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Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: Where do we stand? A literature review

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ABSTRACT

Background: Cervical cancer is the fourth most common cancer affecting women worldwide. Despite advances in screening and human papillomavirus (HPV) vaccination, a significant number of women present with or develop advanced disease. Palliative platinum-based chemotherapy (CT) is the standard first-line treatment for metastatic/recurrent cervical cancer. The prognosis remains poor and effective second line options are urgently needed.
Methods: We searched the English-language medical literature as well as relevant guideline databases, published from January 1981 to December 2015 and identified publications related to cervical cancer and its therapies. Our effort was to highlight the available treatment options in the setting of recurrent/metastatic disease.
Results: Although there have been important advances in the management of women with cervical cancer, the optimal treatment for patients with locally recurrent and metastatic disease after platinum failure is still problematic. Overall, there is a trend in terms of longer overall survival (OS) and better quality of life

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for the combination of cisplatin/paclitaxel (PC) as compared to the doublets of cisplatin/topotecan (TC), cisplatin/vinorelbine (VC), and cisplatin/gemcitabine (GC).
Currently available single agents beyond first-line platinum-based therapy have limited efficacy in this setting and include topoisomerase inhibitors, vinca alkaloids, taxanes, alkylating agents and antimetabolites. Several targeted therapies have demonstrated activity in advanced cervical cancer. Bevacizumab has been evaluated in a phase III trial using doublets of cisplatin with paclitaxel or topotecan and has been approved in the first-line setting by the U. S. Food and Drug Administration.
Selective targeting of angiogenic kinases by tyrosine kinase inhibitors (TKIs) may represent a novel therapeutic tool in this setting, but its use alone or in combination with CT is still investigational. Early reports have implicated PI3KCA somatic mutations suggesting that mTOR-targeted agents should be explored in this disease. Development of the immune checkpoint programmed cell death 1 (PD-1) and T-lymphocyte–associated molecule-4 (CTLA-4) inhibitors have been of considerable interest, leading to ongoing phase II studies in patients with advanced cervical cancer.
Conclusions: Progress in the management of recurrent and advanced cervical cancer patients has been slow and restricted to palliative intent. These patients should be considered for clinical trials of novel targeted agents and/or immunotherapy.

1. Introduction

Data from GLOBOCAN 2012 have demonstrated that cervical cancer is the fourth most common cancer in females worldwide with an estimated 528,000 cases diagnosed annually and with 266,000 disease related deaths (Ferlay et al., 2015). In countries with established screening programmes, the incidence of invasive cervical cancer has dramatically decreased in comparison with 40 years ago. However, a significant number of women presenting with either advanced or locally advanced disease is still present.

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 two years of completing primary treatment (Pfaendler and Tewari, 2016). Surgical resection or radiotherapy may potentially be curative for selected women with locally recurrent or limited metastatic disease, however in the majority of cases this will not be feasible. Women with recurrent and metastatic cervical cancer have limited systemic treatment options and the prognosis is dismal (Pfaendler and Tewari, 2016).

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. Among the standard of care regimens in the first-line setting is combination chemotherapy (CT) with the addition of the anti-vascular endothelial growth factor (VEGF) monoclonal antibody, bevacizumab (Tewari et al., 2014). The landmark phase III GOG240 trial demonstrated an improvement in overall survival from 13.3 months to 17 months with the addition of bevacizumab to first-line CT [cisplatin/paclitaxel (PC) or topotecan-paclitaxel] (HR 0.71; 98% confidence interval [CI], 0.54–0.95; p = 0.004) (Tewari et al., 2014). Importantly, the addition of bevacizumab to CT did not adversely affect health-related quality of life in these women (Penson et al., 2015). This significant improvement in overall survival (OS) with the addition of bevacizumab to first-line CT is likely to result in a greater number of women needing effective second-line treatment options.

Patients with metastatic and non-operable recurrent cervical cancer constitute a high risk population and more research is needed to improve efficacy and reduce the adverse effects associated with treatment in this setting. There is currently no standard of care for second-line treatment, and as such, this represents a significant unmet clinical need. Accruing enough patients to obtain sufficient power to test novel strategies is a challenge.

The purpose of this study is to highlight advances in systemic treatment choices, antiangiogenesis therapy and immunotherapy and evaluate the associated outcome for patients with recurrent/metastatic cervical cancer following first line CT.

2. Literature search strategy

The literature in PubMed database and the Cochrane Database of Systematic Reviews were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed, and the reference lists in those sources and recent review articles were also searched for additional trials. Publications between January 1981 and December 2015 in English were eligible for inclusion.

3. Cervical cancer recurrences

Patients with cervical cancer may develop pelvic recurrence, distant metastases, or a combination of both. The relapse rate of cervical cancer ranges between 11 and 22% in International Federation of Gynecology and Obstetrics (FIGO) stages IB–IIA and between 28 and 64% in FIGO stages IIB–IVA (Quinn et al., 2006). As the bulk of a pelvic tumor increases, the proportion of patients with disease recurrent or persistent in the pelvis as the only site of failure exceeds that of distant metastases. Perez et al., reported a total pelvic failure rate of 10% in stage IB, 17% in stage IIA, 23% in stage IIB, 42% in stage III, and 74% in stage IVA after radiotherapy alone (Perez et al., 1995). The most common extra-pelvic metastases involve *para*-aortic lymph nodes, lungs, liver and bones predominantly involving the lumbar and thoracic spine (Panek et al., 2007; Zola et al., 2007).

The management of recurrent cervical cancer depends mainly on previous therapeutic approaches and on the site and extent of recurrence (Quinn et al., 2006). The vast majority of patients receive pelvic radiotherapy at some point during their treatment, and tumour failure in an irradiated pelvis is usually related to a dismal prognosis. Cervical cancer recurrences may be central pelvic, lateral pelvic and extra-pelvic (Dornhöfer and Höckel, 2008). Central pelvic relapse can be located in the vaginal vault or usually involve the bladder and/or rectum. Lateral pelvic recurrence includes parietal and visceral pelvic side disease developed above and below the level of the obturator nerve, respectively.