Original Article

Determination Relation of the Zinc Serum Level in Acute Leukemia Adult Patients with Mucositis and Neutropenic Prevalence before and after Treatment in Isfahan' Seyed-Al-Shohada Hospital, 2012–2013

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Abstract

Background: Neutropenic fever and mucositis with 70% outbreak average is one of the major reasons of death in the acute leukemia adult patients. The aim of this study was to determine the relationship of serum zinc level with neutropenic fever and mucositis prevalence in acute leukemia adult patients and comparison of the effects of therapeutic intervention with the serum zinc correct level in the group of patients with zinc deficiency. **Materials and Methods:** From May 2012 to May 2013 in a double-blind, randomized, placebo-controlled study, on the basis of zinc serum level, 40 acute leukemia adult patients were divided into two groups of normal and deficiency zinc, and neutropenic fever and mucositis prevalence were taken into consideration in each and every group. The deficiency zinc patients were randomly allocated to zinc or control group in a blocked randomization schedule. The data analysis was performed by SPSS software 20 and with the aid of variance analysis statistical method, logistic regression, and X^2 statistical test. **Results:** Serum zinc level was higher in acute leukemia adult patients without mucositis and neutropenic fever than others but was not statistically significant. There is a positive relation between receiving zinc with recovery; although the relationship has not become statistically significant. **Conclusion:** These data, although preliminary, suggest that zinc therapy could be a valid therapeutic adjuvant to improve the quality-of-life of acute leukemia adult patients.

Keywords: *Acute leukemia, mucositis, neutropenic fever, serum zinc level*

Introduction

One of the major problem in the process of diagnosis and treatment of patients with acute lymphocytic leukemia (ALL) and myeloid, arising neutropenic fever (38° fever and higher accompanied by neutrophils below 500 in microliter) and mucositis. Neutropenic fever incidence in these patients is estimated more than 80% and that of mucositis >60%.[1-3] Neutropenic fever and infections are the most common cause of death in patients in the process of their treatment. Mucositis is also one of the major reasons of disability and life quality decrease in these patients.[4,5] Mucosal inflammation occurs in 60% of patients during treatment and in addition to reduction in quality of patients' life causing the loss of the mucosal immune against pathogens and a higher incidence of infections and also disorder in patients' nutrition and severe pain.[4-7] On the other hand, zinc is one of the necessary microelements of the body participating in the construction of over 70 basic enzymes. Zinc deficiency in its mild form causing the decrease of body immune system through affecting on immune cells resulting to repeated infections and mostly viral ones.[8,9] The people suffering from malignant including leukemia because of several reasons are prone to zinc deficiency. The process of treatment with anticancer drugs commonly cause nausea and vomiting, and anorexia in patients, resulting to worsening of malnutrition in patients.[10,11] So far, several studies of the impact of zinc deficiency on the immune system in patients with chronic renal failure and dialysis and also in patients with chronic blood problems such as sickle cell anemia was shown that the incidence of infections in patients with zinc deficiency has been more and more prolonged[11,12] and also in patients with chronic inflammatory bowel, mucosal inflammation on zinc serum level, zinc malabsorption particularly in patients suffering from chronic disease

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have been reported.[13-15] With due regard to operation of zinc on the process of skin and mucous tissue healing and well-documented effect on immune function, and zinc deficiency high prevalence in chronic disease and malignant have been taken into consideration in this study, so that in this way by treatment interaction toward decreasing the above said complications the possibility of recovery may be provided for the patients suffering from acute leukemia.

Materials and Methods

The study was approved by the Institutional Review Board of the Isfahan University of Medical Sciences. In the present double-blind, randomized, placebo-controlled study, the statistical community including all adult patients with acute leukemia has applied to Sayed-Al-Shohada Hospital, from May 2012 to May 2013. Which in the available method, 40 patients, on the basis of incidence were taken into consideration and studied as per the following formula

$$n = \frac{z\frac{2}{a/2}p(1-p)}{d^2}$$

where the prevalence of both conditions were an average of 70% and the level of type one error and the acceptable rate of error was considered 5%. The patients were hospitalized during the first 14 days, and bone marrow biopsy was performed for response to treatment. During the patients' hospitalization, the routine tests including complete blood count were performed. Daily temperature and other vital signs and mucosa physical examination were performed 4 times a day. After discharge also tests and physical examinations 2 days once were performed at a specialized clinic. All patients were tested by Elisa method serum zinc level and recorded. For each and every test, a simultaneous central test was taken into account. The inclusion criteria for the study were acute lymphoblastic leukemia (ALL) acute myeloid leukemia [AML]) in the patients over 15 years of age and participating in three sampling of serum zinc level and bone marrow biopsy, and chemotherapy treatment was started by treatment standard protocol. Patients with zinc deficiency randomly assigned to receive placebo, and treatment intervention with zinc pharmacological doses 200 mg 3 times/day with the aim of correcting the serum zinc level and the effects of this treatment intervention were also compared on 14 and 28 days of treatment. Signed informed consent was obtained from all participants at the beginning of the study.

The data in the annexed questionnaire were recorded in the patients' file. Statistical analysis was done by the Statistical Package for the Social Sciences (SPSS-version 20, Chicago: SPSS Inc.). Statistical analysis continuous variables were reported as mean ± standard deviation (SD) and categorical data as a percentage. For comparing continuous and categorical data between study groups, independent samples *t*-test, and aid of variance analysis statistical method, logistic regression were performed, respectively $P < 0.05$.

Results

A total of 40 adult patients with acute leukemia participated in the study. Of these, 39 patients completed and one patient discontinued the study.

Table 1 holder of 39 patients' information with an average (SD) 40.15 (13.33) age and 15 (38.5%) women and 24 (62.5%) men concerning the basic demographic and clinical variables were recorded and measured at the state of 3 variables of gender, state of receiving zinc, and type of disease (AML/ALL). Upon studying Table 1, it is observed that despite the difference of variables distribution, the fever status in women and men only were significant from a statistical viewpoint ($P < 0.05$). Despite the differences observed, only mucositis period average until recovery of patients suffering from ALL and AML was statistically significant ($P < 0.05$).

Table 2 shows the average of zinc initial level in all samples based on the patients with or without mucositis, neutropenic fever, cure, and relapse. By using the two independent samples *t*-test was observed the average serum zinc level of AML patients without mucositis was higher, but this difference has not become statistically significant ($P = 0.69$). The same comparison has been made with the patients suffering from ALL, the results of which are similar. But serum zinc level in the AML patients who had without mucositis one unit was lower in average. In both types of the diseases, the whole of sample has not become statistically significant ($P = 0.57$). Comparison of zinc initial level was performed on the basis of being or no fever in the whole of sample and in each of AML and ALL lines. The results showed that the average zinc initial level of individuals without fever has been higher, but this difference has not been significant ($P = 0.43$). In the other part of table, the results of zinc initial level relationship with recovery status have been shown in the whole of sample and in each of AML and ALL lines. In relation with recovery status, no reliable relationship was observed to be presented. In the patients suffering from average type of ALL only, the zinc initial level of individuals who have fully recovered was higher than those who have partly recovered, but in other lines, no comparing allusive status has been observed.

Table 3 shows the results of logistic regression in different models to study the relation of receiving zinc with recovery (full and partial recovery against reappearance). In the raw model is shown the relation of receiving zinc lonely on recovery only. With due regard to the amount of chance ratio, it is observed that there is a positive relation between receiving zinc with recovery; although the relationship has not become statistically significant ($P = 0.42$).

In the next models, the effect of receiving zinc in the presence of altering variables has been studied as pointed

Table 1: Patient's information with an average (SD) concerning the basic demographic and clinical variables, *n* (%)

Variables	Characteristic	Sex		Zinc consumption		Disease type, *n* (%)	
Zinc consumption	Zinc	Female	Male	Yes	No	AML	ALL
	Control	7 (46.7)	13 (54.2)	-	-	-	-
Disease type	AML	8 (53.7)	19 (45.8)	-	-	-	-
	ALL	12 (80)	14 (58.3)	12 (60)	14 (73.7)	-	-
Packed cell transfusion	Yes	2 (20)	10 (41.7)	8 (40)	5 (26.3)		
	No	9 (60)	16 (66.7)	13 (65)	12 (63.2)	17 (65.4)	8 (61.5)
Mucositis	Positive	6 (40)	8 (33.3)	7 (35)	7 (36.8)	9 (34.6)	5 (38.5)
	Negative	4 (26.7)	4 (16.7)	3 (15)	5 (26.3)	8 (30/8)	0
Fever	Positive	11 (73.3)	20 (83.3)	17 (85)	14 (73.3)	18 (69.2)	13 (100)
	Negative	9 (60)	41 (16.7)	6 (30)	7 (36.8)	10 (38.5)	3 (23.1)
Mucositis grade	0	6 (40)	20 (83.3)	14 (70)	12 (63.2)	16 (61.5)	10 (76.9)
	1	11 (73.3)	20 (83.3)	17 (85)	14 (73.7)	18 (69.2)	13 (100)
	2	0 (0)	1 (4.2)	1 (5)	0 (0)	1 (3.8)	0 (0)
	3	3 (20)	1 (4.2)	2 (10)	2 (10.5)	4 (15.4)	0 (0)
Initial neutropenic fever	Yes	1 (6.7)	2 (8.3)	0 (0)	3 (15.8)	3 (11.5)	0 (0)
	No	2 (13.3)	2 (8.3)	1 (5)	3 (15.8)	4 (15.4)	0 (0)
Chemotherapy type	7-,3	13 (86.7)	22 (91.7)	19 (95)	16 (84.2)	22 (84.6)	13 (100)
	Ar.	9 (62.2)	11 (52.4)	12 (63.2)	8 (53.3)	20 (90.9)	0 (0)
	CVAD	1 (7.7)	1 (4.8)	0 (0)	2 (13.3)	2 (9.1)	0 (0)
Age (year)		42.07±13.4	38.95±18.1	39±18.8	41.36±13.7	11.6±3.6	31.3±15.6
Mucositis term to cure (D)		12.7±3.19	8±3.66	9.1±4.1	11.8±3.8	10.2±10.2	6.2±2.9
Neutropenic term to cure (D)		7.5±5.5	9.8±11.2	7.9±5.8	9.6±11.5	84.15±11.4	4.7±2.5
Initial serum zinc level		81.7±7.8	88.8±14.7	86.7±14.8	85.4±10.8	87.2±11.8	89.9±15.3
Mucositis term to cure (D)		83.3±10.1	92.4±13.04	39±18.8	87.1±11.3	44.42±15.2	92.2±14.7

ALL: Acute lymphocytic leukemia, AML: Acute myeloid leukemia, SD: Standard deviation, CVAD: Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone

Table 2: The average of zinc initial level in all samples based on the patients with or without mucositis, neutropenic fever, cure, and relapse

Variable	Disease type		*P*
	AML	ALL	
Mucositis			
Yes	83.9±3.3	85.3±3.9	0.57
No	84.1±8.6	95.3±3.19	
Fever			
Yes	81.3±12.9	81.3±12	0.43
No	84.7±11.9	89.9±15.1	
Semicures			
Yes	90±26.6	86±0	0.8
No	81.7±7.8	90.3±15.2	

AML: Acute myeloid leukemia, ALL: Acute lymphocytic leukemia

Table 3: Relation of the receiving zinc with recovery by logistic regression in different models

Model	Logistic regression (standard error)	OR (96% CI)	*P*
Raw model	0.75 (0.93)	2.12 (0.34-13.2)	0.42
Model 1	0.71 (0.94)	2.05 (0.32-12.94)	0.44
Model 2	01.04 (1.12)	2.84 (0.32-25.65)	0.35
Model 3	1.38 (1.24)	3.98 (0.35-45.6)	0.27

out beneath the table. The amount of chance ratio also showing the positive effect of receiving zinc on recovery, although the relationship has not become statistically significant ($P = 0.27$).

Discussion

Given the heterogeneous nature of acute leukemia in adults, therapeutic decisions need to be individualized after a systematic assessment of disease biology and patient characteristics.[16,17] The decrease in zinc is an early event in the development of malignancy, which is evident in premalignant cells/lesions.

Zinc deficiency in ordinary persons with low protein regimen, and those who are suffering from malnutrition, inflammatory bowel disease such as Crohn's disease, chronic blood disease like sickle cell anemia, and also in other chronic diseases such as kidney failure and cystic fibrosis is widespread up to 40%. Evolving and compelling evidence exists that proves that zinc is implicated as an important cytotoxic/tumor suppressor agent in several cancers. For example, that cellular zinc levels are markedly decreased in prostate cancer is well established.[18,19] This relationship exists because the concentration of zinc that exists in the normal prostate epithelial cells is cytotoxic in the malignant cells. Evolving evidence indicates that this zinc relationship also exists in other cancers, such as gallbladder cancer,[20] ovarian cancer,[21] hepatocellular carcinoma,[22,23] lung cancer,[24] and breast cancer.[25] This

relationship provides the basis and the opportunity for the potential development of zinc-associated chemotherapeutic agents for specific cancers for which no effective treatment currently exists. To the best of our knowledge, this is the first investigation regarding the use of zinc administration in this setting.

Although not statistically significant in two groups, the trend observed in this study appears to indicate that zinc is likely to be beneficial in the reduction of mucositis overall. A larger study is needed verify this benefit. Mucositis is one of the most debilitating and expensive side effects to treat, and any reduction in its incidence, duration or severity is welcomed.

The review article which is the result of studying 280 articles (62 cases in *in vivo*, and 218 cases in *in vitro*), and also 50 human studies from the year 1970 to 2007 in the ground of using the foodstuffs containing antioxidant and nutrients have been published during the radiotherapy and chemotherapy showing that compounds and foodstuffs containing antioxidant do not interfere with the therapeutic methods. In addition, dietary supplements containing antioxidant, increasing the treatment deficiency, decreasing the side effects, and preserving the tissue. Mucositis appears to be the result of sequential biological events that begin in the submucosa and progress to the epithelium. Hence, mechanistically, antioxidant and anti-inflammatory agents could be effective in the prevention of this side effect. Several studies have shown that these agents have some benefits in prevention of mucositis induced by both chemotherapy and radiation therapy.[2]

Infections in the immune compromised host as a result of cancer chemotherapy is an important problem in the present day-to-day treatment care, as they are associated with an increased incidence of neutropenic infectious complication, which in turn influences the outcome of the chemotherapeutic response, and thereby morbidity and mortality, in these patients. Thus, prevention and treatment of infection are vital in the management of acute leukemia, which can be achieved by empirical antibiotic therapy covering the broadest spectrum of organisms because these patients have a 60% likelihood of being infected due to neutropenia.[14,26] Several studies have shown the benefits of zinc supplementation on infectious diseases in humans. In double-blind placebo-controlled trials of zinc supplementation, zinc reduced the incidence and duration of acute and chronic diarrhea and acute lower respiratory tract infections in infants and children. Zinc supplementation of sickle cell anemia patients in a placebo-controlled trial resulted in decreased incidence of *Staphylococcus aureus* pneumonia, streptococcus pneumonia tonsillitis, and *Escherichia coli* urinary tract infections.[11,12]

Normal mammalian cells contain and maintain total cellular zinc levels in the range of approximately 200–800 μM, depending on the cell type. Under these conditions, the normal cells possess mechanisms/factors that protect the cells from the potential adverse effects of zinc. Within the same *in situ* environment, malignancy develops under conditions in which the malignant cells are susceptible to the potential cytotoxic effects of the cellular zinc levels that exist in the normal cells. This suggests that the protective mechanisms/factors that exist in normal cells do not exist in malignant cells. Some *in vitro* studies also provided evidence that similar zinc accumulation from exposure to zinc treatment is more cytotoxic in malignant cells than in nonmalignant cells.[12,27] Therefore, the evolution and development of malignant cells probably involved a selection process in which those neoplastic cells with adaptive mechanisms that prevent zinc cytotoxicity are the surviving cells that become malignant cells. To achieve this, the malignant cells exhibit lower levels of zinc than the normal cells. This adaptive change prevents the manifestation of zinc cytotoxic effects and also maintains the levels of zinc that are essential for the survival and activities of the malignant cells. This is an important distinction as a complete or near-complete loss and absence of zinc should not be expected in malignant cells; that is, a condition under which no cells would survive.

The both mentioned effects, in addition to affecting the patients' death rate causing considerable increase in patients' hospitalization period as well as consumption of antibiotics, hematopoietic pharmaceutical factors, hematic products with high effects, and finally imposing very high financial expenses on patients and treatment system.

The effects during treatment with cytotoxic agents in leukemia patients, due to effect of these medications on the cellular evolution cycle are created in abundance, and in order to face with them and their treatment, using the antibiotics and a series of solutions and topical remedies are usual which evidently are not sometimes successful so much so that the infections lonely in spite of antibiotic serious treatment causing the death about 10% of patients during 1-month of initial treatment.[16,17]

There is a periodical interval about several weeks up to several months from beginning of the malignancy up to diagnosis of final disease and start treating. During this period, by growing the malignant cells and secretion of cytotoxic like tumor necrosis factors-interleukins, etc., causing the decrease of patients' appetite and malnutrition, nausea, fever, and rising the body's catabolism, causing the deficiency of kind of vitamins and micro-elements in the body.

Zinc is one of the skeleton micro-elements, the effect of which has been proved in all therapy. Regardless of treatment, however, outcomes for adult patients with acute leukemia remain in general unsatisfactory. In contrast with the progress made for younger adults, the treatment of acute leukemia in adults has not improved significantly in recent decades.

Conclusion

Development of less toxic and more targeted agents may well provide treatment alternatives for a majority of these patients. The overall dismal outcome with currently available treatment approaches has encouraged patients to participate in prospective clinical trials.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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