Combination chemotherapy with irinotecan and adriamycin for refractory and relapsed non-Hodgkin's lymphoma

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Summary

Twenty-five patients with relapsed or refractory non-Hodgkin's lymphoma were treated by combination chemotherapy with irinotecan hydrochloride (CPT-11) and adriamycin (ADM): CPT-11, 25 mg/m² on days 1 and 2; ADM, 40 mg/m² on day 3. Nine (36%) of twenty-five patients achieved CR. Fairly good responses were seen in relapsed B-cell lymphomas (4 of 8 in diffuse large B-cell lymphoma and 2 of 2 in follicular lymphoma grade 1), and substantial responses in T-cell lymphomas (1 of 4 in peripheral T-cell lymphoma and 2 of 7 in adult T-cell leukemia/lymphoma). Leukopenia was frequent but tolerable, and diarrhea minimal. Combination chemotherapy with a reduced dose CPT-11 and ADM was useful in the treatment of relapsed non-Hodgkin's lymphoma.

Key words: adriamycin, irinotecan hydrochloride (CPT-11), non-Hodgkin's lymphoma, salvage chemotherapy

Introduction

Irinotecan hydrochloride (CPT-11), a unique DNA topoisomerase-I inhibitor, is now widely used in the treatment of colorectal, gastric, breast, lung, ovarian and skin cancer [1]. Early studies have shown that CPT-11 was effective against relapsed or refractory non-Hodgkin's lymphoma [2, 3], but its use in the recommended dose schedule has been limited mainly because of severe leukopenia and diarrhea. In a pilot study of combination chemotherapy with reduced dose CPT-11 and adriamycin (ADM) [4], we found that the toxicity was tolerable and favorable responses were seen in patients with relapsed diffuse large B-cell lymphoma (DLBCL). We extended the study to patients with relapsed or refractory lymphomas including histology of DLBCL, indolent B-cell lymphoma, peripheral T-cell lymphoma (PTCL), and adult T-cell leukemia/lymphoma (ATLL).

Results

All patients were evaluable for effects and toxicity. Nine (36%) of the twenty-five patients attained CR and two (8%) achieved PR. Histologies of the nine CR patients included four DLBCL, one PTCL, and two ATLL. Eight of the nine CR patients were those with relapsed lymphoma after achieving CR with initial ADM-containing regimens, but one ATLL patient attained CR, in whom lymphoma responded to the initial CHOP-ABVP therapy with some remaining disease. The median CR duration in 9 CR patients was 242 days, ranging from 64–630 days.

The major toxicity manifestation was myelosuppression (Table 1). Leukopenia over grade 3 was seen in 10 patients; thrombocytopenia over grade 3 in 9 patients; anemia over grade 3 in 15 patients. G-CSF administration was required in 14 patients, platelet transfusion in 2, and red blood cell transfusion in 9. One patient developed bronchopneumonia and recovered after G-CSF and antibiotics administration. Nausea/vomiting was mild, and diarrhea was minimal. There was no cardiac, hepatic or renal toxicity.
Thrombocytopenia 11 2 2 mg/m² for 3 consecutive days weekly, produced 4 (17%) CR and 4 (17%) PR among 24 patients. In the subsequent phase II study [3], daily infusion of CPT-11 of 40 mg/m² for 3 consecutive days weekly, dose schedule of which was later determined to be standard for malignant lymphoma, produced 9 (13%) CR and 17 (25%) PR among 69 patients with relapsed or refractory non-Hodgkin’s lymphoma. Leukopenia and diarrhea were major adverse effects: 91% and 71%, respectively, in an early phase II study; 80% (over grade 2) and 54% (over grade 3), respectively, in a subsequent phase II study. In the combined phase I–II study of CPT-11 and carboplatin [7], myelosupression was so severe that further dose escalation was halted at the dose of CPT-11 20 mg/m² (days 1–3 and 8–10) and carboplatin 300 mg/m²: grade 4 neutropenia in six patients; grade 4 thrombocytopenia in one; grade 3 diarrhea in two among eight patients. In our pilot study of combination chemotherapy with CPT-11 and ADM [4], CPT-11 was reduced to 25 mg/m² on days 1 and 2, 40 mg/m² of ADM substituted CPT-11 on day 3, and CPT-11 was infused over 120 minutes with appropriate use of loperamide, and the therapy interval was set every three weeks. Toxicity was acceptable: leukopenia (over grade 3) was seen 67%, thrombocytopenia (over grade 3) in 25%, and diarrhea in 8%. Fairly good responses were seen in relapsed diffuse large B-cell lymphoma after initial ADM-containing regimens.

In the present study, we demonstrated fairly good responses in B-cell lymphoma (4 of 8 in DLBCL and 2 of 2 in FL) and substantial responses in T-cell lymphoma (1 of 4 in PTCL and 2 of 7 ATLL). The majority of CR patients were those with relapsed lymphoma after initial ADM-containing regimens. Myelosupression particularly leukopenia was seen frequently even in the combination of reduced dose CPT-11 and ADM, but was tolerable.

The combination chemotherapy using topoisomerase-I inhibitors and -II inhibitors is an interesting idea. Preclinical data suggested additive cytotoxic effects [8], or greater cytotoxic effects with administration of CPT-11 prior to topoisomerase-II inhibitor [9]. We expected to overcome drug resistance in refractory lymphoma to the initial ADM-containing regimens, but the present date failed to demonstrate it. No patients with refractory lymphoma to the initial ADM-containing regimens obtained CR. Results of the present study suggest that use of CPT-11 prior to topoisomerase-II inhibitors produces synergistic cytotoxic effects. The combination of low-dose CPT-11 on days 1 and 2, and ADM on day 3 produced fairly good tumor responses and substantial myelosupression. Further studies will investigate effective combinations of CPT-11 with topoisomerase-II inhibitors other than ADM.

### Discussion

Despite good responses shown in phase II studies [2, 3], CPT-11 has not been widely used to malignant lymphoma mainly because of severe leukopenia and diarrhea. In the early phase II study [2], daily infusion of CPT-11 of 40 mg/m² for 5 consecutive days every 3–4 weeks, or 40 mg/m² for 3 consecutive days weekly, produced 4 (17%) CR and 4 (17%) PR among 24 patients. In the subsequent phase II study [3], daily infusion of CPT-11 of 40 mg/m² for 3 consecutive days weekly, dose schedule of which was later determined to be standard for malignant lymphoma, produced 9 (13%) CR and 17 (25%) PR among 69 patients with relapsed or refractory non-Hodgkin’s lymphoma. Leukopenia and diarrhea were major adverse effects: 91% and 71%, respectively, in an early phase II study; 80% (over grade 2) and 54% (over grade 3), respectively, in a subsequent phase II study. In the combined phase I–II study of CPT-11 and carboplatin [7], myelosupression was so severe that further dose escalation was halted at the dose of CPT-11 20 mg/m² (days 1–3 and 8–10) and carboplatin 300 mg/m²: grade 4 neutropenia in six patients; grade 4 thrombocytopenia in one; grade 3 diarrhea in two among eight patients. In our pilot study of combination chemotherapy with CPT-11 and ADM [4], CPT-11 was reduced to 25 mg/m² on days 1 and 2, 40 mg/m² of ADM substituted CPT-11 on day 3, and CPT-11 was infused over 120 minutes with appropriate use of loperamide, and the therapy interval was set every three weeks. Toxicity was acceptable: leukopenia (over grade 3) was seen 67%, thrombocytopenia (over grade 3) in 25%, and diarrhea in 8%. Fairly good responses were seen in relapsed diffuse large B-cell lymphoma after initial ADM-containing regimens.

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### Table 1. Toxicity.

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Over grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>10</td>
<td>9</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>10 (40)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>15 (60)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>18</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
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### References


Received 12 November 1999. accepted 23 November 1999.

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