Research Article

A prospective study to evaluate the role of curcumin in treatment of locally advanced carcinoma of cervix

Abstract

Objectives: The present study is conducted to determine the role of curcumin alongwith chemoradiation in the management of locally advanced carcinoma cervix in terms of toxicity, tumor response and survival rates.

Methods: Patients were enrolled into study from Jan 2012 to Jan 2014. The patients were randomized into two groups (group I and group II) of 30 patients each. All patients were planned for external beam radiotherapy (EBRT) to total dose of 50Gy/ 25fractions/5weeks with concomitant cisplatin 40mg/m2 IV weekly. HDR brachytherapy with 3 fractions of 6Gy each was given weekly after completion of EBRT. Curcumin (4gm/day) was given orally to group I patients from the start of EBRT till the completion of brachytherapy.

Results: The baseline patients' characteristics were matched in the two groups. The median follow up was of two years. After the completion of treatment, complete tumor response was seen in 70% and 66.67% patients in group I and II respectively. Overall survival and disease free survival rates were 93.3%, 76.7% in group I and 90%, 66.7% in group II respectively. The findings were not statistically significant. Grade 3 skin reactions were seen in 3.33% and 20% of the patients in group I and group II respectively. Acute mucosal toxicity of grade 2 was seen in 23.3% and 50% of patients in group I and II respectively.

Conclusion: The significant difference was found in occurrence of severe acute radiation toxicity to skin and mucosa with comparable survival rates in the two groups, i.e. with and without curcumin.

Keywords: curcmin, cervix, carcinoma, chemoradiation

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Abbreviations: CCRT, concurrent chemoradiotherapy; NF-κB, nuclear factor-kappa B; STAT3, signal transducer and activator of transcription 3; NRF2, nuclear factor E2–related factor-2; Hb, hemoglobin; TLC, total leucocyte count; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; WHO, world health organization; GIT, gastrointestinal tract; GUT, genitourinary tract; RTOG, radiation therapy oncology group; SWOG, south west oncology group, MGUS, monoclonal gammopathy of undetermined significance; RDS, radiation dermatitis severity

Introduction

Cervical cancer is the most frequent gynaecological cancer and the second leading cause of cancer-related deaths among women worldwide.[1] Concurrent chemoradiotherapy (CCRT) with cisplatin based chemotherapy has been the standard line of treatment for locally advanced carcinoma of cervix. The randomized trials have shown that the use of concurrent chemoradiation results in a 30% to 50% decrease in the risk of death as compared to radiotherapy alone. Also, 6% improvement in 5 year survival was seen when compared with radiotherapy alone.[2–7] Although, it is well tolerated, acute and long term side effects have been seen. The attempts have been carried out to decrease toxicity of chemoradiation as well as to improve the outcome at the same time. Administration of curcumin in patients is supposed to kill the tumor cells effectively by enhancing the effect of radiation and, at the same time, protect normal cells against the harmful effects of radiation.

Curcumin is a product obtained from plant *Curcuma longa*. It has radioprotective and radiosensitising properties and thus, may be helpful in decreasing the toxicity and increasing the efficacy profile of the treatment. It acts as a chemosensitizer and radiosensitizer for tumors by downregulating various growth regulatory pathways and specific genetic targets including genes for Nuclear factor-kappa B (NF-κB), Cyclooxygenase-2, Signal transducer and activator of transcription 3 (STAT3), multidrug-resistance proteins, antiapoptotic proteins and growth factor receptors.[8] Curcumin can induce the expression of some antioxidant enzymes and activation of Nuclear factor E2–related factor-2 (NRF2). This mechanism lead to the protective effect of curcumin and has shown to protect normal organs from chemotherapy and radiotherapy induced toxicity, such as liver, kidney, oral mucosa and heart.[8]

Before we started this study, there was no published study of its kind in the literature. The current study was designed to see if the addition of curcumin to standard treatment of locally advanced carcinoma of uterine cervix could improve the tumor control and reduce the toxicity profile in the patients.

Material and methods

Patients with histopathologically proven locally advanced carcinoma of cervix, who were treated from January 2012 to

January 2014 were included in the study. All of the patients were staged according to International Federation of Gynecologists and Obstetricians (FIGO) staging system, 2010. All patients had the following characteristics: stage IIB to IVA, Karnofsky Performance Status ≥70, normal renal function tests, liver function tests and complete hemogram. Their blood investigations were as per the eligibility criteria with Hemoglobin (Hb) >8gm/dL, Total Leucocyte Count (TLC) >4000/cmm, platelet count >100,000/cmm, blood urea <40mg/dL, serum creatinine <1.5mg/dL, SGOT <35 IU/L and SGPT <40 IU/L. Patients with distant metastases, prior chemotherapy, surgery or radiation for the disease, associated co-morbid medical condition, history of prior malignancy were excluded from the study. Ethical clearance was obtained from institutional ethical committee. Informed written consent was obtained from all participants before the commencement of study.

Radiation techniques

External beam radiotherapy (EBRT) by Cobalt-60 unit was used to treat the whole pelvis. A total dose of 50Gy was delivered with the daily fraction of 2Gy, five days per week. The radiation was delivered by Cobalt-60 unit. Intracavitary brachytherapy (ICBT) was started after the EBRT and three sessions of 6Gy, one session per week for three consecutive weeks were given by Ir-192 microselectron HDR remote controlled afterloading brachytherapy machine. All patients were treated with concurrent chemoradiotherapy. Patients were prospectively randomized into treatment schedules:

Group I: Cisplatin+Curcumin

Group II: Cisplatin

In Group I, concurrent cisplatin was given (40mg/m², weekly) during the EBRT, with daily dose of oral curcumin (4gm/day). Curcumin is given continuously during the total treatment duration (EBRT as well as ICBT). Group II patients were treated with concurrent cisplatin (40mg/m², weekly) alone.

Evaluation

During treatment, patients were evaluated weekly for acute radiation reactions. The haematological toxicities were assessesd using World Health Organization (WHO) criteria. Acute radiation reactions of skin, mucosa, upper gastrointestinal tract (GIT), lower GIT and genitourinary tract (GUT) were evaluated according to Radiation Therapy Oncology Group (RTOG) criteria. South West Oncology Group (SWOG) criteria was used for evaluating the weight loss. After the treatment was completed, the disease status was evaluated according to WHO criteria. Late toxicities were assessed according to RTOG/ EORTC (European Organization for Research and Treatment of Cancer) late toxicity criteria.

Statistical analysis

The data thus obtained was analyzed and compared using SPSS software version 20.0. Tumor response rate, radiation toxicities were evaluated between the two groups by the chi-square test. Survival data were calculated by the Kaplan-Meier method and log-rank test to identify any statistical significance between the two groups.

Results

Patient data

A total of 60 patients were included in this study. Thereafter, sixty patients were randomized into group I (with curcumin) and group II (without curcumin) as described above. All data are shown in Table 1.

Table 1 Patient characteristics

Characteristics	Group I	Group II	p- value
Age (years)			
≤30	3.33%	3.33%	
31-40	16.67%	16.67%	
41-50	23.33%	26.67%	0.844
51-60	20%	23.33%	
61-70	30%	30%	
>70	6.67%	0%	
Social background			
Rural	66.67%	66.67%	1
Urban	33.33%	33.33%	
KPS			
80	90%	93.30%	0.64
90	10%	6.70%	
Menopausal status			
Premenopausal	30%	26.67%	0.774
Postmenopausal	70%	73.33%	
Tumor Morphology			
Ulceroproliferative	90%	86.67%	0.688
Infiltrative	10%	13.33%	
Histology			
WDSCC	0%	0%	0.519
MDSCC	76.67%	83.33%	
PDSCC	23.33%	16.67%	
Stage			
IIB	60%	46.67%	
IIIA	6.67%	13.33%	0.67
IIIB	30%	33.33%	
IVA	3.33%	6.67%	

WDSCC, well differentiated squamous cell carcinoma; MDSCC, moderately differentiated squamous cell carcinoma; PDSCC, poorly differentiated squamous cell carcinoma

Treatment received and duration

All patients in both the groups received the intended dose of 50Gy by external beam radiotherapy. In both the groups, all patients received concomitant cisplatin of 40mg/m² weekly. In group I, all patients took 4gm of curcumin per day during the treatment.

In group I and group II, 63.33% and 53.33% of the patients respectively completed the whole treatment within 7-8weeks. In group I and group II, 30% and 33.33% of the patients took 8-9 weeks to complete the treatment respectively. In group I, treatment was interrupted for more than one week in two patients (6.67%). In group II, treatment interruption was seen in four patients (13.33%).

Response of the tumor

After the completion of treatment, complete tumor response was seen in 70% of the patients in group I and 66.67% patients in group II at the end of treatment. In stage IIB, complete response was observed in 83.33% and 64.29 % of patients in group I and group II respectively. In group I, complete response in stage IIIA and stage IIIB were 100% and 44.44% respectively. In group 2, complete response in stage IIIA and stage IIIB were 75% and 70% respectively. In group I and II, complete response in stage IVA was seen in 0% and 50% respectively. Overall, partial response was seen in 30% of the patients in each group. One patient in group II has no response with the treatment. The observations in terms of tumor response were not statistically significant.
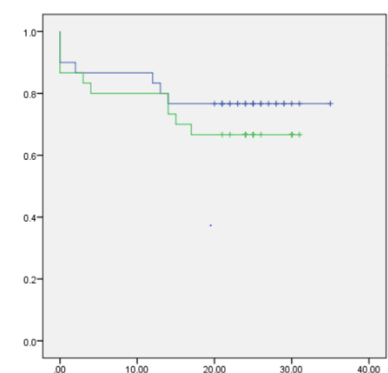
Survival rates

With the median follow up of 24 months, overall survival and disease free survival rates were 93.3%, 76.7% in group I and 90%, 66.7% in group II respectively. The survival rates of the two groups were not statistically significant. These are represented in Figure 1.

Residual disease occurred in 20% and 26.67% of the patients in group I and group II respectively. Recurrence was seen in 3.33% and 6.67% of the patients in group I and group II respectively. The distant metastasis to lung was seen in two (6.67%) patients and to supraclavicular node was seen in one (3.33%) patient; however, these patients did not show any evidence of local disease. Though, findings were not significantly different but they are indicative of slightly better response in group I.
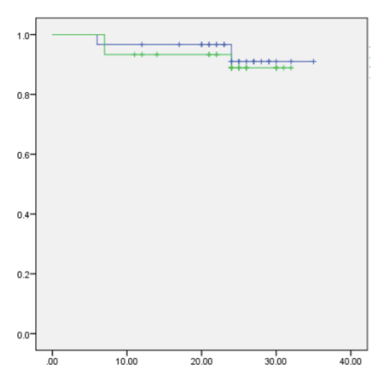
a) Overall Survival rate (p= 0.733)

b) Disease Free Survival rate (p= 0.431)

Figure I Kaplan- Meier curve showing a) Overall survival rate and b) Disease free survival rate of group I (blue line) versus group II (green line).

Toxicity profiles

Acute radiation toxicity: Grade 2 hematological toxicity (Hb) was seen in 13.33% and 20% of the patients in group I and group II respectively. Grade 3 and grade 4 toxicity was not observed in any of the patient. TLC data revealed grade 1 toxicity in 6.7% and 10% of the patients in group I and II respectively.

Grade 1 skin reactions were seen in 76.67% and 33.33% of the patients in group I and group II respectively. Grade 2 skin reactions were seen in 20% and 46.67% of the patients in group I and group II respectively. Grade 3 skin reactions were seen in 3.33% and 20% of the patients in group I and group II respectively. The significant difference was found in occurrence of grade 2 and grade 3 skin reactions in the two groups. Acute mucosal toxicity of grade 1 was seen in 63.4% and 33.3% of the patients in group I and group II respectively. Acute mucosal toxicity of grade 2 was seen in 23.3% and 50% of patients in group I and II respectively, which was significant statistically. Grade 3 mucosal toxicity was seen in 13.3% and 16.7% of patients in group I and group II respectively.

Four patients in group I and two patients in group II developed grade 3 upper GI toxicity. Grade 4 toxicity was not observed in any group. Lower GI grade 3 toxicity was observed in one patient each in group I and group II. Grade 1 genitourinary toxicity was observed in seven patients in group I and nine patients in group II. Grade 2, 3 and 4 toxicity was not observed in any of the groups. The findings were not significant. In both the groups, no significant weight loss was found. All data is shown in Table 2.

Table 2 Acute radiation toxicity of group I versus group II

Acute toxicities	Group I	Group II	p- value
Skin toxicity			
Grade 2	20%	46.70%	0.028
Grade 3	3.30%	20%	0.044
Mucosal toxicity			
Grade 2	23.30%	50%	0.032
Grade 3	13.30%	16.70%	0.717
Upper GIT toxicities			
Grade I	20%	26.70%	0.54
Grade 2-3	53.30%	43.30%	0.44
Lower GIT toxicities			
Grade I	86.70%	83.30%	0.72
Grade2-3	13.30%	16.70%	
GUT toxicities			
Grade I	77%	70%	0.56
Grade 2	23%	30%	

GIT, gastrointestinal tract; GUT, genitourinary tract

Late radiation toxicity

Late cutaneous grade 1 toxicity was seen in 70% and 80% of patients in group I and II respectively. Grade 2 cutaneous toxicity was observed in 13.33% and 10% of patients in group I and II respectively. The observations were not statistically significant. Late subcutaneous grade 2 toxicity was seen in 16.67% and 23.33% of patients in group I and II respectively. The observations were not statistically significant.

Late mucosal grade 1 toxicity was seen in 20% and 23.33% patients of the group I and II respectively. Late mucosal grade 2 toxicity was seen in group II in 3.33% of patients. The observations were not statistically significant.

Grade 2 toxicity of lower GI was observed in one patient of group II and not seen in group I. Grade 1 toxicity was seen in 16.67% and 23.33% of patients in group I and group II respectively. Grade 1 bladder toxicity was observed in 7% and 10% of patients in group I and II respectively. The observations were not statistically significant. All observations are shown in Table 3.

Table 3 Late radiation toxicity of group I versus group II

Late toxicities	Group I	Group II	p- value
Cutaneous			
Grade 0	16.67%	10%	
Grade 1	70%	80%	0.843
Grade 2	13.33%	10%	
Subcutaneous			
Grade 0	23.33%	23.33%	
Grade 1	60%	54%	0.451
Grade 2	16.67%	23.33%	
Mucosal			
Grade 0	80%	73.33%	0.559
Grade 1	20%	23.33%	
Lower GIT			
Grade 0	83.33%	73.33%	
Grade 1	16.67%	23.33%	0.211
Grade 2	0%	3.33%	
Bladder			
Grade 0	93%	90%	0.64
Grade 1	7%	10%	

Discussion

EBRT followed by ICBT was the best option till 1990s, thereafter the treatment paradigm has shifted to concomitant chemoradiation with cisplatin based chemotherapy. Five-year OS of patients treated with chemoradiation now approach 70% to 80% for stage IIB disease, 50% to 60% for stage IIIB disease, and perhaps 15% to 25% for stage IVA disease.[2–7]

This study was conducted to observe the effect of curcumin in locally advanced cervical cancer, when given with concomitant chemoradiation. This is the first study in the published literature trying to evaluate the role of curcumin in cervical cancer patients.

It has been revealed that curcumin sensitizes tumors to different chemotherapeutic agents including paclitaxel, vincristine, doxorubicin, 5-FU, cisplatin and gemcitabine. Chemosensitization has been observed in cancers such as breast, colon, pancreas, cervix, head and neck and in multiple myeloma, leukemia and lymphoma.[9] Curcumin is a highly pleiotropic molecule that modulates numerous targets, including cell cycle (cyclin D1 and cyclin E), apoptosis

(activation of caspases and down-regulation of antiapoptotic gene products), proliferation (Human epidermal growth factor receptor-2, Epidermal growth factor receptor, and Activating protein-1), survival (Phosphatidyl inositol-3-kinase/ protein kinase B pathway), invasion (Matrix metalloproteinase-9 and adhesion molecules), angiogenesis (Vascular endothelial growth factor), metastasis (Chemokine receptor type 4) and inflammation (Nuclear factor - kappa B, Tumor Necrosis Factor, Interleukin-6, Interleukin-1, Cyclooxygenase-2 and 5-Lipoxygenase) [10]. Curcumin has been shown to inhibit cell proliferation, cell cycle arrest and stimulate apoptosis *via* modulation of other transcription factors, such as AP-1, Erg-1, p53, β-catenin, Notch-1, Hif-1, and PPAR-α.[11]

Transcription of pathogenic HPVs during keratinocyte differentiation and thus, progression of cervical cancer can be controlled by curcumin as shown by Prusty et al.,[12] in a study on HeLa cells.[12] Qiao et al.,[13] has shown that curcumin enhanced the response of non hodgkin lymphoma cells to ionizing radiation. It has been observed in the study that the role of curcumin in inducing G2/M phase arrest and inhibiting the mTOR-NF-κB pathway is responsible for the effect. This has offered great potential for curcumin to be used in conjunction with radiotherapy for NHL in order to increase the efficiency of the treatment.[13] It was recently demonstrated by Javvadi et al.,[14] that pretreatment of two cervical cancer cell lines HeLa and SiHa with curcumin prior to ionizing radiation resulted in radiosensitization of cancer cells.[14] Khafif et al.,[15] investigated that curcumin can sensitize squamous cell carcinoma cells to the ionizing effects of irradiation. A significant decrease in the ability to form colonies *in vitro* following pretreatment with curcumin was found at all radiation doses establishing that curcumin may serve as an adjuvant in radiotherapy.[15]

Curcumin has also shown the potential role in the prevention and treatment of colorectal cancer in combination with other agents. The combination of curcumin and quercetin has shown to decrease the number and size of polyps after 6 months of treatment without any appreciable toxicity.[16] Golombick *et al.,*[17] has done a study to determine the effects of curcumin on plasma cells and osteoclasts in patients with Monoclonal gammopathy of undetermined significance (MGUS). This study enrolled twenty-six patients with MGUS, who were randomly assigned to two groups. In group 1, 17 patients were given curcumin at the start of study and were then crossed over to placebo after 3 months. In group 2, nine patients were given placebo initially and then crossed over to curcumin. Paraprotein load was found to be decreased in the ten patients. Out of these ten patients, five had a 12% to 30% reduction in paraprotein levels while receiving curcumin therapy. Also, >25% decrease in urinary *N*-telopeptide of type I collagen was noticed in 27% of patients receiving curcumin. The study suggested the therapeutic importance of curcumin against MGUS.[17]

In our study on locally advanced cervical cancer, the results of concomitant chemoradiation with or without curcumin were comparable. Though, slightly better response was seen in group I in terms of tumor response, disease free survival and overall survival, but no statistically significant difference was observed between the two groups. In group I, the treatment was interrupted in two patients (6.67%) during the external beam radiotherapy. These patients had severe acute skin radiation reactions. These patients complete their dose of external beam radiotherapy in more than six weeks. In group II, treatment duration was increased in four patients (13.33%). Grade 3 skin and mucosal reactions were seen in all of these patients

resulting in the delay of the treatment. These four patients took more than six weeks to complete the planned treatment. In group I and group II, 6.67% and 13.33% of the patients respectively completed the whole treatment in more than 9 weeks due to associated severe acute radiation toxicity. The observations regarding the total treatment duration were similar to the study by Eifel et al.[6]

Perez et al.,[18] noted a major impact of prolongation of treatment time on pelvic tumor control in stages IB, IIA, and IIB. In stage III, although the rate of pelvic failure was higher with prolongation of treatment time, the difference was not statistically significant.[18] In our study, no significant association was found in the tumor response or disease status with prolongation of time.

In a study by Maduro et al.,[19] acute and long-term toxicity of radiotherapy for cervical cancer were assessed. Acute toxicity of radiotherapy was reported in 61% of the patients in the rectosigmoid, in 27% as urological, in 27% as skin and in 20% as gynaecological toxicity.[19] The acute toxicities of GIT and GUT didn't differ much in the two groups. There was insignificant increase in the upper GI toxicity, especially nausea and vomiting in group I. Our study has shown the significant benefit in the acute skin radiation toxicity and acute mucosal radiation toxicity in the group taking curcumin. The results in our study are consistent with the results observed by Ryan et al.,[20] in their study. They found out that the oral curcumin daily during radiotherapy, reduced the severity of radiation dermatitis in breast cancer patients.[20] The arm containing curcumin had fewer moist desquamation and also reduced Radiation Dermatitis Severity (RDS) score at end of the treatment compared to placebo.[20] In the present study, the two groups didn't differ significantly in terms of late radiation toxicity.

Conclusion

The present study revealed statistically significant improvements in the radiation induced skin and mucosal toxicity with the addition of curcumin and, therefore, lesser treatment delay while giving radiotherapy. The limitation of the study included the small sample size. Taking into account the comparable response rate, comparable treatment related toxicities, significantly less radiation induced skin and mucosal toxicity with curcumin, the study is suggestive that the future clinical trials should consider to investigate the potential effectiveness of curcumin in the treatment of locally advanced uterine cancer.

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Conflict of interest

The author declares no conflicts of interest.

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