Combination Chemotherapy in Lymphosarcoma and Reticulum Cell Sarcoma

By Barth Hoosstraten, M.D.; Albert H. Owens, M.D.; Raymond E. Lenhard, M.D.; Oliver J. Glidewell; Louis A. Leone, M.D.; Kenneth B. Olson, M.D.; John B. Harley, M.D.; Stuart R. Townsend, M.D.; Seward P. Miller, M.D.; and Charles L. Spurr, M.D.

The chemotherapeutic management of patients with lymphosarcoma and reticulum cell sarcoma has usually been accomplished with single agents. The alkylating agents cyclophosphamide and chlorambucil have been widely used, while of the vinca alkaloids, vincristine appears most effective. The efficacy of corticosteroids in varying dosages was shown several times. The remission induction rates in these reports have all been around 50 per cent, indicating that in this area little progress has been made in the last decade.

In childhood acute leukemia the combination of agents effective for remission induction has led to greater success than the use of single agents and we can now consistently expect a complete remission rate of 85 per cent or more. This has permitted intensive study of maintenance therapy and twice weekly methotrexate (orally or parenterally) has been shown to be a highly active maintenance regimen.

The present report represents the effort of two large cooperative groups to answer specific questions regarding the chemotherapeutic management of patients with lymphosarcoma or reticulum cell sarcoma:

Study undertaken by the Acute Leukemia Cooperative Group B (Chairman, James F. Holland, M.D.) and the Eastern Cooperative Oncology Group (Chairman, Bruce I. Shnider, M.D.).

Supported by Public Health Service Research Grants from the National Cancer Institute. First submitted April 18, 1968; accepted for publication November 12, 1968.

Acute Leukemia Group B: 1The Mount Sinai Hospital School of Medicine, 100 Street and Fifth Avenue, New York, N.Y. 10029 (CA-04457). 2Associate Biostatistician, Roswell Park Memorial Institute, Buffalo, N.Y. (CA-02593). 3Rhode Island Hospital, Providence, R.I. (CA-08025). 4West Virginia University Medical Center, Morgantown, W.Va. (CA-07757). 5McGill University Hospital, Montreal, Canada. 6Bowman Gray School of Medicine, Winston-Salem, N.C. (CA-03927).

Eastern Cooperative Oncology Group: 1Johns Hopkins Hospital, Baltimore, Md. (CA-06973). 2Albany Medical College of Union University, Albany, N.Y. (CA-06594). 3Maimonides Hospital, Brooklyn, N.Y. (CA-05588).

Other participating institutions were: Dartmouth Affiliated Hospitals, Hanover, N.H. (CA-04326); New York Hospital-Cornell Medical Center, New York, N.Y. (CA-07968); Walter Reed Hospital, Washington, D.C.; Jefferson Medical College Hospital, Philadelphia, Pa. (CA-05462); Medical College of Virginia, Richmond, Va. (Cy-3735); Boston USPHS Hospital; Georgetown University School of Medicine, Washington, D.C. (CA-02824); Lemuel Shattuck Hospital, Boston, Mass. (CA-07190); Long Island Jewish Hospital, New Hyde Park, N.Y. (CA-05903).

Generic and trade names of drugs: Cyclophosphamide—Cytoxan; Vincristine—Oncovin.
COMBINATION CHEMOTHERAPY

Table 1.—Remission Induction Therapy

<table>
<thead>
<tr>
<th>Single Agent</th>
<th>High Combination</th>
<th>Low Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide (I.V.)</td>
<td>15 mg./Kg./wk.</td>
<td>15 mg./Kg./wk.</td>
</tr>
<tr>
<td>Vincristine (I.V.)</td>
<td>—</td>
<td>25 μg./Kg./wk.</td>
</tr>
<tr>
<td>Prednisone (P.O.)</td>
<td>—</td>
<td>1 mg./Kg./day</td>
</tr>
</tbody>
</table>

Table 2.—Definition of Response

COMPLETE REMISSION—Complete disappearance of all lesions, measurable and non-measurable.

PARTIAL REMISSION—Decrease in the sum of the product of tumor diameters by >50 per cent over two or more consecutive measurement periods and no new lesions or disease progression.

NO CHANGE—Decrease of <50 per cent or an increase of <25 per cent over the original measurements.

PROGRESSION—Increase of >25 per cent over the original measurements and/or appearance of a new lesion.

RELAPSE—Appearance of a new lesion persisting for two weeks or an increase of the product of diameters of any old measured tumor by 50 per cent over that which was obtained at the time of maximum regression.

1. Does a combination of drugs induce remissions with greater frequency than one of its single component agents, cyclophosphamide?
2. Is there a difference in the relative efficacies of two dosage levels of combination therapy in inducing remissions?
3. If such a difference exists, does it warrant the higher degree of toxicity caused by high dose combination therapy?
4. Does twice weekly methotrexate maintenance therapy affect the duration of remission?

Methotrexate was chosen for maintenance therapy, because this drug was able to produce tumor regression in 50 per cent of patients with lymphosarcoma or reticulum cell sarcoma.12

METHODS

Only patients over 15 years of age with biopsy-proved lymphosarcoma or reticulum cell sarcoma and having active disease that could be followed by serial objective measurements were eligible for study. Patients who had received prior treatment with corticosteroids or any other chemotherapeutic agent were excluded, but patients could have received prior radiation to localized areas if the objective manifestations were not solely at the irradiation sites. It was also required that there be adequate bone marrow function, as assessed by a leukocyte count over 5,000 per cu.mm. and a platelet count over 100,000 per cu.mm. Patients with lymphosarcoma who had a WBC greater than 15,000 per cu.mm., of which more than 50 per cent were lymphocytes, were excluded. A blood urea nitrogen more than 25 mg. per cent disqualified.

For remission-induction therapy, all patients were randomized to cyclophosphamide alone or to high or low dose combination chemotherapy (Table 1). Therapy was given for six weeks but could be stopped at 28 days if the patient showed evidence of tumor progression. When a complete or partial tumor regression (Table 2) occurred by day 49, the patients from the Acute Leukemia Group B (ALGB) were randomized to oral placebo or to methotrexate, 0.5 mg./Kg. orally or intramuscularly twice weekly. Patients from the Eastern Cooperative Oncology Group (ECOG) were observed without maintenance therapy.
Table 3.—Hematologic Toxicity and Dose Modification

<table>
<thead>
<tr>
<th>W.B.C.</th>
<th>Platelets</th>
<th>Dose of Cyclophosphamide and Vincristine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5,000</td>
<td>&gt; 100,000</td>
<td>100%</td>
</tr>
<tr>
<td>4 – 4,999</td>
<td>&gt; 100,000</td>
<td>75%</td>
</tr>
<tr>
<td>3 – 3,999</td>
<td>75 – 99,999</td>
<td>50%</td>
</tr>
<tr>
<td>2 – 2,999</td>
<td>75 – 99,999</td>
<td>25%</td>
</tr>
<tr>
<td>0 – 1,999</td>
<td>0 – 74,999</td>
<td>None</td>
</tr>
</tbody>
</table>

Vincristine and cyclophosphamide dosages were modified for defined degrees of toxicity (Table 3), but prednisone continued at the prescribed dose.

Patients were seen at weekly intervals and the clinical status, tumor measurements, laboratory data and degree of toxicity recorded. Toxicity was graded 0 = none; 1 = mild; 2 = moderate — drug dose changed; 3 = severe — drug stopped and 4 = life-threatening. The toxicity index was obtained by adding the toxicity grades per treatment group and dividing the total by the number of patients in that group. Performance and food intake were graded 1 = normal; 2 = moderate and 3 = severe impairment. Evaluations were independently made by the study chairman of each Group and the results were recorded only after complete agreement had been reached. Remission duration was calculated from the start of maintenance therapy (day 49) until relapse occurred, regardless of the day of onset of remission (Table 2). A total of 28 cases were disqualified; 13 had received prior chemotherapy; 5 had a BUN over 25 mg. per cent; 4 had no measurable disease; in 3 the protocol was not followed; 2 had leukemia and in one patient prednisone was not given because of preexisting gastric ulcer.

RESULTS

Eighty-eight patients fulfilled the admission criteria and were followed as per protocol, 58 by 13 members of the ALGB and 30 by 7 members of the ECOG. There was a random distribution of patients with lymphosarcoma and reticulum cell sarcoma into the three treatment groups. There was no essential difference between the number of lesions, measurement of enlarged peripheral lymph nodes per patient and degree of hepatosplenomegaly between patients with lymphosarcoma and reticulum cell sarcoma nor between the patients of the three treatment groups. The frequency of extranodal tumor involvement was slightly higher in the cyclophosphamide group, 64 per cent versus 47 per cent for the low combination group and 52 per cent for the high combination group. An analysis was also made of the frequency of hepatomegaly, splenomegaly, involvement in other organs or combinations of these findings in patients with lymphosarcoma or reticulum cell sarcoma, and no differences were found.

Table 4 shows toxicity during the induction period in relation to therapy. Neurotoxicity, alopecia, cushingoid appearance and one instance of nonbacterial hematuria were seen only in patients on combination therapy. One patient in the high combination group developed a perforated peptic ulcer and died postoperatively. Despite the higher toxicity index for this group, the percentage of patients in the high combination group in whom the drug dose had to be reduced was lower than that of patients treated with the single agent, 60 and 80 respectively. This apparent discrepancy was due to the fact that drug dosages were mainly modified for hematologic reasons. The data again shows that prednisone has a hematologic protective effect. In the low combination group 41 per cent of patients required a lowering of drug dosages.
COMBINATION CHEMOTHERAPY

Table 4.—Observed Toxicity: by Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Cyclophosphamide (% Ind.)</th>
<th>High Combination (% Ind.)</th>
<th>Low Combination (% Ind.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Cases</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>Hematologic</td>
<td>21</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>G. I. tract</td>
<td>84</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Neurologic</td>
<td>0</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>27</td>
<td>21</td>
</tr>
</tbody>
</table>

( )=Number of patients.
Index=Mean severity grade/patient.

Table 5.—Response by Disease and Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Lymphosarcoma</th>
<th>Reticulum Cell Sarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Cases</td>
<td>% C.R. &amp; P.R.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>14</td>
<td>33</td>
</tr>
<tr>
<td>High Combination</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Low Combination</td>
<td>21</td>
<td>33</td>
</tr>
</tbody>
</table>

C.R.=Complete Remission
P.R.=Partial Remission.

Table 6.—Selected Sites of Involvement and Frequency of Complete Regression

<table>
<thead>
<tr>
<th>Type</th>
<th>Cyclophosphamide (% Ind.)</th>
<th>High Combination (% Ind.)</th>
<th>Low Combination (% Ind.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Cases</td>
<td>#</td>
<td>#</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>9</td>
<td>33</td>
<td>12</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>12</td>
<td>25</td>
<td>9</td>
</tr>
<tr>
<td>Mediastinum and/or</td>
<td>6</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>6</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Other extra-nodal</td>
<td>6</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>tumor</td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

C.R.=Complete Regression.

The response rates per disease and per treatment modality are shown in Table 5. In lymphosarcoma the response rate in both combination groups is significantly higher than in the cyclophosphamide group, (p < .01). In reticulum cell sarcoma, only high combination therapy was better than cyclophosphamide alone, (p < .05). The day upon which maximum regression occurred for patients responding did not vary appreciably by mode of therapy.

In Table 6 selected sites of involvement in both diseases and the frequency of their complete regression are shown. The high dose combination was superior to the low dose in causing regression of enlarged spleens and/or livers (p < .05). There is a suggestion that hepatomegaly is more resistant to all three therapies than is splenomegaly, since 65 per cent of enlarged spleens returned to normal size compared to only 29 per cent of enlarged livers (p < .01). This may imply non-neoplastic hepatomegaly in some patients. Tumor involvement in sites other than lymph nodes, liver or spleen was highest among cyclophosphamide treated patients. The frequency and degree of response of those lesions were greater among the patients treated with combination therapy.
It is often questioned whether decrease in measured tumor size correlates with improvement in other aspects of the disease. As shown in Table 7, with complete tumor regression improvement was also seen in hemoglobin, performance, food intake, weight and febrile state. Fever decreased sometimes when no remission was attained, but the other parameters mentioned became worse. Thus remission as defined in this study is equated with overall improvement in patient status.

Of the 64 patients who responded during the induction phase, 16 cases from the ECOG were followed without further therapy until relapse; 22 patients from the ALGB were randomly given methotrexate twice weekly, 17 orally and 5 intramuscularly, and 19 cases were given an oral placebo. With methotrexate maintenance the median duration of remissions was 100 days, as compared to 49 days for the placebo group (Fig. 1). This difference is not statistically significant.

**Comments**

A precedent for the use of combination chemotherapy with two or more agents has been well-established in childhood acute leukemia. In remission induction the effect of combining drugs has been consistently superior to that
of its separate components and in each instance the remission induction rate was slightly larger than that predicted from the additive effects of each component alone.10,13 The two cooperative groups contributing to the present study have recently completed an extensive study in which previously untreated patients with lymphosarcoma and reticulum cell sarcoma were treated with single agents, cyclophosphamide 15 mg./Kg./weekly intravenously or vincristine 25 μg./Kg./weekly. The additive remission rate of these two agents was 84 per cent in lymphosarcoma and 70 per cent in reticulum cell sarcoma. The identical dosages were used in our high combination group, to which prednisone was added. The remission rate with the high combination exceeded the additive percentages by 15 per cent in both diseases, 100 and 85 per cent respectively.

The study was undertaken to answer four specific questions. In varying degrees, the answer to three of the questions is affirmative. In lymphosarcoma, both combinations increased the percentage of remissions to a statistically significant degree as compared to cyclophosphamide alone (p < .01), but in reticulum cell sarcoma such increase was only seen with the high combination (p < .05). The total percentage of complete and partial remissions obtained with the high combination is better than any thus far reported in the literature.

The second question, whether there is a difference in efficacy of two dosage levels of combination therapy in inducing remissions, can be answered positively in reticulum cell sarcoma, although at only a low degree of significance (p < 0.10). In lymphosarcoma no difference was found.

The third question, whether the difference in toxicity is acceptable in view of the difference in efficacy of the two combination dosages, is not answerable with assurance. The toxicity index for the high combination was 1.8 times
that for low combination (0.78 vs. 0.43). The difference in remission induction efficacy of the two is not impressive. The answer to this question depends largely upon one’s intent. If chemotherapy in the two diseases is considered palliative only, then the low combination with its lesser degree of toxicity is acceptable and could be pursued. If, on the other hand, the intent is that of maximum possible kill of the malignant cell population, then high combination is to be preferred and should even be intensified. Skipper and colleagues have reported that with intensive high dose chemotherapeutic treatments in mice with leukemia L1210 a maximum cell kill could be achieved and cures predictably obtained. In children with acute lymphoblastic leukemia, intensive combination drug regimens have resulted in several long-term remissions in the absence of continuous maintenance therapy. A similar effort could well be applied in the treatment of the two diseases under discussion, despite an anticipated appreciable toxicity. Certainly chemotherapeutic agents have thus far not been used in dosages which approach maximum host tolerance. Our toxicity data again show the hematologic protective effect of corticosteroids. This had well been shown by others, e.g., Kyle et al. who demonstrated increases in WBC and platelet counts in the majority of their patients with lymphosarcoma.

The last question to be answered in this study related to the effect of twice-weekly methotrexate on the duration of remission, a part of the study undertaken by the Acute Leukemia Group B only. Although the median duration of methotrexate-maintained remissions was twice as long as that of placebo, the difference observed in this number of patients could readily have occurred by chance.

With different degrees of certainty, three of the four questions which led to the design of the protocol have been answered. However, the results gave rise to other questions. As indicated under “methods,” the frequency of extranodal tumor involvement was highest in the cyclophosphamide group. This is a factor which might have influenced the observed response rate in lymphosarcoma, 43 per cent in the present study as compared to 71 per cent in a previous large study by the same observers. But when the effects of cyclophosphamide and combination therapy upon lymph nodes, liver, spleen and extranodal tumors are analyzed separately, the combination is superior in all four categories.

A second obvious question is whether the combination therapy results can be repeated by others. A similar combination is used by another cooperative group in a noncomparative study. They recently reported a remission induction rate of 96 per cent. Thus, there is good evidence that the combination of cyclophosphamide, vincristine and prednisone is an excellent remission induction treatment for lymphosarcoma and reticulum cell sarcoma. Other drug combinations and other schedules, e.g., repetitive courses, are reasonable areas of extension of these findings.

**Summary**

Patients with lymphosarcoma and reticulum cell sarcoma were randomly allocated to treatment with cyclophosphamide alone or to two dosage levels
of combinations of cyclophosphamide, vincristine and prednisone. Remission induction was significantly better for the combinations with lymphosarcoma patients and for the high dose combination with reticulum cell sarcoma patients. Toxicity, more pronounced with high combination, was tolerable. Remissions as measured by decrease in tumor size were associated with improvement in hemoglobin, performance, food intake, weight and fever. The study provides impetus for further trial with other drug combinations and schedules.

SUMMARIO IN INTERLINGUA

Patientes con lymphosarcoma e sarcoma a cellulas reticular esseva allocate aleatorimente a trattamento con cyclophosphamida sol o a un de duo nivellos de dosage de combinationes de cyclophosphamida, vincristina, e prednisona. Le induction de remissiones esseva significativemente plus favorabile in le casos de lymphosarcoma tractate con un del combinationes e in le casos de sarcoma a cellulas reticular tractate con le plus alte dosage del combination. Le toxicitate, plus pronunciate a alte dosages del combination, esseva tolerabile. Le remissiones, judicate per le declino in le dimensions del tumores, esseva associate con melioration in le valores de hemoglobina, le activitate, le acceptation de nutrimentos, le peso corporee, e febre. Le studio provide un stimulo pro essayos additional con altere combinationes e programmas de pharmacotherapia.

REFERENCES

HOGSTRATEN ET AL.


Combination Chemotherapy in Lymphosarcoma and Reticulum Cell Sarcoma

BARTH HOOGSTRATEN, ALBERT H. OWENS, RAYMOND E. LENHARD, OLIVER J. GLIDEWELL, LOUIS A. LEONE, KENNETH B. OLSON, JOHN B. HARLEY, STUART R. TOWNSEND, SHERWOOD P. MILLER and CHARLES L. SPURR