Phase I study of combined radiation, hyperthermia and intra-arterial carboplatin for local recurrence of cervical cancer


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Background: Patients with cervical cancer who develop pelvic recurrence after primary surgery are usually treated with radiation-based therapy. However, their prognoses are dismal. We conducted a phase I study of combined radiation, hyperthermia and intra-arterial (IA) carboplatin for local recurrence of cervical cancer.

Patients and methods: Patients with local recurrence of cervical cancer without extrapelvic recurrence were included in this study. Carboplatin was given as a 5-min IA infusion without hydration just before pelvic radiation every day. External pelvic irradiation (1.8 Gy/day for 28 days) was performed according to local standard schedules. After 20 Gy had been administered, hyperthermia was performed once a week with a radio frequency heating system for four cycles.

Results: Fifteen patients were entered through the four dose levels of carboplatin. The maximum tolerated dose was determined to be 25 mg/m² and the dose-limiting toxicities were leukocytopenia, neutrocytopenia and diarrhea. Grade 3/4 leukocytopenia and diarrhea were observed in nine (60%) and three (20%) of 15 patients. Tumor responses included five complete responses and nine partial responses, and the overall response rate was 93.3% (14 of 15) (95% confidence interval 59.4% to 100%). Tumor reductions were observed only at 20 Gy in 10 cases of 14 responders (71.4%).

Conclusion: The combination therapy of radiation, hyperthermia and IA carboplatin is safe and well-tolerated for locally recurrent cervical cancer.

Key words: carboplatin, cervical cancer, chemoradiation, hyperthermia, recurrence

Introduction

Radical hysterectomy and pelvic lymphadenectomy provide an 80–85% 5-year survival rate for early stage cervical cancer [1, 2]. Between 10% and 15% of women will have a recurrence and approximately 75% of these recurrences are limited to the pelvis [3–5]. Patients who develop pelvic recurrence after primary surgery are usually treated with radiation-based therapy. However, their prognoses are generally dismal in most cases and the reported 5-year survival rates of patients with pelvic recurrence range from 15% to 40%, and pelvic control rates from 21% to 61% [4–8]. Recently several reports demonstrated that chemoradiotherapy improved the rates of survival and progression-free survival among women with locally advanced cervical cancer [9–11]. However, there are no reports to demonstrate the benefit of adding chemotherapy to radiation for local recurrent cervical cancer compared with radiation alone. Wang et al. [12] reported that chemoradiation improved the survival of patients with locally recurrent cervical cancer; however, this report is retrospective and the number of patients is small. Essentially, the efficacy of chemoradiation and its effect on pelvic recurrence is still controversial.

For chemoradiation for cervical cancer, platinum compounds are thought to be key drugs [10]. Intra-arterial (IA) administration of chemotherapy has been shown to result in increased intratumoral concentration and local peak concentration of the drug [13, 14]. In addition, it was reported that hyperthermia enhanced the antitumor effect of carboplatin-based chemotherapy and radiation [15–18]. In this study, we conducted a phase I trial of combined radiation, hyperthermia and IA carboplatin to establish the hyperthermic chemoradiotherapy for locally recurrent cervical cancer. The primary end point was toxicity and response rate.

Patients and methods

Patient selection

Patients with local recurrence of cervical cancer without extrapelvic recurrence were included in this study. The nature and purpose of the study were fully explained to each patient. All patients signed an informed consent form approved by the institutional review boards of Osaka City General Hospital. Pretreatment evaluation included history and physical examination, evaluation of tumor extent, complete hematology and chemistry profiles, chest X-ray, intravenous pyelography, and tumor imaging by means of contrast-enhanced computed tomography (CT) of the pelvis and abdomen.
Criteria for admission were as follows: age younger than 75 years; an Eastern Cooperative Oncology Group performance status of 0–2; and no distant metastases. Patients were also required to meet all of the following laboratory criteria: white blood cell count ≥3000/mm$^3$ or absolute neutrophil count ≥1500/mm$^3$; platelet count ≥100 000/mm$^3$; serum transaminase level ≤50 IU/ml; total serum bilirubin level ≤1.5 mg/dl; serum creatinine level ≤1.5 mg/dl; and blood urea nitrogen level ≤20 mg/dl. Also deemed necessary was adequate cardiopulmonary function that could tolerate radical hysterectomy and the absence of concurrent malignancy or history of other cancer.

**Hyperthermic chemoradiotherapy regimen**

All patients received IA infusion chemotherapy using an implantable catheter port system. Using femoral artery access, the catheter made of polyurethane (Anthron P-U Catheter; Toray Medical Co. Ltd, Tokyo, Japan) was placed in the artery feeding the recurrent tumor. Each catheter was connected with an implantable port made of polyacetal and silicone (Bard MRI Port; Bard Access Systems, Salt Lake City, UT, USA), which was placed subcutaneously at the inguinal region. Pelvic arteriography was performed during catheterization procedures to assess catheter position and tumor perfusion. This procedure was performed by an experienced radiologist. Carboplatin was prepared by diluting in 10 ml saline. Carboplatin was given as a 5-min IA infusion without hydration just before pelvic radiation every day. Dose escalation was performed. The starting dosage was 10 mg/m$^2$ every day. At least three new patients were to be recruited for each dose level. If two of three patients at this level, then a maximum tolerated dose (MTD) was said to have been reached. The following dose levels were evaluated: 10, 15, 20 and 25 mg/m$^2$.

External pelvic irradiation was performed according to local standard schedules. The target volume was tumor and regional pelvic lymph nodes. External-beam radiotherapy was given in daily fractions. Twenty-eight fractions of 1.8 Gy were given to the tumor and regional pelvic nodes; fractions were administered daily except for Saturday and Sunday. After 20 Gy had been administered, the lesion was heated for 60 min with a Thermotron radio frequency (RF)-8 system (Yamamoto Vinita, Osaka, Japan) once a week for 4 weeks. Pelvic heating was performed with 30 cm electrodes operated anterior–posteriorly or laterally. After preparation, including the introduction of thermometry probes and positioning, heating was started. Patients were instructed to mention any unpleasant sensation suggestive of hot spots, such as a burning sensation, a feeling of pressure, or any pain. Any symptom that disappeared within 1 min of power decrease was taken to show that the temperature was too high. Adjustments of treatment settings included changes in power output, fitting of electrodes, application of conductive jelly to electrode surface or placement of additional water boluses. Power outputs were increased up to patients’ tolerances. During the heating process, cold water (0–5°C) was circulated in a cooling pool between the patients’ skin and the electrodes. Intratumor temperature was measured by thermometry probes. The treatment objective was the achievement of a tumor temperature ≥41°C for a period of 30 min. The heat-up time was a maximum of 60 min. If during heat-up a temperature of 41°C could not be achieved, treatment with the highest obtainable temperature was performed for 30 min. When a temperature of 41°C could not be initially achieved, streptococcal preparation (OK432, Picibanil) administration was performed for the next treatment. OK432 treatment involved intravenous administration for 15 min by diluting 5 KE in 100 ml saline before hyperthermia.

DLTs were defined as: (i) non-hematological toxicities grade 3/4 (excluding nausea, vomiting, and alopecia) and (ii) hematological toxicity grade 4 (excluding anemia). Patients who had grade 4 neutropenic toxicity were treated with granulocyte-colony-stimulating factor (G-CSF) at a dose of 5 µg/kg/day.

**Evaluation of response and toxicity**

Recurrent tumor measurements using contrast-enhanced CT were obtained at 20 and 40 Gy, completion of radiation and 1 month following the conclusion of treatment. After the treatment, CT scans were performed every 3 months for 2 years. Measurement of response was based on the product of the two largest perpendicular diameters. Criteria for tumor response were as follows: complete response (CR) was defined as the complete disappearance of all known disease with no development of new disease; partial response (PR) was defined as a ≥50% reduction of the sum of the products of measurement of new lesions. Progressive disease (PD) was defined as a ≥25% increase in the sum of the products of all indicator lesions, or reappearance of any lesion that had disappeared, or appearance of any new lesion. Stable disease was defined as any situation that did not qualify as response or progression. Measurements were performed by an experienced radiologist who was not aware of the patients’ information.

Toxicity evaluation was based on WHO criteria. Complete blood cell counts were performed at least twice weekly. Serum chemistries and liver function tests were obtained before every treatment cycle.

**Results**

**Patient characteristics**

From May 1995 to May 2000, 15 consecutive patients were admitted to the study. Patient characteristics are shown in Table 1. In all cases, 10 cases had radical surgery and regional lymphadenectomy, and five cases had simple total hysterectomy at primary surgery. Subcutaneous fat tissue of all patients was <3 cm.

**Hyperthermia**

A total of 58 cycles of hyperthermia were administered, with a median number of sessions administered per patient of four. Hyperthermia treatment was generally well-tolerated. Two patients at the 20 mg/m$^2$ dose level stopped treatment after three cycles due to diarrhea. In 11 of 15 patients, a temperature of 41°C could be achieved; however, this temperature could not be achieved in four patients despite intravenous OK432 administration. Power was applied to a maximum wattage ranging from 600 to 1200 W with a median of 900 W. Maximum tumor indicative temperatures achieved ranged from 39°C to 42°C with a mean temperature of 40.6 ± 0.9°C (median 41.0°C).

**Toxicity**

The worst toxicity observed in each patient is shown in Table 2. No DLTs were observed at the first two dose levels. DLTs were reported at dose levels 3 and 4 in three patients. These three patients required radiotherapy delay (7, 10, 14 days) and dose reductions after experiencing DLT.

**Hematological toxicity.** Leukocytopenia and neutropenia were the major hematological adverse effects. Grade 3/4 leukocytopenia or neutropenia were observed in 10 of 15 patients (66.7%). Grade 4 hematological toxicity was observed in three cases (dose level 3 one patient; level 4 two patients). However, neutropenic fever was not observed in any of the patients. Three patients received G-CSF treatment. Thrombocytopenia was mild and grade 3 thrombocytopenia was observed in one case.
Non-hematological toxicity. Diarrhea was the major non-hematological side-effect. Grade 3 diarrhea was observed in three of 15 patients (20.0%) (dose level 3 one patient; level 4 two patients). Treatment consisted of the use of loperamide treatment and supportive care with intravenous administration of fluids and electrolytes. Hematuria was observed in six cases; however, all of these cases were grade 1 or 2 (grade 1 four patients; grade 2 two patients). Nausea and vomiting were mild. No renal or liver toxicities were observed in our series.

Hyperthermia-related toxic effects. Subcutaneous burns occurred in five patients; however, discomfort disappeared spontaneously within 2 weeks. No skin burns more than grade 2 occurred in any patient. The clinical symptoms were limited to an induration in the subcutaneous fat, which was tender for 2–3 days and gradually disappeared. Finally, in the first two cases at dose level 4, DLTs occurred.

Response

All 15 patients were evaluable for response (Table 3). Five patients (33.3%) achieved a CR and nine patients achieved a PR.
One patient experienced PD. This PD case had lung metastases; however, pelvic tumor did not recur up to the time of death. Overall response rate was 93.3% (95% confidence interval 59.4% to 100%), and the response rate for tumor in the pelvic cavity was 100%. In 14 responders, PR was achieved in four cases (28.6%) at 20 Gy, in five cases (35.7%) at 40 Gy and in five cases (35.7%) at 50.4 Gy. Tumor reductions were observed at 20 Gy in 10 of 14 responders (71.4%). In all 14 responders, nine patients had recurrence with the second recurrent site present in the pelvic cavity in seven cases, in the liver in one case, and in the lung in one case. In nine second recurrent cases, seven cases received systemic chemotherapy and two cases received interstitial brachytherapy and systemic chemotherapy. In the 14 responders, the median progression-free interval was 8.9 months (range 2–55 months). In all, eight patients died and the median survival time for all patients was 22.3 months (range 7–70 months). Of the five CR cases, three cases are alive without second recurrence (34 months, 55 months, 55 months) and two cases experienced a second recurrence. One case had a second recurrence in the pelvic cavity at 8 months and died at 13 months, and another case had a second recurrence in the lung at 7 months and died at 38 months.

Discussion

There are several reports about radiation therapy for recurrent cervical carcinoma after primary surgery. Most of these studies included a small number of patients (median 37 cases, range 15–115) and took place over several years (median 11 years, range 5–30 years) [5–8, 12, 19–23]. In addition, most of them are retrospective studies [5–8, 12, 19, 21–23] and only two reports mentioned chemoradiotherapy [12, 20]. The following reasons for these study profiles are speculated: (i) the recurrence rate of early-stage cervical cancer after radical hysterectomy is low (10–15%) and most high-risk patients with lymph node metastasis or parametrical involvement usually receive radiotherapy after primary surgery; and (ii) local recurrent cervical cancer patients without history of radiation therapy are thought to be rare cases. Thomas et al. [20] demonstrated that chemoradiotherapy was useful for treating recurrent cervical cancer in a prospective study; however, their chemotherapy regimen did not include platinum compounds. Our phase I study included a small number of patients and was performed over the course of 5 years. However, this is the first prospective study of hyperthermic chemoradiotherapy including a platinum compound for local recurrent cervical cancer.

The first objectives of this study were to determine MTD, DLT and the recommended dose of carboplatin in combination with radiation and hyperthermia in recurrent cervical cancer. MTDs were defined at dose level 4 (25 mg/m²/day for 28 days). Smith et al. [24] reported that the MTD of carboplatin was 30 mg/m²/day for 21 days. Our treatment schedule was a combination of carboplatin, radiation and hyperthermia. Our data are thought to be concordant with the report of Smith et al. The most frequent hematological toxicity was leukocytopenia. Some grade of leukocytopenia was observed in 100% of patients, and 60% of patients experienced grade 3/4 leukocytopenia. The majority of patients (53.3%) experienced grade 3/4 neutropenia; however, no febrile neutropenia occurred. Anemia was frequent (86.7% of patients: grade 1, four patients; grade 2, six patients; grade 3, three patients) but 60% of patients had anemia at study entry because there were no exclusion criteria on hemoglobin value at study entry. Thrombocytopenia was mild. There were no infections. The most frequent non-hematological toxicity was diarrhea. Some grade of diarrhea was observed in 93.3% of patients, and 66.7% of patients experienced grade 2/3 diarrhea. However, diarrhea could be controlled with loperamide treatment and supportive care with intravenous administration of fluids and electrolytes. Other non-hematological toxicities were mild. Three patients required prolongation of therapy (7–14 days) and dose reductions after experiencing DLT.

It is impossible to compare the effect of this study with those of other reports, because the clinical features of treated patients in each report are different. Disease recurrence after hysterectomy is frequently categorized using a system first described by Ciatto et al. [19] as: (A) central recurrence without pelvic wall involvement, (B) recurrence involving one pelvic wall, or (C) massive pelvic recurrence with bilateral pelvic fixation. They reported that 5-year survival rates in groups A, B and C were 81%, 3% and 2%, respectively. Many reports recognized relapse pattern as a significant prognostic factor in recurrent cervical cancer [3–6, 19, 20, 23]. In addition, the prognosis of squamous cell carcinoma is thought to be better than that of adenocarcinoma [12, 22]. In this report, 14 of 15 patients had pelvic side-wall recurrence and six of 15 patients had adenocarcinoma. The patients in our series are thought to have a high risk of recurrence. Tumor reductions were

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### Table 3. Response

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Carboplatin (mg/m²)</th>
<th>No.</th>
<th>Clinical response</th>
<th>Response rate (%)</th>
<th>CR rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3</td>
<td>PR 0 SD 2 PD 1</td>
<td>66.7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>3</td>
<td>PR 0 SD 1 PD 0</td>
<td>100</td>
<td>33.3</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>7</td>
<td>PR 3 SD 4 PD 0</td>
<td>100</td>
<td>57.1</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>2</td>
<td>PR 2 SD 0 PD 0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>–</td>
<td>15</td>
<td>PR 5 SD 9 PD 0</td>
<td>93.3</td>
<td>33.3</td>
</tr>
</tbody>
</table>

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
achieved at 20 Gy in 10 of 14 responders (71.4%), and PR was obtained in four cases (28.6%) at 20 Gy. The PD case also exhibited tumor reduction in the irradiated field at 20 Gy in spite of distant metastasis. These rapid tumor reductions may be from a synergistic effect of the combined modalities (chemotherapy plus radiotherapy).

Experimental studies have shown that hyperthermia—artificial raising of the temperature to 40–45°C—is an effective method of killing cells, especially for cells in hypoxic, nutrient-deprived, and low-pH environments. The combined treatment of radiotherapy and hyperthermia increases the cytotoxic effect [25]. Van der Zee et al. [18] reported that a combined therapy of radiotherapy and hyperthermia revealed a striking therapeutic gain, with an increase in 3-year local control from 41% to 61% for locally advanced cervical cancer compared with radiotherapy alone. In our study, maximum tumor indicative temperatures ranged from 39°C to 42°C with a mean of 40.6 ± 0.9°C (median 41.0°C), falling at the low end of the hyperthermia range. Recently, it was reported that low-temperature hyperthermia was also effective [26, 27]. Van der Zee et al. [18] are planning a study of a combination of three treatments (radiation + chemotherapy + hyperthermia) for malignant tumors. This will be the first prospective report in which the combination of three therapies is examined. In this study, we performed hyperthermia only four times after 20 Gy irradiation for the following reasons. (i) To the best of our knowledge, there were no reports in which a combination of three therapies was examined. We feared that such a combination might induce severe adverse effect. (ii) We thought that hyperthermia might not be effective at the beginning of radiation treatment, because the blood flow into the tumor was too rich to achieve high temperatures at the beginning of the treatment. In addition, under these conditions, hyperthermia induces adverse effects such as distant metastasis. (iii) We thought that the permeation of carboplatin might not be enough in the latter stages of treatment, because of a decrease in blood flow into the tumor. Under these conditions, hyperthermia may be effective in achieving an adequately high temperature. It is possible that the escalation of hyperthermia may induce a stronger antitumor effect. In the next study, we should escalate the dose of hyperthermia.

This phase I study concludes that the recommended IA carboplatin dose is 20 mg/m² for three combined treatments. The combination therapy of radiation, hyperthermia and IA carboplatin is safe and well-tolerated for locally recurrent cervical cancer.

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References

