IMVP-16: An Effective Regimen for Patients With Lymphoma Who Have Relapsed After Initial Combination Chemotherapy

By Fernando Cabanillas, Fredrick B. Hagemeister, Gerald P. Bodey, and Emil J. Freireich

Results of second-line chemotherapy regimens against lymphoma have usually been poor. In this study, we used a combination of ifosfamide, methotrexate, and VP-16 to treat 52 patients with lymphoma who had either relapsed or who had failed to attain a complete remission on front-line treatment. Thirty-two patients (62%) responded (CR 37%, PR 25%) and 10 (19%) had a minor response. The median relapse-free interval of the responding patients was 12 mo, and the median survival of the whole group was 15 mo. Of the 18 patients who achieved complete remission, 10 still remain free of any evidence of disease. The factor that best predicted for response to IMVP-16 was the quality of the remission achieved on front-line therapy. In view of the poor prognosis associated with recurrent lymphoma, the results obtained with this study are considered most encouraging. Patients with recurrent lymphoma can be successfully salvaged by the use of this combination regimen, especially if introduced early after relapse or preferably before progressive disease develops.

CURRENTLY AVAILABLE combination chemotherapy regimens are very effective when used in previously untreated patients with intermediate and high grade malignant lymphomas. Complete remission rates obtained with these regimens range from 60% to 80%. However, approximately 20%-40% of patients who enter complete remission will relapse, while the remainder will experience long-term disease-free survival and probably are cured of their malignancy. The fraction of patients who fail to enter complete remission, or who relapse after initial combination chemotherapy, are uniformly destined to die, usually within 3-7 mo, unless they achieve another complete remission with subsequent therapy. Those patients with low-grade lymphomas might have a more protracted clinical course, but their ultimate fate is similar. Currently available salvage therapies are suboptimal, especially for the intermediate and high-grade tumors, where no uniformly effective second-line regimen has been discovered.

The purpose of this article is to describe the results obtained with a salvage regimen consisting of ifosfamide (a cyclophosphamide analog), methotrexate, and VP-16. These 3 drugs have independent activity against lymphomas as shown by previous studies. Our phase II study of ifosfamide showed a partial response rate of 47% with no complete responses occurring. An advantage of ifosfamide over cyclophosphamide is that its myelosuppression is mild and thus allows for the use of close to full doses of methotrexate and VP-16, which are myelosuppressive. Ifosfamide does not exhibit cross-resistance with cyclophosphamide in the L1210 leukemia model. VP-16 has been studied in lymphomas by various groups and the average overall response rate (CR + PR) is 25%, with a wide range of 0%-63%. Literature data on methotrexate as single agent against lymphoma shows a 41% overall response rate in 29 patients.

MATERIALS AND METHODS

Fifty-two adult patients who had failed to respond or who had relapsed after front-line treatment were treated with the IMVP-16 regimen described below. Included in this group also are 5 patients who had responded to front-line treatment by achieving a partial remission, but who were clearly not improving any further and for this reason, their treatment was changed to IMVP-16 before progression of their lymphoma. The pathologic material was reviewed by a member of our Department of Pathology. The histologic diagnoses of these patients were: large cell lymphoma ("histiocytic") 34, small cleaved cell lymphoma-follicular ("nodular poorly differentiated lymphocytic") 9, others 9 (lymphoblastic 2, small noncleaved ("undifferentiated") 2, Hodgkin's 2, unclassifiable 2, and composite 1). All but 1 of these patients had received front-line combination chemotherapy that included adriamycin in addition to alkylating agents in adequate doses.

The IMVP-16 regimen consisted of ifosfamide, 1 g/sq m in 1000 cc of dextrose in water over 1 hr daily for 5 days, methotrexate 30 mg/sq m on days 3 and 10, VP-16 100 mg/sq m in 1000 cc of normal saline over 2 hr daily for 3 days. Courses were repeated every 21 days if the absolute granulocyte count and platelet count were =1000 and 100,000, respectively. Treatment was given in the outpatient clinic whenever the patient's clinical status permitted it. The methotrexate and VP-16 doses were reduced by 20% when there was a history of prior extensive radiation therapy or previous poor tolerance to chemotherapy. Patients with bone marrow involvement were given full doses of the drugs. Treatment with IMVP-16 was continued until progressive disease developed or to a minimum of 1 yr after achieving complete remission status.

From the Departments of Developmental Therapeutics and Medicine, Section of Hematology, the University of Texas System Cancer Center M. D. Anderson Hospital and Tumor Institute, Houston, Texas. Presented in part at the 17th Annual Meeting of the American Society of Clinical Oncology, Washington, D. C., May 1981. Supported in part by Grant CA 05831, Appropriation 9A from the National Cancer Institute. National Institutes of Health, USPHS, Bethesda, Md. Submitted December 7, 1981; accepted April 27, 1982. Address reprint requests to Dr. Fernando Cabanillas, M. D., Anderson Hospital, 6723 Bertner, Houston, Texas 77030.

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Blood, Vol. 60, No. 3 (September), 1982 693
A complete remission (CR) was defined as the appearance of all evidence of disease and symptoms related to disease for a minimum of 2 mo. In order to evaluate response, all baseline examinations considered abnormal including CT scans, lymphangiograms, and bone marrow biopsies were repeated. A partial remission (PR) was defined as more than 50% reduction in the sum of the product of the diameters of measured lesions lasting for at least 1 mo. No simultaneous increase in the size of any lesion or the appearance of new lesions could occur. Response less than PR was defined as less than 50% regression of the tumor or more than 50% regression of the tumor with regrowth in between courses of treatment. Patients who died before 2 courses of treatment were completed were considered failures if there was evidence of progressive disease before the patient expired. The duration of survival was measured from the time the patient started treatment with the IMVP-16 regimen. The relapse-free survival was measured from the onset of response to the time of progression. The method of Kaplan and Meier was used to plot survival curves.\(^1\) The generalized Wilcoxon test was utilized to test differences in survival.\(^1\)

### RESULTS

#### Response Rates

Nineteen (37%) of the 52 patients achieved a CR on IMVP-16. An additional 13 (25%) attained a PR and 10 (19%) experienced an objective response less than PR. The response rate according to histologic type was: large cell 13/34 (38% CR), 10/34 (29% PR), 7/34 (21% less than PR); small cleaved cell 3/8 (38% CR), 2/8 (25% PR), 1/8 (13% less than PR); others 3/10 (30% CR), 1/10 (10% PR), 2/10 (20% less than PR). The 3 CRs in this last category occurred in 1 lymphoblastic, 1 small noncleaved (undifferentiated) lymphoma, and 1 peripheral T-cell lymphoma. The large cell lymphomas included 31 diffuse and 3 nodular types.

#### Prognostic Factors

Six variables were examined for their ability to predict achievement of CR on IMVP-16. Table 1 shows the 3 variables that were found to be statistically significant or to approach significance. The pretreatment variable most closely associated with a high CR rate to IMVP-16 was the quality of the response to front-line chemotherapy. The highest CR rate was seen in those patients who had achieved a PR on front-line therapy and whose chemotherapy was changed to IMVP-16 before recurrent disease developed. These were patients who had attained their maximum response to front line treatment and after 6 chemotherapy courses no further cytoreduction was observed. The second highest CR rate was in patients who achieved a CR on front-line treatment. When these 2 groups are compared to the rest (Table 1), the \(p\) value is highly significant.

The number of relapses prior to initiating IMVP-16 correlated inversely with the CR rate. The CR rate of those patients who had experienced 3 or more relapses was inferior to those who had experienced 1–2 relapses.

<table>
<thead>
<tr>
<th>Number of relapses</th>
<th>CR (%)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>15 (40)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td>(\geq3)</td>
<td>2 (18)</td>
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Duration of response to first line treatment:

<table>
<thead>
<tr>
<th>Duration</th>
<th>CR (%)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 mo</td>
<td>11 (38)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>1 (12)</td>
<td></td>
</tr>
</tbody>
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Response to first-line treatment:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CR (%)</th>
<th>(p) Value</th>
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</thead>
<tbody>
<tr>
<td>PR-IMVP-16 before relapse</td>
<td>5 (48)</td>
<td>0.001</td>
</tr>
<tr>
<td>PR-IMVP-16 after relapse</td>
<td>2 (11)</td>
<td></td>
</tr>
</tbody>
</table>

Finally, the duration of response to first-line treatment (considering only those patients who had achieved a CR or PR to front-line treatment and later relapsed) was also capable of predicting to some extent the quality of the response to IMVP-16.

#### Survival and Relapse-Free Survival

Survival of the whole group of 52 patients, according to the quality of response to IMVP-16, is shown in the first panel of Fig. 1. The survival of the complete responders is superior to that of partial responders and failures. The projected median survival of complete responders is 15 mo, and 42% are projected to be alive at 36 mo. The median survival of partial responders is 9 mo, and this is also significantly superior to those who had a response less than PR or who had failed to respond.

The relapse-free survival of the responders is shown in the second panel of Fig. 1. All of the relapses in the group of complete responders have occurred in the first year of treatment. The projected median relapse-free survival of this group is 12 mo. Of the 19 complete responders, 7 have experienced relapse-free survival beyond 12 mo. This figure was significantly superior to the median relapse-free survival figures of those with partial and less than partial responses, which are 4 and 3 mo, respectively. Figure 2 shows the data on relapse-free as well as overall survival according to the histologic type. No difference was observed in either of these 2 parameters for the 3 diagnostic categories analyzed.

#### Toxicity

The most frequent side effects of IMVP-16 con-
sisted of myelosuppression, mucositis, and hemorrhagic cystitis. A total of 71 courses of treatment were given to 34 patients without bone marrow involvement. The median lowest white blood count and platelet count in these patients was 700/cu mm (range, 0–3600/cu mm) and 125,000/cu mm (range, 7–630,000/cu mm), respectively. The median day for the lowest blood count was day 13 and by day 21 recovery was seen in the majority of patients. Thirteen documented episodes of infection occurred in 10 patients. These were all associated with neutropenia induced by the chemotherapy. Five of these 10 patients had invasion of marrow by lymphoma, and the rest had received prior extensive radiotherapy or chemothera-
py. The types of documented infection were: 8 septicemias, 2 soft tissue infections, 2 pneumonias, and 1 catheter-related infection. The organisms responsible for the 8 episodes of septicemia were: *Pseudomonas aeruginosa* (3), *Staphylococcus aureus* (2), *Fusobacterium* (1), *Clostridium* (1), and *Enterobacter cloacae* (1). An additional 6 episodes of fever of unknown origin in relation to neutropenia, requiring admission to the hospital for intravenous antibiotics, were recorded. Only 2 patients expired secondary to infection related to myelosuppression. Both had diffuse bone marrow involvement and neutropenia at the initiation of IMVP-16.

Twelve episodes of mucositis occurred in 12
and usually consisted of elevation of alkaline phosphatase and serum glutamic-oxaloacetic transaminase.

Gross hemorrhagic cystitis occurred in 4 instances in 4 patients. These ranged from mild to moderately severe.

Toxicities consisted of drug fever in 1 patient and urticarial rash in another.

Hepatitis-B surface antigen was revealed fatty metamorphosis. The bilirubin gradually reverted to normal over a period of 1 yr after discontinuation of treatment. Liver biopsy in this patient revealed a moderate degree of fatty degeneration.

The quality of the response to front-line treatment and 35% obtained with the IMVP-16 regimen represents a considerable improvement over our previous experience encouraged us to modify that regimen by using a second-line combination chemotherapy regimen instead of a single agent. By properly identifying these factors, one might also avoid the risk of false negative results in phase II trials.

The infectious morbidity associated with IMVP-16 might be before relapse occurs. The morbidity frequently seen after most second-line treatments. If the infectious complications are profound, the patient should be promptly referred to a center where a combination regimen might also be initiated.

The results of salvage treatment of patients with recurrent lymphoma can be successfully salvaged by using a second-line combination chemotherapy regimen instead of a single agent.

The results of this study imply that patients with small but significant fraction of these patients can enjoy long-term disease-free survival and possibly cure. The successful use of this regimen requires its introduction early after relapse or preferably before the morbidity frequently seen after most second-line treatments.

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second-line treatment requires that this regimen be used by experienced oncologists capable of managing the potentially lethal complications. The encouraging results obtained with this salvage regimen suggest that this protocol might have a potential role in the primary management of patients with lymphoma.

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