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ORIGINAL PAPER

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Impact of chemotherapy on antioxidant micronutrient levels in patients with mature lymphoid malignancies

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ABSTRACT

Introduction. Cancer treatments are now intense and are associated with nutritional deficiencies. The nutritional status of a patient may influence the tolerability of chemotherapy.

Aim. We investigated the effects of chemotherapy on serum levels of trace elements (copper, iron, manganese, selenium, and zinc) and vitamins (A, C, and E) in patients with mature lymphoid malignancies (MLMs) at diagnosis and after 3 months.

Material and methods. A case-control study of adults diagnosed with and treated for various MLMs. Thirty-nine cases and 39 age and sex-matched controls were recruited into this study. Venous blood samples were collected from the controls, cases at baseline and after 3 months of chemotherapy. Trace elements were determined by AAS while vitamins were determined by HPLC.

Results. The levels of trace elements and antioxidant vitamins A and E were significantly higher ($p<0.001$) in cases than in controls while vitamin C was lower in cases compared to controls ($p=0.005$). After 3 months of treatment, 28 patients were available for analysis. There was a significant decline ($p<0.001$) in all the levels of trace elements and vitamins after chemotherapy.

Conclusion. Chemotherapy is associated with a significant reduction in antioxidants levels in patients with MLMs.

Keywords. antioxidant micronutrients, chemotherapy, haematologic malignancies

Introduction

Mature lymphoid malignancies are heterogeneous clonal neoplasms of B cells, T cells, and natural killer (NK) cells, which in many respects resemble normal B cells and T cells in stages of differentiation and express the phenotypic markers of mature lymphoid cells. Acute lymphoblastic leukaemias which arise from precursors and express antigenic features of immaturity are excluded.[1,2] Micronutrients are nutrients required by living organisms throughout life in small quantities for a range of physiological functions. Micronutrients include dietary trace elements or minerals and vitamins and other compounds required for normal function in amounts generally less than 100 milligrams/day as opposed to macrominerals which are required in larger quantities.[3] Some of these micronutrients act as antioxidants in the body. Antioxidants are trace elements, vitamins, and enzymes whose combined effect is to neutralize oxidant stress produced from metabolic processes.[4–6]

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The nutritional status of patients with cancer greatly influences the treatment outcomes.[7]micronutrients, food variety and diet diversity score changed significantly after the induction chemotherapy. No significant relationship was found between the changes in dietary indices and nutritional status. Chemotherapy-related side effects as an additional factor to cancer itself could affect dietary intake of leukaemia patients. The effectiveness of an early assessment of nutritional status and dietary intake should be further investigated in order to deter further deterioration. Deficient diets have detrimental effects on immune status and tolerance of treatment and these patients have poorer quality of life and prognosis. The present approach to the treatment of cancer has become more intensive and aggressive with an associated increase in side effects.[8] Nutrients deficiencies may reduce the response to chemotherapeutic agents, delay the schedule of chemotherapy, and at the same time increase the adverse reactions.

Over the decades, researchers have studied the link between the consumption of food rich in antioxidants and the prevention of degenerative diseases including cancers.[9–13] There have been mixed conclusions with some studies stating a positive effect while others show no effect or even a harmful effect of antioxidant supplementation in certain cancer types.[14–17] However, naturally occurring antioxidants in fruits and vegetables may be better than pharmacological preparations in improving antioxidant status.[18] The concept of the administration of antioxidants during cancer treatment remains a very controversial issue. In general terms, antioxidants could promote or suppress the effectiveness of antitumor treatment and even protect healthy tissues against damage induced by oxidative stress.[4]

Aim

In this study, we investigated the effects of chemotherapy on the levels of antioxidant micronutrients in patients with mature lymphoid malignancies.

Material and methods

Patients

Thirty-nine consecutive patients with MLMs who have not had chemotherapy were recruited. Thirty-nine age and sex-matched controls were also recruited. The diagnoses of MLMs were made based on cytomorphological techniques. Blood smears, bone marrow aspirates, lymph node histology, and immunohistochemistry (where available) were used in making the diagnosis. Each case was reviewed by at least two haematologists at the time of diagnosis. The study participants gave written informed consent.

Before administration of chemotherapy to the patients, 5 milliliters of venous blood were drawn from each patient after 12-14 hours of fasting. Fasting samples were taken to avoid recent dietary influence on measurements of trace elements. This was dispensed into a plain serum bottle. The blood samples were allowed to clot and retract and were centrifuged at 4000 rpm for 15 minutes at room temperature to separate the serum. The serum was dispensed into two plain bottles in aliquots for trace elements and vitamins assays. After 3 months of chemotherapy, another 5 ml of blood was taken from the cases and was processed as above. The serum samples were stored at –80°C until analysis.

Chemotherapy Protocols

Each patient was treated according to the cytomorphological /histological diagnosis. Patients with NHL had either of the following regimens: R-CVP or CHOP in the 21 Day cycle. For CLL patients, the following regimens were used: CVP in a 21 Day cycle or PO Chlorambucil 4mg daily for 2 weeks with 2 weeks resting period in a 28-day cycle. Multiple myeloma patients had CTD in a 28 Day cycle or M+P+Thal) in a 28-42 Day cycle. All patients on Thalidomide received thromboprophylaxis with PO Warfarin 2.5 mg nocte throughout the cycle. Radiotherapy was used in a patient with plasmacytoma. The dose was 3Gy/fraction up to 10 fractions on an alternate day, not exceeding 45Gy. The ABVD regimen was used for patients with Hodgkin lymphoma repeated every 2 weeks. Additionally, patients received general advice on good nutrition same as the premorbid state throughout the study period.

Micronutrient Analysis

The micronutrients (Cu, Fe, Mn, Se, and Zn) in the serum samples were measured using atomic absorption spectrophotometry as described by Kaneko [19] while vitamins A, C, and E were measured by high-performance liquid chromatography using Waters 616/626 (USA) machine.[20] This is part of a study investigating antioxidants and markers of oxidative stress in MLMs.

Ethical considerations

Ethical approval for this study was obtained from the ethical committee of the University of Ibadan/University College Hospital Institution Review Board before the commencement of the study (IRB Research approval number: NREC/05/01/2008a).

Statistical Analysis

Statistical analysis was performed with IBM SPSS for Windows Statistics, version 23. Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test and the Levene test was used to test the homogeneity of variance. The mean and standard devia-

tions were used to summarize continuous variables such as levels of trace elements and vitamins at baseline and 3 months. An independent sample t-test was used to calculate the difference in means of both groups. In the case of normally distributed variables, a paired-samples t-test was used to compare the means before and after chemotherapy. Mann-Whitney and Wilcoxon signed-rank tests were used for nonparametric variables. Post hoc analyses were used to test for differences between multiple groups means. A p-value < 0.05 was considered statistically significant.

Results

The demographics and social characteristics of the study population were summarized in Table 1. The study population consisted of equal numbers of males (n = 22, 56.4%) and females (n = 17) in both arms. The M: F was 1.2:1 and it was the same for the two groups. The mean (SD) of the age for the cases was 53.5± 16.4 while for the control was 48.2± 14.8, p=0.143. Most of the cases (41%) had tertiary education compared to the control group where all had tertiary education.

Table 1. Demographics and social characteristics of the study population

Variables	Cases (n = 39)	Control (n = 39)
Age	53.5±16.4	48.2±14.8
Sex		
M	22	22
F	17	17
Level of Education		
1. Primary	7	-
2. Secondary	13	-
3. Tertiary	16	35
Occupation		
1. Professionals/ civil servants	15	35
2. Artisans	9	-
3. Students	2	2
4. Trading	6	-
5. Retired	7	2

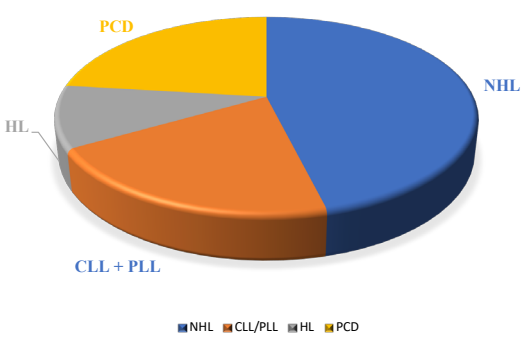

Fig. 1. Proportions of different mature lymphoid malignancies in the study

A total number of 78 participants were included in this study – 39 patients with different mature lymphoid malignancies were recruited and equal numbers of age and sex-matched controls. The cases included 18 patients with NHL, plasma cell dyscrasias (9), CLL (8), Hodgkin Lymphoma (4), this is shown in figure 1. After 3 cycles of chemotherapy, 28 patients were available for analysis.

Assessment of trace elements and antioxidant vitamins in patients with MLMs at diagnosis and control

The serum levels of all trace elements were significantly higher in the cases compared to the controls at diagnosis. The serum concentrations of vitamins A and E were higher in patients with MLMs at presentation relative to the controls. However, the mean level of vitamin C was higher in the controls than in the cases (Table 2).

Table 2. Comparison of serum levels of micronutrients in the controls, cases at diagnosis, and after 3 months of chemotherapy

Parameters	Control n = 39	Before chemotherapy n = 39	3 months PC n = 28
Iron (µg/dl)	111.05 ± 11.5	136.12 ± 13.3#	94.8 ± 1.25¥
Zinc (µg/dl)	94.9 ± 5.9	106.8 ± 6.8#	65.6 ± 6.4¥
Copper (µg/dl)	102.0 ± 11.8	127.8 ± 13.7#	85.3 ± 12.8¥
Manganese (µg/dl)	7.9 ± 0.5	9.16 ± 0.9#	5.5 ± 0.05¥
Selenium (µg/dl)	45.7 ± 5.3	57.4 ± 6.2#	38.4 ± 5.7¥
Vitamin A (µg/dl)	60.62 ± 4.0	63.81 ± 7.9#	33.35 ± 7.23¥
Vitamin C (mg/dl)	1.23 ± 0.1	1.17 ± 0.07*	0.69 ± 0.11¥
Vitamin E (mg/dl)	1.31 ± 0.07	1.54 ± 0.18 #	0.91 ± 0.08¥

PC – post commencement of chemotherapy
- Significantly different from the cases <0.001
* Significantly different from the control <0.005
¥ Significantly different from before chemotherapy <0.001

Effects of chemotherapy on the levels of trace elements and antioxidant vitamins after 3 cycles of chemotherapy

Following chemotherapy, there was a statistically significant reduction (p<0.001 in each case) in serum levels of all trace elements compared to the baseline values. This is shown in Fig 2.

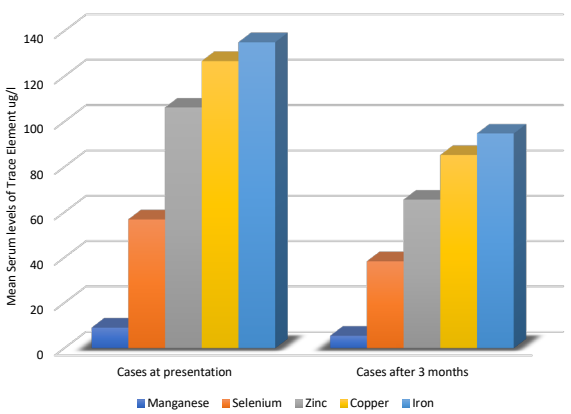

Fig. 2. Levels of trace elements in cases at diagnosis and post 3 months of chemotherapy

A similar trend was seen in all measured vitamins after 3 cycles of chemotherapy as shown in Table 3.

The effects of different chemotherapeutic regimens on trace elements and vitamins

According to Table 3, 8 patients each were treated with CHOP and CVP regimens. Five patients were treated with M+P+Thal, 4 had an ABVD regimen, and 3 were treated with Chlorambucil. The mean (SD) of different analytes were presented in the table below. Post hoc analyses using Scheffe's post hoc criterion for significance indicated that there were no statistical differences in the levels of trace elements, vitamins, and superoxide dismutase using different regimens after 3 months of therapy. The p values for the trace elements were 0.681 for each element, vitamin A (p=0.952), vitamin C (p=0.780), and vitamin E (p=0.680).

Table 3. The effects of different chemotherapeutic regimens on the levels of trace elements and vitamins

	Chemotherapy Regimens					
Parameters	CHOP n = 8	ABVD n = 4	CVP n = 8	M+P+Thal n = 5	Chlorambucil n = 3	p value
Zinc (µg/dl)	67.5±4.0	62.1±4.2	66.5±6.3	67.0±6.3	61.1±13.5	0.681
Copper (µg/dl)	88.9±8.1	78.2±8.4	87.0±12.5	88.1±12.6	76.3±27.0	0.681
Manganese (µg/dl)	5.6±0.3	5.2±0.4	5.5±0.5	5.6±0.5	5.1±1.1	0.681
Selenium (µg/dl)	40.0±3.6	35.2±3.8	39.2±5.6	39.6±5.7	34.3±12.2	0.681
Iron (µg/dl)	98.3±7.9	87.8±8.2	96.5±12.2	97.5±12.2	85.9±26.3	0.681
Vit A (µg/dl)	31.3±12.5	32.7±2.2	35.0±3.3	35.3±3.3	32.2±7.1	0.952
Vit C (mg/dl)	0.7±0.1	0.7±0.1	0.9±0.1	0.6±0.2	0.6±0.2	0.780
Vit E (mg/dl)	0.9±0.1	0.9±0.1	0.9±0.1	0.9±0.1	0.8±0.2	0.680

CHOP = cyclophosphamide, Doxorubicin, Oncovin, Prednisolone. CVP = cyclophosphamide, Vincristine, Prednisolone. ABVD = Adriamycin, Bleomycin, Vinblastine, Dacarbazine. M+P+Thal = Melphalan, Prednisolone, Thalidomide

Discussion

Trace elements and vitamins play crucial roles in cellular metabolism, cell proliferation, differentiation, and immunological functions. These micronutrients together with antioxidant enzymes and other antioxidants in the cells are important in providing defense against oxidative damage to macromolecules such as DNA. The deficiencies of these nutrients have been associated with the risk of malignancies including MLMs.

In this study, the serum levels of copper were found to be significantly higher in patients than controls at presentation and this agrees with several studies in MLMs.[21–23] The elevated serum copper can be explained by the acute phase reaction on the one hand or it could also be due to malignancy. Copper and its carrier protein caeruloplasmin are positive acute phase reactants that are elevated in inflammatory conditions.[21] There is also evidence that serum copper indicates the extent of disease which is independent of the non-specific acute phase reaction.[24,25] Copper is an essential trace element in many metabolic processes from cellular metabolism to antioxidant defence.[25]

The serum levels of zinc, selenium, iron, and manganese observed in this study were significantly higher in cases than in controls. These observations contradict the established findings that these trace elements are negative acute phase reactants, hence are reduced in inflammatory conditions.[26] Additionally, cancers including MLMs are characterized by malnutrition, especially micronutrient deficiencies resulting from a variety of mechanisms such as cancer-associated anorexia and physiological impairment to digestion and/or absorption.[27] The plausible reason for these observed increases in these trace elements may be due to release from their intracellular locations into the bloodstream as a result of increased cell lysis, which is common in lymphomas and leukaemias. Trace elements such as zinc, selenium, and manganese play roles in protecting the cells from oxidative stress. They are integral parts of enzymes such as SOD and glutathione peroxidase involved in the neutralization of free radicals. Iron serves important functions in cell metabolism, proliferation, and growth.[28] It participates in the Fenton reaction where, in its ferrous state it donates an electron to hydrogen peroxide to form hydroxyl radical, a potent DNA damaging agent, and this may lead to oncogenic activation.[29] The findings in this study agreed with Fahmy et al. who reported significantly elevated Zn and Se in newly diagnosed NHL patients higher than the matched controls. Contrary to our findings, Asfour et al. using the same method of atomic absorption spectrophotometry (AAS) found that zinc was reduced in CLL at diagnosis.[21] Furthermore, Stevens et al. found that selenium was reduced in follicular lymphoma and Hodgkin lymphoma but inductively coupled plasma mass spectrometry method was used in their study.[30] This method is more sensitive than the AAS.

It was found that the serum levels of vitamins A and E were higher in cases than in controls, while vitamin C was lower in cases. The reason for these observations in the serum levels of vitamins A and E in this study is not clear. It is a common practice in the locality of this study for ill patients to use over-the-counter supplements or herbal traditional medicines which may be rich in micronutrients before a definitive diagnosis is made.[31] The serum vitamin C in this study agreed with findings in multiple myeloma patients by Sharma et al and Mehdi et al., but the serum vitamin E levels in this study differed with both studies.[32,33] Both studies demonstrated

that vitamins C and E were lower in multiple myeloma patients than in their controls. It must be pointed out that these studies used colorimetric and fluorometric methods in determining the vitamins. These methods are less specific, accurate, and less reproducible than the HPLC method used in this study.[34] Vitamins are organic compounds required in minute amounts for the proper functioning of cells. There is increasing evidence that antioxidant vitamins can protect against certain types of cancers and other diseases. They can act as the first line in protecting against oxidant stress (vitamin C) or as chain breakers in lipid peroxidation (e.g., vitamin E). Vitamin A is effective in quenching singlet oxygen and inhibits lipid peroxidation.[34] As noted above, micronutrient malnutrition predominates in cancer patients. Furthermore, insufficient supplies of antioxidant vitamins prevalent in many cancers have been linked to increased oxidative stress markers.[8] Combining these two pathophysiological mechanisms, serum vitamins are expected to be lower in cancers. However, the findings in this study did not agree with these hypotheses.

It was demonstrated in this study that after 3 months of chemotherapy that the levels of all trace elements (Cu, Zn, Fe, Se, and Mn) and vitamins (A, C, and E) were significantly reduced with chemotherapy. This can be explained by the fact that patients undergoing chemotherapy and radiotherapy are at increased risk of micronutrient malnutrition, thereby worsening the existing micronutrient negative balance. Most chemotherapeutic agents cause nausea and vomiting, thus significantly reducing food intake. Additionally, intestinal losses of vitamins and electrolytes (metals) in the form of diarrhea are common with chemo-radiotherapy. [27] The degree of these losses will depend on the drug dosage, duration of treatment, excretion rate, metabolism, and individual susceptibility. Another possible explanation relates to increased ROS generated using chemotherapeutic agents such as cyclophosphamide, vincristine, and daunorubicin.[8] It is well established that these agents additionally kill cancer cells through the induction of oxidative stress.[35] In terms of generating oxidative stress, antineoplastic agents are divided into very high level, high level, and low-level producers. Daunorubicin and doxorubicin belong to very high levels, while cyclophosphamide and vincristine (and other vinca alkaloids) belong to high levels and low levels respectively. In this study, no difference was detected using different chemotherapeutic regimens as shown in Table 3. The possible reason for the lack of differences in effects on the levels of trace elements and vitamins could be due to the number of patients in each subgroup and the fact that the regimens used in treating these patients have a combination of agents with different oxidative stress generating potentials in each regimen. The implications of these significant reductions in serum micronutrient levels are impairment of immune cells, recovery, and regeneration of new cells as these processes require micronutrients. Restoration of the physiological levels of these elements may relieve or prevent these impairments. Furthermore, nutrient deficiency may also reduce the response to chemotherapeutic agents, delays in the schedule of chemotherapy, and at the same time increasing adverse reactions.[8]

One of the limitations of this study was the dietary patterns of the study population. The dietary patterns were explored but were met with difficulties because of the lack of standardized methods for assessing dietary intakes and their nutritive contents in the locality of this study. In the absence of validated tools for assessing dietary and the fact that the majority of the participants were drawn from the same ethnic group, it was assumed that they have been exposed to food items with similar nutritive values. Another drawback to the generalizability of the study is the number of patients with mature lymphoid malignancies included in it. A larger study is advocated which will include sufficient numbers of cases with a different diagnosis.

Conclusion

In conclusion, there is a multi-micronutrient deficiency in patients with MLMs undergoing chemotherapy. The strength of this study is that it is perhaps one of the few studies in our locality that assessed the effects of chemotherapy on the antioxidant levels during treatment. These results may guide some cautious interventions in the management of patients with MLMs and other haematological conditions.

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