Efficacy and safety of DoceAqualip in a patient with locally advanced cervical cancer: A case report

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Abstract. The standard of care for locally advanced cervical cancer has been the combination of a taxane with platinum based therapy. Conventional docetaxel is known to cause hypersensitivity reactions, fluid retention and other toxicities due to polysorbate-80 and ethanol. Corticosteroid premedication prior to docetaxel administration is required to prevent these toxicities, however, toxicities are still observed, sometimes fatal, despite premedication. DoceAqualip, a nanosomal docetaxel lipid suspension, developed with lipids generally regarded as safe (GRAS) by the US Food and Drug Administration, is devoid of polysorbate-80 and ethanol. DoceAqualip has been demonstrated to be effective and well-tolerated in various cancer types. The authors' report a case of a patient with Stage IIIB cervical cancer who was treated with carboplatin and DoceAqualip (concurrent ChemoRT) and achieved complete response without any serious adverse events.

Introduction

In Indian women, cervical cancer is among the most common malignancies, and is a major cause of mortality (1-3). India has a higher incidence of cervical cancer compared with the developed countries (1). The age-adjusted incidence rate of cervical cancer varies widely among Indian registries, from 4.91 to 23.07/100,000 populations; much higher than the world (7.9/100,000 population). Poor to moderate living standards, lack of proper screening, and a high (≥10% in women aged >30 years) prevalence of human papillomavirus infection could be the potential reasons responsible for the higher incidence in India (4).

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The treatment of choice for early-stage cervical cancer is radical surgery, whereas, concurrent chemoradiation is preferred for locally advanced stages. However, the treatment options are very limited for patients with recurrent or metastatic cancers. In women with recurrent or limited metastatic disease, surgery or radiotherapy may be effective in only in few cases (5,6). After the clinical alert from the National Cancer Institute (NCI) in 1999 (7), concurrent chemoradiotherapy has become the standard of treatment for locally advanced cervical cancer (8); it enhances the radiosensitivity and local tumor efficacy of cytotoxic agents, with eradication of micrometastasis and ultimately improves the pelvic control and survival (9).

Chemotherapy with a platinum agent (carboplatin/cisplatin) and a taxane based regimen is considered the standard of care for cervical cancer in terms of longer overall survival (OS) and a better quality of life for the patients (5,7). Furthermore, carboplatin has advantages over cisplatin in terms of a better safety profile (low incidence of neuropathy, nephrotoxicity and emetogenesis) (10).

Docetaxel has dose limiting toxicities of acute hypersensitivity reactions, and fluid retention due to the excipients (polysorbate-80 and ethanol) used in the conventional formulations, which require corticosteroid premedication (11). DoceAqualip, a nanosomal docetaxel lipid suspension (NDLS), was developed with lipids generally recognized as safe (GRAS) by the US Food and Drug Administration (USFDA) and is devoid of polysorbate-80 and ethanol. DoceAqualip has been shown to be more effective than the conventional docetaxel in the treatment of breast cancer (12) and has demonstrated a promising overall response and safety without the need of corticosteroid in the treatment of breast cancer, advanced gastric adenocarcinoma, ovarian cancer, hormone refractory prostate cancer, and non-small cell lung cancer (11-13).

Here, we report a case of a Stage IIIB cervical cancer patient who was treated with concurrent carboplatin and DoceAqualip chemoradiotherapy.

Case report

A 52-year-old woman presented with complaints of abnormal vaginal bleeding along with white discharge since five months. Her vaginal examination revealed a hard indurated friable

growth replacing the cervix. Per rectal examination revealed involvement of bilateral parametrium.

Her past medical history included type 2 diabetes and she was taking combination tablet of glimepiride 1 mg and metformin 500 mg twice daily for 3 years. Histopathological examination of the cervical biopsy specimen revealed moderately differentiated squamous cell carcinoma. The magnetic resonance imaging (MRI) of pelvis revealed a large mass of 55x45 mm in size in the uterine cervix infiltrating the lower third of the myometrium with enlarged bilateral internal iliac nodes, measuring 1.6 cm on the left side and 1.4 cm on the right side (Fig. 1). Based on these findings, the patient was diagnosed with squamous cell carcinoma cervix Stage IIIB, with Eastern Cooperation Oncology Group (ECOG) score of 2 and was planned for concurrent chemoradiotherapy.

The patient was started on chemotherapy with docetaxel-carboplatin regimen on December 26, 2014. Carboplatin and nanosomal docetaxel lipid suspension (NDLS; DoceAqualip) were administered intravenously (IV) at doses corresponding to AUC 5-6 (area under the curve; total dose 450 mg) and 75 mg/m^2 (body surface area of 1.67 kg/m^2), respectively for 4 cycles (every 3 weekly cycle). DoceAqualip was given without steroid premedication, at a total dose of 120 mg during the first 2 cycles and the dose was reduced to 100 mg for cycles 3 and 4 as the patient developed Grade II neutropenia after 2 cycles of radiotherapy. Post completion of 2 cycles of DoceAqualip, pegylated filgrastim (6 mg) was administered as secondary prophylaxis 24 h after DoceAqualip administration to avoid the risk of neutropenia. The patient did not develop any hypersensitivity reactions (HSR) or any other serious adverse event despite not using any corticosteroids as premedication. No abnormal laboratory investigations were reported throughout the course of the treatment.

The patient also received concomitant radiotherapy from December 31, 2014 to March 10, 2015 at a dose of 50 Gy to the pelvis and 6120 cGy to bilateral parametrium plus 2 high dose rate intracavitary (HDR ICA)- 15 Gy to point A (paracervical reference point) (6).

Post chemoradiotherapy, her MRI done on April 20, 2015 did not reveal any evidence of residual mass in the cervix and no evidence of enlarged internal iliac or para aortic nodes (Fig. 2). The response could best be graded as a complete response (CR) as per RECIST 1.1 criteria. Her fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) scan done on October 12, 2015 revealed no active disease. The follow-up FDG PET CT whole body scan done on June 5, 2017 did not show any evidence of metabolically active lesion in the uterine cervix or anywhere else in the body.

Consent was obtained from the patient for the publication of this case report and informed consent document was signed by the patient.

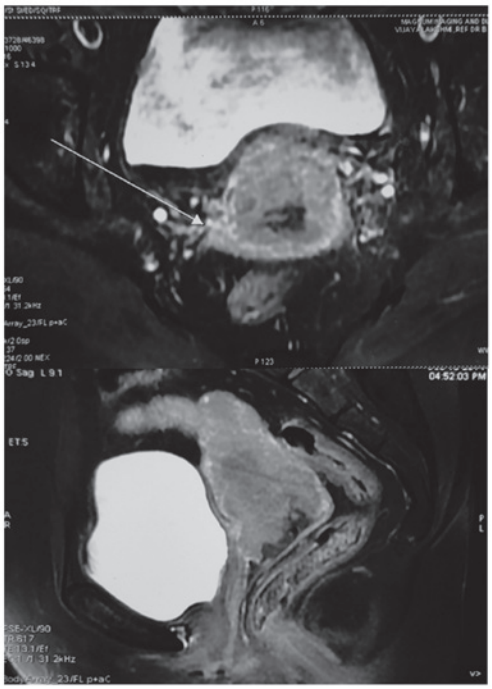

Figure 1. Prechemotherapy MRI pelvis with contrast: Growth in the uterine cervix infiltrating the lower 3rd of myometrium and bilateral parametrium; with enlarged bilateral internal iliac nodes (arrow).

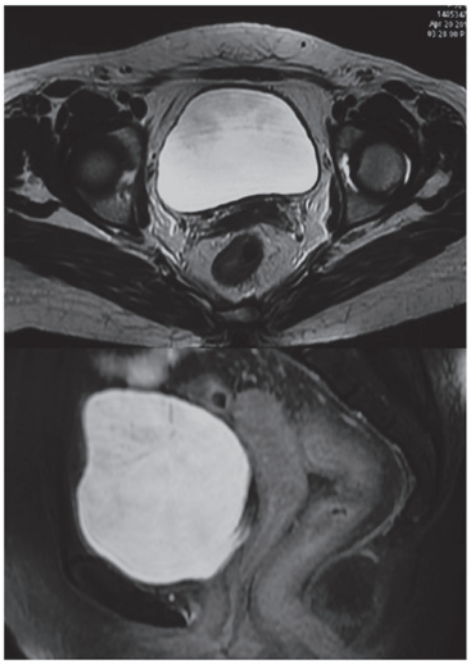

Figure 2. Post-NDLS chemotherapy MRI of abdomen: No evidence of residual mass in the cervix or enlarged internal iliac or paraaortic lymph nodes.

Discussion

Cervical carcinoma is one of the leading malignancies in Indian women with a higher burden as compared to western countries. In India, it accounts for 16% of all cancers in urban women and 37% of the cancers in rural women (3). Concurrent chemoradiation using cisplatin has shown 30-50% reduction in the risk of death, and is regarded the standard treatment for patients with cervical cancer (7,14,15). Carboplatin, an analogue of cisplatin, with a similar mechanism of action, has been used for the treatment of locally advanced cervical carcinoma. It has advantages over cisplatin in terms of decreased nephrotoxicity, neurotoxicity and emetogenesis (16). This favourable toxicity profile when compared to cisplatin may result in better patient adherence to the treatment plan (15). A phase II clinical study

in patients with recurrent or metastatic squamous carcinoma of the uterine cervix revealed substantially better toxicity profile of carboplatin than cisplatin with similar efficacy (17).

Taxanes are commonly used in the treatment of locally advanced cervical cancer in combination with platinum compounds (18). Docetaxel and carboplatin concurrent chemotherapy has shown to be effective in the treatment of cervical cancer with low incidence of nephrointestinal, neurointestinal, and gastrointestinal toxicities (8). In a phase I study in 20 patients with locally advanced or recurrent cervical cancer, weekly docetaxel and carboplatin (145 cycles) showed a high efficacy in a dose-dense setting. The study demonstrated an overall response rate of 65%, and the treatment was well-tolerated (19).

Similarly, in a pilot study that assessed the efficacy and safety of docetaxel and carboplatin combination therapy in advanced or recurrent uterine cervix cancer in 17 patients yielded 76% overall response rate (CR in 2 patients, partial response in 11, and stable disease in 4) with no disease progression reported. Overall, it was concluded that combination chemotherapy with docetaxel (60 mg/m^2) and carboplatin (AUC 6) was effective and well-tolerated in the treatment of uterine cervix cancer. However, the incidence of Grade 3/4 neutropenia was very high (76%), and patients with Grade 4 neutropenia or febrile neutropenia required prophylactic granulocyte colony stimulating factor (G-CSF, 5 μg/kg) administration (20).

Takekida and colleagues further confirmed the efficacy and safety of docetaxel and carboplatin regimen in the treatment of cervical cancer. In a study of 66 patients (62 treatment naïve and 4 recurrent cancer), docetaxel (60 mg/m^2) and carboplatin (AUC 6) combination therapy yielded an overall clinical response rate of 63.7% (44/66, 95% confidence interval, 52.1-75.3). Neutropenia was the major haematological toxicity, which rapidly reversed with G-CSF use (8).

Docetaxel is formulated in polysorbate-80 and ethanol, which are known to cause infusion-related toxicities and hypersensitivity reactions, requiring corticosteroid premedication. Thus, a new formulation nanosomal docetaxel lipid suspension (NDLS) was developed using GRAS lipids that is free of polysorbate-80 and ethanol, and is found to be safe in earlier studies (11-13).

This is the first case report on the use of DoceAqualip in the treatment of cervical cancer. In the current report, the patient who had Stage IIIB cervical cancer, was treated with DoceAqualip and carboplatin combination at generally recommended doses (120 mg followed by 100 mg, and AUC 6, respectively) along with radiation therapy, and achieved CR. Overall, the treatment was well-tolerated, even when there was no corticosteroid premedication, hypersensitivity reaction or any other serious adverse event was not reported. Two-year follow-up investigations did not reveal any recurrence of the carcinoma. Ashraf *et al*, reported that patients receiving DoceAqualip monotherapy did not require G-CSF support whereas dual combination therapy with carboplatin required G-CSF support at each treatment cycle (13). Furthermore, there is a >20% risk of febrile neutropenia in patients receiving combination chemotherapy (21). In this case also, the patient developed Grade 2 neutropenia after 2nd dose of radiotherapy; hence, DoceAqualip dose was reduced from 120 to 100 mg after cycle 2 to avoid radiotherapy interruption and further dose delays. Also, after 2 cycles, the patient was given prophylactic G-CSF (pegylated filgrastim) support after each cycle of dual combination therapy with DoceAqualip and carboplatin. Furthermore, it has been established that external-beam and intracavitary radiation along with the concurrent chemotherapy significantly improves survival in locally advanced cervical cancer patients, which was also followed for this patient (6).

The current report highlights the efficacy and safety of DoceAqualip in the treatment of advanced cervical cancer. These results need to be further confirmed in a larger clinical trial.

In conclusion, NDLS (DoceAqualip), a new formulation developed to overcome toxicity and hypersensitivity reactions caused by polysorbate-80 and ethanol content of the conventional docetaxel formulations, has shown to be effective and well-tolerated in the treatment of cervical cancer without the need for corticosteroid premedication.

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