

Radiotherapy for Localized Relapse in Patients with Non-Hodgkin's Lymphoma: A Preliminary Report

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Purpose: To evaluate the usefulness of radiotherapy for relapse of non-Hodgkin's lymphoma (NHL) at a localized site.

Methods: Of 79 patients with relapsed intermediate- or high-grade NHL, 13 patients (16.5%) with a localized relapse were analyzed retrospectively.

Results: Five patients were treated with radiotherapy alone and eight were treated with radiotherapy plus conventional chemotherapy (CHOP or other combinations). Radiotherapy was delivered to the involved field to a mean total dose of 34.1 Gy (range, 21–51 Gy). The 5-year overall and disease-free survival rates were 80.2% and 76.2%, respectively. Four patients relapsed subsequently. After further salvage therapy, two patients died of NHL and two were alive without active disease.

Conclusion: Radiotherapy may be an important component of treatment for selected patients with NHL who relapse at a localized site.

Key words: malignant lymphoma, non-Hodgkin's lymphoma, radiotherapy, localized relapse

INTRODUCTION

PATIENTS with early stage non-Hodgkin's lymphoma (NHL) have a high likelihood of cure with appropriate therapy. However, frontline therapy fails or disease relapses in a significant fraction of patients. Although patients with low-grade NHL will survive for several years with relapsed disease, the prognosis of patients with intermediate- or high-grade NHL is usually poor after relapse.

Successful treatment of patients with relapsed NHL with salvage chemotherapy has been reported by a number of investigators.¹⁻³ In particular, advances in the era of bone marrow transplantation and high-dose chemotherapy have resulted in high response rates and

cures in a small, selected subgroup of patients.^{2,3} However, bone marrow transplantation is only feasible for a minority of patients with relapsed NHL, since it cannot be used for most elderly patients because of poor tolerance and an unacceptably high treatment-related death rate.⁴

Patients with relapsed NHL usually have disseminated disease, and relapse at a localized site is rare. Therefore, salvage radiotherapy has received little attention in the literature, and there is no general agreement about the role of radiotherapy in patients with relapsed NHL. However, radiotherapy may remain a possible treatment of choice, if a patient does not have disseminated disease. We have employed radiotherapy with or without standard-dose chemotherapy as salvage treatment in patients with a localized relapse of NHL and report our experience in 13 patients.

MATERIALS AND METHODS

Between April 1987 and March 1999, 79 patients with relapse of intermediate- or high-grade NHL were admitted at the Department of Clinical Radiology, Kyushu University Hospital. Sites of failure were varied and multiple in most patients. Only 13 patients (16.5%) were identified with localized relapse, defined as disease

Received February 17, revision accepted March 28, 2000.

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This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientists from the Japan Society for the Promotion of Science.

Table 1. Clinical features of patients before salvage therapy

Patient No.	Age (yrs) / sex	Histology	T/B	Stage	Primary site	Treatment / response	Time from initial therapy to first relapse (mo)
1	73/M	DLCL	B	IIA	Tonsil	30 Gy+CHOP×2 / CR	23
2	55/M	DLCL	B	IA	Neck	40.5 Gy+CHOP×3 / CR	34
3	53/M	DLCL	Unk	IIIB	Neck	15 Gy+CHOP×6 / CR	7
4	69/M	DLCL	B	IA	Maxilla	50 Gy+CHOP×1 / CR	7
5	46/M	DLCL	B	IA	Nasopharynx	50 Gy+CHOP×3 / CR	8
6	58/F	DLCL	B	IA	Orbit	50 Gy+CHOP×3 / CR	10
7	42/F	DLCL	B	IIA	Neck	30 Gy+CHOP-B×1 / CR	9
8	74/M	DM	Unk	IA	Stomach	Gastrectomy+CHOP×2 / CR	46
9	46/F	DSCL	T	IA	Nasal cavity	40 Gy+CHOP×3 / CR	60
10	52/M	DSCL	B	IA	Colon	CHOP×6 / CR	10
11	58/F	DM	B	IA	Rectum	Resection+30 Gy+VEPA×6 / CR	112
12	62/M	DSCL	T	IA	Orbit	Orbital exenteration / CR	18
13	62/F	DM	B	IIA	Breast	Mastectomy+COP ×3 / CR	12

B, B cell; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP-B, cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin; COP, cyclophosphamide, vincristine, prednisone; CR, complete response; DLCL, diffuse large-cell lymphoma; DM, diffuse mixed lymphoma; DSCL, diffuse small-cleaved lymphoma; T, T cell; VEPA, cyclophosphamide, doxorubicin, vincristine, prednisone.

involving only one site or two immediately adjacent sites. All patients were treated with radiotherapy alone or radiotherapy combined with standard-dose chemotherapy, and they form the basis of this report. Patients with low-grade NHL were excluded, because they can sometimes survive for many years with relapsed disease. Initial patient and disease characteristics are shown in Table 1. The eight men and five women in this study group ranged in age from 42 to 74 years (mean, 57.7 years). All tumors were initially evaluated by histopathologic examination of biopsy specimens proven and categorized according to the classification of the Working Formulation. Immunohistologic studies also were performed on frozen or paraffin-embedded specimens. The original stage was stage I in nine patients, II in three, and III in one, according to the Ann Arbor staging system. Nine patients were treated with radiotherapy of the involved field and chemotherapy, two with surgical resection plus chemotherapy, one with chemotherapy alone, and one with surgery alone. All patients achieved complete response, with a mean disease-free interval of 27.4 months (range, 7-112 months).

Relapse disease characteristics, treatment, and outcome are listed in Table 2. Relapse was proven on biopsy in 10 patients and documented radiologically in three patients. Before salvage therapy, patients were carefully evaluated on the basis of a full physical examination, routine blood tests, chest radiographs, computed tomography of the chest and abdomen, 67-

gallium citrate scintigraphy, and gastrointestinal tract studies. A percutaneous bone marrow biopsy was performed in seven patients. Positron emission tomography using ^{18}F -2-fluoro-2-deoxy-D-glucose (^{18}F -FDG) also was performed in one patient. Of 13 patients, only one (patient 1) had bulky disease (≥ 5 cm) and one (patient 11) had a slightly elevated lactate dehydrogenase level.

After elaborate staging procedures, five patients were treated with radiotherapy alone and eight with combined radiotherapy and chemotherapy. Radiotherapy was delivered to the involved field. Total doses ranged from 21 to 51 Gy (mean, 34.1 Gy) in daily fractions of 1.5 to 2.0 Gy. In four patients, reirradiation fields included previously irradiated areas. The cumulative total doses to the reirradiated area ranged from 60 Gy to 80 Gy (mean, 67.8 Gy). Systemic chemotherapy was given to eight patients. Five patients received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), and three received other combinations.

The mean follow-up time from salvage therapy was 4.2 years (range, 1-10 years). Survival and disease-free survival were calculated from the start of salvage therapy using the Kaplan-Meier method.

RESULTS

The 5-year overall and disease-free survival rates following salvage therapy were 80.2% and 76.2%, respectively (Fig. 1). After salvage treatment all patients

Table 2. Details after relapse

Patient No.	Site of relapse	Treatment / response	Time from salvage therapy to second relapse (mo)	Outcome (mo post-treatment)
1	Ileum	51 Gy / CR	NED	Alive in CR (74)
2	Tonsil & neck	30 Gy / CR	21	Alive in CR (117)
3	Inguinal	30 Gy / CR	3	Died of NHL (7)
4	Neck	30 Gy+CHOP×6 / CR	NED	Alive in CR (93)
5	Nasopharynx	21 Gy+ProMACE–MOPP×2 / CR	8	Died of NHL (18)
6	Chest wall	30 Gy+ProMACE–MOPP×2 / CR	66	Alive in CR (93)
7	Neck	30 Gy+VEPA×6+ProMACE×1 / CR	NED	Alive in CR (73)
8	Tonsil	30 Gy+CHOP×3 / CR	NED	Alive in CR (84)
9	Nasal	40 Gy+CHOP×3 / CR	NED	Alive in CR (57)
10	Colon	45 Gy / CR	NED	Alive in CR (12)
11	Mesopharynx	30 Gy+CHOP×3 / CR	NED	Alive in CR (13)
12	Orbit	46 Gy / CR	NED	Alive in CR (11)
13	Neck	30 Gy+CHOP×3 / CR	NED	Alive in CR (6)

MOPP: nitrogen mustard, vincristine, procarbazine, prednisone; NED: no evidence of disease; ProMACE: cyclophosphamide, doxorubicin, methotrexate, etoposide, prednisone. See Table 1 for other abbreviations.

achieved complete response. Four patients relapsed subsequently, three outside the radiation field. Additional treatment included chemotherapy alone in two patients, and combined chemotherapy and radiotherapy in two patients. Two patients died of NHL, and two were disease-free after additional treatment.

Salvage radiotherapy with or without chemotherapy was well tolerated. There was no severe morbidity in any of the patients treated.

DISCUSSION

Optimal treatment of relapsed NHL remains an unresolved issue and the current treatment options include conventional second-line chemotherapy or high-dose chemotherapy with bone marrow transplantation.⁴ Based on the results of prospective randomized trials,^{2,3} treatment with high-dose chemotherapy and bone marrow transplantation is considered today the standard of care in chemotherapy-sensitive relapsing NHL. However, bone marrow transplantation is only feasible for a small, selected subgroup of patients, and the prognosis of patients after standard-dose salvage chemotherapy is still poor.¹

It is well known that radiotherapy plus chemotherapy is an effective treatment in primary localized NHL. Miller *et al.*⁵ have shown that radiotherapy is valuable not only in reducing the number of courses of chemotherapy, but also in producing superior overall survival and progression-free survival. They have concluded that radiotherapy is an important component

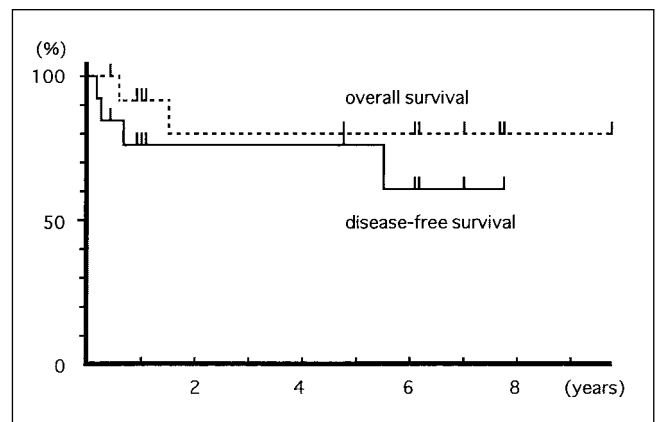


Fig. 1. Overall survival and disease-free survival of 13 patients with recurrent non-Hodgkin's lymphoma from the start of salvage therapy.

of treatment for clinically localized NHL. However, its role in relapsed localized NHL is not well defined. Because of the rarity of relapse at a localized site, this approach has not been systematically investigated as salvage for localized failure.

In contrast to NHL, it is generally accepted that radiotherapy with or without standard-dose chemotherapy remains a possible treatment for relapsed Hodgkin's disease.⁶⁻⁹ Although the clinical presentation and behavior of Hodgkin's disease are different from those of NHL, our series compares favorably with these results.

Although the prognosis of patients with relapsed NHL is usually poor, prognostic factors enable us to

distinguish patients with different response rates.² According to the International Prognostic Index,¹⁰ at relapse patients in the low-risk group were found to have a relatively favorable outcome.² Interestingly, Blay *et al.*² showed that there were no significant differences between conventional chemotherapy and high-dose chemotherapy with bone marrow transplantation in patients with low-risk prognostic values. Even conventional therapy without bone marrow transplantation may be curative for patients in the low-risk group.

Because NHLs are often already generalized at the time of diagnosis, all relapsing patients should be carefully restaged before embarking on curative salvage therapy. For clinical staging, we performed computed tomography of the chest and abdomen, ⁶⁷Ga citrate scanning, gastrointestinal tract studies, and a percutaneous bone marrow biopsy. However, despite elaborate staging procedures, a substantial number of patients with apparently localized NHL may have dissemination after local therapy. In this series, six of eight patients who received both radiotherapy and chemotherapy at relapse were disease-free as compared with two relapses in five patients treated with radiotherapy alone. Probably salvage radiotherapy plus chemotherapy, which increases the potential for eliminating microscopic sites of disease, is of significant benefit for patients with relapsing at a localized site.

Fortunately most of the lymphomas are sensitive to irradiation.¹¹ Although the recommended doses vary according to site and histology, doses of 30 to 40 Gy, frequently increased to 50 Gy, are used.¹² In this study, two series of radiotherapy amounted to 80 Gy or less in spite of reirradiation. Therefore, reirradiation can be undertaken with low risk of complications, even if the reirradiation fields include previously irradiated areas. However, reirradiation must be performed with great caution.

Most investigators now agree that the optimal treatment for relapsed NHL should include high-dose chemotherapy followed by bone marrow transplantation.^{3,13} However, considering the high treatment-related death rate associated with bone marrow transplantation,⁴ radiotherapy with fewer courses of chemotherapy may be an alternative therapeutic approach for selected patients who relapse at a localized site. Although the data are preliminary and the number of patients is small, we believe that this approach should be considered to minimize the risk of toxicity associated with salvage therapy in carefully selected patients,

especially the elderly.

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