Plasma Selenium Concentration and Glutathione Peroxidase Activity in Breast Cancer Patients Before and After Chemotherapy

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Abstract

Background: The chemotherapeutic agents used for treatment of breast cancer are all shown to increase free oxygen radicals and generation of reactive oxygen species. The aim of this study was to evaluate effect of chemotherapy on plasma selenium (Se) concentration and glutathione peroxidase (GPX) activity in breast cancer patients.

Materials and Methods: Seventeen women in stage II and III breast cancer were randomly selected from their population. Plasma Se was measured with Graphite furnace atomic absorption spectroscopy and GPX activity in erythrocyte by using spectrophotometric at baseline (before chemotherapy) and after chemotherapy. normally distributed data was expressed as mean ± standard deviation. Statistical analysis was performed using Paired T-Test.

Results: plasma Se concentration before and after chemotherapy was in normal range and no statistically difference was observed (156.23±25 µg/L vs. 145.23±23 µg/L respectively). After chemotherapy, there was a significant ($p<0.05$) higher erythrocyte GPX activity, as compared to initial activity at baseline. (22.28±4 U/grHb vs. 26.39± 4 U/grHb respectively).

Conclusion: This study indicates that sufficient Se could increase GPX activity with have a protective effect against oxidative damages.

Keywords: breast cancer, chemotherapy, glutathione peroxidase, selenium

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Introduction

The concept of the chemoprevention of cancer as originally proposed refers to prevention of cancer by use of pharmacological agents to inhibit or reverse the process of carcinogenesis. Experimental and clinical studies have shown that a major mechanism for cytotoxic activity of the numerous chemotherapeutic agents is through increased formation of the reactive oxygen species (ROS), including hydroxyl radicals (OH°), hydrogen peroxide (H_2O_2) and superoxide anion (°0²-) (1-3).

The chemotherapeutic agents such as cyclophosphamide (cytoxan), doxorubicin (adriamycin) now commonly used for treatment of breast cancer, have all been shown to increase lipid peroxidation and generation of ROS (4).

The reactive oxygen species play an effective role in pathogenesis of different pathological diseases including cancer. Free radical induced lipid peroxidation causes a loss of cell homeostasis by modifying the structure and functions of cell membrane. The most important characteristic of lipid peroxidation is to cause a considerable DNA-MDA adducts by intraction with cellular DNA (5). However, mammalian cells possess elaborate antioxidant defence mechanisms to neutralize the deleterious effects of free radical induced lipid peroxidation.

Selenium (Se) is a very important component of anti oxidative protective mechanism which belongs to every cell, and there is evidence that this essential trace element have anticancer properties. Se exerts its chemoprevention effect in different ways, such as a protective effect against oxidative damage by decreasing the amount of free radicals and increasing the synthesis of glutathione peroxidise (GPX) (6-9).

The cytosolic GPX is the first and best characterized mammalian selenoprotein, capable of reducing equivalents from glutathione to detoxify hydrogen and lipid peroxides (8).

The present study was, therefore, conducted to evaluate the effect of chemotherapy on plasma Se

concentration and GPX activity in breast cancer patients.

Materials and Methods

Participants

Seventeen breast cancer patients, aged 29 to 55 years (43.23±8 y) were randomly selected from their population. The inclusion criteria for the patient were:1) Cases of breast cancer proven by histopathology/cytopatheology. 2) going under no treatment specific for breast cancer. 3) Not getting suffered a concomitant disease such as diabetes mellitus, rheumatoid arthritis or thyroid and liver disorders. 4) taking no vitamin or mineral supplements during the last year.

For histopathologic analysis, tumors were classified according to TNM (tumore, node and metastasis) system of cancer classification (10). Whereby, nine patients classified as stage II and 8 patients as stage III. These patients underwent 4-5 section of chemotherapy. 14 patients used the chemptherapeutic agents cytoxan + adriamycin + 5-flouro uracil and 3 patients used cytoxan + adriamycin + taxotere during chemotherapy.

Biochemical analysis

At the beginning and after duration of chemotherapy 5 ml venous blood samples were taken and placed in EDTA tubes. Plasma was separated by centrifuging at 1000 x g for 10 minutes at 4°c and was stored at -80°c until analysis. After plasma separation, the white buffy layer (leukocytes) was removed and the packed cells washed twice with physiologic saline. A known volume of erythrocytes was lysed in 4 volumes of ice-cold HPLC-grade water, and was centrifuged at 3000 x g for 10 minutes at 4°c. The supernatant was collected and stored in -80°c until analysis.

Graphite furnace atomic absorption spectroscopy was used to determine the concentration of Se in plasma (11). GPX activity in erythrocyte was measured using the spectrophotometric method as described by Paglia and Valentine (12).

Statistical analysis

Normally distributed data was expressed as mean ± standard deviation. Statistical analysis was performed using Paired T-Test. P value <0.05 was considered as significant. All statistical analyses were done using SPSS version 11 for windows (SPSS Inc., Chicago, 2001).

Ethical aspects

The study protocol and ethical aspects were approved by the research council ethics committee of the research affairs dean of the Shiraz University of Medical Sciences.

Results

Totally, 17 patients were randomly chosen for the study. The mean ±SD age of patients was 43.2±8 years (range: 29-55 yrs). According to TNM system of cancer classification, 9 patients were classified as stage II and 8 patients as stage III. The mean plasma Se and erythrocyte GPX of breast cancer patients before and after chemotherapy are presented in Table 1 and Figure1 and 2.

As Table 1 shows, there was not significant difference between plasma Se concentration before and after chemotherapy. But we observed a significant change regarding erythrocyte GPX activity before and after chemotherapy (P=0.018).

Discussion

Chemotherapy involves administration of cytotoxic drugs that prevents growth and proliferation of cells, and it's especially used in cancer treatment in order to destroy neoplastic cells that show uncontrolled growth. Due to toxicity of drugs, chemotherapy delivered in any setting is usually associated with a number of distressing side effects for the patient (4).

Some investigation showed that chemotherapeutic agents routinely used in cancers increase free oxygen radicals that leads to a damage also of normal tissue (2,13). Se behaves as an antioxidant agent and as its antioxidant role, notably qua GPX, can reduce hydrogen peroxide, lipid and phospholipids hydroperoxides, thereby dampening the propagation of free radicals and reactive oxygen species (8).

The result of the present study showed that Se levels in patients before and after chemotherapy were in normal range and the difference was not statistically significant.

The same results also found in the study of

Table1: Plasma Se concentration and erythrocyte GPX before and after chemotherapy in breast cancer patients.

Parameters	Number	Before chemotherapy	After chemotherapy	Significance
Se (µg/L)	17	156.23±25.43	145.23±23.83	NS*
GPX (U/grHb)	17	22.28±4.18	26.39±4.65	P=0.018

*NS=Not significant
Bold = the significant P (P<0.05)

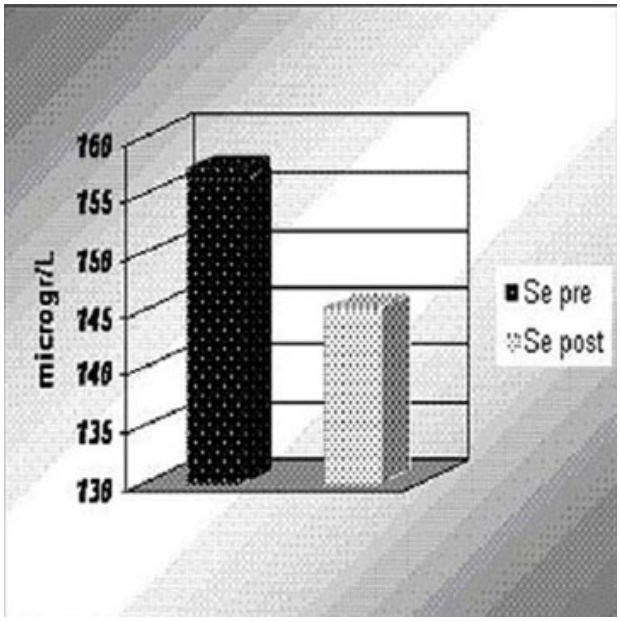

Figure 1: Plasma Se concentration before (Pre) and after (Post) chemotherapy in breast cancer patients.

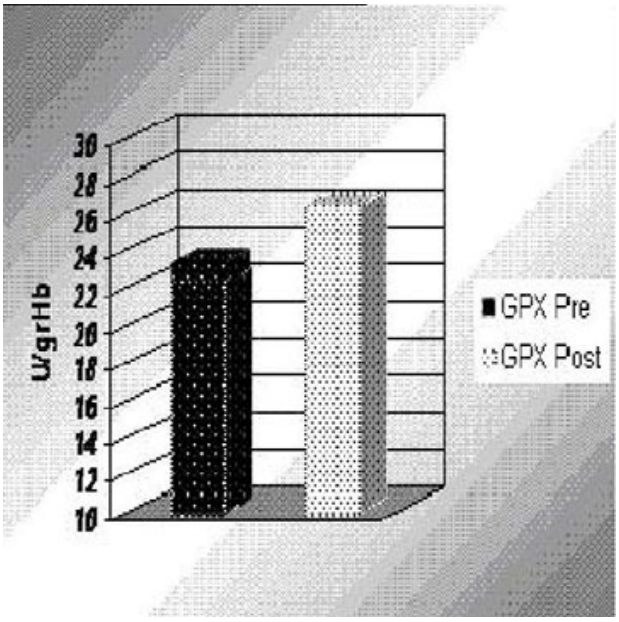

Figure 2: Erythrocyte GPX activity before (Pre) and after (Post) chemotherapy in breast cancer patients.

Breedlove and co-workers (14) which revealed that Se status was within the normal range before and following adjuvant chemotherapy, and was not affected by chemotherapy-induced ovarian failure. In another study, Faber (15) showed that the plasma Se in cancer patients was decreased, but not further modified by chemotherapy.

Our finding showed that erythrocyte GPX activities had significant elevation in breast cancer patients after chemotherapy (P=0.018).

This may be due to the response of higher free radical production caused by using chemotherapeutic agents.

This result is consonant with Jonas and Co-workers (16), who reported plasma GPX activity increase during the time after high-dose chemotherapy in bone marrow transplantation patients.

The study of Breedlove and Faber (14-15), revealed that chemotherapy don't affect plasma GPX status. We suggest that in breast cancer patients, increased GPX activity is due to increased formation of reactive oxygen species that cause increase in the antioxidant enzymes such as GPX, to improve the resistance of neoplastic cells versus drugs that associates with tumor promotion.

In conclusion, Se deficiency was not a problem among our population study and its concentration was in normal range, so in order to detoxify hydrogen and lipid peroxides it was possible for cells to increase GPX, as a Se dependent enzyme.

References

1. Weijl NI, Cleton FJ, Osanto S. Free radicals and antioxidants in chemotherapy-induced toxicity. Cancer Treat Rev. 1997; 23(4):209-240.

2. Sangeetha P, Das UN, Koratkar R, Suryaprabha P. Increase in free radical generation and lipid peroxidation following chemotherapy in patient with cancer. Free Radic Biol Med. 1990; 8(1):15-19.

3. Clemens MR, Ladner C, Schmidt H, Ehninger G, Einsele H, Buhler E, et al. Decreasal essential antioxidant and increased lipid hydroperoxides following high-dose radiochemotherapy. Free Radic Res Commun. 1989; 7(3-6):227-232.

4. Ambrosone CB, Ahn J, Schoenenberger V. Antioxidant Supplements, Genetics and Chemotherapy Outcomes. Current Cancer Therapy Reviews. 2005; 1:251-258.

5. Abidi S, Ali A. Role of oxygen free radicals in the pathogenesis and etiology of cancer. Cancer Lett. 1999; 142:1-9.

6. Patricle I. Selenium Biochemistry and Cancer: A Review of The Literature. Alternative Medicine Review. 2004; 9:239-58.

7. Howard E.Ganther. Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. Carcinogenesis. 1999; 20(9):657-1666.

8. Rayman Margaret P. The Importance of Selenium to Human Health. The lancet. 2000; 356:233-41.

9. Clement IP. Lessons From Basic Research In Selenium And Cancer Prevention. J Nutr. 1998;128:845-1854.

10. Sobin LH, Wittenkind CH, editors. International Union against Cancer (UICC): TNM classification of malignant tumors. 5nd edition. New York. Wiley Liss Publications.1997.

11. Sheehan TM, Halls DJ. Measurment of selenium in clinical specimens. Ann Clin Biochem. 1999; 36:301-315.

12. Paglia DE, Valentine WN. Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin. 1967; 70:158-169.

13. Schumacher K. Effect of selenium on the side effect profile of adjuvant chemotherapy/radiotherapy in patients with breast cancer carcinoma. Design for clinical study. Med Klin. 1990; 94(3):45-8.

14. Breedlove HA, Smith AM, Burk RF, Hill KE, Shapiro CL. Serum selenium measurements in women with early-stage breast cancer with and without chemotherapy-induced ovarian failure. Breast Cancer Research and treatment. 2006; 97(3):225-230.

15. Faber m, Coudray C, Hida H, Mousseau M, Favier A. Lipid peroxidation products, and vitamin and trace element status in patients with cancer before and after chemotherapy, including adriamycin. A preliminary study. Biol Trace Elem Res. 1995; 47(1-3):117-23.

16. Jonas CR, Puckett AB, Jones DP, Griffith DP, Szeszycki EE, Bergman GF, et al. Plasma antioxidant status after high-dose chemotherapy: a randomized trial of parenteral nutrition in bone marrow transplantation patients. Am J Clin Nutr. 2000; 72:181-9.