

HEPATIC STATUS OF PATIENTS RECEIVING CMF PLUS TAMOXIFEN AS ADJUVANT THERAPY IN BREAST CANCER PATIENTS

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ABSTRACT:

Tamoxifen is extensively used in all stages of breast cancer. Its hepatotoxic potential has been shown in various studies. It has produced important results in some clinical trials in which it was used with CMF (a combination of cyclophosphamide, methotrexate and 5-fluorouracil). We tried to evaluate the occult hepatic status of the patients who were maintained on the combination of CMF and tamoxifen. This was compared with controls and those patients who were newly diagnosed or maintained on CMF only. Although, no statistical significant changes in hepatic parameters were observed but their relative alterations were important indicator of enhanced liver damage in the patients who received CMF plus tamoxifen as compared to those who received CMF only.

INTRODUCTION

Tamoxifen, a non-steroidal antiestrogen, is the endocrine therapy of choice for all stages of breast cancer (Jordan, 1995). Various studies have shown its hepatotoxic potential (Sargent et al., 1994, Pratt et al., 1995; Wada et al., 1995). We understand that its hepatotoxic potential is further increased if it is combined with other hepatotoxic drugs or combinations like CMF (a protocol which has been proved to improve the survival in breast cancer patients and contains cyclophosphamide, methotrexate and 5- fluorouracil). We tried to evaluate the cumulative toxicities of such drugs in our breast cancer patients.

MATERIALS AND METHODS

Thirty four patients were recruited in this study. They had following criteria of selection:

- (i) Female of any age with biopsy proven breast cancer.
- (ii) Either newly diagnosed or has received six cycles of CMF or CMF with daily oral tamoxifen.
- (iii) Has no clinically detectable hepatic metastasis or symptoms referring to it.

5 cc blood was taken from each patient. Serum was separated and frozen which was used to determine important hepatic parameters.

Seven healthy volunteers were also recruited as controls who were free from clinically

demonstrable hepatic dysfunction and were not using any pharmacotherapy of adverse hepatic effects. 5 cc blood was taken from each control and dealt in the same way as that of cancer patients.

Liver functions were assessed by bilirubin, transaminases, alkaline phosphatase, LDH and uric acid. These were determined by Merck kits. Protein was not considered as an important parameter due to interference of administered drugs in its metabolism.

RESULTS

Table I shows important hepatic parameters of controls and newly diagnosed patients. ALP shows a statistically significant difference ($P < 0.05$) which is not very important due to wide normal range of this enzyme.

Table II represents important hepatic parameters in newly diagnosed patients and patients receiving CMF. Statistically significant difference ($P < 0.05$) is noted in SGPT, ALP and LDH.

Table III depicts hepatic parameters of newly diagnosed patients receiving CMF plus tamoxifen. Statistically significant difference ($P < 0.05$) is noted in LDH.

Table IV represents hepatic parameters in patients receiving CMF and CMF plus tamoxifen. Although a statistically significant change ($P < 0.05$) is evident only in ALP, but the relative alteration in all hepatic parameters is important.

DISCUSSION

Female hormonal milieu requires an extensive research as yet, to establish its role in breast cancer treatment (Editorial Ovarian Ablation in Early Breast Cancer, 1992). This confusing array is a result of lack of evidences about the definitive role of important steroidal hormones in this malignancy (Mirra et al., 1971; Dewaard, 1975; Bulbrook et al., 1978; Fishman et al., 1978; Morgan et al., 1978; Wynder et al., 1978; Zumoff, 1981; Henderson et al., 1994). Many studies present important role of estrogenic stimulation (Nevinny et al., 1969; Fisher et al., 1974; Fasal and Paffenbarger, 1975; Bonadonna, 1988) while other studies show the significant role of progesterone in this regard (Sherman and Korenman, 1974). However even that there are six million women year of experience with tamoxifen, and the drug has produced survival advantages in node positive and node negative patients who have had 2-5 years of adjuvant tamoxifen therapy (Jordan, 1995). A low incidence of side effects has been reported with tamoxifen, resulting in the proposal to use antiestrogen as a preventive agent for breast cancer. Three separate clinical trials are currently underway in the United States, Italy and United Kingdom (Jordan, 1995). Current report about the development of rat liver tumours (Sargent et al., 1994; White et al., 1995) and liver dysfunction in human patients (Pratt et al., 1995; Wada et al., 1995) compel the scientists for the careful assessment of the benefit and the risk of tamoxifen therapy. Therefore, we

intended to look the hepatic status of our breast cancer patients receiving CMF and CMF plus tamoxifen as adjuvant therapy in this study.

The CMF was developed in (Istituto Nazionale Tumori) in Milan has found to be effective in both premenopausal and postmenopausal breast cancer patients. The different components of this regimen with hepatotoxic potential are:

- (i) Cyclophosphamide: Its active conversion takes place in liver (Connors *et al.*, 1974) where toxic end products are produced (Cohnn *et al.*, 1973). Its hepatotoxicity has been reported in clinical trials (Calabresi and Chabner, 1991).
- (ii) Methotrexate: Its high concentration has been found in liver (Johns *et al.*, 1968) and transient elevation of hepatic enzymes and cirrhosis has been seen in patients receiving it (Dahl *et al.*, 1971; Roerig *et al.*, 1971).
- (iii) 5-Fluorouracil: Its metabolic degradation occurs in liver (Calabresi and Parks, 1985). However its hepatotoxicity is not well documented.

Now a days combination of chemotherapy and endocrine therapy are receiving intense study among patients with advanced disease. A study of 318 women has been reported with follow through 4.5 years. These patients were all randomized to receive either CMF, CMF plus tamoxifen, or CMF plus tamoxifen and BCG for one year after mastectomy. Women who were ER positive had a significantly greater disease free survival if they received chemotherapy and tamoxifen then if they received CMF only (Hubey *et al.*, 1980). This study lacks the toxicity versus benefit evaluation on long- term basis. Our study shows that although no statistical significant changes are found in hepatic parameters in CMF receiving patients as compared to CMF and tamoxifen receiving patients but the collective impression of all important parameters does not permit to declare CMF and tamoxifen as a safe combination. It is represented by slight decrease in direct bilirubin even in the presence of some increase in total bilirubin, slight decrease in transaminases with a reversal pattern of SGOT/SGPT, a significant decrease in alkaline phosphatase, and significant increase in LDH, with an increase in uric acid. these collective changes may be representative of greater liver damage (La Mont *et al.*, 1980) in CMF plus tamoxifen receiving patients, as compared to only CMF receiving patients. This is to be noted that this conclusion has already been proved in our animal experimental model, the results of which are sent for publication in JPMA.

Table I
Hepatic parameters of controls (n=7) and newly diagnosed cancer patients (n=9)

Hepatic parameters	Controls	Newly diagnosed patients
Bilirubin (mg/dl)		
Total	2.91 ± 0.13 ⁺	2.83 ± 0.153
Direct	2.52 ± 0.04	2.72 ± 0.166
Transaminases (mU/ml)		
SGOT	28.90 ± 3.50	27.55 ± 3.380
SGPT	22.14 ± 2.96	19.38 ± 4.390
ALP (mU/ml)	18.28 ± 3.50	97.62 ± 3.440*
LDH (B-B mU/ml)	39.28 ± 7.73	32.85 ± 8.270
Uric acid (mg/dl)	4.89 ± 0.39	4.66 ± 0.420

Mean ± S.E.

* P < 0.05

Table II
Hepatic parameters of newly diagnosed patients (n=9) and patients receiving CMF (n=13)

Hepatic parameters	Newly diagnosed patients	Patients receiving CMF
Bilirubin (mg/dl)		
Total	2.83 ± 0.153 ⁺	2.89 ± 0.12
Direct	2.72 ± 0.166	2.76 ± 0.12
Transaminases (mU/ml)		
SGOT	27.55 ± 3.380	34.96 ± 3.44
SGPT	19.38 ± 4.390	29.76 ± 2.14*
ALP (mU/ml)	97.62 ± 3.440	163.72 ± 23.35*
LDH (B-B mU/ml)	32.85 ± 8.270	135.00 ± 21.89*
Uric acid (mg/dl)	4.66 ± 0.42	4.51 ± 0.37

Mean ± S.E.

* P < 0.05

Table III
Hepatic parameters of newly diagnosed patients (n=9) and patients receiving CMF and tamoxifen (n=20)

Hepatic parameters	Newly diagnosed patients	Patients receiving CMF and tamoxifen
Bilirubin (mg/dl)		
Total	2.83 ± 0.153 ⁺	2.92 ± 0.11
Direct	2.72 ± 0.166	2.73 ± 0.11
Transaminases (mU/ml)		
SGOT	27.55 ± 3.38	33.36 ± 4.41
SGPT	19.38 ± 4.39	29.17 ± 4.50
ALP (mU/ml)	97.62 ± 3.44	105.33 ± 3.18
LDH (B-B mU/ml)	32.85 ± 8.27	161.33 ± 24.78
Uric acid (mg/dl)	4.66 ± 0.42	5.47 ± 0.57

Mean ± S.E.

* P < 0.05

Table IV
Hepatic parameters of and patients receiving CMF (n=13) and patients receiving CMF and tamoxifen

Hepatic parameters	Patients receiving CMF	Patients receiving CMF and tamoxifen
Bilirubin (mg/dl)		
Total	2.89 ± 0.12 ⁺	2.92 ± 0.11
Direct	2.76 ± 0.12	2.73 ± 0.11
Transaminases (mU/ml)		
SGOT	34.96 ± 3.44	33.36 ± 4.41
SGPT	29.76 ± 2.14	29.17 ± 4.50
ALP (mU/ml)	163.72 ± 23.35	105.33 ± 3.18
LDH (B-B mU/ml)	135.00 ± 21.89	161.33 ± 24.78
Uric acid (mg/dl)	4.51 ± 0.37	5.47 ± 0.57

Mean ± S.E.

* P < 0.05

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