Neoadjuvant Chemotherapy with Paclitaxel Plus Platinum Followed by Radical Surgery in Early Cervical Cancer During Pregnancy: Three Case Reports

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To date, only seven women with Stage Ib1 to IIb cervical cancer during pregnancy treated with neoadjuvant chemotherapy followed by radical surgery have been reported. We describe three cases of pregnant women with Stage Ib1 to IIa cervical cancer who were treated with paclitaxel plus platinum neoadjuvant chemotherapy followed by radical surgery. The first patient had a Stage Ib1 small cell neuroendocrine carcinoma of the cervix, the second had a Stage IIa, 8 cm squamous cell carcinoma of the cervix and the third had a Stage Ib2 squamous cell carcinoma and positive lymph nodes. The three patients and their newborns were followed up. All patients had a partial or complete response to neoadjuvant chemotherapy. Two of these patients developed recurrences and one died due to progressive disease at 49 months. All neonates were healthy and had no abnormalities. In conclusion, neoadjuvant chemotherapy with paclitaxel and platinum followed by radical surgery may be an option for pregnant women with invasive cervical cancer.

Key words: cervical cancer – neoadjuvant chemotherapy – pregnancy – small cell neuroendocrine carcinoma

INTRODUCTION

The incidence of cancer during pregnancy is unclear but is estimated to be about 1 in 1000 individuals. After breast and hematological cancers, cervical cancer is one of the most commonly encountered malignancies and the most common during pregnancy (1). Despite this, there is no standard guideline for the treatment of pregnant women with cervical cancer. Neoadjuvant chemotherapy (NACT) had been administered to patients with locally advanced cancer to improve outcome (2). The advantages of NACT include the potential elimination of micrometastases, shrinkage of the primary tumor to achieve radical operability and surgical downstaging of patients (3,4), indicating that NACT may be effective for patients with locally advanced disease who refuse interruption of pregnancy. However, in patients who do not respond to NACT, the curative treatment will have been delayed. Moreover, inducing the radio-resistant clones, a chemotherapeutic drug could have cross-resistance with radiotherapy (5).

Owing to the toxicity of chemotherapeutic agents, there have been few long-term assessments of NACT followed by radical surgery in women with cervical cancer during pregnancy. In addition, several new NACT agents have been administered to patients with cervical cancer, making it difficult to draw definite conclusion. We describe here three pregnant women with cervical cancer who were treated by NACT with paclitaxel and platinum, followed by cesarean section and radical hysterectomy (RH). One of these patients had a rare case of small cell neuroendocrine carcinoma of the cervix (SCNEC) during pregnancy.

CASE REPORTS

Case 1

A 27-year-old woman at 25 + 5 weeks gestation presented with intermittent vaginal spotting, which had persisted for 3 months. Colposcopic examination revealed a 3 × 3 cm
exophytic friable mass in the cervix. Histologically, a cervical biopsy sample showed a small cell carcinoma. The tumor was classified as FIGO (International Federation of Gynecology and Obstetrics) Stage Ib1. Magnetic resonance imaging (MRI) confirmed a 2.5 × 1.0 cm cervical carcinoma and invasion of the posterior vaginal wall (Fig. 1). After extensive discussion, written informed consent was obtained to start chemotherapy. We also obtained Institutional Review Board (IRB) approval from Asan Medical Center, Korea.

NACT consisted of paclitaxel 175 mg/m² plus cisplatin 75 mg/m² administered at 26, 29 and 32 weeks gestation. After the third cycle of NACT, MRI showed a subjective decrease in tumor size.

Three weeks after the third cycle of NACT, the patient underwent a cesarean section at 35 + 5 weeks gestation, followed by type III RH with pelvic lymph node dissection (PLND) and para-aortic lymph node dissection (PALND). The infant was a 2570 g female with no signs of toxicity from chemotherapy.

Histologic examination demonstrated only focal SCNEC (4.5 mm in width and 2.0 mm in depth) with clear vaginal resection margins and negative lymph nodes. The tumor showed no lymphovascular space invasion (LVSI), and no infiltration of the parametrium. Although followed up regularly, the patient was admitted to our medical center on an emergency basis 46 months later with severe numbness of her upper and lower extremities. An MRI scan revealed an intramedullary mass at the C2–3 level, with spinal cord compression. An attempt to biopsy the lesion was unsuccessful due to its location. After consulting with our neurosurgery and radiation oncology departments, we elected radiotherapy of the tumor owing to the high morbidity rates associated with other treatment regimens. The patient therefore received emergency radiotherapy, followed by chemotherapy, but she died 3 months later. The child, however, remains well and healthy.

Case 2
A 32-year-old woman at 28 + 5 weeks gestation was referred to our department for evaluation of a cervical mass. Physical examination showed a 9 × 5 cm sized cancerous mass of the cervix, extending to the posterior vaginal fornix. Cervical biopsy confirmed an invasive squamous cell carcinoma, classified as FIGO Stage Iia. MRI showed a bulky mass involving the entire cervix without parametrial invasion. After written informed consent and IRB approval were obtained, she was started on chemotherapy with paclitaxel 175 mg/m² plus carboplatin at area under the curve 5 at 29 + 2 weeks gestation. A pelvic examination 1 month after the first cycle of NACT showed an approximate 8 cm tumor mass without vaginal involvement. However, because of recent advances in neonatal intensive care and patient’s refusal to receive additional NACT, at 33 + 3 weeks, she underwent a cesarean section followed by type III RH with PLND and PALND. The newborn was male, weighing 2190 g with no sign of toxicity from chemotherapy. Histopathologically, the lesion was found to be a poorly differentiated squamous cell carcinoma, 8.0 × 5.0 × 2.0 cm in size, with negative lymph nodes (Fig. 2). The tumor showed LVSI, but no infiltration of the parametrium or vaginal cuff with clear resection margins. Owing to the presence of two intermediate risk factors (large tumor size and LVSI), the patient was offered adjuvant treatment, but she refused. Unfortunately, 32 months after the surgery, the patient returned to our medical center complaining of a left flank pain. Computed tomography revealed a 7 cm recurrent tumor in the left pelvic cavity, accompanied by hydronephrosis. At last follow-up, the patient underwent left ureteral stent placement and is receiving chemoradiation therapy. Forty-eight months after the primary treatment, the child is developing normally.

Case 3
A 27-year-old woman presented with a FIGO Stage Ib2 squamous cell cervical carcinoma, 5 cm diameter, diagnosed at 28 + 4 weeks of gestation. MRI showed a 5 cm tumor with no infiltration of the parametrium or vagina. The patient refused to terminate the pregnancy and instead elected NACT with pregnancy preservation. After extensive and meticulous counseling, written informed consent and IRB approval were obtained. She was started on paclitaxel 175 mg/m² plus cisplatin 75 mg/m² at 30 + 4 weeks, with a second cycle started at 33 + 4 weeks. MRI assessment after the second cycle revealed a partial response. She underwent
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a cesarean section at 36 + 5 weeks, followed by type III RH, PLND and PALND. The infant was a male, weighing 2600 g with no abnormality. Histologic examination showed that it was a 4.0 × 3.0 × 1.7 cm invasive squamous cell carcinoma. The tumor showed LVSI, no infiltration of the parametrium and clear resection margins. A metastasis was found in one left external iliac nodes. The patient recovered well and received four further cycles of chemotherapy as above. Five years later, the patient remains free of disease, and her child is developing normally.

DISCUSSION

Owing to the rarity of cervical cancer associated with pregnancy, definitive management guidelines for these patients remain unclear. Treatment depends on whether the patient desires to continue her pregnancy, as well as on the stage of the disease and gestational age at diagnosis (6). Because NACT significantly reduces cervical tumor bulk and increases operability, therapeutic options including NACT may be of particular value during pregnancy (7). For example, partial responses to NACT were observed in two pregnant women, indicating a positive impact on the time allowed for fetal viability, with no severe maternal and fetal effects (8).

There are only seven reports of pregnant women with Stage Ib1 to Ib2 cervical cancer treated with NACT followed by radical surgery (Table 1) (6–11). Platinum-based NACT was generally well tolerated and was not associated with toxicities to the newborn or mother (6–11). Including the patients described in this report, 9 of these 10 patients had a partial or complete response to NACT. Chemotherapy plays an important role in the treatment of cancer in pregnancy, but its potential toxicity for the developing fetus must be considered (12). Chemotherapy during the second and third trimesters has been shown to result in a malformation rate of 1.3% and intrauterine growth restrictions (1,13). Additionally, in pregnant women with cervical cancer, planned delay of treatment without NACT to achieve fetal maturity is a reasonable option, in particular for patients with early-stage disease (14). In non-responders, delayed treatment option can be chosen in selected patients because the patient was approaching the term when the fetus will have been considered ‘viable’. However, the level of toxicity is generally considered acceptable when chemotherapeutic drugs are administered after the second trimester because the incidence of malformation is similar to that in the general population (11).

There have been no previous reports about the use of paclitaxel plus platinum chemotherapy in cervical cancer during pregnancy. In general, however, NACT with the combination of paclitaxel and platinum has demonstrated significant activity in cervical cancer patients, with response rates between 40% and 50% (15,16). NACT with paclitaxel plus platinum followed by RH has been found to improve pathologic prognostic factors, reducing the incidence of adjuvant radiotherapy, without worsening the prognosis of patients with locally advanced cervix cancer (17). Case reports of women who received paclitaxel and platinum chemotherapy for epithelial ovarian cancer during pregnancy reported no complications (18,19). The routine use of paclitaxel in pregnant women was not recommended because of the lack of data. Teratogenic effects on fetus have been described for paclitaxel in animal. In rats, paclitaxel use during early pregnancy can cause cranio-facial malformations, diaphragmatic hernias, and renal and cardiovascular systemic malformation. However, the use of the agents seems safe after organogenesis (20,21). At follow-up intervals of 48–60 months, none of the children born to these mothers showed any evidence of metabolic, hematologic, nephrologic or neurologic abnormalities.

Unfortunately, out of three patients, two developed tumor recurrences and one died of disease at 49 months. One of our patients (Case 1) had an SCNEC, a rare malignancy that is present in <5% of patients with cervical cancer and is characterized by frequent and early metastases, resulting in a poor prognosis (22). However, the optimal treatment modality for this tumor type is unclear. One patient, diagnosed with SCNEC at 10 weeks of gestation, was treated with a single course of cisplatin preoperatively, followed by radical surgery and postoperative radiotherapy; this patient, however, developed widespread metastases and died 24 months after diagnosis (23). Moreover, the overall 2- and 5-year survival rates for patients with SCNEC have been reported to be 43% and 29%, respectively (22). Although our patient with SCNEC did not receive any adjuvant treatment, she was disease-free for 43 months. Considering the poor prognosis of SCNEC, NACT with paclitaxel plus platinum followed by radical surgery may be an option in selected patients with invasive SCNEC during pregnancy. However, it is likely that adjuvant treatment would increase survival.

There is no clear consensus regarding postoperative adjuvant chemotherapy after initial NACT. Postoperative adjuvant chemotherapy alone instead of adjuvant radiotherapy may reduce the risk of recurrence (6). We found that adjuvant chemotherapy after NACT plus radical surgery might reduce the risk of recurrence and prolonged survival in two of our patients (Cases 2 and 3).

For patients with early cervical cancer who wish to preserve their fertility, treatment with NACT prior to radical trachelectomy may be helpful. The use of NACT followed by a radical trachelectomy with bulky Stage IB1 cervical cancer also been reported (24). However, long-term results are needed before conclusions.

In conclusion, our results indicate that NACT with paclitaxel and platinum followed by radical surgery may be an option for pregnant women with invasive cervical cancer. Although it is difficult to draw conclusions in patients with SCNEC or high-risk disease, adjuvant chemotherapy after NACT plus radical surgery may improve overall survival and progression-free survival. Identification of optional treatment
Table 1. Cervical cancer in pregnancy treated with neoadjuvant chemotherapy followed by radical surgery: literature review

<table>
<thead>
<tr>
<th>Author</th>
<th>FIGO stage</th>
<th>Pathology</th>
<th>GA at diagnosis (weeks)</th>
<th>Treatment</th>
<th>No. of courses</th>
<th>Tumor response to NACT</th>
<th>Type of surgery</th>
<th>Adjuvant therapy</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
<th>Mother</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bader et al. (6)</td>
<td>IIa</td>
<td>Sq</td>
<td>19</td>
<td>P 50 mg/m², V 1 mg/m²</td>
<td>4</td>
<td>PR</td>
<td>C/S + RH + PLND</td>
<td></td>
<td>P 50 mg/m², V 1 mg/m², B 25 mg/m² every 10 days × 3</td>
<td>80</td>
<td>NED</td>
<td>Normal</td>
</tr>
<tr>
<td>Caluwaerts et al. (7)</td>
<td>Ib1</td>
<td>Sq</td>
<td>15</td>
<td>P 75 mg/m²</td>
<td>6</td>
<td>PR</td>
<td>C/S + RH + PLND + PALND</td>
<td>None</td>
<td></td>
<td>10</td>
<td>NED</td>
<td>Normal</td>
</tr>
<tr>
<td>Tewari et al. (8)</td>
<td>IIa</td>
<td>Sq</td>
<td>20</td>
<td>P 50 mg/m², V 1 mg/m²</td>
<td>6</td>
<td>PR</td>
<td>C/S + RH + PLND</td>
<td>External beam radiation therapy</td>
<td>5</td>
<td>DOD</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ib2</td>
<td>Sq</td>
<td>21</td>
<td>P 50 mg/m², V 1 mg/m²</td>
<td>4</td>
<td>PR</td>
<td>C/S + RH + PLND</td>
<td>None</td>
<td></td>
<td>24</td>
<td>NED</td>
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<tr>
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<td>Ib1</td>
<td>Sq</td>
<td>17</td>
<td>P 75 mg/m²</td>
<td>3</td>
<td>CR</td>
<td>C/S + RH + PLND + PALND</td>
<td>None</td>
<td></td>
<td>12</td>
<td>NED</td>
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<tr>
<td>Palaia et al. (10)</td>
<td>IIb</td>
<td>Sq</td>
<td>19</td>
<td>P 75 mg/m², T 175 mg/m²</td>
<td>3</td>
<td>PR</td>
<td>C/S + RH + PLND</td>
<td>None</td>
<td></td>
<td>10</td>
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<td>Normal</td>
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<tr>
<td>Karam et al. (11)</td>
<td>Ib2</td>
<td>Sq</td>
<td>23</td>
<td>P 40 mg/m², weekly</td>
<td>7</td>
<td>NR</td>
<td>C/S + RH + PLND + PALND</td>
<td>Chemoradiation therapy</td>
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<tr>
<td>Present cases</td>
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<td>Ne</td>
<td>25</td>
<td>P 75 mg/m², T 175 mg/m²</td>
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<td>PR</td>
<td>C/S + RH + PLND + PALND</td>
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<td>49</td>
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<tr>
<td></td>
<td>IIa</td>
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<td>28</td>
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<td>PR</td>
<td>C/S + RH + PLND + PALND</td>
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<td>AWD</td>
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<tr>
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<td>28</td>
<td>P 75 mg/m², T 175 mg/m²</td>
<td>2</td>
<td>PR</td>
<td>C/S + RH + PLND + PALND</td>
<td>P 75 mg/m², T 175 mg/m² every 3 weeks × 4</td>
<td>60</td>
<td>NED</td>
<td>Normal</td>
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</table>

FIGO, International Federation of Gynecology and Obstetrics; GA, gestational age; NACT, neoadjuvant chemotherapy; Sq, squamous; P, cisplatin; V, vincristine; PR, partial response; C/S, cesarean section; RH, radical hysterectomy; PLND, pelvic lymph node dissection; B, bleomycin; NED, no evidence of disease; PALND, para-aortic lymph node dissection; DOD, dead of disease; CR, complete response; T, paclitaxel; NR, no response; Ne, neuroendocrine; C, carboplatin; AUC, area under the curve; AWD, alive with disease.
regimens requires further reports of patients with cervical cancer during pregnancy.

**Conflict of interest statement**

None declared.

**References**


