SPANDIDOS PUBLICATIONS

MOLECULAR AND CLINICAL ONCOLOGY 7: 395-398, 2017

Effects of neoadjuvant chemotherapy on patients with primary vaginal squamous cell carcinoma

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Received September 29, 2016; Accepted July 4, 2017

DOI: 10.3892/mco.2017.1328

Abstract. Vaginal cancer is a rare gynecological malignancy, mainly treated by radiotherapy and surgery. However, the effect of neoadjuvant chemotherapy on patients with vaginal cancer has not been extensively evaluated. The aim of the present study was to assess the feasibility and efficacy of irinotecan and cisplatin in the management of patients with vaginal squamous cell cancer (SCC). Two patients with International Federation of Obstetrics and Gynecology (FIGO) stage I and one patient with FIGO stage II vaginal SCC were treated with irinotecan (240 mg) and cisplatin (100 mg) every 3-4 weeks. The effect of chemotherapy after 2-4 courses was assessed and the next step of treatment was determined according to the outcome. In the present study, all 3 patients had complete remission after 2-4 courses of chemotherapy. In case 1, the patient received a total of 6 courses of chemotherapy and had no recurrence after 45 months of follow-up. In case 2, the patient received 4 courses of chemotherapy and partial vaginal resection, and had no recurrence after 48 months of follow-up. In case 3, the patient underwent laparoscopic radical surgery and peritoneal vaginoplasty after 2 courses of chemotherapy, and no residual tumors were identified in the resected tissues on postoperative pathological examination. Effective neoadjuvant chemotherapy may decrease the size of the tumor, induce tumor regression, or even achieve pathologically-confirmed complete tumor eradication. Thus, neoadjuvant chemotherapy with irinotecan combined with cisplatin is a feasible treatment for patients with early-stage vaginal SCC. In the present study, all the patients achieved good therapeutic results following chemotherapy.

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Key words: vaginal carcinoma, surgery, irinotecan, neoadjuvant chemotherapy

Introduction

Vaginal cancer is a rare disease, accounting for only 2% of all gynecological malignancies (1). Squamous cell carcinoma (SCC) is the most common type of vaginal cancer accounting for 90% of primary vaginal carcinomas (2). The incidence of SCC increases with age, with the peak age being 70-79 years. However, 30% of the patients are aged <60 years (3). The diagnosis of primary vaginal carcinoma should exclude synchronous cervical, vulval or urethral cancer (4). There is currently no consensus regarding the treatment of vaginal carcinoma. Surgery and radiotherapy are mainly used for patients with stage I disease. Good 5-year survival rates have been reported in patients with stage II or higher vaginal carcinoma who are treated by radiotherapy. However, traditional radiotherapy is associated with several side effects, such as irradiation injury to the bladder and rectum, vaginal stenosis and dyspareunia, with severe compromise of the patients' quality of life (5,6). Treatment individualization has been recommended for early-stage vaginal cancer. Surgery has achieved satisfactory results for patients with stage I vaginal carcinoma (7,8). It was reported that surgery following neoadjuvant chemotherapy achieved a good therapeutic effect (9-12). However, the effect of chemotherapy on vaginal SCC has not been extensively evaluated and the majority of available data are derived from studies with small-sized samples or case reports, without a universal consensus regarding the chemotherapy regimens.

Neoadjuvant chemotherapy for cervical cancer is currently considered to be efficient (13-15). It has been suggested that, as the vagina and the cervix are lined with the same type of squamous cell epithelium, the same risk factors are present in both cervical and vaginal carcinomas (16). The aim of the present study was to evaluate the effect of neoadjuvant chemotherapy on patients with primary vaginal SCC.

Case reports

Case 1. A 56-year-old woman presented in December 2011 with postmenopausal vaginal bleeding for 2.5 months. The biopsy result revealed keratinizing SCC. The patient was referred to our hospital and pelvic examination indicated a 5x5x2-cm solid tumor in the upper one-third of the posterior wall of the vagina, without invasion of the paracolpium.

The patient was diagnosed with stage I vaginal carcinoma. The computed tomography showed no lesions in other parts of the body. The patient was treated with irinotecan 240 mg and cisplatin 100 mg for 6 courses every 3-4 weeks. The tumor completely regressed after 2 courses of chemotherapy. Colposcopic biopsy confirmed no residual cancer tissue after 4 courses of chemotherapy. Due to the efficacy of chemotherapy, the patient and her family declined further surgery. The patient was followed up for 45 months (last follow-up, April 2016) and she remained cancer-free with restored sexual function.

Case 2. A 39-year-old woman presented in October 2011 with vaginal bleeding for 20 days. The pelvic examination identified a 5x4x1-cm solid tumor in the upper one-third of the left wall of the vagina, invading the paracolpium, but not reaching the pelvic wall. The biopsy revealed poorly differentiated SCC. The computed tomography showed no lesions in other parts of the body. The patient was diagnosed with stage II vaginal carcinoma and was treated with irinotecan 240 mg and cisplatin 100 mg for 4 courses every 3-4 weeks. The tumor completely regressed after 2 courses of chemotherapy. Colposcopic biopsy confirmed the presence of cell hyperplasia after 3 courses of chemotherapy. Radical resection was advised, but the patient wished to preserve her fertility. Partial vaginal resection was performed and no cancer cells were identified on postoperative pathology. The patient received one more course of chemotherapy after surgery and was followed up for 48 months (last follow-up, April 2016), without tumor recurrence.

Case 3. A 43-year-old woman presented in November 2015 with post-coital vaginal bleeding for 7 years and the biopsy revealed moderately differentiated SCC. The patient was referred to our hospital and on pelvic examination a 3.5-cm solid tumor was identified on the middle third of the anterior wall of the vagina (Fig. 1), without invasion of the paracolpium. The patient was diagnosed with stage I vaginal carcinoma. The computed tomography and magnetic resonance imaging showed no lesions in other parts of the body. The patient was treated with irinotecan 240 mg and cisplatin 100 mg for 2 courses every 3 weeks. The tumor completely regressed after 2 courses of chemotherapy (Fig. 2). The patient then received laparoscopic subradical hysterectomy, bilateral adnexectomy, pelvic lymphadenectomy, complete resection of the vagina and peritoneal vaginoplasty (Fig. 3). Postoperative pathological examination identified no cancer cells in the resected tissue. The patient has had a vaginal mould for 6 months postoperatively, without complications (last follow-up, April 2017).

All 3 patients tolerated the chemotherapy well. There were no serious complications, such as bone marrow suppression or diarrhea, which may affect the course of treatment. All 3 patients achieved clinical and pathological complete response confirmed by pathological examination of colposcopic biopsy specimens or surgically resected tissue. Written informed consent was obtained from the patients and their families regarding the publication of their case details.

Discussion

Primary vaginal cancer is a rare gynecological malignancy and its diagnosis should exclude cervical, vulval or urethral cancer. The main histopathological types of primary vaginal carcinoma include SCC, adenocarcinoma, malignant melanoma and sarcoma. SCC is the most common histotype and accounts for 85-95% of all cases (2,3,16). The incidence of SCC increases with age, with ~50% patients aged >70 years at diagnosis. The main pathogenic risk factors include human papillomavirus infection, injury through use of pessaries, previous gynecological disorders, multiple sexual partners, earlier pelvic irradiation, and smoking (16-18). The high-risk prognostic factors include age at onset, tumor size, clinical stage and pathological type. The 5-year survival rate of vaginal SCC was reported to be 84% for stage I, 75% for stage II and 57% for stage III/IV disease (19).

The standard treatment for patients affected by vaginal cancer is radiotherapy. Hiniker *et al* (5) investigated 91 cases of patients with vaginal cancer and reported that the dose of radiation was 70-80 Gy. Platta *et al* (6) investigated 63 patients with vaginal cancer who were treated with radiotherapy. The 5-year survival rate was 73.3% for stage I-II and 34.4% for stage III-IV disease. However, the incidence rate of serious side effects (grade >3) was 23.1%. It was also reported that surgery alone is preferable to radiotherapy for stage I vaginal cancer (7,8). Due to the particular anatomical location of the vagina, the range of resection without injury to the surrounding structures is limited. However, the side effects of radiotherapy, such as vaginal stenosis, paracolpium fibrosis and radiocystitis, may severely compromise the patient's quality of life. Surgery is the recommended treatment for young patients with early-stage vaginal cancer.

There are currently no randomized controlled clinical trials comparing various treatments due to the low incidence of vaginal cancer. Treatment is mainly focused on the management of cervical or vulval cancer and, thus far, a standard treatment for vaginal cancer has not been established. Currently, the purpose of treatment is not only prolongation of survival, but also planning personalized and individualized treatment. New research in the field of gynecological oncology is aimed at preserving the patient's physiological functions and quality of life to the greatest extent possible.

The number of studies on chemotherapy regimens of primary vaginal SCC is limited. It has been reported that the treatment result is satisfactory when using neoadjuvant chemotherapy for early-stage vaginal cancer. A clinical research was performed by Benedetti *et al* (11). Of 11 patients enrolled, 27% achieved complete remission and 64% achieved partial remission after receiving 3 courses of chemotherapy with paclitaxel and cisplatin every 21 days. All the patients were treated with radical hysterectomy and total vaginal resection following chemotherapy. The average follow-up time was 75 months. One patient succumbed to the disease and 2 patients relapsed. The authors suggested that neoadjuvant chemotherapy followed by radical surgery is a feasible therapeutic strategy, with good short- and long-term results. Lv *et al* (12) reported the case of a patient with stage II vaginal cancer. The tumor size was significantly reduced after 2 courses of chemotherapy with bleomycin and cisplatin. The patient received radical hysterectomy, total vaginal resection and vaginal reconstruction using bilateral pudendal thigh fasciocutaneous flaps. The patient remained tumor-free with restored sexual function after 30 months. Thus, surgery may also be performed following

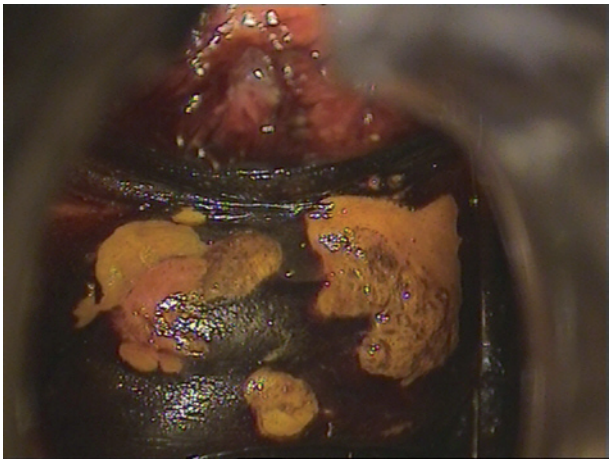

Figure 1. Case 3. Image on colposcopy prior to chemotherapy.

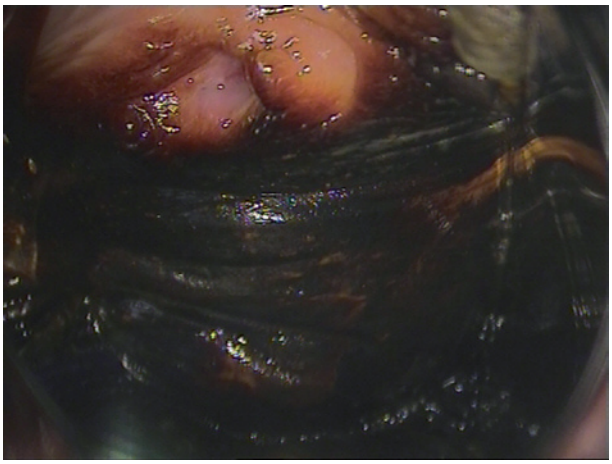

Figure 2. Case 3. Image on colposcopy following chemotherapy.

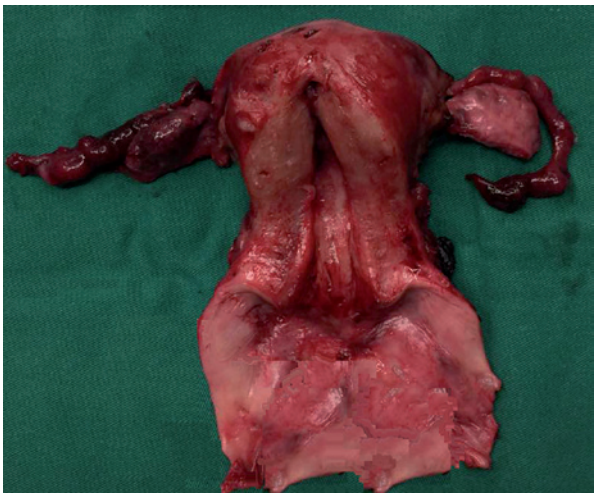

Figure 3. Case 3. Surgical specimen of subradical hysterectomy, bilateral adnexectomy, pelvic lymphadenectomy and complete resection of the vagina.

neoadjuvant chemotherapy for patients with stage II vaginal cancer, but the treatment must be individualized.

Irinotecan is a topoisomerase I inhibitor, specifically acting on the S phase of the cell cycle by impeding DNA synthesis and inhibiting the growth of tumor cells (20). Irinotecan is currently widely applied in the treatment of colorectal, lung, esophageal, cervical and ovarian cancer, as well as other tumors, with good therapeutic outcomes. Tsubamoto *et al* (13) reported 2 cervical cancer patients who wished to maintain their fertility; they received radical trachelectomy after 3 courses of chemotherapy with irinotecan and cisplatin. Postoperative pathological examination confirmed that there were no cancer cells in the resected tissues. Yamaguchi *et al* (21) treated stage IB2 and IIB cervical cancer with irinotecan and nedaplatin, with good therapeutic efficacy. Other studies suggested that the vagina and the cervix are lined with the same type of squamous cell epithelium, and several risk factors are shared by cervical and vaginal carcinoma. Accordingly, the etiology is similar for these two cancers (16). Thus, irinotecan combined with platinum for the treatment of advanced cervical cancer has exhibited confirmed therapeutic efficacy; however, there is little evidence regarding its efficacy against vaginal cancer.

A search through Medline identified only two reports of chemotherapy for vaginal cancer with irinotecan combined with platinum. Umesaki *et al* (9) reported a 48-year-old woman who suffered from stage II vaginal cancer. Pelvic examination identified a 3-cm solid tumor in the middle third of the posterior wall of the vagina. The tumor disappeared after 1 course of chemotherapy with irinotecan and cisplatin. The patient underwent radical hysterectomy, bilateral adnexectomy, pelvic lymphadenectomy and resection of the upper two-thirds of the vagina. Postoperative pathological examination revealed no cancer cells in the resected tissue. The patient was followed up for 1 year and there was no tumor recurrence. Mabuchi *et al* (10) reported a 36-year-old woman who suffered from stage I vaginal cancer. The tumor was sized ~3x4 cm and disappeared after 4 courses of chemotherapy with irinotecan and nedaplatin; however, the vaginal biopsy pathology was vaginal intraepithelial neoplasia (VAIN)III. The patient received partial resection of the vagina and the results of the postoperative pathological examination were also VAINIII. Thus, 2 more courses of chemotherapy were administered. The patient was followed up for 14 menstrual cycles and there was no tumor recurrence. These two reports confirmed the efficacy of irinotecan combined with platinum in the treatment of early-stage vaginal cancer.

In the present study, 3 relatively young patients developed early-stage vaginal cancer. Case 1 was extremely responsive to irinotecan and cisplatin and the tumor completely regressed after 2 courses of chemotherapy. Colposcopic biopsy confirmed absence of residual cancer tissue after 4 courses of chemotherapy. The patient was followed up for 45 months after a total of 6 courses of chemotherapy. No tumor recurrence was found, and the patient's sexual function was restored to normal. Case 2 had stage II vaginal cancer, with a wide range of lesions. There was residual tumor tissue after 3 courses of chemotherapy, but the patient wished to preserve her fertility. The patient was treated with partial vaginal resection, but refused continued treatment after 4 courses of chemotherapy due to amenorrhea; she was followed up for 48 months and there was no tumor recurrence. Case 3 was a 43-year-old patient whose tumor completely regressed after 2 courses of chemotherapy. The patient received laparoscopic subradical hysterectomy, bilateral adnexectomy, pelvic lymphadenectomy, complete

resection of the vagina and peritoneal vaginoplasty. The patient has had a vaginal mould for 6 months postoperatively, without any complications. The 3 patients discussed herein were treated with either chemotherapy or chemotherapy combined with surgery and the curative effect was satisfactory. The lesion size decreased following chemotherapy and the scope and difficulty of the surgery were reduced. Furthermore, the goal of treatment was attained without damaging the bladder, rectum or vagina by radiation. The first 2 patients had no tumor recurrence after long-term follow-up. The treatment outcome and quality of life were satisfactory.

Although there are a few studies available regarding the clinical efficacy of chemotherapy for the treatment of vaginal cancer, the majority included small-sized samples or case reports. Due to the lack of large-sized, multi-centre, randomized controlled trials, no unanimously accepted chemotherapy regimen has been developed to date. The incidence of vaginal cancer is low, mostly affecting elderly patients. However, for young early-stage patients who wish to preserve fertility and sexual function, radiotherapy may affect their quality of life. Thus, treatment should be individualized for such patients; chemotherapy alone or combined with surgery appears to be a feasible option. However, further research is required to determine the standards of chemotherapy regimens, courses and operative methods.

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