Short communication

Esterases and anti-tumoral chemotherapy: an interaction of clinical and toxicological interest

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Received 21 September 1999; received in revised form 21 June 2000; accepted 3 July 2000

Keywords: Anti-tumoral chemotherapy; Arylesterase; Butyrylcholinesterase; Cancer

1. Introduction

In human blood, two types of esterase (type A and type B) are involved in the extra-hepatic hydrolytic transformation of a number of drugs and xenobiotics. Arylesterase (EC 3.1.1.2), a type A enzyme, metabolizes organophosphate pesticides and drugs derived from carboxylic acid [1,2] whereas cholinesterase (also called butyrylcholinesterase) (EC 3.1.1.8), a type B enzyme, hydrolyses many drugs in peripheral blood, and is inactivated by organophosphates [3].

Some studies have reported significant but so far unexplained decreases in butyrylcholinesterase activity. One study implicated nutritional status and the hepatic localization of the tumor in these changes [4], whereas the other blamed the anti-tumoral treatment itself as the possible cause of decreased enzymatic activity [5]. We previously reported that decreased cholinesterase activity can alter serum esterase activity and modify the pharmacokinetics of drugs that are metabolized via this pathway [6].

Cancer patients are treated with many drugs and prodrugs that are metabolized or eliminated by esterases in peripheral blood. Because the possible influence of anti-tumoral chemotherapy on serum esterase activities is currently unknown, we investigated whether chemotherapy modified arylesterase and butyrylcholinesterase activities in patients with primary carcinoma.

2. Materials and methods

2.1. Serum

We studied 65 patients (40 women, mean body weight 64±21 kg; 25 men, mean body weight 67±20 kg; average age of all patients 50±12 years), who were diagnosed as having initial stage (grade 1–2) primary carcinoma of the breast (n=30), digestive tract (n=26), lung (n=5), uterus (n=2) or kidney (n=2). All patients were being treated at the oncology service of the Hospital Universitario de Granada (Spain), and all had undergone simple resection of the tumor before the first session of anti-tumoral chemotherapy. The drugs used for chemotherapy were alkylating agents, anti-metabolites, interleukin, interferon-alpha and hormones, which were given in different combinations depending on the type of tumor (Table 1). Some patients
Table 1
Number of patients with carcinoma in different localizations and chemotherapy given

<table>
<thead>
<tr>
<th>Localization</th>
<th>No. patients (n=65)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>30</td>
<td>CY, ADM, 5-FU</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>26</td>
<td>ADM, 5-FU, IFM-msna, MTX</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
<td>ADM, CY, VP-16</td>
</tr>
<tr>
<td>Kidney</td>
<td>2</td>
<td>IFN-alpha, ILK, VINB</td>
</tr>
<tr>
<td>Uterus</td>
<td>2</td>
<td>CDDP, hormones, IFM</td>
</tr>
</tbody>
</table>

Abbreviations: ADM, Adriamycin; CDDP, Cisplatin; CY, Cyclophosphamide; 5-FU, 5-Fluorouracil; IFM-msna, Ifosphamide-msna; IFN-alpha, Interferon-alpha; ILK, Interleukin; MTX, Methotrexate; msna, 2-Mercaptoethanesulfonic acid; VINB, Vinblastine; Vp-16, Etoposide.

Each patient gave his or her informed consent to participate in the study, which was approved by our hospital’s ethics committee. A 5-ml blood sample was obtained before the first chemotherapy session, 24 h after the first session, and 20–22 days after the last chemotherapy session of the first cycle, before the second cycle was begun. The blood was centrifuged and 2.5-ml aliquots of serum were frozen and stored at −30°C until analysis. None of the patients had antecedents of kidney, liver or connective tissue disease, or abnormalities in enzyme activities. Nutritional status was considered acceptable in all patients, as body weight remained within the normal range for age, sex and height.

2.2. Laboratory analyses

Samples were thawed and analyzed in the same batch according to Ellman et al. [7] to determine cholinesterase activities. Arylesterase activity was determined as described by Junge and Klee [8]. In both methods, activity was determined from the color change as choline and acetate release respectively, and was measured under controlled temperature conditions with a Beckman 3600 spectrophotometer (Irvine, CA, USA).

Prothrombin time and blood concentrations of albumin, transaminases, total bilirubin and alkaline phosphatase before and after treatment with anti-tumoral drugs were recorded from the patient’s hospital record. These laboratory values are habitually determined to detect possible liver damage [9].

2.3. Statistical analyses

One-way analysis of variance was used to test the differences in values at different times (before chemotherapy, 24 h after the first session, and 20–22 days after the last session) for each localization of the primary carcinoma, and to compare the results in men and women across localizations. As a control set of values, we used the results obtained for the same patient before the first cycle of treatment with cytostatics started. Differences with a $P$ value $<0.05$ were considered significant.

3. Results

Serum butyrylcholinesterase and arylesterase activities were clearly decreased ($P<0.05$) 24 h after the first session of chemotherapy. Twenty to 22 days after the end of the first cycle, these enzyme activities had returned to pretreatment levels (Table 2).

Enzyme activities did not differ significantly when the patients were stratified according to age, sex, type of tumor or anti-tumoral treatment given.

Of the laboratory tests used to evaluate hepatic function [9], albumin and transaminase levels were significantly decreased ($P<0.05$) after anti-tumoral treatment, and total bilirubin showed a nonsignificant increase (0.6 vs. 0.9 mg/ml, $P=0.40$). These values had returned to normal at the end of the study (Table
Table 2
Laboratory values (mean±S.D.) in 65 patients with carcinoma before the start of chemotherapy (basal), 24 h after the end of the first session, and 20–22 days after the end of the first cycle

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal</th>
<th>24 h</th>
<th>20–22 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyrylcholinesterase (U/l)</td>
<td>5606±1632</td>
<td>4750±1320*</td>
<td>5930±1770</td>
</tr>
<tr>
<td>Arylesterase (kU/l)</td>
<td>69±31</td>
<td>54±22*</td>
<td>69±30</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42±6</td>
<td>39±5b</td>
<td>44±5</td>
</tr>
<tr>
<td>Total bilirubin (mg/ml)</td>
<td>0.6±0.3</td>
<td>0.9±0.4</td>
<td>0.6±0.4</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/l)</td>
<td>25±4</td>
<td>50±6</td>
<td>26±6</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/l)</td>
<td>30±2</td>
<td>65±6</td>
<td>34±6</td>
</tr>
</tbody>
</table>

* P<0.01.

b P<0.05.

2). We found no changes in alkaline phosphatase activity or prothrombin time during or after treatment.

4. Discussion

We found that serum activity of butyrylcholinesterase and arylase decreased clearly within 24 h after treatment with cytostatics. This suggests that the anti-tumoral drugs studied here had a direct hepatotoxic effect that was independent of sex, age, location of the tumor or type of anti-tumoral chemotherapy given. This hypothetical effect is supported by earlier clinical and experimental studies that provide evidence of the hepatotoxic effects of anti-tumoral drugs such as cytostatics, hormones, interleukins and interferons [10–12], which are known to decrease plasma activities of butyrylcholinesterase and arylesterase in subjects with liver damage [13,14].

Our results are further evidence that anti-tumoral treatment causes liver damage: decreased serum butyrylcholinesterase and arylesterase activity, and changes in blood albumin, transaminases and total bilirubin, appeared in patients who had normal values before treatment was started (Table 2). The hospital records contained no mention of weight loss or change in nutritional status, and we therefore assume that nutritional status was adequate in all patients. The interaction between anti-tumoral chemotherapy and the activities of butyrylcholinesterase, arylesterase in serum should be of concern because in cancer patients who undergo specific anti-tumoral chemotherapy, it may reduce the clearance of drugs and xenobiotics, and may affect the conversion of prodrugs to biologically active forms.

Acknowledgements

This study was supported by the Education and Science Council of the Andalusian Regional Government through Project no. 040. We thank the staff of the Clinical Oncology Service at the San Cecilio University Hospital in Granada for their generous cooperation, and Karen Shashok for translating the original manuscript into English.

References