RESEARCH ARTICLE

Effects of Fresh Yellow Onion Consumption on CEA, CA125 and Hepatic Enzymes in Breast Cancer Patients: A Double-Blind Randomized Controlled Clinical Trial

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Abstract

Onion (*Allium cepa*) consumption has been remarked in folk medicine which has not been noted to be administered so far as an adjunct to conventional doxorubicin-based chemotherapy in breast cancer patients. To our knowledge, this is the first study aimed to investigate the effects of consuming fresh yellow onions on hepatic enzymes and cancer specific antigens compared with a low-onion containing diet among breast cancer (BC) participants treated with doxorubicin. This parallel design randomized controlled clinical trial was conducted on 56 BC patients whose malignancy was confirmed with histopathological examination. Subjects were assigned in a stratified-random allocation into either group received body mass index dependent 100-160 g/d of onion as high onion group (HO; n=28) or 30-40 g/d small onion in low onion group (LO; n=28) for eight weeks intervention. Participants, care givers and laboratory assessor were blinded to the assignments (IRCT registry no: IRCT2012103111335N1). The compliance of participants in the analysis was appropriate (87.9%). Comparing changes throughout pre- and post-dose treatments indicated significant controls on carcinoembryonic antigen, cancer antigen-125 and alkaline phosphatase levels in the HO group (P<0.05). Our findings for the first time showed that regular onion administration could be effective for hepatic enzyme conveying adjuvant chemotherapy relevant toxicity and reducing the tumor markers in BC during doxorubicin-based chemotherapy.

Keywords: Breast cancer - onion - CEA - CA125 - hepatic enzyme - doxorubicin - intervention

Asian Pac J Cancer Prev, **16 (17)**, 7517-7522

Introduction

Doxorubicin (Adriamycin, DOX) is a potent antineoplastic anthracycline drug used in adjuvant therapy of wide a variety of malignancies (Arunachalam et al., 2013). However, there is a remarkable dose-dependent cardiotoxicity in concerning to DOX use, which can result life-threatening clinical relevance of heart failure (Outomuro et al., 2007). In addition to DOX-induced cardiotoxicity, the hepatotoxicity could also be attributed to DOX treatment (Injac et al., 2008; Bulucu et al., 2009). The mediated mechanism to explain DOX-induced hepatotoxicity is the generation of free radicals (Bulucu et al., 2009). Raising prevalence rate of DOX-treated malignancies given an essential intriguingly area to pave a right way to be capable to relief the undesired deleterious effects of DOX administration with less attenuating effects on the efficacy of drug.

One of the vulnerable cells to be influenced by DOX-induced oxidative stress are hepatocytes (Crib et al., 2005), suggesting that monitoring the functionality of liver may be specially involved in the evaluation of DOX-related damages generation in part (Dudka et al., 2012). Hence, there is a notable biochemical parameter like alkaline phosphatase (ALP) which is conventionally addressed to monitor possibly the pathologic features occurred in liver (Singh et al., 2013). The rising levels of serum ALP activities could also associate with poorer prognosis of metastasis in breast cancer (Singh et al., 2013). Evaluations of ALP with other biochemical parameters [such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] are indicators of hepatocellula level of damages. They are considered as highly sensitive and fairly specific preclinical and clinical biomarker of hepatotoxicity (Ozera et al., 2008). They may thus be appropriate determinant variables in monitoring the progression of the disease and treatment efficiency (Tiwari et al., 2011; Singh et al., 2013).

There is unresolved research issue that how possibly could predict the risk of relapse and thus may benefit most

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from adjuvant chemotherapy for breast cancer (McGuire and Clark, 1992; Mansour et al., 1994). Circulating tumor markers could be relatively helpful and carcinoembryonic antigen (CEA) and cancer antigen-125 (CA-125) have become widely used parameters in clinical follow-up care and monitoring therapy specified for breast cancer patients (Ebeling et al., 2002). Actually, they are non-invasive, reproducible for monitoring and easily bioavailable parameters which made them as strong independent prognostic determinants for overall- and disease-free survival in breast cancer patients (Ebeling et al., 2002; Pierga et al., 2012; Zhang et al., 2013).

Several cohort base follow-up studies have revealed that there are strong preventive effects of vegetables on breast cancer risk (Wang et al., 2009; Bradbury et al., 2014; Norat et al., 2014). A growing body of evidence on health promoting effects of Allium vegetables consumption have supported the preventive effects of these vegetables on neoplasm development, such as breast cancer (Challier et al., 1998; Norat et al., 2014; Tajaddini et al., 2015). Of Allium vegetables, onion is being used in traditional medicine and commonly used in Iranian daily dietary habit, has being paid more attention in epidemiologic studies from the standpoints of immunomodulatory, antiproliferative, antioxidant, anti-hormonal effects reported in experimental studies (Lanzotti, 2006; Benitez et al., 2011; Khaki et al., 2012; Elberry et al., 2014). Evidence from case-control studies have shown that a high frequency of onion consumption was associated with a notable decrease in BC risk (Leviac et al., 1993; Tajaddini et al., 2015). Although there is consensus throughout most observational studies to explicate an inverse association between onion intake and cancer risk, no clinical trial has to date supported significantly the controlling effect of onion consumption on growth-related biomarkers in connection with breast cancer prognosis.

Although the experimental studies have shown antioxidative and anticancer functions for active constituents in onion such as quercetin and diallyl trisulfide (Hosseinimehr et al., 2007; Pirouzpanah et al., 2009), to our knowledge, there is no interventional study was carried out to examine the effects of manipulating onion consumption in dietary content of breast cancer patients who treated with doxorubicin. Thereby, the aim of this double blinded randomized controlled clinical trial was to study the effects of raw yellow onion consumption on serum CEA, CA125 and hepatic enzymes in breast cancer who undergone doxorubicin-based chemotherapy.

Materials and Methods

Study subjects

This randomized, double-blind, placebo-controlled clinical trial study was conducted at Tabriz University of Medical Sciences (Faculty of Nutrition, Tabriz, Iran). BC patients whose disease had been approved histopathologically after radical or partial mastectomy in Nour-Nejat hospital and who referred to Shahid Ghazi Cancer Research Centre and private cancer clinics (Tabriz, Iran) aged 30 to 65 years old were enrolled of the primary population of women afflicted with BC (whole date range for patient recruitment was between October 2012 till June 2013). The inclusion criteria consisted of intently completing consent form prior to study, invasive ductal carcinoma (IDC), not being at stage IV (without metastasis), no history of any other malignancy, acute and chronic disease (such as severe liver or kidney failure, hyperthyroidism, polycystic ovary syndrome and gastrointestinal inflammatory disorders), allergy to onion, not being at pregnancy or lactation conditions, no prior history of chemo-, radio-, and hormone-therapy, no medical use of methotrexate and aspirin (Pirouzpanah et al., 2010). Subjects who received vitamin E and flaxseed supplement were excluded from the study. The eligible participants were requested to remain at their common habitual diet and lifestyle in the range of adherence to guidelines. Finally, after obtaining informed consent, fifty-six women with newly diagnosed BC fulfilled the selection criteria and were randomly assigned into either intervention (HO) or placebo (LO) group via block-random allocation (Figure 1). In this probability sampling method, the ratio of 2:1 in stratifying sampling frames was considered to define non-taxol chemotherapy protocols: (vs.) other chemotherapy regimens. The estimated sample size of fifty-six was preceded to mean difference (Adebamowo et al., 2005), and also confirmed by performing number needed to treat in diabetes (Adebamowo et al., 2005; Ebrahimi-Mamaghani et al., 2014). All procedures were subject to the prior approval of the Ethics Committee Center at Tabriz University of Medical Sciences (Ethics no: 5-4-6829). This clinical trial also received license permission from Iranian Registry of Clinical Trials linked to WHO Registry Network (IRCT no: IRCT no: IRCT2012103111335N1). The authors confirm that all the protocol of trials for this intervention was registered in the framework specified in IRCT homepage (http://www.irct.ir).

Study design

The second course of chemotherapy was considered the baseline of interventions and blood sampling was conducted prior to receive a second round of chemotherapy. Prior to the baseline of the study, all participants were placed at a two week run-in period (including the ovulation phase of menses cycle made change in run-in period time without breaking the blinding) in order to collect the information needed to be aware of chemotherapy toleration, lifestyle related risk factors and the respondent rate of patients to follow the basics of treatment. During the run-in period, participants were asked not to have additional onion and less than half a serving of Alliums vegetables (such as spring onion, shallots, garlic, garlic chives, native water-cress leaves and leek) on a daily basis. The amount of Allium had to be less than 90g/d. An expert dietician met each participant individually during this time to undertake a primary dietary assessment (a three-day collection of 24-hour dietary record; for two weekdays and one for a typical weekend), teaching servings, limitations of dietary Allium vegetables, signs of intolerance to Alliums and simplifying the concept of treatment for reaching better adherence in eight weeks. The dietary records were created

based on portion size guide estimated values in household utensils. All participants were individually counselled not to change their habitual diet, with some considerations regarding World Cancer Research Fund International (WCRF) guidelines (specifically, the fat content of their diet) (Wiseman, 2008; Pirouzpanah and Kouhdani, 2011; Ebrahimi-Mamaghani et al., 2014). Participants were also requested not to take any supplements (flax seed extract, soy products, fish liver oil, vitamin E, cartonoids and antioxidants) during the run-in period and also during the entire intervention. A physical activity record was also obtained from each participant during the run-in period, in addition to baseline assessments. Then, BC subjects included in the study were randomly allocated to either the intervention or control group by means of the method of sequence generation of computer-generated randomization software.

Overall, 46 patients who completed the trial received one of the following chemotherapy regimens: four cycles of intravenous (I.V.) doxorubicin every 3 weeks followed by three cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF); four cycles of I.V. doxorubicin along with I.V. cyclophosphamide every 3 weeks, followed by three cycles of CMF; three cycles of I.V. doxorubicin every 3 weeks, followed by four cycles of I.V. docetaxel every 3 weeks, tracked by three cycles of CMF. The eight weeks intervention undertook till docetaxel was prescribed. Radiation therapy was also set as neoadjuvant therapy according to institutional guidelines.

Being respondent to onion intervention was evaluated by weighting the refrigerator-stored left onion at each three weeks visit appointed by who handed in onion packs. Compliance was also monitored by means of collected data from a weakly checklist in order to provide self-reporting of onion consumption in two daily meals. Each participant had three visits between the baseline and end point of eight weeks. In addition, physical examinations at these visits were conducted following chemotherapy-related changes such as cachexia. For not being respondent defined as who consumed was less than 85% (pure weight). At the beginning and end of the study, fasting blood samples were obtained and sera were stored at -70ºC until performing the analyses.

Interventions

At the baseline of the study, the BMI-dependent weighted onion (BMI<24.9 consumed 100-120g/d and BMI>25 consumed 140-160g/d) was handed in for daily usage in high onion group (HO) beside the main meals (lunch and dinner). Participants in the low onion group (LO; placebo group) took 30 to 40g/d onion in addition to meals in a BMI-dependent manner. This superiority trial undertook to compare the treatment effects in HO group rather than LO group. All participants were requested not to consume any onion a day after receiving chemotherapy in order to lessen the possibility of fails in the respondent to the intervention. The duration of this intervention study for both groups was eight weeks. Two onions for daily usage was packed in 5"×5" white foam container (opaque plastic) to provide supplies every three weeks in order to fulfil the concealment criteria. Weight of container was adjusted by pieces of wood to make equal weigh sense and fixed by surrounding cotton (introduced to the protocol). Participants were asked to store all onions in a refrigerator at 4ºC. For consumption, only two outer layers had to be being peeled. Raw yellow onions were obtained from a local market (one seller, Tabriz), who declared obtaining the onions from a particular cultivated farm. Sequence generation and allocation concealment were listed and marked by designer of study and implemented by clinic personnel unaware of the allocated intervention at the time of enrolment. Participants, clinic personnel and laboratory assessors were blinded to the treatment assignments. In order to improve and partially achieve blinding, participants in different date of chemotherapy was included. Nutritionist IV software (version 3.5.2; 1994, N-Squared Computing, San Bruno, CA) was conducted to analyze the average of nutrients intake level for each participant from data obtained from24-hour dietary records at baseline (Table 1). In addition, a validated food frequency questionnaire with 136 food items (Pirouzpanah et al., 2012; 2014a; 2014b) was used to evaluate the concordance of dietary data.

Biochemical assessments

Venous blood samples (8ml) were taken from subjects after at least 12 hours fasting and prior to a second round of chemotherapy in a clot tube (Vacuum Blood Collection Tube – Gel & Clot Activator Tube, AMIS Medical Co., China) at Danesh Laboratory, where is under quality control and verified by the National Reference Laboratory (Tabriz, Iran). The samples were immediately centrifuged (Refrigerated Centrifuge, Sigma, Germany) at 3000×g and at 20°C for 10 min to separate serum supernatant. Aliquots were stored at -70°C until laboratory tests were conducted. Commercially available ELISA kits and standards were used as a follow-up to measure serum tumor markers, i.e., carcinoembryonic antigen (CEA) and cancer antigen 125 (CA 125) using a Diametra ELISA kit (CEA: DKO 051, and CA125: DKO 051; Via Pozzuolo, Italy). Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were determined using Pars-Azmoon kits (Tehran, Iran) at baseline and at the end of intervention to assess possible toxicities. The within and between assays' CVs for all biochemical measures were <10%. For each biomarker, measures were performed at the same time in one laboratory run. The name of the patient in each sera sample was labelled with a specific numeric code. ALT below the 1.5 times of normal upper limit (<35 U/L; n=30) considers as chemotherapeutic toxicity (introduced to the protocol; n=0).

Statistical analyses

A Kolmogorov-Smirnov test was performed to ensure the normality of data distribution in each analysed subclass. A graphed linear histogram was used to examine the skewness and kurtosis. A box plot was used to detect outliers. Descriptive results were expressed in mean±standard deviation (S.D.) and median (95%CI) for the general characteristics of studied variables. Data that were not normally distributed were analysed using

nonparametric tests. Two independent sample t-tests were used to compare variables between the placebo and intervention groups. With-in group comparisons in an interventional arm between the baseline and eight weeks' intervention were carried out by paired t-test. For each comparison, P<0.05 was considered as statistically significant. All statistical analyses were performed using SPSS software (ver.15).

Results

Demographic characteristics

Table 1. Demographic and Clinical Characteristics of BC Patients in LO (placebo; n=23) and HO (intervention; n=23) Groups at Baseline of Intervention

Characteristics	LO (Placebo, n=23) Mean±S.D.	HO (Intervention, n=23) Mean±S.D.	P-value*
Age (years)			
At diagnosis	42.7±5.9	43.9±8.7	0.57
At first delivery	21.7±3.6	22.1±3.7	0.937
At first menses	13.9±1.3	13.5±1.7	0.455
BMI (kg/m^2)	27.4±4.8	27.8±3.7	0.832
Daily dietary intake			
Total calorie intake (kcal/day)	1893±417	1952±442	0.641
Protein intake (g/day)	68.6±21.6	67.9±17.5	0.918
Carbohydrate intake (g/day)	253 ±81	270±98	0.505
Fat intake (g/day)	56.5±20.75	56.6±18.8	0.977
Total dietary fiber (g/day)	4.6±2.9	4.6±2.9	0.956
Soluble fiber (g/day)	0.6±0.5	0.5±0.7	0.286
Crude fiber (g/day)	3.9±2.5	4.1±2.4	0.684

BMI, body mass index; * Independent sample t-test was performed

At last 23 patients in each group completed the study. Mean age at diagnosis for participants included in the study was 42.7±5.9 years (range: 32.0 to 58.0 years) for the LO group and 43.9±8.7 years (range: 30.0 to 63.0 years) for the intervention group (HO). The general and dietary characteristics of the BC participants at the baseline of the study are summarized in Table 1. Two groups were similar with respect to demographic variables and well-known risk factors for BC (Table 1). Daily intakes of total energy, carbohydrates, fat, protein and fibre contents did not differ significantly between the two groups at baseline (Table 1). The habitual dietary and lifestyle-related factors of all the subjects did not differ significantly in terms of the interventions. The compliance of participants in the analysis was as high as 87.85%.

Intervention effect

Raw yellow onion was administered to adjuvant-treated BC patients consistently and begun in the post-second course of chemotherapy (after two days) in a double-blind state. Table 2 summarised average serum levels of variables in terms of cancer specific antigens and hepatic enzymes at baseline compartment of study and 8 weeks after the intervention in women with BC who received onion (HO group) versus LO consumers. Mean serum AST, ALT and ALP levels did not change statistically significant between the placebo and intervention groups after eight weeks. Two indicators of liver toxicity, ALT and AST, increased approximately in each group; however, the elevation of AST in the placebo group was higher than in the intervention (26.08±9.82 to 34.26±14.58 IU/L; P=0.05), in spite of a statistically

Table 2. Serum Levels of Cancer Specific Antigens and Hepatic Enzymes at Baseline Compartment of Study and 8 weeks After the Intervention in Women with BC Who Received Onion (HO group) versus LO Consumers

Variable		LO (Placebo, n=23) Mean±S.D.	HO (Intervention, n=23) Mean±S.D.	Mean difference	P-value [a]
CEA [c]	Pre-dose	2.73±1.33	3.10±2.58	-0.37	0.817
	Week 8	2.61±1.58	2.49±1.85	-0.12	0.823
	Mean difference	0.18	0.69		
	P-value [b]	0.548	0.023		
logCA125 [d]	Pre-dose	18.53±8.94	21.13±16.64	-2.59	0.513
	Week 8	14.64±7.95	16.58±16.21	-1.94	0.616
	Mean difference	4.33	4.93		
	P-value	0.067	0.04		
logALT [e]	Pre-dose	25.65±23.37	25.56±16.38	5.95	0.988
	Week 8	37.26±20.66	26.87±18.25	5.74	0.078
	Mean difference	11.61	1.3		
	P-value	0.086	0.611		
logAST [f]	Pre-dose	26.08±9.82	31.43±12.31	-5.34	0.111
	Week 8	34.26±14.58	30.91±16.29	3.34	0.467
	Mean difference	8.17	0.52		
	P-value	0.051	0.872		
ALP [g]	Pre-dose	155.81±33.92	143.30±49.95	12.51	0.333
	Week 8	150.74±35.53	133.40±49.73	17.33	0.184
	Mean difference	-3.91	-9.68		
	P-value	0.57	0.41		

*LO, low onion group; HO, high onion group. Data are expressed in geometric mean±S.D., whereas CA125, ALT and AST are presented in arithmetic mean; [a] Independent sample t-test was performed between group; [b] Paired t-test was performed to compare within changes in intervention group during the study; [c] Carcinoembryonic antigen; [d] Cancer antigen 125; [e] Alanine aminotransferase
[f] Aspartate aminotransferase; [g] Alkaline phosphatase (ALP)

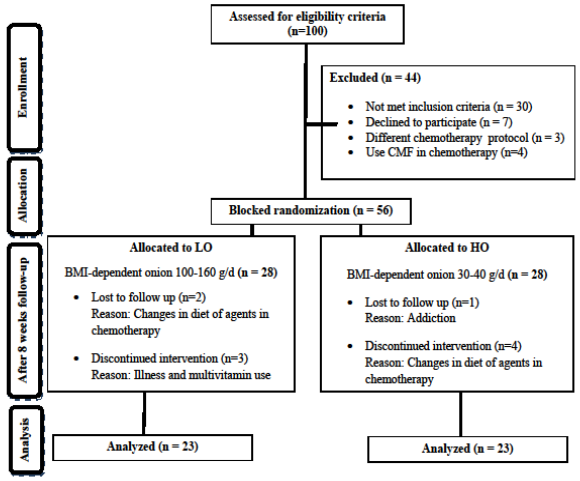

Figure 1. CONSORT Flow Chart Diagram of Intervention

non-significant result.

During the study, serum ALP as a biomarker of cardiotoxicity showed a non-significant reduction that was higher in the HO group (143.09to 133.40 IU/L). A CEA decrease during treatment was a remarkable change obtained only in the high onion feed group ($P<0.05$). Likewise, CA125 also showed a notable decline in the HO group ($P<0.05$).

Discussion

Findings from this randomized controlled clinical trial conducted on newly diagnosed BC patients receiving postoperative chemotherapy and raw yellow onion intervention concurrently showed favourable effects in terms of decreasing certain tumor markers.

Although sera levels of ALT, AST, ALP enzymes apparently increased in LO group during intervention; however, in the HO group they were practically unchanged and ALP levels decreased non-significantly. These findings are consistent with those studies previously conducted (Obioha et al., 2009; Dudka et al., 2012). Resveratrol administration (RV) concomitantly with doxorubicin (DOX; once a week over a period of seven weeks), showed no significant difference in serum activity of AST, ALT and ALP between the DOX and DOX+RV groups (Dudka et al., 2012). However, Obioha et al. (2009) indicated the hepatoprotective effect of onion extracts on cadmium (Cd)-induced oxidative damage in rats (Obioha et al., 2009). Cd is a toxic pollutant that has been addressed as possibly increasing the plasma levels of ALT and AST. Onion extracts have shown to significantly attenuate these adverse effects of Cd, apparently in a dose-dependent manner and seem to exert potent hepatoprotective effects (Obioha et al., 2009). Although, the hepatoprotective effects of onion has been scarcely noticed thus far, the present study suggested the controlling effects of onion consumption on sera levels of hepatic enzymes, particularly on ALP apparently might mask the DOX-related enzymatic changes of liver during intervention.

According to our findings, onion treatment significantly decreases the plasma levels of CEA and CA-125. Although to the best of our knowledge, no study has to date evaluated the hypothesis of tumour marker changes regarding high onion consumption, our findings put forth the possibility of the regulatory effects of onion consumption on the prognosis of BC alongside treatment with DOX over a shorter timeframe. Accordingly, there is a meta-analysis undergone on different population-based studies for gastric cancer risk assessment in Korea which also represented the protective association for Allium vegetables (Woo et al., 2014).

There were some possible limitations in present study. The sample size assigned to each tail of intervention group was relatively small. To provide homogenous adjuvant chemotherapy which was co-administered in this interventional study, there was an attempt to consider only DOX-base regimens. We suggest that at least stratified random allocation could be helpful to weaken the variation conveyed based on chemotherapy type. Although chemotherapy related metabolic changes influence weight loss is an impressive secondary event after receiving the 1st course of chemotherapy, underwent intervention after the 2nd course of regimen was not associated with significant reduced anthropometric changes in controls.

In conclusion, the present study demonstrated the effectiveness of onion to control CEA and CA125 tumor markers. But they were not significant between groups at the end of study among BC patients during doxorubicin-based chemotherapy. Manipulation of diet through high intake of onion is promising to possibly improve a synergistic effect on DOX-based chemotherapy.

Acknowledgements

The authors would like to thank all the subjects involved in this study for their participation and the staff members of Nour-Nejat Hospital, Cancer Clinic, Danesh-2 laboratory, Shahid Ghazi and Emam Reza (peace be upon him) Hospitals for spending their time to this research. This article was outlined using a dataset obtained from a M.Sc. thesis titled "The effect of raw yellow onion consumption on plasma levels of hormonal/metabolic parameters in patients with primary breast cancer: A randomized controlled clinical trial", registered at Tabriz University of Medical Sciences (Registration no.: 5/97/803).The authors' responsibilities were as follows—S.P., and V.M.: designed research; S.P., F.J.S., A.A., A.E. and M.R.R.: conducted research and experiments; S.P., M.R.R. and F.J.S.: analyzed data; and S.P., V.M., M.R.R. and F.J.S.: wrote manuscript.

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