http://www.ijwhr.net
doi 10.15296/ijwhr.2017.55
Open Access Original Article

IJWHR
International Journal of Women's Health and Reproduction Sciences
Vol. 5, No. 4, October 2017, 324–331
ISSN 2330-4456

Comparison of the Complications of Platinum-Based Adjuvant Chemotherapy With and Without Ginger in a Pilot Study on Ovarian Cancer Patients

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Abstract

Objectives: The principal treatment of ovarian cancer is surgery with or without chemotherapy. The chemotherapy, however, might be ineffective and long with serious side-effects. To obviate these shortcomings, more efficient and safer medications are required, among which ginger has recently gained popularity because of its anti-cancer properties. This study aims to compare outcomes and side-effects of adjuvant chemotherapy with and without ginger in ovarian cancer patients.

Materials and Methods: A total of 49 patients (20 patients in case group and 29 patients in control group) with stage I to III, histopathologically proved ovarian cancer underwent cytoreductive surgery followed by platinum-based adjuvant chemotherapy with and without investigator-prepared oral ginger capsules (2 g per day for 6 cycles). Potential side-effects, poor 12-month outcome (serum CA125 levels >35U, radiologic evidence of metastasis and recurrence, or death), and 12-month disease-free survival were documented and compared between the 2 groups.

Results: Poor outcome including serum CA125>35, metastasis, recurrence or death was documented more common in control group (69% versus 40%). metastasis frequency confirmed by computerized tomography (CT) scan 6 month after treatment was significantly lower in case group ($P=0.04$). There was no significant difference regarding mortality and disease free survival during one year follow-up after treatment between 2 groups ($P=0.55$). Chemotherapy complications such as nausea, vomiting, weight loss, and peripheral neuropathy were detected in case group less than control group but the difference was not significant.

Conclusion: Oral administration of ginger is along with a significantly better 12-month outcome in patients on chemotherapy because of ovarian cancer, and accordingly, considering its safety, its administration is recommended.

Keywords: Ovarian Cancer, Ginger, Chemotherapy, Outcome

Introduction

Of all the female malignancies, most clinical discussions focus on ovarian cancer. It has the highest case fatality ratio and it is the fifth most common cause of malignancy-related death among women. The cancer is associated with low parity and infertility. Early menarche and late menopause increase the risk of ovarian cancer. Ovarian cancers include epithelial and non-epithelial tumors. More than 80% of epithelial ovarian cancers are seen in postmenopausal women. The peak incidence of epithelial ovarian cancer is between 55 to 60 years of age. Data show that feature of CA125 increases if the test is performed by transvaginal ultrasound. Its symptoms include complex pelvic mass such as solid pattern, heterogeneous component with irregular thick septum, bilateral masses, and size of lesions exceeding 8 cm. The effective factors in the prognosis of ovarian cancer are divided into the 3 categories of pathological, biological and clinical factors. The pathological factors include the structure and degree of lesion. The biological factors include ploidy and proto-oncogenes such as HER-2neu. The clinical factors include the stage of tumor, the extent of residual disease after primary surgery, volume of ascites, age of the patient, and functional status of patient. Ovarian cancer treatment includes primary cytoreductive and then chemotherapy (1). Chemotherapy may be associated with the complications such as nausea and vomiting, bone marrow depression, peripheral neuropathy, weight loss, hemolytic anemia, and transient cortical blindness (2). Ginger is a plant with anti-carcinogenic and anti-oxidative effects and modern studies have shown other treatment effects such as the ability to inhibit formation of inflammatory products, direct anti- inflammatory effects, and anti-tumoral effects. It has been proved that the active ingredient in ginger can kill cancer cells due to apoptosis and autophagocytosis. This has also been emphasized in ovarian cancers (2).

On the other hand, although chemotherapy drugs suppress inflammatory markers, cancer cells may show resistance to them. It has been proved that ginger can

Received 5 February 2016, **Accepted** 24 September 2016, **Available online** 25 October 2016

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reduce such adverse effects (3). Evaluation of the treatment result for the patients with epithelial ovarian cancer after primary cytoreductive surgery and chemotherapy includes measuring tumor markers (CA125), radiological examination including computerized tomography (CT) scan or abdominal and pelvic Magnetic resonance imaging (MRI), and applying re-evaluation including laparotomy and laparoscopy (1).

The need for further experiences and clinical studies for confirming the effectiveness of ginger in this concern, lack of studies, and high fatality of ovarian cancer in the region made us study the effect of ginger on treating the patients with ovarian cancer compared with the normal treatment without ginger.

Materials and Methods

This randomized controlled clinical trial examined the effect of ginger on platinum-based adjuvant chemotherapy complications in ovarian cancer patients. The study was conducted in Al-Zahra and Shahid Ghazi health centers in Tabriz. It was performed within 16 months. Initial data collection and data analysis were performed from October 2014 to February 2015. At the beginning of the study, an informed consent was collected in written or verbal forms (for illiterate patients) from any patient. The consents were taken from the patients only and filling out the forms by a spouse or a legal representative was not needed. In addition, an additional cost was not imposed on patients in this project, but it was borne by the executor. The study was approved by the Committee of Ethics of Tabriz University of Medical Sciences.

The inclusion criteria included the females with approved ovarian cancer who underwent primary cytoreductive surgery, willingness to participate in the study. The exclusion criteria included allergy to ginger, history of chemotherapy, history of other malignancy in women, reception of vitamin E and omega-3 before or concurrent with chemotherapy, chemotherapy intolerance and patients with stage 4 ovarian cancer.

A total of 49 patients with ovarian cancer who underwent primary cytoreductive surgery with approved serous or mucinous ovarian epithelial cancer in their pathologic reports and candidate for chemotherapy entered the study. The patients were divided into 2 random groups. They were then divided into 2 homogeneous groups (using *Randlist*) based on their satisfaction to receive ginger in terms of the history of lack of neoplastic diseases in women, history of lack of chemotherapy and stage of cancer: (A) Control group including 29 patients who were identified by letter A. They received carboplatin at a dose of 5-6 AUC and paclitaxel at a dose of 175 mg/m^2 for 6 cycles and 2 capsules of placebo daily along with the treatment; (B) Intervention group including 20 patients who were identified by letter B. They were exposed to the same chemotherapy protocol plus edible ginger (1 g ginger capsule made in Tabriz Faculty of Pharmacy) 2 capsules daily along with the 6 cycles of treatment. Both protocols were repeated every 21 days and it was decided to discontinue the drug and exclude the patients in case of unforeseen complications while taking ginger and/or chemotherapy intolerance. Examiners and the patients were unaware of the coding and the real grouping was only specified after statistical analysis. At the end of the treatment, the tumor marker CA125 of any patient was measured and their abdominal and pelvic CT scans were prepared every 3 months up to 12 months after the baseline (or time of death in relevant cases). An adverse complication was considered as metastasis or malignancy recurrence symptoms in the imaging in every stage and CA125 serum level over 35 units in the final examination/death. It should be noted that the abdominal and pelvic CT scan was performed by a radiologist and a single laboratory reported the rate of CA125. The laboratory and radiology results were considered as the primary complication. Meanwhile, any lesion was recorded. Finally, the study variables (continuation) between the 2 groups were compared.

Statistical Analysis

SPSS statistics software version 16.0 was used to analyze the data. Normal distribution of the quantitative data was confirmed by Kolmogorov-Smirnov test. Comparison of the quantitative data for independent groups was made by *t* test. Comparison of the quantitative data was made using the chi-square test or the Fisher exact test. The Kaplan-Meier survival curve was drawn during a 12-month follow-up. $P<0.05$ was considered statistically significant.

Results

Twenty patients in the intervention group and 29 patients in the control group were studied. The average ages of the patients in the intervention and control group were 52.70 ± 10.55 years (26 to 72) and 52.69 ± 15.56 years (24 to 88), respectively. The *t* test result for independent groups showed no statistically significant difference between the 2 groups regarding age ($P=0.99$). The average ages of menarche in the intervention and control groups were 11.90 ± 1.02 years (10 to 14) and 11.90 ± 1.45 years (10 to 16), respectively. The *t* test result for independent groups showed no statistically significant difference between the 2 groups regarding the age of menarche ($P=0.99$). The average ages of menopause in the intervention and control groups were 49.29 ± 3.67 years (45 to 57) and 49.25 ± 3.51 years (40 to 53). The educational level of the patients was the same in both groups (Table 1).

The average previous pregnancies in the intervention and control groups were 3.65 ± 0.63 (0 to 8) and 3.86 ± 0.53 (0 to 10), respectively. The *t* test result for the independent groups showed no statistically significant difference between the 2 groups as far as the average previous pregnancies were concerned ($P=0.80$). The average parity in the intervention and control groups was 3.20 ± 0.57 (0-8) and 3.07 ± 0.48 (0-10), respectively. The *t* test for independent groups showed no statistically significant

Table 1. Comparison the Educational Level of Case and Control Group

Level of Education	Case No. (%)	Control No. (%)
Illiterate	2 (10)	2 (6.9)
High school	1 (5)	11 (37.9)
Diplomas	11 (55)	8 (27.6)
University education	6 (30)	8 (27.6)

difference between the 2 groups as far as parity was concerned ($P=0.86$). The average previous abortions in the intervention and control groups were 0.35 ± 0.13 (0-2) and 0.76 ± 0.20 (0-5), respectively. The *t* test result for the independent groups showed no statistically significant difference between the 2 groups as far as the average previous abortions were concerned ($P=0.13$). No history of infertility was observed in the intervention group and one patient (3.4%) in the control group was reported to have history of infertility. The Fisher exact test showed no statistically significant difference between the 2 groups as far as the history of infertility was concerned ($P=0.59$). As far as the history of hormonal drugs consumption was concerned, only 2 patients (10%) had the history of OCP consumption. One of the members of control group (3.4%) had the history of OCP consumption and one member (3.4%) had the history of infertility treatment. As far as the residence was concerned, 17 patients of the intervention group (85%) lived in urban areas and 3 (15%) lived in rural areas. In the control group, 21 patients (72.4%) lived in urban areas and 8 patients (27.6%) lived in rural areas. The Fisher exact test showed no statistically significant difference between the 2 groups as far as the residence was concerned ($P=0.49$). As far as the cancer stage in the intervention group was concerned, 5 patients (25%), 10 patients (50%), and 5 patients (25%) were in stages I, II, and III, respectively. In the control group, 8 patients (27.6%), 14 patients (48.3%), and 7 patients (24.1%) were in stages I, II, and III, respectively. The chi-square test result showed no statistically significant difference between the 2 groups as far as the cancer stage was concerned ($P=0.98$).

Treatment Complications

Examiners evaluated the patients in the case and control group by history and physical examination during the chemotherapy and detected any complications of treatment. We followed the patients every 3 months by physical exam, serum level of CA125 and CT scan up to12 months.

Nausea and Vomiting

Eight members of the intervention group and 14 members of the control group had nausea and vomiting. The chi-square test result showed no statistically significant difference between the 2 groups ($P=0.57$).

Weight Loss

One member of the intervention group and one member of the control group had weight loss. The Fisher exact test showed no statistically significant difference between the 2 groups ($P=0.66$).

Peripheral Neuropathy

Three members in the intervention group and 5 members in the control group had peripheral neuropathy. The Fisher exact test showed no statistically significant difference between the 2 groups ($P=0.58$).

Bone Marrow Depression

Two patients in the intervention group and 2 members of the control group had bone marrow depression. The Fisher exact test showed no statistically significant difference between the 2 groups ($P=0.54$).

Transient Cortical Blindness

One patient in the intervention group and no member of the control group had transient cortical blindness. The Fisher exact test showed no statistically significant difference between the 2 groups ($P=0.41$).

Any Other Complication

Ten patients in the intervention group and 21 members of the control group were with some other hematologic, renal and digestive complications. The Fisher exact test showed no statistically significant difference between the 2 groups ($P=0.11$).

In the intervention group, CA125 means at baseline, 3 months, 6 months, 9 months, and 12 months after treatment were 418.14 ± 174.18 units (7-3191), 149.78 ± 39.45 units (4-501), 43.60 ± 127.23 units (1-612), 20.96 ± 68.02 units (1-373), and 11.42 ± 28.66 units (9-216), respectively. In the control group, CA125 means at baseline, 3 months, 6 months, 9 month and 12 months after treatment were 336.63 ± 89.82 units (2-2377), 217.47 ± 58.32 units (4-1222), 134.49 ± 36.09 units (2-751), 87.17 ± 22.65 units (2-498), and 63.39 ± 21.20 units (4-502), respectively. The results of repeated measurements showed no statistically significant difference between the intervention and control groups as far as the reduction of level of this serum variable during the study intervals was concerned ($P=0.80$).

The abnormal (increased) CA125 was registered at the end of the follow-up in the intervention group for 5 patients and in the control group for 12 patients. The chi-square test showed no statistically significant difference between the 2 groups ($P=0.24$).

Table 2 summarizes and compares the results of CT scans in terms of the presence of metastasis at different times in the 2 groups. The chi-square test showed metastasis frequency in the baseline and sixth month CT scans after treatment was significantly higher in the control group. No statistically significant difference was seen in other cases. During a 12-month follow-up period,

2 and 3 mortalities were seen in the intervention group and the control group, respectively. The Fisher exact test showed no statistically significant difference between the 2 groups ($P = 0.68$). Figure 1 shows the relevant Kaplan-Meier curves in both groups during a 12-month follow-up period after treatment.

The adverse prognoses for 8 patients in the intervention and 20 patients in the control group were registered. The chi-square test showed that the frequency of adverse prognosis in the control group was significantly higher than the one of the intervention group (odds ratio [OR] = 3.3, $P = 0.04$).

The average disease-free survival during a one-year follow-up after treatment in the intervention and control groups were 11.85 ± 0.49 months (10 to 12) and 11.72 ± 0.84 months (9 to 12), respectively. The *t* test showed no statistically significant difference between the 2 groups ($P = 0.55$).

Table 2. The Results of the CT Scans Performed for the Presence of Metastases at Different Times in the Intervention and Control Groups

Different Times	Intervention (n = 20) No. (%)	Control (n = 29) No. (%)	*P* value
Baseline	9 (45)	21 (72.4)	0.05*
1st quarterly	8 (40)	15 (51.7)	0.42
2nd quarterly	5 (25)	16 (55.2)	0.04*
3rd quarterly	7 (35)	13 (44.8)	0.49
4th quarterly	6 (33.3)	14 (53.8)	0.18
Total	8 (40)	17 (58.6)	0.20

* $P \leq$ is significant.

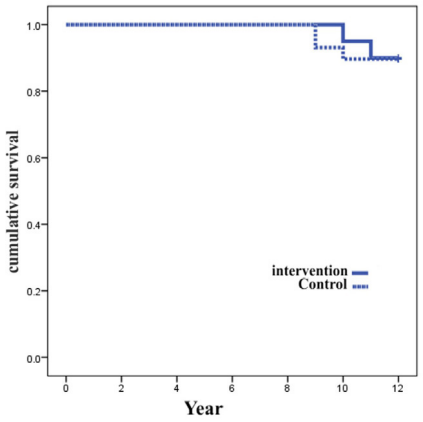

Figure 1. Kaplan-Meier Curves for the 12-Month Mortality in Intervention and Control Groups.

Discussion

This clinical trial examined the effect of edible ginger extract on the complications of platinum-based adjuvant chemotherapy in ovarian cancer patients. The research results showed that ginger improved significantly the adverse prognosis of the patients who received ginger as compared with the control group. The impact on chemotherapy complications was favorable, but statistically non-significant. Ginger or *Zingiber officinale* has been considered effective in preventing a range of chemotherapy-associated complications such as nausea and vomiting (4-7), metabolic disorders (8), and even reproductive system problems (9). It has even been used for appetite stimulation (10) and refreshment in cancer patients (11). In addition, this plant has been used in traditional medicine as an anti-cancer drug for many years and its great effect in modern medicine has been approved (12-16). Finally, its role in exacerbating the effects of chemotherapy is one of the issues of interest in modern medicine (17-20). The benefits of ginger in this field include its nature, strong antioxidant activity, high bioavailability, metabolism simplicity, and low cost as compared with chemotherapy drugs (21).

Studying the available data resources showed that the clinical use of ginger has been mostly for preventing chemotherapy-related complications, especially nausea and vomiting. The role of ginger in this field is not a new case and it has a deep root in traditional medicine. Even today, it is used for making antinausea compounds in the German Pharmacopoeia (22).

The major pharmacological function of ginger in this field is attributed to its active components such as gingerol and shogaol. The components contain antinausea, antipyretic, antitussive, anti-inflammatory, anti-hypertensive and anti-cancer effects. It has also been proved that ginger may reduce the level of prostaglandins and remove digestive problems due to having these types of compounds. Modern studies show that the antiemetic effects of the 2 active ingredients in ginger extract are applied through 2 mechanisms: reducing gastric contractions and increasing the activity of other digestive organs. In addition, the plant has anti-serotonin effects and neutralizes the free radicals leading to nausea (22,23).

Some studies such as the one conducted by Sontakke et al on cancer patients undergoing chemotherapy concluded that ginger administration outperforms the standard antinausea medications such as Metoclopramide (24).

The study of Sripramote and Lekhyananda on 43 cancer patients undergoing chemotherapy proved that ginger administration for this group of patients was effective in reducing late-phase nausea and vomiting (25).

However, the results of different studies in this field have not always had similar outcomes. For example, Eberhart et al concluded that administration of ginger in women who had undergone reproductive system laparoscopy had no effect on the incidence of postoperative nausea and vomiting (26). One of the reasons for such conflicting results is the difference of studies as far as methodology, sample size, and quality of the products containing ginger are concerned. For instance, the study of Nanthakomon and Pongrojpaw concluded that ginger is able to reduce the risk of nausea and vomiting up to 18.4%; however, the difference was not statistically significant due to the low sample size (27).

Other studies proved that ginger administration reduces nausea and vomiting as compared with standard

antinausea medications in the patients undergoing chemotherapy; however, the difference was not statistically significant due to the low sample size (28,29).

The incidence of nausea and vomiting in the intervention group of our study was lower than the one in the control group (40% versus 48.3% with the reduction rate of 8.3%), but the difference was statistically non-significant. Therefore, further studies with larger sample size are needed in this field to reach firm conclusions. This is also important from another point of view. This is the first study, which examines the frequency of other chemotherapy-associated complications in 2 groups of intervention and control. Based on this, the incidence of the complications in the intervention group was generally lower than the control group (50% versus 72.4%). As mentioned earlier, insufficient sample size hinders us from reaching a definitive conclusion in this regard, as some complications such as reversible blindness and neuropathies, unlike nausea and vomiting, are not so common. In addition to affecting chemotherapy-associated complications, the role of ginger in treating cancer patients and contributing to the effects of chemotherapy is more important, as they can be seen while examining the available data resources of many recent studies in this field. A recent research by Rastogi et al in 2015 examined the effect of administering ginger extract on cervix cancer cells. They concluded that ginger applies such antitumorigenic and proapoptotic effects against a range of cancers, as it contains 6-gingerol or 6G alkanol-polyphenolic. Mechanism of action of ginger in this field is summarized as follows:

1) Inhibiting the activity of proteasomes chymotrypsin, 2) Reactivating p53 induction, 3) Increasing p21 levels, 4) Damaging DNA and arresting cell cycle of cancer cells in G2/M phase, 5) Changing levels of apoptotic markers related to p53 such as caspase-3 and PARP, 6) Increasing cytotoxicity of the drugs used in chemotherapy such as cisplatin.

It has been stated that the resultant of all functions enhances death of cancer cells and improves the efficiency of chemotherapy (30).

Other studies emphasized the anti-inflammatory and anti-cancer specifications of 6G. For instance, it has been proved that such an ingredient in ginger extract may inhibit iNOS and IkBα while releasing cytochrome c, activate caspase, increase Apaf-1 expression, induct oxidative stress, damage DNA, stimulate autophagy, and activate tumor-suppressor proteins in the cancer cells. The resultant of all these factors ends in inducting and increasing apoptosis (21,31-37).

In 2015, Wee et al proved that ginger extract might be used in treating colon cancer. This study, which was conducted at a cellular level, reports the anticancer mechanism of ginger in inhibiting mTOR and inducting apoptosis pathways (38).

The anti-cancer effect of ginger on patients with colon cancer and other gastrointestinal cancers was emphasized in other studies (39-42).

In 2015, Ray et al showed that ginger extract is able to inhibit and destroy breast cancer cells. The proposed mechanism in this study is apoptosis induction by ginger (43).

In 2014, Sehrawat et al reported that ginger extract is useful for removing breast cancer cells. Such a beneficial effect has been applied through activating Notch2, which leads to inactivation of proapotic and migration responses of cancer cells (44).

In a study by Chan et al, ginger extract could destroy prostate cancer cells at the cellular level. Such an anticancer effect was achieved through binding to tubulin and establishing a connection between endoplasmic reticulum stress and mitochondrial damage (45). A similar result was reported by Saha et al (46).

Akimoto et al proved that ginger extract at the cellular level can be useful through inducting apoptosis by increasing ROS activity in pancreatic cancer treatment (47). Hsu et alemphasized the anticancer effects of ginger at the cellular level on lung cancer (48). In a similar cellular study, Han et aldiscussed and reported the useful effects of ginger extract for kidney cancer (49).

In 2014, Parvizzadeh et al proved that ginger could improve the chemotherapy effect of cancers. This study reported the favorable effects of ginger extract in this concern through changes in the metabolic pathways of cancer cells in terms of protein and amino acid biosynthesis and metabolism of carbohydrates to enhance the cytotoxic effects of chemotherapy (50).

In 2015, Fan et al highlighted the anticancer effect of ginger extract on osteosarcoma in a cellular study (51).

In 2014, Poltronieri et al emphasized the role of ginger extract in preventing and inhibiting cancer metastasis (52).

As it is noticed, the use of ginger in treating or helping to treat a range of cancers has been emphasized. What is of paramount importance in this concern, as stated earlier, is that all the studies are new, which emphasizes its importance and interest of modern medicine in using such a traditional herbal substance. However, studying the available data resources revealed that only 2 studies have discussed this matter on ovarian cancer. Rhode et al discussed the effect of ginger extract on ovarian cancer cell lines at a laboratory level. The study findings showed that ginger inhibited cancer cells strongly. These effects were applied through inhibiting NF-kB activation and reducing VEGF and IL-8 secretion, which play a major role in angiogenesis of cancer cells (3). Pashaei-Asl et al studied the inhibitory effect of ginger extract on ovarian cancer cell line. They found that the ginger extract has anticancer properties inducing apoptosis through p53 pathway and p53 expression is the main reason for the cytotoxicity effects of ginger in ovarian cancer cells and the cause of cell death in SKOV-3 cells (53). Based on these, the study proposed clinical trials in this field (3,53).

Although the available data on carcinogenesis and its definitive mechanisms on ovarian cancer are limited, it seems that the major components in this regard include inflammation and cancer cells coping strategies. Lack of

response to growth inhibitory signals, evasion of apoptosis, unlimited capacity to proliferate, and continuous angiogenesis were observed among the cases considered in this concern. All these mechanisms have been strongly controlled by NF-κB gene, which is continuously active in most cancers, including ovarian cancers. Therefore, it seems that focusing on this factor plays a major role in controlling and inhibiting ovarian cancer (54).

Ironically, unrelated studies have shown that ginger extract had a major impact on controlling the pathway related to NF-κB and inhibiting cancer-associated angiogenesis. Such a specific impact is apart from other favorable effects of ginger as an anticancer substance such as antioxidant, anti-inflammatory, and anti-carcinogenesis functions (31,55-73).

The present study is of paramount importance, as it is the first randomized clinical trial on examining the effect of ginger on the chemotherapy complications of ovarian cancer and it proved the useful effects of ginger in a clinical manner in reducing unfavorable complications. Although further studies are required using a larger sample size and a longer follow-up period to reach definitive results, it can be administered for these types of cancer patients, as the substance was not associated with a major complication in this study.

Ethical Issues

This study was registered under code No. IRCT2014031510901N4 on the website of Iranian Registry of Clinical Trials (http://irct.ir).

Conflict of Interests

The authors declare no conflict of interests.

Financial Support

Women's Reproductive Health Research Center, Tabriz University of Medical sciences supported this study.

Acknowledgements

We would like to thank authorities of Tabriz University of Medical Sciences for the scientific and ethical approval and financial support of this research. This study has been done as a thesis for specialist degree of Farnaz Shokry in Women's Reproductive Health Research Center, Tabriz University of Medical Sciences.

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