Salvage Chemotherapy in Recurrent Cervical Cancer with Biweekly Pegylated Liposomal Doxorubicin (Lipo-Dox)

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SUMMARY

Objective: To investigate the objective response rate to and tolerance of biweekly Lipo-Dox (TTY Biopharm Co. Ltd., Taipei, Taiwan) at a dosage of 20 mg/m^2 in previously treated patients with recurrent cervical cancer.

Materials and Methods: This study was performed as a Simon's two-stage phase II clinical trial. Ten patients with recurrent cervical cancer were enrolled between April 2003 and December 2005 at the Mackay Memorial Hospital. Lipo-Dox (20 mg/m^2 intravenous) diluted in 250 mL of 5% dextrose solution was administered at 2-weekly intervals.

Results: The mean age of the patients was 51 ± 11.1 years. The mean number of cycles of Lipo-Dox injection was 4.6 (range, 1–12 cycles). Nine patients (90%) had disease progression. Only one patient (10%) achieved a partial response, and this was also the only patient who experienced WHO grade 2 palmar-plantar erythrodysesthesia, which led to treatment delay for 2 months. The median survival time was 2 months (range, 2–6 months). The majority of patients experienced grade 1 or 2 anemia (30%), leukopenia (20%) or thrombocytopenia (20%), and others exhibited symptoms of nausea and vomiting (30%).

Conclusion: Salvage chemotherapy with Lipo-Dox at a dose of 20 mg/m^2 administered at 2-weekly intervals produced limited responses in patients with recurrent cervical cancer. This trial will not proceed to the second stage. These results may discourage the management of recurrent cervical cancer with single-agent Lipo-Dox in future clinical trials. [*Taiwan J Obstet Gynecol* 2008;47(3):322–326]

Key Words: cervical cancer, chemotherapy, Lipo-Dox, recurrent, liposomal doxorubicin

Introduction

Carcinoma of the cervix (Cx Ca) remains a leading cause of cancer mortality in women worldwide. Approximately 500,000 women develop cervical cancer every year, resulting in an annual mortality of about 200,000 [1].

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In Taiwan, cervical cancer is not only the most frequently reported cancer among women [2], but is also the most common female genital tract neoplasm [3,4], with an incidence of 16 per 100,000 women in 2002 [5]. Radical hysterectomy plus pelvic lymph node dissection is the standard treatment when disease is detected at an early stage (stages IA2–IIA). Concurrent chemo-radiotherapy (CCRT) remains the standard for locally-advanced disease (stages IIB–IVA) [6]. Patients with recurrent Cx Ca are difficult to treat with surgery and radiotherapy alone owing to the presence of distant metastases, and single-agent cisplatin represents the most common treatment option and most effective chemotherapeutic agent for treating recurrent or

metastatic Cx Ca. Most patients achieve a clinically complete (CR) or partial response (PR) with cisplatin-based regiments. The response rates to cisplatin range from 40–60%, with average progression-free and overall survivals of 4.1 and 6.7 months, respectively [7]. In addition, the clinical application of cisplatin often results in obstructive uropathy and renal toxicity, which limits its use in some women. There is, therefore, an urgent need to identify new chemotherapeutic agents that are less toxic and have higher response rates and longer response durations for treating platinum-resistant squamous cell carcinoma (SCC) of the cervix.

Polyethylene glycol-coated (pegylated) liposomal doxorubicin (PLD) is designed for the delivery of a liposomal form of doxorubicin [8] (Caelyx, Schering Plough International, Kenilworth, NJ, USA) to the sites of solid tumors [9]. The efficacy of PLD in women has already been demonstrated in studies of ovarian carcinoma [10–12], breast cancer [13], and Kaposi sarcoma [14]. Lower risks of musculoskeletal disorders and alopecia, and fewer grade 3/4 toxicities have been shown in women with relapsed ovarian cancer when comparing single-agent PLD with paclitaxel [10] and topotecan [11,12], respectively.

Lipo-Dox (TTY BioPharm, Taipei, Taiwan) is a second-generation PLD drug containing distearoylphosphatidylcholine that has been commercially available in Taiwan since 1998. We have recently demonstrated, in a multicenter phase II trial, that Lipo-Dox at 45 mg/m^2 every 4 weeks is effective against recurrent, platinum-resistant epithelial ovarian cancer [15]. The purpose of this study was to extend these previous findings by investigating the activity of biweekly Lipo-Dox (20 mg/m^2) in previously treated patients with recurrent Cx Ca at a single institution.

Materials and Methods

Previously treated patients diagnosed with recurrent Cx Ca between April 2003 and December 2005, and aged 18–75 years were eligible for inclusion in the study. Diagnoses were confirmed either by radiologic imaging studies (chest X-ray, computed tomography, technetium Tc 99 whole body bone scan) or by elevated tumor markers (SCC, carcinoembryonic antigen [CEA] or CA-125). All selected patients were required to fulfill the following diagnostic criteria: bone marrow function (granulocyte count > 1,500/mm^3; platelet count > 100,000/mm^3), renal function (creatinine level < 2.5 mg/dL), liver function (bilirubin and liver transaminases < 3.0 times the upper limit of institutional normal), cardiac function (left ventricular ejection fraction > 50%), and Karnofsky performance status (> 60%). Detailed information on the patients was obtained directly from individual medical records and was carefully reviewed. Follow-up information was obtained from chart review of records of clinic visits and from correspondence with patients and physicians. Disease-free survival was defined as the period from the start of primary treatment until clinical or radiologic evidence of recurrence. The follow-up time was defined as the time from initial diagnosis to the time of death or last follow-up. All surviving patients were followed up until June 2006.

Each vial of Lipo-Dox contained 20 mg of PLD. Intravenous premedication was administered with 20 mg dexamethasone (Decadron; NV Organon, Oss, The Netherlands), 50 mg diphenhydramine hydrochloride (Vena; YF Chemical Corp., Taipei, Taiwan), and 300 mg cimetidine (Tagamet; GlaxoSmithKline, London, UK) 30 minutes before PLD infusion. Lipo-Dox (20 mg/m^2) was diluted in 250 mL of 5% dextrose solution and was administered by intravenous infusion over 30 minutes at 2-weekly intervals. Granulocyte colony-stimulating factor was not recommended for prophylactic use but was allowed if grade 4 neutropenia occurred. Patients' responses were measured by pelvic examination, tumor markers (SCC, CEA or CA-125), and radiologic imaging studies including computed tomography scan. The laboratory examinations included complete blood counts and blood chemistry. Complete blood counts were performed biweekly to assess hematologic recovery. Treatment was delayed in patients experiencing serious hematologic and/nonhematologic toxicity. Patients were withdrawn from the study when evidence of disease progression or grade 3 toxicity was observed during treatment. Safety and toxicity were recorded and graded according to the Common Toxicity Criteria (version 2.0) of the U.S. National Cancer Institute. A CR was defined as complete disappearance of all evidence of disease (including image and tumor markers) for at least 4 weeks. A PR was defined as a > 50% decrease in the size of measurable lesions or the reduction of tumor markers for at least 4 weeks. Stable disease was defined as a reduction of < 50% or an increase of < 25% in the tumor size or tumor markers over a period of ≥ 3 months, and progressive disease was defined as an increase of > 25% in the tumor size or tumor markers compared with pretreatment values. All relevant data required for calculating response rates and survivorship were collected in this study.

The clinical trial was approved by the Institutional Review Boards and Ethics Committees of Mackay Memorial Hospital. Written informed consent in line with institutional guidelines was obtained at enrollment.