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PHASE II TRIAL OF CURCUMIN IN ADVANCED HEAD AND NECK CANCER TREATMENT

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ABSTRACT

INTRODUCTION: This study investigates the therapeutic potential of oral curcumin with piperine in the palliative management of advanced squamous cell carcinoma of head and neck region.

METHODS: 40 patients with advanced, incurable or metastatic squamous cell carcinoma of head and neck region or those who have failed all standard treatment were included in this study without randomization. Patients received capsules of curcumin with piperine (3.6 g/day) for a period of 8 weeks.QOL was assessed using EORTC QLQ-C30 (version 3) & QLQ-H&N35 questionnaires.

RESULTS: A significant improvement in global health status, pain, fatigue, constipation and financial difficulty scores was observed at the end of treatment. The study therapy was well tolerated and no grade 3/4 toxicities were observed.

CONCLUSIONS: The present study indicates the therapeutic potential of curcumin and piperine in the palliative treatment of advance head and neck cancer as a cost-effective substitute.

KEYWORDS : Head and neck sq cell cancer (HNSCC), curcumin, quality of life (QOL)

INTRODUCTION

Surgery, radiotherapy and chemotherapy are mainstay treatment for head and neck sq cell cancer (HNSCC). More than 60% patients have recurrence following treatment for advanced HNSCC. A patient with advancing incurable head and neck cancer can present enormous challenges. Although a tracheostomy or gastrostomy tube, nasogastric tube feeding can restore vital functions. In advanced stage majority of these patients suffer from pain, difficulty in chewing and swallowing, oro-cutaneous fistulae, foul smelling fungating wounds, bleeding, aspiration, and cachexia and finally die of locally advanced disease due to obstruction of airways, food passage, cachexia, fungation and haemorrhage.

Loco-regional relapse or distant metastases of HNSCC is considered to have poor prognosis with survival time of less than one year. Treatment is individualized to provide best palliative and supportive care and sometimes may include palliative chemotherapy and radiotherapy with short term benefits. In India patients often present with advanced disease requiring aggressive treatment, which leaves them functionally disabled. In most of these cases, the palliative and supportive care for symptom control and to maintain good quality of life is the main objective of the overall disease management.

There have been numerous studies worldwide, evaluating the role of curcumin as an anticancer agent. Curcumin, a naturally occurring substance found in the herb turmeric (Curcuma Longa) has shown promising results with regards to its anticancer potential as well as safety. Data from the studies have shown that curcumin can suppress carcinogenesis of the skin, liver, lung, colon, stomach, and breast; lower blood cholesterol; promote wound healing; prevent skin wrinkling; inhibit inflammation; suppress rheumatoid arthritis; and inhibit HIV replication. Curcumin mediates this wide variety of therapeutic effects through the regulation of the transcription factors NF-kB and AP-1, suppression of IkBa kinase and c-jun N-terminal kinase, and inhibition of expression of cyclooxygenase 2, cyclinD1, adhesion molecules, matrix metalloproteases, inducible nitric oxide synthase, HER2, EGF receptor, bcl-2, bcl-xl, and TNF. Data have also shown that curcumin can inhibit the cell proliferation of a wide variety of tumour cells in culture and promote apoptosis through BID cleavage, cytochrome C release, and caspase-9 activation followed by caspase-3 activation. Pharmacologically, curcumin is quite safe, and doses as high as 8g/day have been administered orally to human subjects with no side effects[1-10]. Curcumin has demonstrated a myriad of biological effects that warrants its evaluation as a therapy for cancer. Based on these factors, we undertook a phase II study to evaluate the therapeutic potential of oral curcumin with piperine in the palliative management of advanced squamous cell carcinoma of H&N region. The primary objective of the study was to determine the therapeutic potential of oral curcumin with piperine as supportive therapy in maintaining quality of life in advanced epithelial malignancy of the H&N region (oral cavity, pharynx and larynx). The secondary objective was to evaluate the bioavailability of curcumin in the plasma samples of the patients. Study was approved by Institutional ethics committee as well as by Drug Controller General of India & Indian Council of Medical Research and listed on Clinical Trials Registry India No. CTRI/2008/091/000194 .

METHODS

ELIGIBILITY CRITERIA

Eligibility criteria included histologically or cytologically confirmed squamous cell carcinoma of the H&N (oral cavity/ pharynx/ larynx) region, patients who had advanced, incurable or metastatic squamous cell carcinoma of head and neck region at the initial diagnosis or those who have failed all standard cancer specific treatment. Further inclusion criterion were patient's willingness to participate in the study, signed and dated informed consent document and anticipated life expectancy of more than two months on clinical assessment. Patients with other serious or uncontrolled concurrent illness or with potential behavior and cognitive impairment were not eligible for the study. A team of three physicians examined each patient and reviewed the suitability to include in the study. The study was conducted according to the ethical principles stated in the latest version of Helsinki Declaration and the applicable guidelines for good clinical practice (GCP).

Study was planned as single arm, non-randomized with limited numbers in view of anticipated poor or unpredictable compliance rate in advanced terminally ill subjects, since patients with advanced malignancy preferred to stay under care of local family physicians rather traveling to a tertiary health care center.

TREATMENT PLAN

Patients were given capsules of Curcumin with piperine (19:1) packaged in gelatin capsules of 450 mg each. Curcumin with piperine (3.6 g/day) was administered either in capsule or powder form at a dose of 4 capsules twice daily by mouth / feeding tube after meals in morning and evening for 8 weeks . Patients who were unable to swallow curcumin capsules were administered powdered form with water through naso-gastric or gastrostomy tube.

(Provided by sponsor - Department of Biotechnology Govt. of India, procured from Sami Labs Limited, Bangalore India) . Additionally all patients received regular treatment for their symptoms under close supervision of treating physicians.

Minimum 3 weeks of wash out period was observed in patients who received any form of specific treatment (Chemotherapy) for cancer prior to curcumin administration.

STUDY OBJECTIVES AND ASSESSMENT OF RESPONSE

The primary objective of the study was to determine the therapeutic potential of oral curcumin with piperine in maintaining the quality of life in advanced epithelial malignancy of the H&N region (oral cavity, pharynx and larynx). The secondary objective was to evaluate the bioavailability of curcumin in the plasma samples of the patients.Objective assessment of clinical response with Quality of Life

(QoL) score was determined at 1, 2, 4, 6 and 8weeks of treatment. Alteration of local tumor burden was ascertained through clinical assessment. QoLwas assessed using EORTC QLQ-C30 and EORTC QLQ-H&N35 questionnaires. The English and Hindi versions of the EORTC QLQ-C30 and QLQ-H&N35 questionnaires were obtained from the Quality of Life Unit, EORTC Data Center in Brussels, Belgium[11-13]. The EORTC questionnaires were chosen for this research because it is one of the most widely implemented validated questionnaires. The EORTC QLQ-C30 is a 30 item questionnaire composed of multi-item scales that reflects the multidimensionality of the QOL construct. It incorporates five functional scales (physical, role, cognitive emotional and social), three symptom scales – fatigue, pain, nausea and vomiting, global health scale and additional symptoms commonly reported by cancer patients as well as the perceived financial impact of disease and treatment. Score ranges from 0 to 100. A higher score represents a higher level of functioning or a greater degree of symptoms. Similarly, H&N cancer specific module (EORTC QLQ-H&N35) includes 35 items. Patients have to indicate the extent to which they have experienced the symptoms or problems during the past week. Score ranges from 1 to 4. High score for an item means worse QoL or more problems. Curcumin and its metabolites were analyzed in the plasma of patients at the time of accrual and after 1, 2 and 8 weeks of treatment.

STATISTICALANALYSIS

The statistical analysis was performed using Strata version11.0. The mean score and standard deviations of the QoL scales were calculated according to the EORTC QLQ scoring manual [14]. Values of each parameter at every time point were summarized as mean $\pm$ SD. The overall change during treatment period were analysed using Generalized Estimating Equations. Log scores with base 10 were taken for the analysis. Difference between values at baseline and 8 weeks were analysed using Signed Rank Test. A p-value of < 0.05 was taken as statistical significant.

RESULTS

PATIENT CHARACTERISTICS

Total 40 patients were enrolled, 35 men and 5 women with a median age of 53.5 years (range 32-75). Stage at presentation was III in 2 (5%), IIIB in 2 (5%), IV in 2 (5%), IVA in 14 (35%), IVB in 19 (47.5%) and IVC in 1(2.5%) patient respectively. 30 (75%) patients had received prior radiotherapy. The main baseline characteristics of the patients are shown in Table 1.

TREATMENT SUMMARY

Of the 40 patients, 21 patients (52.5%) completed 8 weeks of treatment. 06 patients expired during the study and clinical review by team of physicians concluded natural progression of disease as the cause of death in these terminally ill patients. One patient who died had symptoms of gastritis following consumption of the curcumin , but this was not considered the cause of death in his case. 05 patients did not complete planned 8 weeks of study period and withdrew consent at different stages of the study and another 06 patients were lost to follow up due to various reasons including inability to come for follow up , worsening of symptoms due to natural progression of disease, 02 patients were withdrawn by principal investigator in view expected non-compliance.

EFFICACY

There was significant improvement in the global health status of the patients, whereas other elements of physical functional scale deteriorated at the end of treatment. Worsening in physical functioning and cognitive functioning was significant ($p = 0.01$ and $p = 0.02$), and was noted in patients having progressive cachexia and malnutrition related with natural progression of disease. A significant improvement in pain, fatigue, constipation and financial difficulty scores was observed in the patients. Similarly, except for dry mouth all other parameters of QLQ-H&N35 questionnaire also showed improvement at the end of treatment. A significant improvement in the scores of pain, senses problem, speech problem, less sexuality and felt ill parameters was noted. The results of QoL questionnaires are summarized in Tables 2 and 3.

No significant response was noted in tumour burden as assessed on clinical examination by physicians during follow up.

LEVELS OF CURCUMIN AND ITS METABOLITES IN PLASMA

Curcumin and its metabolites (demethoxycurcumin and bis-demethoxycurcumin) were transiently detectable in the plasma of patients at different time points suggesting a very low systemic bioavailability of curcumin. The range of concentrations of curcumin and its metabolites is summarized in Table 4.

TOXICITY

The study therapy was well tolerated and no grade 3/4 toxicities were observed. One patient had mild symptoms of gastritis following three weeks of treatment with curcumin , endoscopic confirmation could not be carried out due to technical reasons having growth in oral cavity and oropharynx.

DISCUSSION

In the present study, 40 patients with advanced incurable or metastatic cancer of the H&N region were treated with oral capsules containing curcumin and piperine. Curcumin is known to have many effects on human body and Ayurveda has recognized its medicinal use in the treatment of a variety of ailments over last many decades. There has been research in many parts of the world evaluating its anticancer potential, however; data from clinical studies evaluating its role in cancer patients is very limited[1-10,16-20].

The issue of QoL is very important for the management of chronic diseases like cancer especially when the patients present with advanced diseases requiring aggressive treatment that leaves them functionally disabled. Therefore, it has become an important determinant of demand for care, compliance with treatment regimen and overall treatment satisfaction[21]. A number of instruments have been created and adopted for assessing the QoL in different patient populations[22]. Although there is no consensus as yet, the EORTC questionnaires have been widely implemented and utilized in international clinical trials. In the present study, EORTC QLQ-C30 and the QLQ-H&N35 instruments were used to assess QoL[11-13]. The scores for all scales were calculated according to the procedures defined in the EORTC Scoring Manual[14].

A number of studies have investigated the issue of QoL in H&N cancer and its importance on how disease and its treatment affect the individual[23-26]. Using these QoL tools to assess the therapeutic benefit of oral curcumin with piperine , our study demonstrated a significant improvement in the global health status along with pain, fatigue, constipation and financial difficulty scores was observed in the patients. Similarly, except for dry mouth all other parameters of QLQ-H&N35 questionnaire also showed improvement at the end of treatment. A significant improvement in the scores of pain, senses problem, speech problem, less sexuality and felt ill parameters was also noted.

Our second finding was that consumption of 3.6 g of oral curcumin daily for 8 weeks results in very low and transient levels of curcumin and its metabolites in the plasma. This finding was consistent with the results of various studies in rodents[26-30] as well as humans[9-10].

In conclusion, our study indicates the therapeutic potential of curcumin and piperine in the palliative treatment of advance H&N cancers as a supportive therapy.

However from critical point of view, improvement seen in quality of life parameters of these subjects may partly be due to presumably overall better supportive care they received while coming for regular follow up.

Further placebo controlled studies on similar line with larger patient numbers seem warranted, since this study was single arm non randomized,

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Table I. Baseline characteristics of patients (n = 40)

Parameter	No. of patients
Gender, n (%)	
Male	35 (87.5)
Female	5 (12.5)
Age (years)	
Median	53.5
Range	32-75
Method of diagnosis, n(%)	
Aspirate	10 (25)
Biopsy	30 (75)
Stage Group, n(%)	
Stage III	2 (5)
Stage IIIB	2 (5)
Stage IV	2 (5)
Stage IVA	14 (35)
Stage IVB	19 (47.5)
Stage IVC	1 (2.5)
Prior radiation, n(%)	30 (75)

Table II. The comparison of EORTC QLQ-30 at different time-point

	BL	Wk1	Wk2	Wk4	Wk6	Wk8	Average Change per FU	p	Difference BL-Wk8	p
	N=40	N=37	N=36	N=27	N=23	N=21				
Global Health Status	4.5 + 1.16	4.6 + 1.02	4.8 + 0.89	5.3 + 0.76	5.4 + 0.77	5.4 + 0.85	+0.09	<0.001	+0.97	<0.001
Physical Functioning	2.2 + 0.69	2.2 + 0.72	2.1 + 0.76	1.8 + 0.63	1.8 + 0.68	1.7 + 0.65	-0.03	<0.001	-0.49	0.01
Role Functioning	2.2 + 0.94	2.2 + 0.97	2.1 + 0.81	1.9 + 0.68	1.9 + 0.74	1.8 + 0.67	-0.02	0.27	-0.40	0.11
Emotional Functioning	1.9 + 0.77	1.9 + 0.81	1.8 + 0.70	1.5 + 0.55	1.5 + 0.55	1.4 + 0.36	-0.03	0.01	-0.51	0.01
Cognitive Functioning	1.3 + 0.49	1.3 + 0.57	1.3 + 0.45	1.1 + 0.27	1.1 + 0.24	1.0 + 0.22	-0.01	0.25	-0.24	0.02
Social Functioning	2.1 + 1.03	2.0 + 1.02	1.9 + 0.84	1.7 + 0.68	1.7 + 0.70	1.6 + 0.66	-0.04	0.03	-0.47	0.12
Fatigue	2.7 + 0.79	2.6 + 0.85	2.4 + 0.83	2.3 + 0.72	2.3 + 0.76	2.1 + 0.73	-0.05	<0.001	-0.58	0.01
Nausea	1.2 + 0.52	1.2 + 0.52	1.1 + 0.36	1.1 + 0.23	1.1 + 0.24	1.0 + 0.18	-0.01	0.83	-0.08	0.71
Pain	2.6 + 0.92	2.4 + 0.86	2.3 + 0.87	2.1 + 0.67	2.1 + 0.81	2.0 + 0.76	-0.01	0.57	-0.52	0.03
Dysponea	1.4 + 0.70	1.5 + 0.76	1.4 + 0.64	1.4 + 0.49	1.6 + 0.88	1.4 + 0.81	+0.03	0.06	+0.49	0.65
Insomnia	1.9 + 1.12	1.7 + 0.90	1.7 + 0.88	1.6 + 0.92	1.5 + 0.59	1.4 + 0.67	-0.01	0.74	-0.05	0.09
Appetite Loss	2.3 + 1.24	2.0 + 1.01	2.1 + 1.15	1.9 + 0.92	2.1 + 0.90	1.9 + 0.74	+0.01	0.16	+0.29	0.56
Constipation	1.6 + 0.95	1.6 + 0.98	1.6 + 0.94	1.1 + 0.42	1.1 + 0.42	1.2 + 0.68	-0.03	0.01	-0.43	0.04
Diarrhoea	1.2 + 0.43	1.1 + 0.42	1.1 + 0.35	1.1 + 0.45	1.2 + 0.49	1.2 + 0.51	+0.01	0.37	+0.04	0.82
Financial Difficulty	2.6 + 1.1	2.3 + 1.02	2.2 + 0.96	1.7 + 0.65	1.5 + 0.66	1.5 + 0.75	-0.12	<0.001	-1.10	<0.001

Table III. The comparison of EORTC QLQ-35 at different time-point

Parameter	**BL**	**Wk1**	**Wk2**	**Wk4**	**Wk6**	**Wk8**	**Average Change per FU**	**p**	**Difference BL-Wk8**	**p**
	N=40	N=37	N=36	N=27	N=23	N=21				
Pain	2.2 + 0.75	2.0 + 0.77	1.9 + 0.70	1.8 + 0.60	1.9 + 0.71	1.8 + 0.69	-0.01	0.24	-0.32	0.03
Swallowing	1.9 + 0.87	2.0 + 0.85	2.0 + 0.76	1.9 + 0.81	1.9 + 0.86	1.7 + 0.83	+ 0.01	0.39	+ 0.19	0.36
Senses Problem	1.9 + 0.98	1.7 + 0.90	1.6 + 0.75	1.5 + 0.58	1.5 + 0.59	1.3 + 0.45	-0.03	0.11	-0.56	0.04
Speech Problem	1.8 + 0.70	1.8 + 0.77	1.7 + 0.64	1.4 + 0.44	1.3 + 0.44	1.3 + 0.36	-0.04	<0.001	-0.5	<0.001
Trouble Social Eating	2.1 + 1.04	2.1 + 0.98	2.0 + 0.92	1.7 + 0.83	1.7 + 0.83	1.6 + 0.58	-0.01	0.55	-0.52	0.09
Trouble Social Contact	1.8 + 1.03	1.7 + 0.93	1.6 + 0.84	1.3 + 0.49	1.3 + 0.54	1.3 + 0.38	-0.03	0.37	-0.45	0.26
Less Sexuality	1.9 + 1.38	1.7 + 1.29	1.7 + 1.26	1.3 + 0.97	1.1 + 0.62	1.1 + 0.65	-0.04	0.02	-0.78	0.02
Teeth	1.7 + 0.95	1.7 + 0.97	1.6 + 0.88	1.4 + 0.71	1.5 + 0.74	1.6 + 0.82	-0.03	0.05	-0.16	0.58
Opening Mouth	2.0 + 1.20	1.9 + 1.13	1.9 + 1.06	1.6 + 0.87	1.8 + 0.88	1.9 + 0.99	+ 0.02	0.05	+ 0.12	0.83

Dry Mouth	2.5+ 1.13	2.9+ 0.95	2.9+ 0.94	2.8+ 0.96	2.8+ 0.95	2.6+ 0.93	-0.01	0.91	-0.05	0.85
Sticky Saliva	2.7+ 1.03	2.8+ 0.95	2.7+ 0.93	2.5+ 0.97	2.6+ 0.94	2.5+ 0.87	-0.01	0.67	-0.27	0.32
Coughing	1.8+ 0.99	1.9+ 0.97	1.7+ 0.88	1.8+ 1.01	1.9+ 0.90	1.7+ 0.83	-0.02	0.53	-0.11	0.83
Felt ill	2.0+ 1.16	1.8+ 1.15	1.7+ 0.98	1.5+ 0.80	1.4+ 0.84	1.3+ 0.66	-0.05	0.02	-0.69	0.02

Table IV. Range of concentration of curcumin and its metabolites in the plasma of patients

Analyte	Level in plasma sample (ng/ml)
Curcumin (C)	ND- 14.43
Demethoxycurcumin (dmC)	ND- 7.25
Bis-demethoxycurcumin (bdmC)	ND – 2.14

ND: not detectable

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