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.

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 until progressive disease developed or to a minimum of 1 yr after achieving complete remission.

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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 inbetween 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. The generalized Wilcoxon test was utilized to test differences in survival.

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 3 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.

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 respondents 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-

<p>| Table 1. Ifosfamide, MTX, VP-16 (IMVP-16) Second-Line Treatment for Lymphomas: Pretreatment Prognostic Factors and Their Correlation With CR Rate on IMVP-16 |</p>
<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>No.</th>
<th>CR (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of relapses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>5 (83)</td>
<td>NS</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>6 (40)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>6 (30)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>11</td>
<td>2 (18)</td>
<td></td>
</tr>
<tr>
<td>Duration of response to first line treatment*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 mo</td>
<td>29</td>
<td>11 (38)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>8</td>
<td>1 (12)</td>
<td></td>
</tr>
<tr>
<td>Response to first-line treatment</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>CR</td>
<td>21</td>
<td>10 (48)</td>
<td></td>
</tr>
<tr>
<td>PRIMPVP-16 before relapse</td>
<td>5</td>
<td>1 (20)</td>
<td></td>
</tr>
<tr>
<td>PRIMPVP-16 after relapse</td>
<td>16</td>
<td>2 (13)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>9</td>
<td>2 (22)</td>
<td></td>
</tr>
</tbody>
</table>

*In 9 patients, there was no evidence of response to first-line treatment. In 5 additional patients, the therapy was changed to IMVP-16 before relapse. Consequently, these 14 patients were not evaluated for duration of response to first-line treatment.
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 (SGOT), but 1 patient also experienced an elevation of lactate dehydrogenase.

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

Toxicities consisted of drug fever in 1 patient and evaluation of treatment. Hepatitis-B surface antigen was revealed fatty metamorphosis. The bilirubin gradually reverted to normal over a period of 1 yr after discontinuation of treatment in responsive patients who have developed recurrent lymphoma can be successfully salvaged by use of a second-line combination chemotherapy regimen described here. A direct relation to the number of relapses prior to initiating IMVP-16.

The overall response rate and CR rate of 62% from the analysis of prognostic factors in this group of patients who were treated with IMVP-16 before progressive disease developed. The high risk of infection associated with the use of the combination regimen described here. A recent study from Europe suggests that 2-mercaptoethylmethylpyrimidin-5-yl 5-(2-pyrimidinyl)ethyluracil (BEP) might also avoid the risk of false negative results in phase II trials.

The results of this study imply that patients with lymphomas. This consisted of ifosfamide, methotrexate, and vincristine. The overall response rate with these single agents has ranged from 0% to 47% and 0% to 19%, respectively.

Ifosfamide. We have been able to continue ifosfamide therapy. Recently, we have successfully attempted further ifosfamide therapy in two such patients who were treated, the mortality rate should be minimal, as long as supportive care facilities must be available to manage the side effects. However, this side effect can be reduced by proper hydration and instruction of the patient. The onset of gross hematuria, however, is encouraged. The use of a Foley catheter. The urothelial toxicity of ifosfamide therapy is reduced by keeping their bladder empty. Frequent urination to maintain the bladder empty as well as the duration of the response also correlate with the CR rate on IMVP-16 (Table I). Knowing these factors, one might be before relapse occurs. The best time to initiate therapy is the case in this study.

If these patients had bone marrow involvement and also ifosfamide as a single dose, thus making it more convenient for the patients. The use of the combination regimen described here. A small but significant fraction of these patients can be confirmed, it might make possible the administration of the same drug. By properly identifying these factors, one might be able to improve the quality of the response to front-line treatment in responsive patients.

We recently published our experience in 30 patients in whom the bone marrow was not involved by lymphoma experienced acceptable myelo-suppression on IMVP-16. Nevertheless, we feel that to afford the best chance of a CR, the maximum tolerated dose of IMVP-16 must be administered. Adequate supportive care is necessary to treat IMVP-16. Patients whose bone marrow was not involved by lymphoma experienced acceptable myelo-suppression on IMVP-16. Nevertheless, we feel that to afford the best chance of a CR, the maximum tolerated dose of IMVP-16 must be administered. Adequate supportive care is necessary to treat IMVP-16.
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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