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The efficacy and safety of neoadjuvant chemotherapy in the treatment of locally advanced cervical cancer: A randomized multicenter study☆

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HIGHLIGHTS

- NACT reduces rate of patients requiring postoperative radiation by eliminating pathological risk factors, including LVSI and deep stromal invasion.
- IP as neoadjuvant chemotherapy has similar efficacy comparing to TP, but higher rates of neutropenia and diarrhea.
- LVSI was the only factor that indicates prognosis.

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ABSTRACT

Objective. This study sought to evaluate the toxicity and curative effect of irinotecan plus cisplatin neoadjuvant chemotherapy (NACT) for stage Ib2, IIa2, and IIb cervical cancer patients.

Methods. A total of 219 patients were randomly assigned to two groups: 109 patients were treated with 1–2 cycles of chemotherapy (NACT group), and 110 patients in the control group were treated directly with surgery (DS group). Patients in the NACT group were randomly assigned to two groups: 50 patients were treated with irinotecan plus cisplatin followed by surgery (IP group), and 59 patients were treated with paclitaxel plus cisplatin followed by surgery (TP group). Patients with pathological recurrence risk factors received post-operative radiotherapy.

Results. Survival analysis revealed no significant difference in disease-free survival (DFS) or overall survival (OS) between the NACT and DS groups. Analysis of clinicopathologic factors showed that the lymphovascular space invasion (LVSI) and deep stromal invasion rates were significantly lower in the NACT group. Grade 3/4 neutropenia and grade 3/4 diarrhea were both higher in the IP group than in the TP group. DFS and OS were similar in the IP and TP groups. Univariate analysis showed that LVSI was the only factor associated with DFS.

Conclusion. NACT did not improve overall survival but did reduce the number of patients who received post-operative radiotherapy. NACT consisting of irinotecan plus cisplatin for cervical cancer showed similar efficacy and higher toxicity compared with the use of paclitaxel plus cisplatin, although the toxicity was tolerable.

1. Introduction

Cervical cancer is a common malignant tumor and the fourth leading cause of death among women. Surgery is the main treatment for early cervical carcinoma (stages Ia, Ib1, IIa1), whereas the use of surgery remains controversial in the treatment of locally advanced cervical cancer (LACC, stages Ib2, IIa2, IIb). Based on the GLOBOCAN 2014 estimates, the age at which women develop cervical cancer is decreasing. Cervical cancer affects approximately 0.7% (1/157) of the United States population, and 0.3% (1/348) of patients with cervical cancer are younger than 49 years of age [1]. Thus, treatment that protects physiological function and improves quality of life is important. The use of preoperative neoadjuvant chemotherapy (NACT) can improve patient quality of life by inducing tumor regression, reducing the difficulty of surgery, improving the resection rate, restoring the normal ovary for premenopausal patients, and reducing the vaginal injury

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caused by radical radiotherapy [2]. A meta-analysis by Kim et al. [3] showed that the use of NACT in FIGO stage IB1–IIA cervical cancer decreased the incidence of a large tumor size (≥4 cm) and reduced lymph node metastasis and distant metastasis when compared to radical surgery in all studies and randomized controlled trials (RCTs). Furthermore, NACT reduced the need for adjuvant radiotherapy in all studies. Accordingly, one goal of this study was to explore the efficacy of NACT for LACC.

Irinotecan hydrochloride is a derivative of camptothecin. Its active metabolite, SN-38, inhibits DNA topoisomerase I and induces irreversible DNA damage leading to tumor cell death [4]. Irinotecan shows a good curative effect for late, recurrent and metastatic cervical cancers [5]. Yamaguchi et al. [6] reported that NACT with irinotecan hydrochloride and a platinum-based drug followed by radical hysterectomy was effective in more than 75% of cases of locally advanced cervical cancer. Paclitaxel plus platinum is considered an effective regimen and is widely used in clinical practice. However, there have been only a few reports comparing irinotecan to paclitaxel as NACT in a Chinese population with cervical cancer. Thus, another goal of this study was to investigate the role of irinotecan in combination with cisplatin as NACT for locally advanced cervical cancer in China.

This study was a prospective, open-label, randomized, multicenter study to compare the clinical efficacy and safety of neoadjuvant chemotherapy (using irinotecan plus cisplatin, or paclitaxel plus cisplatin) plus radical surgery for locally advanced cervical cancer (stage Ib2, IIa2, or IIb). We hypothesized that NACT would not improve the survival rate. We also hypothesized that NACT consisting of irinotecan plus cisplatin for cervical cancer would show similar efficacy as paclitaxel plus cisplatin.

2. Patients and methods

2.1. Patients

All patients were enrolled from one of three hospitals (Department of Gynecologic Oncology, Affiliated Tumor Hospital of Guangxi Medical University; Department of Gynecology, The Red Cross Hospital of Yulin; Department of Gynecology, 181st Hospital of Chinese People's Liberation Army) between September 2010 and June 2012. The ethics committees of the three hospitals approved this study. All patients received an explanation of the aims of the study and provided signed informed consent. All of the samples were collected from primary lesions during surgery and stored in liquid nitrogen.

2.2. Eligibility criteria

The eligibility criteria included the following: FIGO stage (2009 version) Ib2, IIa2, or IIb cervical cancer through gynecological examination by two veteran gynecologic oncologists; age less than 70 years; performance status score ≤2 assessed by Zubrod-ECOG-WHO; suitable bone marrow reserve (white blood cell count $\geq 4 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L); no obvious abnormalities in the heart, lung, liver and kidney functions; no serious internal medical diseases; no distant metastasis; signed informed consent; good compliance and ability to

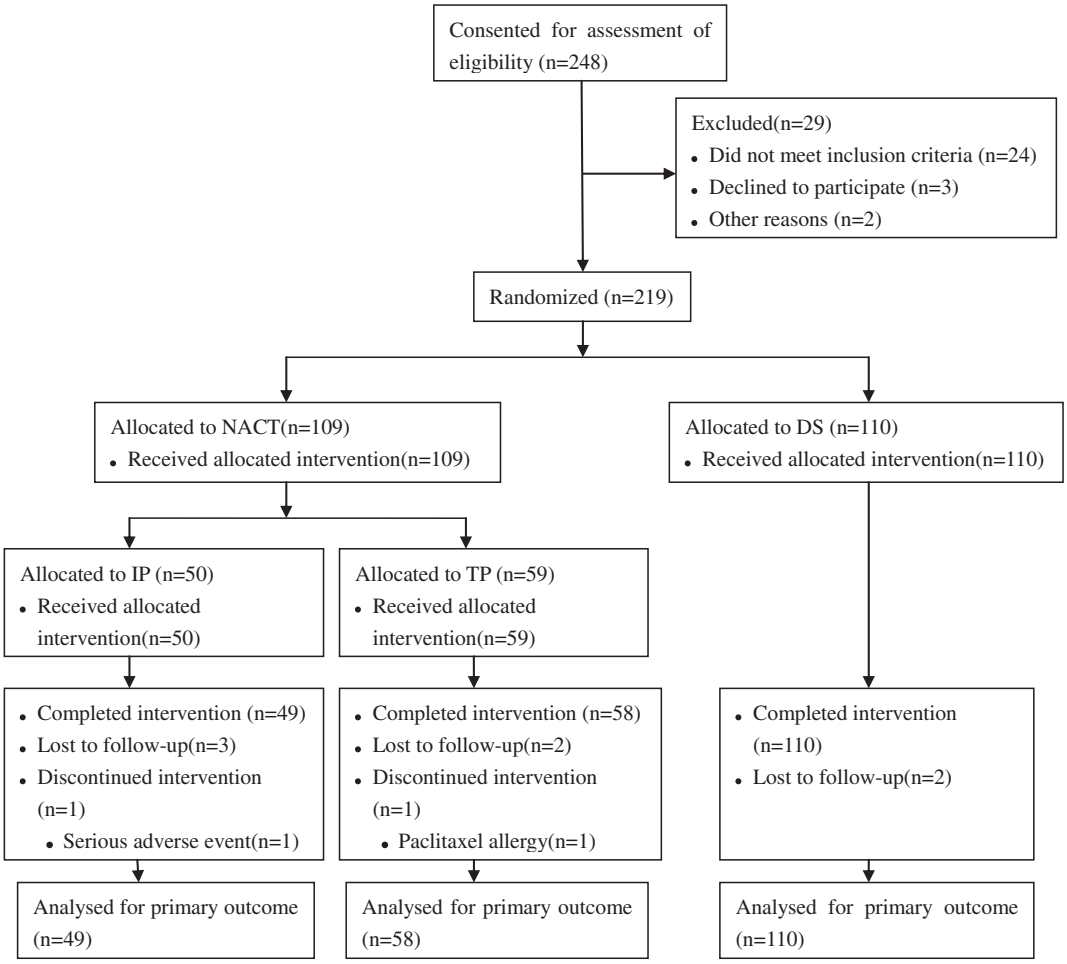

Fig. 1. Consort flow diagram.