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Sustained Complete Response after Maintenance Therapy with Topotecan and Erlotinib for Recurrent Cervical Cancer with Distant Metastases

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Key Words

Recurrent cervical cancer · Epidermal growth factor receptor inhibitor · Erlotinib · Maintenance therapy

Abstract

Introduction: Recurrent cervical cancer is associated with a poor prognosis. Most treatment responses are partial and of short duration. The development of new therapies is vital to improve treatment for recurrent disease. Epidermal growth factor receptor (EGFR) inhibitors may have a role in this setting. **Case Description:** A 53-year-old woman with stage IB2 squamous cell carcinoma of the cervix was initially treated with chemoradiation. Six months after completing treatment, she developed a recurrence in the common iliac and para-aortic lymph nodes above the previous radiation field and was treated with additional radiation therapy. Two years later, she developed recurrent disease in the left supraclavicular lymph nodes and was treated with chemoradiation followed by 3 cycles of adjuvant cisplatin and topotecan. She had a complete response and was placed on maintenance therapy with topotecan and erlotinib, which was well tolerated and produced minimal side effects. After 20 months of maintenance therapy, it was discontinued given the long interval without evidence of disease. The patient is currently without evidence of disease 5 years after completing the topotecan-erlotinib treatment. **Conclusion:** We noted a sustained response

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in a patient with recurrent metastatic cervical cancer treated with radiotherapy, cisplatin, and topotecan followed by maintenance therapy with topotecan and erlotinib. Further evaluation of the role of EGFR inhibitors in this setting should be considered given their favorable toxicity profile and biological relevance.

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Introduction

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death among women worldwide [1]. Many women with cervical cancer present with advanced-stage or recurrent disease due to a lack of screening. In addition, approximately 30% of women who undergo definitive treatment for localized cervical cancer subsequently develop metastatic disease [2]. When metastatic cervical cancer is limited, management includes local treatment such as radiation therapy and/or surgery. If disseminated disease is present, palliative chemotherapy is recommended. Several agents have shown activity in cervical cancer as single agents or in combination therapy. Cisplatin is the preferred single agent, and improved response rates have been shown when cisplatin is used in combination with other agents including paclitaxel and topotecan [3]. Recent data indicate that bevacizumab may improve overall survival, particularly in combination with platinum-based chemotherapy [4]. However, despite these advances, most responses in patients with metastatic cervical cancer are partial and of short duration. Therefore, the development of new agents and new combinations of previously studied drugs is vital to improve outcomes for patients with advanced disease.

Erlotinib is an oral selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. Erlotinib has approval by the Food and Drug Administration for the treatment of lung and pancreatic cancer [5–9]. It is the recommended first-line therapy for non-small cell lung cancer (NSCLC) in patients with an EGFR mutation [5]. In addition, erlotinib is used for refractory disease in patients with advanced NSCLC after failure of at least 1 prior chemotherapy regimen [6]. Furthermore, erlotinib is also recommended as maintenance therapy in patients with advanced NSCLC following a complete response to first-line chemotherapy, regardless of EGFR mutation status [7, 8]. Erlotinib is also approved for first-line therapy in combination with gemcitabine in patients with advanced-stage pancreatic cancer [9].

Previous studies have shown that EGFR is overexpressed in squamous cell carcinomas of the cervix and have indicated that EGFR overexpression may be associated with a poor prognosis [10]. It has been reported that human papillomavirus 16, the primary causative agent of cervical cancer, stimulates EGFR expression on epithelial cells [11]. On the basis of these data, erlotinib has been evaluated in the treatment of cervical carcinoma [12, 13]. In this report, we describe a case of sustained complete response in a patient with distant recurrent cervical cancer treated successfully with local radiation therapy followed by adjuvant chemotherapy and erlotinib-based maintenance therapy.

Case Report

A 53-year-old woman was diagnosed with stage IB2 poorly differentiated squamous cell carcinoma of the cervix with lymphovascular invasion. She received definitive pelvic radiation therapy with concurrent cisplatin chemotherapy followed by brachytherapy. Six months after completion of treatment, positron emission tomography-computed tomogra-

phy (PET-CT) showed recurrent disease to the common iliac and para-aortic lymph nodes above the previous radiation field. The patient was treated with additional radiation therapy to the common iliac and para-aortic lymph nodes. Two years later, PET-CT showed a hypermetabolic left supraclavicular lymph node, and fine-needle aspiration showed poorly differentiated carcinoma consistent with cervical cancer recurrence. The patient received additional chemoradiation with cisplatin encompassing the left supraclavicular area, cervical regions, and upper mediastinum. She subsequently received 3 cycles of adjuvant cisplatin and topotecan. PET-CT showed a complete response. Given the patient's high likelihood of recurrence, she was offered maintenance therapy with erlotinib based on previous study findings in NSCLC. She received therapy with low-dose topotecan (2 mg/m² intravenous every 14 days) combined with erlotinib (100 mg orally daily). PET-CT scans were performed every 3–4 months during maintenance therapy and were negative for disease. Maintenance therapy was well tolerated and produced minimal side effects including mild fatigue and nausea. After 20 months of maintenance therapy, the treatment was discontinued given the long interval without any evidence of disease. Since then, the patient has undergone PET-CT yearly. The patient is currently without evidence of disease 5 years after completing the topotecan-erlotinib maintenance therapy. Of note, EGFR mutational testing was not performed in this case.

A copy of the written consent form is available for review by the Editor-in-Chief of this journal on request.

Discussion

This report describes the case of a woman with recurrent metastatic cervical cancer who developed a sustained complete response following treatment with radiation therapy and adjuvant chemotherapy with cisplatin and topotecan, followed by maintenance therapy with a combination of topotecan and the EGFR inhibitor erlotinib. Erlotinib has been studied in 2 previous phase II studies in women with cervical cancer [12, 13]. The first study was an open-label single-arm trial that enrolled 25 patients with recurrent or metastatic disease who had all previously received chemotherapy. The study failed to show significant activity of erlotinib as monotherapy: no patient had an objective response, and 4 patients (16%) had stable disease [12]. A second study evaluated erlotinib in combination with cisplatin in 36 patients undergoing definitive radiation therapy for locally advanced disease. Thirty-four patients (94%) had a complete response, and 2 patients (6%) had a partial response [13]. In both studies, erlotinib was well tolerated, and the most common side effects were skin rash, fatigue, and gastrointestinal toxic effects.

Erlotinib has also been approved for treatment of NSCLC on the basis of results of randomized trials. A large study compared first-line treatment with erlotinib (n = 86) to platinum-based doublet chemotherapy (n = 87) in patients with metastatic NSCLC whose tumors had EGFR exon 19 deletions or exon 21 substitution mutations [5]. The median progression-free survival (PFS) time was 9.7 months in the erlotinib group and 5.2 months in the platinum-based chemotherapy group (hazard ratio [HR], 0.37; 95% CI, 0.25–0.54; p < 0.0001). However, overall survival did not differ significantly between the treatment groups: median overall survival time was 19.3 months in the erlotinib group and 19.5 months in the platinum-based chemotherapy group (HR, 1.04; 95% CI, 0.65–1.68; p = 0.87) [5]. In another study, patients with advanced NSCLC who previously received 1 or 2 chemotherapy regimens were treated with erlotinib or placebo. The median overall survival time was 6.7

months for the erlotinib group and 4.7 months for the placebo group (HR, 0.70; 95% CI, 0.58–0.85; $p < 0.001$) [6].

Erlotinib has also been evaluated for maintenance therapy for NSCLC. In a trial for patients with nonprogressive NSCLC following first-line platinum-doublet chemotherapy, the median PFS time was better with erlotinib than with placebo: 12.3 versus 11.1 weeks, respectively (HR, 0.71; 95% CI, 0.62–0.82; $p < 0.0001$) [7]. In a more recent clinical trial, patients with advanced NSCLC without tumor progression after 4 cycles of cisplatin-gemcitabine treatment were randomly assigned to observation, gemcitabine, or erlotinib. Median PFS time was significantly longer with gemcitabine than with observation (3.8 vs. 1.9 months, respectively; HR, 0.56; 95% CI, 0.44–0.72; $p < 0.001$) and with erlotinib than with observation (2.9 vs. 1.9 months, respectively; HR, 0.69; 95% CI, 0.54–0.88; $p < 0.003$) [8].

The patient in our reported case was treated with erlotinib and topotecan as maintenance therapy following treatment for recurrent cervical cancer. The treatment was based on the results of maintenance therapy with erlotinib in lung cancer where it was shown to be well tolerated and associated with prolonged PFS [7, 8]. However, the only trial with erlotinib for recurrent cervical cancer failed to show benefit of erlotinib as a single agent [12]. In our case, erlotinib was therefore combined with topotecan, a cytotoxic drug known to be active against cervical cancer. The goal of the treatment plan was to provide a regimen that would be well tolerated and effective. Because the patient did not experience any evidence of disease progression or unacceptable toxic effects, she was kept on treatment. After almost 2 years on this regimen without evidence of disease, both the patient and her medical team felt it was safe to stop the drugs, and she remains without evidence of disease 5 years later.

Conclusion

This erlotinib and topotecan regimen was shown to be safe and potentially effective as maintenance therapy following the treatment of recurrent squamous cell carcinoma of the cervix. Prolonged survival can potentially be achieved with a more aggressive approach such as the one described in this report. Maintenance therapy which includes an EGFR inhibitor should be further studied in women with recurrent cervical cancer given the favorable toxicity profile and biological relevance of this class of drugs.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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