Progression of Disease with Neo-Adjuvant Chemotherapy in Locally Advanced Cervical Cancer: Case Reports and Literature Review

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ABSTRACT

**Background:** Optimal treatment for locally advanced cervical cancer is still a controversial issue as the current standard therapy is associated with radiation toxicity. Neo-adjuvant chemotherapy followed by surgery is an alternative treatment modality which has promising outcomes.

**Cases:** Two cases of cervical carcinoma, aged 33 and 40 years old, stage Ib2 and 1b3, given neoadjuvant chemotherapy (NACT) with combination of platinum-based agents and Taxane, and planned for radical surgery after completion of chemotherapy.

**Result:** Progression of disease observed in both cases after 3rd cycle of chemotherapy required change of treatment modalities to standard chemoradiation therapy (CCRT).

**Conclusion:** NACT followed by surgery has promising outcomes as it gives advantages in lower long-term complication, targeted in younger-aged group and sexually active women for better quality of life, besides offering similar survival rates compared with CCRT. Estimation of response rate to chemotherapy plays a major role in patient selection in order to have successful outcomes.

**Keywords:** Cervical cancer, chemoradiation therapy, neoadjuvant chemotherapy, radical surgery.

I. INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide, ranking after breast cancer (2.1 million cases), colorectal cancer (0.8 million), and lung cancer (0.7 million). It was the leading cause of cancer-related death in women in eastern, western, middle, and southern Africa [1]. Over one-third of tumors diagnosed at International Federation of Gynecology and Obstetrics (FIGO) was stage IB2-IIb [2]. Treatment of cervical cancer has changed over the years based on the results of clinical trials. Radiation therapy used to be given in locally advanced cervical cancer to control pelvic disease, but since 1999, the administration of concomitant platinum-based chemotherapy and radiotherapy (CCRT) has been accepted as a standard treatment, after several studies showed it improves survival [3]. However, the main reasons of treatment failure were persistent pelvic disease and loco regional recurrence [4]. The optimal treatment for locally advanced cervical cancer once again become controversial due to its failure to control local disease, and besides, the early radiation reaction occurs in 51.3% and the late radiation reaction in 14.8% of patients who received adjuvant radiotherapy in gynaecological malignancy [5]. Although the severity much depends on site, volume of tissue exposed, and dosage of radiation received, the morbidity caused by short-term and long-term sexual, gastrointestinal, and urinary dysfunction can affect patients daily activities and impairs quality of life. Neoadjuvant chemotherapy (NACT) has been looked into as one of the treatment methods to improve survival, as well as to reduce complication.

II. CASES

A. Case 1

33 years old, para 1, presented with post coital bleeding with vaginal discharge for two months. Assessment showed she has cervical mass measuring 3.0 x 3.0 cm with contact bleeding, in which biopsy of the mass proven to be non-keratinising squamous cell carcinoma with background of adenocarcinoma, clinically stage 1b2. Computed tomography scan imaging showed the tumour confined to the cervix with no local or distance metastasis. Neoadjuvant chemotherapy with carboplatin 750 mg/m² with AUC 5 and paclitaxel 175 mg/m² with a 3-week interval in between cycles were given for three cycles. However, when assessment was done after completion of the third cycle, the tumour appeared to have
progressively enlarged till 7.0 × 6.0 cm. Repeated computed tomography scan showed involvement of parametrial tissue, upper vaginal wall, and lower uterine body. No distant metastasis was seen. The surgery was then abandoned, and the patient was then given a combination of external beam radiotherapy (EBRT) 46 Gy for 25 fractions and brachytherapy of 5 Gy for 3 fractions in combination with cisplatin 40 mg weekly for five cycles. She had a complete response after the treatment. However, after 12 months of disease free, she had a recurrent disease to the vault, with mass noted 2.5 × 2.1 cm, and to our surprise, biopsy of the mass showed adenocarcinoma of the cervix. No distance recurrence was confirmed via PET scan and computed tomography scan. A radical hysterectomy was then performed, with histopathology examination of the specimens showed an adenocarcinoma type confined to the cervix confirmed. However, the surgical margin was narrow, measuring 1 mm. No disease was found in pelvic lymph nodes and parametrium tissue. Thus, adjuvant chemotherapy was given for four cycles. She is currently well after 3 months of treatment completion.

B. Case 2

40 years old, para 4, presented with per vaginal discharge for two months. During the assessment, she was found to have an exophytic cervical mass measuring 4 cm, with contact bleeding, in which biopsy of the mass proven to be squamous cell carcinoma. Examination under anaesthesia with cystoscopy was then performed and concluded to be clinically stage Ib3 with the tumour confined to the cervix, measuring 4.5 × 4.0 cm. No involvement of bladder wall or rectal wall noted clinically. Magnetic resonance imaging (MRI) showed a cauliflower-like soft tissue mass in the cervix predominantly at the posterior and left lateral lips, measuring 5.0 × 6.4 × 4.7 cm with thickening of surrounding tissue, suggestive of local infiltration. No clear fat plane seen between the mass and the adjacent bladder and rectal wall. No evidence of distant metastasis. Options of treatment were discussed with the patient, and she opted to have neo-adjuvant chemotherapy followed by surgery if feasible. Thus, she then received three cycles of chemotherapy with combination of carboplatin 750 mg/m² with AUC 5 and paclitaxel 175 mg/m² with a 3-week interval in between cycles. Re-assessment after completion of three cycles found the tumour size increased to 6 × 6 cm, thus not suitable for surgery. The direction of treatment then changed to concurrent chemotherapy and radiotherapy (CCRT). She received the standard dose of external beam radiotherapy 46 Gy for 25 fractions and brachytherapy 5 Gy for 3 fractions in combination with cisplatin 40 mg weekly for five cycles. She had a complete response to CCRT and remained disease-free for 6 months.

Neoadjuvant chemotherapy (NACT) in locally advanced cervical cancer has been looked into as an alternative method of treatment to improve survival as well as to reduce complication. NACT has been described in literature as either used before definitive radiotherapy or before radical surgery. Administration of chemotherapy aims in reduction of primary tumour size to allow surgery and eradicates micrometastasis. In addition, it can improve vascularisation and reduce hypoxic cells, thus improves sensitivity to radiation therapy. In clinical practice, NACT has been limitedly used when no benefit was observed comparing NACT followed by radiotherapy and radiotherapy alone [5], [6]. However, promising results had been seen with NACT followed by radical surgery, where several studies conducted showed NACT followed by radical surgery improved clinical outcomes with a significant 23% reduction in the risk of death in patients with locally advanced cervical cancer compared to surgical alone. Furthermore, in those who received NACT, incidence of nodal metastasis, vascular space invasion, and parametrical involvement were lower [4].

NACT followed by radical surgery has also been compared head-to-head with current standard treatment (CCRT) in the literature. Some studies showed no obvious difference between the two treatment modalities, and some showed CCRT has better survival rates [7]-[10]. A meta-analysis involving seven clinical studies, conducted mainly in Asia, by [11] found that NACT followed by surgery is not superior to CCRT, as there was no significant difference in overall survival as well as disease-free intervals between two groups. Late toxicity such as bladder, bowel, pelvic, and vaginal complications were lower in patients who received NACT, while early toxicity did not show significant difference between groups [11]. A preliminary report of meta-analysis by European Organisation for Research and Treatment of Cancer (EORTC) trial (EORTC 55994) that has been released concurred with [11]. A similar 5-year overall survival was observed in both groups, while NACT with radical surgery patients had less long-term toxicity compared to CCRT [12]. Even though this result did not favour NACT followed by radical surgery as a standard treatment for locally advanced cervical cancer, the lower incidence of long-term toxicity may have a significant impact on quality of life of the patients post treatment. The result of this meta-analysis has given NACT followed by surgery a promising alternative treatment modality in especially young and sexually active patients. Both of our reported cases are in the younger age group and may perhaps have benefitted from lower long-term toxicities as mentioned if the tumour responded well to NACT. In addition, NACT followed by surgery may also benefit those in countries with limited resources or in those remote from radiotherapy facilities.

Platinum-based chemotherapy agents have been widely used in cervical cancer as they had shown 10-30% reduction in tumour size. Prolonged survival by few months was observed when they were used in combination with other agents [13]. Good response rates to platinum-based agents when used as NACT in primary untreated cervical cancer were also observed [14]. Various combinations of chemotherapy agents have been described in literature, however, there is no report that the combinations are superior to one another. Platinum-based chemotherapy agents were
also used in both of our patients with combination of taxane, but both developed poor response which ended up with tumour progression. Estimation of possible response rate to chemotherapy plays an important role in clinical practice. Reference [15] described a simple index based on five prognostic factors to identify women who will not respond to platinum-based regimens in recurrent cervical cancer. These factors are patient’s race, site of tumour involvement, GOG performance status, whether radio-sensitiser given, and first recurrence of disease within 1 year of diagnosis. Patients were classified into three risk groups (low risk: 0–1 factor; mid risk: 2–3 factors; high risk: 4–5 factors), and response rate estimated were: low risk 50.6%, mid risk 29.4%, and high risk 13.0% [15]. Median progression-free and overall survival can also be calculated using this index. Even though the study was done among those with disease recurrence, but it can also guide us in patient selection before starting NACT to estimate the response rate. Further evaluation with immunohistochemistry and genetic studies may offer additional prognostic factors for response rate to chemotherapy. In our case report, both cases had poor response to NACT with disease progression requiring change of treatment modality to standard treatment with CCRT. Basically, the initiation of CCRT was delayed around 9–10 weeks in both patients. Generally, delay in initiation of treatment in cancer patients has been correlated with decreased disease control, lower survival, and increased patient’s distress. However, a study conducted by [14] showed that longer time to initiation treatment is not associated with inferior overall survival in patients with cervical cancer treated with CCRT. Even when the delay was more than 90 days, there was no significant worsening of overall survival seen [16]. The pelvic recurrence observed in first case is another issue that needs to be addressed. Either the delay of starting CCRT is associated with pelvic failure or not, this has never been mentioned in literature before. But the factors associated with progression-free survival in those receiving CCRT were mainly stage of the disease, tumour size, and clinical response [17]. Besides, the histology of adenocarcinoma is also associated with poorer prognosis compared to squamous cell type [18].

IV. CONCLUSION

Neo-adjuvant chemotherapy (NACT) followed by surgery has comparable outcomes with standard treatment of chemoradiation therapy in locally advanced cervical cancer. Both have similar overall survival and progression-free survival rates, hence, potentially to be used as alternative treatments. In fact, NACT offers additional benefits with lower long-term toxicity which suits the younger-aged group and sexually active patients. Estimation of response rate to chemotherapy plays a major role in patient selection to have successful outcomes. CCRT can still be administered in those with poor response to NACT without decrease in overall survival.

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CONFLICT OF INTEREST

Authors declare that they do not have any conflict of interest.

REFERENCES
