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Combination Chemotherapy only for Stage II non-Hodgkin's Lymphoma

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Abstract—*Twenty-six previously untreated patients with clinical stage (CS) II B non-Hodgkin's lymphoma (NHL) were treated with systemic chemotherapy only. Patients received bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP). All patients had intermediate- or high-grade lymphoma. Objective response was demonstrated in* 25 *patients* (96%), *with* 21 *patients* (81%) *achieving complete remission (CR). Two of CR patients developed unsalvageable relapse, the remaining* 19 *patients are still alive and disease-free. The median duration of CR has not been reached. Of four patients* (15%) *with documented partial remission* (PR), *three were salvaged using second-line therapy. Over a median follow-up of* 12 months (*range,* 3–30), 22 *patients* (85%) *are alive and disease-free, of whom* 16 (62%) *have survived more than* 1 *yr. Bulky disease or gastrointestinal tract (GIT) involvement did not influence the CR rate. Our results compared favorably with radiation therapy for stage II NHL; however, a larger controlled and randomized study is warranted.*

INTRODUCTION

THE PROGNOSIS for patients with disseminated lymphoma has improved significantly since the introduction of combination chemotherapy. With the use of adriamycin-containing combinations, a high proportion of durable complete remission can be achieved [1–3].

The role of combination chemotherapy in the treatment of the more aggressive localized forms of the disease (stages I and II) has not been clearly defined. Historically, radiotherapy has been considered the treatment of choice. While it has been curative in 45–65% of patients with very localized disease (stage I), radiation therapy has been considerably less successful in patients with stage II disease, particularly with diffuse lymphoma [4–7].

Few investigators have reported their favorable experience using combination chemotherapy alone for clinically staged patients with localized forms of disease. A high response rate as well as disease-free survival has been achieved [8, 9].

In this paper we present our own preliminary results with the use of the BACOP regimen for CS II aggressive types of NHL.

MATERIALS AND METHODS

Between August 1981 and August 1984, 26 patients with CS II NHL were treated using the BACOP regimen [1]. Excluded from the study were those who had previously been treated with radiotherapy and/or chemotherapy, those with stage I disease or those who were rendered disease-free following biopsy. Also excluded were those patients with low-grade NHL based on the National Cancer Institute (NCI) Working Formulation [10]. The histopathological classification originally used was that of Rappaport [11], but on review material, the NCI Working Formulation was adopted. For this purpose all paraffin blocks were retrieved, and sections re-cut and stained. In addition to the routine H/E stain, methyl green pyronin, reticulin and immunohistochemical techniques using immunoglobulins, kappa and lambda light chains and lysozymes were used.

All patients were clinically staged. Staging included complete history and physical examination, routine laboratory studies, chest roentgenogram, IVP, bipedal lymphangiogram, CT scan of the chest and/or abdomen and pelvis, bilateral bone marrow aspiration and biopsy, and percutaneous liver biopsy if it was suspected to be involved. Liver and spleen scan, bone survey and scan, gallium scan, and abdominal ultrasound were done in selected symptomatic patients. Staging laparotomies were not performed to assess the extent of disease; however, patients presenting with abdominal disease had a diagnostic laparotomy. The

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extent of disease was categorized according to Ann Arbor Conference Criteria [12]. Patients with bulky disease were those with disease that has a single site of tumour measuring greater than 10 cm in diameter, palpable abdominal mass displacing intra-abdominal organs or mediastinal mass.

All patients received the BACOP regimen (cyclophosphamide i.v. 650 mg/m^2, adriamycin i.v. 25 mg/m^2 and vincristine i.v. 1.4 mg/m^2) on days 1 and 8. Bleomycin 5 U/m^2 was given i.v. on days 15 and 22. Oral prednisone 60 mg/m^2 was given on days 15–28. The cycle was then repeated.

Blood counts were obtained weekly during therapy. Dosage of adriamycin and cyclophosphamide was reduced by 50% if the WBC count was 2000–3000/mm^3 or platelet count 50,000–100,000/mm^3; dose was delayed if the WBC count was under 2000/mm^3 or platelet count under 50,000/mm^3. The vincristine dose was reduced by 50% if moderate neuropathy developed and was discontinued with severe neuropathy. Bleomycin was omitted with any evidence of pulmonary toxicity or with severe mucous membrane or cutaneous reactions.

All responding patients were scheduled to receive a minimum of six cycles of BACOP or two cycles following clinical remission. Chemotherapy was stopped if there was clear evidence of progression despite 2–3 full courses. At the end of scheduled therapy the treatment was stopped, and 1 month later each patient was re-staged for evidence of residual disease. No maintenance therapy was implemented. Careful re-staging processes were carried out, including physical examination, laboratory studies, chest roentgenogram and other relevant radiological studies such as CT scan, bone marrow aspiration and biopsy, and biopsy of any previously involved extranodal site.

A complete remission (CR) was defined as full regression of all evidence of the disease for a minimum of 1 month. A partial remission (PR) was defined as a greater than 50% reduction in all measurable disease for at least 1 month. Patients demonstrating a response with less than 50% reduction in tumour size or less than 1 month were classified as having a minor response (MR). Progressive disease was defined as no response (NR). Duration of response was calculated from the date of demonstration of that response and survival was dated from the time first seen at our institution.

No patient was excluded from the analysis because of major protocol violation, recent entry, insufficient data, bulky disease, GIT involvement, incomplete therapy, toxicity or early death. Survival curves were calculated by the method of Kaplan and Meier [13]. Tests of significance were determined by the Wilcoxon method, modified by Gehan [14]. The Fisher exact test [15] was used to test the significance of bulky disease and GIT involvement.

RESULTS

All patients entered were evaluable for response. Their clinical characteristics are presented in Table 1. Table 2 demonstrates the distribution of different pathological subtypes based on the NCI Working Formulation.

The median time from start of therapy to response was 6 weeks. Twenty-five patients (96%) achieved objective remission: 21 patients (81%) CR and four patients (15%) PR. Only one patient had no response. The median follow-up time was 12 months, with range of 3–30 months. Disease-free survival is plotted in Fig. 1. The median duration of disease-free survival has not been reached. Of all 21 patients achieving CR, 19 patients remained disease-free. Only two patients

Table 1. *Patients' characteristics*

	No. of patients (n = 26)
Sex	
Male	18
Female	8
B Symptoms	26
Extranodal involvement	
GIT	15 (58%)
Other	2 (8%)
Total	17 (66%)
Bulky disease	
Below diaphragm	12 (46%)
Above diaphragm	2 (8%)
Total	14 (54%)

Median age = 36 yr (range 15–66 yr).

Table 2. *Pathological classification: NCI Working Formulation*

	No. of patients
Intermediate-grade lymphomas	
Diffuse small cleaved cell	4
Diffuse mixed, small and large cleaved cell	4
Diffuse large cleaved cell	5
Total	13
High-grade lymphomas	
Large cell, lymphoblastic convoluted cell	1
Large cell, lymphoblastic non-convoluted cell	2
Large cell, immunoblastic	2
Diffuse small non-cleaved cells (Burkitt's)	4
Large cell, histiocytic	4
Total	13

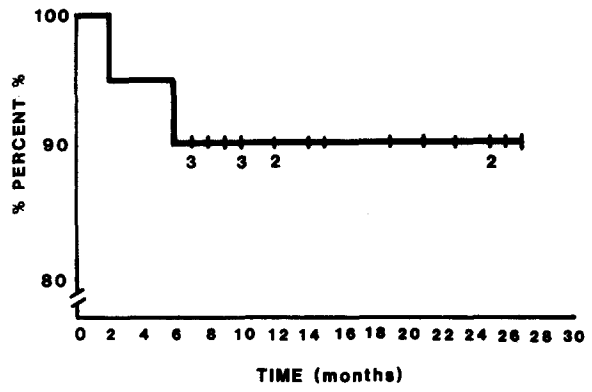

Fig. 1. Disease-free survival of patients achieving complete remission (N = 21).

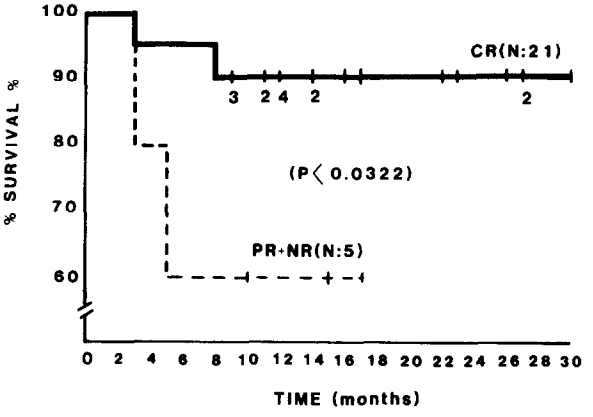

Fig. 2. Percentage survival of patients achieving complete remission (CR) (N = 21), and patients achieving partial remission (PR) + no response (NR) (N = 5).

relapsed after 2 and 6 months respectively. In three of the four patients who achieved PR, complete remission was induced by radiotherapy in one and by second-line chemotherapy (Ara-C and VP-16) in two. These three patients are alive and disease free for 10, 15 and 17 months respectively.

Survival curves for CR and PR + NR patients are presented in Fig. 2. Of 21 patients who achieved CR, 19 (90%) are still alive and disease-free. Two patients died, after 3 and 8 months respectively. In the PR + NR patients two died, after 3 and 5 months respectively. The difference in survival between the two groups was significant ($P < 0.0322$). The median survival of CR patients has not been reached. Of all the series, 16 patients (62%) are alive and disease-free after more than 12 months.

Ten out of 14 patients with bulky disease demonstrated CR, compared to 11/12 patients without bulky disease. The difference was not significant ($P = 0.273$). GIT involvement based on operative, endoscopic, histologic or radiologic evidence was demonstrated in 15 patients. Of those 15 patients, 11 achieved CR, compared to 10/11 patients without involvement — a difference that was not significant ($P = 0.213$).

Leukopenia occurred in 30% of courses, resulting in WBC nadirs below 3000/mm^3. Leukopenia was complicated by serious infection in three patients and resulted in fatal Gram-negative septicemia in one. Only 2% of the courses was associated with a platelet count under 50,000/mm^3. No incidence of serious bleeding occurred. Nadirs occurred mostly at day 14, with full recovery of counts often at the beginning of the subsequent scheduled course.

Reversible total alopecia occurred in most patients. Mild-to-moderate skin and nail changes occurred in six patients. Vomiting was mild-to-moderate in the majority of patients. None of the patients developed cardiomyopathy, pulmonary fibrosis or hemorrhagic cystitis.

DISCUSSION

Traditionally, treatment of early stages of NHL for many years has been radiotherapy. However, in most studies the relapse frequency has remained disappointingly high [4–7]. This has been particularly true for stage II of the unfavorable histologic subtypes [16]. In another series the 2-yr disease-free survival for stage II diffuse histiocytic lymphoma was only 25% and was not influenced by the extent of radiation fields [17].

Several studies have shown a favorable influence of adjuvant chemotherapy on relapse frequency and to some extent on survival of patients with localized disease [7, 18, 19]. However, two other studies failed to demonstrate the same benefit from such an approach [20, 21]. The first study, however, included a small number of patients; furthermore, two of the chemotherapeutic agents used, Ara-C and 6-thioguanine, are known to have only a relatively weak activity against NHL. Although a few stage II patients failing radiotherapy can be effectively salvaged, it would appear that stage II or IIE disease would best be managed by either chemotherapy alone or with chemotherapy and radiotherapy. The histologic subtype should influence the choice of the above therapeutic modalities.

In our series objective remission was achieved in 96% of patients, of which 81% were complete. Two of our CR patients relapsed in the first 6 months. These high response and low relapse rates are similar to those of Miller and Jones, who used chemotherapy only for stage I and II NHL [8].

Of the whole group, only four patients died within the first 8 months. Eighty-five percent of all patients and 90% of complete responders are alive and disease-free. It was of interest to demonstrate a durable remission in three patients using an alternative line of therapy after their partial re-

sponse to the BACOP regimen.

Our series was characterized by a number of factors known to be associated with poor prognosis [16, 22, 23]: B symptoms in all 26 patients, GIT involvement in 58%, bulky disease in 54%, and intermediate- and high-grade histology in all patients. Furthermore, due to the fact that all our patients were clinically staged, the series might have included some patients with more advanced disease. Despite that, our reported high response and low relapse rates were superior to currently reported series employing radiotherapy only as the prime mode of therapy [4–7].

Despite the relatively small number of patients in our series, the efficacy of systemic chemotherapy alone was evident. This approach is particularly suitable for medical oncology satellites where access to radiotherapy facilities is not readily available, a situation which is not uncommon in developing countries. This choice is not likely to compromise the outcome.

This approach needs to be tested further in a larger number of randomized patients. The efficacy of systemic chemotherapy alone for early stages of NHL also needs to be compared with combined radiation therapy and adjuvant chemotherapy.

REFERENCES

1. Shein PS, De Vita VT, Hubbard S *et al.* Bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. *Ann Intern Med* 1976, **85**, 417–422.
2. Skarin AT, Rosenthal DS, Moloney WC, Frei E III. Combination chemotherapy with bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP). *Blood* 1977, **49**, 759–770.
3. Coleman M, Boyd DB, Bernhardt B *et al.* COPBLAM III: combination chemotherapy for diffuse large cell with cyclophosphamide, infusional oncovin, prednisone, infusional bleomycin, adriamycin and matulane. *Proc ASCO* 1984, **25**, 246.
4. Sweet DL, Golomb HM. The treatment of histiocytic lymphoma. *Semin Oncol* 1980, **7**, 302–310.
5. Reddy S, Pellettiere E, Saxena V, Hendrickson FR. Extranodal non-Hodgkin's lymphoma. *Cancer* 1980, **46**, 1925–1931.
6. Gospodarowicz MK, Bush TC, Brown TC. Role of radiation in treatment of patients with intermediate and high grade non-Hodgkin's lymphoma. *Proc ASCO* 1984, **25**, 236.
7. Nissen NI, Ersbøll J, Hansen HS *et al.* A randomized study of radiotherapy versus radiotherapy plus chemotherapy in Stage I–II non-Hodgkin's lymphomas. *Cancer* 1983, **52**, 1–7.
8. Miller TP, Jones SE. Chemotherapy of localized histiocytic lymphoma. *Lancet* 1979, **i**, 358–360.
9. Cabanillas F, Bodey GR, Freirech EJ. Chemotherapy alone for management of Stage I or II malignant lymphoma of unfavorable histology. *Proc AACR* 1979, **20**, 19.
10. National Cancer Institute-sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. The non-Hodgkin's Lymphoma Pathological Classification project. *Cancer* 1982, **49**, 2112–2135.
11. Rappaport H. Tumours of hematopoietic system. In: *Atlas of Tumor Pathology*. Washington, DC, Armed Forces Institute of Pathology, 1966, Sect. III, Fasc. 8.
12. Carbone PP, Kaplan HS, Musshoff K *et al.* Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971, **31**, 1860–1861.
13. Kaplan ER, Meier P. Non-parametric estimation from incomplete observation. *J Am Statist Assoc* 1965, **52**, 457–480.
14. Gehan EA. A generalized Wilcoxon test for comparing arbitrary singly censored samples. *Biometrika* 1965, **52**, 203.
15. Fisher RA, Yates F. *Statistical Tables for Biological, Agricultural and Medical Research.* London, Oliver and Boyd, 1957.
16. Canellos GP, Garvin AJ, Young RC. Malignant lymphoma: II. Prognostic factors and response to treatment of 473 patients at the National Cancer Institute. *Cancer* 1982, **50**, 2708–2721.
17. Jones SE, Fuks Z, Kaplan HS, Rosenberg SA. Non-Hodgkin's lymphomas. V: Results of radiotherapy. *Cancer* 1973, **32**, 682.
18. Bonnadona G, Lattuada A, Monfardini S, Milani F, Banfi A. Combined radiotherapy-chemotherapy in localized non-Hodgkin's lymphomas: 5-year results of a randomized study. In: Jones SE, Salmon SE, eds. *Adjuvant Therapy of Cancer II.* New York, Grune & Stratton, 1979, 145–163.
19. Landberg TG, Hakansson LG, Moller TR *et al.* CVP-remission maintenance in stage I or II non-Hodgkin's lymphomas. *Cancer* 1979, **44**, 831–838.

20. Glatstein E, Donaldson SS, Rosenberg SA, Kaplan HS. Combined modality therapy in malignant lymphomas. *Cancer Treat Rep* 1977, **61**, 1199–1207.
21. Panahon A, Kaufman JH, Grasso JA, Friedman M, Stutzman L. Randomized study of radiation therapy (RT) versus RT and chemotherapy (CT) in Stage IA–IIIB non-Hodgkin's lymphoma. *Proc AACR* 1977, **18**, 321.
22. Bodey G, Rodriguez V. Approaches to the treatment of acute leukemia and lympoma in adults. *Semin Hematol* 1978, **15**, 221–261.
23. Fisher RI, De Vita VT, Johnson BL, Simon R, Young RC. Prognostic factors for advanced diffuse histiocytic lymphoma following treatment with combination chemotherapy. *Am J Med* 1977, **63**, 177–182.