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Effects and toxicity of neoadjuvant chemotherapy preoperative followed by adjuvant chemoradiation in small cell neuroendocrine cervical carcinoma

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Summary

Objective: To determine the efficacy and toxicity of a combined–modality regimen of neoadjuvant chemotherapy (NACT) before primary radical surgery followed by adjuvant chemoradiation in small cell neuroendocrine cervical cancer (SCNEC) patients. *Materials and Methods:* The study was approved by the ethics committee of the present hospital. The records of 23 SCNEC patients who received NACT before primary radical surgery were reviewed at the Zhejiang Cancer Hospital between January 1998 and May 2010. All patients received one to four cycles of NACT and two to eight cycles of chemotherapy (NACT and adjuvant chemotherapy) on the basis of platinum, 17 (73.9%) patients received NACT using a regimen consisting of etoposide and cisplatin (EP). Eighteen (85.7%) patients received adjuvant chemotherapy using a regimen consisting of PE and EP. Kaplan-Meier and Cox regression methods were used for analyses. *Results:* Of the 23 eligible patients, 18 had Stages I-IIA, five had Stages IIB- IIIB disease. Twelve patients (52.2%) developed grade 3 and 4 neutropenia. Fourteen patients (60.9%) developed grade 3 and 4 anemia. The majority of grade 3 and 4 neutropenia and non-hematologic toxicities were usually self-limited. Three patients (13.0%) who postoperative pathology showed pathologic complete response (CR) had better prognosis than those did not show pathologic CR; the median survival was 69.5 months (range, 51.1–177.1), 54.5 months (range: 7.3–81.5), respectively. In univariate analysis, lymphovascular space invasion (LSI) ($p = 0.013$), and deep stromal invasion (DSI) ($p = 0.001$) were considered poor prognostic factors. With a median follow-up for surviving patients was 40.8 months (range, 7–177), 12 patients recurred, 11 of which had died. The estimated three- and five-year overall survival (OS) rates for all patients were 55.8% and 39.9%, respectively. *Conclusion:* NACT before primary radical surgery followed by adjuvant chemoradiation or chemotherapy was well tolerated and seems to be effective for early stage SCNEC patients. Prospective clinical study is necessary and we hope that this research's results help to design a prospective clinical study.

Key words: Neuroendocrine carcinoma; Neoadjuvant chemotherapy; Small cell; Uterine cervix.

Introduction

Small cell neuroendocrine carcinoma of the uterine cervix (SCNEC) is a rare gynecologic malignancy that represents less than 3% of all cervical cancer [1-3]. The histology and biologic behaviors of the tumor are similar to that of small cell lung carcinoma (SCLC), which is highly aggressive. The tumor is characterized by a high incidence of early distant metastases, resulting in poorer prognosis than other subtypes of cervical cancer [3-5]. Due to its rarity studies exploring therapeutic efficacy in this setting generally require long enrollment period to obtain a sufficient number of cases. Therefore, to date most studies of neuroendocrine cervical cancer are comprised of a small series and case reports, making it difficult to draw conclusions on prognostic factors and optional treatment modalities.

Given the aggressive nature of neuroendocrine small cell cervical cancer, it is imperative to identify potential treatments that can improve the outcomes of these patients. The present authors therefore adopted a protocol of neoadjuvant chemotherapy (NACT) most of patients using the etoposide plus cisplatin (EP) regimen in an effort to improve outcomes at the present center.

In this study, we evaluated the efficacy and safety of NACT with EP before radical hysterectomy (RH) follow adjuvant chemoradiation or chemotherapy for Stage I-IIIB SCNEC.

Materials and Methods

Eligibility

Patients from Zhejiang Cancer Hospital from January 1997 to December 2010 for clinical Stage I- IIIB SCNEC. Patients were eligible if they had histologically confirmed small cell carcinoma in the cervix. Of the 23 patients with available paraffin blocks who were diagnosed as having small cell carcinoma on the basis of hematoxylin and eosin (H&E) staining, all had positive staining for one or more neuroendocrine markers. All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system for cervical cancer based on physical examination, chest X-ray, in-

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Table 1. — *Patient characteristics.*

N		23
Age (y)	Median	39
	Range	25-65
Stage	IB1	6
	IB2	4
	IIA	8
	IIB	3
	IIIA	1
	IIIB	1
Histological homology	Pure	16
	Mixed	7
Tumor size (cm)	≤ 4	9
	> 4	14
LNI	No	15
	Yes	8
LSI	No	14
	Yes	9
DSI	≤ 2/3	14
	> 2/3	9
Primary treatment	NACT+RH+RT	2
	NACT+RH+CT	9
	NACT+RH+(CT+RT) / CCRT	12
NACT regimen	EP	17
	TP	4
	BVP	1
	IEP	1
CT regimen	EP	18
	TP	2
	EAP	1
Recurrence	IB1	2 (2/6)
	IB2	2 (2/4)
	IIA	4 (4/8)
	IIB	2 (2/3)
	III	2 (2/2)

NACT: neoadjuvant chemotherapy; RT: radiation; CT: chemotherapy; CCRT: concurrent chemoradiation. RH: radical hysterectomy; LNI: lymph node involvement; LSI: lymphovascular space invasion; DSI: depth of stromal invasion.

Table 2. — *Demographic and treatment factors with associated five-year OS.*

Variables	n	5-year OS	*p* value
Age at diagnosis (years)			0.677
≤ 40	13	46.2%	
> 40	10	60.0%	
Stage			0.174
I-IIA	18	66.7%	
IIB-IIIB	5	0.0%	
Tumor size (cm)			0.196
≤ 4	8	75.0%	
> 4	15	42.7%	
LNI			0.169
No	15	61.1%	
Yes	8	37.5%	
LSI			0.005
No	14	78.6%	
Yes	9	0.0%	
DSI			0.001
≤ 2/3	14	85.7%	
> 2/3	9	0.0%	
Histological homology			0.502
Pure	16	48.2%	
Mixed	7	71.0%	

LNI: lymph node involvement; LSI: lymphovascular space invasion; DSI: depth of stromal invasion.

travenous paleography, cystoscopy, sigmoidoscopy, and abdomino-pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scan. When there were suspicious findings on chest X-ray or the presence of signs and symptoms upon physical examination, a CT scan of the chest and/or brain was carried out.

Treatment

All patients received one to four cycles of NACT and two to eight cycles containing cisplatin (NACT and adjuvant chemotherapy), 17 (73.9%) patients received NACT using a regimen consisting of EP. Eighteen (85.7%) patients received adjuvant chemotherapy using a regimen consisting of EP. Other chemotherapy regimens including paclitaxel and cisplatin (TP), bleomycin vincristine and cisplatin (BVP), doxorubicin etoposide and cisplatin (EAP), and ifosfamide together with IEP as shown in Table 1. After NACT, patients underwent radical hysterectomy and lymphadenectomy. Subsequently, external beam pelvic radiotherapy (EBRT) was initiated within six weeks of surgery. EBRT was delivered to a total dose of 45-48 Gy in 25-27 daily fractions over five to six weeks. External-beam therapy was delivered using anterior-posterior fields, box fields, or conformal radiotherapy and ten MV photons. Intracavitary treatment was delivered using Fletcher-suit after loading high-dose-rate applicators. Patients underwent concurrent or sequential adjuvant chemoradiation . Dose adjustment was based on the greatest toxicity grade, using the National Cancer Institute Common Toxicity Criteria for Adverse Event. Chemotherapy was repeated every three weeks, providing the patient's absolute neutrophil count recovered to > 1,500/mm^3 and platelets were > 100,000/mm^3. The does of each drug was reduced by 20% of previous does in the case of grades 3 and 4 toxicities. Chemotherapy was withheld until resolution of any grade 3 or 4 non-hematologic toxicity.

The clinical and pathological variables analyzed included patient age, tumor size, stage, lymph node involvement (LNI), depth of stromal invasion (DSI), and lymph vascular space invasion (LSI). Clinical and pathological variables analyzed are shown in Table 2.

Follow-up

The primary end point was any cancer-related death. All end points were calculated from the date of diagnosis to death, or censored at last follow-up. The date of death was obtained from the medical records, personal contact, or the National Registry of Death statistics of the China National Statistical Office.

Statistical analysis

All statistical analyses were performed using SPSS v.19 software. Survival curves were estimated using the Kaplan-Meier method, and *p* values were generated using the log-rank test. All tests were two-tailed with *p* values < 0.05 considered significant. All end points were updated in August 2013.

Table 3. — *Major toxicities.*

Adverse event	No. of patients with toxicity (NCI-CTC) (n=23)				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	3	1	7	7	5
Anemia	2	2	5	11	3
Thrombocytopenia	14	5	4	0	0
Hepatic insufficiency	13	8	1	1	0
Renal insufficiency	20	3	0	0	0

Results

From 1998 to 2010, 23 patients were enrolled and received at least one cycle of NACT. The characteristics of the patients included in this study are described in Table 1. The median patient age at diagnosis was 39 years (range: 25–65). The FIGO stage distribution was follows: six were Stage IB1, four were Stage IB2, eight were Stage IIA, three were Stage IIB, one was Stage IIIA, and one was Stage IIIB. The therapeutic regimens and clinical outcomes for all 23 patients are shown in Table1. Five patients with advanced stage disease receiving NACT gained the opportunity of surgery. Three patients of which two were Stage IB1, one was Stage IIA had postoperative pathologic complete responses through one to two cycles NACT of EP regimen with a median follow-up duration 69.5 months (range: 51.1–177.1), without recurrence.However the other eighteen patients who had not postoperative pathologic complete responses through NACT with a median follow-up duration 38.8 months (range: 7.3–81.5)

For all the patients, age, stage, tumor size, LNI, LSI, DSI, and histological homology were assessed; LSI and DSI (stromal invasion depth of cervix > 2/3) were found to be significantly associated with a worse prognosis compared to those patients without LSI and DSI ($p = 0.005$, $p = 0.001$, respectively). Although not statistically significant, age (≤ 40 years), Stage (IIB–IIIB), tumor size (> four cm), LNI, and pure histological homology tended to adversely affect survival (Table 2).

Toxicity

Among 23 patients assessable for toxicity evaluation, the most common toxicity was hematologic, and the levels were mostly acceptable. The incidence of grades 3 and 4 toxicity was follows: anemia, 60.9%; neutropenia, 52.2%; thromobocytopenia, 0%; liver insufficiency, 4.3%, renal insufficiency, 0%; no treatment-related death occurred during therapy. The toxicities are summarized in Table 3.

Pattern of recurrence and survival

The median survival was 40.8 months (range: 7.3–177.1 months) for all patients. The median survival was 48.9 months (range: 7.3–177.1) for Stage IB1–IIA patients. Eleven out of 23 patients were alive without recurrence at the time of analysis. The response rate of NACT as primary therapy was 95.7% (CR 3, PR19, SD 1, PD 0). The median overall survival (OS) periods for those who survived and died during the evaluation period were 51.7 and 21.2 months. The estimated five-year disease-free survival (DFS) and OS rates were 61.1% and 66.7%, respectively for Stage IB1–IIA patients.The estimated five-year DFS and OS rates were 46.2% and 56.5%, respectively, for all patients. Currently 11 patients are alive and disease free, one patient is alive with disease, and 11 have died of disease. With the exception of three patients, relapse sites were unknown and there were one or multiple relapse sites for other nine patients. Relapse sites included the lung (n=5), liver (n=5), bone (n=3), para-aortic nodes (n=2), and brain (n=2). Eight patients (72.7%) with relapse were dead within three years of the first treatment.

Discussion

Based on reports from different hospitals, SCNEC is a rare disease [6]. That is associated with a poor prognosis. Because SCNEC occurs infrequently, it is difficult to perform a randomized controlled clinical trial to determine optimal therapy. The current study analyzed a large series of patients diagnosed with SCNEC from a single institution experience, which included an update of a previous reported series [7].

NACT has been recommended for patients with tumor size > four cm [5, 8], However, another previous study that found that patients who received NACT tended to have a worse median OS that those who did not receive NACT [9]. Whether NACT can improve the prognosis for cervical cancer patients remains a matter of debate. We therefore carried out a retrospective trial to identify the efficacy and toxicity of NACT for patients with early-stage SCNEC. Although radical surgery is not associated with prolonged survival relative to definitive radiation for patients with SCNEC [10, 11], most gynecologic oncologists and patients in China favor radical surgery. Most patients with FIGO Stage IB1–IIA tumors underwent radical surgery as the main mode of treatment. Although favorable results have been reported for patients with SCNEC who received concurrent chemoradiation followed by several additional cycles of chemotherapy [4, 11], other studies have reported that radical surgery is an important component in the multimodal treatment of SCNEC [5, 12, 13]. However, patients with large lesions (> four cm) did poorly despite radical surgical treatment in this current series. Bermudez *et al.* [14] recommended NACT containing vincristine, bleomycin, and platinum for patients with large lesions > four cm. Based on his series of 13 patients who received NACT, it seems that preoperative chemotherapy may be a useful treatment method to enhance the resectability of the large tumors to improve outcome. However, Lee *et al.* [9] found that two of five patients with Stage IB1 and all six patients with Stage IB2–IIA tumors

treated with NACT died of their disease. They thought that although NACT might be useful for enhancing the resectability of bulky tumors, it did not improve survival.

The present results indicate that through preoperative chemotherapy, 18 patients with early-stage SCNEC received NACT including nine cases with bulky tumors; only one case had pelvic recurrence, seven cases died of their disease, all due to distance metastases, with a median survival of 48.9 months (range: 7.3–177.1) and an OS rate at five years of 66.7%. Although limited by the small number of patients included in this analysis, we did show improvement in the OS rate over the previously reported five year survival of 31.6–46.6% for Stage (I–IIA) patients [5, 9, 15]. In addition the present data showed that for 18 early–stage patients who received NACT, three (16.7%) patients achieved a complete response (CR) after one to two cycles of NACT of EP regimen. These three patients achieved long-term survival without recurrence, with a median follow-up duration 69.5 months (range: 51.1–177.1). Therefore, NACT may be an approach for assessing response to treatment.

We applied NACT to five patients with advanced stage disease (IIB- IIIB), of which gained the opportunity of surgery. While only one patient with Stage IIB disease is alive at the end of follow up, the remaining four patients died of their disease, two of which with pelvic recurrence. These results suggest that hysterectomy after NACT may confer little benefit in the setting of advanced stage SCNEC.

We also observed that DSI and LSI were poor prognostic factora. The five-year survival rate for patients without DSI was 78.6% compared to 11.1% for patients with DSI ($p = 0.001$). The five-year survival rate for patients without LSI was 71.4% compared to 22.2% for patients with LSI ($p = 0.005$). These results were consistent with those of a previous a study [16]. Although not statistically significant, LSI tended to adversely affect survival.

We recognize the limitations of this study. Firstly, this was a small, single institute study that had inherent limitations. There was no comparative group for use as a control. Therefore, the favorable survival obtained in this study can only be compared indirectly with historical controls. Secondly, due to the fact that this study was not a prospective study, the chemotherapy regimens were not unified. However, despite these limitation, to the best of the authors' knowledge, this is the first retrospective study that has tested a EP regimen in preoperative NACT follow postoperative adjuvant therapy for SCNEC.

Conclusion

We demonstrated a favorable outcome in OS in early-stage patients treated with EP regimen preoperative NACT follow postoperative adjuvant therapy. Toxicities are manageable. Therefore, this study suggests that a prospective, randomized controlled study should be designed to evaluate efficacy of this approach compared with the current primary radical surgery, followed by adjuvant chemotherapy for patients with early-stage SCNEC.

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