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Treatment of Non-Hodgkin's Lymphoma of Waldeyer's Ring: Radiotherapy Versus Chemotherapy Versus Combined Therapy

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Treatment of stage IA non-Hodgkin's lymphoma (NHL) of Waldeyer's ring remains controversial, probably because of the small number of patients and the scarcity of controlled studies. Between 1981 and 1991, 316 patients with stage I NHL of Waldeyer's ring were randomised for treatment with radiotherapy alone (extended fields), 101 patients; combined chemotherapy with a regimen of CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone) or CHOP-like (epirubicin instead of doxorubicin), 106 patients; and combined therapy (radiotherapy followed by the same combination chemotherapy), 109 patients. Median follow-up was 6.8 years. Complete response was achieved in 93, 87 and 97%, respectively. Relapses were least frequent in patients treated with combination therapy. The 5-year rate for failure-free survival was 48% for radiation therapy, 45% for the patients who were treated with chemotherapy, which was statistically significantly less than the 83% for patients treated with combined therapy ($P<0.001$). Overall survival was also better in the combined therapy arm: 90%, statistically different to 58% for the patients treated with chemotherapy alone and 56% for patients treated with radiation therapy ($P<0.001$). Toxicity was mild and late side-effects were not observed in any patients. From these results combined therapy should be considered as the best therapeutic approach in patients with localised NHL of Waldeyer's ring.

Keywords: malignant lymphoma, non-Hodgkin's lymphoma, chemotherapy, radiotherapy, doxorubicin, epirubicin

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INTRODUCTION

The authors' experience of non-Hodgkin's lymphoma (NHL) has shown that more than 40% of localised disease presented in sites other than lymph nodes. Gastrointestinal involvement was the most common site, however, Waldeyer's ring and neck involvement accounted for one-third of all cases [1].

For more than three decades the treatment of localised malignant lymphoma of the Waldeyer's ring has included intensive radiotherapy for permanent control of the local disease, but there has been a tendency for a spread to more distant lymph nodes and extra-lymphatic tissues. Thus, not all of the tumour is detected at the time of presentation, and the local treatment delivered may be insufficient [2–5]. For this reason, in some clinical trials combination chemotherapy has been carried out in addition to radiation therapy to improve the outcome. However, randomised trials are scarce, or the number of patients involved is too small for definitive conclusions to be drawn [6–10]. With these considerations in mind, patients with clinical stage I of the Waldeyer's ring, who were randomised to receive local radiation therapy in comparison with combination chemotherapy or combined therapy (radiotherapy followed by chemotherapy), were enrolled into a clinical trial.

The results presented here demonstrate that the use of a combined therapy appears to be the best therapeutic approach for these patients.

PATIENTS AND METHODS

From 1981 to 1991, 316 patients with NHL involving the Waldeyer's ring and clinical stage I, diagnosed and treated in the Oncology Hospital, National Medical Center, were enrolled into this prospective clinical trial. Pathological material was classified according to the Working Formulation [11]. Because prognostic factors have demonstrated their

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usefulness in therapeutic decisions using our risk model, patients were assessed according to this prognostic system [1].

The general staging procedures included a history and clinical examination, the ears, nose and throat were carefully examined under local anaesthesia. Radiographs were taken postero-anterior and lateral of the chest. Complete blood counts and serum chemistries, including renal and hepatic tests were performed. In the last few years beta-2-microglobulin [12] and human immunodeficiency virus tests have been included. Gastroscopy with multiple gastric biopsies were performed in all cases. Bone marrow smear and biopsy were taken in all cases.

Computed tomography of the abdomen and pelvis, and the head and neck, were also performed in all cases. The localisation and extent of the disease in the Waldeyer's ring was documented according to the TN model system for the oropharynx and nasopharynx.

Patients were randomly allocated according to a blind envelope system to receive the following treatments.

Group 1 received radiation therapy alone. All patients were treated with Co^{60} or 6 MeV equipment. The treatment field consisted of parallel opposed lateral fields covering the Waldeyer's ring and upper neck. The lower neck and supraclavicular areas were treated through an anterior field. A larynx block was used in the anterior neck fields to provide protection of the larynx and to prevent overlapping of the upper and lower fields at the spinal cord. Treatment was initiated at the rate of 200 cGy tumour dose fraction for a total dose of 4500 cGy.

Group 2 received combination chemotherapy which consisted of: cyclophosphamide, 600 mg/m^2, i.v., day 1; doxorubicin, 50 mg/m^2, i.v., day 1; vincristine, 1.4 mg/m^2, day 1 (maximum dose 2 mg); prednisone, 40 mg/m^2, p.o., daily, days 1–5; Bleomycin, 10 mg/m^2, i.v., day 14.

During the last 3 years, doxorubicin has not been available at our institution and so instead epirubicin, 70 mg/m^2, i.v., day 1, was used.

This treatment was administered every 3 weeks for six cycles.

Group 3 received radiation therapy as the initial treatment as for patients in group 1, followed, 6 weeks after radiotherapy, by the same schedule of combined chemotherapy. At the completion of all therapy, patients were carefully restaged by repeating those tests that had been abnormal during the staging evaluation. If suspicious or residual disease existed in any anatomical site, including the ears, nose or throat, a biopsy was performed.

Complete response (CR) was defined as the disappearance of all evidence of disease for at least 6 months.

Partial response was defined as the diminution of the tumour mass by $\geqslant 50\%$ of the initial tumour burden without the appearance of new lesions.

Failure was considered when the tumour mass reduced by less than 50% or there was the presence of new lesions.

Survival and failure-free survival (FFS) curves were constructed using the Kaplan–Meier method [13]. Multivariate analysis was performed to determine the influence of prognostic factors in duration of remission and survival using the Cox method [14].

The Ethical Committee approved the protocol and informed consent was received for all patients.

RESULTS

Between 1981 and 1991, 336 patients were considered candidates for the study. 20 cases were excluded: stage II (10 cases), follicular large cell lymphoma in pathological review (4 cases) and major protocol violations (6 cases). Table 1 shows

Table 1. *Patients' characteristics*

	Radiotherapy No. (%)	Chemotherapy No. (%)	Combined therapy No. (%)
Total	108	112	116
Excluded	7	6	7
Evaluable	101	106	109
Sex: male	58 (57)	50 (47)	56 (52)
female	43 (43)	56 (52)	53 (48)
Age (years): range	29–77	21–69	30–73
median	53	58	55
Histology:			
diffuse large cell	48 (47)	69 (65)	64 (58)
diffuse mixed	19 (18)	11 (10)	21 (18)
immunoblastic	30 (30)	22 (20)	20 (18)
small non-cleaved	4 (4)	4 (3)	4 (3)
Risk:			
low	93 (92)	100 (94)	101 (92)
intermediate	8 (7)	6 (6)	8 (7)
Anatomic sites:			
tonsil	56 (55)	60 (57)	62 (56)
base of tongue	5 (5)	3 (2)	8 (7)
nasopharynx	11 (11)	16 (12)	7 (6)
multiple sites	29 (29)	27 (26)	32 (28)
Chemotherapy:			
doxorubicin	—	60 (56)	63 (57)
epirubicin	—	46 (43)	46 (42)
Bulky disease ($\geqslant 7$ cm)	36 (36)	43 (32)	50 (36)

the clinical and laboratory characteristics of the 316 patients who were eligible for evaluation. No significant differences were observed between the three arms of the protocol. Median follow-up was 6.8 years. Table 2 shows the types of response. No differences were observed between the treatment modalities in the CR rates. However, relapses were most frequent in patients treated with radiation therapy or chemotherapy alone compared with patients who were treated with combined therapy. Figure 1 shows the FFS. The 5-year FFS was 48% in patients treated with radiotherapy, 45% for patients who were treated with chemotherapy alone, both were significantly different to the 83% FFS rate in patients who were treated with combined therapy ($P<0.001$). The patterns of relapse can be seen in Table 3. In patients treated with radiotherapy alone, relapses were most frequent in anatomical sites ouside the radiation fields. In the chemotherapy group the relapses occurred most frequently in the gastrointestinal tract and retroperitoneum. On the other hand, relapses in the patients treated with combined therapy were disseminated in most cases. Figure 2 shows the overall survival. The 5-year rate was 51% for patients treated with chemotherapy and 56% for patients who were treated with radiation therapy, statistically different to the 90% for patients treated with combined therapy ($P<0.001$).

Table 2. Type of response

	Radiotherapy No. (%)	Chemotherapy No. (%)	Combined therapy No. (%)
Complete response	94 (93)	93 (87)	106 (97)
Partial response	2 (1)	3 (2)	0
Failure	5 (5)	10 (9)	3 (2)

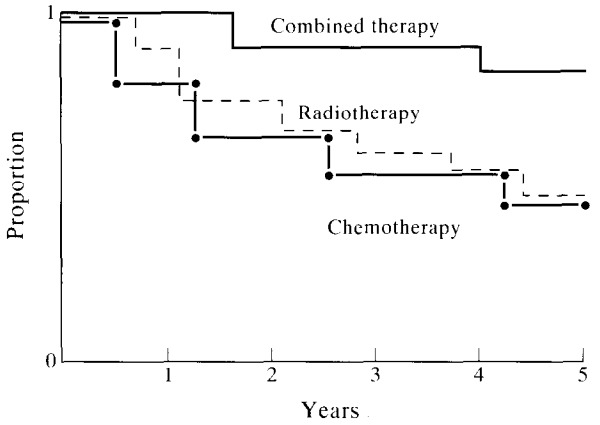

Fig. 1. Failure-free survival in patients with non-Hodgkin's lymphoma of the Waldeyer's ring.

Table 3. Patterns of relapse

	Radiotherapy No. (%)	Chemotherapy No. (%)	Combined therapy No. (%)
Waldeyer's ring	3 (5)	12 (23)	1 (5)
Gastrointestinal tract	21 (35)	16 (30)	5 (29)
Bone marrow	6 (10)	2 (1)	0
Lung	3 (5)	1 (1)	0
Retroperitoneum	12 (20)	15 (28)	7 (6)
Multiple sites	14 (23)	6 (11)	11 (61)

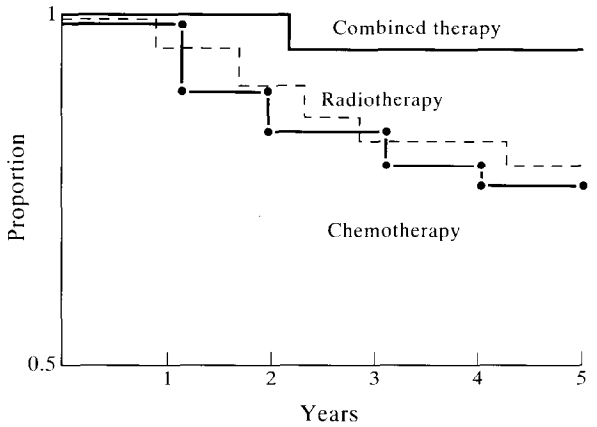

Fig. 2. Overall survival.

Toxicity was mild, 35% of the patients who received radiation therapy (groups 1 and 3) showed moderate mucositis. Xerostomia was observed in 15% of the patients, but only 5% had chronic damage. 41 of the patients who were treated with chemotherapy (groups 2 and 3) developed haematological toxicity grades I–II. None of the patients developed toxicity grades III or IV. Until now no evidence of a second tumour or acute leukaemia has been observed.

Multivariate analyses were performed, including age, sex, performance status, bulky disease, levels of lactic dehydrogenase and beta-2-microglobulin, anthracycline treatment or therapeutic modalities. Only type of treatment (combined therapy) was statistically significant in the duration of remission and survival (data not shown).

DISCUSSION

The management of patients with localised intermediate- or high-grade NHL has undergone considerable change over the last 20 years. Prior to 1970, radiotherapy was the usual treatment for clinical stages I and II patients [15–18]. However, long-term analysis has shown that only about 50% of patients are alive and free of disease after more than 20 years [16, 18, 19]. The results for patients with poor prognostic factors were particularly poor, with only a 10–15% chance of 5-year survival [18, 20].

Multiagent chemotherapy has proved an effective treatment for stages I or II, but, despite excellent CR rates, the incidence of relapse at local sites has been significant, particularly for patients who had bulky disease [20–22].

For this reason, combined therapy, including different schedules (chemotherapy followed by radiotherapy, radiation therapy followed by chemotherapy, different combinations of cytotoxic drugs or radiation therapy) were introduced in an attempt to improve the outcome of these patients [23–26]. In most studies complete remission and survival were better when combined therapy was used. However, as most studies were retrospective analyses, or the number of patients studied was too low, no definitive conclusions have been achieved [25].

In the present study the results of the first randomized and prospective clinical trial in patients with NHL of Waldeyer's ring, carried out with an adequate number of patients, were examined.

Malignant lymphoma of the Waldeyer's ring is usually very responsive to both radiation and chemotherapy. For many years radiation therapy has been considered the choice treatment for all early-stage disease. Local control could be achieved with radiation therapy in about 90% of the patients, as has been confirmed in our study. However, relapses often occurred outside the radiation fields [4, 9, 10]. Thus, local radiation therapy is highly effective at the local regional level, but is insufficient in about 50% of the patients because relapses at more distant sites tend to occur. The use of more aggressive staging procedures, as laparatomy, to define the exact extent of disease, has not proved to be more effective [19]. The results of most studies, including our own, suggests that at least half of the patients with stage I NHL of the Waldeyer's ring have truely localised disease and can be cured with radiation therapy alone, but the other 50% of the patients need more aggressive treatment. Chemotherapy alone might be considered for patients with small non-life threatening lesions, but most patients with NHL of the Waldeyer's ring present large tumoral masses at diagnosis. In these patients the use of complementary irradiation appears warranted for two reasons: most recurrences occurred at the site of initial bulky disease and these large lesions when not shrinking rapidly under chemotherapy could cause compression and severe discomfort to the patients. Thus, the use of radiotherapy to control and rapidly shrink the tumour mass locally followed by systemic chemotherapy to avoid the distant relapses may be reasonable.

Recently the introduction of group risk based decisions has been developed to predict the outcome of patients with NHL. However, we cannot validate this concept in our study because most of the patients were in low-risk groups and so no comparison is possible.

In this study the combination of radiation chemotherapy as the initial treatment followed by a combined chemotherapy can be considered to have had excellent results. Both the FFS and the overall survival were improved compared to other therapeutic modalities. The tolerance was good, with minimal local and systemic toxicities. Long-term side-effects were mild, and no second tumours or acute leukaemia has been observed in the patients.

Quality of life was good as the patients did not have to spend time in hospital, all treatment was given on an out-patient basis.

Over the years the use of radiation therapy in intermediate- and high-grade NHL has been considered only in selected cases [19–21, 24, 25]. However, radiation therapy should be considered as an excellent option for more patients, including patients with advanced disease and bulky disease [27] or aggressive behaviour [28].

In conclusion, our experience in a large randomised clinical trial of patients with limited Waldeyer's ring NHL clearly indicate that loco-regional irradiation followed by conventional chemotherapy is safe, highly effective and probably curative for most patients, including those with bulky disease. We hope that more clinical trials will be carried out to demonstrate the usefulness of this treatment modality.

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