likehood of CNS relapse.

Key words: chemotherapy plus radiotherapy, intermediate- to high-grade NHL, localized

Introduction

Approximately 25%–30% of patients with intermediate- to high-grade NHL at diagnosis appear, upon clinical staging, to have a localized stage of the disease [1, 2].

Until 15 years ago the treatment of choice for these patients was radiotherapy alone. However, the incidence of relapses was reported to be high (50%–70%), expecially for patients staged only clinically without laparotomy [3, 4]. Distant relapses were frequently observed after primary radiotherapy or even during the irradiation program [5, 6]. In subsequent studies a combined modality approach with prior chemotherapy plus locoregional radiotherapy was investigated [6–13]. The addition of chemotherapy was based on the observation that the majority of relapses were disseminated [7].

At the beginning of the 1980s, three randomized studies [7–9] showed the superiority of a combined approach with chemotherapy plus radiotherapy *versus* radiotherapy alone in terms of relapse-free survival (RFS) and overall survival.

More recent studies using anthracycline (doxorubicin, epirubicin) [6, 10–12] containing regimens (CHOP-like) with or without radiotherapy, confirm these observations. The complete remission rate was high, usually over 95%, and the RFS ranged between 60% and 85%. However, the length of chemotherapy used varied among studies from three to eight courses.

To maintain a similar efficacy, while reducing toxicity and the time of the treatment, a brief combined modality treatment consisting of a six-week chemotherapy regimen, ACOP-B, originally described by Connors et al. [13], followed by locoregional radiotherapy, was investigated. Here we report the results achieved in 84 patients with localized intermediate- to high-grade NHL.

Patients and methods

A cooperative trial was initiated for the treatment of localized stage intermediate- to high-grade non-Hodgkin's lymphoma (NHL). From January 1, 1988 to November 30, 1994, 84 patients with stages I and II nodal and extranodal lymphoma were treated with ACOP-B chemotherapy followed by locoregional radiotherapy (RT). They were followed through December 31, 1995 or until death.

The criteria for inclusion were: a histologic diagnosis of intermediate- to high-grade NHL according to the Working Formulation [2] (WF) (diffuse mixed 'F', diffuse large cleaved or non-cleaved 'G', immunoblastic 'H'); lymphoblastic, Burkitt's and Burkitt's-like lymphomas were excluded; age between 15 and 80 years; no systemic B-symptoms; perfomance status less than 3 on the Eastern Cooperative Oncology Group (ECOG) scale; and no past or present medical history of severe cardiac, renal or hepatic disease. Patients were required to have localized stages I or II disease according to the Ann Arbor criteria [32]. Patients with primary gastrointestinal lymphoma or more than three involved anatomic lymphoid sites and those with AIDS or who were human immunodeficiency virus (HIV)-positive were not included in this study.

In all patients, in addition to a complete physical exam, staging included routine blood chemistry tests; blood cell counts and differential; ECG; chest X-ray; computed tomography (CT) of chest, abdomen and pelvis and bilateral bone marrow biopsy. Percutaneous liver biopsy, lumbar puncture with CSF examination and brain CT scan were performed only when there was clinical indication of the presence of liver or CNS involvement.

The patients were given with a six-week regimen, ACOP-B, as originally proposed by Connors et al. [13], consisting of doxorubicin 50 mg/sqm and cyclophosphamide 350 mg/sqm in weeks 1, 3, 5; vincristine 1.4 mg/sqm and bleomycin 10 mg/sqm in weeks 2, 4, 6; and prednisone 50 mg p.o. daily throughout the first two weeks and thereafter every other day.

The dose reduction guidelines for cyclophosphamide and doxorubicin were as follows: if the neutrophil counts were more than 0.99×10^9/l, 100% of the planned dose was delivered; if between 0.5 and 0.99×10^9/l, they received 66% of the dose; and if less than 0.5×10^9/l chemotherapy was delayed by one week. Doses were not reduced because of thrombocytopenia.

Patients with sinus involvement were given CNS prophylaxis consisting of six doses of intrathecal methotrexate 12 mg plus prednisolone 25 mg twice weekly during the treatment program, starting after sinuses were cleared of disease.

In the absence of tumor progression, radiotherapy to initial sites of disease involvement and to proximal uninvolved nodal regions was delivered approximately one month after completion of the chemotherapy program.

Patients were treated with a ^{60}Co teletherapy unit or a 6-Mev linear accelerator. Doses of radiation ranged from 36 to 40 Gy, over 4 or 5 weeks at a schedule of 1.80 to 2 Gy/d for 5 days per week.

One month after completion of the treatment, patients were fully restaged. Restaging tests included complete physical exam; blood chemistries in all patients and repetition of any previously abnormal staging studies. The restaging tests, including CT scan of chest, abdomen and pelvis, were perfomed at 12 and 24 months off therapy if initially abnormal. Patients with no evidence of active disease for a minimum of four weeks were judged to be in a complete remission (CR). A partial remission (PR) was defined as a 50% or greater decrease in the sum of the products of the maximun perpendicular diameters of measured lesions lasting at least four weeks. Failure was defined as anything less than PR.

Patients in CR at the end of the treatment received no further therapy.

Statistical methods

All patients started on treatment were considered evaluable. Overall survival (OS) includes all patients, with 'event' defined as death due to any cause. Survival duration was measured from the beginning of the treatment to the date of death or last follow-up alive. Relapse-free survival (RFS) includes all patients and was calculated from the beginning of treatment to the date of relapse, progression or toxic death.

Survival and RFS curves were plotted according to the method of Kaplan and Meier [14].

Statistical significance among curves was determined by the Breslow generalized Wilcoxon tests [15].

All calculations were by the BMDP program (1985) developed at the Health Science Computing Facility, University of California at Los Angeles (National Institute of Health) Special Research Resources.

Results

The clinical characteristics of the 84 patients are listed in Table 1.

The median age was 58 years, with a range of 25–79. Thirty-five percent were over 65 years. The majority of the patients (62%) were in stage I and 38% stage II. Primary sites of disease were nodal in 54%, nodal and extranodal in 8% and extranodal alone in 38% of

Table 1. Clinical characteristics of the 84 patients.

	No	%
Patients	84	
Age		
Median	58 years	
Range	25–79	
>65 years	29	35
Sex		
Male	44	52
Female	40	48
Histologic subtype (WF)		
F	18	21
G	42	50
H	24	29
ECOG Performance status		
0–1	81	96
2	3	4
Stage		
I	52	62
II	32	38
Primary site		
Nodal	45	54
Nodal + extranodal	7	8
Extranodal	32	38
Extranodal sites		
Waldeyer's ring	14	17
Bone	9	11
Soft tissue	5	6
Testis	4	5
Skin	3	3
Breast	2	2
Lung	1	1
Other	1	1
LDH level[a]		
Normal	74	94
Above normal	5	6
Bulky		
No	81	96
Yes	3	4

[a] LDH level was not determined in five patients.

the patients. The most common sites of extranodal involvement were Waldeyer's ring (17%), followed by bone (11%). Bulky disease, defined as a mass greater than 10 cm, was documented in 4% and LDH level above normal values in 6% of the patients.

All patients received ACOP-B chemotherapy, and 77 were given locoregional RT. Eight patients received no RT: three, with stage I splenic lymphoma, underwent splenectomy followed by chemotherapy; one, with primary lung involvement, was given chemotherapy alone; one refused RT; two were not given RT due to protocol violation and one progressed immediately after completion of chemotherapy.

Response to treatment

Eighty-three patients (99%) achieved CR at the end of the combined treatment, 79 patients (94%) did so with ACOP-B chemotherapy and 4 (6%) after radiotherapy.

Only one patient, with a stage II subdiaphramatic nodal diffuse large-cell lymphoma, failed to achieve CR. She showed disease progression with supraclavicular nodal involvement and attained continuous CR with an alternative chemotherapy regimen.

RFS and survival

With a median follow-up of 45 months, the four-year relapse free survival rate was 79% for all 84 patients (Figure 1).

Sixty-eight of the complete remitters remained in continuous CR. Fifteen patients relapsed, 47% of them within the first year off therapy.

The majority of relapses (93%) involved distant nodal and/or extranodal sites (Table 2). Local recurrence was detected in only one patient.

Two of the four patients who achieved a CR only after RT subsequently relapsed, at 13 and 30 months.

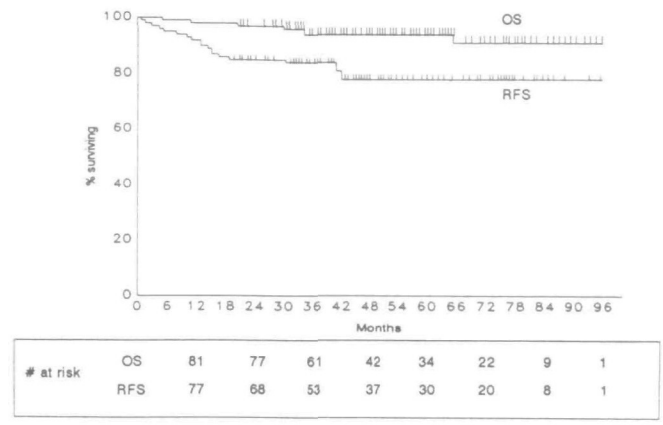

Figure 1. The overall survival (OS) of all 84 patients at four years is 90%. The relapse-free survival (RFS) of all 84 patients (1 NR and 15 relapses) at four years is 79%.

Four patients had an immunoblastic lymphoma with testicular involvement without clinical signs of CNS disease at presentation and all achieved CR. Two of them presented a CNS relapse, at 3 and 10 months off therapy: one achieved a second CR with brain RT, and the second had disease progression and died of lymphoma.

The outcome of the 15 relapsed patients was generally good: 9 were converted to a second CR (7 with second-line chemotherapy, 1 with RT alone and another with high-dose therapy followed by ABMT); 2 of them subsequently relapsed and are still alive with persistent lymphoma. Three did not respond to second-line therapy and died of lymphoma. One patient is still receiving salvage chemotherapy. One patient was given no further treatment and died of the disease and one, immediately after relapse, died of myocardial infarction.

No clinical characteristics at diagnosis (age, stage, LDH, PS, bulky, nodal vs. extranodal primary sites)

Table 2. Modality of relapse.

Pts	WF	Stage	Age	Primary site	RT	Pattern of relapse	Salvage therapy	Response
1 PP	H	II	55	Extra	Yes	Distant	CT	II cCR
2 GP	F	II	55	Nodal	Yes	Distant	CT	II CR-relapse
3 BB	H	I	51	Extra	Yes	CNS	RT	II cCR
4 BC	H	I	59	Extra	Yes	Distant	CT	NR-death
5 AC	G	I	79	Extra	Yes	Local rec.	–	death for MI
6 CC	H	II	58	Nod + ext	Yes	Distant	CT	II cCR
7 NL	G	II	63	Nodal	Yes	Distant	CT	NR-death
8 AM	G	I	53	Nodal	Yes	Distant	CT	II cCR
9 BG	H	II	73	Nodal	No	Distant	CT	II cCR
10 CA	H	I	58	Extra	Yes	Distant	–	death for NHL
11 CO	H	I	45	Extra	Yes	CNS	CT	NR-death
12 GL	H	I	69	Nodal	Yes	Distant	CT	II cCR
13 FM	H	I	45	Extra	Yes	Distant	ABMT	II CR-relapse
14 DG	G	II	45	Extra	Yes	Distant	CT	II cCR
15 PA	H	I	67	Extra	No	Distant	CT	PR

Abbreviations: extra – extranodal; nod + ext – nodal and extranodal; local rec – local recurrence; CT – chemotherapy; cCR – continuous complete remission; MI – myocardial infarction.

Table 3. Prognostic factor for RFS in all pts treated with ACOP-B plus radiotherapy.

	Four-year RFS	*P* value
Age		
<65 years	78%	
>65 years	82%	n.s.
Stage		
I	80%	
II	78%	n.s.
Primary site		
Nodal	80%	
Extranodal ± nodal	78%	n.s.
Radiotherapy		
No	69%	
Yes	80%	n.s.

were found to be predictive for RFS (Table 3). The eight patients who received no radiotherapy had a lower RFS rate (69% vs. 80%), but the differences were not significant.

The overall four-year survival for all 84 patients was 90% (Figure 1). Four patients died of lymphoma, one of myocardial infarction, as previously described, and one of unrelated causes while in CR.

Toxicity

Overall, treatment was well tolerated. No toxic deaths were recorded, and there were no severe toxic effects (World Health Organization grades 3 and 4).

The most frequent side effect was mild mucositis (WHO grade 1 and 2) due to chemotherapy, which occurred in 38% of the patients. Mild paraesthesias and/or mild constipation (WHO grade 1) were observed in 27% of the patients. Seven patients developed minor infections, none of them requiring hospitalization.

Ten percent of the patients had a neutrophil nadir of less than 1.0×10^9/l but only 2% experienced a neutrophil nadir of less than 0.5×10^9/l. None of the patients had a platelet count less than 100×10^9/l or haemoglobin level less than 9 g/dl. No platelet or PRBC transfusions were required.

Delay of chemotherapy was kept to a minimum. Ninety two percent of the patients completed ACOP-B chemotherapy on time.

Discussion

This study reports the results obtained in localized intermediate- to high-grade malignant lymphoma with a brief weekly chemotherapy regimen, ACOP-B, followed by locoregional radiotherapy. This combined modality approach is highly effective, yielding a 99% complete remission rate. The complete remissions are durable with a four-year RFS of 79% and four-year overall survival of 90%. The ACOP-B regimen was originally proposed by Connors et al. [13] as a modification of MACOP-B [16] by omitting methotrexate and lowering the prednisone dose. The duration of therapy was reduced from 12 to 6 weeks to develop a brief chemotherapy with low toxicity. In a series of 46 patients the authors reported a CR rate of 100% with RFS and OS rates of 80% and 88%, at a median follow up of 17 months.

Our experience, in a larger series of patients with a longer follow-up, confirms these data.

At the beginning of the 1980s, several randomized studies [7–9] showed the superiority of a combined-modality treatment with chemotherapy plus locoregional radiotherapy over that of radiotherapy alone, with a lower relapse rate in favour of the combined modality approach.

Further studies using CHOP-like chemotherapy regimens followed by locoregional radiotherapy confirmed these observations. In 142 patients with diffuse large cell lymphoma treated with 2–8 courses of CHOP with or without involved field (IF) RT, Jones et al. [12] achieved a high CR rate (99%) with a RFS of 82% at five years. CR and five-year DFS rates of 98% and 83% were reported by the Istituto Nazionale dei Tumori of Milan [17] in 183 patients with stages I–II intermediate- to high-grade NHL treated with 4–6 courses of CHOP followed by locoregional radiotherapy. Recently Lambertenghi et al. [18] confirmed these data in a series of 150 patients using four courses of CEOP (cyclophosphamide, epirubucin, vincristine, prednisone) plus RT (CR 90%; DFS 77% at seven years).

An unanswered question is whether combined modality treatment offers an advantage over chemotherapy alone in patients with localized stage. Mauch et al. [10] analyzed 71 patients with intermediate- to high-grade NHL: 43 were treated with chemotherapy plus radiotherapy and 28 with chemotherapy alone. The FFR for patients receiving the combined therapy was 66% at six years compared to 43% for those treated with chemotherapy alone ($P < 0.01$) and the risk of local recurrence in the combined therapy group was 12% vs. 50% ($P < 0.01$). Jones et al. [12] compared 34 patients treated with CHOP alone *versus* 108 patients treated with CHOP plus RT: no significant differences were observed in terms of RFS, but there is a trend in favour of combined therapy.

Randomized clinical trials are needed [19] to determine the best form of treatment: two studies are now underway in the ECOG and the SWOG, and preliminary results of these trials were recently reported. In the ECOG [20] study 345 patients with early-stage intermediate-grade NHL were treated with eight courses of CHOP with or without low-dose RT (30 Gy) consolidation to sites of pretreatment involvement for patients in CR. All patients in partial response after CHOP received high-dose RT (40 Gy). The combined therapy was significantly more effective than CHOP alone, with a six-year DFS of 73% vs. 58% ($P < 0.01$),

and a trend toward significance for OS (84% vs. 70%).

More recently, at the 1996 ASCO [20] and Lugano [21] meetings, the preliminary results of the SWOG 8736 were reported. Four hundred one patients with localized intermediate- to high-grade NHL were randomized to receive combined modality treatment (three courses of CHOP plus IF RT) vs. chemotherapy alone (eight courses of CHOP). Patients treated with the combined approach experienced a significantly better four-year survival (87% vs. 75%) than patients treated with chemotherapy alone.

There was a trend toward significance also for progression-free survival. In the CHOP arm some deaths occurred after completion of chemotherapy, primarily cardiac. Grade 4 toxicity was also higher with CHOP alone than with CHOP plus RT (40% vs. 31%). The authors conclude that CHOP plus RT is more effective and less toxic than CHOP alone.

We cannot address this. In our series eight patients were given no radiotherapy after the ACOP chemotherapy. Relapse in primarily involved sites was observed in only one of our patients and RT thus appeared to be useful for averting local recurrence, as described by others [5, 6] Moreover, RT converted four partial responders to CR; however, two of the four had diffuse recurrences. Thus the failure rate was higher in question because our plan was a combined modality treatment for all patients. Patients who obtained a late CR with radiotherapy compared unfavourably with those with a prompt CR after chemotherapy (50% vs. 16%), suggesting that patients with late CR remain at high risk for systemic relapse. Thus, radiotherapy may be useful for the local control of disease, and the combined modality treatment appears to lower the risk of recurrence.

Another point of discussion is the difference in outcome between stages I and II patients. With radiotherapy alone a significant difference was observed between pathological stages I and II by Vokes et al. [23, 24] (OS at 10 years 70% vs. 46%, DFS 72% vs. 31%).

A difference between stages I and II was not uniformly reported if a combined modality treatment had been used. An important difference in DFS (94% stage I vs. 76% stage II) was shown by Jones et al. [12] in 142 patients treated with CHOP plus RT. A poorer outcome for stage II patients was observed in other studies with CHOP-like regimens plus RT than for those with stage I disease [25–27] The MDAH study [28] reported better results in 147 stage I patients treated with CHOP-bleo plus RT in term of OS (72% vs. 43%) and RFS (79% vs. 66%) than in stage II patients. In contrast, no differences were reported by the Istituto Nazionale dei Tumori of Milan [17] and Vancouver groups [6].

The variation among studies may reflect different incidences of patients with adverse prognostic features. The inclusion criteria for stage II may differ from one study to another; in some cases the criteria have not been specified and some have included patients with bulky disease or systemic symptoms. In the present series stage II patients had a more superimposable outcome than those with stage I, but our series includes a small number of patients with bulky disease (4%) and none with B-symptoms at presentation. Moreover, stage II patients were enrolled in the study only if they had a limited extent of disease (less than four involved lymphoid sites).

In this study four patients had testicular involvement at diagnosis, an unusual presentation of NHL. All of them achieved CR after orchiectomy and before ACOP-B plus radiotherapy to the contralateral testis. No CNS involvement was noted at presentation and no intrathecal chemotherapy was given. However, two had CNS relapses, with one succumbing to lymphoma and the other achieving a second CR with brain RT. A few published studies have reported CNS relapses, ranging between 20% and 40%, in patients with testicular involvement at diagnosis [29–32]. On the basis of these data we recommend prophylactic intrathecal chemotherapy for all patients with testicular involvement.

ACOP-B plus locoregional radiotherapy was very well tolerated, with low toxicity, no treatment-related toxic deaths and ease of administration in the outpatient clinic, also in elderly people. None of the patients required hospitilization for adverse toxic events.

Our results in terms of CR, OS and RFS rates at four years are superimposable upon those reported with CHOP plus RT. However, the duration of treatment with CHOP ranges from three to six months (3–8 courses) while ACOP-B chemotherapy lasts only six weeks.

In conclusion, our experience in a large consecutive series suggests that a very brief course of chemotherapy followed by locoregional radiotherapy is safe, effective and probably curative in localized intermediate- to high-grade NHL.

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