Anti Cancer Chemotherapy Induced Hepatotoxicity in Breast Cancer patients.
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Abstract

Breast Cancer requires an aggressive treatment both in pre-menopausal and postmenopausal patients. ‘CMF’ is a well known combination which is used for chemotherapy of the patients. We tried to evaluate accumulative hepatotoxicity of this combination, both in acute and Chronic phases. Insignificant toxicity was noted in acute therapy. Significant toxicity in terms of hepatic enzymes was evident in patients who were receiving this therapy since long. Our study shows that benefit versus risk should be assessed before deciding about CMF, regimen. No doubt toxicity seems to be enhances if this combination is used with analgesics or neuroleptics, or other drugs with little or more hepatoxic potential.

Keywords

Anti Cancer Chemotherapy, Hepatotoxicity, Breast Cancer

Introduction

According to consensus development conference, held at the National Cancer Institute in Bethesda in Sept-1985, the CMF regimen has reduced 25% mortality, as adjuvant chemotherapy in breast cancer Patients. No other adjuvant treatment has been able to achieve survival rates 12 years after mastectomy which are comparable to this regimen.

Materials And Methods

Phase I: Evaluation of acute toxicities

Six patients were included in this phase of study. They were female of biopsy proven breast cancer. They were receiving CMF as adjuvant to surgery and/or radiotherapy. Blood sample was collected from each patient. The CMF was administered in these patients having following doses of different component drugs.

a) Cyclophosphamide 1000 mg
b) Methotrexate 50 mg
c) 5-fluorouracil 750 mg

All these drugs were given I.V. drip tube of Dextrose saline or normal saline. The second blood sample was collected after the completion of therapy.

Phase II: Evaluation of chronic toxicities

Twenty two patients were recruited in this part of study. They were female of biopsy proven breast cancer. They were newly diagnosed or have been received three or six cycles of CMF in the following dosage schedule.

a) Cyclophosphamide 1000 mg
b) Methotrexate 50 mg
c) 5-fluorouracil 750 mg

All the drugs were given through I.V. drip tube of Dextrose saline or normal saline. Blood sample was collected for each patient. Seven healthy female volunteers were also recruited, who were free from clinically demonstrable hepatic dysfunction and were using no pharmacotherapy of adverse hepatic effects. 5 cc blood was taken from each control and dealt in the same manner as in case of patients.

Liver function was assessed by Bilirubin, Transaminases, Alkaline Phosphatase, LDH, and Uric Acid. These parameters were determined by Merck Kits. Protein was not considered to be an important parameter due to interferences of administered drugs in protein metabolism.

Results

Important hepatic parameters just before and after the administration of regimen has been shown. No significant change (p>0.05) is noted in most of the parameters, except a decrease

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TABLE-1  ACUTE HEPATIC TOXICITIES IN CMF TREATED PATIENTS (n=6)

<table>
<thead>
<tr>
<th>Hepatic Parameters</th>
<th>Before CMF</th>
<th>After CMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billirubin (mg/d1)</td>
<td>0.91±0.140</td>
<td>0.67±0.10</td>
</tr>
<tr>
<td>Total</td>
<td>0.75±0.140</td>
<td>0.59±0.10</td>
</tr>
<tr>
<td>Direct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases (u/m1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGPT</td>
<td>36.33±4.070</td>
<td>32.50±5.25</td>
</tr>
<tr>
<td>SGOT</td>
<td>33.33±2.810</td>
<td>37.50±5.25</td>
</tr>
<tr>
<td>Ackaline Phosphatase (U/2)</td>
<td>180.91±48.52</td>
<td>186.16±38.0</td>
</tr>
<tr>
<td>LDH (B-B U/M1)</td>
<td>113.33±21.51</td>
<td>31.66±7.25*</td>
</tr>
<tr>
<td>Uric Acid (mg/d1)</td>
<td>3.83±0.880</td>
<td>5.25±0.38</td>
</tr>
</tbody>
</table>

+Mean+S.E
*p<0.05

(p<0.05) in LDH after drug administration. (Table-1)
Same hepatic parameters in controls & in patients 2.
Same hepatic parameters in controls & in patients receiving
less than three cycles of CMF have been shown (Table-2)
statistically significant difference (p<0.05) is found in SGOT,
SGPT, and LDH.

Hepatic parameters in controls and in patients receiving
more than three cycles of CMF have been shown (Table, 3)
statistically significant difference (p<0.05) is present in ALP
and LDH. However important changes although statistically
insignificant (p>0.05) are observed in Bilirubin (both total
& direct), SGPT and Uric acid.

Discussion

A major advance in decades is the use of combination of
drugs. This assertion is extensively supported by extensive experimental2 and clinical3 evidences. For a combination
which is designed on pharmacological basis, it is considered
to contain the component drugs, which do not produce the
same toxic effects. However for a combination which is
derived on clinical trials with prime importance of its response
to particular malignancy, this important fact is sometime
overlooked. Such combinations sometimes contain the
components having same loci of toxicities, e.g. CMF. It contains three component drugs which are all hepatotoxic,
viz.

1) Cyclophosphamide: It is converted by the mixed hepatic
function oxidase system to active metabolites4 and therefore
hepatocytes are exposed to higher concentration of the toxic
end products viz Phosphoramid, mustard and acrolein5.
Perhaps higher activity of aldehyde oxidase of hepatic tissue
 PROVIDES SAFETY FROM THESE PRODUCTS6,7. However hepatotoxicity
of this drug has been reported8.

2) Methotrexate: Autoradiographic studies in mice9 and
aminopterin labelled with a gamma emitter ([I]-3-
iodoaminopterin studies in human patients10 reveal its
centration in liver. Hepatotoxicity of transient elevations
of hepatic enzymes have been noted with high dose infusions
severe hepatic pathology including cirrhosis has been found
in low dosage therapy11,12.

3) 5-Fluorouracil: Although hepatotoxicity of this drug has
not been noted as yet, but metabolic degradation of the drug
occurs in liver13 which may enhance the toxicities of other
drugs or may produce toxic substances after interaction with
other metabolites of combination drugs.

In our studies the acute toxicities of these drugs when given
simultaneously do not present an establish picture of toxic
hepatic pathology but the ultrachanges of hepatic parameters show that these changes may lead to cirrhosis\(^{14}\) if persist for a long period or exaggerate on subsequent therapies or combinations. One may expect that these changes may easily be exaggerated if these patients are given hepatic enzyme inducing drugs especially neuroleptics or analgesics\(^{15}\) as they are usually prescribed to relieve pain or tension associated with a diagnosis of malignancy and depression linked with a loss of an important sexual part of the body as a result of mastectomy. The chronic toxicities as found by us do not depict, statistical significant alterations in different parameters, however their mode is important with reference that cumulatively they show an enzyme depletion phenomenon. However on summarizing the whole discussion, we can say that CMF does not produce considerable toxicity. This is in support to the studies done by Bonadonna\(^{16}\) on CMF toxicity. However this crucial question remains to be interrogated that is this combination is safe to combine with the supportive drugs which are used in addition to this regimen to relieve different symptoms? Theoretically keeping the results of our study in mind, our answer is “no”. However the benefit versus risk should be considered in such cases.

**TABLE-2 ACUTE HEPATIC TOXICITIES OF CONTROLS (n=7) & AND PATIENTS RECEIVING LESS THAN THREE CMF (n=7)**

<table>
<thead>
<tr>
<th>Hepatic Parameters</th>
<th>Controls</th>
<th>Patients receiving less than three CMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billirubin (mg/dl)</td>
<td>2.91±0.13+</td>
<td>2.644±0.11</td>
</tr>
<tr>
<td>Total</td>
<td>2.52±0.04</td>
<td>2.50±0.120</td>
</tr>
<tr>
<td>Direct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases (u/ml)</td>
<td>28.90±3.50</td>
<td>39.20±4.70*</td>
</tr>
<tr>
<td>SGOT</td>
<td>22.14±2.96</td>
<td>31.16±3.62*</td>
</tr>
<tr>
<td>SGPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline Phophatase (u/l)</td>
<td>118.28±3.500</td>
<td>134.16±23.53</td>
</tr>
<tr>
<td>LDH (B-B  u/ml)</td>
<td>39.28±7.730</td>
<td>145.71±32.06*</td>
</tr>
<tr>
<td>Uric Acid  (mg/dl)</td>
<td>4.89±0.39</td>
<td>4.78±0.470</td>
</tr>
<tr>
<td>+Mean+S.E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* p&lt;0.05</td>
<td></td>
<td></td>
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</tbody>
</table>
TABLE - 3  HEPATIC TOXICITIES OF CONTROLS (n=7) & AND PATIENTS RECEIVING MORE THAN THREE CMF (n=7)

<table>
<thead>
<tr>
<th>Hepatic Parameters</th>
<th>Controls</th>
<th>Patients receiving less than three CMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billirubin (mg/dl)</td>
<td>2.91±0.13+</td>
<td>3.24±0.14</td>
</tr>
<tr>
<td>Total</td>
<td>2.52±0.04</td>
<td>3.13±0.13</td>
</tr>
<tr>
<td>Transaminases (u/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT</td>
<td>28.90±3.50</td>
<td>30.00±4.26</td>
</tr>
<tr>
<td>SGPT</td>
<td>22.14±2.96</td>
<td>28.57±2.41</td>
</tr>
<tr>
<td>Alkaline Phophatase (u/l)</td>
<td>180.28±3.500</td>
<td>189.05±35.76*</td>
</tr>
<tr>
<td>LDH (B-B u/ml)</td>
<td>39.28±7.730</td>
<td>120.00±25.99*</td>
</tr>
<tr>
<td>Uric Acid (mg/dl)</td>
<td>4.89±0.39</td>
<td>4.20±00.58</td>
</tr>
</tbody>
</table>

+Mean+ S.E

* p < 0.05

References

1) National Cancer Institute:Consensus Conference: CMF regimen as adjuvant chemotherapy. In Handbook of Medical Oncology (G Bonadonna & G Robustellidella Cunna eds) 487

2) Goldin A, Venditti JM, Mantel N. Combination chemotherapy: Basic considerations; In Antineoplastic and Immuno suppressive agents, Part I(eds) A C Sartorelli and DG Johns Berlin Springer Verlag 1974; pp 411-448


