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Research paper

Silymarin (Milk Thistle) can revoke liver enzyme changes during chemotherapy of breast cancer with Taxanes

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ABSTRACT

Introduction: Drug associated liver injury is common and anticancer agents have been associated with inducing liver dysfunction, too. The present study was designed to evaluate the effect of silymarin (Milk Thistle) in reducing the hepatic side effects of taxane when used in chemotherapy of breast cancer.
Methods: This study was conducted on 99 patients with invasive breast carcinoma receiving chemotherapy contained adriamycin, epirubicin, cyclophosphamide, docetaxel, and paclitaxel. The patients were randomized into 2 groups and given silymarin 70 mg PO three times daily or placebo during their treatment course. The patients were assessed by liver function tests (LFT) after each dose of taxane and results were analyzed statistically.
Results: The patients had mild rises in serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminases (SGPT), and bilirubin in both groups during the study. However, the changes were less notable in the study group. The differences were statistically significant for rises in SGOT and SGPT (23.3 ± 2.3 vs. 1.7 ± 1.5 for SGOT and 27.8 ± 0.6 vs. 23.7 ± 0.3 for SGPT in the control and case groups respectively).
Conclusion: There was a rise in some of the LFT indices after the chemotherapy, with more than 2-fold rise in SGOT, SGPT, and bilirubin which indicated liver injury. The addition of silymarin alleviated these effects considerably.

1. Introduction

Increased occurrence of cancer worldwide prevalence during the last decade has posed a great challenge to the health care professionals [1]. Breast cancer is the most common malignancy afflicting women and one of the leading causes of cancer mortality [2]. Over recent years there have been some remarkable changes both in the treatment and the philosophy of metastatic breast cancer (MBC) and in the availability of therapies, contributing to improvements in survival rates and quality of life [3].

As a metabolizer of harmful and foreign substances in the blood, the liver is particularly susceptible to drug-induced injury, regardless of the site of action for therapeutic effect. Liver adverse reactions are linked to approximately 1100 drugs, 3% of all hospitalizations, and 3% of all jaundiced patients [4]. The liver is fundamentally important in drug metabolism. In oncology, the astute clinician must not only understand the meaning and limitations of commonly ordered liver biochemical tests, but also be aware of which anticancer agents might induce liver dysfunction, and of the strategies for appropriate dosing of patients with pre-existing liver dysfunction [5]. The presentation of possible drug-induced liver injury may vary from asymptomatic liver enzyme elevation (which incidentally may come to the attention of clinicians during planned laboratory tests for other medical reasons) to acute liver failure causing hospital admission and potentially requiring transplantation [6–8]. Although the use of newer chemotherapeutic agents can potentially reduce metastases, these agents can also affect the normal adjacent liver parenchyma, leading to hepatotoxicity. Pre-existing liver disease, genetic variability, the presence of extensive hepatic metastases, sepsis, immunosuppression, exposure to blood products, and administration of agents metabolized in the liver are factors that affect the hepatic function [9].

Treatment options of breast cancer include surgery, radiotherapy and systemic treatment. The taxanes; paclitaxel and docetaxel are among the most commonly used cytotoxic drugs for breast cancer [10]. Paclitaxel, as an example of taxane family, is mainly metabolized by the liver through the cytochrome 2C8 and 3A4 pathways; it undergoes biliary excretion. A prospective study

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of its toxic effects and pharmacokinetics showed that patients with abnormal bilirubin (i.e., >25 μmol/L) or aspartate aminotransferase levels 2-times or higher than the upper limit of normal had more toxic effects (particularly myelosuppression) compared with other groups [4]. We have tried to find a safer way for administration of taxanes in patients with abnormal liver function. The present study was designed to evaluate the addition of silymarin, the most researched herbal treatment for liver diseases [11], for alleviation of hepatic side effects of taxane in chemotherapy of breast cancer.

2. Materials and methods

The present study was conducted in a cancer treatment center, Arak city, Iran in 2014. Patients ($n = 99$) with invasive breast carcinoma who were candidates for chemotherapy according to the planned cancer treatment regimen by their physicians were recruited into the study.

They received chemotherapy as adriamycin 60 mg/m^2 or epirubicin 100 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 times. Then, they were divided into two groups randomly. Both groups received docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 every 3 weeks for 4 times. Moreover, the patients in the study group were given silymarin 70 mg PO three times daily during their treatment course. The control group received placebo.

Silymarin with trade name Livergol was obtained from Goldaru pharmaceutical co., Iran in form of 70 mg tablets. Other drugs were prescribed from the clinic pharmacy.

Before the study, the patients were examined for liver metastasis by liver function test (LFT) and abdominal CT scan. Any patient with abnormal findings was excluded from the study. The patients were assessed by LFT after each dose of taxane.

The study had been approved by local ethical committee of Arak's university of medical sciences. All the studied patients provided informed consent for participation to the study.

The results were analyzed by SPSS software version 16.0. Any differences between the groups were determined by *t*-test. Statistical significance was set at *p*-value less than 0.05.

3. Results

Ninety nine patients (49 in the study group and 50 in the control group) ended their treatment course and were included in the study analysis. There was no loss to follow up. The mean age of the patients was 54.1 ± 11.3 and 57.5 ± 9.7 in the case and control groups respectively. Their general characteristics are given in Table 1. There was no notable difference between the groups. Most of the studied patients had invasive intraductal carcinoma in both groups. Moreover, most studied individuals were in B2, A3 and A2 stage of the cancer in both groups.

Analysis of LFT before, during, and after the study has been shown in Table 2. It confirms that the patients treated with taxanes

Table 2
Results of LFT analysis (mean ± SD) in the study and control groups before and during the study.

	Study group	Control group	*P* value
SGOT			
Before the treatment	24.42 ± 4.51	22.0 ± 5.01	0.14
After the 1st dose of taxane	24.22 ± 3.27	25.7 ± 3.56	0.21
After the 2nd dose of taxane	31.08 ± 3.26	33.56 ± 4.11	0.09
After the 3rd dose of taxane	38.12 ± 4.51	40.20 ± 6.43	0.09
After the 4th dose of taxane	44.46 ± 2.65	48.04 ± 4.32	0.04
1 months after end of the treatment	43.96 ± 3.44	46.70 ± 3.23	0.03
SGPT			
Before the treatment	24.54 ± 3.19	23.94 ± 2.98	0.22
After the 1st dose of taxane	33.00 ± 4.58	32.76 ± 3.94	0.12
After the 2nd dose of taxane	39.50 ± 3.59	41.00 ± 4.13	0.11
After the 3rd dose of taxane	45.10 ± 4.01	48.92 ± 3.58	0.04
After the 4th dose of taxane	49.94 ± 4.18	55.44 ± 3.54	0.03
1 months after end of the treatment	48.88 ± 3.28	54.70 ± 3.55	0.03
Alkaline phosphatase			
Before the treatment	266 ± 21	105 ± 11	0.12
After the 1st dose of taxane	307 ± 18	126 ± 16	0.06
After the 2nd dose of taxane	346 ± 23	223 ± 20	0.06
After the 3rd dose of taxane	371 ± 31	278 ± 25	0.09
After the 4th dose of taxane	405 ± 25	322 ± 31	0.11
1 months after end of the treatment	424 ± 28	309 ± 33	0.07
Total bilirubin			
Before the treatment	0.87 ± 0.09	0.84 ± 0.10	0.18
After the 1st dose of taxane	1.10 ± 0.15	1.09 ± 0.14	0.19
After the 2nd dose of taxane	1.36 ± 0.22	1.31 ± 0.09	0.12
After the 3rd dose of taxane	1.56 ± 0.11	1.55 ± 0.07	0.18
After the 4th dose of taxane	1.74 ± 0.08	1.85 ± 0.05	0.11
1 months after end of the treatment	1.87 ± 0.12	1.99 ± 0.12	0.20
Indirect bilirubin			
Before the treatment	0.55 ± 0.08	0.53 ± 0.11	0.22
After the 1st dose of taxane	0.73 ± 0.10	0.72 ± 0.09	0.16
After the 2nd dose of taxane	0.94 ± 0.12	0.94 ± 0.08	0.21
After the 3rd dose of taxane	1.11 ± 0.07	1.10 ± 0.10	0.18
After the 4th dose of taxane	1.26 ± 0.11	1.35 ± 0.14	0.04
1 months after end of the treatment	1.43 ± 0.20	1.51 ± 0.12	0.11

Table 1
General characteristics of the studied groups.

	Study group $n = 49$	Control group $n = 50$ (including 1 male)
Age (SD)	49.64 (11.21)	49.20 (12.09)
Cancer type		
Invasive intraductal	42	44
Invasive lobular	6	6
Medullary	1	0
Cancer stage[a]		
A2	9	8
A3	10	11
A4	1	2
B1	2	4
B2	17	15
B3	7	8
C3	1	1
D4	2	1
Chemotherapy drug		
Docetaxel	26	24
Paclitaxel	23	26

[a] According to Breast Cancer Staging Guide published by American Joint Committee on Cancer, 7th edition, 2009.

developed more than two-fold rise in SGOT, total bilirubin and SGPT, and more than 3-fold rise in alkaline phosphatase and indirect bilirubin during the treatment. The patients who had received silymarin concomitantly had less notable rises.

4. Discussion

The present study was conducted to evaluate potential liver injury after chemotherapy with taxanes in patients with breast cancer and the possible role of silymarin in the process. We confirmed that there are rises in some indices of LFT after the proposed chemotherapy regimen. There were more than 2-fold rises in SGOT, SGPT, and bilirubin which indicate the liver injury. The addition of silymarin modulated the effects considerably.

Due to the large variety of agents, drug hepatotoxicity remains a significant challenge for the scientific community, namely, physicians, health authorities, and pharmaceutical firms [4]. The majority of liver adverse drug reactions are present in only a small percentage of patients, which makes it challenging to spot during drug development [4]. Many chemotherapy agents are substrates for liver uptake, metabolism, and excretion, and dysfunction of the liver can result in drug toxic effects. A typical patient presents with several variable causes of liver impairment, including direct hepatic involvement by their disease, effects of cancer-induced inflammatory cytokines, comorbidities, and concurrent medications [5]. The frequent identification of chemotherapy associated liver injuries poses a number of other management quandaries to the surgeon and oncologist such as: what is the ideal dose and duration of therapy; should all patients be formally assessed for chemotherapy associated liver injuries [12]? The taxanes paclitaxel and docetaxel are some of the most effective chemotherapeutic agents against breast cancer and are indicated in both metastatic and adjuvant settings with few side effects [13]. However, increased aspartate aminotransferase or bilirubin has also been attributed to the taxanes' administration [5]. With reducing this effect, safer or higher dose administration of the drug becomes possible.

The most researched herbal treatment for liver diseases is *Silybum* or milk thistle. Its active constituents are collectively known as silymarin [11]. *Silybum* has been reported in a number of uncontrolled studies and case reports as effective in the treatment of acute hepatic failure due to *Amonita phalloides* mushroom poisoning [11]. Silymarin has also been used for treatment of non-alcoholic steatohepatitis and acetaminophen induced hepatotoxicity [14,15].

So, its effects on the liver enzymes elevation associated with chemotherapy/cancer were studied. The present study confirmed that there was some evidence of beneficial effects. We did not find any similar studies with which to compare our results. In future research, the use of silymarin with higher permissible doses should be studies to explore whether this could magnify the effect.

5. Conclusion

In conclusion, the addition of silymarin to a chemotherapy regimen containing taxanes may have a positive effect on hepatic function. Future studies are recommended to confirm the efficacy of this herbal based drug in pre-treatment or concomitant treatment in cancer chemotherapy, particularly those contained taxanes.

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