Anti-Cancer Drugs 1999, **10**, pp. 641–646

Clinical study

Phase II trial of neoadjuvant chemotherapy in early-stage small cell cervical cancer

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Clinical complete response (CR) to chemotherapy is not uncommon in small cell carcinoma. To understand its pathologic response, we conducted a phase II trial with neoadjuvant chemotherapy followed by hysterectomy in patients with small cell cervical cancer and reviewed all reported cases receiving neoadjuvant chemotherapy followed by hysterectomy through a MEDLINE search. From December 1993 to December 1997, the enrolled patients were treated with two to three courses of vincristine, adriamycin and cyclophosphamide alternating with cisplatin and etoposide (VAC/PE) before hysterectomy. Another three courses of chemotherapy were added after surgery. A total of seven patients was enrolled. Clinical CR was observed in six patients, but microscopic residual tumor was present in all. Lymphatic permeation, scattered residual tumor clusters and residual superficial invasive adenocarcinoma over the cervix presented in five cases, and another had a metastatic pelvic node with no residual cervical tumor. Three of these seven patients have been alive with no evidence of disease for 16.2, 45.2 and 56.6 months, respectively. The other four died from disease 10.3–23.6 months after diagnosis. These findings indicate the discrepancy between clinical and pathologic responses in small cell cervical cancer after chemotherapy and emphasize the necessity of local treatment. [© 1999 Lippincott Williams & Wilkins.]

Key words: Cervical neoplasms, hysterectomy, neoadjuvant chemotherapy, small cell carcinoma.

Introduction

Small cell carcinoma of the uterine cervix was first reported to be associated with a poor prognosis in 1959[1,2] and was described as a new tumor entity in 1976.[3,4] Histologically, it is characterized by densely packed, uniform, small, oval cells with hyperchromatic nuclei and scanty cytoplasm, identical to pulmonary small cell undifferentiated carcinoma.[5] A high mitotic rate, aneuploidy and diffuse lymph-vascular infiltration with a high frequency of lymph node metastasis are common in most tumors.[6–10] Small cell cervical cancer is an aggressive tumor with a propensity for rapid distant recurrence and a high mortality rate.[11–13] Patients with small cell cervical cancers treated as cervical cancers of common histologic types have a median survival of 10.5–13 months.[5,13,14] Because small cell cervical cancers and small cell lung cancers (SCLC) have indistinguishable histological and similar clinical features, chemotherapeutic regimens for SCLC have been advocated for small cell cervical cancer. Standard regimens for SCLC include a combination of cisplatin and etoposide (PE), a combination of vincristine, adriamycin and cyclophosphamide (VAC), and alternating VAC and PE (VAC/PE) with no difference in their efficacy.[15–17]

Neoadjuvant chemotherapies involving two to three courses of cisplatin-based regimens prior to surgery are effective in reducing tumor size and in providing better circumstances for surgical removal of early-stage bulky cervical tumors of common histologic types. A lower than expected incidence of lymph node metastasis was also noted in patients who received neoadjuvant chemotherapy.[18–22] As a result of the rarity of small cell cervical cancer, the role of neoadjuvant chemotherapy has not yet been defined.

Up to July 1998, 68 cases of small cell cervical cancer treated with chemotherapy had been reported

Part of this manuscript was presented at the First Annual Terry Fox and Chang Gung Memorial Hospital International Cancer Symposium on Cervical Cancer, Taipei, Taiwan, 16–18 October, 1997. Supported in part by grant NSC 86-2314-B182A-056 from the National Science Council, Executive Yuan, Taiwan, and grant NMRP87-6(H) from Chang Gung Memorial Hospital.

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in the English literature,[5,13,23-37] but only five[29,33,34,38] patients had received neoadjuvant chemotherapy, followed by hysterectomy and had available information on the pathologic response to the chemotherapy. The others were treated with chemotherapy alone, chemotherapy with radiation or surgery followed by adjuvant chemotherapy.

In order to understand the efficacy of chemotherapy on untreated small cell cervical cancer, we conducted a phase II trial to administer two to three courses of neoadjuvant chemotherapy before hysterectomy. We also retrieved all the cases treated with neoadjuvant chemotherapy and followed by hysterectomy for small cell cervical cancer reported in the English literature through a MEDLINE search from 1976 to October 1998 for review.

Materials and methods

Eligible patients were those age over 18 years and had an untreated, small cell undifferentiated carcinoma of the uterine cervix of FIGO[39] stage Ib-IIa. The definition of small cell carcinoma was adopted from the World Health Organization (WHO) and the International Association for the Study of Lung Cancer (IASLC) criteria for small cell lung cancer.[40,41] Histologically, the tumor consists of small, rather uniform cells with scanty cytoplasm and with centrally located nuclei containing finely dispersed chromatin and inconspicuous nucleoli. All histologic slides were reviewed by one of the authors (SH) before chemotherapy. The patients should have no medical or other contraindications to radical hysterectomy. Patients should also have adequate marrow, renal and hepatic function before chemotherapy: hemoglobin $\geqslant 10$ g/dl, white blood cell (WBC) count $\geqslant$ 3000/mm^3, platelet count $\geqslant 100\,000$/mm^3, serum creatinine $\leqslant 1.5$ mg/dl, serum bilirubin $\leqslant 2.0$ mg/dl, serum glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and alkaline phosphatase $\leqslant 2$ times the upper limits of normal, and an Eastern Cooperative Oncology Group (ECOG)[42] performance status of 0 to 2 (asymptomatic to symptomatic in bed less than 50% of the day) before treatment. Computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis were performed, and used only as a reference of disease status and not for determining stage and treatment. Written informed consent regarding the experimental nature of the study and the possible toxicities was required. Patients with uncontrolled infection, those with concurrent medical conditions unrelated to the malignancy which would impose an unacceptable risk of treatment to the patient, those who had received chemotherapy or radiotherapy for other malignancies and those with allergic reactions to the scheduled chemotherapy were excluded from the study. This study protocol was approved by the Institutional Committee of Human experiment and Medical Ethics.

The VAC regimen consisted of vincristine 1.0 mg/m^2 up to 2 mg maximum i.v. bolus, adriamycin 40 mg/m^2 i.v. infusion and cyclophosphamide 1000mg/m^2 i.v. bolus within 1 day. The PE regimen was a combination of cisplatin 100 mg/m^2 i.v. infusion on day 1 and etoposide 100 mg/m^2 i.v. infusion on days 1-3. Pre- and post-cisplatin hydration with normal saline and osmotic diuresis with 300 ml of 20% mannitol immediately after cisplatin were administered for renal protection, and dexamethasone and a 5-HT_3 antagonist were given for emesis prevention. The VAC/PE was the alternating schedule of VAC and PE. Chemotherapy was repeated every 21 days if the patient's laboratory data and performance score permitted. Chemotherapy was delayed if any of the aforementioned criteria was not met, repeated blood checks were undertaken at least every 7 days and dose reductions of 20% for all agents were required if grade IV neutropenia (<500/mm^3) or grade III thrombocytopenia (25 000-49 999/mm^3) occurred. Patients were withdrawn from neoadjuvant chemotherapy and underwent hysterectomy if there was a greater than 2 week delay in chemotherapy.

Clinically complete response (CR) was defined as complete disappearance of all evaluable disease by pelvic examination and/or image study before hysterectomy. Partial response (PR) was a greater than 50% decrease of the product of the greatest length and greatest perpendicular width of the cervical tumor, and no appearance of new lesions during treatment. Progressive disease (PD) was a more than 25% increase in the product of the greatest length and greatest perpendicular width of the cervical tumor, appearance of a new lesion or significant worsening of condition presumed to be related to malignancy. Stable disease (SD) was defined as the state of response which was less than PR or PD. Histological CR was defined as no residual tumor in all of the surgical specimens and PR was defined as the presence of tumor either in the cervix or in other tissues among patients with clinical CR or PR.

The patient was treated with VAC/PE up to three cycles to achieve a clinical complete remission, followed by radical hysterectomy and pelvic lymph node dissection. The surgical specimen was then used for the evaluation of pathologic response. Adjuvant therapy after surgery was administered according to the attending physician's decision and a total of six

cycles of chemotherapy, including the neoadjuvant therapy, was recommended. The end points of observation were tumor response to neoadjuvant chemotherapy and patients' survival. Survival was calculated from the initial diagnosis of cervical cancer.

Results

From December 1993 to December 1997, seven patients were enrolled in this study (Table 1, patients 1–7). Six had FIGO stage Ib disease and one patient with stage IIa disease presented with liver metastasis on CT that was confirmed by liver biopsy. The mean age of these seven patients was 41 years (range 35–56 years).

Case 1 presented with a cervical tumor measuring 5 × 4 cm. After two cycles of neoadjuvant therapy, there was no gross tumor, but yellowish pigmentation in part of the cervical stroma was noted. Microscopically, it was seen that the cervical stroma was diffusely infiltrated by foamy histiocytes, and clusters of residual tumor cells were scattered throughout the cervix and in the lymphovascular space (Figure 1). There were two metastatic lymph nodes, one over the left lower pelvis and one in the left parametrium, and both nodes were less than 1 m in size. Case 2 had a clinical CR and no residual small cell carcinoma, but adenocarcinoma *in situ* and a focus of superficially invasive adenocarcinoma over the cervical canal. Case 3 initially presented with a 3 × 2.5 cm cervical tumor with vaginal fornix extension. CT showed multiple low-density hepatic nodules and the biopsy from one of these nodules showed metastatic small cell carcinoma. During neoadjuvant therapy, she also received whole liver irradiation to 1800 cGy. At hysterectomy, excision of the residual lesions over the liver surface was also undertaken and ultrasonography taken during surgery confirmed no intra-hepatic tumor. There was no grossly visible tumor over the cervix. Microscopically, residual tumor clusters were present in up to 50% of the cervical wall thickness and prominent lymphatic permeation in the full thickness of the cervical stroma was noted. She received adjuvant chemotherapy after surgery, had hepatic and para-aortic lymph node relapses 18 months after diagnosis, and died of disease 5.6 months after relapse despite salvage chemotherapy. Cases 4 and 6 also showed prominent lymphovascular space infiltration and scattered residual tumors, and died from distant metastases (case 4, liver and lung; case 6, liver metastases). Case 5 initially presented with a 3 cm protruding, cervical myoma-like tumor which was excised through a vaginal approach. There was no residual cervical tumor in the hysterectomy specimen, but a metastatic pelvic lymph node was present. Case 7 also had clinical complete tumor regression after chemotherapy. Histologically, there were superficial small cell carcinoma and adenosquamous carcinoma over the cervix, and no lymph node metastasis. She had generalized malaise 7 months after diagnosis and

Table 1. Patient characteristics, treatments and tumor response to neoadjuvant chemotherapy

Patient no. or investigator	Age at diagnosis	Stage	Tumor size (cm)	Neoadjuvant therapy	Clinical/ pathologic response	Adjuvant therapy after RAH	Survival status	Follow-up[a] (months)
1	38	Ib2	5 × 4	VAC/PE × 2	CR/PR	VAC/PE × 4	NED	56.6
2	36	Ib	3.5 × 3	VAC/PE × 3	CR/PR	VAC/PE × 3	NED	45.2
3	44	IIa	3 × 2.5	PE × 3+liver R/T	CR/PR	(CARBO+VP-16) × 2, (Taxol+CARBO) × 2	DOD	23.6
4	40	Ib	3.5 × 3	PE × 2	CR/PR	PE × 2	DOD	9.7
5	37	Ib	3 × 3	PE × 2	CR/PR[b]	pelvic R/T	NED	18.2
6	56	Ib	1.5 × 1	VAC/PE × 3	PR/PR	VAC/PE × 3	DOD	17.4
7	35	Ib	2.5 × 2	VAC/PE × 3	CR/PR	VAC/PE × 3	DOD	10.3
Jacobs	25	Ib	3 × 3	cisplatin	SD	pelvic R/T	DOD	18
Lewandowski	44	IIa	7 × 5	PAE × 3	CR/PR	PAE × 1, pelvic R/T, oral VP-16	NED	14
Lewandowski	57	IIb	10	PAE × 2	CR/CR	oral VP-16 for 10 m	NED	12
Tabbara	54	Ib	–	POMACE	CR/CR	–	NED	15
Abulafia	39	Ib	3 × 2	(CTX, VP-16, VCR) × 1	SD	PE × 3	NED	61

CARBO, carboplatin; CR, complete response; CTX, cyclophosphamide; DOD, died of diease; NED, no evidence of disease; PAE, cisplatin, doxorubicin and etoposide; POMACE, cisplatin, vincristine, methotrexate, doxorubicin, cyclosphosphamide, etoposide; PR, partial response; RAH, radical abdominal hysterectomy; R/T, radiation therapy; SD, stable disease; VCR, vincristine; VP-16, etoposide.

[a]Starting from the time of diagnosis.

[b]No residual tumor over the cervix, but a metastatic focus over one pelvic node.

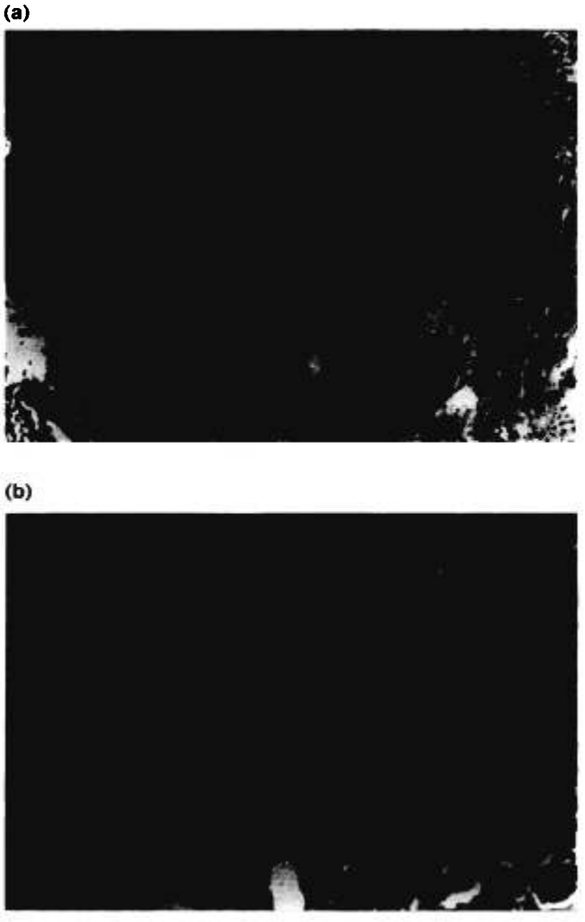

Figure 1. Clusters of residual tumor in the stroma (a and b, right) and in lymphovascular space (b, center) of a small cell cervical cancer after neoadjuvant chemotherapy, which showed clinical CR. The cervical epithelium (a, left lower) is intact.

multiple hepatic metastatic tumors were disclosed by CT, which were not present before treatment. Pulmonary metastasis developed rapidly thereafter and she was dead of disease with no evidence of pelvic recurrence.

A clinical CR was observed in six of our seven patients after two to three courses of therapy; however, there was no pathological complete response in any patient. Lymphatic permeation and scattered residual tumors over the cervical stroma were present in four cases, and residual superficial invasive carcinoma was seen in another two (cases 2 and 7). The other (case 5) showed no residual cervical tumor but had a metastatic pelvic node.

Amongst the five cases from the literature (Table 1), two patients who received one course each of neoadjuvant therapy showed SD. One had several metastatic pelvic nodes,[38] and another had perineural and lymphovascular invasion in the cervix.[34] Clinical CR was observed in the other three patients, including a 57-year-old patient with a 10 cm cervical tumor and multifocal para-aortic lymphadenopathy on CT. Two of these three patients also showed pathological CR and one 44-year-old patient had a residual, microscopic focus of submucosal tumor over the cervix.

Three of our study patients and four of previous reported cases were alive at their last follow-up. Their median follow-up was 18.2 months (range 12-61 months). Those who died of disease were dead 2 years after initial diagnosis (range 9.7-23.6 months) and all presented with distant metastases (cases 3, 4 and 7, lung and liver metastases; case 6, liver metastasis; and one reported by Jacobs, disseminated metastasis).

Toxicity of the neoadjuvant therapy was generally tolerable, and there was no grade III toxicity. Grade II nausea, vomiting and leukopenia were observed in three, three and one of our seven patients, respectively.

Discussion

Neoadjuvant chemotherapy has been used in the management of cervical cancer of common histologic types.[19,43-45] In early stage (FIGO stage I-II) bulky (4 cm or larger) tumors, two to three courses of cisplatin-based therapy resulted in a higher than 80% response rate, around 20% clinical CR and a 4-6% pathologic CR. However, the role of neoadjuvant chemotherapy in the treatment of small cell cervical cancer has not yet been determined.

Small cell carcinoma may arise from many organs,[46] while the lung is the most common site and accounts for 20% of all lung cancers. Small cell cervical cancer and small cell lung cancer are histologically indistinguishable, and both show a propensity for distant dissemination even in early stage disease. Therefore, chemotherapy for small cell lung cancer has been advocated for small cell cervical cancer.

In this prospective trial, we tested the efficacy of neoadjuvant chemotherapy on seven patients with early stage small cell cervical cancer, and compared the clinical and pathologic responses. It was noticed that six cases showed gross complete disappearance of their cervical tumor, but none had pathologic CR. Lymphovascular infiltration, scattered clusters of tumor cells in the cervical stroma, superficial residual tumor or lymph node metastasis were present in all patients.

Although more courses of chemotherapy might probably eradicate the residual tumor, it is unknown

whether more chemotherapy alone, instead of hysterectomy after two or three courses of therapy, will benefit these patients. Experience from small cell lung cancer showed that chemotherapy for more than 4 months is not effective. Furthermore, the accumulative toxicity of chemotherapy may limit the use of adjuvant therapy after surgery. It is also unknown whether neoadjuvant chemotherapy followed by radical hysterectomy or hysterectomy followed by adjuvant chemotherapy may provide a better treatment result in patients with early-stage small cell cervical cancer. A multi-centered randomized trial with sufficient case numbers is needed to answer this question. However, according to earlier trials on early stage small cell cervical cancer treated in our institute that showed 10 of the 14 patients who received hysterectomy followed by adjuvant VAC/PE survived with a median follow-up of 41 months,[37] hysterectomy followed by adjuvant chemotherapy seems to be a better treatment modality based on this histological comparison.

Conclusion

This study indicates the discrepancy between clinical and pathologic responses in small cell cervical cancer after chemotherapy, which also provides a valuable reference in estimating the treatment response of small cell carcinoma of other organs that direct visualization during therapy is nearly impossible and surgery is seldom undertaken.

Acknowledgments

We thank Dr Jacqueline Ming Liu, Cancer Research Center, National Health Research Institutes, for her assistance in English editing and recommendations.

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(Received 21 January 1999; revised form accepted 23 March 1999)