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The Result of Combined Modality Treatment for Non-Hodgkin's Lymphoma of Head and Neck

Jae Cheol Kim, M.D., Sang Bo Kim, M.D.
Samuel Ryu, M.D. and In Kyu Park, M.D.

Department of Therapeutic Radiology, Kyungpook National University Hospital, Taegu, Korea

From April 1985 to September 1989, 26 patients with stage I and II non-Hodgkin's lymphoma of unfavorable histology localized in head and neck region were treated with combined modality (combination chemotherapy plus radiotherapy) at the Department of Therapeutic Radiology in Kyungpook National University Hospital. Of the 26 patients, 23 showed complete response and 3 partial response. Between these two groups there were no statistical differences according to the variables. Three-year survival and disease-free survival rate were 62.4% and 65.2%, respectively. Unilateral involvement of neck node ($p<0.05$), radiation dose over 5000 cGy ($p<0.01$), and 6 or more cycles chemotherapy ($p=0.06$) had a favorable effect on 3-year survival rate. There were 8 recurrences including 3 partial responders, 1 local failure, 1 distant failure, 1 contiguous failure, and 2 simultaneous local and distant failure. It could be suggested that combined modality treatment might be necessary for the treatment of stage I and II Non-Hodgkin's lymphoma of unfavorable histology.

Key Words: Non-Hodgkin's lymphoma, Stage I and II, Combined modality treatment

INTRODUCTION

A large proportion of non-Hodgkin's lymphoma (NHL) are in advanced stages with generalized involvement of both nodal and extranodal sites at the time of presentation[1].

When localized, they are highly curable with radiotherapy (RT). Traditionally, patients with stages I and II disease have received RT alone with modest success[1~5]. However, the strategy for initial treatment of patients with localized diffuse NHL of unfavorable histology is controversial[6]. Many authors[7~15] have suggested that combined modality treatment (CMT) should be considered since clinically staged patients treated only with localized RT are at high risk for distant relapse.

We have analyzed stage I and II diffuse histiocytic and diffuse poorly differentiated lymphocytic lymphomas arising from head and neck area treated with CMT.

The purpose of this study is to evaluate the efficacy of CMT for NHL in terms of survival and pattern of failure.

MATERIALS AND METHODS

From April 1985 to September 1989, a total of 53 NHL patients were treated at the Department of Therapeutic Radiology in Kyungpook National University Hospital. Of the 53 patients, 26 had stage I and II disease of unfavorable histology localized in head and neck region, and were treated with radiation plus chemotherapy (CHX).

Table 1 lists the characteristics of the 26 patients: 18 were men and 8 were women. Median age

Table 1. Patient Characteristics

Characteristics		No. of patients (%)
Age		
	Range	23 – 70 years
	Median	54 years
Sex		
	Male	18 (69)
	Female	8 (31)
Sites of Primary Lesion		
	Nodal	10 (38)
	Extranodal	16 (62)
Stage		
	I	11 (42)
	II	15 (58)
Pathologic Distribution		
	Diffuse histiocytic	6 (23)
	Diffuse poorly differentiated lymphocytic	20 (77)

was 54 years with a range of 23 to 70. Median follow-up period was 32 months with a range of 11 to 62 months.

All the patients had disease confined to the head and neck region except one patient who had also enlarged paratracheal lymph node on chest CT scan. Extranodal presentation was more common than nodal presentation and the sites of extranodal lesions were as follows: tonsil, 9: nasopharynx, 3: base of tongue, 3: and nasal cavity, 1.

The histology was reviewed and classified according to the Rappaport classification[16]. There were 20 diffuse lymphocytic poorly differentiated and 6 diffuse histiocytic lymphomas.

Patients were clinically staged according to the Ann Arbor staging system[16]. The clinical evaluation included pertinent history, physical examination, complete blood count, blood chemistry, chest X-ray, chest CT scan, bone marrow aspiration and biopsy, and liver and bone scan. Most patients had abdominal CT scan instead of lymphangiogram to evaluate the paraaortic lymph nodes. None of the patients had exploratory laparotomy. There were 11 stage I and 15 stage II patients.

All were treated with CMT, i.e., combination CHX and RT. Several combinations of CHX were applied and the range of cycles was 1~12 (median 8 cycles). Initial CHX regimen were CHOP-Bleo (cyclophosphamide, adriamycin, oncovin, prednisone, bleomycin) in 24 patients, CHOP (cyclophosphamide, adriamycin, oncovin, prednisone) in 1 patient, and COP (cyclophosphamide, oncovin, prednisone) in 1 patient. Radiation was delivered after 1~6 cycles of CHX (median 2 cycles) with 6 MV X-ray encompassing primary tumor and adequate normal tissue margin plus regional lymph nodes. Radiation dose varied depending on the histology and tumor size ranging from 3240 to 6500 cGy (median 5000 cGy). A boost dose of 500 to 1000 cGy was given for the residual lesion. After RT 19 patients received additional 1~10 cycles of CHX (median 7 cycles) consisting of CHOP-Bleo, COP-Bleo, COP, CVB (cyclophosphamide, vincristine, bleomycin), AVBD (adriamycin, vincristine, bleomycin, dactinomycin).

Complete response was defined as the complete disappearance of all objective evidence of active disease for a period of at least 2 months. Partial response was defined as an average decrease of measureable lesions to less than 50% of their pretreatment size.

Overall survival and disease-free survival were calculated from the start of initial treatment. The survival curves were plotted using Kaplan-Meier method and were analyzed by the log-rank test[17]. Differences between response rates were assessed by the Fisher's exact test[18].

RESULTS

Of the 26 patients, 23 (88%) achieved complete

Table 2. Response Rate

Response	No. of patients (%)
CR	23 (88)
PR	3 (12)

CR : Complete response PR : Partial response

Table 3. Response Rate According to Variables

	No. of patients (%)		
	CR	PR	Total
Age			
< 60	16 (94)	1 (6)	17
⩾ 60	7 (78)	2 (22)	9
Sex			
Male	16 (89)	2 (11)	18
Female	7 (88)	1 (12)	8
Histology			
DPDL	17 (85)	3 (15)	20
DH	6 (100)		6
Site of disease			
Nodal	8 (80)	2 (20)	10
Extranodal	15 (94)	1 (6)	16
Stage			
I	10 (91)	1 (9)	11
II	13 (87)	2 (13)	15
Neck status			
Negative	4 (100)		4
Unilateral	15 (88)	2 (12)	17
Bilateral	4 (80)	1 (20)	5
Radiation dose			
⩽ 4500	5 (83)	1 (17)	6
⩾ 5000	18 (90)	2 (10)	20
Cycles of CHX			
< 6	7 (78)	2 (22)	9
⩾ 6	16 (94)	1 (6)	17

CR : Complete response, PR : Partial response
DPDL : Diffuse poorly differentiated lymphocytic
DH : Diffuse histiocytic

response, 3 (12%) partial response as shown in Table 2. The response rates according to the prognostic variables are illustrated in Table 3 but there were no statistical differences according to the variables.

At the time of this analysis, 8 patients were dead and 18 patients remained alive. Overall and disease-free survival rate at 3 years were 62.4% and 65.2%, respectively, as shown in Fig. 1. The 3-year survival rates according to the various prognostic factors are shown in Table 4. Favorable factors were unilateral neck node involvement ($p<0.05$)(Fig. 2), radiation dose 5000 cGy or more ($p<0.01$)(Fig. 3), and 6 or more cycles of CHX ($p=0.06$)(Fig. 4). Other variables did not show any statistical differences.

Of the 26 patients, 15 patients remained free of disease, 3 patients were lost to follow up, and 8 patients were recognized as failure including 3 partial responders. Of the 5 recurrences , 1 patient relapsed within the irradiated field, and 1 patient relapsed at distant sites, and 1 patient who had a lesion in the nasal cavity relapsed in unirradiated

Table 4. 3-Year Survival Rate According to Variables

Variables	3-Year Survival Rate (%)	p-value
Overall	62.4	
Disease-free	65.2	
Age		
< 60	82.4	
⩾ 60	33.3	NS
Sex		
Male	55.9	
Female	85.7	NS
Histology		
DPDL	70.6	
DH	31.3	NS
Site of disease		
Nodal	60.0	
Extranodal	67.3	NS
Stage		
I	81.8	
II	50.8	NS
Radiation dose		
⩽ 4500	0.0	
⩾ 5000	84.4	<0.01
No. of CHX cycles		
< 6	37.0	
⩾ 6	77.2	0.06
Neck status		
Unilateral	71.7	
Bilateral	20.0	<0.05

DPDL : Diffuse poorly differentiated lymphocytic
DH : Diffuse histiocytic
NS : Nonspecific

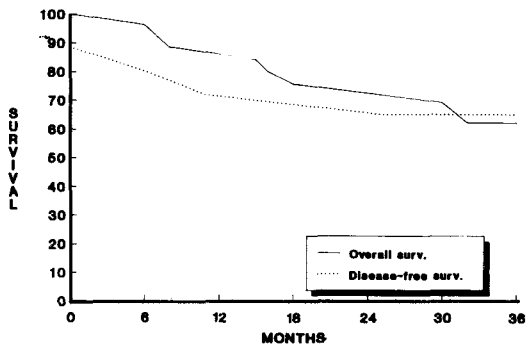

Fig. 1. Overall and disease-free survival.

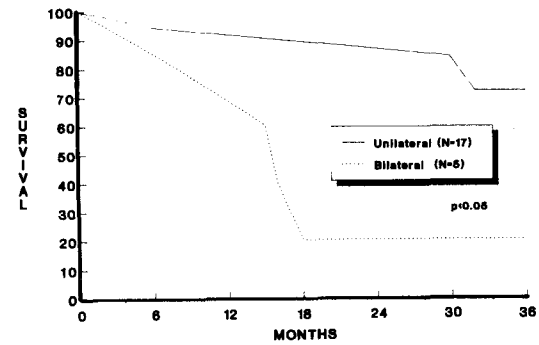

Fig. 2. Survival by neck status.

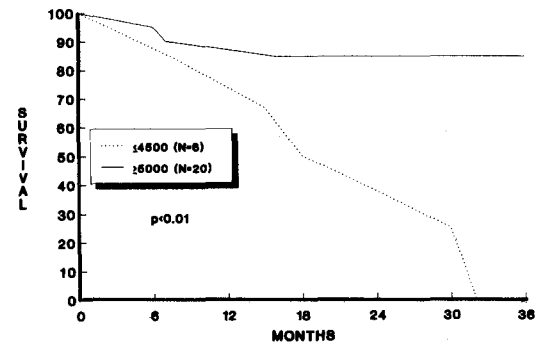

Fig. 3. Survival by radiation dose.

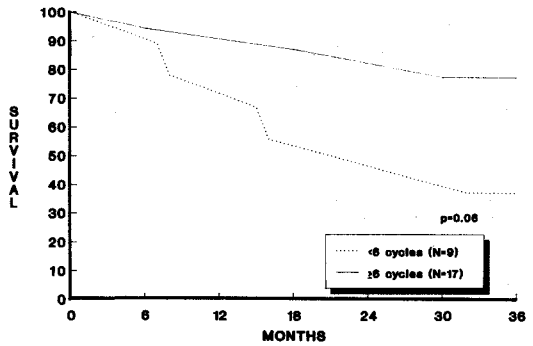

Fig. 4. Survival by number of chemotherapy cycles.

contiguous area (tonsil and neck). Two patients relapsed in areas of both irradiated and distant sites simultaneously. Median time to relapse was 7 months with a range of 3 to 11 months.

Six of the 8 failed patients were treated again with RT and/or CHX, but all died of disease except one who remained alive with stable disease in the neck for a follow up period of 22 months.

DISCUSSION

Until effective combination chemotherapy programs for the treatment of NHL of unfavorable histology were identified, most patients with localized disease (stage I-II) were treated with RT alone. Although well selected patients had a favorable outcome, the overall experience in stage I-II remained unsatisfactory[1~5,19]. Since most likely sites of failure after RT appear to be nonirradiated nodes and extranodal sites, and since the most likely sites of failure after CHX appear to be sites of initial involvement, both CHX and RT should be used as the initial treatment of patients with NHL[20]. Several randomized[8~10] and non-randomized[11~15] trials have showed improved overall and disease-free survival.

Overall and disease-free survival rate at 3 years of 62.4% and 65.2%, found in this study, are slightly lower than those reported in most CMT series[8~15]. It is quite likely that a fair segement of our patients were pathologically more advanced than clinically evident since clinical staging is known to underestimate true disease extent[21]. The Stanford group[22] reported that 6 of 37 patients (16%) with diffuse histiocytic lymphoma were advanced to a higher pathologic stage after staging laparotomy. They suggested that one of the reasons for relapse in diffuse histiocytic lymphoma was that patients might have advanced disease at the time of presentation which was missed in routine clinical staging.

The fact that survival and disease-free survival were almost parallel (Fig. 1) indicates that when recurrence occurs in this group, survival is not influenced by further therapy. Indeed, all the recurrent patients in our study failed to respond to aggressive treatment except one patient who remained alive with disease in the neck after retreatment. This is consistent with other reports[1,2,23] and a better salvage CHX regimen would be anticipated.

Analysis of the initial sites of relapse for 5 recurrent patients did not reveal an obvious pattern of failure: 1 local failure, 1 distant failure, I contiguous failure, and 2 simultaneous local and distant faliure. Moreover, an analysis of the clinical features of the 8 patients (3 partial responders and 5 recurrences) did not indicate any significant difference in the distribution of potentially adverse features between patients who remain disease-free and those who eventually relapse.

NHL is a conglomerate of diverse entities and the identification of the relevant prognostic factors is a far more difficult challenge, even with the modern tool of statistical analysis. Tubiana et al[24] stated that at least 3 main factors should be taken into account: clinical stage based on Ann Arbor classification, histologic subtype, and bulk of disease.

Stage is widely accepted as the most valuable indicator for relapse or survival in the patients with stage I-II NHL of the head and neck[21,25~27]. In the current analysis, the rate of complete response was similar between stage I and II, but stage I patients had better survival than stage II (81.8% vs. 50.8%) though it was not statistically significant. The poor survival of stage II patients may be due to the extent of the disease but another possibility is that a greater proportion of the patients may have had more advanced disease than clinically staged.

Reddy at al[1,2] reported that diffuse poorly differentiated lymphocytic lymphoma and diffuse histiocytic lymphoma had similar survival and disease-free survival rates. In this analysis, the survival of diffuse poorly differentiated lymphocytic lymphoma was better than that of diffuse histiocytic lymphoma (70.6% vs. 31.3%), but log-rank test revealed no statistical significance.

Shimm et al[21] reported that extent of metastatic involvement of neck correlated with survival, i.e., unilateral cervical adenopathy fared better than

bilateral adenopathy. This is consistent with our result that unilateral involvement of neck fared better than bilateral involvement in survival (71.7% vs. 20%, $p<0.05$) as shown in Fig. 2.

The optimum radiation tumor dose is influenced by the histology, the extent of local disease, the tissue volume to be treated, and the observed rate of regression during therapy[24]. Usually 3500 to 4000 cGy delivered in fractionated doses over 4 to 5 weeks is sufficient to achieve local control in patients with follicular lymphoma. However, larger doses may be required for patients with bulky tumors and those with a large cell component to the histology. At the Princess Margaret Hospital, 80% of patients with medium or large bulky nodal involvement had local control of nodal disease after total doses of 4500 to 5000 cGy[16]. This is consistent with other analysis of dose-effect relationships in NHL, which show that a minimum dose of 4000 to 4500 cGy is required for local control of diffuse disease[24]. Nonetheless, a true tumoricidal dose level for diffuse lymphomas has not been established. Peters et al[28] suggested that when RT is required to supplement CHX, all the tumor doses quoted can be reduced to approximately two-thirds of the average dosage required for primary RT. Tubiana et al[24], however, stated that even with CHX is combined with RT, a dose of at least 4500 cGy appears to be required to obtain a local control of the bulky lesions. In our result, the survival of patients who received 4000 to 4500 cGy was significantly worse than that of those received 5000 to 6500 cGy ($p<0.01$)(Fig. 3), which suggests that higher radiation dose is associated with better survival even with CHX.

The minimum number of courses of CHX prior to RT remains to be defined. It may be that 3 cycles of CHX before RT are required when used in a CMT program[7,15]. Our study showed that the survival of patients who received less than 6 total cycles of CHX was lower than that of 6 or more cycles with marginal significance ($p=0.06$)(Fig. 4). It would seem that high dose RT and CHX yielded better survival.

In conclusion, CMT would seem to be necessary in stage I and II NHL of unfavorable histology, and higher radiation dose and 6 or more cycles of CHX would be necessary for a better survival.

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= 국문초록 =

두경부 악성 임파종에 대한 병용치료의 결과

경북대학교 의과대학 치료방사선과학교실

김재철 · 김상보 · 류삼열 · 박인규

1985년 4월부터 1989년 9월까지 경북대학교병원 치료방사선과에서 두경부 악성 임파종으로 진단되어 복합화학요법 및 방사선 병용치료를 받은 26명을 대상으로 치료성적을 분석하였다. 완전관해율은 88%, 부분관해율은 12%였고 관해율에 영향을 미치는 예후인자는 없었다. 3년 생존율 및 3년무병생존율은 각각 62.4% 및 65.2%였다. 생존율이 높았던 군은 편측성 임파절침범($p<0.05$), 방사선량 5000 cGy 이상 ($p<0.01$), 화학요법 6회 이상 ($p=0.06$)등이었다. 26예 중 8예(부분관해 3예 포함)에서 재발을 했으며 재발 양상은 국소재발 1예, 원격 전이 1예, 인접조직에 재발 1예, 국소 재발 및 원격전이 2예 등이었다.