Effective Salvage Therapy for Lymphoma With Cisplatin in Combination With High-Dose Ara-C and Dexamethasone (DHAP)

By William S. Velasquez, Fernando Cabanillas, Patricio Salvador, Peter McLaughlin, Michael Fridrik, Sue Tucker, Sundar Jagannath, Fredrick B. Hagemeister, John R. Redman, Forrest Swan, and Barthel Barlogie

Ninety patients with progressive recurrent lymphoma were treated with a combination of cisplatin 100 mg/m² intravenously (IV) by continuous infusion over 24 hours, followed by cytosine arabinoside in two pulses each at a dose of 2 g/m² given 12 hours apart. Dexamethasone, 40 mg orally or IV, was given on days 1 through 4. Vigorous hydration was reinforced by routine use of mannitol. Treatments were repeated at 3- to 4-week intervals for six to ten courses. Most patients had not achieved complete remission (CR) with prior therapies, which included Adriamycin (all patients) and methotrexate and VP-16 (58 patients). Median patient age was 55 years. Intermediate-grade lymphoma was the most frequent pathologic diagnosis. Seven patients died within two weeks of therapy; of the remaining 83 patients, 28 (34%) or 31% if all patients are considered, achieved CR, and 22 (26.5%) achieved partial remission (PR). Response was evident after the first two cycles of chemotherapy and appeared to be independent of the histopathologic type of lymphoma. To date, only eight of the complete responders have relapsed at a median follow-up of 11 months. The overall 2-year survival is 25%. Further analysis showed that patients with low tumor burden and normal lactic acid dehydrogenase (LDH) had a high CR response rate (67%) and a survival rate of 61% at 2 years. In contrast, patients with both high tumor burden and elevated serum LDH levels had a negligible CR rate, and only 5% are surviving at 1 year. Patients with either high tumor burden with normal LDH or low tumor burden with elevated LDH had an intermediate survival. Myelosuppression-related infection was the most frequent serious complication of this regimen (31%) and the cause of death of ten patients. Acute lysis syndrome was also observed in five patients with high tumor burden and was the cause of death in three of these patients. DHAP has proven to be an effective non-crossresistant regimen for patients with relapsing or refractory lymphoma, particularly for patients who have favorable prognostic characteristics.

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Tumor burden was determined in accordance with our prior prognostic model.19

Durations of survival and remission were calculated from the beginning of treatment. Patients who died early in the course of therapy were considered as treatment failures for survival calculations, which were done according to the method of Kaplan and Meier.18 Survival times for distinct patient groups were compared using the generalized Wilcoxon test.19 Fisher's exact test was used to compare frequencies in $2 \times 2$ tables.

**RESULTS**

Among the 90 patients treated, there were seven early deaths, including three patients who died with lysis syndrome, an acute event characterized by rapid disappearance of tumor masses associated with renal and pulmonary decompensation, hyperkalemia, hyperphosphatemia, and disseminated intravascular coagulation. Two other patients died of sepsis. One patient died of pulmonary thromboembolism and the other died of acute subdural hemorrhage. All but two of these patients had bone marrow involvement.

Among the remaining 83 patients, 28 achieved CR and 22 achieved a PR. Thus, a 55% response rate and a 31% CR rate were observed if all patients are considered. After a median follow-up of 11 months, 8 of the 28 patients who achieved CR had relapsed at 4 to 24 months after initiation of their treatment.

Response to therapy was usually evident after the first course of treatment, and maximum antitumor effect was often observed after three courses of therapy. The CR rate seemingly was independent of histology, although the number of patients with "transformed" lymphoma and those with low and high grade lymphoma were relatively small (Table 4). Among the 54 patients with diffuse large cell lymphomas and immunoblastic lymphoma who were evaluable, 17 patients (31.5%) achieved CR. Two patients in the miscellaneous group had diagnoses of mycosis fungoides; one achieved CR.

The presence of bone marrow or CNS involvement did not have an adverse effect on the CR rate, and two patients with meningeal involvement achieved CR. When CR rates were analyzed in relation to the patient's pretreatment characteristics, elevated LDH values and tumor burden became the most important determinants for response (Table 5). Thus, the CR rate was higher for the patients with normal serum LDH (58%) than for patients with LDH $>225$ mU/mL. Furthermore, the elevation in LDH was inversely related to the probability of remission. For the 18 patients with values

**Table 2. Treatment Scheme**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>IV</td>
<td>24 h</td>
<td>1</td>
</tr>
<tr>
<td>Ara-C</td>
<td>2 g/m² x 2</td>
<td>IV</td>
<td>3 h, q 12 h</td>
<td>2</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg</td>
<td>IV</td>
<td>15 min</td>
<td>1-4</td>
</tr>
</tbody>
</table>

Abbreviation: CI, Continuous infusion.
TABLE 4. Treatment Results

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Evaluable</th>
<th>Complete Remission</th>
<th>Partial Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade*</td>
<td>13</td>
<td>4 (31)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Intermediate grade:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCL de novo</td>
<td>43</td>
<td>12 (28)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>DLCL Transformed</td>
<td>15</td>
<td>5 (33)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>FLCL</td>
<td>5</td>
<td>2 (40)</td>
<td>2 (40)</td>
</tr>
<tr>
<td>DMCL</td>
<td>5</td>
<td>3 (60)</td>
<td>0</td>
</tr>
<tr>
<td>High grade†</td>
<td>5</td>
<td>1 (25)</td>
<td>1 (20)</td>
</tr>
<tr>
<td>Miscellaneous‡</td>
<td>3</td>
<td>1 (33%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>28 (31%)</td>
<td>22 (24%)</td>
</tr>
</tbody>
</table>

DLCL, diffuse large cell lymphoma; FLCL, follicular large cell lymphoma; DMCL = diffuse mixed cell lymphoma.

*Low-grade lymphoma includes follicular small cleaved cell lymphoma and follicular mixed cell lymphoma.
†High-grade lymphoma includes diffuse small noncleaved cell and lymphoblastic lymphoma.
‡Miscellaneous includes two patients with mycosis fungoides and one patient with diffuse lymphoma, cell type undetermined.

Between 225 mU/mL and 299 mU/mL, the CR rate was 39%, whereas the CR rate for patients with an LDH >300 mU/mL was 18%. Even more striking was the fact that all CRs, with the exception of one, were observed in the patients with low tumor burden (46% CR rate) (Table 5).

The presence of constitutional B symptoms correlated with high tumor burden. Therefore, lower remission rates were observed when compared with rates for patients who had no constitutional symptoms. Patients who had never achieved CR with frontline induction therapy had a CR rate of 27%, but patients with lymphoma relapsing after achieving CR with frontline therapy had a CR rate of 37%. These differences, however, did not reach statistical significance. Of interest is the fact that of the six patients who failed previous treatment with cisplatin two achieved CR.

The projected 24-month overall survival rate for the 90 patients is 25% (Fig 1). When survival of patients is analyzed by risk group and according to tumor burden and LDH level, the most favorable group was patients with low tumor burden and normal LDH values who had a calculated survival of 61%. In contrast, patients having high tumor burden and elevated serum LDH had a 5% survival at 1 year. The 48 patients who had either high tumor burden with normal LDH or low tumor burden with elevated LDH had a 27% survival rate (Fig 2). These survivals related closely to the CR rate for each group: 66% for the favorable group, 37.5% for the intermediate group, and 0% for the high-risk group.

To date, eight patients have relapsed after CR. Only three patients developed CNS involvement during administration of DHAP as one of the multiple areas of progression of their disease. With a median follow-up of 11 months, no definite

TABLE 5. Prognostic Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients</th>
<th>CR (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional B Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>51</td>
<td>20 (39)</td>
<td>.09</td>
</tr>
<tr>
<td>Present</td>
<td>39</td>
<td>8 (20)</td>
<td></td>
</tr>
<tr>
<td>Prior CR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
<td>14 (37)</td>
<td>.4</td>
</tr>
<tr>
<td>No</td>
<td>52</td>
<td>14 (27)</td>
<td></td>
</tr>
<tr>
<td>Serum LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>19</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td>225-300 mU/mL</td>
<td>18</td>
<td>7 (39)</td>
<td>.006</td>
</tr>
<tr>
<td>&gt;301 mU/mL</td>
<td>53</td>
<td>10 (18)</td>
<td></td>
</tr>
<tr>
<td>Tumor burden</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>58</td>
<td>27 (47)</td>
<td>.01-4</td>
</tr>
<tr>
<td>High</td>
<td>32</td>
<td>1 (3)</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete remission; LDH, lactic acid dehydrogenase.
plateau has been observed (Fig 3). Three patients have relapsed after 1 year of unmaintained remission, and second remissions were observed in all three. Thus, the projected 2-year survival rate for all patients who achieved a CR is 50%.

Toxicity. DHAP chemotherapy induced profound myelosuppression with marked neutropenia and thrombocytopenia (Table 6). Patients with marrow involvement by lymphoma or patients with extensive prior radiotherapy experienced particularly severe and more long-lasting myelosuppression. As a result of severe neutropenia, 43 patients, 28 of whom had documented bacterial or fungal infection, had to be admitted to the hospital for IV antibiotic therapy. Among those with documented infection, ten patients died of septic complications.

An unexpected complication was tumor lysis syndrome, which occurred in five patients and was fatal in three, owing to multiorgan failure. All five patients initially had high tumor burden and elevated LDH.

Renal insufficiency with baseline serum creatinine at twice the baseline level occurred in 18 patients and was more prominent in patients aged >60 years and in patients with cisplatin cumulative doses >300 mg/m². Renal insufficiency was reversible in most patients but was permanent in six patients. In four patients, renal failure was associated with acute respiratory distress syndrome, without any evidence of lysis syndrome, which eventually caused the deaths of two patients.

Acute neurologic toxicity due to Ara-C is rare but was expressed in one patient who had signs of severe cerebellar dysfunction and who had had prior intrathecal Ara-C for previous meningeal lymphoma. Although mild weakness was a frequent symptom, severe peripheral neuropathy from cisplatin occurred in four patients and necessitated discontinuation of their treatment. Tinnitus was marked in four patients and severe hearing loss was noted in another three patients.

### DISCUSSION

The DHAP combination showed remarkable efficacy in relapsing and primary refractory lymphoma that greatly exceeds the results obtained with any of the drugs given as single agents. This possible synergism has also been observed in Hodgkin’s disease and chronic lymphocytic leukemia.

In a previous report, high-dose Ara-C showed a modest (22%) response, all PRs only. Adelstein et al reported the results of high-dose Ara-C alone or in combination with an anthracycline agent or amascrine. Five patients among the 14 achieved CRs of short duration (median 3 months). High-dose Ara-C, administered for four to eight doses, proved very toxic in this regimen and required >4 weeks for the patient to recover from severe myelosuppression. Cisplatin given as a single drug has also shown marginal antitumor activity in lymphoma. Other investigators combined cisplatin with bleomycin and vincristine in the treatment of relapsing lymphoma, and the CR rate ranged from 0% to 21%. All three CR patients among 17 patients in the last study relapsed within 10 months. Cisplatin has also been combined with VP-16 with similar results. Thus, the experimentally demonstrated synergistic interaction between cisplatin and Ara-C appears to occur clinically in several lymphoid neoplasms. A possible beneficial effect from high-dose Dexamethasone in this combination, however, cannot be ruled out. The explanation of the synergistic effect remains unknown, although the simultaneous presence of both agents is postulated to induce the formation of multimeric platinum pyrimidine complexes in a structure similar to the “dimers of dimers” described by Lock et al for cisplatin-DNA adducts.

Our DHAP results compare well with the MIME regimen as one of the most active salvage programs for refractory lymphoma yet published, particularly when we consider that 64% of our patients had already failed a methotrexate and VP-16 combination. Whereas MIME produced a CR rate of...
only 10% in low-grade lymphoma, the activity of DHAP appears to extend across the entire histologic spectrum of subtypes, although this estimation must be made with caution owing to the much smaller number of patients with low and high grade lymphomas. Furthermore, in contrast to MIME, which has a CR rate of <15% in primary refractory lymphoma, 27% of 52 patients who had never achieved a CR responded to DHAP, a finding of major clinical importance for the design of chemotherapeutic trials for high-risk patients with predicted lower-than-optimum CR and survival rates. Similarly, patients with indolent lymphoma had the same CR rates as those with aggressive histologies, even when a transformation to a more aggressive type had occurred. When the patient characteristics were studied in relationship to the prognostic model derived from front-line induction treatment, namely LDH and tumor burden, they played a major role in the degree of tumor response and survival. Patients with low tumor burden and normal LDH value had an excellent CR rate, but patients with a high LDH value and/or high tumor burden had a much lower CR rate (Table 4). Further analysis showed that both factors were independent, as demonstrated in the survival curves of the three prognostic groups. Patients with low tumor burden and normal LDH value had the best survival. Patients having both adverse factors, however, namely elevated serum LDH level and high tumor burden, had only a 5% survival rate at 12 months. Adding other drugs to DHAP (VP-16, doxorubicin, ifosfamide, etc.) might improve the complete response rate for patients with such poor prognoses for whom DHAP may not be recommended.

The fact that high-dose Ara-C can reach significant levels in the CNS has been another attractive feature of this combination. As expected, DHAP was also active in patients with CNS disease, of whom two of six achieved CR. In addition, CNS disease progression in patients responding to DHAP occurred in only three patients. Currently, DHAP is now used for all primary CNS lymphomas in our institution, with excellent results (W.S. Velasquez, unpublished observations).

With the availability of supportive care, side effects of DHAP treatment were manageable. A surprising life-threatening complication from DHAP, however, was the development of a tumor lysis syndrome in five patients, all of whom had higher tumor burden with bone marrow involvement. These patients responded dramatically and developed hyperkalemia and hyperphosphatemia, disseminated intravascular coagulopathy, and acute renal and pulmonary failure. Although all patients promptly underwent hemodialysis, only two patients recovered from this syndrome. Tumor lysis has been well recognized in patients undergoing initial therapy for high-grade lymphoma, but it has not been reported in association with salvage therapy for intermediate-grade lymphoma.

Another serious complication of DHAP therapy was infection, mainly associated with neutropenia. Although most of the patients responded to antibiotic therapy, infection was the most frequent complication and the cause of death in ten patients. This fact may imply the need for prophylactic antibiotic therapy in a future study. The myelosuppressive toxicity of 6 to 12 doses of high-dose Ara-C is well recognized, but it was unexpected with only two doses and might indicate synergistic toxicity with cisplatin. The observed renal toxicity was similar to previous reports with cisplatin alone.

The true test of any therapeutic regimen is increased survival. The long-term benefit cannot yet be properly assessed after a median follow-up of only 11 months. Our preliminary results are nevertheless superior to any other salvage regimen evaluated in any other series of patients with relapsing and primary refractory lymphoma and comparable to the MIME regimen. The projected 2-year survival rate of 25% for the entire group and 50% for patients achieving CR is indeed remarkable for these patients.

Recently, the use of high-dose chemotherapy followed by autologous bone marrow transplantation (ABMT) was investigated as a potential salvage strategy for refractory lymphoma; however, it has many restrictions, including younger age, absence of bone marrow involvement, and good performance status. With these selection criteria, a pool data from many institutions using high-dose chemotherapy and ABMT was reported by Phillip et al. In this study, the overall disease-free survival rate for the 100 patients was 19% at 3 years with median follow-up of 33 months for the responding patients. Further analysis, however, identified a significant subgroup of patients who had responded to “conventional salvage protocol.” Among these 44 patients, the disease-free survival was 38% at 3 years. In contrast, for the 56 patients who had not responded either to conventional salvage or even primary inductive treatments, the disease-free survival was <15%. Although direct comparison with our patient population is not possible, it is reasonable to suspect that the group with greatest treatment benefit comprised patients with low tumor burden and/or low serum LDH determinations who are likely to respond to a “salvage regimen” and have a better prognosis. ABMT, however, could serve as consolidation therapy leading to a significant proportion of long-term survivors. Currently, DHAP is being considered as the initial treatment for relapsing intermediate-grade and high-grade lymphomas in a multinational study using ABMT as consolidation in a randomized trial for patients responding to salvage therapy.

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Effective salvage therapy for lymphoma with cisplatin in combination with high-dose Ara-C and dexamethasone (DHAP)

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