Combination of Ifosfamide, Methotrexate, and Etoposide (IMVP) as a Salvage Therapy for Relapsed and Refractory Aggressive Non-Hodgkin Lymphoma: Retrospective Study

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Aim. There are contradictory reports on the outcomes of IMVP (ifosfamide, methotrexate, and etoposide) treatment in patients with aggressive non-Hodgkin’s lymphomas. Our aim was to evaluate retrospectively the results of this treatment in our institution.

Methods. Twenty-eight patients with refractory or relapsed aggressive non-Hodgkin’s lymphomas received IMVP between April 1997 and June 2001. Median follow-up of the survivors was 24 months. There were 15 women and 13 men, aged 15-68 years. Twelve patients were refractory to primary treatment. The number of previous treatment lines varied between one and five. The overall response rate to IMVP treatment was 39%, with 6 patients achieving complete and 5 partial response/remission. Eleven patients received a subsequent hematopoietic stem cell transplant after IMVP therapy.

Results. Median duration of the survival for all patients was 6 months, and the response duration for responders 6 months. Nine patients had grade 3 hematologic toxicity or higher, 5 developed significant infectious complications, and one developed the tumor lysis syndrome. There was one treatment-related death due to infection. The patients with a low or low-intermediate international prognostic index at the start of IMVP had a significantly better survival and progression-free survival rates than those with high or high-intermediate score. Seven patients with hematopoietic stem cell transplant were alive in December 2001.

Conclusion. IMVP is an active regimen with acceptable level of toxicity in patients with relapsed or refractory aggressive non-Hodgkin’s lymphoma. However, outcomes of this treatment are unsatisfactory and better treatment is still needed.

Key words: etoposide; ifosfamide; lymphoma, B-cell; lymphoma, diffuse; lymphoma follicular; lymphoma, high-grade; lymphoma, intermediate-grade; lymphoma, large-cell; lymphoma, non-Hodgkin; lymphoma, T-cell; methotrexate

Currently available first-line combination therapy regimens are an effective treatment for aggressive non-Hodgkin’s lymphoma, especially in patients with low-risk features (1-5). The “gold standard” is a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), which results in 60% of patients achieving complete remission (1). Even so, about 40% of the patients who achieve complete remission relapse. Such patients, as well as those not responding to first-line therapy, need second-line therapy. Several salvage chemotherapy regimens have been introduced, based either on a platinum compound (e.g., combination of dexamethasone, cytarabine, and cisplatin – DHAP) or ifosfamide (e.g., combination of ifosfamide, methotrexate, and etoposide – IMVP; or combination of ifosfamide, carboplatin, and etoposide – ICE) (5-7). None of them is uniformly effective and all are associated with significant toxicity and poor long-term survival. A randomized comparison of these regimens has never been done. The only therapy improving the long-term survival is high-dose chemotherapy followed by autologous bone marrow or blood stem cell rescue, but it is efficacious only in patients with a chemosensitive relapse (8,9).

We have been using IMVP routinely as a second-line treatment regimen in patients with aggressive non-Hodgkin’s lymphoma for more than 4 years. Since only two studies have been published on the efficacy of this regimen in relapsed and refractory non-Hodgkin’s lymphoma cases, with contradictory results (10,11), we decided to perform a retrospective analysis of our patients treated with IMVP at our institution.
Patients and Methods

Patients

Between April 1997 and June 2001, 28 consecutive patients with aggressive non-Hodgkin’s lymphoma were treated with IMVP combination therapy. The median age of patients was 47 years (range 15-68). Histologic type of lymphoma, stage, and international prognostic index (IPI) score at diagnosis were determined in all patients before IMVP was introduced (Table 1). All patients had been treated for their illness prior to IMVP, receiving between 1 and 5 lines of therapy (median 2), with at least one containing anthracyclines. There were 16 patients who relapsed after having achieved complete (12 patients) or partial remission (4 patients), and 12 who were refractory to previous therapy. Three patients had been previously autografted. Twelve patients were in the first and 4 in second relapse. Median duration of illness from diagnosis to IMVP therapy was 12.5 months (range 3-60). Before IMVP therapy was started, all patients were routinely restaged: 18 patients had stage IV disease, 4 had stage III, 5 had stage II, and one had stage I according to Ann Arbor classification (13). Twenty-two patients had B symptoms (unexplained fever, unexplained weight loss, drenching night sweats, or severe pruritus). Eleven patients had a low or low-intermediate IPI score (0-2), and 17 had a high or high-intermediate score (3-5) (Table 1). Median follow-up was 24 months.

Response to treatment were analyzed according to the standard criteria (15). Complete remission and complete remission-unconfirmed were considered complete responses.

Further Treatment

After IMVP therapy, patients who were younger than 60, had never received an autograft, and had performance status 0-2 were considered candidates for autografting. Those in complete remission received cyclophosphamide and G-CSF, whereas others received mini-BEAM (combination of carmustine, etoposide, cytarabine, and melphalan) for stem cell mobilization (16). Autografting was performed after conditioning all patients with the BEAM. Eight out of 10 eligible patients received an autograft, whereas 2 had an insufficient number of stem cells for safe grafting.

Toxicity

Toxicity was graded according to the National Cancer Institute “Common Toxicity Criteria” (14).

Response Criteria

Responses to treatment were analyzed according to the standard criteria (15). Complete remission and complete remission-unconfirmed were considered complete responses.

Results

Toxicity

Hematologic toxicity of IMVP therapy was frequent (Table 2). In nine out of 28 patients significant hematologic toxicity resulted in treatment postponement. There were a total of 9 episodes of neutropenic fever in 78 cycles, one of them with a lethal outcome. The cause of infection was established in only 3 cases. Hemorrhagic cystitis did not occur in any of the patients. Except for nausea and vomiting, there was only a single episode of severe non-hematologic, non-infectious toxicity. One patient developed a tumor lysis syndrome, with severe hyperkalemia and increased concentrations of uric acid and creatinine (toxicity grade III).

Response and Survival

The overall response rate to IMVP treatment was 39%. Six out of 28 patients achieved a complete remission, and 5 achieved a partial remission. Median overall survival duration for the whole group was 6 months (range 1-42). Median progression-free survival for responders was 6 months (range 1-33) (Fig. 1). Eight patients were subsequently autografted and three were allografted. In December 2001, seven patients were still alive, six autografted, and one allografted. Three were in a complete remission, one in a partial remission, and three did not respond to IMVP (one of the non-responders was allografted).

We analyzed the prognostic significance of different histologic subtypes of lymphoma, IPI score at

Table 1. Histologic type, stage, and international prognostic index (IPI) score of patients with relapsed or refractory aggressive non-Hodgkin’s lymphoma treated with IMVP

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>low</th>
<th>high</th>
</tr>
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<tr>
<td>ALCL</td>
<td></td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Follicular</td>
<td></td>
<td>14</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>B-LCL</td>
<td></td>
<td>28</td>
<td>1</td>
<td>5</td>
<td>4</td>
<td>18</td>
<td>11</td>
</tr>
</tbody>
</table>

Abbreviations: IMVP – ifosfamide, methotrexate, and etoposide; ALCL – anaplastic large cell lymphoma; B-LCL – B-large cell lymphoma.

Table 2. Hematologic toxicity of IMVP treatment (ifosfamide, methotrexate, and etoposide) in patients with relapsed or refractory aggressive non-Hodgkin’s lymphoma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>3</td>
<td>9</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Platelets</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
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</table>
the start of IMVP therapy, and disease status (refractory vs relapsed) for overall survival.

**Histologic Subtypes**
Response rate for different histological groups (follicular, B-large cell, and anaplastic large cell lymphoma) was 3 out of 8, 7 out of 14, and 1 out of 6, respectively. Median survival was 3.5, 6.5, and 9 months, respectively. These differences were not significant (Fig. 2).

**IPI Score**
The response rate in 11 patients with a low IPI score (0-2) was 36%. Three of them achieved a complete response lasting for a median of 25 months (range 8-35), and one achieved a partial remission. The response rate in 17 patients with a high IPI score (3-5) was 41%. Three of them achieved complete responses of the median duration of 6 months (range 3-24), and 4 had partial responses. Median survival of patients with low IPI scores (0-2) was 10 months (range 2-42), and of those with high scores (3-5) was 4 months (range 1-31). The difference in survival was significant (p < 0.05, Fig. 3).

**Disease Status**
The response rate in 16 relapsing patients was 44%. Four achieved a complete response and 3 achieved a partial response. The median survival was 8 months (range 2-42).

Out of 12 patients with refractory disease before IMVP, 2 achieved a partial response and 2 had a complete response. The median survival was 3.5 months (range 1-24). These differences were not significant (Fig. 4).

**Figure 1.** Overall survival and progression-free survival of patients with non-Hodgkin’s lymphoma treated with IMVP (ifosfamide, methotrexate, and etoposide). Overall survival – full line; progression-free survival – dashed line.

**Figure 2.** The influence of histologic types on overall survival of patients with non-Hodgkin’s lymphoma treated with IMVP (ifosfamide, methotrexate, and etoposide). Anaplastic large-cell lymphoma – full line; large B-cell lymphoma – dotted line; follicular lymphoma – dashed line.

**Figure 3.** The influence of international prognostic index scores on overall survival of patients with non-Hodgkin’s lymphoma treated with IMVP (ifosfamide, methotrexate, and etoposide). IPI 0-2 – full line; IPI 3-5 – dashed line. The difference was significant (p = 0.0422, log-rank test).

**Figure 4.** The influence of disease status on overall survival of patients with non-Hodgkin’s lymphoma treated with IMVP (ifosfamide, methotrexate, and etoposide). Patients in relapse – full line; refractory patients – dashed line. The difference was not significant (p = 0.321, log-rank test).
Discussion

The results of ifosfamide-based second-line regimens for the treatment of aggressive non-Hodgkin’s lymphoma vary substantially, with response rates ranging from 20% to 70%. Unfortunately, there is no proof that these differences result from differences in treatment efficacy rather than from differences in patient selection (7). In our institution, IMVP was a moderately effective second-line therapy with tolerable toxicity. Less than half of patients with relapsed and refractory aggressive non-Hodgkin’s lymphoma responded to treatment, and the median overall survival was 6 months. The incidence of toxic death was low. These outcomes are comparable with those of the British report (11), but different from the “MD Anderson Cancer Center” study (10), probably due to the difference in patient selection. Our results are comparable with most second-line regimens (19-23).

Different histological types of aggressive non-Hodgkin’s lymphoma have different prognosis, but histology has lower prognostic impact than IPI does (24). Due to the small number of patients in each category, we were unable to show a significant difference in outcomes between patients with follicular, B-large cell, and anaplastic large cell non-Hodgkin’s lymphoma. The same is true for the disease status. The patients with refractory disease are generally considered to have a worse prognosis than those who are in remission. Our data followed such a trend, which did not reach statistical significance, probably due to the limited number of patients.

In our study, IPI score (12) seemed to be the most powerful prognostic indicator for this group of patients, which is in accordance with other studies (25, 26). It is quite surprising that such a simple index should be of supreme prognostic importance in almost all histological groups of non-Hodgkin’s lymphoma, irrespective of the disease phase and treatment given.

The only long-term survivors are patients who were transplanted after chemotherapy. This emphasizes the need to make every attempt to collect stem cells and transplant them to a patient with aggressive non-Hodgkin’s lymphoma who failed first-line treatment.

Finally, the outcomes of our patients with non-Hodgkin’s lymphoma were not satisfactory. Today, the attempts to improve the outcomes of such patients are focusing on more aggressive chemotherapy regimens with high-dose ifosfamide, e.g. ICE (27), and their combination with monoclonal antibodies, like rituximab (28). According to some reports, such regimens have response rates of almost 100% but are also significantly more toxic. Regarding previous unfavorable experience from the cases where aggressive treatment was adopted as a standard based only on phase II data (1), it is very encouraging that a large intergroup phase III trial is being planned to compare RICE (ICE + rituximab) with a “standard dose” regimen combined with rituximab (R-DHAP). The results of this trial will have an important impact on the treatment of patients with relapsing or refractory aggressive non-Hodgkin’s lymphoma.

Acknowledgment

This research was supported in part by grants No. 9188 and 108133 from the Croatian Ministry of Science.

References


Received: May 23, 2002
Accepted: September 19, 2002

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