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Role of curcumin as an adjuvant in treatment of advanced head and neck squamous cell carcinoma

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ABSTRACT

Background: Chemoradiation forms the major line of treatment in advanced head and neck squamous cell carcinoma, but the benefit of chemotherapeutic agents is at the expense of various toxicities. Curcumin has demonstrated promising results in in-vivo and in-vitro studies as a radiosensitiser. The objective of the study was to determine the role of curcumin as an adjuvant in patients undergoing chemo radiation for advanced head and neck cancers.
Methods: Study involved 21 patients who underwent chemo radiotherapy for advanced head and neck cancers. They were randomized into two groups. Group A received 500 mg of curcumin while, Group B received placebo along with chemoradiation. The response was assessed using RECIST criteria at three months post treatment using contrast enhanced computerized tomography scan.
Results: Overall 58.3% patients had partial response and 41.7% patients had stable disease in group A. In group B, 33.3% patients had a partial response and 66.6% patient had a stable disease.
Conclusions: Patients receiving curcumin along with chemoradiation had a marginal decrease in tumour volume and 58.3% patients had partial response and 41.7% had stable disease. A statistical significance could not be achieved due to lack of stage-match controls. Further studies are required to validate the role of curcumin as an adjuvant in the treatment of head and neck squamous cell carcinomas.

Keywords: Head and neck squamous cell carcinoma, Radiation, Chemo radiation, Radiosensitiser, Curcumin

INTRODUCTION

Head and neck squamous cell carcinoma is one of the commonest malignancy in Indian population.[1] Radiation and chemotherapy forms the major line of treatment in inoperable patients and is known to affect tumour response through various mechanisms.[2,3] The benefit of chemotherapeutic agents is at the expense of toxicities like mucositis, haematological toxicity and nephrotoxicity.[3] This resulted in the need for alternative agents as an adjuvant with low toxicity profile and created a special interest in finding out the efficacy of phytochemical agent curcumin as radiosensitiser, which was found to have radiosensitisation potential both in vitro studies and in vivo studies.[4-9]

Objective

To determine the role of curcumin as an adjuvant in patients undergoing chemo radiation for advanced head and neck cancers.

METHODS

This study is a randomized, single blinded clinical study coordinated by a multidisciplinary team including Head and Neck surgeon, medical oncologist and radiation oncologist to evaluate all eligible patients during December 2012 to June 2014 in the Department of Otorhinolaryngology and Head and Neck Surgery of R.L. Jalappa Hospital and Research Centre. The study was approved by the Institutional ethical committee. Detailed clinical examination was carried out and patients were staged according to AJCC 2012 TNM classification. All adult patients undergoing radiotherapy or concurrent chemo-radiotherapy for Head and Neck Squamous Cell Carcinoma were included in the study. All of them underwent biopsy for histopathological diagnosis. Other required tests like complete blood investigations, including liver and renal function tests, x-ray mandible, chest x-ray, electrocardiogram, were done. Written informed consent was taken from all the patients included in the study. The exclusion criteria were patients with non-squamous head and neck cancers, patients not giving consent for the treatment, patients with severe acid-peptic disease, patients with distant metastasis and patients with recurrent tumors.

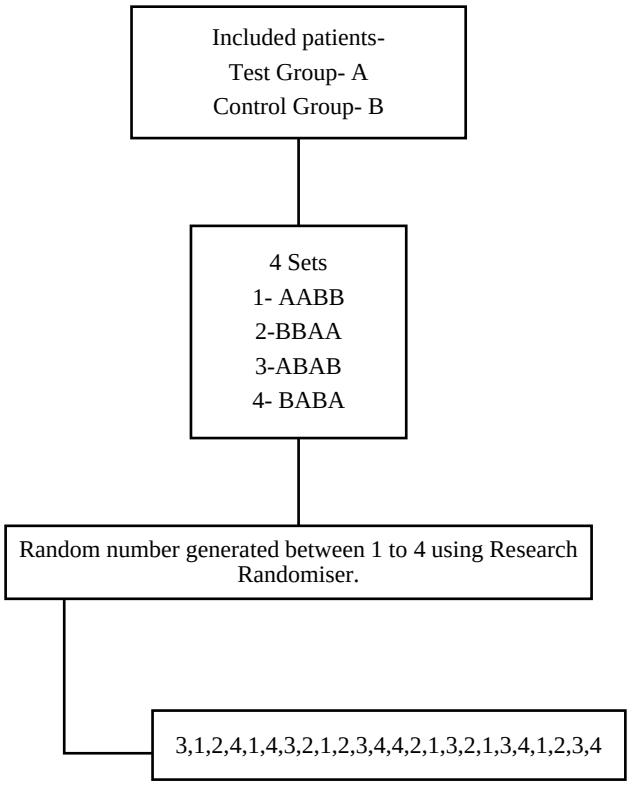

Figure 1: Showing the randomisation method carried out in the study.

All patients enrolled in the study were randomized using 4x4 block randomization as shown in Figure 1. In this method four groups were made and allotted into one, two, three and four groups, then random numbers were generated from one to four using Research Randomizer. The patients were randomised into two groups - Study group (Group A) and Control group (Group B). Patients in group A received daily dose of 500 mg of curcumin capsules thrice a day (total dose 1.5 gm/day) and were asked to take after food, while patients in control group received placebo capsules thrice a day. The curcumin used in our study was obtained from Arjuna naturals, Aluva, Kerala. Each capsule of curcumin contained 500mg of curcumin powder, it comes under the group of nutraceutics and has been approved by FSSAI (Food Safety and Standards Authority of India). The placebo capsule contained starch powder. Both the capsules are identical in colour and shape. The patients started consuming the capsules on the first day of radiation till the completion of radiotherapy. All the patients received external beam radiotherapy (EBRT) using Cobalt 60. They received one fraction (2Gy) of radiotherapy per day, five times a week, for a total dose of 66 Gy, spinal cord was excluded after 46Gy. All Patients received Cisplatin infusion (50mg/m^2) weekly along with radiotherapy.

Table 1: RECIST criteria used for assessing the tumor response.[10]

Response assessment	RECIST guideline, version 1.0
Target lesions	
Complete response (CR)	Disappearance of all target lesions
Partial response (PR)	≥30 percent decrease in the sum of the longest diameter (SLD) of the target lesions compared with baseline
Progressive disease (PD)	≥20 percent increase in the sum of the longest diameter (SLD) of the target lesions compared to the smallest sum of the longest diameter recorded since treatment started OR The appearance of one of more new lesions
Stable disease (SD)	Neither partial response (PR) nor progressive disease (PD)

Twenty-one patients were included in the study and were randomized to group A with 12 patients and group B with 9 patients. They underwent Base-line Contrast enhanced computerized tomography (CECT) scan and pre-treatment anteroposterior diameter, transverse diameter and volume of tumour were documented. Three months post treatment, patient underwent a repeat CECT scan to know the response. RECIST criteria (response evaluation criteria in solid tumours) as shown in Table 1 was used to assess the response and the response were documented as complete response (CR), partial response (PR), progressive disease (PD) or stable disease (SD).[10]

Statistical analysis

We used the IBM SPSS software (v.22) to perform the statistical analysis. Independent t-test for quantitative data and 2 tailed p value. P value less than or equal to 0.05 was considered as statistically significant.

RESULTS

After randomization, group A included 11 patients of stage IV cancers and one patient had stage III cancer. In group B, eight patients had stage IV cancers and one patient had stage III cancer (Table 2). The mean anteroposterior diameter and transverse diameter was documented and the mean tumour volume was calculated prior to treatment and post treatment, a statistical significance could not be attained due to few number of stage matched patients (Table 3 and 4). To assess the tumour response post treatment, we could get stage match only for stage IV cancers. At three months post treatment both groups showed in a reduction in tumor size. In Group A, the mean tumor volume before and after treatment was 41.47 and 12.74 respectively, while in Group B mean tumor volume before and after treatment was 41.47 and 12.74 respectively as depicted in Table 3. At three months post treatment in Group A, a PR was seen in 54.5% and SD was seen in 45.5% (Table 4 and Figure 2). In group B, 37.5% had PR and 62.5% had SD. In group B, 37.5% had PR and 62.5% had SD. The CECT scan showing the reduction in tumour volume pre and post treatment are shown in Figure 3 and 4. None of the patients in both the groups had progressive disease at the end of treatment.

Table 2: Stage matched distribution of patients included in the study to assess the radiosensitivity of curcumin.

Stage of disease	Group A (N=12)	Group B (N=9)
	Number of cases	Number of cases
Stage III	1	1
Stage IV	11	8

Table 3: Overall reduction in tumor volume 3 months post chemoradiation.

Overall reduction in tumor volume 3 months post chemoradiation	Mean tumor volume before treatment	Mean tumor volume after treatment
Group A (in cm^3)	41.47	12.74
Group B (in cm^3)	18.73	8.40

Table 4: Overall tumour response 3 months post chemoradiation.

Tumor response 3 months post chemoradiation	Group A (N=12)		Group B (N=9)	
	Number of cases	%	Number of cases	%
Partial response	7	58.3	3	33.3
Stable disease	5	41.7	6	66.6

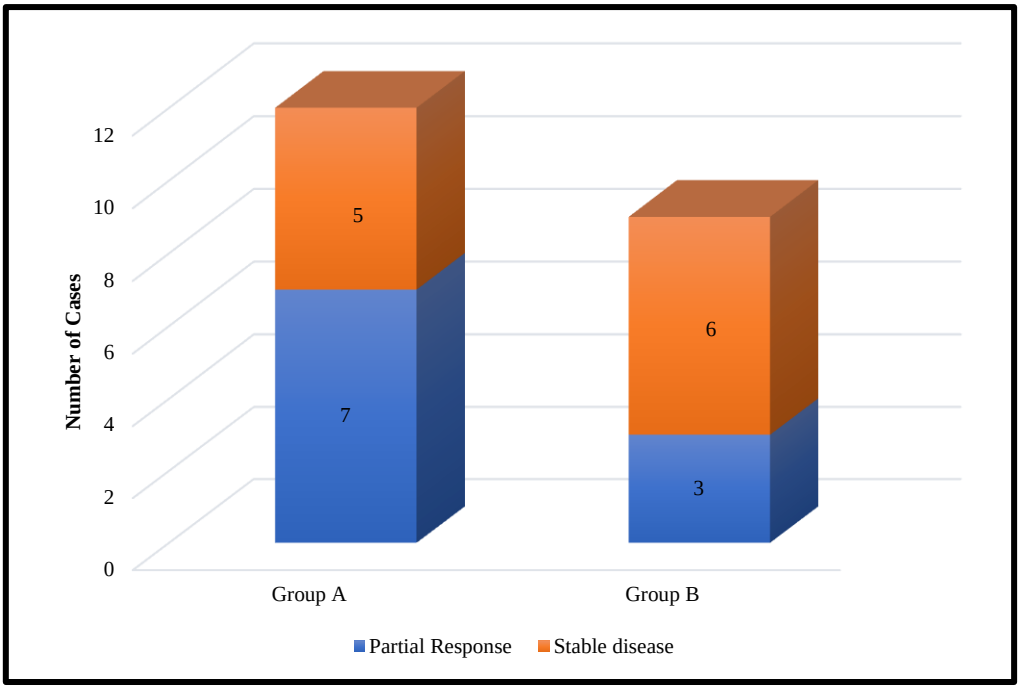

Figure 2: Overall tumour response 3 months post chemoradiation.
In group A, the overall PR was seen in 58.3% and SD was seen in 41.7%. In group B, 33.3% had PR and 66.6% had SD.

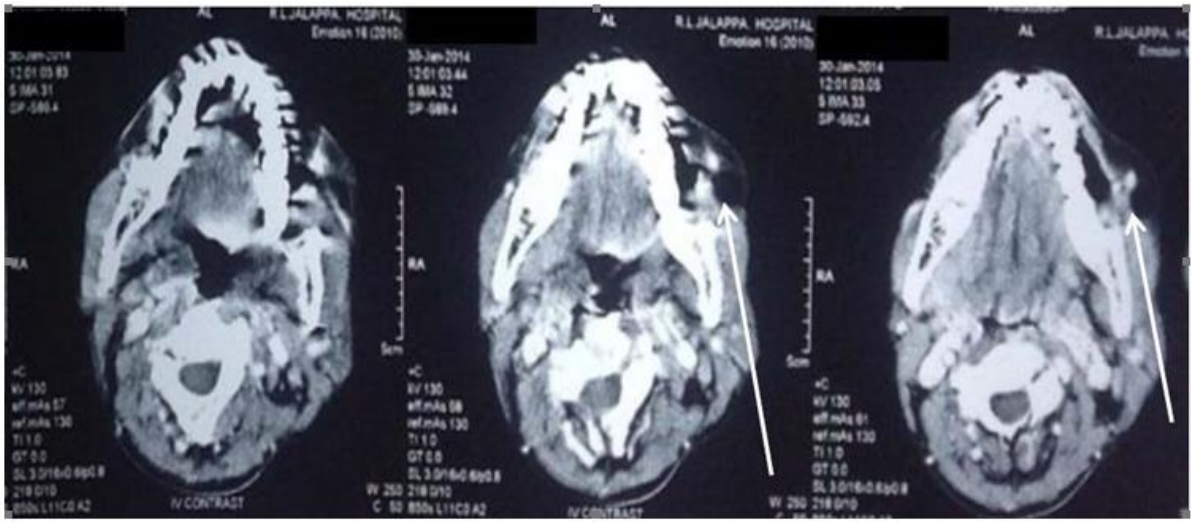

Figure 3: Baseline CT scan of patient with carcinoma buccal mucosa before initiation of treatment, arrow pointing towards tumor site.

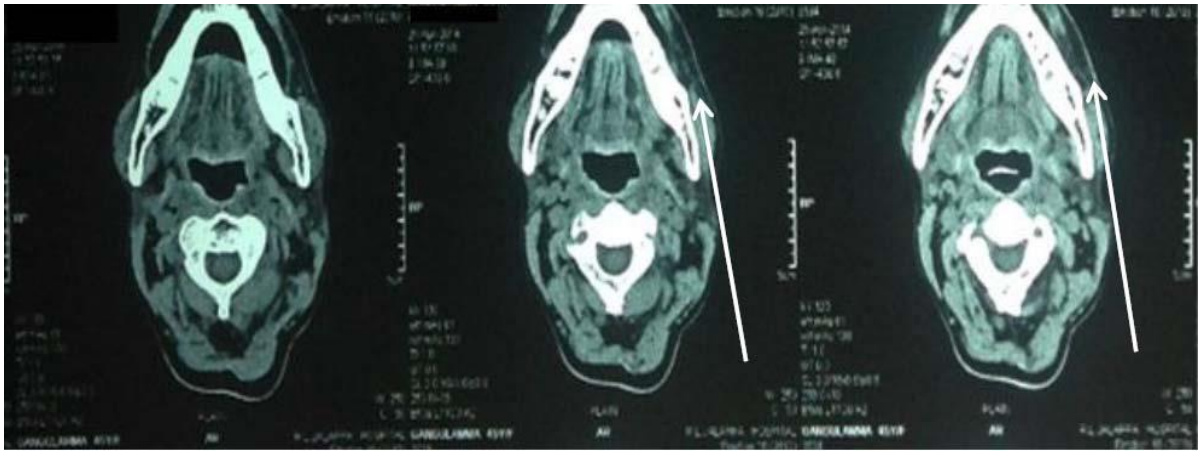

Figure 4: Post treatment CT scan showing reduction in tumor size, arrow pointing towards tumor site.

DISCUSSION

Multimodality of treatment using combination of surgery, radiation, chemotherapy has become the preferred treatment for HNSCC, more so in the advanced tumours. Chemotherapeutic agents are commonly used as an adjuvant along with radiation. They play a key role of radiosensitiser. The most commonly used radiosensitisers are cisplatin, 5 –fluorouracil, paclitaxel and gemcitabine. Cytotoxic action of radiosensitiser are usually associated with damage to normal cells with varying consequences, which can be acute or delayed. Randomised trials RTOG 9501 and EORTC 22931 have shown satisfactory evidence of improvement in terms of loco regional control and disease-free survival in patients undergoing chemotherapy along with EBRT, but grade 3 toxicity was reported in 77% and 44% of patients.[11] Hence there is a continued search for potential alternatives with less toxicity profile, one such agent of interest is curcumin.

Studies have shown that multiple molecular pathways such as NF-kB activation, STAT 3 expression, MAP kinase cascade and VEGF mediated angiogenesis are dysregulated in HNSCC and are potential targets of therapeutic intervention. In vitro and in vivo studies have shown curcumin to have a diversified inhibitory effect on the various molecular pathways of tumorogenesis.[4-8] In vitro studies on various head and neck cancer cell lines such as CCL23 (laryngeal), CAL27, UM-SCC14A and UMSCC1 (oral), treated with curcumin have demonstrated inhibitory effect on molecular pathways involved in cell proliferation. The inhibitory action of curcumin was shown to be mediated via inhibition of NF-kB and STAT3 signalling protein.[5] In SAS oral cancer cell lines, curcumin has shown to up-regulate insulin like growth factor and C/EBPα protein, which are potent suppressors of head and neck cancers. This inhibitory effect of curcumin was mediated via activation of p38.[5] Several phase I and phase II trials are underway in several countries, studying the role of curcumin as an

adjuvant in treatment of premalignant conditions of GIT and oral cavity and also in advanced malignancies of pancreas and colon.[13]

Curcumin as a radiosensitiser has been studied only in human cancer cell lines and in animal models. Curcumin significantly enhanced the effect of gamma radiation in xenograft nude mice models with colon cancer by suppressing NF-kB activity. In prostate cancer cell line PC-3, curcumin showed anti-cancer and radio sensitising effect by down regulating MDM2 levels, and also by inhibition of TNF-α mediated NF-kB activity.[9]

Curcumin has had promising result as a radiosensitiser in both in vitro and in vivo studies on head and neck cancer cells. In vitro studies on HNSCC cell lines such as SCC1, SCC-9, A431 and KB, which were treated with curcumin, radiation and combination of both have shown that curcumin along with radiation had an independent and addictive effect and inhibited cell viability in all cell lines. In the same study, orthotopic mouse models implanted with SCC-1 cells, treated with curcumin and RT, also showed significant reduction in tumour weight and size.[9] The mechanism of radiosensitisation by curcumin in this study was attributed to the inhibitory action on COX-2 pathway and also on phosphorylation of EGFR. Studies have shown COX-2 and EGFR up regulation in most head and neck cancers. Curcumin as a combined inhibitor of COX-2 and EGFR has a potential role in the treatment of these cancers. The down regulation of COX-2 expression has also shown to enhance chemo radiotherapy response while sparing the normal tissues.[4]

Curcumin has been shown to cause alteration in the mitotic spindle structures and arrest cells in G2/M and S phase of cell cycle, which is the most radiosensitive phase of cell cycle. This mechanism is very similar to the action of taxols, which are potent radiosensitisers. In a phase I trial on 14 patients of advanced/metastatic breast cancer, combination of docetaxel and curcumin have shown to arrest progression of cancer. Out of the 14 patients enrolled in the study, 5 patients had PR, and 3 patients had SD and none of the patients had progressive disease.[14]

Nearly 6-7 phase I clinical trials have tested the safety profile of curcumin in treatment of various cancers and found no dose-limiting toxicity. Our study was a pilot study, to study the radiosensitisation potential of curcumin. At the end of treatment, none of the patients in both the groups had progressive disease. Stage match could be achieved only with patients having stage IV head and neck squamous cell cancers. The partial response (PR) in study group was 54.5% compared to 37.5% in control group. The overall tumour response (Stage III +Stage IV), the study group had PR of 58.3% and SD of 41.7%, while the control group had 33.3% PR, and 66.6% SD. The difference in the groups was not statistically significant due to lack of adequate number of cases. The diverse inhibitory effect on various pathways of carcinogenesis, lack of systemic toxicity and synergistic effect with radiation makes curcumin an ideal adjuvant in the treatment of head and neck squamous cell cancers. Further studies are required with larger sample size to understand the radiosensitising effect of curcumin. The limitation of our study was lack of number of stage matched patients for assessing the radio sensitisation property of curcumin.

CONCLUSION

Patients receiving curcumin along with chemo radiation had a marginal decrease in tumour dimensions and volume, but a statistical significance could not be achieved due to inadequate number of cases and lack of stage-match controls. Curcumin has shown to have a diversified inhibitory effect on various molecular pathways of tumorogenesis. No systemic toxicity was noticed with intake of curcumin. Further elaborate studies with more stage matched patients are required to validate its role as an adjuvant in the treatment of head and neck squamous cell carcinomas

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Ethical approval: The study was approved by the Institutional Ethics Committee

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