

Research Article

Clinical Evaluation of Neoadjuvant Chemotherapy Followed by Radical Hysterectomy in the Management of Cervical Cancer Stage IIB***Evaluasi Klinis Kemoterapi Neoadjuvan Diikuti oleh Radikal Histerektomi dalam Pengelolaan Kanker Serviks Stadium IIB***

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Abstract

Objective: To evaluate the clinical efficacy, operability, radicality, toxicity, and incidence of recurrences of neoadjuvant chemotherapy (NAC) followed by radical hysterectomy (RH) among patients with stage IIB cervical cancer.

Method: This is an observational clinical study at Dr. Moh. Hoesin Hospital, Palembang. Data were analyzed from 27 patients who matched the inclusion criteria and underwent 3 cycles of neoadjuvant chemotherapy (NAC) with Paclitaxel (75 mg/m²) in combination with Cisplatin (50 mg/m²) and Docetaxel (75 mg/m²) combined with Carboplatin (300 mg/m²) according to AUC 6, followed by radical hysterectomy from January 2012 until December 2013.

Result: The operability rate after NAC was 96.4%. Lymph node metastases were negative in 75% of patients, and we found bilateral lymph node metastases in 14.3% of patients. Parametric infiltrations were negative in 85.7% of the patients, and positive in 14.3% of patients. No vaginal infiltrations were found. As much as 89.3% of the patients did not experience any side effect, while anemia and thrombocytopenia were found in 10.8% of the patients. We found that 7.1% of patients had recurrences within 6 months interval.

Conclusion: NAC followed by radical hysterectomy showed significant advantages for patients with stage IIB cervical cancer, with fewer side effects. However, long-term evaluation and a larger number of patients are required to confirm this result.

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Keywords: cervical cancer, neoadjuvant chemotherapy, radical hysterectomy

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Abstrak

Tujuan: Untuk mengetahui efikasi klinis, operabilitas, radikalitas, toksisitas, dan angka rekurensi dari pemberian kemoterapi neoadjuvan diikuti dengan histerektomi radikal pada pasien kanker serviks stadium IIB.

Metode: Penelitian ini adalah penelitian observasional klinis yang dilakukan di RSUP Dr. Moh. Hoesin, Palembang. Data dianalisis dari 27 pasien yang memenuhi kriteria inklusi, dan menjalani kemoterapi neoadjuvan dengan regimen Paclitaxel (75 mg/m²)-Cisplatin (50 mg/m²) dan Docetaxel (75 mg/m²)-Carboplatin (300 mg/m²) berdasarkan AUC 6, sebanyak 3 siklus dilanjutkan dengan histerektomi radikal dari Januari 2012 sampai Desember 2013.

Hasil: Angka operabilitas setelah dilakukan kemoterapi adjuvan adalah 96,4%. Pada 75% pasien tidak ditemukan metastasis ke kelenjar getah bening, dan didapatkan metastasis ke kelenjar getah bening bilateral pada 14,3% pasien. Tidak ditemukan infiltrasi parametrium pada 85,7% pasien, dan ditemukan infiltrasi pada 14,3% pasien. Tidak ditemukan infiltrasi vagina pada seluruh pasien. Didapatkan efek samping berupa anemia dan trombositopenia sebanyak 10,8%, sedangkan pada 89,3% pasien tidak didapatkan efek samping. Sebanyak 7,1% pasien mengalami rekurensi dalam interval 6 bulan setelah pembedahan.

Kesimpulan: Kemoterapi neoadjuvan diikuti dengan histerektomi radikal memberikan manfaat yang signifikan pada pasien kanker serviks stadium IIB. Namun, untuk mengkonfirmasi hasil dari penelitian ini dibutuhkan evaluasi jangka panjang dan jumlah sampel yang lebih besar.

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Kata kunci: histerektomi radikal, kanker serviks, kemoterapi neoadjuvan

INTRODUCTION

Globally, cervical cancer is the third most common female cancer, with over 500,000 new cases diagnosed every year according to the WHO.¹ More than 85% of these cases and deaths occur in economically developing and medically underserved countries, largely in sub-Saharan Africa, South America, and South-Central Asia, where it is often

the second most common female cancer. There are still almost 300,000 deaths from this disease recorded annually.²

According to the staging of cervical cancer by the International Federation of Gynecology and Obstetrics (FIGO) in 2009, stage IIB is a locally advanced stage of disease, characterized by tumor larger than 4 cm, with involvement of the upper 2/3 of the va-

gina, bilateral or unilateral parametrial involvement without extension to the pelvic sidewall.³ Currently, there is no international agreement on how FIGO stage IIB patients should be treated. The National Comprehensive Cancer Network (NCCN) guidelines recommend cisplatin-based chemoradiotherapy as a primary treatment for FIGO stage IIB disease. More recently, several opinions have been voiced on the efficacy of neoadjuvant chemotherapy (NAC) followed by surgery compared to concomitant radiotherapy and chemotherapy in patients with FIGO IIB cervical cancer.³⁻⁵

In this study, we aim to evaluate the clinical efficacy, toxicity, and recurrences of neoadjuvant chemotherapy followed by radical hysterectomy (RH) among patients with cervical cancer stage IIB.

METHODS

This is an observational clinical study at Dr. Moh. Hoesin Hospital, Palembang, Indonesia. Data were analyzed from 28 patients with stage IIB cervical cancer who underwent treatment between January 2012 and December 2013. Approval was provided by the Research Ethics Committee.

Patients were evaluated by board-certified gynecologic oncologists. The evaluation consists of physical examination, transvaginal ultrasonography, and thoracic radiography. Intravenous pyelography, magnetic resonance imaging, and computed tomography were performed as considered appropriate.

The inclusion criteria were all patients who underwent neoadjuvant chemotherapy for 3 cycles followed by type III radical hysterectomy, unless it was contraindicated, as determined by physical examination. The regimens of NAC were cisplatin-paclitaxel, and docetaxel-carboplatin with a three weekly interval. The exclusion criteria were patients who received more than 3 cycles of NAC, and refused to undergo radical hysterectomy.

Periodic follow-up of patients included post-operative adjuvant therapy, physical examination, vaginal cytology, and imaging such as thoracic ra-

diography, computed tomography, or magnetic resonance imaging continued until March 2014. All data from the patients were recorded and analyzed using SPSS version 18.0.

RESULTS

During the study period, 28 patients with stage IIB cervical cancer were treated in Dr. Moh. Hoesin Palembang, Indonesia. All of them received 3 series of NAC with the regimen Docetaxel-Carboplatin and Paclitaxel-Cisplatin. The kinds of regimen the patients received are detailed in Table 1. Twenty-seven of them then underwent radical hysterectomy. As many as 26 patients (92.9%) underwent type II radical hysterectomy, and one of them (3.6%) underwent type I radical hysterectomy.

The age of the patients ranged from 29 to 59 years old. The majority of our patients had squamous cell carcinoma of the cervix (82.1%). The clinical features of our patients before NAC and the type of histopathology are summarized in Table 2.

After being treated with NAC, the patients were evaluated; and 27 of them were assessed as operable and underwent radical hysterectomy. One of them was found to be inoperable.

The toxicities associated with NAC were predominantly grade 1 and grade 2, including bone marrow suppression with leukopenia, thrombocytopenia, and a decrease in hemoglobin, which were in 3.6% of the patients for each group. No grade 3 and 4 toxicities were observed.

Metastasis was evaluated according to the pathologic data reported from surgical specimens including lymph nodes metastasis, positive surgical margin, and parametric infiltration. Positive surgical margin was found in one patient (3.6%) and 26 patients did not have infiltration in the surgical margins. Four of the patients (14.3%) showed parametric infiltration. Four patients (14.3%) showed bilateral lymph node metastases, and 2 patients showed unilateral lymph nodes metastases. The clinical features of our patients after surgery are presented in Table 3.

Table 1. Main Regimens of NAC

Regimen	Number of Patients Based on Histopathologic Types		
	Squamous	Adenocarcinoma	Clear cell
Docetaxel - Carboplatin	2		
Paclitaxel - Cisplatin	21	4	1

Table 2. Clinical Features of the Study Subjects (n=28)

	n (%)
Age	
29-39	4 (14.3%)
40-49	14 (50%)
50-59	10 (35.7%)
Tumor diameter, cm	
≤ 4 cm	17 (60.7%)
>4 cm	11 (39.3%)
Histology	
Squamous	23 (82.1%)
Adenocarcinoma	4 (14.3%)
Clear cell	1 (3.6%)
Cancer free space (CFS)	
25%	3 (10.7%)
50%	13 (46.4%)
75%	4 (14.3%)
100%	8 (28.6%)
Operability	
Operable	27 (96.4%)
Not operable	1 (3.6%)
Type of hysterectomy	
Type II	1 (3.6%)
Type III	26 (92.9%)
Not performed	1 (3.6%)
Toxicities	
Grade I	1 (3.6%)
Grade II	1 (3.6%)
None	26 (92.8%)

Table 3. Clinical Features after Radical Hysterectomy

	n (%)
Positive lymph nodes	
Bilateral	4 (14.3%)
Unilateral	2 (7.1%)
Negative	21 (75%)
Unknown	1 (3.6%)
Parametrial invasion	
Positive	4 (14.3%)
Negative	23 (82.1%)
Unknown	1 (3.6%)
Surgical margin	
Positive	1 (3.6%)
Negative	26 (92.8%)
Unknown	1 (3.6%)

Local recurrence to the vagina after 6 months was observed in two patients, and 26 patients showed no incidence of recurrence. Until May 2014, the survival rate of the patients showed that 27 of the patients (96.4%) were still alive with no progression of disease, while one patient (3.6%) died due to disease complication.

Table 4. Treatment Outcome

	n (%)
Local recurrence after 6 months	
Positive	2 (7.2%)
Negative	26 (92.8%)
Death	
Positive	1 (3.6%)
Negative	27 (96.4%)

DISCUSSION

Neoadjuvant chemotherapy is widely used in stage IIB cervical cancer patients. In this study all patients were given three cycles of intravenous NAC with three weekly intervals. This method is convenient and does not require any special equipment. In this study, NAC showed greater clinical values.^{4,6,7}

It remains controversial as to whether NAC confers any clinical benefits in the treatment of cervical cancer. In a phase III trial in stage IB2 cervical cancer comparing NAC followed by surgery with surgery alone. Eddy et al reported similar recurrence rates and death rates between the two groups, and no evidence that NAC conferred any additional objective benefits.⁷ Nevertheless, NAC continues to be used as it may contribute to ease surgical intervention by reducing tumor size. It may also be useful as a preliminary treatment while the patient is on a waiting list for surgery.⁸⁻¹⁰ Matsumura et al showed an average of 1.4 courses of NAC with as many as 58.7% (27/46) of the patients receiving only one cycle of NAC, suggesting that the benefit conferred was that of tumor reduction rather than survival benefit.¹¹ Platinum-based chemotherapy was considered the most effective regimen in chemotherapy for cervical cancer. Sugiyama et al reported a 78% response rate for this combination in NAC for cervical cancer.¹²

The few studies using NAC (platinum-based) to treat cervical cancer have reported a response rate

of 66.6% to 94%. In this study, after receiving 3 cycles of NAC prior to radical hysterectomy, we found that 96.4% of patients were operable, and only one patient was not operable. Grade 1 and grade 2 toxicities were found in 3.6% of patients in both groups. Positive surgical margins were found in one patient (3.6%). Whereas, four of the patients (14.3%) showed parametric infiltration, 14.3% of patients showed bilateral lymph nodes metastases, and two of them showed unilateral lymph node metastases. Local recurrence to the vagina after 6 months was found in two patients. The survival rate of the patients showed that 27 of the patients (96.4%) were still alive with no progression of disease after 6 months, while one of the patients (3.6%) died due to disease complication.

CONCLUSION

In summary, the results of the current study indicate that NAC followed by radical hysterectomy is a viable option in the treatment of stage IIB cervical cancer. This treatment may allow avoidance of the long-term toxicities that can arise from radiotherapy and chemotherapy alone. NAC appears to offer an advantage in terms of tumor reduction prior to surgical intervention, with mild toxicity.

Further studies are needed, with a bigger sample size in a multicenter randomized clinical trial setting, and with longer duration of follow up.

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