Combination Chemotherapy ("CHOP-Bleo") in Advanced (Non-Hodgkin) Malignant Lymphoma

By Victorio Rodriguez, Fernando Cabanillas, Michael A. Burgess, Eugene M. McKelvey, Manuel Valdivieso, Gerald P. Bodey, and Emil J Freireich

Forty-seven adults with advanced malignant lymphoma (the majority in stage IV) were treated with a combination of cyclophosphamide, hydroxydaunorubicin (Adriamycin), vincristine (Oncovin), prednisone, and bleomycin (CHOP-Bleo). The complete remission (CR) rate was 66%. The overall response (complete + partial remission) was 92%. The CR rate in patients with diffuse histiocytic lymphoma (DHL) was 69%. Only 3 of the 18 patients with DHL in CR have relapsed; the projected median duration of response was calculated to be greater than 2 yr. In patients with nodular poorly differentiated lymphocytic lymphoma (NPDL), the CR rate was 62%. One of the eight patients with NPDL in CR has relapsed; the projected median duration of complete response will be greater than 4 yr. The median survival for all patients entered in this study has not been reached; however, it was estimated that it will be greater than 3 yr. The survival curves became flat at 70 wk for the patients with DHL and at 1 yr for the patients with NPDL. Major complications during chemotherapy with CHOP-Bleo were myelosuppression and alopecia. Only six severe infections occurred during myelosuppression. No hemorrhagic problems were observed. This study indicates that combination chemotherapy with these agents is effective in increasing the CR rate and survival in patients with diffuse histiocytic lymphoma. In patients with NPDL, further observation will be needed to assess the effect of this combination on survival.

THE MALIGNANT ("NON-HODGKIN") LYMPHOMAS constitute a variety of lymphoproliferative disorders that most often present as clinically advanced disease. Consequently, systemic therapy for these diseases has been investigated during recent years. These malignancies are treatable with various single antitumor agents, such as the alkylating agents, vinca alkaloids, and corticosteroids, with response rates ranging from 15% to 50%.1,3

Combination chemotherapy with these agents was introduced in 1966 and
has been clearly demonstrated as superior to single therapy, both in the proportion of complete remissions achieved and in prolongation of survival in patients achieving complete remission. Most recently, new agents, such as the nitrosoureas, bleomycin, and Adriamycin, which also appear to be quite effective in the malignant lymphomas, have become available. Therefore, various modalities of combination chemotherapy based on the COP combination plus either of these new agents have been investigated in the recent past with various degrees of success. We have combined cyclophosphamide, vincristine, and prednisone with Adriamycin and bleomycin in an attempt to improve the results in advanced malignant lymphoma. The results of this study are reported in this paper.

MATERIALS AND METHODS

Adults with advanced malignant ("non-Hodgkin") lymphoma admitted to the Department of Developmental Therapeutics at the University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute in Houston, from October 1973 to October 1975 were eligible for this study. Patients previously untreated with chemotherapy were eligible. However, four patients who had received prior minimal chemotherapy were entered in the study. Patients who had received prior radiotherapy also were eligible.

Patients were staged according to the recommendations outlined by the Ann Arbor classification for Hodgkin disease, which in addition to standard clinical parameters includes bilateral pedal lymphangiograms, gallium scanning, and bone marrow aspiration and biopsy. Five patients also had staging laparotomies and five had percutaneous liver biopsies as part of the staging procedure.

Chemotherapy consisted of a combination of cyclophosphamide, hydroxydaunorubicin (Adriamycin, Adria Laboratories, Wilmington, Del.), vincristine (Oncovin, Eli Lilly, Indianapolis, Ind.), prednisone, and bleomycin (CHOP-Bleo). The dosages and routes of administration are shown in Table 1. In patients older than 60 yr, the dose of bleomycin was reduced to 4 units/sq m on days 1 and 5. A course of chemotherapy consisted of the 5-day administration of the regimen, followed by 10-14 days of observation for recovery from side effects. The doses of cyclophosphamide and Adriamycin were increased or decreased by 20% and 25%, respectively, for subsequent courses according to the degree of myelosuppression from the previous course. The doses of vincristine, prednisone, and bleomycin were not escalated. The cumulative total dose of Adriamycin administered was 450 mg/sq m and that of bleomycin was 180 units. Courses of therapy were repeated at 2-to-3-wk intervals until response occurred. If progression of disease occurred after two courses, therapy was discontinued and the patients were treated with other therapy.

Complete response was defined as the disappearance of all evidence of disease, documented clinically and by normalization of all laboratory and radiographic parameters that had been abnormal prior to therapy. Partial response was defined as decrease of >50% in measurable disease. Patients with bone lesions whose disease completely disappeared were not considered in complete remission until calcification of bone lesions was apparent. Restaging procedures

<table>
<thead>
<tr>
<th>Table 1. CHOP-Bleo Regimen</th>
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<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Cyclophosphamide*</td>
</tr>
<tr>
<td>Hydroxydaunorubicin (Adriamycin)*</td>
</tr>
<tr>
<td>Oncovin (vincristine)</td>
</tr>
<tr>
<td>Prednisone</td>
</tr>
<tr>
<td>Bleomycin†</td>
</tr>
</tbody>
</table>

*Starting dose to be reduced by 20% for patients with prior extensive radiotherapy or hypocellular bone marrow (<20%).
†Dose to be reduced to 4 units/sq m on days 1 and 5 for patients older than 60 yr.
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...were performed in all patients to document response; however, laparotomies were not repeated for restaging purposes. The pathology review of biopsy specimens of the patients was done by Dr. James J. Butler or Dr. Jerome S. Burke or members of the staff in the Department of Anatomical Pathology at M. D. Anderson Hospital.

After achieving complete remission, most patients had a spinal tap performed, at which time prophylactic Ara-C (100 mg in 20 cc of Elliot's B solution) was injected once, unless central nervous system involvement was documented, in which case appropriate intrathecal and radiation therapy were instituted. Patients who achieved complete or partial response continued to receive intermittent courses of maintenance therapy every 3 to 4 wk at the highest tolerated dose. When the limiting dose of Adriamycin and bleomycin was reached, they continued on maintenance therapy with monthly courses of COP (cyclophosphamide 1 g/sq m i.v. x 1 day, Oncovin 2 mg i.v. x 1 day, prednisone 100 mg/day p.o. x 5 days). After 1 yr of maintenance chemotherapy, all therapy was discontinued. Complete blood counts with differential and platelet count were performed twice weekly during remission induction and at least once weekly thereafter; renal (BUN, creatinine) and liver chemistries (bilirubin, serum transaminases, alkaline phosphatase) were repeated at least once prior to each course of therapy. Chest x-rays and flat plates of the abdomen (to follow-up lymphangiograms) were done prior to each course of therapy during remission induction, and then every 2 to 3 mo while in remission. Gallium scans were repeated to document remission, and thereafter approximately every 6 mo while the patients were in remission. Allopurinol in doses of 300 mg/day was administered to all patients with the initial course of chemotherapy; appropriate hydration was emphasized to all patients during chemotherapy. Adequate supportive therapy, such as transfusion of blood products and administration of antibiotics, was provided as required during myelosuppression.

The duration of complete remission was measured from the time the patients achieved remission. The duration of survival was measured from the time they entered the study.

RESULTS

Fifty-one adults with advanced malignant lymphoma were entered in this study from October 1973 to October 1975. Four patients were considered unevaluable. Three patients were lost to follow-up after the first course of chemotherapy when they decided to receive other therapy from their referring physicians. The fourth patient, who had been referred after unilateral orchiectomy and abdominal radiation for histiocytic lymphoma in the testis and paraaortic nodes, was unevaluable because no measurable disease could be followed. The 47 evaluable patients ranged in age from 20 to 79 yr (median 56), and 25 were males. The overall characteristics of the evaluable patients are summarized in Table 2. The majority of patients had malignant lymphoma of the diffuse histiocytic or nodular poorly differentiated lymphocytic type. All patients had advanced disease, and most of them (85%) were in stage IV. Only

<table>
<thead>
<tr>
<th>Type</th>
<th>No. Patients</th>
<th>No. in Stage III/IV</th>
<th>No. With Prior XRT</th>
<th>No. With Prior Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DH</td>
<td>26</td>
<td>2/24</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>NPD L</td>
<td>13</td>
<td>3/10</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>DPDL</td>
<td>3</td>
<td>0/3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NM</td>
<td>3</td>
<td>1/2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>UNDIFF</td>
<td>2</td>
<td>0/2</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>6/41</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

DH, diffuse histiocytic; NPD L, nodular poorly differentiated, lymphocytic; DPDL, diffuse poorly differentiated, lymphocytic; NM, nodular mixed; UNDIFF, undifferentiated; XRT, radiotherapy.
five patients had received prior extensive radiotherapy, and four had received chemotherapy (one with chlorambucil, one with nitrogen mustard, and two with cyclophosphamide in small doses). The sites of involvement in the 40 patients with stage IV disease are listed in Table 3. Most patients with bone marrow involvement had lymphocytic disease; most patients with histiocytic lymphoma had other nonlymphoid organs involved.

The overall rate of response (complete + partial remission) to combination chemotherapy, CHOP-Bleo, in this study was 92%. Thirty-one of the forty-seven patients (66%) had a complete response. The responses are listed for the various types of malignant lymphoma in Table 4. The complete response in patients with diffuse histiocytic lymphoma was 69%, and an overall response of 88%. In the 13 patients with nodular poorly differentiated lymphocytic lymphoma, the complete response rate was 62%, with an overall response of 100%. All of the six remaining patients with lymphocytic or mixed disease also responded. Of the two patients with undifferentiated lymphoma, one had a complete remission and one failed to respond.

All patients have been followed for more than 9 mo, and the majority have been followed for more than 1 yr. The durations of complete response for patients with histiocytic disease and nodular poorly differentiated lymphoma are shown in Fig. 1. Only 3 of the 18 patients with histiocytic lymphoma have relapsed (as of September 1976), as has one of the eight patients with nodular poorly differentiated lymphoma. The projected median duration of response for the patients with diffuse histiocytic lymphoma in this study is calculated to be > 2 yr. For patients with nodular poorly differentiated lymphocytic disease, it is calculated to be > 4 yr. Four of the five patients with histiocytic diffuse lymphoma who achieved partial remission have relapsed; the median duration of remission in these five patients is 24 wk (range 12–74+). Of the five patients with nodular poorly differentiated lymphoma who achieved partial remission,
Fig. 1. Duration of complete remission (CR) in malignant lymphoma, diffuse histiocytic and nodular poorly differentiated lymphocytic. The tick marks indicate patients still in CR as of September 1976.

three have relapsed at 4, 27, and 91 wk; two remain in partial remission at 32+ and 82+ wk.

The three patients with diffuse poorly differentiated lymphocytic lymphoma had a complete remission duration of 53+ and 64+ wk and a partial remission of 14 wk. In the three patients with nodular mixed lymphoma, the duration of complete remission was 52+ and 64+ wk, and the partial remission was 8 wk. The patient with undifferentiated lymphoma who responded remains in remission at 93+ wk. No central nervous system relapse of the disease has occurred in our patients.

The duration of survival for all patients is shown in Fig. 2. The median

Fig. 2. Survival in all patients entered, measured from the time they entered the study. The tick marks indicate patients still alive (as of September 1976).
survival has not yet been reached since only 13 of the 47 patients have died. However, it is estimated that it will be > 3 yr. The survival curve becomes flat at 70 wk for the patients with diffuse histiocytic lymphoma, and at 50 wk for the patients with nodular poorly differentiated lymphocytic lymphoma. The duration of survival of those patients who achieved complete remission has been compared to the survival of those patients who did not achieve complete remission (Fig. 3). It is obvious that achieving complete remission results in prolonged survival of the patients.

The major complications during chemotherapy with CHOP-Bleo were myelosuppression and alopecia. Myelosuppression occurred in all patients to a degree that varied with the dosage of the chemotherapeutic agents given (Table 5). Myelosuppression was transient (3-5 days). In spite of myelosuppression, severe infection occurred only in six patients. In two of these patients, the infection (pneumonia) was fatal. No hemorrhagic problems attributable to thrombocytopenia were encountered. Alopecia was universal, but in most patients the hair gradually grew again while they were on maintenance therapy. Two episodes of congestive heart failure occurred during this study that may have been related to Adriamycin therapy, one in a man 59 yr of age, the other in a man of 79 who also had arteriosclerotic heart disease. In both patients, this

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>WBCt</th>
<th>Day</th>
<th>Platelet</th>
<th>Day</th>
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</thead>
<tbody>
<tr>
<td>40/600</td>
<td>1.9 (0.7-3.5)</td>
<td>12 (8-17)</td>
<td>150 (100-290)</td>
<td>15 (11-16)</td>
</tr>
<tr>
<td>50/750</td>
<td>1.6 (0.3-3.9)</td>
<td>12 (8-17)</td>
<td>112 (23-195)</td>
<td>11 (8-18)</td>
</tr>
<tr>
<td>65/1000</td>
<td>0.6 (0.1-3.0)</td>
<td>12 (9-14)</td>
<td>144 (55-310)</td>
<td>12 (3-16)</td>
</tr>
</tbody>
</table>

*Values are in mg/sq m.
†WBC, white blood cell count; values are the median lowest counts × 1000/cu mm.
‡Day, median day for leukopenia or thrombocytopenia.
complication occurred after having received three courses of CHOP-Bleo and, therefore, if attributable to Adriamycin, it was not dose related. Mild peripheral neuropathy was seen in about a third of the patients and was reversible with discontinuation of the vincristine. No pulmonary toxicity attributable to the administration of bleomycin was clinically evident in the patients in this study.

DISCUSSION

The results of this study indicated that a significant number of patients with advanced malignant lymphoma achieved complete remission with combination chemotherapy, CHOP-Bleo. In our study, the majority of patients had diffuse histiocytic or nodular poorly differentiated lymphoma. The complete response rate in diffuse histiocytic lymphoma was 69%, and the overall response rate was 88%. These were impressive results for a disease in which until a few years ago no more than 40% complete remission rates could be obtained with combination chemotherapy. Furthermore, remissions seemed to be of good clinical significance, since the majority of these patients remain in complete remission, and the survival appears to have been prolonged. Until recently, complete remission rates in diffuse histiocytic lymphoma were best obtained with a combination, COP, or MOPP. At best, 40% of the patients entered in these combinations achieved a complete remission. However, prolonged survivals have been described among those few patients who entered complete remission. Most recently with the introduction of Adriamycin, a higher proportion of remissions have been achieved in patients with diffuse histiocytic lymphoma. Thus Gottlieb et al., in a pilot study of Adriamycin, reported about 40% complete remissions in patients who had extensive prior therapy. The Southwest Oncology Group has performed a randomized study comparing a three-drug combination (HOP) (Adriamycin, vincristine, and prednisone) versus a four-drug combination (CHOP) (cyclophosphamide, Adriamycin, vincristine, and prednisone). The complete remission rates for patients with diffuse histiocytic lymphoma were 66% and 68%, respectively. Our complete remission rate of 69% was not significantly higher than that accomplished by the Southwest Oncology Group investigators; however, the patients entered in our study were older. Nevertheless, the duration of remission and survival were impressive. The survival curve for patients with histiocytic disease appears unchanged after 1 yr, as has been described by other investigators, and may indicate that a proportion of patients with this disease are now curable with chemotherapy.

Patients with nodular poorly differentiated lymphocytic lymphoma usually respond to therapy with varying degrees of success. Complete remission rates ranging from 50% to 80% have been reported with the various combinations. Certainly, most of the patients achieve at least a partial remission status prior to entering complete remission. Thus it is not uncommon to obtain remission rates close to 100% with any combination regimens in this type of malignant lymphomas. In our study, the combination, CHOP-Bleo, also induced 100% response with a complete remission rate of 62% in patients with nodular, poorly differentiated lymphocytic disease, stage IV. These results are comparable to those reported from other groups including the Southwest Oncology Group study where the CHOP-HOP combination produced 76% and 71% complete remissions.
remission rates, respectively. In our study, the duration of remission and survival in these patients have also been prolonged. Since the natural history of this disease indicates that the median duration of remission and survival are in the range of 2–4 yr, additional time will have to elapse before the overall effects of CHOP-Bleo chemotherapy on survival can be ascertained.

Central nervous system relapses have been recognized more frequently in the malignant lymphomas in recent years. However, thus far this has not been observed in this group of patients. Since 1973, lumbar punctures have been performed routinely on patients with lymphoma for diagnostic purposes and in order to administer prophylactic cytosine arabinoside intrathecally. The impact of this approach on the natural history of this disease and the future development of CNS lymphoma remains to be seen. However, the lack of CNS relapse in these patients suggests that this might be an appropriate prophylactic measure against the development of this complication.

The combination, CHOP-Bleo, was very well tolerated. The degree of myelosuppression and the incidence of infection resulting during myelosuppression were not any higher than has been reported with other combinations. The addition of bleomycin at the doses used in this study did not enhance any other major toxicity. However, the addition of bleomycin did not appear to have increased the complete remission rate over that attained with CHOP. Whether the addition of bleomycin to this regimen has increased the survival remains to be seen.

This study indicates that combination chemotherapy has a definite place, not only in the palliation of advanced lymphoma, but also in the permanent control of these diseases in some patients. Effective combinations which include adriamycin are available today to control these advanced diseases fairly well. The efficacy of such regimens suggests that with effective treatment, prognostic factors that have been recognized to be important in the natural history of these diseases (the histological type, the bulk of the disease) might become less important. This concept is supported by the fact that most patients in our study had advanced disease, extranodal disease, and histological types (such as diffuse histiocytic) that have been resistant to other therapies; nevertheless, the responses have been excellent. Because regimens like CHOP-Bleo are so effective in advanced disease, and since the malignant lymphomas are usually disseminated diseases, no matter how early the stage of disease is detected initially, it becomes important to consider a chemotherapeutic approach in early stages of the disease. Therefore, the addition of combination chemotherapy to radiotherapy for early stage disease or perhaps the use of chemotherapy alone in patients with malignant lymphoma, stages I and II deserve consideration, particularly when one considers that in patients with early disease treated with radiotherapy alone there is an unacceptable relapse rate of more than 50% at 5 yr.

REFERENCES

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