Int J Clin Exp Med 2015;8(8):13690-13698
www.ijcem.com /ISSN:1940-5901/IJCEM0010822

Original Article

Clinical efficacy and safety of paclitaxel plus carboplatin as neoadjuvant chemotherapy prior to radical hysterectomy and pelvic lymphadenectomy for Stage IB_2-IIB cervical cancer

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Received May 29, 2015; Accepted July 20, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: Objective: To assess the efficacy and toxicity of the combination of paclitaxel plus carboplatin as neoadjuvant chemotherapy (NACT) for locally advanced cervical cancer (LACC) prior to radical hysterectomy and pelvic lymphadenectomy. Methods: We reviewed patients with cervical cancer of the International Federation of Gynecology and Obstetrics (FIGO) stage IB_2-IIB who underwent neoadjuvant chemotherapy (NACT) with paclitaxel plus carboplatin followed by radical hysterectomy (NACT group) or only received primary radical surgery (PRS group) in our hospital between Jan 2007 and Jan 2012. Toxicity, NACT response, surgery pathological factors and survival data were collected and analyzed. Results: In the NACT group, the overall response rate was 71.3% (82/115). Eighteen (15.7%) patients achieved complete remission. Well differentiated tumors showed a more favorable response to NACT (P=0.011). Myelosuppression was the most common adverse effect (51.7%) and serious adverse effects were rare (3.4%). The median follow-up period was 44 months (range, 6-75). The NACT responders had significantly longer OS and PFS when compared to the non-NACT responders and patients in the PRS group. Conclusion: Patients with LACC can benefit from neoadjuvant chemotherapy with paclitaxel plus carboplatin when they have response to the chemotherapeutic agents.

Keywords: Neoadjuvant chemotherapy, paclitaxel plus carboplatin, locally advanced cervical cancer, prognosis, efficacy

Introduction

Cervical cancer is the most common gynecologic malignancy in low-resource countries, and China accounts for 29% of approximately 50 million new cases in the world every year [1]. Despite advances in screening, several patients have a locally advanced cervical (LACC) at presentation [2]. For LACC, concurrent chemoradiation is recommended by The National Comprehensive Cancer Network (NCCN). However, owing to limited technologic development in some area of China, and for the patients who worried the serious side effect of radiotherapy, such as radio-cystitis and radiation proctitis, neoadjuvant chemotherapy (NACT) followed by radical surgery has become one of the alternative treatment options [3]. Until now, the use of NACT remains controversial. Mori et al. reported neoadjuvant chemotherapy with paclitaxel and carboplatin on a weekly schedule followed by radical surgery for patients with LACC was a promising mode of therapy that may improve the prognosis [4]. Paclitaxel plus carboplatin as neoadjuvant chemotherapy is getting more and more attention of researchers. Thus, we performed a retrospective study to assess the efficacy and toxicity of paclitaxel plus carboplatin as the neoadjuvant chemotherapy for patients with LACC, and compare survival outcomes between patients undergoing radical hysterectomy and pelvic lymphadenectomy, with or without upfront neoadjuvant paclitaxel plus carboplatin.

Materials and methods

Patients

We reviewed the medical files of all patients with cervical cancer of stage IB_2-IIB received

NACT with paclitaxel plus carboplatin (NACT group) or primary radical surgery (PRS group) in Wuhan Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, from January 2007 to January 2012. The clinical staging of the cervical cancer was accomplished according to The International Federation of Gynecology and Obstetrics. The original diagnosis of invasive cervical cancer was pathologically confirmed in all patients. Archiving of patient data were performed with written informed consent and were approved by the hospital ethics committee.

Finally, 116 and 69 eligible patients were identified in the NACT and the PRS group respectively. Basic information was as follows: (1) clinical stage IB_2 to IIB according to the International Federation of Gynecology and Obstetrics (FIGO); (2) bidimensionally measurable lesion; (3) performance status of 0 to 2 according to the World Health Organization criteria; (4) normal hematologic, hepatic, and renal function; (5) no heart or lung disease by clinical examination; (6) no preexisting; and (7) no active infection.

Management

Once every 4 weeks, patients received paclitaxel (paclitaxel liposome for injection, Luye Pharma Group Ltd., Nanjing, China) at 135-175 mg/m^2 intravenously over 4 hours on the first day in addition to carboplatin (carboplatin for injection, Qilu Pharma Ltd., China) at AUC=5 intravenously over 30 minutes with the simultaneous monitoring of blood pressure, electrocardiograph and blood oxygen saturation. The doses and schedules of the drug administration were modified according to a drug toxicity evaluation before each course. Laboratory studies, consisting of a complete blood count and renal, liver function tests, were monitored before and during each chemotherapy cycle. If the count of white blood cell was lower than 3.0 G/L, granulocyte colony-stimulating factor (G-CSF) was administered. The re-evaluation was carried out ten days after NACT. The toxicity of the regimen was determined according to the WHO Toxicity Criteria by Grade.

The response to NACT was evaluated using the RECISR criteria for solid tumors (version 1.1) via comparison tumor size before and after the chemotherapy investigated by MRI and pelvic examination. Briefly, a complete regression (CR) was defined as complete regression of the tumor mass and no lymph node metastasis. Partial regression (PR) was defined as at least 50% decrease in the largest diameter of tumor mass. Stable disease (SD) was defined as less than 50% decrease or more than 25% increase of the tumor size. Progressive disease (PD) was defined as more than 25% increase of the lesion or new mass appearing. NACT responders included the patients with CR or PR, while non-responders were the patients with SD or PD.

After completion of chemotherapy courses, the operable patients underwent radical hysterectomy and pelvic lymphadenectomy (classification of radical hysterectomy C2) [5] ten days after NACT. For the inoperable patients, radiotherapy was administered. The patients in the PRS group underwent radical surgery immediately after diagnosis.

Patients with lymph node metastasis, parametrial involvement or positive surgical margins were subjected to post-operative radiation.

Follow up

Follow-up was performed at stage-specific gradations in accordance with the FIGO guidelines. The patients underwent follow-up examinations every three months for two years, every six months in the third year, and then once a year after the fourth post-operative year. The contents of the follow-up examinations included gynecological examination, vaginal stump brushing cytological examination, B-ultrasound examinations for the pelvis, and chest X-ray. Overall survival (OS) was defined as the time from study entry to death from any cause or to the date of last contact. Progression-free survival (PFS) was defined as the time from study entry to the first appearance of progressive disease or to the date of last contact.

Statistical analysis

Statistical analysis was performed using the SPSS statistical software 11.0. Independent t-test and Chi-square test were used to compare the covariates. Survival curves were produced with the Kaplan-Meier method, and the log-rank test was used to test the significance of differences in survival. $P<0.05$ was considered statistically significant.

Table 1. Patients' characteristics

Characteristics	NACT N=116 (%)	PRS N=69 (%)	*P*-value
Age (years)			0.509
Median (range)	45 (23-68)	44 (30-62)	
≤35	11 (9.5)	7 (10.1)	
>35	105 (90.5)	62 (89.9)	
FIGO stage			0.759
IB_2	39 (33.6)	21 (30.4)	
IIA	54 (46.6)	36 (52.2)	
IIB	23 (19.8)	12 (17.4)	
Histology			0.129
Squamous	104 (89.7)	53 (76.8)	
Adenocarcinoma	7 (6.0)	10 (14.5)	
Adenosquamous	3 (2.6)	4 (5.8)	
Others	2 (1.7)	2 (2.9)	
Histological Grade			0.650
Well differentiated (G1)	39 (33.6)	20 (29.0)	
Moderately differentiated (G2)	41 (35.3)	29 (42.0)	
Poorly differentiated (G3)	36 (31.0)	20 (29.0)	
Tumor size			0.012
d≤2 cm	7 (6.0)	5 (7.2)	
2 cm<d<4 cm	29 (25.0)	25 (36.2)	
4 cm≤d≤6 cm	65 (56.0)	39 (56.5)	
d>6 cm	15 (12.9)	0	

NACT: neoadjuvant chemotherapy with paclitaxel plus carboplatin followed by radical hysterectomy, PRS: only received primary radical surgery.

Results

Patients' characteristics

In total, 116 eligible patients with LACC in the NACT group and 69 in the PRS group were involved in this study. The two groups were comparable with respect to median age, clinical stage, histological type and tumor grade. However, the patients in the NACT group had larger tumors when compared to those receiving PRS (**Table 1**).

Toxicity of NACT

In general, patients tolerated the NACT well and no deaths related to toxicity occurred. The most common side effect was myelosuppression. Anemia occurred in 51.7% (60/116) of patients. Leukopenia and neutropenia occurred in 50.0% (58/116) and 46.6% (54/116) of patients, respectively. Grade 3-4 anemia, leukopenia and neutropenia were respectively observed in 11 (9.5%), 15 (12.9%) and 16 (13.8%) patients. Thrombocytopenia occurred in 17.2% (20/116) of patients, and no grade 4 thrombocytopenia developed. Due to grade 3-4 leukopenia or neutropenia, 16 patients (13.8%) received G-CSF until the blood counts were normal and thus the NACT was delayed for one week in these patients, but the dose was not reduced. Twenty-six (22.4%) patients had mild to moderate nausea and vomiting. Four (3.4%) patients had grade 3 liver toxicity and NACT was delayed until the ALT/AST was less than 90 U/L. Hair loss was observed in 21 (18.1%) patients, and totally hair loss was seen in 6 (5.2%) patients. One patient showed allergic to paclitaxel, and did not complete NACT. Four patients had headache after paclitaxel infusion.

Response to NACT

The patient who was allergic to paclitaxel was excluded. As summarized in **Table 2**, after NACT 82 (71.3%) patients achieved clinic remission, including 18 (15.7%) cases of CR, 11 of which were pathologically confirmed, and 64 (55.7%) cases of PR. Thirty-three patients with SD were identified as non-NACT responders, and no PD was observed. Furthermore, we analyzed the correlation between response to chemotherapy and clinicopathological parameters of patients. The overall response rate (CR+PR) was 79.3% in well differentiated tumors, and it decreased to 68.3% and 60.0% in moderately and poorly differentiated tumors, respectively and the difference was statistically significant (P= 0.011). Though squamous tumors did not show significantly higher responsibility than non-squamous ones, CR was only observed in squamous tumors.

Surgery data and post-surgery pathological factors

After NACT, 102 patients were subjected to radical surgery, and 14 patients received radiotherapy. The surgery didn't start in three patients because of ureter or bladder invasion detected during surgery. Thus, the operability rate in NACT group was 89.2% (99/111). In the

Table 2. Response to NACT

Variables	*N*	Response to NACT				Response rates (%)	*P* value
		CR	PR	SD	PD		
	115	18	64	33	0	71.3	
Age (years)							0.875
≤35	10	1	6	3	0	70.0	
>35	105	17	58	30	0	65.2	
FIGO stage							0.125
IB_2	38	7	17	14	0	63.2	
IIA	54	7	37	10	0	81.5	
IIB	23	4	10	9	0	60.9	
Histology							0.798
Squamous	103	18	57	28	0	72.8	
Adenocarcinoma	7	0	4	3	0	57.1	
Adenosquamous	3	0	2	1	0	66.7	
Others	2	0	1	1	0	50.0	
Grade							
G1	39	12	21	6	0	79.3	
G2	41	3	25	13	0	68.3	0.011[a]
G3	35	3	18	14	0	60.0	
Tumor size							0.060
d≤6 cm	101	17	58	26	0	74.3	
d>6 cm	14	1	6	7	0	50.0	

NACT: neoadjuvant chemotherapy with paclitaxel plus carboplatin followed by radical hysterectomy. [a]Well differentiated tumors compared to moderately and poorly differentiated tumors.

Table 3. Surgery data and post-surgery pathological parameters

Group	NACT (N=99)	PRS (N=64)	*P*-value
Operative time			0.111
Median (range), min	240 (180-510)	240 (170-360)	
Operative blood loss			0.668
Median (range), ml	300 (150-1200)	300 (100-2000)	
Number of lymph nodes removed			0.402
Median (range)	23 (11-66)	24 (9-62)	
Positive surgical (n, %)	2 (2.0)	1 (1.6)	0.832
Margins of the vagina (n, %)			
Parametrial involvement	3 (3.0)	5 (7.8)	0.168
Lymph node metastasis	28 (28.3)	14 (21.9)	0.361

NACT: neoadjuvant chemotherapy with paclitaxel plus carboplatin followed by radical hysterectomy, PRS: only received primary radical surgery.

PRS group, the operability rate was 92.8% (64/69), which was not significantly different from the NACT group. The median operative time was 240 minutes and the median estimated blood loss was 300 milliliters in both groups. The median number of lymph nodes removed was 23 and 24 in the NACT group and in the PRS group respectively. In the NACT group, injury of obturator nerve, bladder and ureter were occurred in one case (1/99, 1.01%) each. In PRS group, intra-operative complication occurred in just one patient (1/64, 1.56%), which was the bladder injury. The post-surgery pathological parameters were listed in **Table 3**. There was no significant difference between the two groups in the positive rate of surgical margins of the vagina, the parametrial involvement or the lymph node metastasis rate. However, when we made further analysis in lymph node involvement, we found that the lymph node metastasis rate was as high as 57.1% (12/21) in non-NACT responders, and it decreased to 19.8% (16/81) in NACT responders (P=0.001).

Survival

The median follow-up period was 44 (6-75) months. By the last follow-up, 25 patients developed recurrent diseases, including 14 (12.1%) in the NACT group and 11 (15.9%) in the PRS group. Eighteen cases had isolated pelvic recurrences and 7 had distant metastases. No patient with CR developed recurrent disease. Twenty-two patients died from cervical cancer, including 12 (1.03%) in the NACT group and 10 (1.45%) in the PRS group. The 5-year overall survival (OS) was 85% in the NACT group and 82% in the PRS group. The 5-year progression-free survival (PFS) was 86% in the NACT group and 83% in the PRS group. The differences in OS and PFS between groups were not statistically significant (**Figure 1A**, **1B**).

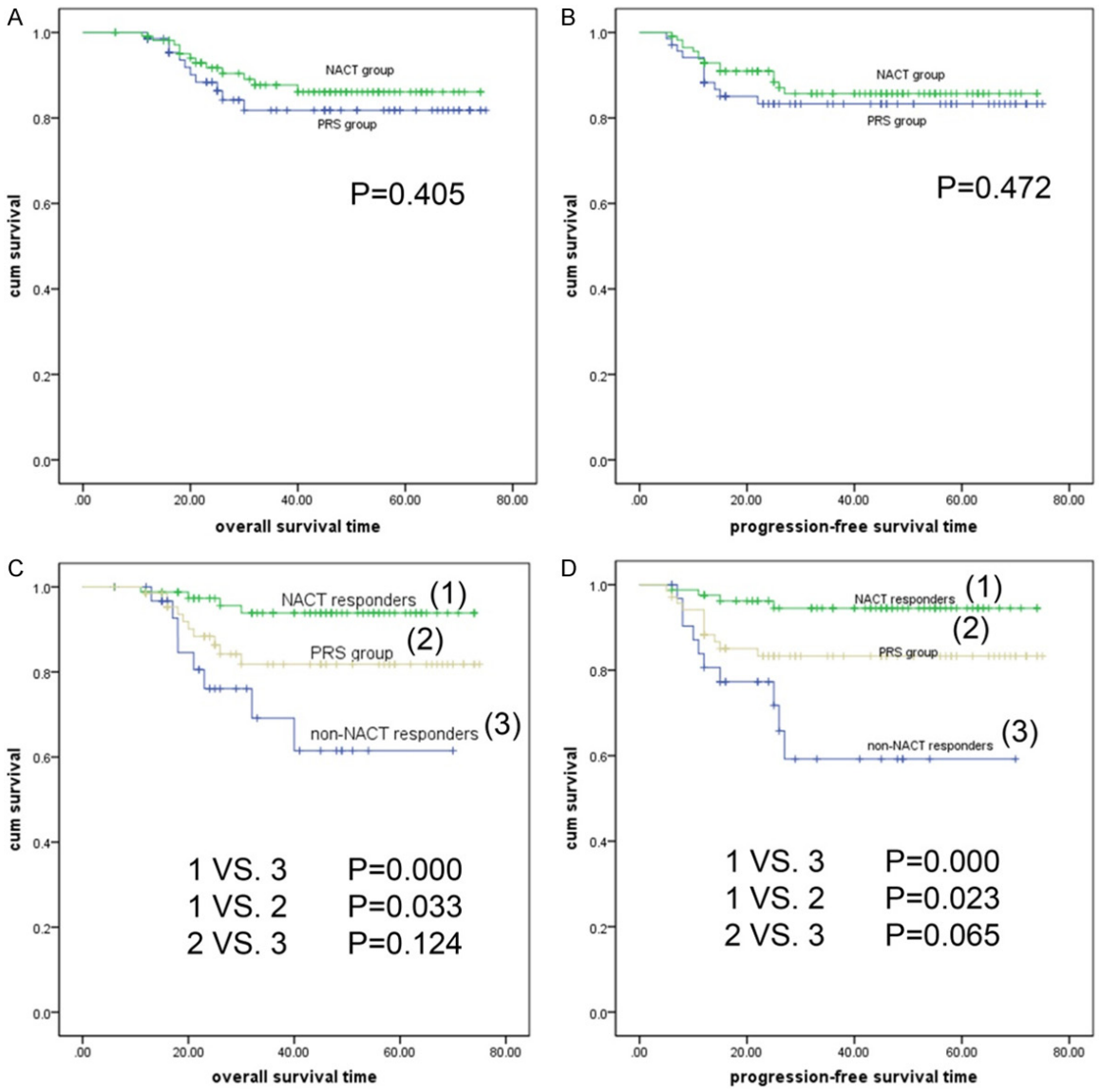

Figure 1. Kaplan-Meier curves for comparison of survival between groups. Log-Rank test was used to calculate statistical significance. There was no significant difference in OS (A) and PFS (B) between the NACT and the PFS groups (POS=0.405, PPFS=0.472). The OS (C) and PFS (D) of NACT responders was significantly longer than that of non-NACT responders (POS=0.000, PPFS=0.000) and patients in surgery group (POS=0.033, PPFS=0.023). However, there was no significant difference in OS or PFS between the non-NACT responders and the patients undergoing primary surgery (POS=0.124, PPFS=0.065).

In the subsequent analysis, we stratified the NACT group based on chemotherapeutic response, and compared them with the PRS group (**Figure 1C**, **1D**). NACT responders had significantly longer OS and PFS time than non-NACT responders (POS=0.000, PPFS=0.000) and patients in the PRS group (POS=0.033, PPFS=0.023). There was no significant difference in OS and PFS between non-NACT responders and the PRS patients (POS=0.124, PPFS=0.065).

Discussion

The application of NACT for cervical cancer is debated, although it is often used in Asia, South America and Italy [6]. NACT regimens for cervical cancer vary, ranging from single-agent to many forms of multiagent regimens. The study conducted by an Italian group (SNAP02) indicated the two-drug combination of cisplatin plus paclitaxel (TP) as a possible alternative to standard chemotherapy (paclitaxel, ifosfamide

and cisplatin (TIP)), with a reported response rate ranging between 78 and 100 % after three chemotherapy cycles [7-9]. Although TP has been proven to be active in locally advanced cervical cancer as a neoadjuvant regimen, but toxicities are still high, with the most common side effects, haemotoxicity and nephrotoxicity [10, 11], there is an urgent need for new chemotherapeutic regimens with similar efficacy but less toxicity. To resolve this issue, some studies proposed the use of carboplatin instead of cisplatin in neoadjuvant setting and reported similar response rates associated with lower side effects [10, 12, 13]. But the most relevant bias is that in all of these trials, carboplatin is always associated to many other chemotherapy regimens. Recently Angioli et al. [14] used the combination of carboplatin (AUC6) + paclitaxel 175 mg/mq in a neoadjuvant setting in patients affected by LACC and the NACT induced toxicity and the response to treatment were evaluated. Their results suggest that carboplatin is a well-tolerated drug with a response rate similar to standard cisplatin [14]. In our study, we verified the effectiveness of this NACT regimen for treatment of LACC and found it could be well tolerated by Chinese patients; moreover, patients with LACC could benefit from it when they have response to the chemotherapeutic agents.

Paclitaxel has been recognized as one of the most active cytotoxic agents and a component of the first-line therapy for patients with ovarian cancers [15]. The most common side effect produced by paclitaxel and carboplatin was hematologic toxicity, which was normally tolerable as previously reported [16]. One phase II trial was designed to evaluate the toxicity and activity of NACT with cisplatin-adriamycin-paclitaxel in patients with locally advanced cervical adenocarcinoma [17]. That combination seems to be feasible with an acceptable toxicity profile and hematologic toxicity was the most relevant adverse effect [17]. Angioli et al [14] reported the feasibility and safety of carboplatin plus paclitaxel as neoadjuvant chemotherapy for locally advanced cervical cancer in a pilot study, in their study, G3 and G4 haematological toxicities are registered only in 8.7% of patients, while they rise up to 63% in TP regimen [16, 18]. Also, our results showed that the grade 4 hematologic toxicity was just seen in 4 of 116 patients and did not result in any infection. Through the Granulocyte Colony-Stimulating Factor (G-CSF) therapy, patients could recover soon. Thrombocytopenia was uncommon; however, 5 patients developed grade 3 thrombocytopenia. So we should pay attention to platelets account. In the present study, the rate of vomiting and nausea was lower than that has been reported [19]. That may due to different chemotherapy regimens.

High response rate is the most vital factor for the improvement of curative effects [18]. It has been reported that for patients with LACC, neoadjuvant 3-weekly paclitaxel and carboplatin followed by radical surgery produced a high response rate (95%), but the long-term prognosis has not yet been reported [16]. Due to many influence factors, including the application of different chemotherapy regimens, the reported response rate of NACT in LACC ranged from 69.4% to 95.0 % [14, 16, 19-21]. The total response to NACT was 71.3% in our research and the complete regression rate was 15.7%. It suggested that NACT using paclitaxel and carboplatin was effective in reducing tumor size. The factors influencing the response of cervical cancer to chemotherapy have been previously investigated. It has been reported that NACT response was more favorable in squamous carcinomas than in adenocarcinoma [22]. Recently, a meta-analysis [23] was applied to calculate the efficacy of NACT in different histological types of cervical cancer. In that review, He et al. [23] found squamous cell carcinoma (SCC) was associated with a higher short-term response rate than non-squamous cell carcinoma in RCTs, for the long-term outcome of NACT, patients with SCC experienced a significant 5-year overall survival (OS) and progress-free survival (PFS) when compared to patients with non-SCC in pooled and observational studies other than RCTs. In our study, though squamous tumors did not show significantly higher response than non-squamous tumors, CR was only observed in squamous tumors. In addition, we found patients who suffered a well differentiated tumor showed a more favorable response than patients with moderate and poor differentiated tumors, suggesting that well differentiated tumors may be more suitable for NACT.

In recent years, genomics have been performed to find useful molecular information to predict the response to chemotherapy in cervical can-

cer patients. Masatomo et al. [24] found Sirtuin1 expression was significantly higher in the group contained patients in which NAC was ineffective compared to the group in which NAC was effective (P<0.001), these results indicate that Sirtuin1 expression may predict the efficacy of NAC as a treatment for locally advanced uterine cervical cancer. The XRCC1R399Q polymorphism, XRCC1 Arginine 194 Tryptophan polymorphism and GGH-401 Cytosine/Thymine polymorphism have been reported to be associated with the response to platinum-based neoadjuvant chemotherapy in cervical cancer [25, 26]. However, until now, there is not ideal biomarker to predict the chemotherapy response.

The theoretical benefits of NACT are reduction of bulky tumor mass and with increased operability, control of pelvic lymph node metastasis, and possible improvement of long-term survival. In previous studies, 73% to 100% cumulative operability rates were obtained for bulky stage IB to IIA patients after NACT [27, 28]. Similarly, in our study operability rate in the NACT group was 91.9%. Patients with LACC have a high risk of lymph node metastasis, and NACT may be effective to alleviate the risk [29, 30]. Several studies have reported a pelvic lymph node metastasis rate ranging from 22% to 25% after NACT for the locally advanced stage IB to IIA patients [31, 32]. In our study, lymph node metastasis rate of patients was 27.5% in the NACT group and 21.9% in the PRS group. However, the difference was not statistically significant, which may be due to the smaller tumor size in the PRS group which represents a significant factor affecting lymph node metastasis. In the NACT group, the lymph node metastasis rate was significantly lower in the NACT responders than in the non-responders, being in agreement with results in previous study [21]. However, the parametrial infiltration of patients received NACT showed no improvement compared with patients underwent radical surgery directly. Randomized trials are needed to verify the benefits of NACT.

Although some researchers claimed cervical cancer is sensitive to chemotherapy, the use of NACT remains controversial because the question whether the NACT before surgery or radiotherapy benefits survival still remains unaddressed. Lin et al. [23] reported the clinical evaluation of cisplatin-based NACT followed by radical surgery in the management of 202 patients with stage IB_2-IIB cervical cancers. They found no significant advantages of NACT in terms of 2-year PFS and OS, which may due to the variation of NACT regimen as only 9 (4.46%) patients received taxane-containing chemotherapy in their study. In our study, we found that the OS and PFS in non-NACT responders was significant lower than NACT responders, and the non-NACT responders had significantly higher recurrence rate than the NACT responders. These results may indicate that response to NACT possibly benefit PFS and reduce recurrence. And this is in accordance with the reports of others [33]. However, more randomized trials should be carried out to confirm this conclusion.

Our results suggest that NACT using paclitaxel and carboplatin can improve the prognosis of patients with LACC with generally good toleration and safety when they respond to the chemotherapy. It might be time to stop arguing about the effectiveness of NACT for the treatment of patients with LACC and to head toward identifying those patients who will benefit from a NACT. Searching for meaningful biomarkers to predict the NACT response is urgent and prospective randomized studies can lead to better alternative clinical therapy for these patients.

Acknowledgements

This work was supported by National Natural Science Foundation of China (81202058, 81272860, and 81472443).

Disclosure of conflict of interest

None.

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References

[1] Kim K, Zang R, Choi SC, Ryu SY, Kim JW. Current status of gynecological cancer in China. J Gynecol Oncol 2009; 20: 72-6.

[2] Rose PG. Chemoradiotherapy: the new standard care for invasive cervical cancer. Drugs 2000; 60: 1239-44.

[3] Loizzi V, Cormio G, Vicino M, Selvaggi L. Neoadjuvant chemotherapy: an alternative option of treatment for locally advanced cervical

cancer. Gynecol Obstet Invest 2008; 65: 96-103.
[4] Mori T, Hosokawa K, Sawada M, Kuroboshi H, Tatsumi H, Koshiba H, Okubo T, Kitawaki J. Neoadjuvant weekly carboplatin and paclitaxel followed by radical hysterectomy for locally advanced cervical cancer: long-term results. Int J Gynecol Cancer 2010; 20: 611-6.
[5] Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol 2008; 9: 297-303.
[6] González-Martín A, González-Cortijo L, Carballo N, Garcia JF, Lapuente F, Rojo A, Chiva LM. The current role of neoadjuvant chemotherapy in the management of cervical carcinoma. Gynecol Oncol 2008; 110: S36-40.
[7] Park DC, Kim JH, Lew YO, Kim DH, Namkoong SE. Phase II trial of neoadjuvant paclitaxel and cisplatin in uterine cervical cancer. Gynecol Oncol 2004; 92: 59-63.
[8] Lissoni AA, Colombo N, Pellegrino A, Parma G, Zola P, Katsaros D, Chiari S, Buda A, Landoni F, Peiretti M, Dell'anna T, Fruscio R, Signorelli M, Grassi R, Floriani I, Fossati R, Torri V, Rulli E. A phase II, randomized trial of neo-adjuvant chemotherapy comparing a three-drug combination of paclitaxel, ifosfamide, and cisplatin (TIP) versus paclitaxel and cisplatin (TP) followed by radical surgery in patients with locally advanced squamous cell cervical carcinoma: the Snap-02 Italian Collaborative Study. Ann Oncol 2009; 20: 660-5.
[9] Angioli R, Plotti F, Montera R, Aloisi A, Luvero D, Capriglione S, Terranova C, De Cicco Nardone C, Muzii L, Benedetti-Panici P. Neoadjuvant chemotherapy plus radical surgery followed by chemotherapy in locally advanced cervical cancer. Gynecol Oncol 2012; 127: 290-6.
[10] Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, Mannel RS, DeGeest K, Hartenbach EM, Baergen R; Gynecologic Oncology Group. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003; 21: 3194-200.
[11] Shen Y, Yang L, Wang Z. Treatment of early bulky cervical cancer with neoadjuvant paclitaxel, carboplatin and cisplatin prior to laparoscopical radical hysterectomy and pelvic lymphadenectomy. Oncol Lett 2012; 3: 641-5.
[12] Kitagawa R, Katsumata N, Ando M, Shimizu C, Fujiwara Y, Yoshikawa H, Satoh T, Nakanishi T, Ushijima K, Kamura T. A multi-institutional phase II trial of paclitaxel and carboplatin in the treatment of advanced or recurrent cervical cancer. Gynecol Oncol 2012; 125: 307-11.
[13] Takekida S, Fujiwara K, Nagao S, Yamaguchi S, Yoshida N, Kitada F, Kigawa J, Terakawa N, Nishimura R. Phase II study of combination chemotherapy with docetaxel and carboplatin for locally advanced or recurrent cervical cancer. Int J Gynecol Cancer 2010; 20: 1563-8.
[14] Angioli R, Plotti F, Luvero D, Aloisi A, Guzzo F, Capriglione S, Terranova C, De Cicco Nardone C, Benedetti-Panici P. Feasibility and safety of carboplatin plus paclitaxel as neoadjuvant chemotherapy for locally advanced cervical cancer: a pilot study. Tumour Biol 2014; 35: 2741-6.
[15] Ozols RF. Paclitaxel (Taxol)/carboplatin combination chemotherapy in the treatment of advanced ovarian cancer. Semin Oncol 2000; 27: 3-7.
[16] Dueñas-Gonzalez A, López-Graniel C, González-Enciso A, Cetina L, Rivera L, Mariscal I, Montalvo G, Gómez E, de la Garza J, Chanona G, Mohar A. A phase II study of multimodality treatment for locally advanced cervical cancer: neoadjuvant carboplatin and paclitaxel followed by radical hysterectomy and adjuvant cisplatin chemoradiation. Ann Oncol 2003; 14: 1278-84.
[17] Lorusso D, Ramondino S, Mancini M, Zanaboni F, Ditto A, Raspagliesi F. Phase II trial on cisplatin-adriamycin-paclitaxel combination as neoadjuvant chemotherapy for locally advanced cervical adenocarcinoma. Int J Gynecol Cancer 2014; 24: 729-34.
[18] Elliott P. Lymph node metastases, cell type, age, HPV status and type, neoadjuvant chemotherapy and treatment failures in cervical cancer. Int J Gynecol Obstet 1995; 49 Suppl: S17-25.
[19] Choi CH, Kim TJ, Lee JW, Kim BG, Lee JH, Bae DS. Phase II study of neoadjuvant chemotherapy with mitomycin-c, vincristine and cisplatin (MVC) in patients with stages IB2–IIB cervical carcinoma. Gynecol Oncol 2007; 104: 64-69.
[20] Bae JH, Lee SJ, Lee A, Park YG, Bae SN, Park JS, Namkoong SE. Neoadjuvant cisplatin and etoposide followed by radical hysterectomy for stage 1B-2B cervical cancer. Gynecol Oncol 2008; 111: 444-448.
[21] Chen H, Liang C, Zhang L, Huang S, Wu X. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: A randomized study. Gynecol Oncol 2008; 110: 308-315.
[22] Namkoong SE, Park JS, Kim JW, Bae SN, Han GT, Lee JM, Jung JK, Kim SJ. Comparative study of patients with locally advanced stages Ib and II cervical cancer treatment by radical surgery with and without preoperative adjuvant chemotherapy. Gynecol Oncol 1995; 59: 136-42.
[23] He L, Wu L, Su G, Wei W, Liang L, Han L, Kebria M, Liu P, Chen C, Yu Y, Zhong M, Wang W. The efficacy of neoadjuvant chemotherapy in dif-

ferent histological types of cervical cancer. Gynecol Oncol 2014; 134: 419-425.
[24] Teramae M, Fukuda T, Wada T, Kawanishi M, Imai K, Yamauchi M, Yasui T, Sumi T. Sirtuin1 expression predicts the efficacy of neoadjuvant chemotherapy for locally advanced uterine cervical cancer. Mol Clin Oncol 2015; 3: 73-78.
[25] Chung HH, Kim MK, Kim JW, Park NH, Song YS, Kang SB, Lee HP. XRCC1 R399Q polymorphism is associated with response to platinum-based neoadjuvant chemotherapy in bulky cervical cancer. Gynecol Oncol 2006; 103: 1031-1037.
[26] Kim K, Kang SB, Chung HH, Kim JW, Park NH, Song YS. XRCC1 Arginine194Tryptophan and GGH-401Cytosine/Thymine polymorphisms are associated with response to platinum-based neoadjuvant chemotherapy in cervical cancer. Gynecol Oncol 2008, 111: 509-515.
[27] Hwang YY, Moon H, Cho SH, Kim KT, Moon YJ, Kim SR, Kim DS. Ten-year survival of patients with locally advanced stage IBeIIB cervical cancer after neoadjuvant chemotherapy and radical hysterectomy. Gynecol Oncol 2001; 82: 88-93.
[28] Edelmann DZ, Anteby SO. Neoadjuvant chemotherapy for locally advanced cervical cancer-where does it stand? A review. Obstet Gynecol Surv 1996; 51: 305-13.
[29] Sardi JE, Giaroli A, Sananes C, Ferreira M, Soderini A, Bermudez A, Snaidas L, Vighi S, Gomez Rueda N, di Paola G. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. Gynecol Oncol 1997; 67: 61-9.
[30] Yamakawa Y, Fujimura M, Hidaka TMD, Hori S, Saito S. Neoadjuvant intraarterial infusion chemotherapy in patients with stage IB2-IIIB cervical cancer. Gynecol Oncol 2000; 77: 264-70.
[31] Panici PB, Scambia G, Baiocchi G, Greggi S, Ragusa G, Gallo A, Conte M, Battaglia F, Laurelli G, Rabitti C, et al. Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. Prognostic factors for response and survival. Cancer 1991; 67: 372-9.
[32] Eddy GL, Manetta A, Alvarez RD, Williams A, Creasman WT. Neoadjuvant chemotherapy with Vincristin and Cisplatin followed by radical hysterectomy and pelvic lymphaden- ectomy for FIGO stage IB bulky cervical cancer: a gynecologic oncology group pilot study. Gynecol Oncol 1995; 57: 412-6.
[33] Ye Q, Yuan HX, Chen HL. Responsiveness of neoadjuvant chemotherapy before surgery predicts favorable prognosis for cervical cancer patients: a meta-analysis. J Cancer Res Clin Oncol 2013; 139: 1887-98.