Paclitaxel, Ifosfamide and Cisplatin Regimen is Feasible for Japanese Patients with Advanced Germ Cell Cancer

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Background: Paclitaxel, ifosfamide and cisplatin (TIP) has been tested with successful results on metastatic testicular cancer in Western countries. Because paclitaxel, the key drug of this regimen, has not been approved for testicular cancer in Japan, there are no established data concerning TIP. The purpose of this study was to assess the feasibility of a TIP regimen for Japanese patients with advanced germ cell cancer.

Methods: Eight patients with advanced germ cell cancer were treated with TIP that was originally reported by Motzer et al (1). The treatment was used for three refractory cases and two late relapse cases as salvage therapy and for three poor-risk cases with extra-pulmonary visceral metastases as a part of induction chemotherapy. TIP consisted of paclitaxel 175 mg/m² by 24 h infusion on day 1, followed by ifosfamide 1.2 g/m² infusions over 2 h and cisplatin 20 mg/m² given over 2 h on days 2–6.

Results: Five patients (62%) achieved a disease-free status after chemotherapy and surgical resection of residual tumor. Three of five patients have remained continuously free from disease progression at a median follow-up duration of 24 months and one additional patient is free of evidence of disease. Most patients developed grade 3 or 4 leukocytopenia and thrombocytopenia; however, they could be managed with routine supportive care. Sensory neuropathy was frequently seen, but no patient experienced over grade 3 neurotoxicity.

Conclusions: TIP regimen as salvage chemotherapy is feasible for Japanese patients with advanced germ cell cancer. TIP as a part of induction chemotherapy for poor-risk patients is also feasible; however, larger and longer-term follow-up studies are needed to define the role of TIP in this setting.

Key words: testicular cancer – paclitaxel – ifosfamide – cisplatin

INTRODUCTION

About 70–80% of patients with disseminated testicular cancer can currently be cured because of the progress in cisplatin-based chemotherapy (2). However, patients who relapse after initial treatment or patients who did not respond completely to chemotherapy have a poor prognosis. Current standard-dose salvage chemotherapy with cisplatin, ifosfamide and either etoposide or vinblastine (VIP or VeIP) can achieve complete response in ~50% of patients (3–5). However, remission is of short duration in many cases, resulting in a long-term disease-free survival rate of 10–25%.

One possible approach to improve outcome is drug-dose increment. In recent years, high-dose chemotherapy (HDCT) with autologous stem-cell rescue has been used with some success in the first relapse cases and refractory cases (6,7). Although the non-randomized data are promising, the clinical benefit of HDCT remains to be confirmed in an ongoing randomized study. Another strategy is to include a new active drug in the chemotherapy regimen. Recently, Motzer et al. reported that a regimen of paclitaxel, ifosfamide and cisplatin (TIP) as first-line salvage therapy produced a highly durable complete response (CR) rate of up to 73% in patients with good prognostic factors (1). The results suggest that there might be some advantage in the use of TIP as salvage for patients with unfavorable prognostic features such as refractory tumor and late relapse and also used as part of induction chemotherapy for poor-risk patients with an incomplete response to first-line chemotherapy. However, the regimen has not been available in Japan, since paclitaxel, the key drug of the regimen, has not been approved by the Japanese government for testicular cancer. The purpose of our study was to test the feasibility of this regimen in Japanese patients with advanced germ cell cancer. This study was carried out using the University Hospital Investigative Fund for purchasing paclitaxel.

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Table 1. Characteristics and treatment outcome of the refractory and/or relapsed cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Histology/category</th>
<th>Prior therapy</th>
<th>Treatment</th>
<th>Marker normalization</th>
<th>Response</th>
<th>Outcome (duration)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>Ch/refractory</td>
<td>BEP×3, MAC×3, TP×3</td>
<td>TIP×4, thoracotomy</td>
<td>Yes</td>
<td>PR</td>
<td>DOD (8 Mos)</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>E/refractory</td>
<td>COMPE×4, EP×1, VEIP×1</td>
<td>TIP×3 RPLND + heptectomy</td>
<td>Yes</td>
<td>PR</td>
<td>NED (33 Mos)</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>TC,Y/refractory (extragonadal)</td>
<td>BEP×4, ICE×1, VIP×4</td>
<td>TIP×1</td>
<td>No</td>
<td>NC</td>
<td>AWD (12 Mos)</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>TC/relapse (13 years)*</td>
<td>PVB×5</td>
<td>TIP×3</td>
<td>No</td>
<td>PR</td>
<td>NED after surgical salvage (12 Mos)</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>TC/relapse (4 years)*</td>
<td>BEP×3</td>
<td>TIP×3, RPLND</td>
<td>Yes</td>
<td>NC</td>
<td>NED (5 Mos)</td>
</tr>
</tbody>
</table>

Ch, choriocarcinoma; E, embryonal carcinoma; TC, teratocarcinoma; Y, yolk sac tumor; BEP, bleomycin + etoposide + cisplatin; EP, etoposide + cisplatin; VEIP, vinblastin + ifosfamide + cisplatin; CEC, carboplatin + etoposide + cyclophosphamide with autologous stem-cell rescue (ASCR); MAC, methotrexate + actinomycin D + cisplatin; TP, paclitaxel + cisplatin; COMPE, cisplatin + vincristine + methotrexate + peplomycin + etoposide; ICE, ifosfamide + carboplatin + etoposide with ASCR; RPLND, retroperitoneal lymph node dissection; PR, partial response; NC, no change; DOD, died of disease; NED, no evidence of disease; AWD, alive with disease. *Time to relapse. *Mos = months.

PATIENTS AND METHODS

PATIENTS

Eight male patients with advanced germ cell cancer were enrolled in the phase II study with TIP at Tsukuba University Hospital between January 2000 and March 2002. According to the Tsukuba University Hospital system, the use of paclitaxel for germ cell cancer patients was reviewed and approved by the Committee of the University Hospital Investigative Fund. Written informed consent was obtained from each patient. The median age at the treatment was 31 years (range, 25–44 years). All patients had histologically confirmed germ cell cancer with measurable disease and raised concentrations of tumor markers in serum. Seven patients had testicular primary tumors and one patient was diagnosed with extragonadal germ cell cancer originating from the retroperitoneum. Pretreatment evaluation included a history and physical examination, chest X-ray, serum tumor markers and routine blood chemistry. Depending on the sites of metastatic disease, all patients underwent computed tomography of the chest and abdomen and/or pelvis.

TREATMENT PROGRAM

Chemotherapy consisted of paclitaxel 175 mg/m² by 24 h infusion on day 1, followed by ifosfamide 1.2 g/m² infusion over 2 h and cisplatin 20 mg/m² given over 2 h on days 2–6. The dosages and schedule for cisplatin and ifosfamide administration were identical with the TIP regimen reported by Motzer et al. (1), but the dose of paclitaxel was fixed at 175 mg/m² in the present study. Mesna 400 mg was administered intravenously before ifosfamide infusions and every 4 h thereafter for a total of three doses per day. All patients received prophylactic premedication with 20 mg dexamethasone 12 and 6 h before paclitaxel, intravenous ranitidine and oral diphenhydramine (each 50 mg) 30 min prior to paclitaxel administrations. Patients received granulocyte colony-stimulating factor (G-CSF) daily by subcutaneous injection from day 7. If the WBC count exceeded 10 000/µl, G-CSF therapy was discontinued. Courses were repeated every 21 days. The subsequent cycle was withheld until the granulocyte count was >500/µl and the thrombocyte count was >50 000/µl.

EVALUATION OF RESPONSE AND TOXICITIES

Clinical response was evaluated according to the criteria in the General Rules for Clinical and Pathological Studies on Testicular Tumors. Survival duration was measured from the date of the initiation of TIP. Evaluation of toxicities was classified according to National Cancer Institute Common Toxicity Criteria (Second Version, 1999).

RESULTS

PATIENTS’ CHARACTERISTICS

Seven patients had non-seminoma and one patient had seminoma histologies. The characteristics of refractory or relapsed patients at the initiation of TIP treatment are described in Table 1. There was evidence of disease progression during or within 4 weeks of the last cisplatin-based chemotherapy in three refractory patients. All patients had been treated with more than eight cycles of cisplatin-based standard dose chemotherapy. Of them, two had received HDCT but failed to be cured. One patient was treated with three courses of paclitaxel and cisplatin (TP) prior to TIP but developed progressive disease during the third course of TP. Two relapsed patients were considered to have a late relapse, defined as a progression of germ cell cancer more than 2 years after a complete response to the induction chemotherapy (8). Table 2 summarizes the characteristics of poor-risk patients who received TIP as a part of the induction chemotherapy. All patients had extra-pulmonary visceral metastases in addition to multiple lung or lymph node
metastases. Thus, two non-seminoma patients and the seminoma patient were defined as having poor and intermediate prognosis, respectively, according to the International Germ Cell Consensus Classification (9). Two patients received three courses of bleomycin, etoposide and cisplatin (BEP) as first-line chemotherapy (10). In one patient, EP was substituted for BEP from the second course because of bleomycin-induced dermatitis.

TREATMENT AND TOXICITY

In total, 23 cycles of TIP were administered with a median of three cycles per patient (range, 1–4 cycles). The median number of days between cycles was 26 days (range, 21–41 days). The toxicity of TIP was considered tolerable except in one patient. This patient developed grade 2 sensory neuropathy at the first course of TIP and refused further treatment. Myelosuppression was the major toxicity, as is shown in Table 3. All patients developed grade 3 or 4 leukocytopenia. Three patients developed neutropenic fever, all of whom were successfully treated with empirical broad-spectrum antibiotics. Platelet transfusion was needed for three of five patients who developed grade 3 thrombocytopenia. Otherwise, no grade 3 or greater toxicity was observed. Six patients developed grade 1 and one patient developed grade 2 sensory neuropathy, although motor neuropathy was not observed in these patients.

RESPONSE AND SURVIVAL

Response was assessable in all patients (Tables 1 and 2). Six patients achieved tumor marker normalization by chemotherapy. Responses of measurable disease were defined as partial response (PR) in five patients and no change (NC) in one patient. They underwent post-chemotherapy surgery. Surgery included thoracotomy in three patients (cases 1, 6 and 7), retroperitoneal lymph node dissection (RPLND) in two patients (cases 5 and 8) and RPLND and partial hepatectomy (case 2) in one patient. Pathological examinations revealed necrosis or fibrosis in four patients. Residual viable germ cell tumor was revealed in the remaining two patients. In one patient (case 1), histology of completely resected lung metastases contained viable choriocarcinoma elements. In the other patient (case 7), thoracotomy resulted in incomplete resection because of the multiplicity of residual masses. The histology of the removed mass was immature teratoma. In two other patients, TIP failed to achieve tumor marker normalization. One patient (case 4) received three additional courses of VelP, which failed to achieve tumor marker normalization. The patient subsequently underwent RPLND and partial hepatectomy as surgical salvage. The other patient (case 3) received radiation for residual RPLN mass. Therefore, five of eight patients achieved a disease-free status after TIP and subsequent surgical resection of residual tumor. Of them, three patients remained continuously free from disease progression at a median follow-up duration of 24 months (range, 12–33 months) and the other patient is currently without evidence of disease. The one remaining patient who had viable choriocarcinoma cell in resected lung metastases, relapsed and died of the disease at 8 months after TIP therapy. Among three patients who failed to achieve a disease-free status, one (case 3) is alive with progressive disease. The second patient (case 4) was rendered free of disease by surgical salvage and is currently without evidence of disease. A third patient (case 7) developed leukemia with a typical etoposide-associated karyotype at 13 months after chemotherapy and is currently receiving chemotherapy for leukemia. The residual lung metastases of the patient are still stable with normal tumor markers for 20 months.

Table 2. Characteristics and outcome treatment of the poor-risk cases

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (years)</th>
<th>Histology</th>
<th>Metastases</th>
<th>Marker</th>
<th>Treatment</th>
<th>Marker normalization</th>
<th>Response</th>
<th>Outcome (duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>25</td>
<td>Ch, E</td>
<td>Liver, brain, lung, RPLN</td>
<td>hCG 24×10^4 IU/l, AFP 45 ng/ml</td>
<td>BEP×3, TIP×4, radiation&lt;sup&gt;†&lt;/sup&gt; thoracotomy</td>
<td>Yes</td>
<td>PR</td>
<td>NED (24 Mos)</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>Immature T, S, Y</td>
<td>Liver, bone, lung</td>
<td>hCG 58 IU/l, AFP3.2×10^4 ng/ml</td>
<td>BEP×1, EP×3, TIP×2 thoracotomy</td>
<td>Yes</td>
<td>PR</td>
<td>SD (20 Mos)</td>
</tr>
<tr>
<td>8</td>
<td>44</td>
<td>S</td>
<td>Liver, RPLN</td>
<td>LDH 1700 IU/l*</td>
<td>BEP×3, TIP×3, RPLND</td>
<td>Yes</td>
<td>PR</td>
<td>NED (12 Mos)</td>
</tr>
</tbody>
</table>

Ch, choriocarcinoma; E, embryonal carcinoma; T, teratoma; S, seminoma; Y, yolk sac tumor; RPLN, retroperitoneal lymph node; PR, partial response; NED, no evidence of disease; SD, stable disease. *Normal range <232 IU/l. <sup>†</sup> Gamma knife radiosurgery for brain metastases. <sup>‡</sup>Mos = months.

Table 3. Toxicity (WHO grade)

<table>
<thead>
<tr>
<th>Grade</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>62</td>
</tr>
<tr>
<td>Non-hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/ALT</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>Creatinine</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Myalgia/artralgia</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>Neuropathy (sensory)</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

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DISCUSSION

Paclitaxel showed antitumor activity with response rates of 11–25% in refractory or relapsed germ cell cancer patients in several single-agent phase II studies (11,12). Paclitaxel also showed synergy for cisplatin and alkylating agents in in vitro studies using cisplatin-resistant teratocarcinoma cell lines (13). Based on these preclinical and clinical data, paclitaxel has been increasingly studied in different combination programs for the treatment of relapsed and refractory germ cell cancer (14–16).

In the present study, we tested the feasibility of TIP as salvage treatment for patients with unfavorable prognostic features and also as part of the induction chemotherapy for poor-risk patients. In the refractory and relapsed cases, a group of heavily pretreated patients, TIP was well tolerated without grade 3 or higher non-hematological toxicities. Although most patients developed grade 3 or 4 leukocytopenia and thrombocytopenia, they could be managed with routine supportive care. Sensory neuropathy was frequently seen, but no patient experienced over grade 3 neurotoxicity. One patient with grade 2 sensory neuropathy had received cisplatin with a cumulative dose of 800 mg/m² before TIP, hence the neuropathy may be attributable to cisplatin or the combination of cisplatin and paclitaxel. Since a possible synergistic neurotoxic effect was suggested in the combination of cisplatin and taxanes (17,18), close symptom assessment and neurological examination are recommended in TIP, especially when used as salvage therapy.

In this series, three of five patients with refractory or relapsed disease achieved a disease-free status after TIP followed by surgery. Although the response was of short duration in one patient, the other two patients remain in continuous disease-free status. One patient who had developed progressive disease during prior VeIP was subsequently salvaged with TIP. Another patient was a late relapse, a condition that is generally characterized by a high degree of resistance to standard-dose salvage chemotherapy (8). Motzer et al. also reported promising TIP activity for late relapse case (1). In contrast, considering the less favorable results with TIP in patients with HDCT failure, the role of TIP as salvage for the situation is considered to be negligible. New and more active agents are needed in patients who relapse after HDCT (19).

Based on the promising results with TIP on the refractory or relapsed cases, we tested the role of TIP as consolidation for poor-risk patients. Three patients who all had extra-pulmonary visceral metastases other than lung or lymph node metastases were treated with three courses of BEP followed by TIP. The results are encouraging, with two of three patients achieving durable disease-free status. The other patient had multiple residual lung tumors, which were stabilized with a normal tumor marker for 18 months after TIP. We were planning a second-look thoracotomy for lung tumors highly suspicious of teratomatous residua. Unfortunately, the patient developed leukemia with typical findings of etoposide-related secondary leukemia. The patient is now receiving chemotherapy for leukemia. The lung tumors are still stabilized with normal tumor markers. Thus, BEP followed by TIP induced a durable response with no relapses of germ cell cancer in all three consecutive patients with extra-pulmonary visceral metastases. The treatment was better tolerated as the induction chemotherapy for poor-risk patients when compared with our prior experience with HDCT (20). de Wit et al. also reported similarly encouraging results with addition of a standard dose of paclitaxel to induction chemotherapy for poor- or intermediate-prognosis testicular cancer (14). Phase II/III randomized studies of BEP versus paclitaxel plus BEP in patients with intermediate-prognosis germ cell cancer are now under way by the EORTC and collaborating groups.

In summary, TIP was effective salvage chemotherapy for relapsed and selected refractory testicular cancers. TIP therapy as consolidation for poor-risk patients is also feasible and challenging; however, larger and longer-term follow-up studies are needed to define the role of paclitaxel-containing protocols as induction chemotherapy for poor-risk testicular cancer.

References