Efficacy of high-dose methotrexate, ifosfamide, etoposide and dexamethasone salvage therapy for recurrent or refractory childhood malignant lymphoma

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Background: Children with recurrent or refractory malignant lymphoma generally have a poor prognosis. There is a need for new active drug combinations for this high-risk group of patients.

Patients and methods: This study evaluated the activity and toxicity of the methotrexate, ifosfamide, etoposide and dexamethasone (MIED) regimen for childhood refractory/recurrent non-Hodgkin’s lymphoma (NHL) or Hodgkin’s lymphoma (HL). From 1991 through 2006, 62 children with refractory/recurrent NHL (n = 24) or HL (n = 38) received one to six cycles of MIED. Based on MIED response, intensification with hematopoietic stem cell transplantation (HSCT) was considered.

Results: There were 10 complete (CR) and 5 partial responses (PR) among the 24 children with NHL [combined response rate, 63%; 95% confidence interval (CI) 38% to 73%]. There were 13 CR and 18 PR among the 37 assessable children with HL (combined response rate, 84%; 95% CI, 68% to 94%). Although 59% courses were associated with grade IV neutropenia, treatment was well tolerated and without toxic deaths.

Conclusions: MIED is an effective regimen for refractory/recurrent childhood malignant lymphoma, permitting a bridge to intensification therapy with HSCT.

Key words: childhood, lymphoma, recurrent, refractory

introduction

Significant advances have been made in the treatment of malignant lymphomas in children. However, approximately 20%–30% of patients will have refractory or recurrent disease [1–7], which confers a poor prognosis. These patients are therefore generally considered eligible for a novel or relatively aggressive salvage regimen, including hematopoietic stem cell transplantation (HSCT), for those with chemosensitive disease. Hitherto, only a limited number of salvage regimens have been studied, including ICE (ifosfamide, carboplatin and etoposide), DECAL (dexamethasone, etoposide, cisplatin, cytarabine, and L-asparaginase) and DHAP (dexamethasone, high-dose cytarabine, and cisplatin) [8–12]. Here, we describe a new effective regimen incorporating high-dose methotrexate, ifosfamide, etoposide, and dexamethasone (MIED) for children with refractory or recurrent non-Hodgkin’s lymphoma (NHL) and Hodgkin’s lymphoma (HL). The post-MIED salvage therapy including the HSCT (i.e. preparative regimen and type of HSCT) varied among patients studied; therefore, detailed analyses of post-MIED therapy and outcomes are not a focus of this report.

patients and methods

patients

Sixty-two children with refractory or recurrent malignant lymphoma (NHL, 24; HL, 38) were treated with the MIED regimen from 1991 through 2006. The St Jude Institutional Review Board approved this retrospective review of outcomes after MIED treatment. Written informed consent for therapy was obtained from all patients or their legal guardians before treatment began.

 treatment

The MIED treatment schema is shown in Table 1. Hydration given with methotrexate included infusion of 0.45% NaCl with 40 mEq/l NaHCO3 and 20 mEq/l KCl at 250 ml/m2/h for 2 h, then at 125 ml/m2/h for 24 h. Urine pH was checked with each void, and methotrexate was started only after it exceeded 6.5. Methotrexate levels were drawn before and at 24, 44 and 72 h after the start of the methotrexate infusion, and leucovorin and hydration were adjusted accordingly. On days 2 through 4, etoposide followed by
therapy, which in some cases included an intensification phase with HSCT.

age-adjusted dosages on day 1.

received intrathecal methotrexate, hydrocortisone, and cytarabine at

Mesna 500 mg/m\textsuperscript{2}/dose i.v. Immediately after and at 3

Ifosfamide 2000 mg/m\textsuperscript{2}/day i.v. over 2 h Days 2–4

Dexamethasone 40 mg/m\textsuperscript{2}/day i.v. Divided into three doses and

G-CSF 5 mcg/kg/day i.v./SQ Starting 24 h after last

<1.010 and urine red blood cells

The time to first relapse (\(P = 0.022\)). Among HL patients, the rate of response (CR + PR) was significantly higher among those with a >12-month time period to first relapse (\(P = 0.038\)). Among patients with NHL, the rate of response (CR + PR) was significantly higher among those with a >12-month time period to first relapse (\(P = 0.022\)).

A total of 152 courses of MIED were delivered to 61 patients. The most frequently encountered toxicity (Table 2) was reversible grade 3/4 hematologic toxicity. Grade 3/4 neutropenia was associated with 65% of courses, grade 3/4 thrombocytopenia with 68% of courses, and grade 3 fever with neutropenia with 46% of courses. The latter was successfully managed with broad-spectrum antibiotics; there were no septic

Based on MIED response, patients were considered for further salvage therapy, which in some cases included an intensification phase with HSCT.

response evaluation

Among NHL patients, those with complete disappearance of all disease were considered to have a complete response (CR); those with at least a 50% reduction in product of greatest perpendicular diameter were considered to have a partial response (PR); others were considered to have no response. Among HL patients, those with negative gallium or positron emission tomography (PET) imaging and at least a 75% reduction in the product of the perpendicular diameter on computed tomography scan were considered to have a CR; those with 50%–75% reduction in the product of the perpendicular diameter were considered to have a PR, regardless of the activity identified on gallium or PET scanning.

statistical analysis

Fisher’s exact test was used to test the association between the rate of CR and the type of disease (HL or NHL), and the association between the CR rate and the time to first relapse (> versus \(\leq 12\) months).

results

Most patients received two cycles of MIED (range, 1–4 cycles). One patient with HL developed acute renal failure after receiving high-dose methotrexate and was unable to complete the first course of MIED. This patient was not considered assessable for response but is included in the toxicity summary.

All 24 children with NHL and 35 of 37 assessable patients with HL (95%) received MIED at the time of first treatment failure (i.e. relapse or induction failure). Twenty of the 24 children with NHL and 31 of the 37 assessable children with HL received further salvage therapy, which in some cases included an intensification phase with HSCT support (autologous, 48; allogeneic, 3) at some point after MIED (Figure 1). Patients who received allogeneic HSCT included one with relapsed Burkitt’s lymphoma, one with recurrent lymphoblastic lymphoma, and one with refractory leukemic anaplastic large-cell lymphoma (ALCL).

Forty-six (75%) of the 61 assessable children with refractory or recurrent lymphoma responded to MIED (CR, 23; PR, 23). Among the 24 children with NHL (18 large cell [8 ALCL, 6 B-cell, 1 T-cell, 3 large cell not otherwise specified]; 3 Burkitt; 2 lymphoblastic; and 1 other), 10 had a CR and 5 a PR for a combined response rate of 63% [95% confidence interval (CI), 38% to 73%]. Among the eight patients with ALCL, there were five CRs and two PRs for a combined response rate of 88%. Among the 37 children with HL (29 nodular sclerosis; 4 mixed cellularity, 1 lymphocyte predominant, and 3 HL not otherwise specified), there were 13 CRs and 18 PRs for a combined response rate of 84% (95% CI, 68% to 94%).

The time to first relapse (> 12 months versus \(\leq 12\) months) among HL patients was not significantly associated with response (either CR or PR) to MIED (\(P = 0.383\)). Among patients with NHL, the rate of response (CR + PR) was significantly higher among those with a >12-month time period to first relapse (\(P = 0.022\)).

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<table>
<thead>
<tr>
<th>Drug/agent</th>
<th>Dose</th>
<th>Route</th>
<th>Schedule (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-dose methotrexate</td>
<td>8000 mg/m\textsuperscript{2}/day</td>
<td>i.v. over 4 h</td>
<td>Day 1</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>15 mg/m\textsuperscript{2}/dose</td>
<td>i.v./p.o.</td>
<td>Day 2, 20 h after the completion of HD-MTX (every 6 h \times 12 doses)</td>
</tr>
<tr>
<td>Etoposide</td>
<td>200 mg/m\textsuperscript{2}/day</td>
<td>i.v. over 2 h</td>
<td>Days 2–4</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2000 mg/m\textsuperscript{2}/day</td>
<td>i.v. over 2 h</td>
<td>Days 2–4</td>
</tr>
<tr>
<td>Mesna</td>
<td>500 mg/m\textsuperscript{2}/dose</td>
<td>i.v.</td>
<td>Immediately after and at 3 and 6 h after ifosfamide</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/m\textsuperscript{2}/day</td>
<td>i.v.</td>
<td>Divided into three doses and given every 8 h \times 12 doses, starting on day 1</td>
</tr>
<tr>
<td>G-CSF</td>
<td>5 mcg/kg/day</td>
<td>i.v./SQ</td>
<td>Starting 24 h after last dexamethasone dose and continuing for 7 days or longer, based on count recovery</td>
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</table>

Table 1. MIED chemotherapy regimen

*Intensive methotrexate, hydrocortisone and cytarabine were given on day 1 to non-Hodgkin’s lymphoma patients, at age-adjusted dosages. G-CSF, granulocyte colony stimulating factor; HD-MTX, high-dose methotrexate; MIED, methotrexate, ifosfamide, etoposide and dexamethasone; SQ, subcutaneous.

ifosfamide with mesna was given. The start of chemotherapy on days 2–4 required that urine-specific gravity be <1.010 and urine red blood cells be <50/microscopic high power field. Post-ifosfamide hydration comprised 1000 ml/m\textsuperscript{2} of 0.45% NaCl given i.v. over 6 h immediately after ifosfamide on days 2 through 4; hydration was piggybacked on other i.v. fluids so that total daily i.v. fluid intake equaled 2500 ml/m\textsuperscript{2}. Patients with NHL received intrathecal methotrexate, hydrocortisone, and cytarabine at age-adjusted dosages on day 1.

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The MIED regimen is effective and well tolerated in children with recurrent or refractory malignant lymphoma. The combined response rate (PR + CR) supports the efficacy of the regimen in both NHL (63%) and HL (84%). However, the limited scope of histological subtypes of NHL in our cohort precludes conclusions about subtype-specific efficacy. The predominant histological subtypes were large-cell NHL and nodular sclerosing HL. However, the two children with lymphoblastic lymphoma in our cohort had no response to MIED. Study of additional cases will be required to establish the activity of MIED in children with this and other NHL histological subtypes.

The prognosis of children with recurrent lymphoma is thought to correspond to time to first relapse. In our study of MIED however, response to salvage therapy with respect to time to first relapse varied with histology. Among patients with HL, rate of response to MIED did not differ with respect to the time from diagnosis to time to first relapse (i.e. > versus <12 months). In contrast, among patients with NHL, those with a time >12 months to first relapse had a significantly higher rate of response to MIED.

The most frequent toxic effects of the MIED regimen included reversible grade 4 hematologic toxicity and grade 3 fever with neutropenia, which was successfully managed with broad-spectrum antibiotics; there were no septic or toxic deaths. Oral mucositis, another frequently encountered toxicity, was managed with standard supportive care. The toxicity profile of the MIED regimen was generally acceptable and reversible, such that patients with chemosensitive disease were eligible for institutional HSCT protocols. One patient, however, experienced acute renal failure after administration of high-dose methotrexate, and a complete course of MIED could not be delivered. Although renal toxicity was not common, this case highlights the importance of optimizing drug clearance and closely observing both methotrexate levels and clinical status to minimize toxicity.

There is relatively little available data on successful salvage for children with recurrent or refractory malignant lymphoma. Previous publications have focused primarily on NHL. The Pediatric Oncology Group (POG) reviewed its experience with ICE in 21 children aged 2–20 years (median, 12 years) with recurrent NHL (histological subtypes not specified) [12]. They reported a combined response rate of 71% (CR, 43%; PR, 28%). Fever with neutropenia was a common toxicity; however, there were only three episodes of sepsis, and none was fatal. The ICE regimen was well tolerated with no clinically significant nephrotoxicity. The response rate and toxicity profile of ICE is comparable with that observed with MIED. Because the POG study was limited to NHL, the activity of ICE in children with HL is unclear. A phase II study of ICE in adults and children with recurrent HL at Memorial Sloan Kettering Cancer Center had a combined response rate of 88%; however, only a small subset of the study population were children [9].

The Children’s Cancer Group published the results of the DECAL salvage regimen in children with recurrent NHL (n = 68) and HL (n = 29) [10]. The rate of response appears somewhat lower than that achieved with MIED when analyzed on the basis of intent to treat: the combined response rate was 65.5% in those with HL (CR, n = 10; PR, n = 9) and 41.6% in those with NHL (CR, n = 23; PR, n = 6). However, when only patients with available response data were analyzed, the response rate for DECAL (79.2% and 50% for HL and NHL, respectively) approached that seen with MIED.

Table 2. Grades 3 and 4 toxic effects associated with 152 courses of MIED in 61 patients

<table>
<thead>
<tr>
<th>CTC v.3 toxicity</th>
<th>Grade 3, n (%) of courses</th>
<th>Grade 4, n (%) of courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>9 (6)</td>
<td>89 (59)</td>
</tr>
<tr>
<td>Anemia</td>
<td>65 (43)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>40 (26)</td>
<td>64 (42)</td>
</tr>
<tr>
<td>Fever with neutropenia</td>
<td>70 (46)</td>
<td>—</td>
</tr>
<tr>
<td>Mucositis</td>
<td>27 (18)</td>
<td>—</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>13 (9)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>2 (1)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Grade 2 mucositis occurred with 52 courses (34%). CTC, Common Terminology Criteria; MIED, methotrexate, ifosfamide, etoposide and dexamethasone.
Some NHL salvage regimens have been used primarily for specific histological subtypes. For example, the DHAP regimen has been shown to be active in adults and (in a small study) in children with recurrent large-cell lymphoma [11]. In the study reported here, seven of eight children with ALCL responded to MIED (five CRs and two PRs). The French Society of Pediatric Oncology (SPOP) has tested regimens specifically designed for children with ALCL [13]. They identified CVBA (CCNU, vinblastine, bleomycin and cytarabine) and CVA (CCNU, vinblastine and cytarabine) as particularly active regimens for recurrent ALCL. Notably, they also identified single-agent vinblastine as very active, even against multiply relapsed disease. Among 12 children with recurrent ALCL, 10 had a CR after receiving weekly single-agent vinblastine for 6–18 months, and some of these remained in CR 15–36 months after completing therapy. We and others have demonstrated that autologous HSCT strategies can be successfully used to salvage some patients with recurrent ALCL [14, 15]. However, SPOP found no survival advantage for intensive therapy with autologous HSCT as compared with more conventional chemotherapy incorporating vinblastine. Excellent results were achieved in a recent Berlin–Frankfurt–Munster study of allogeneic HSCT for patients with relapsed ALCL with high-risk features, suggesting a possible graft-versus-lymphoma benefit in this setting [16]. Additional prospective trials are needed to more fully address the role of allogeneic HSCT in children with refractory/recurrent disease.

In summary, MIED is an active regimen for children with refractory or recurrent lymphoma, and is a bridge therapy to intensification with HSCT support. Its toxic effects are generally manageable and do not preclude subsequent intensification with HSCT.

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disclosure
C-H Pui is the American Cancer Society Professor. The authors have declared no conflicts of interest.

references