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A Prospective Randomized Study Evaluating the Role of Oral Curcumin along with Chemoradiationin Management of Locally Advanced Head and Neck Carcinoma

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Authors' contributions

This work was carried out in collaboration between all authors. Authors DK and PK did the study design and wrote the protocol. Authors NB, JVK and AK did literature searches. Authors DK, PK and JVK did the statistical analysis. Final editing done by authors PK and NB analyses of study was by author AK. All authors read and approved the final manuscript.

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ABSTRACT

Aim: This study was to evaluate the role of Curcumin along with or without chemoradiation in the management of locally advanced head and neck cancers (LHNC) in terms of tolerability, toxicity and response. Sixty treatment naive histopathologically proved cases LHNC were included in this prospective randomized study.
Materials and Methods: Patients were randomly assigned to receive radical external beam radiotherapy (EBRT) with weekly cisplatin and capsule Curcumin from the first day of EBRT till the

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completion in the dose of 1gm every 8 hourly (Group I/Study Group) and EBRT with weekly cisplatin only (Group II/Control Group).
Results: There were lower grades of statistically insignificant haemoglobin *(grad*e 2 *p value- 0.300)* and total leucocyte count *(grade 1 p value- 0.313)*, toxicities in group II in compared to group I during treatment. The acute skin and mucosal reactions were less in group I than group II without any statistically significant association during treatment and follow ups. Statistically significant less blood urea *(grade 1 p value- 0.019)* toxicities observed in group I, in compared to group II during treatment. There were statistically significant fewer grade 3 and 4 vomiting (*p value- 0.037)* in group II. At one year follow up 67% was disease free in group I in comparison to 56% in group II.
Conclusion: Curcumin, in management of LHNC, seems to decreases haematological, renal, skin and mucosal chemoradiation induced toxicities results in timely completion of intended treatment without any financial burden on patients and improves the disease control.

Keywords: Curcumin; cisplatin; concomitant chemoradiation; head and neck cancer.

1. INTRODUCTION

Head and neck cancers are among the most common cancers in developing countries, especially in Southeast Asia. Majority of these patients are diagnosed with locally advanced disease. This resulted in high incidence of loco regional recurrence and treatment failures. Concomitant chemoradiation is standard of care in inoperable cases of head and neck carcinoma. However this treatment schedule associated with more treatment induced an acute and late adverse effect which leads to treatment interruptions and thus prolonged treatment time. The prolongations of treatment time have adverse effect on success of treatment [1-3]. Various strategies have been tried to increase response and to reduce treatment related toxicities when integrate with chemotherapy and radiotherapy and therefore increase outcome. Curcumin is widely tried drug in various diseases as well as in various cancers.

Curcumin is commonly used in the Indian and Eastern Asia as spice commonly known as turmeric. Various studies showed that curcumin is supposed to have properties of radiosensitization and chemosensitization to tumors, and radioprotection and chemoprotection to normal organs thus; helpful in decreasing the toxicity and increasing the efficacy profile of the regimen [4-6]. Based on the information and literature available so far this prospective study has been conducted to determine the role of curcumin along with chemoradiation in the management of locally advanced head and neck cancers in terms of tolerability, toxicity and local control.

2. MATERIALS AND METHODS

The study was carried out on locally advanced, histopathologically proven sixty (60) cases of squamous cell carcinoma of Head and Neck region having stage III-IVB (AJCC-2010) disease treated in Department of Radiotherapy, Pt. B. D. Sharma Postgraduate Institute of Medical Sciences Rohtak (India), from May, 2013 to June, 2014. The patients included in study had pretreatmentKarnofsky performance status >70, hemoglobin>10 mg/dl. Pretreatment complete hemogram, kidney and liver function were within normal range. Chest X-ray and USG abdomen showed no apparent metastatic disease. Patients with co-morbid disease and metastatic disease were excluded from study.

The patients were divided randomly in two groups of 30 patients each by draw of lots (see Fig. 1).

EBRT was delivered by Cobalt – 60 teletherapy machines. Assessment of toxicities was done weekly during treatment in both the groups as per WHO toxicity criteria, RTOG Acute Radiation Morbidity Scoring Criteria weekly during treatment and then monthly during follow up. Tumor response is assessed as per WHO response criteria. Disease status (clinically) and late radiation toxicities (RTOG/EORTCcriteria) assessed during last follow up at six months. Radiological examination, fine needle aspiration or biopsy was carried out in case of any suspicious clinical examination. All the patients were followed up monthly after completion of concurrent chemoradiotherapy and up to one year.

2.1 Quality Assurance

Senior radiation oncologist in the department reviewed the records and also conducted examination of patients at random to verify treatment planning and findings of response and toxicities.

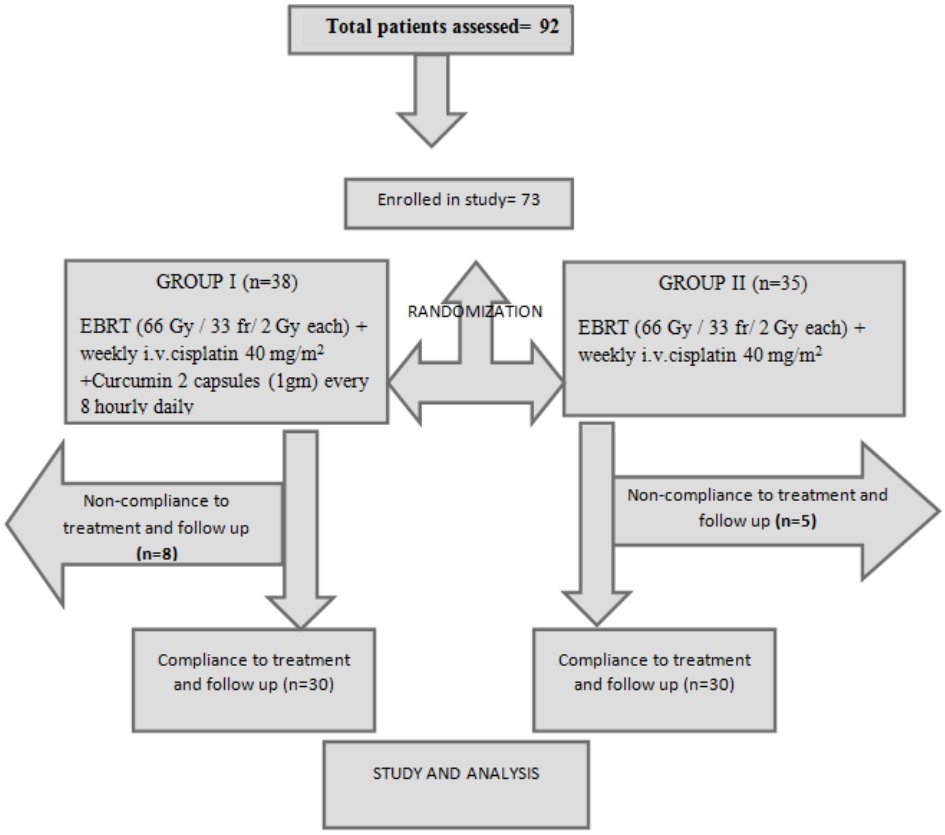

Fig. 1. Study design

2.2 Statistical Analysis

Pretreatment patient and clinical characteristics between two groups were compared. For continuous variables, mean and median values compared between two groups. Endpoints of study were tumor & nodal response, and acute & late radiation toxicities. Subgroup analysis was carried out on various prognostic indicators. La Morte statistical software was used for data analyse. P value of <0.05 was considered as statistical significant.

3. RESULTS

The base line patients and tumour characteristics in between the two groups were matching shown in Table 1. The mean age at presentation in group I and group II was 55.9 years and 56.7 years respectively. Overall, fifty five out of sixty (92%) patients were males, remaining five (8%) being females. Overall 93% patients were smokers (all more than 10 years history of smoking). Base of tongue was the most common primary site; 66.7% in the Group I and 76.6% in the Group II. The histopathological reports revealed that the most common histopathological type was moderately differentiated squamous cell carcinoma, being 83% in both groups.

Acute treatment induced grade III skin and mucosal toxicities observed 3.3% vs 20%; and 10% vs 20% in group I and II respectively more in group II. However more Upper gastro-intestinal toxicity (grade 3 and 4) was observed in group I (20%; 6.7%) v s (6.7%; 00%) in group II. Hematological toxicity as fall in hemoglobin was seen less in group I patients- grade 3 toxicity: 00% versus 3.33% in group II. Grade 3 neutopenia was similar in both groups (3.33%).

In Curcumin group 90% patients completed indented treatment in 7.3 weeks in comparison to 80% in group II. Treatment was delayed in 10% by one week and completed in 8 -9 weeks. In group II treatment interrupted in 20% for up to 2 weeks because of grade 3 skin reaction. Intended treatment completed 8 – 9.5 weeks in group II.

Table 1. Shows patients and tumour characteristics

Patient characteristics		Group I	Group II	p value
Age (Years)	Mean	55.9	56.7	0.269
	Range	40-85	32-70	
Gender	Male	27	28	0.640
	Female	3	2	
Social background	Rural	26	28	0.389
	Urban	4	2	
Smoking habits	Smoker	29	27	0.300
	Non-smoker	1	3	
Chief complaint	Difficulty in swallowing	10 (33.3%)	06 (20%)	-
	Pain in swallowing	03 (10%)	04 (13.3%)	
	Pain Throat	08 (26.7%)	11 (36.7%)	
	Neck mass	03 (10.0%)	04 (13.3%)	
	Earache	02 (6.7%)	02 (6.7%)	
	Change in voice	04(13.3%)	03 (10%)	
Site OF primary tumor	Oral cavity	02 (6.6%)	03(10%)	-
	Oropharynx	20(66.7%)	23 (76.6%)	
	Hypopharynx	02 (6.7%)	02 (6.7%)	
	Larynx	06 (20%)	02 (6.7%)	
Pretreatment stage (AJCC2010)	Stage III	15 (50%)	14 (46.7%)	0.796
	Stage IV	15 (50%)	16 (53.3%)	
Histopathology	Well differentiated SSC	02 (6.7%)	05 (8.3%)	
	Moderately differentiated SCC	27 (90%)	23 (76.6%)	
	Poorly differentiated SCC	01 (3.3%)	02 (3.3%)	
Tumor morphology	Ulcerative	16 (53.3%)	18 (60%)	
	Indurative	03 (10.0%)	04 (13.3%)	
	Proliferative	11 (36.7%)	08 (26.7%)	
KPS (Pretreatment)	80	10 (33.3%)	10 (33.3%)	1.0
	90	20 (66.7%)	20 (66.7%)	

Overall tumour and nodal response (Table 3) observed at one year of follow up showed 66.7% showed no evidence of disease in group I, 56.7% in group II. Residual diseases seen in 16.6% vs 26.7% patients.

Patients were followed from May 2013 to June 2015. Mean duration of follow up was eighteen months (range, 6 to 20); all patients were followed for at least for 12 months.

Late grade 1 and 2 skin toxicities were seen in 22/30 (73.3%) patients in group I and 25/30 (83.3%) patients in group II. There was no statistically significant association *(p value- 0.347)*. Late grade 1 and 2 late mucosal toxicities were seen in 19/30 (56.7%) patients in group I and 22/30 (73.3%) patients in group II (*p value- 0.405)*. None of the patients experienced grade 3, 4 and 5 late skin and mucosal toxicity. In group I, grade 2 late salivary gland toxicities were seen in 4 (13.3%) patients compared to 6 (20%) patients in group II (*p value- 0.488)*. There were no any grade 3, 4 and 5 late salivary gland toxicities in both the groups.

4. DISCUSSION

To the best of our knowledge, this is first study that is evaluating the role of oral Curcumin along with chemoradiation in locally advanced head and neck cancer.

In this study there were lower grades of haemoglobin *(grade 2 p value- 0.300)* and total leukocyte count *(grade 1 p value- 0.313)*

toxicities in group II in compared to group I during treatment though statistically insignificant. As well as less blood urea (grade 1 *p value- 0.019)* toxicities in group I, in compared to group II observed at third week of treatment.

Ueki et al studied the effect of curcumin administration (100 mg/kg ip) on the inflammatory mechanisms involved in the pathogenesis of cisplatin-induced renal injury in mice. Curcumin prevented cisplatin-induced tubular necrosis, decreased renal dysfunction and the increase of pro inflammatory markers including of TNF-α in serum, and TNF-α and MCP-1 in renal tissue, and a rising of intracellular adhesion molecule 1 (ICAM-1) mRNA in kidney. Oxidative stress has been proven to be involved in Cisplatin induced toxicity including nephrotoxicity. It is hypothesized that the reno-protective effects of curcumin may be related to its predisposition to scavenge free radicals, and upregulate antioxidant machinery in kidney mitochondria [7].

Possibly these protective mechanisms of curcumin on kidney may be related to less cisplatin induced renal toxicities in patients in group I in comparison to group II.

The acute skin and mucosal reactions were less in group I than group II without any statistically significant association. The statistically significant fewer grades 3 and 4 vomiting (*p value- 0.037)* were observed *in* group II. It is generally recognized that curcumin does not cause significant short-term toxicity at doses up to 8 g day 1; this dose of curcumin is considered suitable for trials in which curcumin is administered for short periods of time. Studies have shown that curcumin at doses ranging from 0.9 to 3.6 g day 1 for 1–4 months have some adverse effects including nausea and diarrhoea [8].

Table 2. Toxicities

Toxicities	Group I	Group II
Haematological toxicities		
Hemoglobin		
Grade 2	02 (6.66%)	03 (10%)
Grade 3	-	01 (3.33%)
Total leucocyte count		
Grade 2	01 (3.33%)	04 (13.33%)
Grade 3	01 (3.33%)	01 (3.33%)
Renal toxicities		
Blood Urea		
Grade1	00	05 (16.66%)
Grade2	-	
Grade3	-	-
Serum Creatinine		-
Grade1	01 (3.33%)	01 (3.33%)
Grade2	00	00
Grade3	00	00
Skin		
Grade2	17 (56.7%)	22 (73.3%)
Grade3	01 (3.33%)	06 (20%)
Mucosal toxicities		
Grade 2	19 (63.3%)	23 (76.7%)
Grade 3	3 (10%)	06 (20%)
Upper Gastrointestinal toxicities(N/V)		
Grade 2	09 (30.0%)	07 (23.3%)
Grade 3	06 (20.0%)	02 (6.7%)
Grade 4	02 (6.7%)	00

Table 3. Disease status at one year of follow up (Locoregionally control – overall tumour and nodal)

Group I	Disease status			
	NED	RD	REC	PD
	20 (66.7%)	05 (16.66%)	03 (10%)	02 (6.7%)
	17 (56.7%)	08 (26.7%)	04 (13.3%)	01 (3.33%)

NED= No evidence of disease, RD= Residual disease, REC= Recurrent disease, PD=Progressive disease

The onset and intensity of occurrence of severe reactions is significantly lesser in the study group. This is similar to the results observed by Ryan et al in breast cancer patients. Ryan et al conducted a randomized, double-blind, placebo-controlled clinical trial to assess the ability of curcumin to reduce radiation dermatitis severity in 30 breast cancer patients. Radiation dermatitis occurs in approximately 95% of patients receiving radiotherapy (RT) for breast cancer. Eligible patients were adult females with noninflammatory breast cancer or carcinoma *in situ* prescribed RT without concurrent chemotherapy. Randomized patients took 2.0 grams of curcumin or placebo orally three times per day (i.e., 6.0 grams daily) throughout their course of RT. Weekly assessments included Radiation Dermatitis Severity (RDS) score, presence of moist desquamation, redness measurement, McGill Pain Questionnaire-Short Form and Symptom Inventory questionnaire. The 30 evaluable patients were primarily white (90%) and had a mean age of 58.1 years. Standard pooled variances *t* test showed that curcumin reduced RDS at end of treatment compared to placebo (mean RDS = 2.6 vs. 3.4; $P = 0.008$). Fisher's exact test revealed that fewer curcumin-treated patients had moist desquamation (28.6% vs. 87.5%; $P = 0.002$). No significant differences were observed between arms for demographics, compliance, radiation skin dose, redness, pain or symptoms. In conclusion, oral curcumin, 6.0 g daily during radiotherapy, reduced the severity of radiation dermatitis in breast cancer patients [9].

Curcumin is supposed to have properties of radioprotection and chemoprotection to normal organs thus, helpful in decreasing the toxicity profile of the regimen. Administration of curcumin in patients is able protect normal cells against the harmful effects of radiation [6].

Electronic databases (Medline, PubMed, and CancerLit) and reference lists of published reports, review articles, and relevant books were searched. Clinical trials of curcumin evaluating the skin reactions are not available in literature for head and neck carcinoma. So, direct comparison was not possible.

For all stages, the no evidence of disease (NED) at the last follow up at one year in group I and group II were: 20 (66.7%)versus 17/30 (56.7%).

In study on the potential cooperative effect of cisplatin and curcumin, two HNSCC cell lines (*In vivo* study) were treated with curcumin or cisplatin alone or in combination. Cisplatin treatment led to cellular senescence, indicating an effect mediated by p53 activation. The mechanisms of the two agents through different growth signaling pathways suggest potential for the clinical use of sub therapeutic doses of cisplatin in combination with curcumin, which will allow effective suppression of tumor growth while minimizing the toxic side effects of cisplatin [10].

As per Radiation Therapy Treatment Oncology (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) criteria late radiation toxicities were observed during follow up at six months of each patient.

Patients were followed from May 2013 to June 2015. Mean duration of follow up was eighteen months (range, 6 to 20); all patients were followed for at least 12 months.

Late grade 1 and 2 skin toxicities were seen in 22/30 (73.3%) patients in group I and 25/30 (83.3%) patients in group II. There was no statistically significant association *(p value-0.347)*. Late grade 1 and 2 late mucosal toxicities were seen in 19/30 (56.7%) patients in group I and 22/30 (73.3%) patients in group II (*p value-0.405)*. None of the patients experienced grade 3, 4 and 5 late skin and mucosal toxicity.

It may be inferred from studies that possible radioprotective, chemoprotective, anti-inflammatory, antioxidant, wound-healing, antimicrobial, analgesic and antiseptic activities of curcumin preventing acute skin and mucosal reactions may possibly also related to comparatively less late skin, mucosal and salivary gland toxicities in patients receiving curcumin. Keeping in view the high chances of treatment induced mucositis which result in

treatment interruptions; curcumin may be effective in prevention of mucositis and hence may help in the timely completion of the intended treatment.

5. CONCLUSION

Therefore, it may be concluded from the present study that Curcumin, in management of locally advanced head and neck carcinoma, decreases chemoradiation induced haematological, renal, skin and mucosal toxicities which results in less treatment interruption and improvement of the disease control. However, upper gastrointestinal toxicity in terms of vomiting is significant in curcumin group. To further explore and establish the role of Curcumin in management of locally advanced head and neck carcinoma, a larger study with more number of patients is needed.

CONSENT

All authors declare that written consent was obtained from every patient or their relative when they enrolled in the study.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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