

Mini Review

Management of Metastatic Cervical Cancer: Mini Review

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Cervical cancer is one of the most frequent malignancies among women worldwide. It is one of the most common causes of cancer related mortality among women. With advances in diagnostic and the effective therapeutic modalities, the prognosis of cervical cancer has been improved. Selected targeted therapies that target specific molecular pathways involved in carcinogenesis have improved overall survival. Standard conventional treatment in the form of radical surgery, chemotherapy and radiotherapy is administered to the early-stage and locally advanced cervical cancer patients. But up to one - third of the patients develop progressive and recurrent cervical cancer and the prognosis of patients with advance recurrent and metastatic cervical cancer remains poor because of heterogeneous manifestations. With current therapeutic options, 80-90% of the stage I, early the stage II and 60% of stage II women with cervical cancer get cured of the disease [1]. But patients with progressed disease land up in poor outcome.

Metastatic cervical cancer patients are those with any stage of tumor size (T stage), any lymph node (LN) and M1 that is distant metastasis of peritoneal spread and involvement of supraclavicular, mediastinal or para-aortic lymph nodes, lung, liver, bone or brain at primary presentation or those with recurrent/persistent disease outside pelvis. Cervical recurrence can be central pelvic, lateral pelvic and extra-pelvic [2]. Prevalence of advanced stage cervical cancer is highly variable from region to region, as it chiefly depends upon the socioeconomic factors. One of Indian study reported it 89% with 23.16% in stage IIB and 35.13% in stage IIIB [3]. In developing and underdeveloped countries, women present at late stage when the prognosis of the disease is worse. Recurrence rate of cervical cancer ranges from 11 to 22% among women with FIGO stages Ib-IIa and 28-64% in FIGO stages IIb-IVa [4]. Now median survival time for advanced cervical cancer patients is only 8 to 13 months. Majority of recurrences occur within 2 years of the diagnosis of the disease [5].

MANAGEMENT

Metastatic cervical cancers are referred as lymphatic metastasis when affected sites are all lymph nodes outside of pelvic organs. Such metastatic lesions are diagnosed by computed tomography, magnetic resonance imaging (MRI) and positron emission tomography with CT/MRI. For isolated lymph node recurrence, salvage radiation therapy with concurrent

chemotherapy after radical surgery is also practiced. In case of para-aortic disease, either surgical resection or concurrent chemoradiotherapy are the choices. Also extended-field radiation therapy is offered for metastatic cervical cancer who only present with para-aortic metastasis. Hematogenous metastasis is relatively uncommon, involves lungs, brain, bone, liver and other sites associated with the very poor outcome. Such patients have 5.3-fold higher risk of death compared to patients with lymphatic metastasis [6]. Radiotherapy with multiagent chemotherapy is preferred choices for managing cases with hematogenous spread.

Management of metastatic cervical cancer mainly depends upon the previous treatment received for the primary site, and extent of metastatic lesions, comorbidities, and disease free interval age and general condition of the patients. For patients with central or lateral pelvic recurrence after primary radical surgery, treatment of choice is intensity modulated radiotherapy or concurrent cisplatin-based chemo-radiation. Patients primarily treated with radiotherapy, but presented with small persistent or recurrent lesions of central cervical cancers can be managed by radical surgery with radiation resulting in long-term survival. Women who primarily had received chemo-radiation or surgery with adjuvant radiation therapy and presenting with lateral pelvic recurrence involving lateral pelvic wall cannot receive exenteration, hence receiving palliative chemotherapy will be choice of therapy. Among 2-12% of the patients, isolated para-aortic recurrence may be observed after primary management of the disease. Such type of progressive disease is very worst, as it is associated with wide systemic spread. Patients with distant or loco-regional recurrence have to be managed by palliative chemotherapy. Several factors decide the plan of palliative chemotherapy like poor bone marrow function, compromised drug distribution due to previous irradiation and renal dysfunction due to obstruction in the urethra [7].

Chemotherapy in combination with radiotherapy is the most preferred modality of treatment among women with advanced cervical cancer. Traditionally cisplatin is considered as the most active and popular drug of choice for management of metastatic cervical cancer. Other drugs included are ifosfamide, paclitaxel, topotecan, irinotecan, carpecitabine and Pemetrexed. Topotecan can cross blood brain barrier, hence used in brain metastasis. In case of metastasis to any organ, if a lesion is operable, surgical

resection with appropriate chemotherapy and radiation therapy is an optimal choice of treatment. But among patients who received prior chemotherapy, chemo-resistance may develop and those who received prior radiation therapy there is chance of failure to radiotherapy [8].

EMERGING THERAPIES

Number of factors influence prognosis of the disease. There is no single chemotherapeutic agent that can improve the overall survival of patients with metastatic cervical cancer. But combination of cisplatin and paclitaxel is more effective to lengthen progression free survival compared to single agent chemotherapy. But many of targeted agents have been found to have limited activity against metastatic cervical cancers. Novel agents like Bevacizumab in combination with chemotherapy are found to be highly active in advanced cervical cancer [9]. Immunotherapy is a promising for the management of locally advanced, recurrent or metastatic cervical cancer. Recently human papilloma virus-targeted tumor-infiltrating lymphocyte therapy, live attenuated *Listeria monocytogenes*-based immunotherapy have been evaluated and found useful as active agents against metastatic cervical cancer [10]. Also other immunotherapeutic agents like nivolumab and ipilimumab, monoclonal antibodies are under evaluation for their ability to boost immune system for defense against the tumor [11,12].

CONCLUSION

Despite the number of advances in the treatment of cervical cancer, management of metastatic cervical cancer is problematic and challenging with the poor outcome. Identification of patients with potentially curable radical treatment is the most crucial step while dealing with such cases. Those with advanced progressive disease need to be offered palliative therapy to reduce the symptom burden and improve quality of life.

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