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Alternative Therapy and Abnormal Liver Function During Adjuvant Chemotherapy in Breast Cancer Patients

Although hepatotoxicity has been rarely reported during adjuvant chemotherapy in breast cancer patients, we observed a high frequency in our patients who were also taking alternative agents. We therefore sought to determine the association between hepatotoxicity and alternative agents during adjuvant chemotherapy in breast cancer patients. All breast cancer patients were treated with the same chemotherapeutic regimen and had normal baseline liver function test (LFT). LFT was checked repeatedly during each cycle of chemotherapy. Patients showing LFT abnormalities were asked about use of alternative agents, and, after the end of chemotherapy, a questionnaire was administered to each patient on their use of alternative agents. Of 178 patients, 65 (36.5%) admitted using alternative therapy, and significantly more patients in this group developed LFT abnormalities (37/65, 56.9%) than those who denied taking alternative therapy (25/113, 22.1%, p=0.001). Although LFT abnormalities were mild to moderate and normalized in most patients after cessation of alternative agents, it remained a serious problem in one patient. In conclusion, alternative therapy may be one of the etiologies for abnormal LFT in breast cancer patients receiving adjuvant chemotherapy.

Key Words : *Breast Neoplasms; Complementary Therapies; Drug Therapy; Hepatitis, Toxic*

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INTRODUCTION

The use of alternative therapy in cancer patients has become increasingly popular, although this approach has not been scientifically tested and has the potential to interact with conventional treatment (1-6). To date, there have been no studies prospectively investigating the use of alternative therapies in breast cancer patients receiving adjuvant chemotherapy, or determining the risk of abnormal liver function in concomitantly treated patients. Also, there are few published reports focusing on hepatotoxicity from chemotherapy with adriamycin or the CMF (cytoxan+methotrexate+5-fluorouracil) regimen in adjuvant chemotherapy trial (7, 8). We previously found that 34% of patients who had received adjuvant adriamycin followed by CMF chemotherapy for breast cancer developed abnormal liver functions (9). Since many of our patients were also taking various kinds of herbal medicines, a majority of which are sold as "health food" without evidence of proven efficacy or safety, we thought that the association between these alternative therapies and abnormal liver function warranted further study. We designed this study to determine the frequency of hepatotoxicity during adjuvant chemotherapy in breast cancer patients, and we compared results between patients who had and had not taken alternative agents.

MATERIALS AND METHODS

This study was conducted at an outpatient oncology clinic on breast cancer patients who received adjuvant chemotherapy from April through December 2002 with AC (adriamycin 60 mg/m^2+cyclophosphamide 600 mg/m^2, every 4 weeks) after curative surgery and had normal liver functions prior to chemotherapy. Each patient had a baseline history, a physical examination, complete blood count (CBC) and liver function test (LFT). The latter included assays for serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total bilirubin, as well as the hepatitis B virus (HBV) markers, HBsAg and anti-HBs, anti-HCV antibody, and a baseline liver ultrasonography within 2-4 weeks before chemotherapy. LFT was repeated before each cycle of chemotherapy, one month after the last cycle and at every 3 month follow-up visit after chemotherapy. Abnormal LFT was defined as the elevation of aminotransferase (AST and/

or ALT>40 IU/L) or bilirubin (>1.5 mg/dL) concentration.

Alternative agents were defined as any product, not approved for use in conventional medicine, including herbs, other botanical agents or any biological preparations sold as "health food." Any patients found to have abnormal LFT during the chemotherapy period were asked about the use of any alternative agent and requested to cease its use. If the liver function did not return to normal after these agents were stopped, ultrasonography of the liver, and hepatitis panels for HBV and HCV were repeated at the attending physician's discretion. Also, HBV DNA probe and HBeAg were assayed if the patient was an HBV carrier. After the end of chemotherapy, all patients were interviewed by an oncology nurse specialist and questionnaires were filled in for the history of use of any alternative agents. We used SPSS (version 11.0) statistical software package for data entry and analysis. Chi-square test was used for comparing the categorical variables between patients who admitted taking alternative therapy and those who did not. Statistical significance was defined as a p-value less than 0.05.

The protocol was reviewed and approved by the Clinical Performance Improvement Project of our center. All patients provided verbal informed consent before entering onto the study.

RESULTS

Patient characteristics

During the study period, there were 203 patients with breast cancer who had undergone curative surgery and received adjuvant AC chemotherapy. Of these, 25 patients were excluded because of abnormal LFT prior to chemotherapy. Thus, a total of 178 breast cancer patients (median age, 46 yr; range, 29-72), were included in this study. Six patients were HBsAg carriers and one patient was positive in an anti-HCV antibody test. Of the 150 patients for whom we had results of baseline liver ultrasonography, 37 had underlying fatty liver disease. Five patients received red blood cell transfusions during hospitalization for breast surgery, but none had transfusions during the chemotherapy period.

Table 1. Alternative agents taken by our patients

Alternative therapy	Examples
Herbs (70)	*Panax ginseng* (ginseng steamed red 35), *Daucus carota* (carrot juice 15), other kinds of ginseng (6), *Ulmus davidiana* (Slippery elm 6), *Angeliaca keiskei* (2), *Acer pictum* (1), Yeast (1), *Elentherococcus sessiliflorus* (root bark of various araliaceous shrubs 1), *Euonymus hamiltonianus* (1), *Morus alba* (Mulberry leaves 1), Mistletoe (1)
Diets (19)	Various uncooked grains and raw vegetables (12), "Pumpkin juice", ingredients unknown (3), Vegetarian diet (2), "Pear juice", ingredients unknown (1), "Grapefruit juice", ingredients unknown (1)
Mushroom (13)	*Phelinus linteus* (8), *Ganoderma lucidum* (5)
Others (7)	Agaricus (3), Crucian juice (2), Royal jelly (1), Shark cartilage (1)

*Numbers in the parenthesis are the numbers of patients.

Alternative therapy

At the first follow-up visit after the end of 4 cycles of chemotherapy, 65 (36.5%) patients admitted they had taken some type of alternative agent(s) during chemotherapy period, whereas 113 patients (63.5%) denied taking any alternative agents. Duration of alternative therapy varied from 1 week to 3 months. Steamed red Ginseng (*Panax ginseng*) was the most common herbal therapy (35/65, 53.8%), and many patients had taken several different agents (Table 1). Baseline characteristics were similar between patients who admitted using alternative therapies and those who did not (Table 2).

Abnormal liver function

We found that 62 of 178 patients (34.8%) developed abnormalities in LFT (Table 3). According to NCI common toxicity criteria (Table 4), 43 patients (69.4%) had grade 1 toxicity, 16 (25.8%) had grade 2, 2 (3.2%) had grade 3, and 1 (1.6%) had grade 4. Of the 65 patients who took alternative therapy, 37 (56.9%) developed an LFT abnormality, compared with 25/114 (22.1%) who denied taking alternative therapy (p=0.001). Development of hepatotoxicity of grade 2 or higher was significantly more common in the alternative therapy group (13/65, 20.0%) than in the other group (6/113, 5.3%; p=0.002). All patients who admitted using alternative agents had started taking them one or two months before the LFT

Table 2. Patient characteristics according to the use of alternative therapy

	With alternative therapy	Without alternative therapy
Total number of patients	65 (36.5%)	113 (63.5%)
Age (yr), median	44 (29-72)	46 (30-72)
BMI (kg/m^2)*	23.4 (18.9-28.6)	23.2 (17.5-35.7)
Hemoglobin, median	12.0 g/dL (9.0-14.1)	12.0 g/dL (9.0-14.4)
RBC transfusion	1 patient	4 patients
AST*	20 IU/L(12-37)	20 IU/L (10-37)
ALT*	15 IU/L (6-40)	14 IU/L (3-40)
ALP*	50 IU/L (30-162)	52 IU/L (14-128)
Total bilirubin	0.7 mg/dL (0.2-1.3)	0.7 mg/dL (0.1-1.4)
HBV carrier	1 patient	5 patients
HCV Ab (+)	0	1 patient
Fatty liver disease	12/54 (22.2%)	25/97 (25.8%)

*Numbers are median value of BMI and liver function test.
BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HBV, hepatitis B virus; HCV Ab, hepatitic C virus antibody.

Table 3. Abnormal liver function according to the use of alternative therapy

Abnormal liver function test (LFT)	With alternative therapy (No. of patients)	Without alternative therapy (No. of patients)
Incidence*	37/65 (56.9%)	25/113 (22.1%)
Grade 1/2/3/4	24/11/1/1	19/5/1/0
Grade ≥2*	13/65 (20.0%)	6/113 (5.3%)
Time to normalization of liver function	median 1.9 months (range 1-8 months)	median 2.9 months (range 1-10 months)

*p-value< 0.05.

abnormality was detected. After discontinuing the agents, however, the liver function abnormality was normalized within a median 1.9 months (range, 1-8 months). In contrast, normalization of liver function abnormalities took a median 2.9 months (range, 1-10 months) in the other group.

The patient with grade 4 hepatotoxicity was an HBV carrier who had used *Panax ginseng* and *Ulmus davidiana* (Slippery elm) for 3 months from the beginning of adjuvant chemotherapy. After the third cycle of chemotherapy, AST and ALT were increased to 134 IU/L and 164 IU/L, respectively, and the patient was asked to stop taking the alternative agents. After the fourth cycle of chemotherapy, the patient presented with further increases in AST and ALT to 748 IU/L and 732 IU/L, respectively, and her bilirubin was 3.6 mg/dL. This resulted in a delay in the administration of tamoxifen, and hospitalization was required. No evidence for the replication of HBV was observed, judging by the negative results of HBeAg and HBV DNA probe, and liver ultrasonography showed a pattern of non-specific chronic liver disease. It took more than 6 months for the increased aminotransferases and bilirubin to return to their normal ranges.

Significantly more patients who had underlying fatty liver disease (18/37, 48.6%) developed abnormalities in LFT than patients who did not (35/113, 30.7%; p=0.047). The frequency of underlying fatty liver disease was not different between the patients who took alternative agents (22.2%) and those who did not (25.8%). Of the 6 HBV carriers, 2 developed abnormal LFT during chemotherapy, but there was no evidence of viral replication.

DISCUSSION

Since data regarding hepatotoxicity during adjuvant chemotherapy in breast cancer patients is scarce, it is difficult to determine how often it occurs and what agents are involved. Mild liver function abnormalities have been reported in 7% of breast cancer patients after adjuvant CMF chemotherapy (7), whereas the frequency of mild abnormal LFT within one year after the cessation of CAF (cytoxan+adriamycin+5-fluorouracil) chemotherapy was found to be 77%, suggesting that LFT abnormalities were manifestations of drug toxicity (8). Of these patients, however, 33% (33/97) had abnormal liver functions

Table 4. Hepatotoxicity according to NCI common toxicity criteria

Grade	1	2	3	4
AST, ALT* (IU/L)	≤2.5×N† (≤100)	2.6-5.0×N (100-200)	5.1-20.0×N (200-800)	> 20.0×N (>800)
Total bilirubin (mg/dL)		<1.5×N (<1.8)	1.5-3.0×N (1.8-3.6)	>3.0×N (>3.6)

*AST, aspartate aminotransferase; ALT, alanine aminotransferase; †N, upper normal limit.

prior to the start of chemotherapy, an unusually high percentage. In contrast, only 25 of our 203 patients (12.3%) had abnormal LFT before chemotherapy.

In our study, 36.5% of breast cancer patients admitted using alternative therapy during the adjuvant chemotherapy period. The development of abnormal LFT was significantly more frequent in these patients than in those who denied taking alternative agents (56.9% vs. 22.1%, p=0.001). In most cases, LFT abnormalities were mild to moderate, rarely led to interruption of chemotherapy, and normalized after the cessation of alternative agents or spontaneously within several months, even in patients who denied using alternative agents. These results strongly indicate that alternative agents could cause liver toxicity during adjuvant chemotherapy.

In our study, two of six HBV carriers showed elevation of aminotransferases during adjuvant chemotherapy, but there was no evidence of HBV replication. The reactivation of HBV infection in subjects receiving cytotoxic treatment has been well documented in patients with hematologic malignancies receiving steroid-containing high-dose chemotherapy (10-12). Although the numbers of HBV carriers in our study is too small to draw a firm conclusion, HBV carrier status alone does not seem an additional risk factor for abnormal LFT.

Interests in alternative therapies have been increasing. In previous population-based surveys, 48% and 72% of breast cancer patients admitted using at least one type of alternative therapy (4, 13). Among these alternative therapies were dietary therapies, herbal remedies, spiritual healing, and psychological methods, with the prevalence of each type dependent on ethnicity (4). In our study, we considered only orally ingested alternative therapies, perhaps explaining why the percentage of our patients taking alternative treatment was lower than those observed elsewhere.

Some herbal and botanical agents possess complex biological activities that could affect many aspects of carcinogenesis and treatment (14, 15). Despite an extensive series of laboratory studies, few clinical trials have tested the efficacy and safety of these herbal and botanical agents. Heavy-metal contamination is not uncommon in Asian herbal or botanical agents, and these agents can act through a variety of mechanisms to alter the pharmacokinetic profile of concomitantly administered drugs (16, 17). Since several herbal remedies are associated with hepatotoxicity (18, 19), it was not surprising that our patients who took alternative agents had a higher rate of

developing abnormal liver function during the chemotherapy. The alternative agents taken by our patients varied widely, such that we could not sort out the agents responsible for hepatotoxicity. The determination of patients who ingested alternative agents was based totally on their own statements, and it is our practice to discourage our patients from taking alternative agents. Thus, we cannot completely rule out the possibility that our patients under-reported usage of alternative agents. In addition, we did not perform serial liver ultrasonography on all patients who developed LFT abnormalities. Therefore, we cannot determine precisely whether individual LFT abnormalities are due to the use of alternative therapies, to hepatotoxicity induced by chemotherapeutic agents, or to aggravation of underlying fatty liver disease, either by chemotherapy or alternative agents.

In conclusion, our results indicate that the use of alternative agents can be one of the etiologies for the development of abnormal LFT while on AC adjuvant chemotherapy in breast cancer patients. Our findings suggest the need for more prospective studies regarding the relative contribution to hepatotoxicity by adjuvant chemotherapy and by alternative agents.

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