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Original Article

The Impact of Systemic Therapy Beyond First-line Treatment for Advanced Cervical Cancer

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Abstract

Aims: Despite recent advances in the primary and secondary prevention of cervical cancer, a significant number of women present with or develop metastatic disease. There is currently no consensus on the standard of care for second-line systemic treatment of recurrent/metastatic cervical cancer. The purpose of this study was to evaluate the second-line systemic therapy used and the associated outcomes in a single cancer centre.

Materials and methods: A retrospective review of patients with cervical cancer who received one or more lines of treatment for recurrent or metastatic cervical cancer at the Royal Marsden Hospital between 2004 and 2014 was carried out. The primary objective was to establish the types of second-line systemic treatment used. Secondary end points included objective response rate, progression-free survival and overall survival after second-line therapy.

Results: In total, 75 patients were included in the study; 53 patients (70.7%) received second-line therapy for recurrent/metastatic disease. The most common second-line therapy was weekly paclitaxel (28.3%). Carboplatin-based chemotherapy (24.5%), targeted agent monotherapy within clinical trials (22.6%), docetaxel-based chemotherapy (13.2%), topotecan (9.4%) and gemcitabine (1.9%) were also used. The objective response rate to second-line therapy was 13.2%, which included three partial responses to carboplatin and paclitaxel, two partial responses to docetaxel-based chemotherapy, one partial response to weekly paclitaxel and one partial response to cediranib. Twenty-two patients (41.5%) achieved stable disease at 4 months. The median progression-free survival for women treated with second-line therapy was 3.2 months (95% confidence interval 2.1–4.3) and median overall survival was 9.3 months (95% confidence interval 6.4–12.5). Thirty-nine per cent of patients received third-line therapy.

Conclusion: Seventy per cent of patients treated with first-line systemic therapy for recurrent/metastatic cervical cancer subsequently received second-line treatment but response rates were poor. There remains no standard of care for second-line systemic therapy for advanced cervical cancer. Patients should be considered for clinical trials whenever feasible, including novel targeted agents and immunotherapy.

Key words: Cervical cancer; chemotherapy; metastatic; second-line; targeted therapy

Introduction

Cervical cancer is the fourth most common cancer in women, accounting for 528 000 new cases and 266 000 deaths annually worldwide [1]. The incidence of cervical cancer in the UK has reduced significantly after the introduction of cervical screening, and it is anticipated that it will reduce even further with human papillomavirus (HPV) vaccination [2,3].

Despite advances in the primary and secondary prevention of cervical cancer, a significant number of women present with or develop metastatic disease. Although stage IV disease accounts for only 5% of new diagnoses of cervical cancer [4], metastatic disease develops in 15–61% of women, usually within the first 2 years of completing primary treatment [5]. Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent or limited metastatic disease, but in most cases this will not be feasible. Women with recurrent and

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metastatic cervical cancer have limited systemic treatment options and the prognosis is poor, with a 5 year survival of 5% [5,6].

For women with recurrent or metastatic disease not amenable to therapy with curative intent, the goal of treatment is palliation of symptoms and prolongation of survival with systemic therapy. The standard of care in the first-line setting is combination chemotherapy with the addition of the anti-VEGF monoclonal antibody, bevacizumab [7]. The landmark phase III GOG240 trial showed an improvement in overall survival from 13.3 months to 17 months with the addition of bevacizumab to first-line chemotherapy (cisplatin-paclitaxel or topotecan-paclitaxel) (hazard ratio 0.71; 98% confidence interval 0.54–0.95; $P = 0.004$) [7]. Importantly, the addition of bevacizumab to chemotherapy did not adversely affect health-related quality of life in these women [8]. This significant improvement in overall survival with the addition of bevacizumab to first-line chemotherapy will probably result in a greater number of women needing effective second-line treatment options.

There is currently no standard of care for second-line treatment, and as such, this represents a significant unmet clinical need. So far, there is no evidence that treatment in the second-line setting improves overall survival compared with best supportive care. However, women in this situation are often symptomatic and relatively young – treatment options that offer improvement in disease-related symptoms, quality of life and prolongation of progression-free survival (PFS) are worthwhile. Several phase II studies of cytotoxic or targeted agents as second (or subsequent) line treatment have shown response rates typically less than 10% (range 0–28%) and stable disease rates between 11 and 44% [9–26]. The median PFS of women treated with second-line systemic therapy is 1.2–5.4 months and the median overall survival is 3.5–11.7 months [9–26]. The purpose of this study was to establish the types of second-line treatment received by women with recurrent and metastatic cervical cancer in clinical practice at the Royal Marsden Hospital over a 10 year period and to evaluate the outcomes of these treatments.

Materials and Methods

In this retrospective study, approved by the Royal Marsden Clinical Research Committee, all women treated for cervical cancer between January 2004 and June 2014 at the Royal Marsden Hospital were identified using electronic patient records. Patients who received one or more lines of systemic therapy for recurrent or metastatic disease were included. The primary objective was to establish the types of second-line systemic treatment received by patients with recurrent or metastatic cervical cancer. Secondary end points included objective response rate (ORR), PFS and overall survival after second-line therapy.

Data including baseline patient characteristics, treatments, radiological response to treatments, date of progression and date of death or last follow-up were retrieved from the electronic patient records. The platinum-free interval (PFI), defined as the time period between completion of the last platinum-based chemotherapy and radiological progressive disease, was also collected.

Statistical Methods

The best overall response to second-line treatment (complete response, partial response, stable disease or progressive disease) was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The ORR was defined as the number of patients with a complete or partial response divided by the total number of patients who underwent second-line treatment. PFS was defined as the time from the initiation of second-line treatment to the first documented radiological progression, according to RECIST 1.1. Overall survival was defined as the time from the initiation of second-line treatment until death from any cause. Patients alive at the time of evaluation were censored at the last follow-up. Patients with loss of follow-up were censored at the last follow-up. PFS and overall survival analyses were carried out using the Kaplan–Meier method. All statistical analyses were carried out using SPSS software package, version 21.0 (Chicago, IL, USA).

Results

Between January 2004 and June 2014, 508 patients were treated for cervical cancer at the Royal Marsden Hospital. Of these, 75 patients were treated with one or more lines of systemic therapy for recurrent or metastatic disease, and included in the study. Baseline characteristics are shown in Table 1. The median age at diagnosis was 44 years (range 19–79). The predominant histological subtype was squamous cell carcinoma (65.3%), followed by adenocarcinoma (20%). Eight patients (10.7%) had stage IV disease at initial diagnosis (six stage IVA, two stage IVB). Sixty-eight per cent of patients received chemotherapy as part of primary treatment. The median overall survival for the 75 patients in the study from diagnosis to death was 3.8 years (95% confidence interval 2.8–4.4). The 5 year overall survival rate was 30%.

First-line Systemic Treatment for Recurrent or Metastatic Disease

The treatments used in the first-line setting for recurrent or metastatic disease are outlined in Table 1. Thirty-one patients (41.3%) received carboplatin and paclitaxel as first-line treatment. One patient received bevacizumab in combination with carboplatin and paclitaxel. The median number of cycles received was six (range two to eight). The median PFS for women treated with first-line systemic therapy for metastatic or recurrent disease was 6.6 months (95% confidence interval 5.5–7.6). The PFS rate at 6 months was 54% (95% confidence interval 42–65).

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