A Dose-finding Study of Nedaplatin and Cyclophosphamide for Patients with Gynecological Malignancies

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Background: Nedaplatin is a new analogue of cisplatin with similar efficacy but less renal toxicity. We investigated the appropriate dose of nedaplatin in combination with cyclophosphamide for patients with gynecological malignancies.

Methods: Nine patients (five with ovarian cancer and four with uterine cervical cancer) were studied. Three patients received 60 mg/m² of nedaplatin combined with 500 mg/m² of cyclophosphamide every 4 weeks. Another three patients were each administered 80 or 100 mg/m² of nedaplatin with the same dose of cyclophosphamide. A total of 27 courses was given.

Results: No patient needed dose reduction due to myelosuppression and no severe adverse events were observed.

Conclusions: Treatment with 100 mg/m² of nedaplatin and 500 mg/m² of cyclophosphamide is feasible for patients with gynecological malignancies. However, phase II studies are needed to clarify the efficacy of this combination chemotherapy.

Key words: nedaplatin – cyclophosphamide – combination chemotherapy – ovarian cancer – uterine cervical cancer

INTRODUCTION

Cisplatin is the most effective drug not only for ovarian cancer but also for other solid tumors, such as lung cancer, breast cancer, seminoma and many other malignancies. However, the renal and neurotoxicities of cisplatin become severe at high dose, hence it is sometimes difficult to continue cisplatin therapy. Although many analogues of cisplatin have been produced, only a few agents, such as carboplatin (1) and oxaliplatin (2), have been used clinically. Nedaplatin (cis-diammineglycolatoplatinum) is a platinum analogue produced by Shionogi Pharmaceutical (Osaka, Japan) (3). It was approved for clinical use against ovarian cancer and uterine cervical cancer in 1995 by the Japanese government. However, there have been only a few reports on combination chemotherapy including nedaplatin (4, 5).

A platinum- and cyclophosphamide-containing regimen has been the standard treatment for patients with ovarian cancer (6) and it has also been reported that platinum- and cyclophosphamide-containing regimens are effective for patients with uterine cervical cancer (7). Therefore, we conducted a dose-escalation study of nedaplatin and cyclophosphamide in patients with ovarian cancer and uterine cervical cancer to assess the efficacy and adverse events of this regimen.

PATIENTS AND METHODS

Eligibility Criteria

Patients had epithelial ovarian cancer or uterine cervical cancer that was histologically confirmed. The other eligibility criteria included a performance status <2, age <75 years, normal bone marrow function (WBC >3.0 × 10⁹/l; platelets >100 × 10⁹/l), creatinine clearance >40 ml/min, normal hepatic function (SAST <2 × normal; SALT <2 × normal) and no prior chemotherapy or radiotherapy. Exclusion criteria included concomitant malignancies and other severe cardiac or respiratory disease. All patients gave written informed consent.

Treatment Plan and Dose Escalation

Nedaplatin was administered intravenously over 120 min with 500 ml of normal saline solution and 500 mg/m² of cyclophosphamide with 500 ml of 5% glucose solution were administered concurrently over 120 min. Then 1000 ml of fluid were given for
hydration and protection of renal function. To reduce gastrointestinal toxicity, an anti-emetic agent (5-HT3 antagonist) was used prophylactically. Granulocyte colony-stimulating factor was administered subcutaneously (2 μg/kg) when the WBC count was <1.0 × 10^9/l or the neutrophil count was <0.5 × 10^9/l. Platelet transfusion was performed when the platelet count was <25 × 10^9/l and red cell transfusion was performed when the hemoglobin was <8 g/dl.

The doses of nedaplatin tested were 60, 80 and 100 mg/m². Three patients were initially enrolled at each dose level. If none of these three experienced dose-limiting toxicity (DLT), defined as grade 4 hematological toxicity and grade 3 or 4 non-hematological toxicity according to WHO criteria, then the next three patients were enrolled at the next higher level. If one patient developed DLT, up to five additional patients could be entered at the same dose level. The maximum tolerated dose (MTD) was defined as that dose at which over one third of the patients experienced hematological or non-hematological DLT. The recommended dose for phase II studies was defined as the dose level below the MTD.

When the platelet count was <100 × 10^9/l or the WBC count was <3.0 × 10^9/l, further treatment was withheld until it recovered to 100 × 10^9 or 3.0 × 10^9/l, respectively. In the presence of prolonged severe myelosuppression (the platelet count did not exceed 100 × 10^9/l or the WBC count did not exceed 3.0 × 10^9/l for more than 6 weeks), no further therapy was administered. Also when the creatinine clearance was <40 ml/min, no further therapy was administered. Patients were removed from the study if they had disease progression or unacceptable toxicity.

RESULTS

CLINICAL CHARACTERISTICS

Between January 1, 1996 and July 31, 1997, nine patients were enrolled in this study. Their age, histology, stage and performance status are listed in Table 1.

ADVERSE EVENTS

At 60 mg/m² of nedaplatin and 80 mg/m² of nedaplatin, no patient had grade 3/4 hematological or non-hematological toxicity and none of them required G-CSF, platelet transfusion or red cell transfusion. At 100 mg/m² of nedaplatin, two patients (Nos 8 and 9) experienced grade 3 leukopenia in the first three courses. Also, patient No. 8 experienced grade 3 thrombocytopenia in the first course and patient No. 9 experienced grade 3 thrombocytopenia in the third course. However, none of them received G-CSF or platelet transfusion and none of them had neutropenic fever (temperature >38.0°C) or a bleeding episode (Table 2). Grade 1 alopecia was observed in five patients, but all of them recovered after completion of treatment. No patient experienced more than grade 2 liver toxicity, renal toxicity, ototoxicity or neurotoxicity. Gastrointestinal toxicity was manageable and no other hematological toxicity was observed.

RESPONSE

Patient No. 5 with recurrence of ovarian cancer in the pelvis had stable disease for 12 months, but she died of disease 17 months after entry into the study. Patient No. 4 with residual tumor after surgery had a partial response that continued for 7 months. Patient No. 7 with uterine cervical adenocarcinoma was suspected to have recurrence when the tumor marker CA 125 increased from 20 to 157 U/ml. She had three courses of this treatment and the CA125 level decreased to <7 U/ml. Patient No. 8 with lymph node recurrence of cervical cancer had stable disease for 6 months. However, patient No. 3 with uterine cervical cancer had progression of bone metastasis despite chemotherapy (Table 3).

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Median (range) age, years</th>
<th>Performance status (WHO)</th>
<th>No. of patients with grade 3/4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose of nedaplatin</td>
<td>No. of patients</td>
<td>WBC</td>
<td>Platelets</td>
<td>Hb</td>
</tr>
<tr>
<td>60 mg/m²</td>
<td>3</td>
<td>0/0</td>
<td>0/0</td>
<td>0/-</td>
</tr>
<tr>
<td>80 mg/m²</td>
<td>3</td>
<td>0/0</td>
<td>0/0</td>
<td>0/-</td>
</tr>
<tr>
<td>100 mg/m²</td>
<td>3</td>
<td>2/0</td>
<td>2/0</td>
<td>0/-</td>
</tr>
</tbody>
</table>
Table 3. Characteristics of each patient

<table>
<thead>
<tr>
<th>No.</th>
<th>Dose (mg/m²)</th>
<th>Origin</th>
<th>Histology</th>
<th>Stage (FIGO)</th>
<th>Age (years)</th>
<th>No. of courses</th>
<th>Response</th>
<th>Status</th>
<th>Time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>Ovary</td>
<td>Serous</td>
<td>IB</td>
<td>39</td>
<td>3</td>
<td>–</td>
<td>NED</td>
<td>(26 months)</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>Ovary</td>
<td>Endomet.</td>
<td>IA</td>
<td>42</td>
<td>3</td>
<td>–</td>
<td>NED</td>
<td>(27 months)</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>Uterus</td>
<td>Squamous</td>
<td>Recurrence</td>
<td>64</td>
<td>3</td>
<td>PD</td>
<td>DOD</td>
<td>(5 months)</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>Uterus</td>
<td>Squamous</td>
<td>IVA</td>
<td>58</td>
<td>3</td>
<td>PR</td>
<td>DOD</td>
<td>(17 months)</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>Ovary</td>
<td>Serous</td>
<td>Recurrence</td>
<td>57</td>
<td>3</td>
<td>NC</td>
<td>DOD</td>
<td>(17 months)</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>Ovary</td>
<td>Mucinous</td>
<td>IC</td>
<td>58</td>
<td>3</td>
<td>–</td>
<td>NED</td>
<td>(21 months)</td>
</tr>
<tr>
<td>7</td>
<td>100</td>
<td>Uterus</td>
<td>Adeno.</td>
<td>Recurrence</td>
<td>49</td>
<td>3</td>
<td>CR</td>
<td>NED</td>
<td>(21 months)</td>
</tr>
<tr>
<td>8</td>
<td>100</td>
<td>Uterus</td>
<td>Squamous</td>
<td>Recurrence</td>
<td>46</td>
<td>3</td>
<td>NC</td>
<td>DOD</td>
<td>(12 months)</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>Ovary</td>
<td>Serous</td>
<td>IIIA</td>
<td>62</td>
<td>3</td>
<td>–</td>
<td>NED</td>
<td>(9 months)</td>
</tr>
</tbody>
</table>

Serous, serous cystadenocarcinoma; mucinous, mucinous cystadenocarcinoma; endomet., endometrioid adenocarcinoma; adeno., adenocarcinoma; CR, complete response; PR, partial response; NC, no change; PD, progression of disease; NED, no evidence of disease; DOD, died of disease.

DISCUSSION

Nedaplatin is a new analogue of cisplatin, which has the same efficacy with less neurotoxicity and nephrotoxicity (3). The dose-limiting toxicity of nedaplatin is reported to be thrombocytopenia (8). Nedaplatin has been approved for the treatment of ovarian cancer, uterine cervical cancer and many other cancers in Japan. Although in vitro studies have shown that nedaplatin has a higher efficacy than cisplatin (9), there have been few clinical reports about their comparative efficacy (10). In phase II studies, nedaplatin achieved a comparable response to carboplatin in patients with ovarian cancer, [38% for nedaplatin (11) and 38% for carboplatin (12)]. Nedaplatin has also been reported to have a higher efficacy than cisplatin and carboplatin in patients with uterine cervical cancer [46% for nedaplatin (11), 39% for cisplatin (13) and 19% for carboplatin (14)]. Although it was a non-randomized study, Hirabayashi et al. found that nedaplatin in combination with ifosfamide and pepleomycin had a high efficacy for advanced and recurrent uterine cervical cancer (4).

All of the patients with uterine cervical cancer who were enrolled in the present study had prior radiation therapy and were thought to have a poor prognosis. Despite this, the median survival period after therapy was 15 months (5 months, DOD; 12 months, DOD; 17 months, DOD; 21 months, NED). These data suggest that this regimen should be tried in untreated patients with uterine cervical cancer.

In the 1980s, platinum-containing regimens were reported to be superior to non-platinum-containing regimens for ovarian cancer (15). Several studies have shown that cisplatin and cyclophosphamide have the same efficacy as and less toxicity than cisplatin, cyclophosphamide and doxorubicin for advanced ovarian cancer (16,17). On the other hand, carboplatin has been shown to have the same efficacy as with less neurotoxicity, nephrotoxicity and gastrointestinal toxicity than cisplatin plus cyclophosphamide. Therefore, the combination of carboplatin and cyclophosphamide was established as the standard regimen for advanced ovarian cancer in 1992 (18).

In this study, we tried to assess the optimum dose of nedaplatin in combination with cyclophosphamide. There was no dose-limiting toxicity observed when 100 mg/m² of nedaplatin was given with 500 mg/m² of cyclophosphamide, which was the recommended dose from a phase I study of nedaplatin alone. Recently, moderate-dose platinum has been recommended for ovarian cancer, such as an area under the curve (AUC) of 4–6 mg x min/ml for carboplatin (19,20) and a dose of 75 mg/m² for cisplatin (21). There may be no survival benefit in escalating the platinum dose above moderate levels for advanced ovarian cancer. Accordingly, there may be no benefit in increasing the dose of nedaplatin above that suggested on the basis of the phase I study. We measured the serum concentration of total platinum (Pt) and filtered Pt at seven points after the administration of nedaplatin and cyclophosphamide in this study’s patients with the written informed consent. The total Pt and filtered Pt concentrations in serum with this combination chemotherapy were equivalent to pharmacokinetic data in a phase I study of nedaplatin alone (data not shown). Therefore, we stopped this.
study at a nedaplatin dose of 100 mg/m². Recently, taxol- and platinum-containing regimens have shown a higher efficacy than cyclophosphamide- and platinum-containing regimens in patients with stage III and stage IV, that is, advanced ovarian cancer (22). However, it is not yet certain whether taxol- and platinum-containing regimens are better than cyclophosphamide- and platinum-containing regimens for early stage ovarian cancer. Currently, the standard cytotoxic regimen recommended for recurrence of uterine cervical cancer is a platinum-containing regimen (23). However, the best combination drugs and dosage have not yet been clarified. Also, platinum- and cyclophosphamide-containing regimens have been shown to be effective for uterine cervical cancer. Therefore, nedaplatin and cyclophosphamide should be verified for their efficacy on response rate and ultimately survival in gynecological malignancies. The present study was the first to use combination therapy with nedaplatin and cyclophosphamide and the data obtained might be useful for planning further studies of this combination.

References