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Comparative Study with CHOP-Pepleo and COP-Pepleo Combination Chemotherapy for Non-Hodgkin's Lymphoma

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Abstract Combination chemotherapy with CHOP-Pepleo regimen (cyclophosphamide, adriamycin, vincristine, prednisolone and pepleomycin), or COP-Pepleo regimen (cyclophosphamide, vincristine, prednisolone, and pepleomycin), was used as a remission induction therapy for patients with mostly advanced non-Hodgkin's lymphomas. Among 23 patients treated with CHOP-Pepleo or CHOP without Pepleo (5 patients), 57% achieved complete remission with 78% overall response (complete remission plus partisl remission). Among 12 patients treated with COP-Pepleo, 50% achieved complete remissions with 83% overall response. No significant difference was observed in response rates between two groups. Median follow-up durations were 14 months for CHOP-Pepleo and 16 months for COP-Pepleo. Of all patients who achieved complete remission, three patients (23%) treated with CHOP-Pepleo and 4 patients (67%) treated with COP-Pepleo relapsed within 20 months after achieving complete remission. Relapse-free survival rates at 4 years were 65% for CHOP-Pepleo and 33% for COP-Pepleo. Survival rates at 4 years were 54% for CHOP-Pepleo and 34% for COP-Pepleo. Each survival curve in the patients treated with CHOP-Pepleo or COP-Pepleo showed a plateau after 24 months.

Though the addition of adriamycin did not improve complete remission rate significantly as a whole, the complete remission rate in stage IV, overall survival and relapse-free survival were favorably inproved by the addition of adriamycin. Further study will be needed to assess the effect of adriamycin on response and survival in patients with non-Hodgkin's lymphomas.

Key Words : Non-Hodgkin's Lymphoma, Chemotherapy, CHOP-Pepleo, COP-Pepleo

Introduction

Many forms of combination chemotherapy have been developed in the management of patients with non-Hodgkin's lymphoma. The combination therapy with cyclophosphamide,

vincristine, and prednisolone (COP) has been regarded as one of standard chemotherapies.[1,2] Over the years, several anti-tumor drugs such as bleomycin and adriamycin were added to this combination, and the COP-Bleo or CHOP combination chemotherapy had obtained a higher rate of complete remission.[3,4] Recently, the adriamycin-containing combinations such as CHOP-Bleo, BACOP, M-BACOD and MTX-CHOP have been widely used for remission induction therapy.[5-10] Although some evidence revealed the superiority of the combination which includes adriamycin,[6,11] the advantage of its addition to the response is not definitely established.

This study was performed to evaluate the therapeutic value of CHOP-Pepleo regimen (CHOP with pepleocycin, an analogue of bleomycin[12]) comparing to that of the COP-Pepleo regimen for remission induction therapy.

Materials and Methods

Between January 1982 and December 1986, 35 patients with stage II, III and IV non-Hodgkin's lymphomas were treated with CHOP-Pepleo or COP-Pepleo combination chemotherapy for remission induction. Patients without the previous chemotherapy were eligible and those who had received prior radiotherapy were included.

All biopsy specimens were diagnosed and classified according to the criteria of LSG.[13] Staging of lymphoma's was carried out according to the criteria adopted at the Ann Arbor Conference on Hodgkin's Disease.[14] Staging procedures included routine physical examination, chest X-ray, lymphangiography, bone marrow aspiration and biopsy. Intravenous pyelogram and scintigram of the liver and spleen were performed in the selected patients. Lumber puncture with the cytologic examination of the spinal fluid and brain CT were done in patients with symptoms due to meningeal or central nervous system involvement.

CHOP-Pepleo or COP-Pepleo regimen was assigned to the patients as shown in Table 1. Treatment courses were repeated at approximately 3-week intervals. When the peripheral white blood cell count fell below 1,000/mm^3, or when the bone marrow was extremely hypocellular, the dosages of adriamycin and cyclophosphamide in the next course were reduced by at least 25%. In two cases with serious arrhythmia probably due to CHOP-Pepleo therapy, COP-Pepleo regimen was substituted for the CHOP-Pepleo regimen, Then, these two cases were included into the group with COP-Pepleo regimen. Vincristine and prednisolone were reduced or discontinued, when moderate or severe side effects ascribable to them were evident. Total cumulative doses of adriamycin and pepleomycin were limited to 500mg and 200mg, respectively.

Response to these chemotherapies was evaluated according to the following criteria. Complete remission was defined as the complete disappearance of symptoms and all measurable evidence of lesions. Partial remission state was given to the patients who had more than 50% reduction in measurable disease, which continued at least for one month. Patients whose measurable lesions regressed less than 50% during the course of treatment or recurred within a month were considered to have had "no response".

When a complete remission was obtained after at least 2 courses, the same schedule was repeated more than 3 courses as a consolidation

Table 1 CHOP-Pepleo and COP-Pepleo Chemotherapy for Non-Hodgkin's Lymphoma

C	cyclophosphamide	750 mg/m^2	day 1	iv
H	adriamycin	50 mg/m^2	day 1	iv
O	vincristine	1.4 mg/m^2	day 1 & 5	iv
P	prednisolone	100 mg/day	day 1 - 5	po
Pepleo	pepleomycin	10 mg/m^2	day 1, 3 & 5	iv
C	cyclophosphamide	750 mg/m^2	day 1	iv
O	vincristine	1.4 mg/m^2	day 1 & 5	iv
P	Prednisolone	100 mg/day	day 1- 5	po
Pepleo	pepleomycin	10 mg/m^2	day 1, 3 & 5	iv
Course repeated every 3 weeks				

therapy at 3-week intervals. As a maintenance therapy, all patients who obtained complete remission received CHOP or COP regimen with or without pepleomycin, considering the age and bone marrow cellularity. To the patients with partial remission, the same treatment was also continued until complete remission or relapse. Patients who did not respond to 2 courses of remission induction therapy were treated with other combinations.

The duration of survival was calculated from the date of onset of the chemotherapy to the date of death. The duration of remission was calculated from the date of response to the date of relapse.

Chi-Square tests were used in testing for the differences in response rates. Survival and relapse-free survival curves were calculated using the methods of Kaplan and Meier.[15] The curves were compared using the generalized Wilcoxon test.[16]

Results

Thirty-five patients were entered in this study ; their median age was 53 years (range 9-78). The male : female ratio was 2.2 : 1.0. No patients had received a previous chemotherapy and only 5 patients (14%) had received radiotherapy prior to this study. The majority of the patients had advanced disease : 11% were stage II, 29% were stage III, and 60% were stage IV including 4 patients who were in leukemic state.

Therapeutic results of CHOP-Pepleo and COP-Pepleo are shown in Table 2. We chose CHOP-Pepleo regimen to treat 23 patients including 5 patients without pepleomycin, and 12 patients were treated with COP-Pepleo. These two groups of patients were almost comparable with respect to sex, age, stage, and histology. Nineteen (54%) of the 35 patients achieved a complete remission ; complete remission was achieved in 13 (57%) of patients treated with CHOP-Pepleo and in 6 (50%) of the patients treated with COP-Pepleo. No significant difference in the complete remission rate was noted between the two groups. Two (50%) of four patients who had received prior radiotherapy achieved complete remission, and the remainder had partial response. The complete remission rates by stage of lymphomas were different and appeared to be lower in the advance stage ; 100%, 70% and 57% in stage II, III and IV, respectively, although there was no significant difference statistically ($P=0.08$). In patients with stage IV lymphoma, however, the complete remission rate by CHOP-Pepleo regimen was much higher than by COP-Pepleo (50% and 20%, respectively).

Table 2 Response to CHOP-Pepleo and COP-Pepleo by Prior Therapy, Stage and Age

	CHOP-Pepleo			COP-Pepleo		
	n	CR	PR	n	CR	PR
Total	23	13	5	12	6	4
Prior therapy						
no prior therapy	21	12	4	10	5	3
radiotherapy	2	1	1	2	1	1
Stage II	2	2	0	2	2	0
III	5	3	2	5	3	1
IV	16	8	3	5	1	3
B symptom	11	5	2	4	3	0
Leukemic state	4	2	1	0		
Age 60>	16	11	1	6	4	2
60≦	7	2	4	6	2	2

n : No. of patients, CR : complete remission, PR : partial remission

Table 3 Response to CHOP-Pepleo and COP-Pepleo by Pathologic Type

Histology	CHOP-Pepleo			COP-Pepleo		
	n	CR	PR	n	CR	PR
Follicular	3	2	1	1	1	0
medium	2	1	1	1	1	0
mixed	1	1	0	0		
Diffuse	19	10	4	11	5	4
small	2	0	2	0		
medium	3	2	0	1	1	0
mixed	3	2	1	4	2	2
large	10	5	1	4	2	1
pleomorphic	1	1	0	1	0	0
Burkitt	0			1	0	1
Unknown*	1	1	0	0		

*Lymph nodes biopsy was not practiced because of the state of leukemic change.
n : No. of pateints, CR : complete remission, PR : partial remission

The complete remission rates in the patients above 60 years (31%) and under 60 years (68%) showed significant difference statistically (P=0.07). The distribution of the evaluable patients according to the classification of the LSG and their responses are shown in Table 3.

The survival of all patients is shown in Figure 1. The 4-year survival rates were estimated as 54% and 34% for patients treated with CHOP-Pepleo and COP-Pepleo, respectively, with no significant difference between the two groups (P=0.45). The survival curves became flat after 24 months in both groups of the patients. The relapse-free survival of the 19 patients who achieved complete remissions is show in Figure 2. Three (23%) of the 13 complete responders treated with CHOP-Pepleo subsequently relapsed at 6, 6, and 20 months after achieving a complete remission. Four (67%) of the 6 complete responders treated with COP-Pepleo relapsed at 7, 7, 9, and 12 months. Overall survival rate without relapse was 60% at 4 years. Respective survival rates between the two groups with CHOP-Pepleo treatment (65%) and COP-Pepleo treatment (33%) showed no significant difference (P=0.20). Relapse free survival curve in complete responders showed a plateau after 21 months.

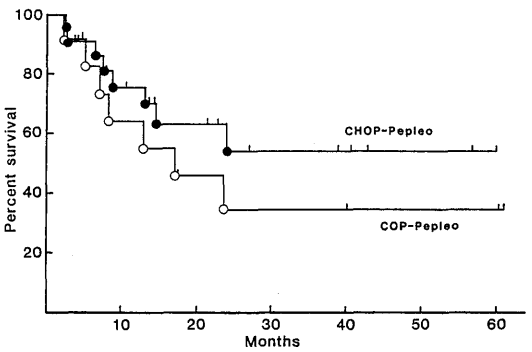

Fig.1 Survival of patients from the start of therapy

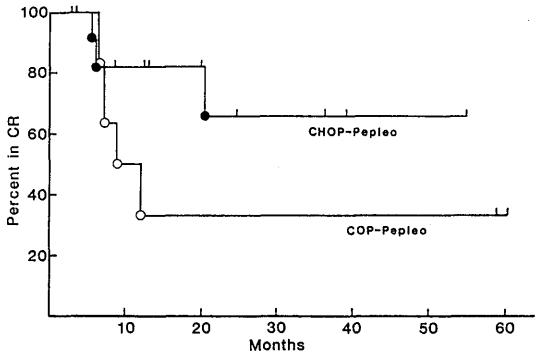

Fig.2 Duration of complete remission in complete responders.

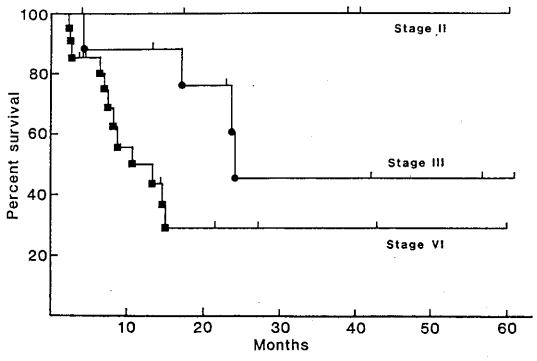

Fig.3 Survival of patients by the stage.

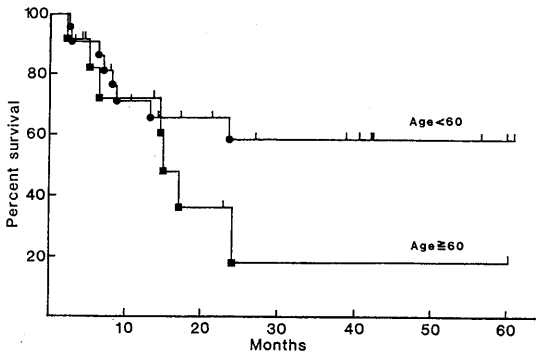

Fig.4 Survival of patients by the age.

The survivals of all patients by stage and by age were shown Figures 3 and 4. The survival of the patients above 60 years of age was not significantly different from that of patients under 60 years of age. The significant difference in survival rates by stage was noted ; patients in stage IV had the lower survival rates compared to those in stage II or III ($P=0.02$). There was no significant difference in survivals between stage II and stage III ($P=0.12$).

Both CHOP-Pepleo and COP-Pepleo regimens were tolerable. As expected, leukopenia and thrombocytopenia generally occurred from 10 to 14 days following therapy. Although, myelosuppression was not so severe, seventy-one percent of all patients had white blood cell counts below 2000/mm^3 after the first or second treatment. Thrombocytopenia was less frequent, and only 11% of patients had platelet counts below 100,000/mm^3 in courses of therapy.

Nausea and vomiting were common side effects of treatment due to large doses of adriamycin and cyclophosphamide, but did not limit chemotherapy. Severe hair loss was usually associated with CHOP-Pepleo regimen.

Cardiac toxicity attributable to adriamycin were noted in 5 (22%) patients treated with CHOP-Pepleo. Serious arrhythmia developed in 2 patients during the first chemotherapy by CHOP-Pepleo regimen. Drug-related congestive heart failure was not noted.

Numbness or paresthesia of peripheral extremities due to vincristine was noted in 12 (34%) patients. Paralytic ileus developed in four patients (11%). One patient who was administered with pepleomycin developed slight restrictive lung failure.

Discussion

Our results of CHOP-Pepleo regimen and COP-Pepleo regimen in non-Hodgkin's lymphoma were comparable to those previously reported by others.[3-11] The variation in complete remission rate is probably explicable on the basis of a small number of patients, differences of protocol, and interobserver variation in relation to staging, histological classification, and evaluation of remission status.

In this study, the prognosis of patients with follicular lymphoma who gained complete or partial remissions was more favorable than those with diffuse lymphoma, while no significant differences in remission rates were obtained by difference in the histologic types or regimens. The poor prognosis in diffuse lymphoma was emphasized in COP combination program,[2,17] and the higher complete remission rate in diffuse lymphoma was obtained by CHOP-Pepleo regimen than by COP combination.[6,11] Our results were consistent with the previous reports.

The complete remission rate and the survival of the patients with stage II and III were more favorable than those of patients with stage IV. In stage II and III, these two parameters showed no significant difference between CHOP-Pepleo and COP-Pepleo regi-

mens. However, in stage IV, the complete remission rate of CHOP-Pepleo was more favorable than that of COP-Pepleo, as seen in other studies.[5,8] In this study, the complete remission rate in patients treated with CHOP-Pepleo was 50% as compared to 20% in the group treated with COP-Pepleo, although no significant difference was observed statistically between the two groups.

Age was also an important factor that reflects to complete remission rate in non-Hodgkin's lymphomas. Complete remission rate and survival in the patients under 60 years of age were more favorable than above 60 years (Table 2). These results may be explained partly by the fact that the full doses of anti-tumor drugs were given to the majority of the patients under 60 year of age in contrast to the elder patients in whom doses were reduced to avoid more pronounced marrow toxicity (data not shown).

Our results indicate that the addition of adriamycin does not significantly improve the response rate. However, the relapse rate in complete responders was lower in patients treated with CHOP-Pepleo than in the patients treated with COP-Pepleo, and the relapse-free survival rate at 4 years was higher in CHOP-Pepleo than in COP-Pepleo. Furthemore, in poor prognostic states, such as stage IV or diffuse lymphomas, the response by adding adriamycin was more favorable. These results were consistent to the previous reports.[6,11]

Both survival curve in all patients and relapse free survival curve in complete responders became flat after 24 months, which suggested the curability of non-Hodgkin's lymphomas. Mckelvey and coworkers reported that the relapse rate decreased after 3 years and became a plateau in complete responders of diffuse histiocytic lymphoma.[18] According to Arimitage et al., 61% of patients who achieved complete remission with the CHOP regimen were long-term disease-free survivors.[19] These reports suggested the possibility has a curative effect that adriamycin-containing combination chemotherapy of non-Hodgkin's lymphomas.

The addition of pepleomycin, an analogue of bleomycin,[12] at the doses used in this study did not enhance any other major toxicities. It is reported that the addition of blemycin to CHOP combination chemotherapy does not increase the complete remission rate that attained with CHOP.[5-8] Previously, we reported that COP-Bleo had advantages to COP in the overall response (complete and partial remissions), the time until the complete remission and the duration of the median survival, though there was no difference in the complete remission rate between COP-Bleo and COP.[20] In this study, we were unable to determine whether the addition of pepleomycin to CHOP chemotherapy improved the therapeutic results because the numbers of the patients treated without pepleomycin was so small. The role of pepleomycin is worthy of further investigation.

The combination therapy of CHOP-Pepleo was well tolerated. Cardiac toxicity induced by adriamycin was comparable as the other studies. With regard to the degree of myelosuppression, there was no difference between CHOP-Pepleo and COP-Pepleo.

Finally, our results conclude that adriamycin-containing combination therapy is recommended in the patients with non-Hodgkin's lymphoma, especially, in advanced stages. COP-Pepleo combination may be still useful in the patients in a relatively lower stage (II or III) of the desease.

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