Treatment of Advanced Non-Hodgkin's Lymphomas With Favorable Histologies: Preliminary Results of a Prospective Trial

By Carol S. Portlock, Saul A. Rosenberg, Eli Glatstein, and Henry S. Kaplan

From July 1971 to August 1975, 63 previously untreated patients with stage IV non-Hodgkin's lymphomas with favorable histologies were prospectively randomized to three treatment programs: cyclophosphamide, vincristine, and prednisone alone (CVP); split course CVP and total lymphoid irradiation (CVP-TLI); or single alkylating agent (SA) therapy. More than 95% of all patients responded to therapy, and pathologically documented complete remissions were achieved in 78.3% of CVP, 65% of CVP-TLI, and 55% of SA patients (p > 0.2). The actuarial probability of obtaining a complete remission was the same (>80%) for SA patients as it was for those receiving CVP or CVP-TLI, but the time required to achieve a complete remission was more prolonged for SA patients (up to 40 mo). Only six (14.3%) complete responders have relapsed; the others have remained relapse-free for periods of 1–35 mo. There have been no statistically significant differences noted among the groups in terms of the probability of disease-free survival or survival, and 82.7% of all patients are alive at 30 mo (84.6% CVP, 73% CVP-TLI, and 90% SA). All three treatment programs have thus been highly effective in achieving excellent responses and prolonged disease-free survivals in patients with stage IV non-Hodgkin's lymphomas with favorable histologies. Over the 4-yr period of study, single agent therapy has been associated with as good or better overall survival when compared to the more aggressive treatment programs (CVP and CVP-TLI).

THE RAPPAPORT CLASSIFICATION of the non-Hodgkin's lymphomas permits the identification of disease entities whose responses to treatment and prognosis are well correlated with histopathology. As first reported by Jones et al. and later confirmed by others, a nodular architecture and a lymphocytic cytology are associated with a significantly better prognosis and response to chemotherapy than are the diffuse or histiocytic lymphomas. Jones et al. have identified four histopathologic groups which are favorable in their response to single alkylating agent chemotherapy and in their survival—well-differentiated lymphocytic lymphomas of the nodular (NLWD) or diffuse (DLWD) type, nodular poorly differentiated lymphocytic lymphoma (NLPD), and nodular mixed lymphocytic and histiocytic lymphoma (NML). Similarly, combination chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP) has resulted in excellent responses and prolonged disease-free sur-

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PORTLOCK ET AL.

Survivals in patients with advanced non-Hodgkin's lymphomas with favorable histologies.

In July 1971, a prospective randomized clinical trial was initiated at Stanford Medical Center to study three treatment programs for the therapy of stage IV non-Hodgkin's lymphomas with favorable histologies: combination chemotherapy alone with CVP versus split course CVP with total lymphoid irradiation (CVP-TLI) versus continuous single alkylating agent (SA) chemotherapy. Reported here are the preliminary results of that study, representing a maximal follow-up of 48 mo and a median of 24 mo for all patients.

MATERIALS AND METHODS

From July 1971 to August 1975, 63 patients with previously untreated stage IV non-Hodgkin's lymphomas with favorable histologies (NLWD, NLPD, NML, and DLWD) were prospectively randomized to receive CVP alone, CVP-TLI, or SA chemotherapy. The details of the study, histopathologic criteria, diagnostic methods, and staging designations, have appeared in previous reports.

Three treatment programs were utilized:

1. CVP alone—Treatment consisted of cyclophosphamide 400 mg/sq m once each day orally (p.o.q.d.) x 5 days, vincristine 1.4 mg/sq m intravenously (i.v.) on day 1 (total dose limited to 2 mg per injection), and prednisone 100 mg/sq m p.o.q.d. x 5 days. CVP was repeated every 21-28 days for at least six cycles, or until pathologic documentation of complete remission; then four consolidation cycles were given at the same dosage schedule every 21-28 days; and finally all complete responders have received or will receive maintenance CVP at the same drug dosage repeated every 3 mo for 2 yr from the initiation of CVP consolidation.

2. Split course CVP-TLI—Three cycles of CVP at the same drug dosage as in CVP alone were given at 21-28 day intervals; then TLI was begun to include 4400 rads to Waldeyer's ring, mantle, and wide-inverted Y field, and 3000 rads to a whole abdominal field to encompass the mesenteric lymph nodes. A 30-60 day rest period followed TLI to allow recovery of blood counts; then CVP was reinstituted at 21-28 day cycles; however, the dose of cyclophosphamide was reduced to 300 mg/sq m p.o.q.d. x 5 days because of expected diminished bone marrow reserve. CVP was continued for three or more cycles until pathologic documentation of complete remission; then the patient went on to receive consolidation and maintenance as for those patients receiving CVP alone.

3. Continuous SA—Cyclophosphamide (1.5-2.5 mg/kg/day) or chlorambucil (0.1-0.2 mg/kg/day) was given by mouth indefinitely. The dose was titrated to disease activity and to bone marrow tolerance (usually maintaining WBC > 3,000 and platelets > 100,000).

The characteristics of the patient population are described in detail in Table 1.

No patients were excluded from the study because of treatment toxicity, incomplete therapy, or insufficient data. A complete remission was defined as complete regression of all known disease and pathologic documentation of complete regression of all known extranodal sites of disease. Bone marrow or liver biopsies were necessary to confirm that complete regression of disease had occurred when these studies had previously been positive. A partial remission was defined as greater than 50% reduction of all measurable tumor for at least 1 mo. The partial remission group included any patient who was in clinical complete remission but who had not had pathologic documentation of complete remission or whose bone marrow biopsy was still positive while on treatment. Patients with no response were defined as those who had less than a 50% reduction in measurable tumor.

Duration of complete response was calculated from the date of pathologic documentation of complete remission to the first objective evidence of relapse. Survival was determined from the date of the patient's first visit to Stanford Medical Center to death (the duration from diagnosis

*The randomization procedure involved drawing a sealed envelope with the treatment option determined from a series of random numbers.
Table 1. Characteristics of the Patient Population

<table>
<thead>
<tr>
<th></th>
<th>CVP</th>
<th>CVP-TLI</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>52</td>
<td>52.5</td>
<td>48.4</td>
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<tr>
<td>Range</td>
<td>29–65</td>
<td>32–65</td>
<td>24–65</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLPD</td>
<td>21</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>NML</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>DLWD</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Extranodal sites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow</td>
<td>15</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Marrow and liver</td>
<td>6</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Liver only</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Skin only</td>
<td>1</td>
<td>0</td>
<td>0</td>
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to date first seen at Stanford was less than 3 mo for all patients). Curves for the probability of disease-free survival and for actuarial survival were calculated by the method of Kaplan and Meier. Tests for significance between survival curves, using the method of Gehan, are reported. All survival data refer to actuarial probability of survival unless otherwise stated.

RESULTS

Treatment Toxicity, Drug and Radiation Dosage

In general, the three treatment programs were well tolerated, with acceptable toxicities being those observed previously for CVP, total lymphoid irradiation, and continuous single alkylating agent therapy. Significant toxicities encountered are listed in Table 2.

The hematologic toxicity of CVP was manifested primarily by reversible leukopenia which was maximal at 10–14 days. The cyclophosphamide dose was reduced for leukopenia at 21 days or CVP was withheld for 1 wk to allow recovery of the white count. Patients in the CVP group received 74.7% of the calculated ideal dosage of 400 mg/sq m cyclophosphamide, as did those patients in the split course group prior to total lymphoid irradiation (78.5%). However, after radiation therapy, the dose of cyclophosphamide was reduced significantly (54.1% of the ideal 400 mg/sq m dose) because of low blood counts; and in four patients, persistent cytopenia with documented bone marrow hypoplasia required discontinuance of planned treatment. On the other

Table 2. Toxicities of Treatment

<table>
<thead>
<tr>
<th></th>
<th>CVP (23)</th>
<th>CVP-TLI (20)</th>
<th>SA (20)</th>
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<tbody>
<tr>
<td>Bacterial infections</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Persistent cytopenia</td>
<td>—</td>
<td>4</td>
<td>—</td>
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hand, the non-marrow-suppressive drugs were administered in comparable
dosage to both groups of patients (Table 3).

The planned course of 4400 rads TLI was carried out in 60\% of the patients
in the split course group, while modified radiation therapy courses were neces-
sary in seven patients because of blood count depression. In two patients the
dose was 3500 rads TLI, and in five patients the mantle and Waldeyer’s ring
received less than 2200 rads, while the abdomen received 4400 rads. Only one
patient, who died after two cycles of CVP, received none of the planned radia-
tion therapy.

Treatment Results

The response in each of the three treatment groups has been excellent, with
greater than 95\% of all patients responding to therapy. As outlined in Table 4,
pathologically documented complete responses were obtained in 78.3\% of the
CVP group, 65\% of the CVP-TLI group and 55\% of the SA group (p > 0.2). In
Fig. 1 the time to complete remission is displayed actuarially, and it can be seen
that the CVP and CVP-TLI groups enter complete remission more rapidly than
the patients given a single agent, but that one is just as likely to obtain a com-
plete remission with SA therapy, although the time to complete remission is
more prolonged. An 80\% actuarial probability of obtaining a complete re-
sponse does not occur until 40 mo with continuous SA treatment as compared
to 16 mo for the CVP and CVP-TLI groups. Since the median follow-up for
all patients to date is only 24 mo, the number of patients obtaining a pathologi-
cally documented complete response in each group still reflects both the efficacy

<table>
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<th>Table 3. Drug Dosage and Hematologic Toxicity</th>
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<tr>
<td>Cyclophosphamide per Cycle (% of 400 mg/sq m)</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>CVP alone</td>
</tr>
<tr>
<td>CVP-TLI Before TLI</td>
</tr>
<tr>
<td>CVP-TLI After TLI</td>
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<tr>
<td>*Average lowest count at 3 wk.</td>
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<td>†Excluding four patients in whom CVP was discontinued following total lymphoid irradiation because of persistent cytopenia.</td>
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<th>Table 4. Response to Treatment</th>
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<tr>
<td>Complete response</td>
</tr>
<tr>
<td>CVP (23)</td>
</tr>
<tr>
<td>Disease progression</td>
</tr>
<tr>
<td>CVP (20)</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>CVP (20)</td>
</tr>
<tr>
<td>On treatment</td>
</tr>
<tr>
<td>CVP (20)</td>
</tr>
<tr>
<td>Disease progression</td>
</tr>
<tr>
<td>CVP (20)</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>CVP (20)</td>
</tr>
<tr>
<td>Disease progression</td>
</tr>
<tr>
<td>CVP (20)</td>
</tr>
<tr>
<td>Total disease progression</td>
</tr>
<tr>
<td>CVP (20)</td>
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</tbody>
</table>
Fig. 1. Actuarial probability of achieving a complete response from date first seen to date of pathologic documentation of complete response for CVP (23), CVP-TLI (20), and SA (20).

of treatment, as well as the relative rapidity of remission induction. As a result, a longer period of follow-up will be necessary to assess fully the complete response rates for each group, in particular for those receiving SA therapy. Six complete responders (14.3% of the complete responders) have relapsed, while the others have remained disease-free for periods of 1–35 mo. There were three complete responders in the CVP group who relapsed 6, 8, and 23 mo after pathologic documentation of complete remission (two in lymph nodes and one in bone), as well as two complete responders in the split course group who relapsed at 6 and 27 mo (both in lymph nodes and one in bone marrow as well), and one single agent complete responder who relapsed in bone marrow 3 mo after documented complete remission. To date, there are no significant differences between the three treatment groups in terms of disease-free survival ($p > 0.6$) (Fig. 2).

Partial responses were seen in 21.7% of CVP patients, 30% of CVP-TLI, and 40% of SA patients. Of the 19 partial responders, seven are currently receiving treatment, and all are clinically free of disease, but without pathologic documentation of complete remission. The other 12 partial responders have had progression of their disease: four in the CVP group, one of whom has died; four in the CVP-TLI group, of whom three have died; and four in the SA group, one of whom has died. There were only two nonresponders in the entire study population: one CVP-TLI patient died with disease after two cycles of CVP before receiving planned radiation therapy, and one SA patient is alive with disease currently receiving combination chemotherapy.

To date, then, with a maximal follow-up of 48 mo and a median of 24 mo for all patients, there are 21 patients who have had progression of disease after ini-
Fig. 2. Actuarial disease-free interval from date of pathologic documentation of complete response to relapse for CVP (18), CVP-TLI (13), and SA (11).

Fig. 3. Actuarial disease-free survival from the date first seen to disease progression for CVP (23), CVP-TLI (20), and SA (20).
Fig. 4. Actuarial survival from the date first seen for CVP (23), CVP-TLI (20), and SA (20).

...tial therapy: seven patients in the CVP group, eight patients in the CVP-TLI group, and six patients in the SA group. When one looks at the actuarial time to relapse from the initiation of treatment to disease progression for the study population as a whole, one can see that more than half of the patients remain alive without evidence of disease progression at 35 mo, and that there are no significant differences in the disease-free survival for any of the three treatment groups ($p > 0.5$) (Fig. 3).

Likewise, there are no significant differences in the probability of survival between the three treatment groups ($p = 0.07$), where the median survival has not been reached and more than 70% of all patients remain alive at 30 mo (Fig. 4). There have been two deaths in the CVP group: one in a complete responder who relapsed in bone 8 mo after documented complete remission, and one in a partial responder who had progressive disease on CVP. There have been five deaths in the split course group: one in a complete responder who died from unrelated causes and had unsuspected microscopic evidence of disease at post-mortem, one in a nonresponder after two cycles of CVP and prior to initiation of planned radiation therapy, and three in partial responders who died from complications of bone marrow hypoplasia with active lymphoma. There has been one death in the single agent group in a partial responder who had progressive disease.

DISCUSSION

As one might expect in patients with histologically favorable non-Hodgkin's lymphomas, all three treatment programs have resulted in excellent responses to therapy, with an overall response of greater than 95% for all patients (Table 4). Somewhat surprising, however, is the observation that patients receiving
continuous single alkylating agent therapy can obtain pathologically documented complete remissions, and that the probability of obtaining such a complete response is the same for patients given a single agent as it is for those receiving combination chemotherapy, with or without radiation therapy, but that the time to complete remission is more prolonged. Previous studies of single agent chemotherapy reporting response rates of 10%-20% did not identify patients with favorable histologies utilizing the Rappaport classification, and, in general, patients were treated for only brief periods of time (less than 42 days) before a response to treatment was assessed. Likewise, reports of combination chemotherapy in the non-Hodgkin's lymphomas suggesting that such treatment is superior to single agent therapy refer to concurrent or historical controls in which results were not analyzed with reference to the Rappaport classification and in which single agent treatment was of limited duration.

The retrospective review by Jones et al. pointed out, however, that when results were analyzed according to the Rappaport classification, approximately 40% of patients with nodular lymphomas obtained clinical complete remissions with single agent therapy and that the time required to reach such a remission varied from 2 to greater than 20 mo. Our experience in the present prospective study confirms this observation and further demonstrates that pathologically documented complete remissions can be obtained with continuous single agent therapy. However, we cannot yet assess the durability of these complete remissions, because the follow-up for all patients is less than 48 mo, and the longest complete remission for any patient receiving a single agent to date is only 12 mo.

Of the 31 complete responders who have received combination chemotherapy (with or without total lymphoid irradiation), five (16.1%) have relapsed less than 27 mo following pathologic documentation of complete remission: three in the CVP group (two in lymph nodes and one in bone) and two in the split course CVP-TLI group (both in lymph nodes and one in bone marrow as well). Other CVP studies have similarly noted that, although patients with favorable histologies do have initially high rates of complete remission, these remissions are not as uniformly sustained as are those obtained in patients with unfavorable histologies. In particular, Schein et al. have observed a pattern of continuous relapse from complete remission after CVP therapy for patients with NLPD, and pointed out that such relapses occur only in sites which were previously known to be positive. Furthermore, since 69% of these relapses occurred in lymph nodes, they suggested that adjunctive radiation therapy might be of benefit. The present results in the split course CVP-TLI group do not appear to support this conclusion; however, it should be noted that the two CVP-TLI complete responders who have relapsed did so after receiving markedly reduced cyclophosphamide dosages following total lymphoid irradiation (19% and 40% of the calculated 400 mg/sq m) as a result of pancytopenia.

Moreover, for those patients who achieve a partial remission only, the split course CVP-TLI technique is associated with significant morbidity. Four of these patients developed persistent cytopenia with documented bone marrow hypoplasia following radiation therapy, and three have subsequently died from complications of marrow hypoplasia with active lymphoma. Recognizing that
the purpose of adjunctive radiation therapy is to consolidate a complete remis-
sion and that CVP is excellent induction chemotherapy, the split course tech-
nique has been abandoned in favor of considering lymphoid irradiation only
after complete response to CVP alone.

Even though all patients in this study had widely disseminated lymphoma,
there have been only 21 patients (33.3\%) who have had progression of disease
after initial therapy (with a median follow-up of 24 mo); and no significant
differences have been seen between the three treatment groups in terms of the
probability of treatment failure as illustrated in Fig. 3. Furthermore, there have
been only eight deaths (12.7\%) in this study and as one can see in Fig. 4, the
probability of survival is similar in the three treatment groups (p = 0.07) with
more than 70\% of patients alive at 30 mo. These results reflect the good prog-
nosis of the favorable non-Hodgkin’s lymphomas and serve to emphasize the
prolonged survival of even those patients who achieve only a partial remission
or who relapse after a complete response to chemotherapy.

Although a longer period of follow-up will be needed to judge the relative
efficacies and risks of the three treatment approaches, certain tentative con-
clusions can be made: (1) the three treatment programs are all effective in
achieving excellent responses and prolonged disease-free survivals in patients
with stage IV non-Hodgkin’s lymphomas with favorable histologies; (2) the
combined approach of split course CVP and high dose total lymphoid irradia-
tion does not appear to improve the duration of complete remission as com-
pared to CVP alone and makes salvage of partial responders difficult because
of treatment-induced bone marrow hypoplasia; and (3) single agent chemo-
therapy, given continuously, is capable of inducing pathologically documented
complete remissions in these patients, and, over the 4-year period of this study,
single agent therapy has been associated with as good or better overall survival
as compared to the more aggressive treatment programs.

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