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ORIGINAL ARTICLE

Can Zinc Supplementation widen the Gap between Control and Complications in Head and Neck Cancer Patients treated with Concurrent Chemo-radiotherapy

Mohsin Khan[1], Shahid A. Siddiqui[1], Mohd Akram[1], Mohd Shadab Alam[1]

[1]*Department of Radiotherapy and Clinical Oncology, JN Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India*

Introduction: Zinc as an antioxidant can attenuate the effects of ionizing radiation. Contrary to theoretical radiobiological concepts, studies have pointed to the differential effects of zinc on normal and tumor cells, respectively. Therefore the present study was conducted to highlight the effects of zinc supplementation on adverse events and response rates of head and neck cancer patients who had undergone definitive concurrent chemo-radiotherapy (CCRT). **Materials and Methods:** Case records of patients with head and neck cancer who underwent definitive chemo-RT were analyzed from July 2015 to July 2018. Those who received zinc supplements were categorized as Arm A and those who did not as Arm B. All patients received a total of 6600–7000 cGray RT with weekly cisplatinum. Radiation Morbidity Scoring System was used to summarize data on adverse events. Computed tomogram scans were compared for documenting response rates. **Results:** Data were collected from 95 patients under Arm A and 107 in Arm B. 15.8% in Arm A and 21.5% in Arm B had RT interrupted for >1 week. Although the results were not statistically different for > Grade 2 toxicities, patients in Arm A fared better than those in Arm B. Interestingly, when the two groups were analyzed for salivary gland adverse events, 74 patients in Arm B complained of ≥ Grade 2 toxicities as compared to 37 in Arm A, the results being statistically significant ($P = 0.000017$). Overall, response rates were 88.4% in Arm A and 92% in Arm B. **Conclusions:** Zinc supplementation lends some of its radioprotective effects in normal tissues with salivary glands deriving the major benefits.

Key words: Chemoradiotherapy, head and neck cancer, zinc

INTRODUCTION

Radiotherapy (RT) is one of the most important treatment strategies involved in the management of head and neck cancers. Either alone or concurrent with chemotherapy, it has become the treatment of choice at various sites and stages of head and neck cancer. Ionizing radiation interacts with matter/cell to form reactive oxygen species (ROS), which are the free radicals and toxic substances leading to the oxidative stress damage to cellular components such as DNA, RNA, and proteins.[1] A host of endogenous defense systems then acts to protect from these ROS. These include various antioxidants, enzymes, vitamins, glutathione, and some trace elements.[2] One such element zinc (Zn) has been extensively studied for its antioxidant activity, anti-inflammatory effects, and DNA-stabilizing ability.[3-5]

RT with or without chemotherapy besides having its anti-tumor effects is known to induce normal tissue toxicities within the radiation portals. These can range from being mild to severe including ulceration/necrosis depending on various intrinsic/extrinsic factors pertaining to host and treatment parameters.

Zn as an essential component of various enzymes participates in cell proliferation, wound healing, free radical protection, immunity, and epithelial organization.[6,7] To mitigate the side effects of radiation, these properties of Zn have been explored time and again but with mixed results.[8-11] There are even reports in the literature where Zn supplementation has

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Corresponding Author: Dr. Mohsin Khan, Department of Radiotherapy, JN Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India. Tel: 8266891077. E-mail: khan.mohsin_1786@yahoo.com

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shown improvement in local tumor recurrence and overall survival in patients with head and neck cancer.[12] Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology gave evidence in favor of systemic Zn supplements for prevention of side effects in head and neck cancer patients receiving RT.[13]

Still, the data are insufficient and there is no level 1 evidence either in favor or against the use of trace elements. Therefore the present study was conducted to highlight the effects of zinc supplementation on adverse events and response rates of head and neck cancer patients who had undergone definitive concurrent chemo-radiotherapy (CCRT).

MATERIALS AND METHODS

This was a retrospective study. Data was retrieved from the case record files of head and neck cancer patients enrolled from July 2015 to July 2018 who had undergone definitive concurrent chemo RT at a tertiary hospital located in North India.

Patients

Patients with oral cavity, oropharynx, hypopharynx, and larynx primaries who underwent definitive concurrent chemo-RT were included except for nasopharyngeal and paranasal sinus tumors. All patients had squamous cell histology. Those with concurrent illnesses such as diabetes mellitus, hypertension, and chronic inflammation were excluded. Patients reported with oral candidiasis/other oral lesions such as stomatitis and necrosis at the time of treatment initiation were also excluded from data collection.

Treatment

In the past 3 years, those patients who either received Zn supplements or who did not but were treated with definitive concurrent chemo-RT for head and neck inclusive sites were included in this analysis. For ease of comparison, patients were divided into two arms, Arm A - who received Zn supplements and Arm B - who did not receive zinc supplementation during the course of their treatment. Patients who received upto 40mg of elemental Zinc (irrespective of the prescribed salt/ brand) daily during the course of concurrent chemo-radiotherapy were included in Arm A. Regarding the radiation therapy protocols, all patients received treatment with parallel opposed lateral fields up to a total of 6600–7000 centiGray (cGy), on a daily 180–200 cGy fraction, five times/week with or without concurrent chemotherapy, i.e., cisplatin dosed at 40 mg/m^2 intravenous weekly during the course of radiotherapy. All patients were treated on Cobalt60 tele-therapy machine.

Assessment

Patient's record was retrieved from respective case sheets, and their weekly/monthly progress charts were analyzed for data collection. Routinely adverse events during radiotherapy, at our institute, are reported using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Radiation Morbidity Scoring System. We included the patients till July 2018, so only the acute effects are reported here. The worst toxicity experienced by the patients pertaining to skin, mucous membrane, salivary glands, larynx, and pharynx/esophagus were analyzed. Computed tomograms (CT) scans of the patients were utilized for reporting the responses and overall response rate (including the complete plus partial response).

Data analysis

Descriptive statistics was used to present the data. Pearson Chi-square test was used to assess correlation of numerical variables. Significance level was set at 0.05.

RESULTS

Patient, tumor, and treatment characteristics

Data were collected from the head and neck cancer patients who were treated with concurrent chemo-RT from July 2015 to July 2018. Case sheets of a total 95 patients under Arm A and 107 patients under Arm B were studied. Majority of the patients were male. About 69.3% of the patients had oral cavity/oropharyngeal cancers with 57% having Stage IV disease with both the arms well balanced for all of the above variables [Table 1]. Only those patients were included who completed their entire treatment with a minimum dose of 6600 cGy of RT and whose CT reports were available for response assessment.

Toxicity analysis

Majority of patients in both the arms completed a minimum of 5 cycles of concurrent chemotherapy. Nearly 15.8% of patients in Arm A and 21.5% in Arm B had RT interrupted for >1 week [Table 2]. Although the results were not statistically different for >Gr 2 toxicities pertaining to skin, mucous membrane, and pharyngeal/esophageal sites, patients in Arm A fared slightly better than those in Arm B [Table 3].

Interestingly, when the two groups were analyzed for salivary gland adverse events, 74 patients in Arm B complained of ≥Gr 2 toxicities as compared to 37 of those in Arm A, the results being statistically significant (P = 0.000017) [Table 3]. About 5.3% of patients in Arm A and 7.5% in Arm B required blood transfusions for ≥Gr 2 hematological toxicity. 6.1% of patients in Arm A and 13.1% in Arm B required granulocyte colony stimulating factor support for ≥Gr2 leukopenia.

Response assessment

For response assessment, posttreatment CT scans (done 2–3 months postcompletion of treatment) were compared with pretreatment scans [Table 4]. Complete response was noted in 71% of patients in Arm A and 75% in Arm B. Overall response rates were 88.4% in Arm A and 92% in Arm B, results being statistically not significant ($P = 0.22$).

Table 1: Patient and tumor characteristics

	Arm A	Arm B
Total patients	95	107
Males	87	81
Females	8	26
Median age in years (range)	58 (40-80)	61 (36-75)
Anatomic site		
Oral cavity	28	31
Oropharynx	35	46
Hypopharynx	7	8
Larynx	25	22
Clinical stage		
II	7	18
III	25	37
IV	63	52
III+IV	88	89
P	0.04	

Table 2: Compliance with treatment

	Arm A (%)	Arm B (%)	*P*
Median RT dose (Gy)	70	70	
Patients with RT interruption duration ≥1 week	15 (15.8)	23 (21.5)	0.30
Patients with chemotherapy interruption ≥3 days	31 (32.6)	42 (39.3)	0.33
Patients who complete minimum 5 cycles of weekly concurrent chemotherapy	88 (92.6)	97 (90.6)	0.64

RT=Radiotherapy

DISCUSSION

A number of trials and one systemic review have generated positive evidence for prescribing systemic Zn in head and neck cancer patients. At our institute too, off any research protocol, Zn was being prescribed to patients of head and neck cancer undergoing radical RT, with the intent of lessening the side effects. We have observed some favorable results in the past. To substantiate the effects of Zn supplementation in mitigating the side effects and to note if it makes any difference in response rates, we carried out this retrospective report.

Zn as an essential element is involved in a plethora of cellular tasks. It contributes to the maintenance of epithelial and tissue integrity, promotes cell growth, and suppresses apoptosis and acts as an antioxidant against free radical damage.[7] It is a vital component for wound healing and immune system. It induces metallothionein, which can act as scavenger for damaging free radicals.[14] Although it looks impressive, but theoretically, it can be a detriment to the effects of ionizing radiation on tumor cells as radiobiologically free radical injury in the form of indirect effects is the major component of cell killing in tumor cells. Contrary to the theoretical radiobiology concepts, there are studies which have pointed to the differential radioprotection effects of Zn on normal and tumor cells.[15] Provinciali *et al*.[16] demonstrated that Zn exerts a direct action on cancer cells inducing ROS-mediated apoptosis by induction of p53 and Fas/Fas ligand. There are reports that Zn even downregulates hypoxia inducible factor 1α and inhibits its activity in tumor cells.[17]

The above-mentioned differential effects of Zn on tumor and normal cells, respectively, make it a wonderful element to explore in management protocols. It can be well theorized that Zn supplementation during RT can increase the therapeutic ratio, protecting the normal tissues and simultaneously increasing the lethality for tumor cells.

Since we included patients till July 2018, we have reported only acute adverse effects in the present study. CT scan of last patient was obtained before the compilation of final data;

Table 3: Acute toxicity

	Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B	Arm A	Arm B
Skin (%)	0	0	32 (33.7)	15 (14.01)	38 (40)	57 (53.3)	25 (26.3)	33 (30.8)	0 (0)	2 (1.9)
Mucous membrane	0	0	19 (20)	7 (6.5)	38 (40)	57 (53.27)	38 (40)	36 (33.6)	0	7 (6.54)
Salivary gland	0	0	58 (61)	33 (30.8)	37 (38.9)	74 (69.2)	NA	NA	0	0
Pharynx/esophagus	0	0	48 (50.5)	33 (30.8)	36 (37.9)	57 (53.3)	11 (11.6)	17 (15.9)	0	0
Hemoglobin	33 (34.7)	21 (19.6)	57 (60)	78 (73)	5 (5.3)	8 (7.5)	0	0	0	0
Leukocytes	34 (35.8)	7 (6.5)	55 (57.9)	86 (80.4)	4 (4.2)	12 (11.2)	2 (2.1)	2 (1.9)	0	0

NA=Not available

Table 4: Response rates

	Arm A	Arm B	*P*
Complete response (%)	67 (71)	80 (75)	0.49
Partial response	17 (18)	18 (17)	0.84
Overall response rates	84 (88.4)	88 (92)	0.22

hence, response analysis was included for more details.

Ertekin *et al*.[6] reported that Zn sulfate supplements help in postponing the start of radiodermatitis and even decreases its severity. Moslemi *et al*.[8] in double-blinded randomized controlled trial (RCT) concluded that Zn sulfate is effective in reducing the severity of radiation-induced oropharyngeal mucositis. Our results showed that the severity of radiodermatitis, mucositis, and pharyngitis was slightly lower in patients who received Zn. Proportionately, more number of patients in Arm B reported Gr2 and Gr3 acute skin, mucosal, and pharyngeal toxicities.

A randomized placebo-controlled trial[9] concluded that Zn supplementation can prevent radiation-induced taste alterations. While another trial[18] reported that placebo-treated patients experienced a greater worsening of taste acuity than those treated with Zn sulfate. Through this study, we observed that those patients with Zn supplementation had better salivary gland function than those without Zn, results being statistically significant. Sadic *et al*.[19] showed that with Zn supplementation levels of edema, pan-acinar inflammation, necrosis, atrophy, fibrosis, sclerosis, and stenosis were lower in salivary glands. This could be one explanation that patients in Arm A had lesser salivary gland adverse events.

Lin *et al*.[20] concluded in a RCT that Zn supplementation improved local-free survival at 3 years in head and neck cancer patients. In another trial, [12] Zn supplementation in conjunction with chemo-RT attenuated local tumor recurrence and improved overall survival of patients with advanced nasopharyngeal carcinoma. Although we observed no statistically significant difference in complete or overall response rates whether Zn was supplemented or not, the results might have been influenced by proportionately more number of patients with stage 3 and 4 disease in Arm A.

It is interesting to note that systemic Zn supplementation lends some of its radioprotective effects in normal tissues with salivary glands deriving the major benefits. Yes there are questions to be answered especially on its long-term effects both in terms of toxicity and survival. This will follow.

CONCLUSIONS

Being retrospective, study has its own limitations and biases. Nevertheless, we observed some positive beneficial effects of systemic Zn supplementation. Whether or not Zn supplementation leads to favorable therapeutic index needs to be tested in large RCTs.

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Conflicts of interest

There are no conflicts of interest.

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