Bone Marrow Transplantation for Peripheral T-Cell Lymphoma in Children and Adolescents


We report nine children with relapsed (n = 8) or high-risk (n = 1) peripheral T-cell lymphoma (PTCL) who underwent autologous (n = 6) or allogenic (n = 3) bone marrow transplantation (BMT). These children received transplants as part of a prospective phase 1/II study of thioTEPA (TT) and total body irradiation (TBI) with escalating doses of VP-16. The median age of these patients at time of BMT was 6.5 years (range 2.5 years to 14 years). Three were transplanted with active disease after failing salvage chemotherapy. Of the other six, one was transplanted in first complete remission (CR) and five in second or subsequent CR. Of these nine patients, eight are free of disease a median of 25 months after BMT (range, 6 to 48 months), with an estimated 2-year relapse-free survival (RFS) of 89%. Six of these eight patients have been followed for 12 or more months after BMT, and in each their current remission exceeds their longest previous remission duration. The toxicity of the TT/TBI ± VP-16 regimens was significant but manageable, predominately consisting of severe mucositis. For a comparison, we reviewed retrospective data on the six additional children and adolescents with PTCL who underwent BMT during the 3-year period preceding this phase I/II study. The median age at BMT of these six patients was 19 years (range 15.5 years to 20 years). These patients were prepared for BMT with a variety of other regimens. One had no response to BMT and the other five relapsed at 1.5 to 5 months after BMT (median, 3 months) with an RFS of 0%. Our data suggest that thioTEPA plus TBI, with or without VP-16, is an effective preparative regimen for BMT for young patients with relapsed or high-stage PTCL and leads to prolonged RFS.

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PERIPHERAL T-cell lymphoma (PTCL) is a malignancy of mature post-thymic T cells. It is the most common type of peripheral lymphoma seen in adults in the United States, representing 10% to 20% of all diffuse non-Hodgkin’s lymphomas (NHLs). In contrast, PTCL is relatively rare in childhood, with the large majority of childhood T-cell lymphomas being lymphoblastic lymphomas arising from pre-thymic or thymic lymphocytes.

Although adults with PTCL may respond to chemotherapy, the majority will relapse and die of their disease. The prognosis of patients with high-stage, disseminated PTCL is even worse, with a 4-year disease-free survival (DFS) after conventional chemotherapy of less than 20%.

Patients with NHL who relapse after combination chemotherapy also have a very poor outcome, with 10% or less surviving long term after salvage chemotherapy. However, high-dose chemoradiotherapy followed by allogeneic or autologous bone marrow transplantation (BMT) may salvage 35% to 55% of patients with relapsed NHL, and this form of therapy is especially efficacious in those with disease that is sensitive to chemotherapy. There have been few studies reporting on the efficacy of BMT in patients with PTCL, and none specifically addressing the response to BMT of children and young adults with relapsed PTCL.

Since 1988, we have been conducting a phase I/II dose escalation study of VP-16 in combination with high-dose thioTEPA (TT) and total body irradiation (TBI) as preparation for BMT for pediatric patients with lymphoma or a variety of solid tumors. ThioTEPA, a polyfunctional alkylating agent, was originally introduced in the 1950s and has a broad spectrum of activity. Antitumor activity has been observed in patients with Hodgkin’s lymphoma and NHL, acute and chronic leukemias, breast cancer, ovarian cancer, central nervous system tumors, and melanoma.

However, severe myelosuppression at clinically effective doses limited the utility of this agent. Like other alkylating agents, TT demonstrates a clear dose-response relationship. This observation led to the reexamination of this agent, in high-dose regimens, along with bone marrow rescue. In this setting, high-dose TT-containing regimens have shown efficacy against a variety of tumors, including Hodgkin’s lymphoma and NHL, with tolerable nonhematologic toxicity. Alkylating agents are often non-cross-resistant, therefore this agent may be effective even in patients who have failed cyclophosphamide (CPM) containing chemotherapy regimens. We have also used this regimen, or a similar regimen with TT/VP-16 and CPM, to treat children with a variety of solid tumors. The results, especially for patients with Wilms’ tumor and Ewing’s sarcoma, have been very encouraging.

As part of this dose escalation study, we have transplanted nine children with PTCL. Preliminary analysis of these nine patients is provided here. In addition, as a comparison, we reviewed retrospective data on six additional children and young adults with PTCL who underwent BMT at our institution during the 3-year period preceding this TT study. A variety of preparative regimens were used for this earlier group of patients, reflecting ongoing studies during that time period.
PATIENTS AND METHODS

Classification of the cases as PTCL was made based on morphologic and immunophenotypic studies of the tumor cells in lymph nodes and/or skin lesions. The tumor cells in all patients expressed one or more pan-T-cell markers and were negative for B-cell-associated markers using paraffin or frozen section immunohistochemical techniques. If possible, cases were further classified as helper/inducer phenotype (CD4 positive) or suppressor/cytotoxic phenotype (CD8 positive). Tumors were also stained for CD30 antigen as recognized by the Ki-1 and/or Ber-H2 antibodies (DAKO Corp, Santa Barbara, CA).

After transplantation, the continued remission status of all patients was documented by physical examination, chest radiographs, computed tomographic scans of the abdomen and chest, gallium scans, and bone marrow examinations, as appropriate. Remission durations are analyzed to July 1, 1992. RFS was defined as the time from BMT to relapse. The RFS was estimated using the product-limit method of Kaplan and Meier. Transplant protocols were approved by the Institutional Review Board at the University of Nebraska Medical Center (UNMC). The benefits and the risks of the therapies used were explained in detail to parents and older children and written consent was obtained for both recipients and donors.

The nine patients in the phase I/II study underwent autologous or allogeneic BMT at UNMC between July 1988 and January 1992, by the Pediatric BMT group. The clinical characteristics of these patients are shown in Table 1. At time of diagnosis, these patients ranged in age from 18 months to 13 years (median 6 years). Using the St Jude staging system,26 two patients presented with stage I or II, three with stage III, and four with stage IV disease. Three tumors were helper/inducer phenotype, one suppressor/cytotoxic phenotype, and five could not be further phenotyped. Eight were CD30 positive and one was CD30 negative (patient no. 4). One patient (no. 8) presented with a right frontal lobe mass and cerebrospinal fluid (CSF) cytology showed My7 (CD13)-positive cells. Although bone marrow showed no evidence of disease, an initial diagnosis of acute monocytic leukemia was made. At time of relapse, inguinal and cervical lymph nodes showed large anaplastic lymphoma cells that stained with antibodies against T-cell markers CD2 (T11) and CD45 (UCHL1), as well as CD30 (Ki-1) and monocye marker CD14 (LeuM3). This histology and immunophenotype was felt most consistent with PTCL coexpressing monocyte markers.

All nine patients were treated with multiagent chemotherapy with or without radiotherapy, following the initial diagnosis of PTCL. All patients had resolution of clinically apparent disease.

Patient no. 9 (with stage IV disease) received a transplant in first remission 5 months after diagnosis. For the other eight patients, the first remissions lasted from 3 to 13 months (median, 5 months). Four of the patients who relapsed did so while on therapy, and another two within 6 months of completing therapy. The time from diagnosis to transplantation for all patients ranged from 5 to 35 months (median, 9 months). At time of BMT, the patients ranged in age from 2.5 to 14 years (median, 6.5 years).

All patients received TT (300 mg/m² per day for 3 days) and TBI (200 cGy twice a day for 3 days) either alone (one patient) or with VP-16 1,000 mg/m² (one patient), 1,500 mg/m² (five patients), or 1,800 mg/m² (two patients). The preparative regimen is shown in Table 1. Six patients received histologically normal, unpurged, autologous marrow (including three patients [nos. 4, 8, and 9] with marrow involvement with lymphoma at diagnosis). Of the three remaining patients, one with stage IV disease (no. 3) received marrow from an HLA-phenotypically identical unrelated donor, one with extensive stage III disease (no. 2) received marrow from an HLA-identical sibling donor and one (no. 5) received syngeneic marrow from an identical twin.

RESULTS

Phase I/II study. Of the nine patients in the phase I/II study prepared with TT/TBI ± VP-16, eight patients are free of disease a median of 25 months after BMT (range, 6 to 48 months), with an estimated 2-year RFS of 89% (Fig 2). Three were transplanted with active disease after failing salvage chemotherapy. All three had resolution of all bulk disease, but one (patient no. 7) relapsed 1 month after BMT. Six patients have been followed for 12 or more months after BMT and in each their current remission exceeds their longest previous remission duration.

The toxicity of the TT/TBI ± VP-16 regimens was significant but manageable. Mucositis was severe, and all patients required morphine for pain control and aggressive oral debridement with topical nystatin and betadine treatment to prevent superinfection.27 One patient (no. 3) had a cardiorespiratory arrest at 7 days after BMT and sustained anoxic brain damage, presumably secondary to airway compromise from oropharyngeal mucositis. No other patient required intubation for airway control. Other hematologic toxicity from these preparative regimens was limited to generalized erythroderma with cutaneous bronzing in all patients, as has been previously reported.18

Table 1. Clinical Characteristics of Nine Patients in Phase I/II Study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Duration of Response To Primary Therapy (mos)</th>
<th>Status at BMT</th>
<th>Age at BMT (yrs)</th>
<th>Time Dx to BMT (mos)</th>
<th>Preparative Regimen</th>
<th>BMT Type</th>
<th>Response To BMT and Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 (2 mos off therapy)</td>
<td>2nd REL</td>
<td>13</td>
<td>6</td>
<td>TT/TBI</td>
<td>Auto</td>
<td>CR, NED at 48+ mos</td>
</tr>
<tr>
<td>2</td>
<td>6 (2 mos off therapy)</td>
<td>2nd CR</td>
<td>8</td>
<td>8</td>
<td>TT/TBI/VP(1,000)</td>
<td>Allo</td>
<td>NED at 36+ mos</td>
</tr>
<tr>
<td>3</td>
<td>5 (relapse on therapy)</td>
<td>2nd REL</td>
<td>2</td>
<td>12</td>
<td>TT/TBI/VP(1,500)</td>
<td>Allo</td>
<td>CR, NED at 30+ mos*</td>
</tr>
<tr>
<td>4</td>
<td>12 (9 mos off therapy)</td>
<td>2nd CR</td>
<td>11</td>
<td>14</td>
<td>TT/TBI/VP(1,500)</td>
<td>Auto</td>
<td>NED at 28+ mos</td>
</tr>
<tr>
<td>5</td>
<td>3 (relapse on therapy)</td>
<td>2nd CR</td>
<td>6</td>
<td>6</td>
<td>TT/TBI/VP(1,500)</td>
<td>Sync</td>
<td>NED at 23+ mos</td>
</tr>
<tr>
<td>6</td>
<td>13 (3 mos off therapy)</td>
<td>2nd CR</td>
<td>4</td>
<td>15</td>
<td>TT/TBI/VP(1,500)</td>
<td>Auto</td>
<td>NED at 16+ mos</td>
</tr>
<tr>
<td>7</td>
<td>4 (relapse on therapy)</td>
<td>2nd REL</td>
<td>6</td>
<td>9</td>
<td>TT/TBI/VP(1,500)</td>
<td>Auto</td>
<td>CR, relapse at 1 mo</td>
</tr>
<tr>
<td>8</td>
<td>3 (relapse on therapy)</td>
<td>3rd CR</td>
<td>11</td>
<td>35</td>
<td>TT/TBI/VP(1,800)</td>
<td>Auto</td>
<td>NED at 9+ mos</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1st CR</td>
<td>4½</td>
<td>6</td>
<td>TT/TBI/VP(1,800)</td>
<td>Auto</td>
<td>NED at 6+ mos</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; NR, no response; REL, relapse; Auto, autologous; Allo, allogeneic; Sync, syngeneic. See Fig 1 for details of the preparative regimen.

*Had cardiopulmonary arrest after transplant as mentioned in text.
**PREPARATIVE REGIMEN**

| ThioTEPA | 300 mg/m² |
| VP-16 | Q DAY |
| TBI | 200 cGy BID |
| -7 | -6 |
| -5 | -4 |
| -3 | -2 |
| -1 | 0 |
| VP-16 dose (as 24 hr infusion): |
| 1800 mg/m² | 2 patients |
| 1500 mg/m² | 5 patients |
| 1000 mg/m² | 1 patient |
| None | 1 patient |

**Fig 1.** TT/TBI ± VP-16 preparative regimen (phase I/II study).

Because of the overall good responses and the small number of patients at each dose level, we could not assess the effect of increasing VP-16 dose on outcome. The one patient who failed did so at the 1,500 mg/m² level. Mucositis was significant at all dose levels, and did not appear significantly worse at the highest dose levels. The patient who suffered airway compromise from severe oropharyngeal mucositis was administered 1,500 mg/m² of VP-16.

**Retrospective review.** Data were collected retrospectively on six children and young adults receiving transplants for PTCL between 1985 and 1988. These six patients represented all other pediatric patients receiving transplants for PTCL at UNMC (five patients) or at Clarkson Memorial Hospital (one patient). These patients were all transplanted by the Internal Medicine Bone Marrow Transplant group. Four of these patients have been previously reported. All patients had relapsed after initial CRs, and ranged in age from 15.5 to 20 years (median, 19 years) at time of BMT. Patients were prepared for BMT with a variety of preparative regimens (CPM/VP-16/TBI, 1 patient; melphalan/TBI, 1 patient; BCNU/VP-16/cytosine arabinoside/CPM, 2 patients; CPM/BCNU/VP-16, 1 patient; cytosine arabinoside/CPM/TBI, 1 patient). The diversity of regimens reflected on-going studies by the Internal Medicine BMT group during that time period. Of these six patients, one had no response to BMT and the other five relapsed at 1.5 to 5 months after BMT (median, 3 months) with an RFS of 0% (Fig 2).

**DISCUSSION**

The majority of childhood T-cell lymphomas arise from precursor or early T cells and can be easily distinguished morphologically and immunologically from tumors arising from mature peripheral T cells. The peripheral T-cell lymphomas originate from differentiated post-thymic T cells and, while relatively common in adults, are rare in children. The optimal treatment and prognosis of children with PTCL is unclear. Some investigators have found a worse prognosis for adults with PTCL as compared to those with B-cell lymphoma, although others have noted no differences. Certainly, some subgroups of PTCL, such as those with Ann Arbor stage IV, do particularly poorly. There have only been a few small pediatric series of PTCL and these have also suggested a poor outcome. Leake et al reported six pediatric patients with PTCL, three of whom died, with a mean survival of 22 months. Bucsky et al described an additional six pediatric patients with PTCL and reported a continuous complete remission rate of 44%, as compared to 83% for a much larger group of children with other types of NHL.

In general, once a patient with NHL has relapsed, the clinical outcome is poor. BMT is a viable salvage option in such cases. Up to 56% of children treated with high-dose chemoradiotherapy and allogeneic BMT for relapsed NHL are long-term survivors. Vose et al recently reported their experience with autologous BMT in adults with relapsed T-cell lymphoma, 14 of whom had PTCL. All 14 were transplanted with active disease, although four had at least a partial response to pretransplant chemotherapy. A variety of BMT preparative regimens were used. Eight of the 14 patients (57%) had complete responses to BMT and four (29%) were in continuous CR at 21 to 48 months after transplantation. Both the CR rate and DFS of these patients were equivalent to that seen in a concurrent group of patients transplanted for relapsed B-cell NHL.

Herein, we describe nine children who underwent BMT for relapsed or high-stage PTCL, after preparation with regimens containing TT/TBI ± VP-16. TT, a polyfunctional alkylating agent, has efficacy against Hodgkin's dis-
ease and NHL at standard doses, and at high doses in combination with BMT.\textsuperscript{18,20,34} The use of TT/TBI \textsuperscript{15} or VP-16 preparative regimens in our patients with PTCL was associated with a good outcome after BMT, with eight of nine in remission a median of 25 months. Six of these patients have been followed for 12 or more months after BMT and in each, their current remission exceeds their longest previous remission duration.

Although the RFS for these nine children is very encouraging, the lack of other large series of children undergoing BMT for PTCL makes determination of the value of this particular preparative regimen difficult. As a comparison, we retrospectively reviewed all the cases of PTCL in children and young adults who received transplants at our institution. These patients were treated by the Internal Medicine BMT group during the 3 years preceding our phase I/II study, using a variety of different BMT preparative regimens. These patients were older (median age, 17 years \textsuperscript{17} v 6 years) and were more often transplanted in relapse than were the patients in our phase I/II study. Nevertheless, all of the six patients in the retrospective review relapsed after transplantation.

Patients described in both the phase I/II study and the retrospective review had tumors that expressed a T-cell immunophenotype. In addition, eight of nine in the phase I/II study expressed the CD30 antigen as demonstrated by positivity with the Ki-1 or Ber-H2 antibody. We have shown a high frequency of positivity for this antigen in pediatric patients with PTCL,\textsuperscript{35} but it is not clear whether this antigen confers any prognostic significance. Several small studies have suggested that tumors which bear the CD30 antigen have a more favorable prognosis, especially in young patients.\textsuperscript{36–38} However, a recent review of 24 patients treated on Children’s Cancer Study Group protocols could show no prognostic significance of the CD30 antigen.\textsuperscript{39} Chakravarti et al\textsuperscript{40} recently reported two patients who were transplanted for relapsed Ki-1-positive lymphoma. Both patients had tumors of peripheral T-cell origin as shown by the presence of T-cell receptor \( \beta \) gene rearrangements and expression of T-cell activation antigens. Both were transplanted in second remission and both are alive without evidence of disease at 40 and 56 months after transplantation.

In conclusion, we have presented data on 15 pediatric patients with PTCL who underwent BMT. Our data suggest that TT plus TBI, with or without VP-16, is an effective preparative regimen for BMT for young patients with relapsed or high-stage PTCL and leads to prolonged RFS. Further evaluation of this preparative regimen for children and older patients appears to be warranted.

### REFERENCES


Bone marrow transplantation for peripheral T-cell lymphoma in children and adolescents

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