Srinagarind Hospital experience in concurrent chemoradiation for 100 patients with stage IB2 to IVA uterine cervical cancer

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Abstract
Purpose. The aim of this study was to determine responses, acute adverse effects, and survival outcomes of women with stage IB2 to IVA treated with weekly cisplatin concurrent with pelvic irradiation at Srinagarind Hospital.

Materials and methods. The medical records of 100 women with cervical cancer stage IB2 to IVA who were treated with weekly cisplatin 40mg/m² concurrent with pelvic radiotherapy at Srinagarind Hospital between January 2003 and June 2006 were reviewed and analyzed.

Results. During the study period, 100 women were eligible for analysis, with a mean age of 46 years (range 24–60 years). Distribution according to International Federation of Gynecology and Obstetrics (FIGO) staging was IB2 1.0%, IIB 47.0%, IIIB 51.0%, and IVA 1.0%, respectively. A total of 86 patients received five or more cycles of weekly cisplatin. Grade 3 and 4 hematologic toxicities were found in 6.0%. The overall response rate was 97.0%. Complete response was achieved in 86 patients (86.0%) and partial response in 11 patients (11.0%). Stable disease was found in 1 patient (1.0%) but no progressive disease was found. Progression-free survival and overall survival rate were 69.6% and 96.1%, respectively.

Conclusion. Weekly cisplatin (40mg/m²) concurrent with pelvic irradiation for locally advanced cervical cancer was effective with acceptable toxicity in Thai women.

Key words Cervical cancer · Concurrent chemoradiation · Cisplatin · Response

Introduction
Cervical cancer remains a major health problem worldwide, particularly in Asia, Africa, and Latin America. In 2000, the estimation of new cases was 230 000 cases (8.7% of women cancer) and 200 000 deaths per year. In Thailand, the incidence of cervical cancer was 20.9 per 100 000 women-years. Khon Kaen University's Cancer Unit reported that the incidence of cervical cancer in Khon Kaen province was 17.2 : 100 000, making it the most frequent cancer among women in 2004. The cervical cancer incidence is high because Thailand’s cervical cancer screening coverage is still low. About 80%–90% of Thai patients diagnosed with cervical cancer present with advanced disease. Whereas cure rates approach 90% for patients with stage I disease, survival dramatically diminishes for patients with higher-stage disease. Patients with bulky tumors have a particularly poor prognosis.

In February 1999, the current practice of treating cervical cancer has been challenged by five large randomized Phase III trials from the U.S. National Cancer Institute. The results of these trials showed an overall survival advantage of 30%–50% for cisplatin-based therapy given concurrently with pelvic irradiation when compared to either irradiation alone or irradiation concurrent with non-platinum-containing chemotherapy. Based on these five experimental trials, the new guideline recommended incorporation of concurrent cisplatin-based chemotherapy with irradiation for the treatment of locally advanced cervical cancer. Cisplatin is presently
the most active cytotoxic agent against cervical cancer with only moderate bone marrow toxicity; therefore, cisplatin is the drug of choice for concurrent chemoradiation. Additionally, cisplatin was hypothesized to have the mechanisms of radiosensitizing activity, such as inhibition of the repair of sublethal and potentially lethal radiation damage and hypoxic cell sensitization.11,12 Cisplatin has also shown synergy with 5-fluorouracil (5FU) when given concurrently in animal models and in Phase I/II studies.13,14 GOG-120 demonstrated improved survival for the two arms containing cisplatin but with lower toxicity for the arm utilizing weekly cisplatin at 40 mg/m² for 6 weeks.7 Cisplatin could be administered in either a weekly or a daily schedule with similar effectiveness, but weekly cisplatin seems to be the more convenient schedule.15

Concurrent chemoradiation for locally advanced cervical cancer was initiated at Srinagarind Hospital in 2002. The purpose of the present study was to determine responses, acute adverse effects, and survival rates of weekly cisplatin (Placis; Boryung Pharm, Kyungki-Do, Korea) concurrent with pelvic irradiation for patients with locally advanced cervical cancer treated at the authors’ institution.

Materials and methods

Eligibility

The analysis included 100 women with International Federation of Gynecologic and Obstetrics (FIGO) stage IB2 to IVA who were treated with weekly cisplatin (40 mg/m²) concurrent with pelvic irradiation between January 2003 and June 2006. The medical records of these women were reviewed. The inclusion criteria were age <60 years, Karnofsky performance status ≥60, adequate bone marrow function (absolute granulocyte count ≥1500 cells/mm³, platelet count >100 000 cells/mm³), renal function [serum creatinine <1.5 mg/dl, calculated glomerular filtration rate (GFR) >40 ml/min], no ureteric obstruction even on one side, and adequate liver function [bilirubin < twice the institutional upper limit of normal, serum glutamate oxalic transaminase (SGOT) < three times the upper limit of normal].

Patients with human immunodeficiency virus (HIV) infection; patients who were intolerant to chemotherapy due to underlying disease; patients who were pregnant; patients who had had a malignancy within the past 5 years, prior pelvic irradiation, prior systemic chemotherapy, previous hysterectomy, evidence of distant metastases, ureteric obstruction even on one side, or an active serious infection; and those who were breast-feeding were excluded. Pretreatment evaluation included a history, physical and pelvic examinations, evaluation of performance status, clinical tumor measurements, laboratory workup (including complete blood count, urinalysis, renal function tests, liver function tests, intravenous pyelography, chest radiography), and cystoscopy and paraaortic lymph node evaluation by surgery or computed tomography (CT) scan, if clinically indicated.

The study was approved by the Ethical Review Board of the Faculty of Medicine, Khon Kaen University.

Chemotherapy

Cisplatin (40 mg/m²) was given for 6-week cycles concurrent with radiotherapy. The time required for cisplatin prehydration by 2000 ml of 5% dextrose in half-strength saline (DNSS/2) intravenous infusion was approximately 12 h overnight. Dose was calculated by body surface area not to exceed 2.0 m². Toxicity was monitored by gynecologic oncologists. Chemotherapy was initiated during the first week of radiation therapy and then was given every 7 days thereafter for 6 weeks prior to the irradiation of the same day (either external beam or brachytherapy). Supportive treatment was given according to institutional policy.

Radiotherapy

External irradiation and brachytherapy were delivered in a manner consistent with guidelines of the Radiotherapy Division. External beam radiation consisted of 5000 cGy to the whole pelvis delivered in 25 daily fractions over 5 weeks using high-energy photons (10–25 MV) with an additional 600–1000 cGy boost to the sides of grossly involved parametrium. Pelvic radiotherapy was delivered without the use of a midline block if the mass was larger than 5 cm. Midline block was used after 4000 cGy in masses >4 cm, after 3000 cGy in masses >3 cm, and after 2000 cGy in masses <3 cm. Typical field borders (four fields) for the anteroposterior-posteroanterior (AP-PA) field were as follows: The superior border (50% isodose line) was at the L4–L5 interspace; inferior border was at the lower obturator foramen; and lateral borders were 1.5 cm lateral to the bony pelvis. For the lateral fields, the superior and inferior borders were the same, the anterior field border was at the anterior symphysis pubis, and the posterior border included the anterior sacral silhouette. Modifications to the field size were allowed for better coverage of lower vaginal or uterine extension. No paraaortic radiation was given.

External beam radiation was combined with high-dose-rate (HDR) brachytherapy boost to take the point