RETROSPECTIVE CASE SERIES OF 15 PATIENTS TREATED WITH CHEMORADIATION USING 5-FU AND NEDAPLATIN FOR GYNECOLOGICAL MALIGNANCY: WITH REGARD TO HEMOTOXICITY

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ABSTRACT

We conducted a retrospective comparison of the hemotoxicity of the sequential administration of 5-Fluorouracil (5-FU) prior to Nedaplatin (NDP) (FN therapy) and that of its reverse sequence (NF therapy) for gynecological malignancy. From February 2002 to November 2004, a total of 15 gynecological malignancy patients were treated with radiation therapy combined with NDP and 5-FU. Of these 15 patients, 5 were treated with NF therapy, and 10 were treated with FN therapy. No significant differences were detected between the FN and NF groups with regard to white blood cell count (WBC), hemoglobin level (Hb), and platelet count. The results of this study do not show that the FN group has a lesser degree of hemotoxicity than the NF group.

Key Words: Radiotherapy, Chemotherapy, 5-FU, Nedaplatin, Hemotoxicity

INTRODUCTION

Nedaplatin (NDP) was selected from a series of platinum analogs based on its pronounced pre-clinical antitumor activity against various solid tumors with lower nephrotoxicity than cisplatin. Pre-clinical experimental studies revealed that NDP shows synergistic antitumor efficacy against various cancers in combination with etoposide,¹ 5-fluorouracil (5-FU),² paclitaxel,³ or gemcitabine.⁴ Moreover, in combination with NDP and 5-FU, the sequential administration of 5-FU prior to NDP (FN therapy) resulted in more antitumor efficacy and less toxicity than its reverse sequence (NF therapy)² in an experiment of human head and neck squamous cell carcinoma xenograft in nude mice. We also performed this combination phase I study⁵ for head and neck cancer at Aichi Cancer Center Hospital. In administering 5-FU at a fixed dose (700 mg/
m² on days 1–5), the recommended dose of NDP was 150 mg/m². Furthermore, we performed a Phase I/II study⁷ of alternating chemoradiotherapy using FN therapy for patients with cervical cancer. The recommended dose of NDP was 140 mg/m² in this alternating chemoradiotherapy.

In the present study, we performed concurrent chemoradiation for gynecological malignancy, administering 5-FU at a dose (700 mg/m²/d on days 1–4) and administering NDP on day 4 at a dose of 100 mg/m², by reference to prior studies.⁶,⁷ We retrospectively and historically compared the hemotoxicity of prior FN therapy with that of NF therapy for gynecological malignancy.

SUBJECTS AND METHODS

Patients

From February 2002 to November 2004, a total of 15 gynecological malignancy patients were treated with radiation therapy combined with NDP and 5-FU. Of these 15 patients, 5 were treated with NF therapy (NF Group), and 10 were treated with FN therapy (FN Group). Histological exams were conducted for all patients; there were 14 cases of squamous cell carcinoma and one of undifferentiated carcinoma. Of 15 patients, 12 were diagnosed with cervical cancers, and 3 with vaginal cancers. Patients were diagnosed in a clinical stage, according to the classification system of the International Federation of Gynecology and Obstetrics (FIGO). Eligibility requirements included an ECOG performance status 0 to 2 (Criteria of Eastern Cooperative Oncology Group), an age of less than 75 years, adequate marrow function (white blood cell count (WBC) ≥ 3,000/mm³, platelet count ≥ 100,000/mm³), a creatinine clearance greater than or equal to 60 ml/min, adequate hepatic function, and no prior treatment with radiotherapy or chemotherapy. Patient characteristics are shown in Table 1. Patients 1–4 were treated at the Toyohashi Municipal Hospital, and patient 10 was treated at the Ichinomiya Municipal Hospital. The others were treated at the Nagoya University Hospital.

Chemotherapy (Table 1)

Two different schedules using 5-FU before/after NDP-combined radiotherapy for 15 patients with gynecological malignancy were evaluated. One group received 5-FU 700 mg/m²/day intravenous (IV) continuous infusion on days 1–4 plus NDP 100 mg/m² IV bolus on day 1 (NF Group: 5 pts). The other group received 5-FU at the same dose on days 1–4 and NDP on day 4 (FN Group: 10 pts). These two schedules were started concomitantly with whole pelvic irradiation, and repeated every third week. Although NDP was administered by IV in principle, there were also cases administered by intra-arterial infusion if no lymph node metastasis occurred. Each treatment consisted of 2 courses of chemotherapy.

Radiation therapy (Table 1)

Patients with cervical cancer, except for patient 9, were treated with a combination of external irradiation and high-dose-rate (HDR) intracavitary brachytherapy (RALS). Whole pelvic irradiation was delivered using conventional anterior-posterior parallel opposed fields with 6 or 10 MV photons. The usual field is about 16×16 – 17×18 cm at the isocenter. A central shield was inserted to avoid an overdose of radiation to the bladder and rectum during intracavitary irradiation. Straight shields 4 cm wide at the axis of the beam are often used. An additional 10–20 Gy was then delivered to the pelvis until the dose reached 50 Gy. However, in patients 14 and 15, with a large field size (22 × 22 cm), whole pelvic irradiation was delivered using four fields with anterior-posterior and two lateral portals to reduce complications. HDR intracavitary irradiation was initiated in all patients after 30 Gy of external irradiation, using a Toshiba HDR...
system (NF group: patients 1–4) and a micro-selectron HDR system (NF group: patient 5; FN group: all patients except for patients 7, 10, and 12). HDR intracavitary brachytherapy was performed with a combination of a tandem and Henschke-type ovoid applicator. A single dose of 6 Gy was delivered primarily at point A once weekly. In patient 10, a very large tumor had invaded the rectum with liver metastasis; therefore, external irradiation alone was delivered.

Toxicity

Adverse events of hematologic toxicity were evaluated according to the toxicity grading criteria of Common Terminology Criteria for Adverse Events v3.0 (CTACE). In the usual case, the patients underwent a blood test once a week during the treatment, but two times per week when hematologic toxicity increased. In hematologic toxicity, the statistical significance between the FN and NF groups was obtained using Fisher’s exact test, with $p < 0.05$ considered significant.

RESULTS

**NF group**

In the NF Group, the initial dose of NDP was reduced for patients 1–4 because of 50–60 mg/min of creatinine clearance. In patient 5, Grade 3 toxicity developed in WBC and platelets after the first course; therefore, the doses for both NDP and 5-FU were reduced to 75% in the

Table 1  Clinical features in all patients

| Case No. | Age | PS | Disease | Stage | Dose (Gy) | RALS (Gy) | 5-FU (mg/m²) | NDP (mg/m²) |
|----------|-----|----|---------|-------|-----------|-----------|--------------|-------------|
| **NF Group** |     |    |         |       |           |           |              |             |
| 1        | 74  | 1  | CC      | III B | 50.4      | 18        | 700          | 50          |
| 2        | 63  | 2  | CC      | III B | 50.4      | 18        | 700          | 50          |
| 3        | 72  | 1  | CC      | II B  | 50.4      | 24        | 700          | 70          |
| 4        | 66  | 1  | CC      | III B | 50.4      | 18        | 700          | 70          |
| 5        | 66  | 1  | CC      | III B | 50.4      | 28        | 700          | 70          |
| **FN Group** |     |    |         |       |           |           |              |             |
| 6        | 66  | 1  | CC      | III B | 50.4      | 28        | 700          | 100         |
| 7        | 54  | 0  | VC      | IV A  | 60.0      | –         | 700          | 100         |
| 8        | 54  | 0  | CC      | II B  | 50.4      | 24        | 700          | 100         |
| 9        | 53  | 0  | CC      | III B | 50.4      | 15        | 700          | 100         |
| 10       | 39  | 0  | CC      | IV B  | 60.0      | –         | 700          | 100         |
| 11       | 57  | 0  | CC      | III B | 50.4      | 18        | 700          | 100         |
| 12       | 60  | 1  | VC      | II B  | 60.0      | –         | 700          | 100         |
| 13       | 68  | 1  | CC      | III B | 50.4      | 24        | 700          | 100         |
| 14       | 65  | 0  | CC      | III A | 50.4      | 24        | 700          | 100         |
| 15       | 71  | 2  | VC      | III   | 45.0      | 24        | 700          | 100         |

PS: Performance status (ECOG), CC: cervical cancer of the uterus, VC: vaginal cancer
RALS: Remote afterloading system (high-dose-rate intracavitary brachytherapy)
second course. In all cases in the NF group, irradiation was uninterrupted. Hematological toxicity is shown in Table 2.

**FN group**

Hematological toxicity is shown in Table 3. In patients 9, 12, 14, and 15, Grade 3 toxicity developed in WBC, but severe toxicity did not develop in platelets. In one case, irradiation was interrupted for 5 days due to postoperative ileus (the patient had undergone surgery for cholelithiasis), and chemotherapy was limited to one cycle (patient 15). No significant difference was detected between the FN and NF groups with regard to WBC (p=1), Hb (p=0.241758), or platelets (p=0.333333). In addition, there was no case which developed worse nephrotoxicity in this study.

**DISCUSSION**

Several randomized studies have demonstrated that concurrent chemoradiotherapy significantly improves treatment outcome compared with radiotherapy alone for patients with locally advanced uterine cervical cancer. Concurrent chemoradiotherapy is, therefore, now considered to be a standard treatment for locally advanced uterine cancer. According to the standard chemotherapy regimen in clinical practice, in a combination of cisplatin and 5-FU, cisplatin was administered on day 1. Severe hemotoxicity rates of several concurrent chemoradiation studies using NDP alone for cervical cancer are shown in Table 4. Kamiura et al. indicated that, when NDP alone was given at 70 mg/m² on days 1 and 29, none of the planned radiotherapy was postponed or discontinued due to side effects. In a dose escalation study involving 8 institutions with concurrent chemoradiation therapy using the same regimen, Hatae et al. reported that a recommended NDP dose of 80 mg/m² and that the dose-limiting toxicity indicated leukopenia (Table 4). On the other hand, in this study, the WBCs in the FN group were less toxic even though the NDP dose was 100 mg/m² and 5-FU was also administered. No significant difference was detected between the FN and NF groups with regard to WBCs in this study. However, in the NF group the dose of NDP was 50 mg/m² or 70 mg/m², in only one case that of NDP was 100 mg/m², and for this patient the doses for both NDP and 5-FU were reduced to 75% in the second course due to thrombocytopenia. Although there were few cases and no conclusion could be drawn, the toxicity of platelets showed few tendencies.

In general, the greater the dose of the anti-cancer agent, the more severe the toxicity. We performed a Phase I/II study of alternating chemoradiotherapy using FN therapy for patients with cervical cancer at Aichi Cancer Center Hospital. The recommended dose of NDP was 140 mg/m² in the alternating chemoradiotherapy. But in the present study, we performed concurrent chemoradiation for gynecological malignancy at the reduced doses for both 5-FU and NDP. Though we could not show its usefulness, the FN therapy did not increase hemotoxicity compared with NF therapy. As NDP could be given with lower hydration compared with CDDP, NDP could be used even in cases of slightly impaired renal or cardiac function. The optimal methods for the two drugs have yet to be established. A prospective study would rectify this shortcoming.

In conclusion, the statistical analysis conducted as a part of this study did not show that the FN group had less hemotoxicity than the NF group.

Conflict of Interest: None
### Table 2  Hematological toxicity in NF Group

| Case No. | WBC (Grade) | Hb (Grade) | Plts (Grade) |
|----------|-------------|------------|--------------|
| 50 mg/m² | 1           | 2          | 3            | 1            |
|          | 2           | 2          | 3            | 2            |
| 70 mg/m² | 3           | 2          | 2            | 0            |
|          | 4           | 3          | 1            | 0            |
| 100 mg/m²| 5*          | 3          | 1            | 3            |

*a*: Doses of NDP and 5-FU were reduced to 75% in 2nd course.

*b*): NCI-common toxicity criteria for adverse events (version 3.0, 2003)

### Table 3  Hematological in FN Group

| Case No. | WBC (Grade) | Hb (Grade) | Plts (Grade) |
|----------|-------------|------------|--------------|
| 100 mg/m²| 6           | 2          | 1            | 0            |
|          | 7           | 2          | 1            | 0            |
|          | 8           | 2          | 1            | 0            |
|          | 9           | 3          | 2            | 0            |
|          | 10          | 2          | 2            | 1            |
|          | 11          | 2          | 3            | 1            |
|          | 12          | 3          | 2            | 0            |
|          | 13          | 1          | 0            | 0            |
|          | 14          | 3          | 2            | 2            |
|          | 15          | 3          | 1            | 1            |

### Table 4  >= Grade 3 hematological toxicity

| Chemoradiation | WBC (%)       | Hb (%)        | Plts (%)       |
|----------------|--------------|---------------|----------------|
| 70 mg/m²       | 33.3 (4/12)  | 8.3 (1/12)    | 0 (0/12)       |
| 80 mg/m²       | 8.3 (1/12)   | 0 (0/12)      | 8.3 (1/12)     |
| *90 mg/m²      | 100 (2/2)    | 0 (0/2)       | 0 (0/2)        |
| Present study  | 40 (2/5)     | 40 (2/5)      | 20 (1/5)       |
| **FN Group     | 40 (4/10)    | 10 (1/10)     | 0 (0/10)       |

*a*): Concurrent chemoradiation therapy with Nedaplatin for high-risk cervical cancer – clinical investigation of adverse events (ref. 12)

*b*): A dose escalation study of concurrent chemoradiation therapy with Nedaplatin for cervical cancer (ref. 13)

* vs. ** not significant in WBC
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