Long-term follow-up of neoadjuvant intraarterial chemotherapy using an original four-lumen double-balloon (4L-DB) catheter for locally advanced uterine cervical cancer

Introduction

Uterine cervical cancer is one of the most common cancers in women worldwide.\(^1\) Although the 5-year survival rate exceeds 76% for patients with early disease (stages 0-IIA), the 5-year survival for patients with more advanced disease (stages IIIB-IVA) is only 22%–40%.\(^2\) In general, patients with locally advanced cervical squamous cell carcinoma receive primary radiation therapy as standard therapy. Because it is clear that current treatment modalities, including external radiotherapy and brachytherapy, have limited potential for further improvement,\(^3\) new therapeutic approaches for the primary treatment of advanced uterine cervical cancer are needed. For these reasons, new strategies are being tried by several oncology groups around the world. To date, the benefit of cisplatin-based concomitant chemoradiation compared to radiation therapy alone for locally advanced cervical cancer has been shown in some trials.\(^4\) In 1999, a National Cancer Institute Alert, based on the results of these randomized trials, recommended that concomitant chemoradiation should be considered instead of radiotherapy alone in women with cervical cancer. However, by giving chemotherapy prior to radiotherapy, rather than concomitantly, increased radiotherapy toxicity may be less likely.\(^8\) Cisplatin, in both single-agent and combination chemotherapy, has been the most effective and widely used drug for patients with uterine cervical cancer.\(^7\) Recently, neoadjuvant intraarterial chemotherapy (NAIC) followed by radical hysterectomy has been proposed to improve local pelvic control and eradicate distant micrometastases (10–18). Chemotherapy given prior to surgery may render inoperable tumors (stages IIB-IVA) operable and treat metastases. However, it has not yet been clarified whether NAIC has improved long-term survival. In the present study, to reduce the dose-limiting toxicity and increase the antitumor effect, we developed balloon-occluded arterial infusion therapy (BOAI) with an original four-lumen double-balloon (4L-DB) catheter (Clinical Supply Japan, Gifu, Japan; Fig. 1). Also, we evaluated the tumor response, long-term survival benefit, toxicity, and
platinum concentration in the surgical specimens after NAIC using our original 4L-DB catheter in locally advanced cervical cancer.

Patients, materials, and methods

Patients

Between April 1995 and March 2001, 60 patients with primary cervical cancer were enrolled. Eligibility criteria were as follows: (1) International Federation of Obstetricians and Gynecologists (FIGO) stage IIB, stage III, or IVA cervical squamous cell carcinoma; (2) age less than 75 years; (3) World Health Organization (WHO) performance status 0–2; (4) no previous treatment; (5) fulfillment of pretreatment laboratory requirements, including leukocyte count more than 3000/mm³, platelet count more than 100 000/mm³, serum creatinine less than 1.5 mg/dl, serum bilirubin less than 1.5 mg/dl, and normal SGOT and SGPT; (6) patients without other major organ disease; and (7) the patient gave written informed consent for participation. Table 1 summarizes the characteristics of the patients enrolled. The median age was 56 years (range, 27 to 73 years). The clinical stage was IIB with bulky mass in 11 patients, IIIB in 48 (IIIA,1; IIIB, 47), and IVA in 1.

Intraarterial chemotherapy

For intraarterial infusion therapy, we developed an original 4L-DB catheter (Clinical Supply Japan) for the simple and efficient injection of an anticancer agent at a high concentration to target spots in patients with advanced uterine cervical cancer (Fig. 1).

Under local anesthesia, according to Seldinger’s technique, polyethylene catheters of 6-French diameter were inserted through both femoral arteries. Each catheter tip was placed in the internal iliac artery. While the guidewire was detained in the peripheral artery of the internal iliac artery, the catheter was passed through the junction of the uterine artery, which was the target vessel, just distal to the branching out of the superior gluteal artery. To confirm the correct position of the catheter and effective perfusion, pelvic arteriography was performed during catheterization procedures. Each time after the completion of treatment, the catheters were removed and sandbags were used to apply firm pressure over each groin area for 6 h. The regimen included the following: cisplatin 60–70 mg/m² on day 1, mitomycin-C 10–20 mg/m² on day 1, and pirarubicin hydrochloride (THP) 10–20 mg/m² on day 1, for two courses every 21 days. All drugs were administered intraarterially within 30 min in divided doses via the bilateral internal iliac arteries. Hydration with normal saline and 5% dextrose began 3 h before chemotherapy, with careful monitoring of urine volume.

Treatment response

Complete blood cell counts and renal and hepatic function tests were repeated before each course. Toxicity was graded according to the WHO criteria. Disease was monitored with magnetic resonance imaging (MRI; SIGNA MR/i; GE, Slough, UK). Response was measured as the product of the two largest perpendicular diameters of the cervical mass lesion. Patients were evaluated for response with a physical examination and MRI after two courses of therapy. A complete response (CR) was defined as the complete disappearance of all clinically detectable disease. A 50% or more decrease in tumor size constituted a partial response (PR). Stable disease (SD) was defined as no significant change, and progressive disease (PD) was defined as a more than 25% increase in tumor size or the appearance of new lesions.

In addition, histological changes were also evaluated in surgical specimens, using the following criteria of the Japan Society for Cancer Therapy: grade 0 was defined as the absence of degenerative or necrotic change after chemotherapy; grade 1a was defined as degeneration, necrosis, or...