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Long-term remission of clear cell carcinoma of the cervix after chemoradiation with 109 cycles of paclitaxel: a case report and literature review

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Summary

Background: Clear cell carcinoma of cervix (CCCC) is a rare cervical neoplasm that is usually associated with diethylstilbestrol (DES) exposure in utero as a primary risk factor. Advanced stage disease typically has poor outcomes and no evidence-based approach exists to guide clinicians in treating this rare disease. *Case:* The authors report a case of locally advanced CCCC in a 37-year-old Caucasian female. She underwent chemoradiation therapy that included 109 courses of paclitaxel chemotherapy until no disease could be detected on imaging studies. She is now disease-free 13 years after discontinuing chemotherapy. *Conclusion:* A prolonged course of single agent paclitaxel after completing standard radiation therapy was successful in achieving remission in a patient with this rare disease.

Key words: Clear cell carcinoma of the cervix; Paclitaxel; Chemotherapy.

Introduction

Clear cell carcinoma of the cervix (CCCC) is a rare entity with diethylstilbestrol (DES) exposure as a main risk factor [1]. It has two incidence peaks, with mean ages of 26 and 71 years at each peak, respectively [2]. Its prevalence has been reported as approximately 4% of cervical adenocarcinomas; however, this percentage is expected to fall with DES no longer in use [3]. Reports have demonstrated that for early stage disease, radical surgery may result in good outcomes [4-5]. Based on these reports, a recent Gynecologic Cancer InterGroup (GCIG) Consensus Review recommends surgical resection as the first line treatment for early stage CCCC [6]. However, advanced stage disease typically has poor outcomes [7], and the GCIG Review could not provide an evidence-based approach to direct the management of patients with advanced stage disease at presentation or with recurrent disease [6]. Therefore, it is important for clinicians who have had successful outcomes in treating this rare disease to share their experience.

Case Report

The present patient was a healthy 37-year-old G0 Caucasian female. She presented in May 1995 to another institution with a complaint of being tired and concerns of being anemic. She also reported a vaginal discharge for two days. Her menses were regular and she did not complain of excessively heavy menses. The patient self-reported that all of her PAP smears had been normal including one approximately two years prior to presentation. Her history was remarkable for DES exposure in utero. She had no medical problems. Her only prior procedure was a wisdom tooth extraction in 1976. She was single and an active smoker. Her family history was notable for a paternal grandmother with uterine cancer.

A clinical exam revealed a foul smelling yellowish discharge. A small mass with a cauliflower-like appearance was extruding from the vaginal opening. A speculum could not be inserted fully into the vaginal opening. A CBC revealed a hemoglobin and hematocrit of 7.6 and 25.7%. She was admitted for transfusion and received two units of pRBCs. The next day, a CT scan revealed enlarged para-aortic nodes up to the renal vessels and up to 2.5 cm in diameter. She was subsequently taken to the operating room the following day and underwent an exam under anesthesia, multiple cervical and vaginal biopsies, fulguration of the tumor with electrocautery in the vagina and cervix, cystoscopy, proctosigmoidoscopy, exploratory laparotomy with peritoneal cytology, and aortic lymphadenectomy. Operative findings were notable for an anterior vagina replaced with a polypoid, very friable, necrotic tumor extending from the cervix to two cm from the urethra. The cervix was replaced by carcinoma and was five- to six-cm in size. There was no appreciable parametria, bladder or bowel involvement. On laparotomy, there was palpable lymphadenopathy from the pelvis to above the renal vessels.

Cervical, vaginal, and para-aortic lymph node biopsies demonstrated clear cell carcinoma. She was clinical staged as IIIA carcinoma of the cervix, surgically staged to IIIC disease. She was referred to the present institution for treatment. She was initially treated with 25 fractions of external beam radiation therapy followed by brachytherapy from June 1995 until August 1995. In November 1995, given the presence of persistent disease, she then subsequently started on paclitaxel chemotherapy following Gynecologic Oncology Group (GOG) protocol 128-B [1]. Per this

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protocol, for patients with prior pelvic radiation, the dose of paclitaxel was 135 mg/m^2 given as a 24-hour continuous intravenous infusion with courses repeated every three weeks. Dose escalation to 200 mg/m^2 and de-escalation to 110 mg/m^2 were allowed based on adverse effects.

CT scans were performed prior to chemotherapy and after the second, fourth, sixth, and eighth cycles. Each one demonstrated persistent disease in the lymph nodes. On the CT scan after the eighth cycle, there was an enlarged aorto-caval lymph node measuring 1.5×1.0 cm, peri-aortic lymph node measuring 1.8×1.3 cm, and a 2.0×1.5 cm left obturator lymph node.

Given the minimal toxicity related to the chemotherapy, a decision was made with the patient to continue paclitaxel chemotherapy, and to continue to follow with serial clinical exams, cervical cytology, and CT scans. Imaging demonstrated persistence of disease in these lymph nodes over the next seven years. She was still on chemotherapy when the results of GOG-128-B were published in 2001 [8].

Suspected disease was last visualized in September 2002 with the presence of an enlarged one-cm left peri-aortic and a one-cm left external iliac lymph node. The patient had a PET/CT scan that was negative in December 2002 following the 109th cycle of paclitaxel. A decision was made at that time to discontinue chemotherapy and start surveillance only. Her most recent imaging was a CT/PET in October 2009. Her most recent clinical exam was performed in June 2015. She is now 57-years-old and without evidence of disease for over 13 years. She has had complications related to her treatment but has continued to do well.

Discussion

The U.S. National Cancer Institute-funded screening program was started in 1937. Pacitaxel was discovered in 1962 as part of this program when it was isolated from the bark of the Pacific Yew, Taxus brevifolia, and received the name "taxol." It was not until 1977 that pacitaxel's mechanism of action was understood, in that it binds to and stabilizes a cell's microtubule assembly thereby slowing cell division and growth and preventing the separation on the chromosomes. In 1984, phase I clinical trials of paclitaxel against a number of cancer types began and demand for paclitaxel spiked in 1989 after investigators reported that the drug produced partial or complete responses in 30% of patients with advanced ovarian cancer. It was FDA approved in December 1992 and remains a first line treatment for many gynecologic malignancies [9-10].

To the present authors' knowledge, there are no reports in the literature that have suggested that long-term or maintenance paclitaxel could or should be use in treatment of cervical carcinoma. Taxane-therapy is generally a safe and well-tolerated chemotherapy drug, and its use has been suggested as a maintenance regimen in ovarian cancer [11-13]. Studies have been conflicting regarding its efficacy. A recent Cochrane review concluded that pacitaxel requires additional investigation to determine its efficacy as a maintenance therapy in ovarian cancer [14].

For locally advanced cervical cancer, chemoradiotherapy with platinum-based chemotherapy significantly improves survival compared to radiotherapy alone and is considered the standard of care [15]. However, there are numerous studies than have shown promising results with the addition of paclitaxel for locally advanced, metastatic, or recurrent disease [16-19], and a recent Cochrane Review concluded that paclitaxel may provided additional benefit in treating advanced, metastatic, or recurrent cervical cancer [20]. A large phase III study by the GOG is ongoing to see if the addition of four extra cycles of carboplatin and paclitaxel to standard chemoradiation provides additional survival benefits [21].

CCCC is a rare subtype of cervical cancer. Advanced stage CCCC typically has poor outcomes and no evidence-based approach exists to guide clinicians in treating this rare disease. The present case report demonstrated a successful remission in a patient with advanced disease with single agent paclitaxel for a prolonged course after completing standard radiation therapy and may be one possibility for future providers in treating this rare disease.

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