Combination Chemotherapy of Advanced Non-Hodgkin Lymphoma with Bleomycin, Adriamycin, Cyclophosphamide, Vincristine, and Prednisone (BACOP)

By Arthur T. Skarin, David S. Rosenthal, William C. Moloney, and Emil Frei, III

Seventy-three patients with advanced non-Hodgkin lymphoma were treated with bleomycin, Adriamycin, cyclophosphamide, vincristine (Oncovin) and prednisone (BACOP), administered intensively during a 7-wk induction course followed by intermittent cycles every 3 wk for a total of 28 wk. The objective response in 44 evaluable nonleukemic patients with diffuse histology was 86%, with 66% achieving a complete remission (CR), varying from 80% for diffuse poorly differentiated lymphocytic (DPDL) to 56% for diffuse histiocytic (DH) lymphoma. In patients with nodular histology 89% (8/9) achieved a CR with a projected 75% of patients in CR at 14 mo. Median follow-up from time of CR for nodular histology was 17 mo. The projected median duration of CR in diffuse histology was 14 mo, with median survival 14 mo. Patients with a partial response survived a median of 7 mo, compared to 3 mo for nonresponders. Of 29 patients with diffuse histology, 17 (59%) have remained disease free for 5–34 mo with a median follow-up of 12 mo. Survival beyond 20 mo has been projected for 42% of patients with diffuse histology (58% with DPDL and 32% with DH). The central nervous system (CNS) was involved in a total of 11/44 (25%) patients with diffuse histology, including 5 with primary CNS relapse. BACOP resulted in a higher CR rate and longer survival than a previous three-drug program (COP), especially in patients with diffuse histology.

Several studies have shown that combination chemotherapy was superior to single-agent therapy in the management of advanced non-Hodgkin lymphoma (NHL). In 1969, a three-drug program, cyclophosphamide, vincristine (Oncovin), and prednisone (COP), was initiated at the Sidney Farber Cancer Center, and the results were published in 1974. A com-
Fig. 1. Diagram of BACOP schema for advanced non-Hodgkin lymphoma. Maintenance therapy consisted of cyclophosphamide 2 mg/kg orally daily.

complete remission rate of 77% was achieved in patients with nodular histology. While transient partial responses were frequent in patients with diffuse histology, only 14% of such patients achieved complete remission and long-term survival.

With the availability of bleomycin and Adriamycin, which showed significant activity in NHL,5'8 a new combination chemotherapy program was developed in late 1972. The program employed bleomycin, Adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP); it consisted of an intensive 7-wk induction phase followed by intermittent cycles of drugs every 3 wk for a total of 28 wk (Fig. 1).

The rationale for combining five agents was based upon qualitatively different mechanisms of action and toxicity, exploitation of cell cycle kinetics, and experimental evidence of synergism for Adriamycin and cyclophosphamide.9,10 The use of continuous prednisone and frequent doses of vincristine and bleomycin during the induction phase was designed to control the rapid proliferative thrust of these diseases, particularly between doses of cyclophosphamide and Adriamycin.

This report presents the results of BACOP in patients with advanced NHL.11

MATERIALS AND METHODS

The BACOP protocol was initiated in January 1973, and by November 1, 1975, 73 consecutive patients with advanced NHL had been registered. Ten patients were nonevaluable for response: six because concurrent or previous radiotherapy created a nonmeasurable disease status, two because of major protocol violation; and two because of recent entry into the protocol. Thus 63 patients were evaluable for response and survival data. No patient was excluded from analysis because of early death (ten died from progressive disease within 2 mo). All 73 patients were evaluable for toxicity.

All original sections were reviewed and classified according to the histologic criteria of Rappaport.12 Various histologic groups are indicated in Table I. Ten cases were classified as lymphosarcoma cell leukemia (LSL) based upon the following criteria: diffuse infiltration of bone marrow by poorly differentiated lymphocytic cells and white blood counts greater than
Table 1. Histopathologic Classification

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number</th>
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<tbody>
<tr>
<td>Nodular</td>
<td>53</td>
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<tr>
<td>Well-differentiated lymphocytic</td>
<td>15</td>
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<tr>
<td>Poorly differentiated lymphocytic</td>
<td>5</td>
</tr>
<tr>
<td>Mixed lymphocytic–histiocytic</td>
<td>6</td>
</tr>
<tr>
<td>Histiocytic</td>
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<tr>
<td>Diffuse</td>
<td>44</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>3</td>
</tr>
<tr>
<td>Well-differentiated lymphocytic</td>
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</tr>
<tr>
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<td>15</td>
</tr>
<tr>
<td>Mixed lymphocytic–histiocytic</td>
<td>6</td>
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<tr>
<td>Histiocytic</td>
<td>18</td>
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Clinical staging included chest roentgenogram, intravenous pyelogram, liver and spleen scan, bone survey and bone scan in selected symptomatic patients, bone marrow biopsy and aspiration, and percutaneous liver biopsy if liver involvement was suspected. Bilateral pedal lymphangiography was performed in patients who did not have superior vena cava syndrome or massive abdominal adenopathy which might result in complications. In the latter circumstances an intravenous pyelogram and abdominal ultrasound were employed to define retroperitoneal disease. Routine staging laparotomy was not carried out. The extent of disease was categorized according to the Ann Arbor staging classification.13

The clinical characteristics of the 53 evaluable patients with diffuse and nodular histology are presented in Table 2. Although histologic subtypes were grouped together, some differences were noted among the two largest subtypes: diffuse histiocytic lymphoma (DH) and diffuse poorly differentiated lymphocytic lymphoma (DPDL). Patients with DH had more skin lesions, malignant effusions, and involvement of other extranodal sites, while patients with DPDL had a higher incidence of bone marrow infiltration (11/15, 73%) compared to DH (6/18, 33%).

Combination chemotherapy with BACOP consisted of a 7-wk remission-induction period followed by a consolidation phase for a total of 28 wk of treatment (Fig. 1). Bleomycin, administered at a dose of 15 mg/sq m in the first 10 patients, was reduced to 4 mg/sq m (intravenously, i.v., on days 1 and 5) because of pulmonary and cutaneous toxicity. The main thrust of the program, cyclophosphamide and Adriamycin, were administered together through a running i.v. every 3 wk for a total of 10 doses (total dose of adriamycin 450 mg/sq m).
Vincristine was administered weekly for 7 wk and then on days 1 and 5 of each cycle during the consolidation period. Prednisone was given at a dose of 50 mg/sq m orally (p.o.) for 4 wk with tapering by the end of the induction period. Five-day courses at the same dose level were administered during the consolidation phase. Patients with a complete remission or a stable partial remission were maintained on cyclophosphamide, 2 mg/kg orally daily, until relapse. Nonresponders (as defined below) were removed from the protocol and treated by alternative programs.

Blood counts were obtained weekly during the remission-induction phase and in most instances weekly during the consolidation phase. Doses of Adriamycin and cyclophosphamide were reduced at the time of injection according to the following schedule: white blood count (WBC) 2000–3500/cu mm or platelets 50,000–100,000/cu mm, 50% decrease; WBC under 2000/cu mm or platelets under 50,000/cu mm, dosage delayed. Vincristine was reduced by 50%, if moderate neuropathy developed and discontinued with severe neuropathy such as paresis. Bleomycin was omitted with the first evidence of pulmonary toxicity or with severe mucous membrane or cutaneous reactions. Prednisone was reduced or withheld if severe side effects were encountered.

Complete remission (CR) was defined as disappearance of all measurable disease persisting for a minimum of 1 mo after the completion of BACOP. All procedures involved in initially defining the extent of disease were repeated short of laparotomy and laparoscopy to confirm complete remission. Patients who had a greater than 50% reduction in measurable disease which lasted for a minimum of 1 mo or those with complete disappearance of disease which recurred after at least three cycles of BACOP, brief PR or CR lasting less than 1 mo, or failure of remission induction with progressive disease or appearance of new lesions. Remission duration was calculated from the time of first evidence of CR or PR to relapse, and survival was calculated from the first day of BACOP therapy. Survival rates and graphic presentations were developed by standard life-table formulas. Statistical significance was determined by the Wilcoxon test, modified to deal with life-table data by Gehan.

RESULTS

Response and Survival

The objective response rate (CR + PR) to BACOP in 44 evaluable patients with diffuse histology was 86%, with 66% achieving a CR (Table 3). The CR rate varied from 56% (10/18) in DH to 80% (12/15) in DPDL. In nodular lymphomas the CR was 89% (8/9). The median time from start of therapy to CR was 6 wk. All patients achieved CR by the end of 3 mo except for 2 patients who required 4 and 6 mo. Time to CR did not differ significantly among the various histologic groups. Previous therapy did not adversely affect response rate or survival.

Partial response occurred in 1/9 (11%) patients with nodular histology, and 9/44 (20%) patients with diffuse histology. Among the latter were four patients who showed initial complete disease regression but relapsed during the consoli-

<table>
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<th>Table 3. Results of BACOP in Evaluable Patients</th>
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<tbody>
<tr>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>Nodular (all)</td>
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<tr>
<td>Diffuse (all)</td>
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<tr>
<td>DPDL</td>
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<td>DH</td>
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<td>DM</td>
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<td>DWDL</td>
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Fig. 2. Duration of complete remission plotted from onset of CR in patients with nodular and diffuse histology. Number in parentheses, number at risk; vertical bar, individual follow-up time.

Fig. 3. Actuarial survival curves for patients with nodular and diffuse histology calculated from the first day of treatment. Number in parentheses, number at risk; vertical bar, individual follow-up time.

dation phase of BACOP. No response occurred in 6/44 (14%) patients with diffuse histology, and 5 of these were DH.

The duration of CR is plotted in Fig. 2. A projected 75% of patients with nodular lymphoma remained in CR at 14 mo with a median follow-up time of 17 mo. One patient with nodular mixed pathology (NM) relapsed at 11 mo with change to a diffuse type (DM), and died of progressive disease at 18 mo, while a second patient in relapse achieved partial response after additional therapy but died of recurrent disease at 30 mo.

The projected median duration of CR in patients with diffuse histology treated by BACOP was 14 mo. Of 29 BACOP patients with diffuse histology achieving CR, 17 (58%) have remained disease free for periods of 5–34 mo with a median follow-up time of 12 mo. Six have remained in CR for more than 20 mo. Disease relapse occurred in 9 (31%) patients 6–13 mo after achieving CR and 5 of these have died. Three patients died of complications while in early CR and had no autopsy evidence of malignant lymphoma. All 9 partial responders relapsed in a median time of 4 mo, and 7 are dead. Two of the latter had received successful therapy for central nervous system (CNS) relapse and died of pulmonary complications with no evidence of lymphoma at autopsy.

Actuarial survival curves are presented in Fig. 3. Median survival of patients with nodular histology has not been reached but will exceed 25 mo. Six of nine (67%) patients are alive and have been disease free for periods of 9–31 mo. Median survival of all patients with diffuse histology is 14 mo, with projected survival beyond 20 mo in 42% of patients.
Survival related to diffuse histology subgroups is presented in Fig. 4. Projected survival in 75% of patients with DPDL is 20 mo. Median survival in patients with DH and DM is 9 mo. Although life-table analysis projects prolonged survival (after 20 mo) for 58% of patients with DPDL and 32% with DH, larger numbers and longer follow-up time are required to determine statistical significance.

**Dose Adjustment and Toxicity**

The initial dose of cyclophosphamide and Adriamycin was reduced by half in 24% of patients owing to previous chemotherapy and/or radiotherapy, in order to avoid undue myelosuppression. From 12% to 26% (median 20%) of subsequent courses were administered at half-dose based upon dose reduction criteria.

Leukopenia was more common than thrombocytopenia, with 27% of courses resulting in WBC nadirs below 3000/cu mm and 15% below 2000/cu mm. Platelet counts under 100,000/cu mm occurred during 14% of courses, with only 3% under 50,000/cu mm. Nadirs occurred at 14 days with return to normal in most instances by 3 wk. Cumulative toxicity was not observed.

Significant untoward reactions in the entire group of 73 patients included the following: transient fever to 101°–103°F (10 patients, 8 while receiving high-dose bleomycin, but with no anaphylactic reactions); severe oral mucositis (4 patients, 3 while receiving high-dose bleomycin); skin and nail changes (10 patients, 5 while receiving high-dose bleomycin); cardiomegaly with controllable congestive heart failure attributable to Adriamycin (1 patient); reversible peripheral neuropathy (10 patients, 6 of whom had received previous vincristine); perforated duodenal ulcer (1 patient); diabetes mellitus (2 patients); and hemorrhagic cystitis necessitating discontinuation of cyclophosphamide (2 patients). The majority of patients had total alopecia, which was reversible following the consolidation phase.

Pulmonary infiltrates developed in 21/73 (29%) patients and were ascribable to bleomycin toxicity in 8 (11%) patients. In 5 patients the radiographic changes were reversible, but 3 patients expired of pulmonary insufficiency. Two of the latter had received initial high-dose bleomycin. The median time to diagnosis was 6 wk and the average total dose of bleomycin in the reversible cases was 72 mg, compared to 93 mg in the fatal cases. Details concerning differential diagnosis and therapeutic approach will be published elsewhere.
Three patients expired of complications from pneumocystis carinii infection, while two developed fatal bacterial infection during periods of drug-induced pancytopenia. The mortality rate from complications ascribable in whole or in part to the chemotherapy was 11% (8/73). All fatalities occurred in patients with diffuse histology (1 diffuse undifferentiated [DU], 1 DM, 4 DH), or LSL (2) with variable responses (3 CR, 2 PR, 3 NR). Of significance, 7/8 drug-related fatalities had received prior radiotherapy and/or chemotherapy.

Relapse Patterns and Central Nervous System Involvement

Of 37 patients achieving CR on BACOP, 11 relapsed—2/8 (25%) with nodular histology and 9/29 (31%) with diffuse histology. The latter included 5/12 patients with DPDL and 4/10 with DH. The time to relapse in diffuse histology was shorter than nodular histology (median 7.5 mo, versus 11.5 mo). Initial relapse in nodular histology occurred predominantly in areas of previous disease, while this was true in only 4/9 relapses with diffuse histology. Five patients had new sites of involvement, including bone, breast (1 each) and CNS (3 patients).

A total of 11 patients developed CNS lymphoma, including 1 who presented with CNS disease, 5 who had concomitant progressive systemic disease (1 CR, 2 PR, 2 NR) and 5 who had primary CNS relapse. The latter consisted of 3 patients who relapsed in the CNS at 6, 7.5, and 9 mo after achieving CR and 2 patients arbitrarily defined as PR since they were receiving BACOP consolidation when CNS relapse occurred at 4 and 5 mo. Both patients later died of pulmonary complications and had no evidence of lymphoma at autopsy, while progressive systemic disease developed in two of the three remaining patients with primary CNS relapse. All patients had diffuse histology (5 DH, 1 DU, 5 DPDL) with an incidence of 25% (11/44). Of interest, 7/11 patients had had initial bone marrow involvement. Only one patient had intracerebral lesions, while ten had meningeal involvement with malignant cells identified in spinal fluid. Details of therapy and survival in CNS lymphoma will be published separately.

DISCUSSION

The main objective of this study has been to increase the CR rate and thus survival in advanced NHL, based upon evidence that only patients who achieve CR have a major increase in survival. While the latter may be true in diffuse histology, recent data suggest it may not be true in nodular histology. The 66% CR rate achieved with BACOP in diffuse histology greatly exceeds the 14% CR rate of our earlier COP program, as well as other COP studies which revealed CR rates of 27%-35% in diffuse histology. The low CR rate with our initial COP protocol may be related to less intensive therapy.

Combination programs employing Adriamycin or bleomycin with COP have resulted in improved CR rates, varying from 43% to 64%. Recently, Berd et al. have reported a CR rate of 60% (9/15) in patients with diffuse histology employing combined cyclophosphamide, vincristine, methotrexate and leucovorin rescue, and cytosine arabinoside. Preliminary results of a program employing the same five drugs as the present BACOP protocol have revealed a CR of 43% in previously untreated patients with diffuse histology.
Although 8/9 (89%) patients with nodular histology had a CR with BACOP, an equally impressive CR of 77% was achieved with COP. The CR rate in other COP programs has varied from 43% to 62%. With the addition of bleomycin or Adriamycin, rates of 50% or 73%, respectively, have been achieved. The favorable prognosis of nodular histology in advanced NHL was emphasized in our COP study, and subsequently Jones et al. identified a group of histologies, mainly nodular (nodular well-differentiated and poorly differentiated lymphocytic lymphomas and NM) but including DWDL, that demonstrated improved survival compared to diffuse histology (DPDL, DM, DH, DU). Although clinical characteristics of advanced disease and definition of CR may vary among institutions, single-agent chemotherapy of these favorable histologies has been generally satisfactory. Current prospectively randomized studies at Stanford reveal that single alkylating agent therapy is equally as effective as either COP alone or COP and total lymphoid irradiation in achieving excellent response and prolonged survival. Other recent studies have shown that equally effective results may be achieved either by COP or total-body irradiation. Thus programs less intensive than BACOP may provide comparable benefits with less toxicity to patients with favorable histology.

Chemotherapy of patients with unfavorable histologies (i.e., diffuse histologic patterns) presents a major challenge. A 66% CR rate achieved by BACOP appears to be an improvement over older programs, particularly those not employing Adriamycin, bleomycin, or cycle-active agents. The CR for various histologic subgroups varies from 80% for DPDL to 56% for DH (Table 3). Data from Schein et al. reveal a CR of 22% (2/9) in patients with DPDL treated by cyclophosphamide, vincristine, and prednisone and 35% (9/26) in those with DH treated by nitrogen mustard or cyclophosphamide, vincristine, procarbazine, and prednisone. Of interest, however, is long-term survival in 10 of 11 complete responders with DH for periods of 26–105 mo. With BACOP, survival continues beyond 20 mo in 42% of patients with diffuse histology (32% with DH and 58% with DPDL), but longer follow-up is required to determine statistical significance. Median survival of all patients with diffuse histology is significantly higher with BACOP than in our earlier COP study (14 mo versus 7 mo) and exceeds 8 mo recently reported with another COP program.

Relapse occurred in 30% of patients achieving CR and predominantly involved new sites in diffuse histology compared to previously involved areas in nodular histology relapse is due to primary failure to control all disease, while risk of relapse in patients with diffuse histology has occurred early and has diminished markedly after 1–2 yr of complete remission. This finding contrasts with nodular histology, wherein the risk of relapse per unit time did not significantly diminish up to 30 mo of follow-up (Fig. 2). Patients with nodular histology treated by our previous COP program have continued to relapse, and after 4 yr only 1/13 patients was alive and free of disease. It is possible that in nodular histology relapse is due to primary failure to control all disease, while in diffuse histology reinduction of new disease occurs by a remaining etiologic factor.

Whether longer disease-free survival in nodular histology can be achieved
with irradiation of areas of prior bulk disease, as proposed in Hodgkin disease, or by maintenance chemotherapy, will require further clinical trials. Maintenance therapy with intermittent courses of combined agents may be more effective in decreasing the relapse rate than continuous alkylating agent as employed in the present study and previous COP protocol. Possibilities for improved results in diffuse histology are discussed below.

CNS involvement in this study occurred in 25% (11/44) of patients with diffuse histology, with 5 having relapse initially in the CNS. Two of the latter had relapsed during the consolidation phase of BACOP. Recently, Bunn et al. reported a high overall incidence of CNS involvement (29%), including 20% (5/25) in patients previously achieving CR. Involvement of the CNS by NHL has generally been quite low, with an autopsy incidence of 12% (20/172) reported in one series, and has usually been associated with advanced systemic disease. The increased incidence in our patients in remission, as well as those cited above, may be related to longer survival with relapse in a "pharmacologic sanctuary" similar to patients with both ALL and AML. Another factor may be a predilection for CNS involvement in patients with DH and DU lymphoma, although only 6/11 of our patients had these histologies. One other associated factor appears to be bone marrow involvement, present in 7/11 (64%) patients in this series and 13/15 (87%) from the NCI series.

Survival after CNS relapse is generally poor. Eventual systemic disease occurred in all patients reported from NCI and 8/11 patients in this study. Therapy of CNS lymphoma has not been standardized, but remissions have occurred with irradiation, intrathecal methotrexate and arabinosyl cytosine, and systemic high-dose methotrexate with citrovorum factor rescue (MTX/CF), as noted in our patients as well as other studies. Future chemotherapy programs for patients with diffuse histology, especially those with bone marrow involvement, should be designed to include prophylactic therapy of the CNS and spinal cord.

A significant problem encountered in this study concerned diffuse pulmonary infiltrates which were related to bleomycin toxicity in eight (11%) patients. Three expired, 2 having received an initial dose of 15 mg/sq m. Decreasing the dose of bleomycin to 4 mg/sq m did not eliminate lung toxicity, which may have been related to an excessive dose rate or additional factors. The total dose of bleomycin prior to lung toxicity (72 mg in reversible cases and 93 mg in fatal cases) was well below the reported toxic level of 200 mg. There appeared to be a constant 3%-5% incidence of pulmonary toxicity at all dose levels, however, which increased significantly above 450 mg. Recent studies have shown that gallium-67 lung scans may be of value in detecting bleomycin lung toxicity.

Intensive combination chemotherapy with BACOP in advanced NHL, diffuse histology, results in a high CR rate when compared to other programs. Further follow-up is required to determine if long term disease-free survival has been achieved.

Treatment failures including disease relapse may be due to several factors, which may be overcome in the future: (1) High proliferative thrust between courses of therapy remains a problem and interposition of MTX/CF may overcome this. (2) CNS involvement may be controlled by intermittent courses of
MTX/CF and the use of dexamethasone instead of prednisone. Preliminary data suggest the former has been achieved in acute leukemia but more data are required concerning the efficacy of dexamethasone. (3) Inadequate cyto reduction may be overcome by escalating the dosage of cyclophosphamide and Adriamycin upward and by the addition of MTX/CF, which is nonmyelosuppressive and would not compromise the dosage of other elements of the program. (4) Fatal complications from BACOP adversely affect remission and survival curves and should be reduced by deletion of continuous prednisone and frequent doses of bleomycin. Patients with prior radiotherapy and chemotherapy appear to be at increased risk of toxicity and should be monitored carefully. Improvement in granulocyte transfusion techniques should also control complications from myelosuppression.

Modifications in BACOP based upon the above have been the subject of our present study. Only with a multidisciplinary approach employing maximal therapy and supportive care can significant long-term disease-free survival and eventual cures be achieved in patients with diffuse histology, especially diffuse histiocytic lymphoma.

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