The Treatment of Advanced Stage Favorable Histology Non-Hodgkin’s Lymphoma: A Preliminary Report of a Randomized Trial Comparing Single Agent Chemotherapy, Combination Chemotherapy, and Whole Body Irradiation

By Richard T. Hoppe, Paula Kushlan, Henry S. Kaplan, Saul A. Rosenberg, and Byron W. Brown

Between 1975 and 1978, 51 patients with favorable histology non-Hodgkin’s lymphomas, pathologic stage III-IV, were treated prospectively on a randomized treatment protocol. Treatment options were single alkylating agent chemotherapy, combination chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP), or fractionated whole body irradiation followed by low dose involved field irradiation. The median follow-up interval in this group of patients is now 41 mo. Actuarial survival is excellent, 84% at 4 yr for the entire group, with similar survival observed for each of the three treatment options. Initial complete remission rates (64%, 88%, and 71%) were not significantly different in the three treatment arms. Frequent relapse after initial remission induction was noted, however, with a freedom from relapse at 4 yr of only 25%. The toxicities of the three therapies were most numerous in the group of patients treated with CVP; however, long-term hematologic depression was most commonly observed in patients treated with whole body irradiation. In general, hematologic complications were more frequent among patients who had marrow involvement and intact spleens at the time of initial therapy. The relationship of this study to other clinical trials in the management of patients with advanced stage favorable histology lymphomas and its implications for future clinical trials are discussed.

Patients with nodular lymphocytic poorly differentiated (NLPD), nodular mixed lymphocytic-histiocytic (NM), or diffuse lymphocytic well differentiated (DLWD) lymphoma according to the Rappaport system have a favorable prognosis. The median survival of these patients is reported to be in excess of 8 yr, despite advanced disease (pathologic stage III-IV) at presentation in most patients.2

The optimal therapy for these patients has not been defined. Treatment programs reviewed recently in the literature include single alkylating agent chemotherapy, combination chemotherapy, total lymphoid irradiation, whole body irradiation, combined modality therapy, and immunotherapy.3 14 In addition, one recent report has suggested that these patients may not necessarily require therapy at the time of diagnosis, but that treatment may safely be withheld until symptomatic problems develop.15

In a previous trial initiated at Stanford in 1971 (J6 study), pathologic stage (PS) IV patients with these “favorable” lymphomas were randomized to treatment with either single alkylating agent (cyclophosphamide or chlorambucil), combination chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP), or CVP combined with total lymphoid irradiation.12 No significant differences in survival or freedom from relapse between any of the treatment groups were identified. These patients demonstrated the familiar pattern of good survival in the face of persistent or relapsing disease. A new trial comparing treatment with a single alkylating agent, CVP, or whole body irradiation plus low dose involved field boosts for PS III–IV patients was initiated in 1975 (J8 study). This report will detail the preliminary results of that trial.

Patients and Methods

From January 1975 through January 1978, 51 patients were accepted into this study. Criteria for acceptance included age 65 yr or less, residence within a 300-mile radius of Stanford, the absence of any significant illness with the exception of lymphoma, approval of the referring physician, and informed consent of the patient. All patients had a diagnosis of either NLPD, NM, or DLWD lymphoma. Lymph node biopsies showing poorly differentiated lymphocytic or mixed lymphocytic-histiocytic lymphoma with a nodular and diffuse pattern were considered nodular for the purpose of this study.16 17

Routine staging included a thorough history and physical examination with careful attention to all lymphoid regions including Waldeyer’s ring. Blood studies included a complete hemogram, platelet count, erythrocyte sedimentation rate, serum copper, and liver chemistries. Routine radiographic evaluation included PA and lateral examination of the chest with mediastinal and full lung tomography if any abnormalities were detected on the plain chest film. Bipedal lymphography was performed in all patients. In the presence of bulky retroperitoneal pelvic lymphadenopathy, an intravenous pyelogram was performed to rule out obstructive uropathy. Appropriate other blood studies or radiographic evaluations were obtained as indicated.
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All patients underwent percutaneous needle bone marrow biopsy with a Jamshidi needle. Occasionally, multiple biopsies were obtained. Those patients with stage I–III disease then underwent staging laparotomy and splenectomy. Following the completion of staging, patients were randomized to treatment with either single alkylating agent chemotherapy (SA), combination chemotherapy with CVP, or whole body irradiation with boosts (WBI).

Patients randomized to treatment with SA received either cyclophosphamide (1.5–2.5 mg/kg/day) or chlorambucil (0.1–0.2 mg/kg/day) orally. The similar efficacy of these two single agents has been reported in many studies. Doses were adjusted according to hematologic tolerance in order to maintain the white blood cell count above 3000/cu mm and the platelet count above 100,000/cu mm. Single alkylating agent therapy generally was continued until a complete remission was achieved and for 2 yr, thereafter as maintenance. Treatment was discontinued when disease progressed, severe toxicity intervened, or after a total duration of 2 yr if a complete remission was not attained.

Patients randomized to treatment with CVP received the cyclic regimen described by Bagley et al. The cyclophosphamide (400 mg/sq m) and prednisone (100 mg/sq m) were administered orally for 5 consecutive days. Vincristine (1.4 mg/sq m, maximum single dose 2 mg) was administered i.v. on day 1 only. This cycle was repeated every 21–28 days until a complete remission was achieved. Patients then received four consolidation cycles of CVP followed by maintenance CVP once every 3 mo. The total duration of consolidation and maintenance therapy was 2 yr.

Patients receiving whole body irradiation were treated in the sitting position via opposed lateral fields with a 6 MeV linear accelerator. Compensators were employed to correct for inhomogeneity of dose. Patients were treated 2-3 times/wk, with a weekly dose of 30 rad and prescribed total dose 150 rad. Following completion of the whole body irradiation, "boost" irradiation was administered to all initial sites of clinical or pathologic involvement excluding the bone marrow. Boost irradiation was administered with 6 MeV photons to standard opposed anterior-posterior or lateral fields including the mantle or minimantle, Waldeyer region, whole abdomen, and pelvis. Patients received 2000 rad in 2–3 wk to each field.

A complete remission was defined as the total regression of all clinically enlarged nodes, including a return to normal of lymphographically opacified retroperitoneal and pelvic nodes. A repeat lymphogram was obtained whenever there was inadequate residual dye for evaluation. Bone marrow and liver biopsies were repeated in those patients with initially positive studies in order to confirm remission status.

Following the completion of therapy, all patients were followed in the conjoint lymphoma clinic at Stanford University Medical Center. Physical examination, blood studies, and radiographic examinations were repeated on a regular basis. Lymphography was repeated as necessary and bone marrow biopsies were obtained annually. Initial relapses were documented pathologically.

Survival and freedom from relapse were calculated by the technique of Kaplan and Meier. Tests of significance of difference between results were done using the generalized Wilcoxon test of Gehan and the actuarial test of Cox.

RESULTS

Staging

Seventy percent (35/51) of the patients had advanced stage disease (III–IV) by clinical staging criteria alone. Percutaneous needle bone marrow biopsy identified bone marrow involvement in 27% (4/15) of clinical stage (CS) I–II patients and in 70% (21/30) of CS III patients. A staging laparotomy was performed in the remaining 20 CS I–III patients.

Twelve patients had two or more percutaneous needle bone marrow biopsies. In two instances both a negative and positive sample were obtained, yielding a false negative rate for a single biopsy of 17%. In addition, 2/22 patients with negative bone marrow biopsies had positive open bone marrow biopsies at the time of staging laparotomy.

Characteristics of the Patient Populations

Table 1 summarizes the patient characteristics in the three different treatment groups. There was an even distribution according to clinical characteristics. There was a male predominance and two-thirds of the patients had NLPD. Most patients had stage IV disease, usually because of bone marrow involvement, and most were asymptomatic.

Patient Status

Table 2 summarizes the treatment results and current patient status. The median follow-up interval is 41 mo from the institution of therapy. Complete remissions were documented in 11/17 (64%) of the SA, 15/17 (88%) of the CVP, and 12/17 (71%) of the WBI patients. The most common reason for failure to achieve a complete remission was a persistent positive marrow biopsy (5/13 patients). The median time

| Table 1. Characteristics of 51 Patients With Favorable Lymphoma |
|-----------------|------|------|------|
| Treatment       | SA   | CVP  | WBI  |
| Total No. patients | 17   | 17   | 17   |
| Age (median)    | 53   | 50   | 49   |
| Sex ratio (M:F) | 11/6 | 11/6 | 8/9  |
| Histology       |      |      |      |
| NLPD*           | 11   | 11   | 12   |
| NM              | 4    | 4    | 3    |
| DLWD            | 2    | 2    | 2    |
| Pathologic stage|      |      |      |
| III             | 7    | 5    | 5    |
| IV              | 10   | 12   | 12   |
| Symptoms        |      |      |      |
| A               | 15   | 17   | 15   |
| B               | 2    | 2    | 2    |
| Extralod sites  |      |      |      |
| Marrow          | 10   | 11   | 10   |
| Liver           | 0    | 0    | 4    |
| Skin            | 0    | 1    | 2    |
| Gl tract        | 1    | 0    | 0    |
| Bone            | 0    | 1    | 0    |

*NLPD, nodular lymphocytic, poorly differentiated; NM, nodular mixed; DLWD, diffuse lymphocytic, well differentiated.
required to achieve a complete remission was 12 mo (SA), 5 mo (CVP), and 3 mo (WBI). The median duration of total therapy, including maintenance treatment, was 23 mo (SA), 26 mo (CVP), and 3 mo (WBI). Approximately half of the patients who achieved an initial complete remission have relapsed. Relapse was most common in previous sites of involvement, including lymph nodes (13 patients) and bone marrow (2 patients). Continuous complete remission in the different treatment groups has been documented in 35%–47% of patients. The median follow-up intervals after completion of therapy for patients in complete remission are 10 mo (SA), 8 mo (CVP), and 36 mo (WBI). These differences are due to the prolonged maintenance treatment in the two chemotherapy groups.

After failure of the initial treatment program, it was our policy in these patients not to initiate a secondary therapy until the disease became symptomatic. Among the 13 patients who failed to achieve a complete remission 4 have died without subsequent therapy, 2 have required treatment, and 7 others are alive with disease. Among the 18 patients who relapsed, 3 have died with disease. Seven others have received treatment with either palliative irradiation (3 patients), multiagent chemotherapy (1 patient), or combined modality therapy (3 patients). Eight of the 18 relapsing patients have required no subsequent therapy.

Actuarial survival at 4 yr for the entire group of 51 patients is 84%; however, only 25% are relapse-free. Initial stage or the presence of constitutional symptoms had no influence on outcome. Figure 1 summarizes survival and freedom from relapse in the three different groups. Statistical tests fail to reveal any significant differences in either survival or freedom from relapse (Fig. 1). The log rank test\(^2^\) for differences among these treatment groups yielded \(p\) values of 0.31 and 0.67, for survival and freedom from relapse, respectively. When the groups were compared pair-wise, the three log rank tests yielded \(p\) values of 0.17–0.57 for survival and 0.39–0.81 for freedom from relapse. Pair-wise tests by the generalized Wilcoxon method\(^2^\) yielded \(p\) values of 0.34–0.95 and 0.10–0.66, respectively.

**Complications of Therapy**

All of the treatments were tolerated well. Table 3 summarizes the major complications in each of the treatment groups. Hospitalization for infection or evaluation of fever occurred most frequently among patients receiving CVP—7 instances in S patients. Persistent cytopenia, defined as either white blood cell count less than 3000/cu mm or platelet count less than 100,000/cu mm for at least 6 mo, occurred primarily among patients treated with WBI. Whole body treatment schedules of 15 rad twice a week and 10 rad three times a week were equivalent in their hematologic toxicity, including the degree of lymphopenia induced. The single patient who developed acute nonlymphocytic leukemia was treated with single agent cyclophosphamide for 8 mo, followed by chlor-

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**Table 2. Current Status of 51 Patients With Favorable Lymphoma**

<table>
<thead>
<tr>
<th></th>
<th>SA (17)</th>
<th>CVP (17)</th>
<th>WBI (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial complete remission</td>
<td>11</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Continuous complete remission</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Relapse, alive with disease</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Relapse, dead with disease</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Induction failure, alive with disease</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Induction failure, dead with disease</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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of the 17 irradiated patients developed severe thrombocytopenia. As shown, lowest recorded blood counts were
and eventually a diagnosis of leukemia was confirmed. She died shortly thereafter.

of recurrent lymphoma, she developed pancytopenia and underwent splenectomy. However, because of the small number of patients, it was impossible to ascertain the independent effect of these two variables.

Secondary Therapy

Among patients receiving whole body irradiation of CVP chemotherapy there was a marked difference in hematologic tolerance that appeared dependent on prior splenectomy and the absence of marrow involvement. Patients tolerated treatment better (higher doses of drugs, less blood count depression) when their bone marrow was uninvolved and they had undergone splenectomy. However, because of the small number of patients, it was impossible to ascertain the independent effect of these two variables.

Table 3. Complications of Therapy Among 51 Patients With Favorable Lymphoma

<table>
<thead>
<tr>
<th>Complication</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization for infection/fever</td>
<td>SA</td>
</tr>
<tr>
<td>Cystitis</td>
<td>CVP</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>WBI</td>
</tr>
<tr>
<td>Severe leukopenia (white blood cell count &lt; 2000/cu mm)</td>
<td>SA 3 CVP 3 WBI 3</td>
</tr>
<tr>
<td>Severe thrombocytopenia (platelet count &lt;50,000/cu mm)</td>
<td>SA 0 CVP 0 WBI 3</td>
</tr>
<tr>
<td>Persistent cytopenia</td>
<td>SA 1</td>
</tr>
<tr>
<td>Acute nonlymphocytic leukemia</td>
<td>CVP 5</td>
</tr>
</tbody>
</table>

*See text for definition.

DISCUSSION

The management of patients with favorable histology non-Hodgkin’s lymphomas is a challenging problem. Although 80% of these patients present with advanced disease, frequently with bone marrow involvement, initial response rates are very high. Complete response rates with single alkylating agent chemotherapy are in the range of 40%-70%, and with CVP they are 40%-85%. Despite good initial responses, however, these patients are at continued risk for relapse, even many years after initial therapy.

The use of whole body irradiation in the treatment of these diseases was revived after reports from several centers confirmed its clinical efficacy. However, while complete clinical remission rates were high, pathologic confirmation with biopsy of the marrow and liver was often lacking. When bone marrow biopsies were obtained after treatment, persistent disease was often documented.

In 1968, a trial was initiated at the National Cancer Institute (NCI) comparing treatment with chemotherapy (CVP or C-MOPP) and irradiation (total nodal, total body, or hemibody irradiation). A few patients received supplementary local irradiation following whole body treatment. The survival and freedom from relapse were identical in the two treatment groups and exhibited the familiar pattern of excellent survival but poor relapse-free survival. A subsequent trial at the NCI, which combined whole body irradiation with CVP or C-MOPP and compared that treatment to

Table 4. Hematologic Toxicity* of Treatment Among Patients With Favorable Lymphoma

<table>
<thead>
<tr>
<th></th>
<th>SA</th>
<th>CVP</th>
<th>WBI + Boosts</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT (%)</td>
<td>37.0</td>
<td>35.6</td>
<td>33.3</td>
</tr>
<tr>
<td>WBC (x 10^3/µl)</td>
<td>3.300</td>
<td>2.900</td>
<td>2.900</td>
</tr>
<tr>
<td>PLT (x 10^9/µl)</td>
<td>182,000</td>
<td>179,000</td>
<td>185,000</td>
</tr>
</tbody>
</table>

*Median (range) lowest recorded blood counts.
CVP or C-MOPP alone failed to reveal any advantage to the combined modality approach.13

Another report from the NCI, however, has shown excellent results in a group of 31 patients with PS II–IV NML treated with C-MOPP, CVP, or BACOP chemotherapy.3 The initial complete response rate was 77%, and 79% of those patients (61% of the total) maintained their remission. No relapses occurred after 3 yr; however, only 8 patients were at risk longer than 5 yr. No other center has reported long-term disease-free data comparable to these. Moreover, a recent update of the NCI experience with C-MOPP for NML indicates that relapse may occur as long as 6 yr after therapy.31

At Stanford University Medical Center, we have employed a variety of treatment programs in an effort to obtain durable remissions in these patients. Our first prospective trial, the J6 study, randomized stage IV patients to receive either single alkylating agent, CVP, or CVP combined with total lymphoid irradiation. Details of that study, including initial complete response rates and complications of therapy have been published previously.13,32,33 With maximum follow-up in that group of patients now exceeding 8 yr, neither survival nor freedom-from-relapse differences can be detected (Fig. 2).

Since the J6 study and the J8 study had two of their arms in common (SA and CVP), these data were analyzed together by the log rank test, adjusting for the time period. The differences were not statistically significant (p = 0.43 for survival and p = 0.46 for freedom from relapse). Although the initial complete remission rate was higher in CVP than SA (90% versus 78%), the actuarial relapse-free experience was actually slightly better in the SA group (Fig. 3).

In this current trial, the J8 study, we felt that an important modification of our whole body treatment compared to that used by others was the routine delivery of supplementary irradiation to all initial sites of involvement (exclusive of marrow). This was in an effort to control disease in involved lymphoid tissues, a frequent site of initial relapse.34 These sites were boosted with 2000 rad in 2–3 wk. Despite the boost treatment, however, 2 of the 6 relapses in the WBI group were initially limited to previously involved nodes (compared to 7 of 12 relapses in the chemotherapy groups).

In this study, toxicities of the three treatment programs were acceptable. Hospitalization for sepsis or evaluation of fever were most common among patients receiving CVP and resulted from granulocytopenia during therapy. In general, however, hematologic depression was transient in this group. Persistent cytopenias were most common in the WBI group, but were limited to the nonsplenectomized patients. The mean nadir white blood cell and platelet counts during WBI were 6500 versus 3100/cu mm and 294,000 versus 56,000/sq mm for patients with or without splenectomy, respectively (p < 0.01). Although these differences were marked, it was impossible to know if the better tolerance for both the primary and secondary therapies was related to splenectomy per se or to the lower frequency of marrow involvement in this group. A protective effect of splenectomy has been demonstrated previously for patients receiving total lymphoid irradiation,35 but not whole body irradiation. Poor hematologic tolerance to WBI among patients with splenomegaly, however, has been noted.36 The severity of thrombocytopenia in our irradiated group was less than that reported from other centers utilizing WBI programs.3,13,27 This may have been due to the splenectomy status of many of our patients and/or the inclusion of previously treated patients in the other series.
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SURVIVAL

PERCENT PROBABILITY

YEARS

SA

CVP

SA

CVP

FREE FROM RELAPSE

Fig. 3. J6 and J8 studies. Survival (top panel) and freedom from relapse (bottom panel) of 77 patients with stage III-IV favorable histology non-Hodgkin's lymphoma treated with either single alkylating agent (SA) or cyclic combination chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP).

The similar results of treatment in our three different patient groups make it impossible to recommend any one as the treatment of choice for patients with advanced stage, favorable histology non-Hodgkin's lymphoma. However, it should be emphasized that these groups of patients are not large. It is quite possible for clinically important differences in response or survival rates to be masked by the statistical variations inherent in the results for groups of this size. For example, even after pooling results for the two studies of SA and CVP, with approximately 40 patients in each group, if a true difference in response rate as great as 16% existed. The likelihood of observing an insignificant difference statistically would be 50%. Similarly, if a true difference in death rates as great as 2.5-fold was present, the probability of observing an insignificant difference statistically would also be 50%.

Finally, one cannot ignore the usual indolent course of patients with these types of lymphoma. Treatment intervention may not even be necessary at the time of diagnosis. Portlock and Rosenberg have reported a group of asymptomatic patients with advanced stage “favorable” non-Hodgkin's lymphoma who were followed closely after their initial diagnosis. The majority of these patients did not require therapy during the first 2.5 yr of follow-up. A few patients still have not required treatment, more than 10 yr after presentation. The delay in initiating therapy in these patients has not compromised their prognosis, since their overall survival is similar to that of a group of patients who did receive initial treatment.

Prospective clinical trials at Stanford since 1971 have failed to identify a potentially curative approach to the management of patients with advanced stage favorable lymphomas. In addition, with the exception of the experience reported from the NCI for patients with NML, no convincing data have been published to suggest that other current treatment programs hold great promise either. Since initial treatment programs may have little effect on ultimate outcome, it is acceptable to initiate treatment in these patients only when symptomatic problems develop. Prospective trials testing this hypothesis are needed, but have already been initiated at the NCI and Stanford.

REFERENCES

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The treatment of advanced stage favorable histology non-Hodgkin's lymphoma: a preliminary report of a randomized trial comparing single agent chemotherapy, combination chemotherapy, and whole body irradiation

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