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Case Report Open Access

Neoadjuvant Chemotherapy with Paclitaxel and Nedaplatin plus Radical Surgery in Cervical Cancer during Pregnancy: A Case Report and Review of the Literature

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Abstract

Introduction: Cervical cancer in the 3rd trimester of pregnancy is rare and the management is thorny. The disease control and fetal outcome are cautiously considered by the clinicians.

Case presentation: A 36-year-old Han Chinese female with cervical cancer staged as IB1 at the gestational age of 30 + 3 weeks was referred to our department. The patient and the family refused to term pregnancy and wanted pregnancy-preserving management, she was treated by neoadjuvant chemotherapy with paclitaxel 230 mg plus nedaplatin 120 mg first, and caesarean section; radical hysterectomy and pelvic lymph node dissection were performed three weeks later. Based on the pathology report, the patient underwent further radiotherapy, and the neonate was healthy.

Conclusions: The patient with cervical cancer diagnosed in the 3rd trimester of pregnancy can be performed with neoadjuvant chemotherapy (Paclitaxel/nedaplatin) before operation, while the proper chemotherapy doses must be carefully studied considering the pharmacokinetic alteration during pregnancy and the adverse effects for the pregnant patient and the fetus. Thus, further investigation is required regarding the safety and outcome.

Keywords

Cervical cancer, Pregnancy, Neoadjuvant chemotherapy

Abbreviations

NACT: Neoadjuvant Chemotherapy; CIN: Cervical Intraepithelial Neoplasia; CL: Clearance; RSE: Relative Standard Error; BDP: Biparietal Diameter; FL: Femoral Length; IMRT: Intensity-Modulated Radiation Therapy

Introduction

Cervical cancer is one of the most common tumors during pregnancy with the incidence from 1.6 to 10.6 per 10,000 pregnancies [1,2]. Owing to the scarcity of cases reported in the literature, most of gynecological oncologists are still confused about the standard management of the pregnant patients with cervical cancer [1,2]. Here, we reported a case of cervical cancer staged at IB1 diagnosed in the 3rd trimester of pregnancy treated by neoadjuvant chemotherapy (NACT) once, the regimen was nedaplatin (80 mg/m^2) and paclitaxel (150 mg/m^2), and then performed a caesarean section with radical hysterectomy plus bilateral pelvic lymphadenectomy 3 weeks later. After that, the patient received concurrent chemo radiation therapy (CCRT) for the lymph-vascular space invasion (LVSI). By now, the patient shows no evidence of recurrence, and the neonate was healthy.

Case Report

A 36-year-old female of Chinese Han nationality at the gestational age of 30 + 3 weeks, gravid 4, para 0, without the history

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Table 1: Laboratory data.

Variable	Before chemotherapy (2014-10-18)	After chemotherapy (2014-11-10)	After operation (2014-11-16)	Reference range	Units
White cell count	7.29	7.70	9.77	4.00-10.00	10^9/L
Red blood cell count	3.21	3.58	3.30	3.68-5.13	10^{12}/L
Hemoglobin	89	96	89.0	113.0-151.0	g/L
Platelet count	195	184.0	143.0	100.0-300.0	10^9/L
Hematocrit	0.291	0.320	0.29	0.335-0.450	L/L
Glutamic-pyruvic transaminase	39	328	139	0-60	IU/L
Glutamic-oxaloacetic transaminase	24	215	44	0-60	IU/L
Total bilirubin	12.8	31.8	13.9	3.4-20.5	umol/L
Direct bilirubin	5.9	20.9	8.3	0.0-6.8	umol/L
Indirect bilirubin	6.9	10.9	5.6	0.0-13.7	umol/L
Blood urea nitrogen	2.65	3.13	3.23	2.86-7.14	mmol/L
Creatinine	48	50	51	45-84	umol/L
Squamous cell antigen	4.6	2.8	/	0-1.5	ng/ml

Note: The date for NACT: 2014-10-19; the date for surgery: 2014-11-12.

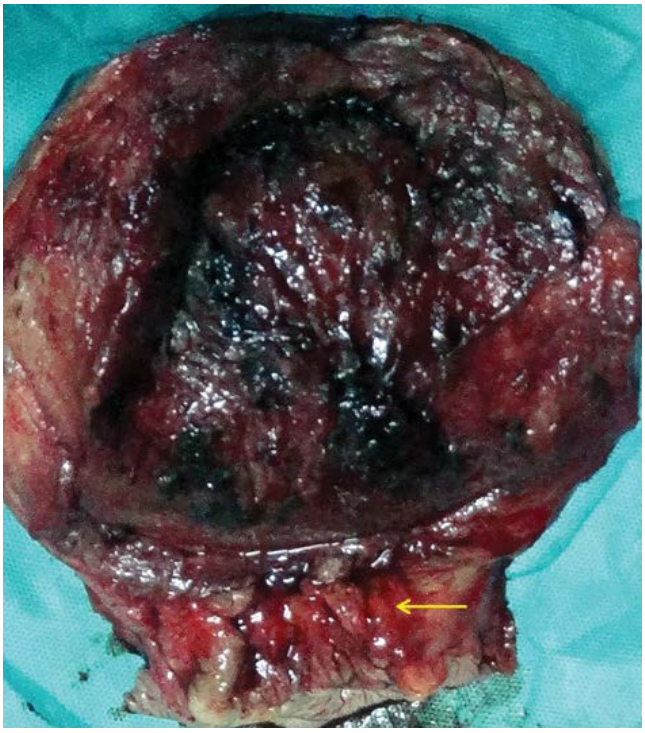

Figure 1: On gross examination, the tumor was displayed in the front lip of the cervix. (Arrow showed).

of family hereditary, smoking and drinking, presented an invasive squamous cervical carcinoma. The patient complained intermittent vaginal spotting 2 years ago without any physical examination and treatment, and has a history of vaginal bleeding one month ago. She was sent to our hospital and diagnosed by colposcopy biopsy. Pelvic examination revealed a 3.5 cm cervical mass without parametrial or vaginal involvement. An ultrasound scan revealed a live intrauterine pregnancy of size consistent with gestational age, and normal fetal anatomy (Biparietal diameter 76 mm and femoral length 56 mm). The patient was staged by two gynecological oncology specialists as cervical cancer IB1 (FIGO 2014). After a complete consultation, the patient and her family refused to term pregnancy and wanted pregnancy-preserving management, they agreed with neoadjuvant chemotherapy with paclitaxel 230 mg plus nedaplatin 120 mg (body surface area = 1.58 m^2). Three weeks later she came back for operation and found tumor decrease (3 cm mass) and liver dysfunction such as higher ALT, AST, TBIL, and DBIL as listed in table 1. The BDP was 84 mm, and the FL was 64 mm according to the ultrasonic examination.

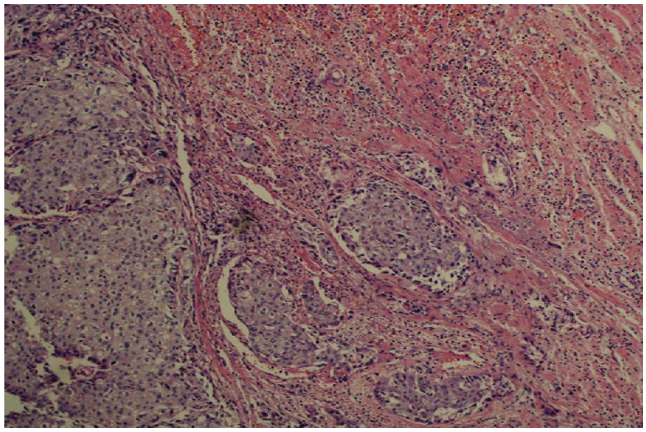

Figure 2: Viewed microscopically, the carcinomatous components showed with Hematoxylin-eosin (× 100).

Glucocorticoid therapy (Dxm 10 mg, 5 times before operation) was administered for fetal lung maturation. We also administered 20 mg vitamin K1 and the pharmacies for liver function protection before operation. The patient had a history of vaginal delivery 9 years before, and wanted no more children. Thus, caesarean section, radical hysterectomy and pelvic lymph node dissection were performed at 34 + 3 weeks' gestation. A female infant weighing 2,030 g with Apgar score at 1 and 5 min of 9' and 9' was delivered. The infant was healthy and transferred to the preterm birth ward. The final pathological report on the hysterectomy specimen (Figure 1) indicated that non-keratinizing squamous cervical cancer (Figure 2), neither infiltration of parametrium and nor the resection margin of the vaginal involvement was found, the 16 left and 12 right pelvic lymph nodes were free of disease, both lymph-vascular and the serous layer of the cervix were involved. The patient underwent further radiotherapy with Intensity-Modulated Radiation Therapy (IMRT), the target included total pelvic lymph nodes, vaginal cuff and parametria tissue, 95% PTV 5040cGy/28f/5.5w.

Discussion

The currently recommended neoadjuvant chemotherapy (NACT) regimen for cervical cancer is platinum-based chemotherapy (cisplatin 75 mg/m^2), preferably with paclitaxel (175 mg/m^2) at a 3-week interval [2-4]. However, the evaluation of the efficacy and safety of NACT in pregnancy is difficult for the rarity of reports and less clinical trial; we have considered all of the data and publications available about NACT during pregnancy in the Pubmed (Table 2). We chose nedaplatin (80 mg/m^2) and paclitaxel (150 mg/m^2) for chemotherapy in view of the heart overload during pregnancy and

Table 2: Cervical cancer in pregnancy treated by neoadjuvant chemotherapy plus surgery: literature review.

Authors	Age	Histology	FIGO stage	GADD	NACT regimen (mg/m2, course, intervals)	Response to NACT	Type of surgery	Pelvic lymph nodes	Adjuvant therapy	Outcome of patient/child
Giacalone, et al. [5]	34	SCC	1B1	17,32	Cisplatin (75,3,21 days)	PR	CD+RH+PLND	Neg.	None	DF 1 year/ND
Caluwaerts, et al. [6]	28	SCC	1B1	15,32	Cisplatin (75,6,10 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
Tewari, et al. [7]	34	SCC	IIA	16,34	Vincristine (1,3,21 days) + cisplatin (50,6,21 days)	PR	CD+RH+PLND	Neg.	RT	Recurrence and DOD/ND
	36	SCC	1B2	21,32	Vincristine (1,4,21 days) + cisplatin (50,4,21 days)	PR	CD+RH+PLND	Neg.	None	DF 2 years/ND
Marana, et al. [8]	26	SCC	IIB	14,38	Cisplatin (50,2,21 days) + bleomycin (30,2,21 days)	PR	No surgery	N/A.	Patient refused further treatment	DOD/ND
Bader, et al. [9]	38	SCC	IIA	19,33	Vincristine (1,4,21 days) + cisplatin (50,4,21 days)	PR	CD+RH+PLND	Pos.	CT	DF(80 months)/ ND
Benhaim, et al. [10]	31	SCC	IIIB	22,28	Cisplatin (50,2,14 days)	PD	No surgery	/	CCRT	DOD/ND
Chun, et al. [4]	32	SCC	IIA	28,33	Paclitaxel (175,1) + carboplatin (at AUC 5)	PR	CD+RH+PLND+PALN	Neg.	None	Recurrence /ND
	27	SCC	IB2	28,36	Paclitaxel (175,2,21 days) + cisplatin (75,2,21 days)	PR	CD+RH+PLND+PALN	Pos.	CT	DF 5 years/ND
	27	SCENC	IB1	25,35	Paclitaxel (175,3,21 days) + cisplatin (75,3,21 days)	PR	CD+RH+PLND+PALN	Neg.	None	DOD/ND
Palaia, et al. [11]	30	SCC	IIB	19,35	Paclitaxel (175,1,21 days) + cisplatin (75,3,21 days)	PR	CD+RH+PLND	Neg.	None	DF 10 months /ND
Cid, et al. [12]	24	ADCA	IB1	23,34	Vincristine (1,2,28 days) + cisplatin (50,2,28 days)	PR	CD+RH+PLND	Neg.	CT	DF /ND
Luiza, et al. [13]	27	ADCA	IB2	19,34	Cisplatin (75,6,14 days) + doxorubicin (35,6,14 days)	CR	CD+RH+PLND	Neg.	None	DF 20 months /ND
Fruscio, et al. [14]	29	SCC	IB2	13,30	Vincristine (1,NA,14 days) + cisplatin (50,NA,14 days)	SD	CD+RH+PLND	Pos.	RT	DOD/ ND
Li, et al. [2]	37	SCC	IB2	18,32	cisplatin (75,NA,21 days)	SD	CD+RH+PLND	Neg.	None	DF/ND
	28	SCC	IB2	16,33	Paclitaxel (175,NA,21 days) + cisplatin (75,NA,21 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
	36	SCC	IB2	16,34	Paclitaxel (175,NA,21 days) + cisplatin (75,NA,21 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
Kong, et al. [15]	32	SCC	IB2	20,35	cisplatin (75,NA,21 days)	SD	CD+RH+PLND	Neg.	CCRT	DOD/ ND
	34	SCC	IB1	22,36	cisplatin (75,NA,21 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
	39	ADCA	IB1	20,36	cisplatin (75,NA,21 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
	34	ADCA	IB1	26,36	cisplatin (75,NA,21 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
	37	SCC	IB1	8,36	cisplatin (75,NA,21 days)	SD	CD+RH+PLND	Pos.	CCRT	DF/ND
	36	SCC	IB2	27,33	Paclitaxel (75,2,14 days) + cisplatin (50,2,14 days)	PR	CD+RH+PLND	Neg.	CCRT (LVSI)	DF/ND
	39	SCC	IB2	29,33	Paclitaxel (75,2,14 days) + cisplatin (50,2,14 days)	PR	CD+RH+PLND	Neg.	None	DF/ND
	31	SCC	IB1	19,33	Paclitaxel (135,3,21 days) + cisplatin (60,3,21 days)	PR	CD+RH+PLND+PALN	Neg.	None	DF/ND
	38	SCC	IB2	13,35	Paclitaxel (135,4,21 days) + cisplatin (60,4,21 days)	PR	CD+RH+PLND	Neg.	CT	DF/ND
	26	SCC	IB1	25,34	Paclitaxel (135,1,21 days) + cisplatin (60,1,21 days)	PR	CD+RH+PLND	Neg.	CT	DF/ND
Karam, et al. [16]	28	SCC	1B2	23,33	cisplatin (40,7,7 days)	SD	CD+RH+PLND+PALN	Neg.	CCRT	DF/ND
Boyd, et al. [17]	26	Clear cell	IIB	21,35	cisplatin (100,3,21 days)	N/A	No surgery	N/A	CCRT	DF for 15 months/ND
Seamon, et al. [18]	30	Glassy cell	IIIB	23,31	cisplatin (30,3,21 days) + Vincristine (1.5,3,21 days) cisplatin (40,3,21 days). weekly cisplatin and every other week vincristine.	PR	No surgery	Pos.	CCRT	DF for 4.1 years/ND
Smyth, et al. [19]	26	Small cell	IB2	23,35	adriamycin (60,3,21 days) + cyclophosphamide (600,3,21 days)	PR	No surgery	N/A	CCRT	DF/ND
Rabaiotti, et al. [20]	27	SCC	IB2	15,32	cisplatin (75,4,21 days)	SD	CD+RH+PLND	Pos.	CCRT	DOD/ ND
Favero, et al. [21]	35	ADCA	IB1	14,19	cisplatin (NA)	N/A	Laparoscopic nodal evaluation, then CD+RH	Neg.	CT	DF/ND
	31	SCC	IB1	18,32	cisplatin (NA)	N/A		Neg.	CT	DF/ND
	34	SCC	IB1	22,36	cisplatin (NA)	N/A		Neg.	CT	DF/ND
	31	SCC	IB1	14,32	cisplatin (NA)	N/A		Neg.	CT	N/A
	29	ADCA	IB1	18,34	cisplatin (NA)	N/A		Neg.	CT	N/A
Current study	36	SCC	IB1	30,34	paclitaxel (150,1,21 days) + nedaplatin (80,1,21 days)	PR	CD+RH+PLND	Neg.	RT (DSI and LVSI)	DF/ND

FIGO: International Federation of Gynecology and Obstetrics; NACT: Neoadjuvant Chemotherapy; GADD: Gestational Age at Diagnosis and Delivery; M: Mother; C: Child; SC: Squamous Cell Carcinoma; P: Cisplatin; T: Paclitaxel; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ND: No Evidence Of Disease; DOD: Death Of Disease; CD: Cesarean Delivery; RH: Radical Hysterectomy; PLND: Pelvic Lymph Node Dissection; PALN: Para-Aortic Lymph Node Dissection; SCENC: Small Cell Neuroendocrine Carcinoma; CT: Chemotherapy; CCRT: Concurrent Chemo Radiation Therapy; NA: Not Available; ADCA: Adenocarcinoma; LVSI: Lymph-Vascular Space Invasion; DSI: Deep Stromal Invasion; N/A: Not Available; CDDP: Cisplatin; VCR: Vincristine; BLM: Bleomycin; 5-FU: 5-Fluorouracyl; CBDCA: Carboplatin; ADR: Adriamycin; CTX: Cyclophosphamide.

the anemia for this patient (Table 1). It has not been reported about the chemotherapy with nedaplatin during pregnancy before, which has the benefit of without need of hydration, less nausea, vomiting and nephrotoxicity than other platinum-containing drugs. The fetus did not show intrauterine growth restriction after chemotherapy. Unfortunately, the patient showed damage to liver function three weeks after chemotherapy (Table 1).

The physiologic alterations during pregnancy have an effect on the most important pharmacokinetic processes including absorption, distribution, metabolism, and excretion. Alterations in drug metabolism begin at 4 weeks of gestation, progressively increase, and are more pronounced in the third trimester of pregnancy [22]. Pharmacokinetic analysis has shown that no gestational effect could be estimated on clearance (CL) for doxorubicin; for epirubicin, docetaxel and paclitaxel, a fold-change of 1.1 (relative standard error, RSE 9%), 1.19 (RSE 7%) and 1.92 (RSE 21%) were respectively, estimated on CL. Calculated dose modification requirements for doxorubicin, epirubicin, docetaxel and paclitaxel were + 5.5%, + 8.0%, + 16.9% and + 37.8%, respectively [23]. It has not been reported about the CL for nedaplatin, and we chose the common doses for the patient without pregnancy. However, the adverse effects of chemotherapy with the adjustment doses should also be considered, and it needs further study and more clinical data.

This patient was diagnosed as cervical cancer at gestation of 30 + 3 weeks. At this 3rd trimester of pregnancy, a complete pelvic and paraaotic lymphadenectomy is difficult to perform; therefore, the management cannot rely on the nodal status. Although the neoplasm diameter was 3.5 cm, the patient refused to term pregnancy and wanted to pregnancy-preserving management. We performed NACT and find the tumor decrease before operation.

A good number of the pregnant patients diagnosed as cervical cancer were in the early stages [24]. Management with conization or trachelectomy may be indicated for microinvasive or invasive disease [25]; while management is dependent on the clinical stages and gestation weeks for invasive cervical cancer. For the patients at gestational age more than 22 weeks, early-stage (Ia2-Ib) with negative lymph node status, delay of treatment until fetal maturity may be appropriate; Ib > 2 cm with negative lymph node status NACT is recommended until fetal maturity. The patient with positive lymph node status is suggested to term the pregnancy [22,24,26,27]. Laparoscopic lymphadenectomy during pregnancy is difficult for the enlargement of uterus. According to the reports, either laparoscopic or laparotomic lymphadenectomy can safely be performed between the 13th and 25th weeks of pregnancy. Lymphadenectomy in minimal number of 10 lymph nodes were suggested by International Federation of Gynecology and Obstetrics [22,28-31].

In summary, NACT for the treatment of cervical cancer during pregnancy seems to be a sensible choice for the patients who refuse to give up their pregnancies. Nevertheless, the reasonable chemotherapy doses, drugs and regimens should be carefully selected, the corresponding side effects should also be considered.

Conclusion

The patient with cervical cancer staged at IB1 diagnosed in the 3rd trimester of pregnancy can be performed with NACT before operation, while the proper chemotherapy doses must be cautiously considered in view of the pharmacokinetic alteration during pregnancy and the adverse effects for the pregnant patient and the fetus.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

ZY and WDB designed the report; ZY, CG, ZXF, CL, CY,SKL and WDB were attending doctors for the patient; WHY performed the pathology diagnosis; XF and ZY organized and wrote the report; WDB gave the final approval. All authors read and approved the final manuscript.

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