

A STUDY OF COX-2 INHIBITOR CELECOXIB AND CHEMORADIATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

Kuppa Prakash¹, M. Venkatesh², M. Vijaya Kumar³

¹Associate Professor, Department of Radiotherapy, MNJ Institute of Oncology/S. V. Medical College.

²Senior Resident, Department of Radiotherapy, MNJ Institute of Oncology and Regional Cancer Center, Hyderabad.

³Professor, Department of Radiotherapy, MNJ Institute of Oncology and Regional Cancer Center, Hyderabad.

ABSTRACT

AIMS AND OBJECTIVES

To evaluate efficacy of concurrent oral Cox-2 Inhibitor (celecoxib) and chemoradiation in locoregional control, distant control, disease free survival and/or overall survival in patients with locally advanced cervical cancer. To determine treatment related toxicity rates in patients with locally advanced cervical cancer treated by oral celecoxib, intravenous cisplatin and concurrent pelvic radiation therapy.

MATERIALS AND METHODS

Study was done for a period of 2 years in a tertiary care cancer hospital which caters to the cancer patients. Advanced squamous, adenocarcinoma or adenosquamous carcinoma of uterine cervix, Patients with age <70 years, ECOG performance status 0-2, Normal haematological investigations, Normal renal function test, Normal liver function test, No disease outside of pelvis.

RESULTS

This prospective study consisted 30 patients, 15 patients on either arm. Overall pooled mean age for both study and comparison group was 50.3 years with a probability value $P=0.91$ for age. 14 patients (93.33%) in both the arms had a performance status of ECOG 0 or 1 and 1 patient in both arms had ECOG PS-2. Stage distribution of the patients in study arm was 3 in IB2, 2 in IIA, 5 in IIB, 4 in III and 1 in stage IVA. In control arm, out of the 15 patients 2 are in IB2, 2 in IIA, 5 in IIB, 5 in III and 1 in stage IVA. The mean probability value was $P=0.65$ for stage distribution. 15 patients in arm-A (study arm) received pelvic RT 50Gy 2Gy/Fr 5#/week followed by HDR –ICR 3 Fr. 700 cGy/Fr after pelvic RT on an average of 1 week along with weekly cisplatin 40 mg/m² (50 mg) (D1, D8, D15, D22) and Cox-2 inhibitor oral celecoxib 400 mg twice daily (800 mg/d) starting from day 1 to throughout the duration of the chemoradiation. 15 patients in arm-B (Control arm) received pelvic RT 50Gy 2Gy/Fr 5#/week followed by HDR –ICR 3 Fr. 700 cGy/Fr on an average of 1 week after pelvic RT along with weekly cisplatin 40 mg/m² (50 mg) (D1, D8, D15, D22). The probability value (86.67% vs. 73.33%) was $P=0.37$ for local control, which is not significant. 2 patients (13.33%) failed at local control in study arm and 4 patients (26.67%) failed locally in control arm. In both arms, 4 patients (26.67%) had local/distant relapse. The probability value $P=1.00$ for local /distant relapse, non-significant, but locoregional control is high in study arm compared to control arm with a probability value $P=0.37$ which is not significant. Most of the relapses were observed with stage III and stage IVA disease. The median time to response from the end of the radiation was 3 months.

CONCLUSION

Celecoxib is a safe drug to use along with chemoradiation without any serious cardiovascular side effects.

KEYWORDS

Cox-2 Inhibitor, Cervical Cancer, Concurrent, Chemoradiotherapy, etc.

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INTRODUCTION: Cervical cancer is one of the most common malignant neoplasms. It is the 2nd most common malignancy in women worldwide and most common gynaecological malignancy in India and it is the 2nd most frequent cause of cancer deaths in women.

Cervical cancer rates are decreasing among women in the United States, but rates are still high among Hispanic/Latin, Black and Asian Women.¹ 78% cases occur in developing countries. An estimated 12,200 new cases of cervical cancer were diagnosed in United States in 2012, 4200 deaths result from the disease. Global yearly incidence of cervical cancer for 2002 was 4,93,200. The annual death rate was 2,73,500. Persistent HPV infection is regarded as the most important contributing factor for the development of cervical cancer. Early age at first intercourse, Multiple sexual partners, Sexual contact with an infected partner, unprotected sexual contacts,

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Corresponding Author:

Dr. Kuppa Prakash,

Associate Professor, Department of Radiotherapy,

MNJ Institute of Oncology, Hyderabad.

E-mail: kuppa_prakash@yahoo.in

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Multiparity.² Pregnancy at an early age, HPV infection, Smoking and Immunosuppressant etc. are the common aetiological factors resulting in cervical cancer. Combined chemoradiation is the current cornerstone in management of locally advanced cervical cancer. Improving locoregional control and local/distant relapse in locally advanced cervical cancers has led to increasing interests in exploring the use of novel antineoplastic agents in the patients. Cyclooxygenase (Cox-2) is one interesting potential target for the treatment of cervical cancer. Cox-2 enzyme overexpresses in many malignant tumours as well as cervical cancer and is associated with more aggressive tumour behaviour and poor prognosis. Several preclinical studies on selective Cox-2 inhibitors such as celecoxib have shown that these agents have antitumour, antiangiogenesis and radiosensitising effects.³ In addition, there are evidences that cox-2 inhibitors have been associated with significant reduction in vascular permeability and decrease in acute and chronic inflammation. Celecoxib has been progressively used in clinical studies for improving the response to therapy in many cancers. This study aimed to determine the efficacy and treatment related toxicity of Cox-2 inhibitors, celecoxib (400 mg BD) and chemoradiation in locally advanced cervical cancer.

Rationale of Combining COX-2 Inhibitor (Celecoxib) to Chemoradiation in Locally Advanced Cervical Cancer:

Chemoradiotherapy has been shown in RTOG 90-01 and several GOG studies to be more effective than radiation therapy alone in the treatment of women with advanced carcinoma of the cervix.⁴ The combination of cisplatin and 5-fluorouracil decreased both local and distant recurrence rates and improved overall survival in RTOG 90-01. GOG 120 demonstrated superior survival for weekly cisplatin and radiotherapy compared with radiotherapy alone, and weekly cisplatin and radiotherapy yielded a lower frequency of combined grade 3 and grade 4 toxicity compared with the combination of Radiotherapy, cisplatin, 5-FU, and hydroxyurea. In the arm that received radiotherapy and cisplatin, the rate of progression-free survival was 67%, and thus, within two years 33% of the patients with advanced cervical cancer had failed therapy.^{5,6}

Angiogenesis has been linked to increased metastasis formation and decreased overall survival in patients with various tumours, including the uterine cervix. Angiogenesis is a unique process by which new blood vessels are formed. Tumours stimulate angiogenesis by directly secreting angiogenic substances or activating and releasing Angiogenin compounds stored within the extracellular matrix. Angiogenesis is a prerequisite for tumour growth greater than 1-2 cubic millimetres. Therefore, tumour angiogenesis is a very important therapeutic target. Numerous growth factors play a role in angiogenesis including tumour necrosis factor alpha, acidic and basic fibroblast growth factor (big), placental growth factor (PGF) and vascular endothelial growth factor (Angiogenin or VEGF). Cyclooxygenase (COX) is the enzyme that

catalyses the synthesis of prostaglandins (PGs) from arachidonic acid.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit COX-mediated synthesis of PGs. While cyclooxygenase-1 (COX-1) is constitutively expressed in a wide range of tissues, cyclooxygenase-2 (COX-2) is cytokine inducible. Enhanced COX-2 expression has a key role in the development of oedema by impeding blood flow and causing immunomodulation that is observed in pathologically altered disease states. COX-2 is overexpressed in a variety of different tumours, including colon, pancreatic, prostate, lung and head and neck cancers. COX-2 is also observed within human tumour neovasculature.^{7,8} suggesting that COX-2 derived prostaglandins contribute to tumour growth by inducing formation of new blood vessels. Celecoxib, a COX-2 inhibitor, which spares COX-1 at therapeutic doses in humans, is a potent inhibitor of angiogenesis. Furthermore, celecoxib inhibited neoplastic cells and neoangiogenic vasculature proliferation by 40-60% in these tumours. Celecoxib suppressed the growth and metastasis of Lewis lung carcinoma in C57/BL6 mice. Celecoxib caused at least a 70% decrease in both tumour growth and metastasis. These and other data suggest that COX-2 dependent angiogenesis plays a major role in development of cancer.

The ability of celecoxib to block neoangiogenesis and tumour proliferation, regardless of the expression of the enzyme in the cancer cells, suggests the potential utility of this anti-inflammatory drug in the treatment of human cancer. The combination of Celecoxib and cisplatin-based chemotherapy with radiotherapy has the potential to improve tumour control and reduce complications in women with advanced carcinoma of the cervix. Preliminary evidence suggests that inhibition of COX-2 can down-regulate angiogenesis and work cooperatively with radiation therapy without enhancing the normal tissue toxicity.

METHODOLOGY: MNJIO&RCC, Hyderabad is a tertiary care cancer hospital which caters to the cancer patients of Andhra Pradesh and its neighbouring states with a patient load of around 10,000 per year. This prospective two arm study included a total of 30 patients with 15 patients in each arm registered at MNJIO&RCC, Hyderabad with confirmed diagnosis of squamous cell and/or adenocarcinoma of cervix. The intention was comparing the results of Cox-2 inhibitors (celecoxib) and chemoradiation with only chemoradiation in locally advanced cervical cancer. Study period - from October 2010 to December 2012.

Inclusion Criteria: Advanced squamous, adenocarcinoma or adenosquamous carcinoma of uterine cervix, Patients with age < 70 years, ECOG performance status 0-2, Normal haematological investigations, Normal renal function test, Normal liver function test, No disease outside of pelvis.

Exclusion Criteria: Patients with active GI ulcers, GI bleeding, inflammatory bowel disease, Patients with history of allergy to sulphonamides or NSAIDs or celecoxib use 2 months prior to study entry, Patients taking Dilantin or lithium or with active cardiac disease, Patients with age above 70 years.

Associated Comorbid Conditions: Untreated tuberculosis, HIV, HBsAg positive patients, uncontrolled hypertension, and uncontrolled diabetes mellitus; history of previous treatment with any of the modalities like surgery, radiotherapy, chemotherapy; patients with prior malignancies without disease-free intervals more than 3 years; pregnant or lactating females.

Pre-Treatment Evaluation: A complete detailed history which includes presenting complaints, past history, family history, personal history and socioeconomic history with emphasis on sexually transmitted infections.

General physical examination; local examination including abdomen, pelvic, rectal examination; systemic examination.

Haematological investigations: Complete Blood picture, renal function tests and Liver function tests; Screening for HIV/HbsAg.

Biopsy from the primary tumour (edge of gross tumour or 4 quadrants).

X-ray Chest (PA view). Ultrasound abdomen & pelvis. CT perfusion scans - Abdomen & Pelvis (optional). MRI/PET CT (optional). When all the investigations were within normal limits, patient's written consent was taken after explaining the nature of disease, its treatment and side effects in his own vernacular language.

RESULTS: A prospective comparative study of 30 patients with squamous cell and/or adeno, adenosquamous carcinoma of cervix following strict selection criteria as outlined previously was done.

The patients were treated with celecoxib and chemoradiation as per the protocol mentioned previously. Informed consent was taken after explaining in detail the treatment benefits & risks. Emphasis was laid on documenting the toxicity of the treatment and nutritional status of the patients during treatment.

| Age Group | Arm-A | | Arm-B | |
|-------------------------|-----------------|-------|-----------------|-------|
| | No. of Patients | % | No. of Patients | % |
| 30-39 | 2 | 13.33 | 2 | 13.33 |
| 40-49 | 5 | 33.33 | 5 | 33.33 |
| 50-59 | 6 | 39.96 | 5 | 33.33 |
| 60-69 | 2 | 13.33 | 3 | 20 |
| Histology | | | | |
| Squamous Cell Ca. | 12 | 80 | 12 | 80 |
| Adeno Ca. | 3 | 20 | 3 | 20 |
| Stage | | | | |
| IB2 | 3 | 20 | 2 | 13.33 |
| IIA | 2 | 13.33 | 2 | 13.33 |
| IIB | 5 | 33.33 | 5 | 33.33 |
| III | 4 | 26.67 | 5 | 33.33 |
| IVA | 1 | 6.66 | 1 | 6.66 |
| Toxicity Grading | | | | |
| I | 9 | 60% | 9 | 60% |
| II | 6 | 40% | 6 | 40% |
| III | 0 | 0 | 0 | 0 |

Table 1: Details in the Study

| Local Control & Local/Distant Relapse | Arm-A | | Arm-B | |
|---------------------------------------|-----------------|-------|-----------------|--------|
| | No. of Patients | % | No. of Patients | % |
| Initial local control after treatment | 13 | 86.6% | 11 | 73.33% |
| Local/Distant relapse during followup | 4 | 26.6% | 4 | 26.6% |

Table 2: Shows Local control & Local/Distant Relapse

| Parameter | IB2 | | IIA | | IIB | | III | | IVA | |
|-----------------------|-----|---|-----|---|-----|---|-----|---|-----|---|
| | No. | % |
| Loco-regional control | 3 | 2 | 2 | 2 | 5 | 4 | 3 | 3 | 0 | 0 |
| Local/Distant relapse | 0 | 0 | 0 | 0 | 1 | 1 | 2 | 2 | 1 | 1 |

Table 3: Analysis of Parameters

| | | | | | | | | |
|----------------|---|---|---|---|---|---|---|---|
| Nausea | 9 | 9 | 6 | 6 | 0 | 0 | 0 | 0 |
| Vomiting | 8 | 7 | 5 | 5 | 0 | 0 | 0 | 0 |
| Diarrhoea | 7 | 6 | 5 | 4 | 0 | 0 | 0 | 0 |
| Renal toxicity | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| CVS Toxicity | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Table 4: Toxicity in Study

This prospective study consists of 30 patients, 15 patients on either arm. In test arm, the mean age was 50.4 years and in control arm the mean age was 50.1 years. Overall pooled mean age for both study and comparison group was 50.3 years with a probability value $P=0.91$ for age. 14 patients (93.33%) in both the arms had a performance status of ECOG 0 or 1 and 1 patient in both arms had ECOG PS-2. Stage distribution of the patients in study arm was 3 in IB2, 2 in IIA, 5 in IIB, 4 in III and 1 in stage IVA. In control arm, out of the 15 patients 2 are in IB2, 2 in IIA, 5 in IIB, 5 in III and 1 in stage IVA. The mean probability value $P=0.65$ for stage distribution. 15 patients in arm-A (Study arm) received pelvic RT 50Gy 2Gy/Fr 5#/week followed by HDR –ICR 3 Fr. 700 cGy/Fr after pelvic RT on an average of 1 week along with weekly cisplatin 40 mg/m² (50 mg) (D1, D8, D15, D22) and Cox-2 inhibitor oral celecoxib 400 mg twice daily (800 mg/d) starting from day 1 to throughout the duration of the chemo radiation.

15 patients in arm-B (control arm) received pelvic RT 50Gy 2Gy/Fr 5#/week followed by HDR –ICR 3 Fr. 700 cGy/Fr on an average of 1 week after pelvic RT along with weekly cisplatin 40 mg/m² (50 mg) (D1, D8, D15, D22). The mean follow up was 13 months. In both arms among 15 patients, 6 patients had grade 2 haematological and gastrointestinal toxicities and 9 patients had grade 1 toxicities. The probability value $P=1.00$ for the toxicity. Acute treatment related toxicities were manageable in both groups. The patients in the study group tolerated celecoxib well and none of them had significant complaint of treatment related toxicities. Anorexia, nausea, vomiting, fatigue, diarrhoea were the most frequent treatment related toxicities in both the groups. None of the patients developed grade 3 and grade 4 toxicities and treatment related death was not observed. There was no difference in terms of toxicity between the two groups.

Among 15 patients, who completed the treatment, 13 patients (86.67%) showed loco regional control in study arm and 11 patients (73.3%) showed loco regional control in control arm. The probability value (86.67% vs. 73.33%) $P=0.37$ for local control, which is not significant. 2 patients (13.33%) failed at local control in study arm and 4 patients (26.67%) failed locally in control arm. In both arms 4 patients (26.67%) had local/distant relapse. The probability value $P=1.00$ for local/distant relapse, non-significant, but loco regional control is high in study arm compared to control arm with a probability value $P=0.37$ which is not significant. Most of the relapses were observed with stage III and stage IVA disease. The median time to response from the end of the radiation was 3 months.

DISCUSSION: Concurrent Chemoradiation is accepted as a standard treatment option for locally advanced cervical cancer. The Institution of combined modality therapy has resulted in significant improvements in tumour control and survival benefit compared with RT alone. Despite improvements in survival after the introduction of chemoradiation in the treatment of patients with cervical cancer, locoregional control of this disease continues to be

a major problem. To further optimise, the efficacy of chemoradiation, there is growing interests in novel molecularly targeted approaches, one of such most promising agents is Cox-2 inhibitors (Celecoxib).^{9,10} Cox-2 overexpression is seen in many malignancies including cervical cancer. Over 150 articles were reviewed; studies in vivo & in vitro confirmed the role of Cox-2 in the development of cervical cancer. In addition, Cox-2 overexpression in cervical cancer patients is a poor prognostic marker associated with increased risk for recurrent or metastatic disease. Elevated tumour Cox-2 prostaglandin PGE2 levels have been implicated in angiogenesis, tumour invasion, resistance to apoptosis and suppression of antitumour immunity.

Preclinical animal model studies show tumour reduction when animals are treated with either nonspecific or specific inhibitors of Cox-2. These studies suggest that NSAIDs may act on multiple tumour progression targets via both Cox-2 dependent and independent pathways.¹¹ In addition several studies found that Cox-2 inhibitors significantly enhanced the response of tumour cells to radiotherapy. The exact mechanism(s) responsible for the anti-proliferative effect of Cox-2 inhibitors remains to be defined. Several clinical trials studied the role of Cox-2 inhibitors in improving the response to radiotherapy or chemotherapy in many different cancers, such as cervical, breast, lung, rectal, Head & Neck, oesophageal, pancreatic CA, etc.¹²

Cervical Cancer: Two studies of celecoxib and chemoradiation in cervical cancer, one is a phase II trial at Princess Margaret Hospital, the efficacy and toxicity of celecoxib in combination with definitive chemoradiation were evaluated in 31 women with locally advanced cervical cancer. All the patients received oral celecoxib 400 mg twice daily for 2 weeks before and during chemoradiation. They found acute grade $\frac{3}{4}$ haematological, GI toxicities were most frequent and were largely attributed to chemotherapy. Twenty five of 31 patients (81%) achieved complete response during the first year of followup. In second study, RTOG 0128 the treatment related toxicity associated with celecoxib and chemo radiation was evaluated for 84 women, they found that the celecoxib and chemo radiation was excessively toxic, disease free survival and overall survival was 69% and 83% at the end of 2-year followup. In both the studies, the chemotherapy regime was cisplatin and 5-FU every 3 weekly 3 times along with radiation. Authors concluded that addition of celecoxib to CRT did not improve response rate and is excessively toxic, but trials are done with full dose of cisplatin & 5-FU, most of the toxicities in the study were attributable to chemotherapy.

Lung Cancer: A phase I trial of thoracic radiotherapy and celecoxib in patients with locally advanced lung cancer results show that celecoxib can be safely administered with thoracic radiotherapy when given up to the highest FDA approved dose of 800 mg/d. Treatment resulted in

actuarial local progression free survival of 66% at 1 year and 42.2% at 2 years. An encouraging outcome that warrants further assessment in a phase II/III trial. In another phase II study of celecoxib, carboplatin, paclitaxel, RT in locally advanced lung cancer, the addition of celecoxib to chemoradiation therapy in locally advanced lung cancer did not improve survival; primary end point was not reached.

Oesophageal Cancer: Phase II trial studied response rate, toxicity, overall survival rate in patients with cisplatin and 5-FU, Celecoxib 200 mg twice daily on day 1 until surgery and then 400 mg twice daily until disease progression or unexpected toxicities or for a minimum of 5 years.¹³ 22 patients underwent oesophagectomy 4-6 weeks after completion of chemoradiation. Most patients experienced grade 3/4 toxicities of which diarrhoea, neutropenia, nausea, vomiting, oesophagitis, and dehydration were most frequent.

There were 7 treatment related deaths of 22 patients who underwent oesophagectomy. 5 had pathological complete response (22%). Authors concluded that celecoxib 400 mg twice daily to chemoradiation was well response rate of 22% in their study was similar to that reported with use of preoperative chemoradiation alone in other trials.¹⁴ Rectal Cancer: A Phase II study of Radiation, 5-FU, celecoxib in locally advanced rectal cancer, results are addition of celecoxib to preoperative CRT is feasible for patients with locally advanced rectal cancer. Patients treated with celecoxib tend to show a better response (61%) when compared to those treated with placebo.

Head & Neck Cancer: The addition of celecoxib to CRT for locally advanced HNSCC was associated with increased incidence of toxicities. Pancreatic Cancer: A phase II study of Gemcitabine plus Celecoxib in patients with advanced or metastatic pancreatic adenocarcinoma. Results are addition of Celecoxib to gemcitabine did not demonstrate significant improvement in measured clinical outcomes.

Prostate Cancer: A phase I trial on prostate cancer, the addition of celecoxib to radiation was not associated with increased level of side effects. Glioblastoma: A phase I study of celecoxib and post chemoradiation adjuvant therapy for newly diagnosed glioblastoma. Results showed celecoxib can be safely administered with temozolomide in glioblastoma.

Familial Adenomatous Polyposis: Six months of twice daily treatment with 400 mg BD celecoxib leads to a significant reduction in number of colorectal polyps, a risk reduction of 33% to 45% in polyp recurrence.

Nasopharyngeal Cancer: In a study Soo et al found celecoxib 400 mg twice daily for 14 days, reduced microvessel density and induced changes in gene expression in patients with newly diagnosed, untreated nasopharyngeal carcinoma.¹⁵ In another study, mohammadinnah et al found that addition of low dose

celecoxib 100 mg twice daily to chemoradiation with weekly cisplatin (30 mg/m²) in locally advanced nasopharyngeal cancer improved locoregional control; however, response rate, survival are statistically not significant. Most of the trials that concluded excessive toxicity of celecoxib and chemoradiation, studied with full dose of chemotherapy and a complex regimen of chemotherapy along with radiation and in those studies most of the toxicities were attributable to chemotherapy. There are less number of studies actually studied with weekly cisplatin (30 mg/m²) or (40 mg/m²) or weekly paclitaxel 30 mg/m² or weekly carboplatin (AUC=2) and radiation therapy along with oral Cox-2 inhibitors (Celecoxib).

In this prospect there are encouraging results. The present study is evaluating efficacy and treatment related toxicity, safety of celecoxib 400 mg twice daily (800 mg/d) with concurrent chemoradiation in locally advanced cervical cancer.¹⁶ The addition of celecoxib 400 mg twice daily did not change the rates of overall survival or treatment related toxicities.

The addition of celecoxib 400 mg twice daily to concurrent chemoradiation improved locoregional control, which is non-significant with a probability value P=0.37 for this study concerned. Celecoxib in combination with definitive chemoradiation is associated with acceptable treatment related toxicity. There is still a need for future trials of celecoxib and chemoradiation with promising results for confirmation of efficacy of the drug in different cancers.

CONCLUSION: The addition of celecoxib 400 mg twice daily (800 mg/d) to concurrent chemoradiation improved locoregional control, which is non-significant with a probability value P=0.37 for this study concerned. Its effect on response rates and overall survival was statistically not significant. Celecoxib in combination with definitive chemoradiation is associated with acceptable treatment related toxicity. Celecoxib is the safe drug to use along with chemoradiation without any serious cardiovascular side effects. With this study it may or may not be considered adding celecoxib to chemoradiation in locally advanced cervical cancer, but there is still a room for future trials of celecoxib and chemoradiation with promising results for confirmation of efficacy of the drug in different cancers.

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