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Neoadjuvant chemotherapy followed by radical surgery in patients affected by vaginal carcinoma

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Abstract

Background. Radiotherapy represents the standard treatment for patients affected by FIGO stage II vaginal cancer. Several authors have suggested that neoadjuvant chemotherapy followed by radical surgery might be a valid treatment option in patients affected by cervical cancer. The objective of this study was to analyse the feasibility and results obtained by neoadjuvant chemotherapy followed by surgery in patients affected by invasive vaginal cancer with paravaginal tissue involvement not reaching the pelvic side wall.

Methods. Eleven patients affected by FIGO stage II vaginal cancer were treated with paclitaxel 175mg/m^2 and cisplatin 75mg/m^2 every 21days for three courses followed by radical surgery.

Results. All patients were subjected to the 3 planned chemotherapy courses. Three (27%) patients achieved a complete clinical response and seven (64 %) patients achieved a partial clinical response. All patients were subjected to radical hysterectomy and vaginectomy. At a median follow up of 75months two (18%) patients suffered a disease recurrence and one of these died of disease.

Conclusions. Neoadjuvant chemotherapy followed by radical surgery is a feasible therapeutic strategy with good short- and long-term results. In women affected by vaginal cancer, a larger series reporting the result of this therapeutic strategy or the results obtained by surgery alone will aid physicians to choose the best therapeutic strategy for each individual patient.

Keywords: Vaginal cancer; Neoadjuvant chemotherapy; Radical surgery

Introduction

Vaginal cancer is a rare gynecologic malignancy. In United States 2420 new cases are diagnosed and 820 deaths occur annually [1]. According to the International Federation of Gynecology and Obstetrics (FIGO), cases should be classified as vaginal carcinomas only after having excluded a cervical, urethral or vulvar tumor involvement [2]. Squamous cell carcinomas account for more than 70% of vaginal primary tumors and usually occur in elderly patients.

The standard treatment for patients with stage II vaginal carcinoma is radiotherapy [3]. Unfortunately, this treatment is associated with a high risk of severe acute and late complications such as lymphedema, local irritation, and desquamation; buttock or groin pain due to sacral and pubic fractures can also occur [4]. Furthermore, several women complain vaginal stenosis and dyspareunia. Some authors [5,6] have advocated radical surgery with or without associated radiation as an alternative to standard treatment. In order to increase survival and reduce iatrogenic morbidity, new therapeutic strategies are being considered [7].

Neoadjuvant chemotherapy followed by radical surgery (NACT followed by RS) has demonstrated to be an effective treatment strategy in terms of survival in women affected by locally advanced cervical tumors [8]. In these patients, Sardi et al. [9], reported a significantly higher response rate of

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central lesions (cervix and vagina) as compared to parametrial ones. This observation justifies the attempt to extend the indication of NACT followed by RS also to women affected by primary vaginal cancer.

The objective of the present trial is to report the results of neoadjuvant chemotherapy followed by radical surgery in patients affected by FIGO stage II vaginal cancer. The aim of this study is to evaluate short- and long-term morbidity and survival efficacy of this therapeutic strategy.

Patients and methods

Patients

From May 1998 to December 2002 consecutive patients affected by vaginal cancer FIGO stage II were assessed for eligibility. The internal review board approved (IRB) the study. Eligibility criteria were: stage II vaginal carcinoma, age $\leq$75years, no concurrent or previous malignant disease, no previous radiation therapy, WHO performance status $\leq$1, adequate renal, hepatic and cardiac function, signed informed consent, and BMI <35. Enrolled patients were submitted to NACT+RS.

Before chemotherapy the treatment strategy was explained to the patients and written informed consent was obtained. All patients were subjected before and after the three planned chemotherapy cycles to instrumental, clinical and surgical staging. This included blood chemistries, chest X ray, EKG, MRI, and when indicated proctoscopy, cystoscopy with biopsy and diagnostic laparoscopy. All patients were subjected to a pelvic examination under anesthesia before and after chemotherapy by senior gynecologic oncologists.

Chemotherapy

Before chemotherapy, standard premedication was given to prevent hypersensitive reactions to paclitaxel. This premedication consisted in dexamethasone 20mg orally administered 12 h and again 6 h before chemotherapy, as well as diphenhydramine 50mg and ranitidine 50mg administered by intravenous injection 30 min before paclitaxel.

The chemotherapy regimen consisted of paclitaxel 175 mg/m^2 administered as a continuous intravenous (IV) infusion in 500 mL of dextrose over a 3-hour period. Following the treatment the patients received 900mL of 0.9% NaCl with mannitol 100 mL IV over a 1-hour period, followed by cisplatin 75mg/m^{2}in 1000 mL 0.9% NaCl IV over a 2-hour period. After completion of cisplatin, the patients received an additional 2 L of 0.9% NaCl that contained potassium and magnesium. Appropriate antiemetics were used before and after the administration of chemotherapy. Courses of paclitaxel and cisplatin were given every 21 days for three cycles.

Chemotherapy was discontinued in cases of progressive disease or unacceptable toxicity. This condition never occurred in the present series. Clinical reassessment was performed at the time of every treatment. Complete blood counts were performed weekly throughout the treatment, and in addition all patients underwent a complete blood count, platelet count, and chemical survey the day chemotherapy was administered. Indication for delaying chemotherapy were creatinine clearance <50 mL/min, WBC$<3\times10^3$/mm^3, granulocyte $<1\times10^3$/mm^3, platelets $<150\times10^3$/mm^3, or if any other clinically relevant toxicity or morbidity occurred. Between cycles, postchemotherapy therapies included erythropoietic growth factor to reduce the grade of anemia; granulocyte-colony-stimulating factor to treat neutropenia; granisetron, dexamethasone, and metoclopramide to reduce nausea and vomiting; and pantoprazole to reduce the symptoms of gastritis. Toxicity was evaluated according to common toxicity criteria (CTC) [10].

Tumor response evaluation

Complete response was defined as the complete disappearance of all measurable disease. Partial response was recorded as >50% reduction in the product of the two longest perpendicular diameters of all measurable lesions. No response or stable disease was defined as <50% decrease or <25% increase in the product of the two longest perpendicular diameters of the measurable lesions. Progressive disease was defined as >25% increase in the product of the two longest perpendicular diameters of one measurable lesion or the appearance of new ones. The evaluation was performed by the same gynecologic oncologists through pelvic examination under anesthesia and MRI results before and after the three courses of chemotherapy.

Surgery

Before surgery, all patients were submitted to mechanical bowel preparation, deep venous thrombosis prophylaxis with low molecular weight heparin (2 h before the operation and postoperatively until complete ambulation), and a short-term antibiotic prophylaxis was performed 2 h prior to surgery (cefazolin 2 g).

All patients were submitted to diagnostic laparoscopy prior to radical surgery as for internal guidelines. In patients with clinically resectable disease radical surgery was carried out. The extirpative procedure was type III radical hysterectomy [11] and radical vaginectomy and bilateral extraperitoneal pelvic lymphadenectomy [12]. If the inferior third of vagina was involved before NACT, also the inguinal lymph node was removed.

Radical vaginectomy technique was as follows: the patient is placed in a lithotomic position and the vaginal wall is exposed using three vaginal retractors. The lesion is delimited by colposcopy after impregnation of the vaginal wall with acetic acid 3%. Methyl blue is injected in the bladder with a Foley catheter. The anterior, posterior and lateral margins of lesions are recognized and the involvement of the vaginal vault is evaluated. Submucosal injection at the 3, 6, 9, and 12o'clock quadrant of adrenalin solution (1/400,000) to reduce bleeding is performed. First of all, a parallel incision of the posterior vaginal wall is performed at least 10mm caudally to the lesion with cold scalpel. The caudal vaginal margin is clamped with Allis forceps to highlight rectovaginal septum. The vagina is