Combination Chemotherapy Using Intravenous Nedaplatin (254-S) and Intraarterial Cisplatin (CDDP) with Transcatheter Arterial Embolization (TAE) for a Patient with Uterine Cervical Cancer: a Case Report

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A 45-year-old Japanese woman with a bulky (75 × 40 mm) stage 2a uterine cervical cancer was treated with 87 mg (50 mg/m²) of nedaplatin (254-S) intravenously and 120 mg (70 mg/m²) of cisplatin (CDDP) intraarterially with transcatheter arterial embolization (TAE). She received three courses of this combination chemotherapy and showed a complete response, as confirmed by magnetic resonance imaging. A radical hysterectomy was performed and the pathological findings revealed the absence of carcinoma cells. This type of combination chemotherapy seems to be effective for the treatment of locally advanced uterine cervical cancer.

Key words: uterine cervical cancer – intraarterial chemotherapy – nedaplatin – cisplatin – transcatheter arterial embolization

INTRODUCTION

Although radiotherapy to treat locally advanced uterine cervical cancer has now been standardized, the prognosis for these patients remains poor (1). Squamous cell carcinoma of the cervix is sensitive to radiotherapy, but bulky tumors of the cervix, especially those more than 40 mm in diameter, cannot usually be cured by radiotherapy alone (2).

There have been some reports of intraarterial chemotherapy as a neoadjuvant treatment applied to cases of locally advanced cervical cancer in order to improve the clinical response and survival duration (3,4). Intraarterial chemotherapy followed by surgery has been considered to increase the response rate and to yield survival rates longer than those obtained with radiation therapy alone (3,5). However, the rate of complete response (CR) with intraarterial chemotherapy alone is low and it is rare for patients with bulky tumors exceeding 40 mm to achieve pathological CR (3,4). We report a case of bulky cervical cancer in which pathological CR was achieved with a combination chemotherapy using intravenous nedaplatin (254-S) and intraarterial cisplatin (CDDP) with transcatheter arterial embolization (TAE).

CASE REPORT

A 45-year-old Japanese woman complaining of vaginal bleeding came to Hyogo College of Medicine in October 1996. A large vaginal tumor extending from the uterine cervix was observed and a cervical biopsy specimen revealed invasive squamous cell carcinoma of the large cell non-keratinizing type (Fig. 1). She was diagnosed as having uterine cervical cancer of FIGO stage 2a and was admitted to the College Hospital in November 1996. Laboratory studies showed an elevated squamous cell carcinoma antigen (SCC) level of 9.2 mg/ml. Other physical evaluations included computed tomography and chest radiography; both revealed no evidence of metastatic disease. Magnetic resonance imaging (MRI) showed a 75 × 40 mm uterine cervical tumor with high density (Fig. 2). We initiated a phase 1 study of combination chemotherapy using intravenous nedaplatin (254-S) and intraarterial cisplatin (CDDP) with transcatheter arterial embolization (TAE). The eligibility criteria were previously untreated locally advanced uterine cervical cancer, FIGO stage 1b or 2a with bulky disease (>4 cm), or a disease stage exceeding 2b. Her performance status (ECOG) was 0 and other physical conditions met the criteria for the phase 1 study.

Treatment was planned and initiated in November 1996. On December 2nd, 87 mg of 254-S (50 mg/m²) were administered intravenously. On December 4th, 120 mg of CDDP (70 mg/m²) were administered through both uterine arteries by Seldinger’s method and thereafter gelfoam was administered for embolization. Three weeks later, both anti-cancer agents and gelfoam
Figure 1. Microscopic features of the biopsy specimen show squamous cell carcinoma non-keratinizing type.

Figure 2. T2-weighted sagittal MRI before chemotherapy reveals a large, high signal intensity cervical mass, measuring 75 × 40 mm.

were administered at the same doses and subsequently a third course of therapy was administered 4 weeks after the second. MRI showed a complete clinical response on February 7th (Fig. 3). Tumor markers had decreased to within the normal range (SCC: 0.9 mg/ml) by February 4th. A cervical Papanicolaou smear test showed class 2 and a radical hysterectomy was performed on February 25th. Side effects of the chemotherapy were tolerable and bone marrow toxicity (ECOG) measurements were all less than grade 2. Histological findings revealed no metastases to the pelvic lymph nodes and a complete pathological response in the uterine cervix (Fig. 4). Post-operative recovery was uncomplicated and the patient was discharged from hospital on March 19th, 1997.

Figure 3. Two weeks after the third course of chemotherapy, T2-weighted sagittal MRI at the same level shows absence of the tumor.

Figure 4. Microscopic features of the surgical specimen show that the previous cancer tissues have been replaced with layers of squamous metaplastic cells and edematous tissues including lymphocytes and stromal cells. Also, there are no active cancer cells.
DISCUSSION

Many reports have suggested that radiotherapy alone cannot lead to a complete cure of bulky cervical cancers, especially those more than 40 mm in diameter (2,6), and that the surgery is superior to radiation therapy alone in the cases of stage 2 cervical cancer (7). However, radiotherapy is usually selected for the treatment of bulky tumors because radical hysterectomy is very difficult to perform in such cases. Neoadjuvant chemotherapy for locally advanced cervical cancer has been used to increase operability in patients with bulky tumors. CDDP is the most active agent for the treatment of cervical cancer and Bonomi et al. (8) showed that 100 mg/m² CDDP was able to achieve a response rate higher than that using 50 mg/m² CDDP as a neoadjuvant chemotherapy in cervical cancer.

Intraarterial chemotherapy exposes the tumor to a higher drug concentration and may be less toxic than intravenous chemotherapy. Many researchers have reported good results with intraarterial chemotherapy including a CDDP regimen for locally advanced cervical cancer (3–5,9–11). Kigawa et al. (3) have also demonstrated very good results with intraarterial chemotherapy using CDDP and bleomycin for the treatment of locally advanced cervical cancer. This treatment achieved an 80% clinical response and 72% operability and the 3 year survival of those who underwent this regimen was as high as 76%, compared with 49% in patients who received radiation therapy alone. However, after surgical resection, all specimens revealed only a pathological PR and no pathological CR was observed in their study.

To intercept the tumor blood supply, TAE therapy is usually applied to patients with hepatocellular cancer (12). This method is very appropriate from a pharmacological viewpoint and easy to apply to patients with cervical cancer when intraarterial chemotherapy is performed. Hashii et al. (10) used TAE along with intraarterial chemotherapy consisting of CDDP and mitomycin or adriamycin for the treatment of cervical cancer. They observed the pathological CR in 73% of 15 patients with cervical cancer, although four patients with stage 1b cancer were also enrolled. This finding suggested that intraarterial chemotherapy in combination with TAE might increase the pathological CR rate in patients with cervical cancer. Therefore, we included TAE in our treatment schedule.

Intraarterial chemotherapy gives good results with respect to local control, but advanced cervical cancer treated by this method is often accompanied by metastases to lymph nodes and other distant sites (13). Lymph node metastases are associated with a poor prognosis in cases of advanced cervical cancer and the efficacy of intraarterial chemotherapy for treatment of such metastases is unknown. However, we considered that intravenous chemotherapy might be pharmacologically more effective than intraarterial chemotherapy for the treatment of lymph node and distant metastases. Therefore, intravenous chemotherapy should be given in combination with intraarterial chemotherapy for the treatment of advanced cervical cancer in order to improve both the response rate and survival duration.

254-S is an analogue of CDDP and has been reported to give a very high response rate (46%) in patients with cervical cancer (14) as compared with CDDP (35%) in a phase 2 study in Japan (15). Intravenous chemotherapy with 254-S, ifosfamide and peplomycin has been shown to give a high response rate in cervical cancer (16). However, intraarterial chemotherapy with 254-S alone is not associated with a higher survival benefit than radiotherapy alone (17). On the basis of these clinical observations, we conducted a phase 1 study of combination chemotherapy using intravenous 254-S and intraarterial CDDP with TAE.

This case was the first patient entered into the study and a bulky tumor measuring 75 × 40 mm was found to disappear completely upon pathological examination. The responses of other cases to this combination chemotherapy remain to be evaluated, but the fact that pathological CR was attained in the present case suggests the potential efficacy of this treatment.

References