CHANGES IN SERUM COPPER LEVELS IN PATIENTS WITH MALIGNANT DISEASES UNDERGOING RADIOTHERAPY

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ABSTRACT

Present study reports changes in serum copper levels (SCL) in various neoplastic diseases undergoing radiotherapy. We estimated SCLs in 140 individuals comprising of 90 previously untreated patients with various malignancies and 50 healthy controls. Patients received radiation in doses of 40-70 Gy in 4-7 weeks. SCLs were again estimated in patients following irradiation. the mean SCL was significantly higher ($P<0.001$) in cancer patients as compared to healthy controls. It declined significantly ($P<0.001$) following irradiation. However, it remained significantly higher as compared to healthy controls ($P<0.01$). Highest fall in SCL was seen in complete clinical responders and least in non-responders to radiation treatment. Serial estimation of SCLs may be useful in the treatment monitoring of the neoplasms undergoing radiation treatment.

KEY WORDS : Serum copper, malignancy, radiotherapy

INTRODUCTION

Cancer is known to be the second most common cause of death after heart disease world-over. Radiation has been used for a century to treat various malignant disorders as a single modality or in combination with surgery and/or chemotherapy. In majority of the neoplastic diseases, we lack exact biochemical parameters to monitor the radiation therapy and its outcome.

It is well established that the element copper is biologically essential for normal growth and development of human body and its function. Very little is known about the clinical significance of serum copper level (SCL) in various disease states including malignancy. Several investigations (1-8) studied serum copper in various malignant disorders. They consistently found it to be elevated in such patients except in few urogenital malignancies (1).

Tessmer et.al. (2) studied the usefulness of SCLs in malignant diseases to assess the response to radiation treatment. Hrgovic et.al. (3) and Thorling and Thorling (9) found the clinical usefulness of SCLs in Hodgkins disease to assess the response to therapy. And, Sharma et.al., (10) found a role for SCL in treatment monitoring of breast cancer.

Recently Martin-Lagos et.al.(5) did not find significant elevation in mean SCLs in cancer patients as compared to controls. Jacobs et.al. (11) failed to find a useful role for SCLs in the treatment monitoring of epithelial ovarian malignancy. Jayadeep et.al.(7) did not find any significant role for SCL as a biomarker of disease progression in the squamous cell carcinoma of oral cavity.

It is clear from above that the interest on the role of trace elements in malignancies is revived, but there is no unanimity regarding their use in monitoring disease. In view of these controversial reports, the present study investigates the role for serum copper in the treatment monitoring of patients with various malignancies undergoing radiotherapy.

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MATERIALS AND METHODS

Patients

The present study is based on the estimation of SCLs in 140 individuals included in the study and control group. Study group comprised of 90 previously untreated, histologically proven patients with various malignancies otherwise free from any concurrent illness. All patients underwent routine haematological and biochemical work up of liver and kidney functions, a chest X-ray PA view and other investigations including Barium swallow, ultrasonography of abdomen, CT scan and endoscopies as indicated. All patients were clinically staged. They gave an informed consent to participate in this study.

Methods

SCLs were estimated both pre and post-irradiation in all the patients by Atomic Absorption Spectrometry method(12) from the venous blood samples. We also estimated SCLs in the blood samples from the healthy voluntary blood donors in our hospital who served as controls.

Interventions

All the patients underwent radiation treatment with the help of telecobalt (Theratron 780-C, AECL, Ottawa). A dose of 40-70 Gy in fraction sizes of 2 Gy was delivered 5 days in a week over a period of 4-7 weeks. Spinal cord was spared after a dose of 40 Gy where required.

Response assessment

Responses were assessed for the disease one month following the completion of radiotherapy and were categorized as a complete response (CR) i.e. complete disappearance of all tumours on clinical examination, partial response (PR) i.e. greater than 50% reduction in the tumour size, or no response (NR) i.e. less than 50% reduction, stable disease or progression.

Statistical methods

For difference between means of measured values of SCLs in various groups or pre-and post-therapy, the student's test was used.

RESULTS

A total of 90 patients were in the study group. The characteristics of these patients are shown in Table 1. Fifty healthy blood donors served as the controls.

The mean pre-treatment SCL was significantly higher ($P < 0.01$) in the subjects (total) with the malignancy ($182 \pm 24.2 \mu\text{g} \%$) as compared to the control ($107 \pm 13.3 \mu\text{g} \%$) (Table 2). There was no statistically significant difference between the mean SCLs of the various age groups or sexes, either in controls or subjects with malignancy.

SCLs were analysed between the various types of malignancies being studied. Nearly similar mean serum copper values were observed in the patients suffering from various cancers. An effort was made to see the variations in SCLs in different clinical stages (stage I-IV) of the disease; and early (stages I & II) versus late disease (stages III & IV). No significant differences were observed in various such subsets of the patients.

Following radiotherapy, there was a decline in SCLs in 82% patients (74/90), while there was an elevation in serum levels in remaining 18% of

Table 1. Patient characteristics (n=90)

Age	Mean (yrs.)	45.7	
	Range (yrs.)	22-73	
Sex	Males	59	65.5%
	Females	31	34.5%
Site of malignancy	Head & Neck	64	71.1%
	Cervix	9	10.0%
	Oesophagus	8	8.9%
	Bronchus	6	6.7%
	Lymphoma	3	3.3%
Stage of disease	I	3	3.3%
	II	21	23.3%
	III	37	41.1%
	IV	29	32.3%
Histopathology	Head & Neck	All squamous	cell carcinomas
	Cervix	All squamous	cell carcinomas
	Lymphoma	All Hodgkins	
	Bronchus & Oesophagus	All squamous	cell carcinomas

Table 2. Serum copper levels in controls and cancer patients

Sex	SCLs in controls ($\mu\text{g}\%$)				SCLs in patients ($\mu\text{g}\%$)			
	No.	Mean	$\pm$ S.D.*	Range	No.	Mean	S.D.	Range
Males	30	105	$\pm$ 13.9	64-129	59	187	$\pm$ 22.5	60-300
Females	20	110	$\pm$ 12.3	80-140	31	173	$\pm$ 27.7	104-240
Total	50	107	$\pm$ 13.3	64-140	90	182	$\pm$ 24.2	60-300

*S.D.=standard deviation

Table 3. Clinical response Vs. decline in SCLs following radiotherapy

Clinical Response	No	Pre-therapy	SCLs#	Post-therapy	SCLs#	Decline in SCLs#	
		Mean	Range	Mean	Range	Mean	Range
CR*	39	182	120-230	110	78-180	73	(-)35-135
PR*	30	185	90-240	146	80-240	34	(-) 45-129
NR*	21	180	60-300	165	110-260	15	(-) 50-65

#serum copper level in $\mu\text{g}\%$ (-)inspite of fall in SCL following radiotherapy the actual values are higher than in normals *CR=complete clinical response *PR=partial clinical response *NR=no clinical response

the subjects (16/90) over the pre-treatment level. The total mean post-therapy SCL came down to $136 \pm 27.9\mu\text{g}\%$ from the mean pre-treatment level of $182 \pm 24.2\mu\text{g}\%$. This decline in the mean of $46 \pm 19.6\mu\text{g}\%$ (not shown in table 3) was statistically highly significant ($P < 0.01$). However, the mean post-treatment level was significantly higher than the mean SCL of healthy controls ($P < 0.01$).

An effort was made to see the correlation between the clinical response and changes in serum copper levels following the radiotherapy (Table 3). It was observed that the decline in mean SCL was highest in patients achieving CR versus those with PR or NR. There was a statistically significant difference between the decline in the mean in patients with CR and PR ($P < 0.01$) and also between PR and NR ($P < 0.05$). There was no significant difference between the mean post-therapy SCLs in patients with complete clinical response ($110 \pm 17.2\mu\text{g}\%$) and mean levels in healthy controls. However, mean post-therapy level in patients with PR was $146 \pm 24.2\mu\text{g}\%$, which was significantly higher than the mean SCL in controls ($P < 0.01$).

The decline in mean SCLs was compared between early stages (stage I & II) and late stages (stage III & IV) of the disease. There was a significantly higher fall in mean SCL of patients with early disease ($54 \pm 25.6\mu\text{g}\%$) as compared to late stages ($41 \pm 21.4\mu\text{g}\%$) ($P < 0.05$ not shown in table). An effort was also made to see the differences in mean decline in SCLs with various doses of radiation. But no correlation was observed.

DISCUSSION

A total of 90 subjects with various malignancies were included in the present study. The mean SCLs were significantly higher in patients with various cancers as compared to healthy controls ($P < 0.001$). Many researchers (1-8) found significant elevation in SCLs in various malignancies except in patients with prostatic carcinoma and few renal neoplasms(6).

No significant differences were observed in the SCLs in the various clinical stages of the

disease in the present study. However, Margalioth et.al. (13) studied SCLs in various gynaecologic malignancies and found that SCLs correlated well with the stage of the cancer except in cases with ovarian neoplasm. Thorling and Thorling(9) found statistically significant correlation between the stage of the Hodgkins disease and SCL. However, we did not find any such correlation. Sanada et.al. (6) also did not find a distinct relationship between SCLs and extent of the disease in transitional cell carcinoma of the bladder.

Hrgovcic et.al.(3) and Thorling and Thorling, (9) in their studies of Hodgkins disease found that serum copper is regularly reduced to within normal limits at complete remission and they proposed that this parameter be included in the criteria for complete remission. Sood et.al.(4) studied prospectively changes in SCLs in patients with various malignancies including carcinomas, sarcomas and lymphomas treated with surgery, radiotherapy or chemotherapy. They concluded that SCL is a potentially valuable biochemical index for assessing the efficacy of therapy and as a guide to prognosis. Sanada et.al.(6) evaluated the changes in SCLs in patients with malignant neoplasms of the urogenital tract. They found that SCLs decreased in testicular cancer patients responding to therapy and increased again in relapse. In a study of SCLS in breast malignancy, Sharma et.al.(10) postulated that the levels of this trace element may help in diagnosis

and prognosis of disease. However, Jacobs et.al. (11) in their study of SCLs in ovarian malignancy concluded that serum copper determination has no use in the treatment monitoring of epithelial ovarian carcinoma. Jayadeep et.al. 1997(7) in their study of SCLs in 92 patients of squamous cell carcinoma of oral cavity concluded that serum copper determination has a little value as biomarker of disease progression.

In the present study, the greatest decline in mean SCL was observed in patients with complete clinical response while least decline of mean was found in patients with no response to radiotherapy (Table 3). The mean post-therapy SCL in patients with CR was near normal, whereas it remained significantly elevated in patients with PR or NR ($p < 0.001$) as compared to controls. And significantly higher decline in mean SCL was observed in patients with early malignancy (stages-I & II) as compared to patients with advanced disease (stages III & IV).

From the results of the present study, it may be concluded that decline in SCLs are strongly related to the response to radiotherapy. Measurement of serum copper levels during radiotherapy may be helpful in treatment monitoring of such cancers. However, this study needs to be conducted on a larger patient population to assess a clinical role for this biomolecule in the treatment monitoring of various neoplasms undergoing radiation treatment.

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