Serum Galactosyltransferase as a Prognostic Marker in Patients with Solid Tumors

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ABSTRACT

The serum level of galactosyltransferase was measured in a group of 218 patients with a variety of solid tumors and most with advanced disease. The pretreatment enzyme level showed little potential as a diagnostic tumor marker, and its change with treatment did not reflect the initial response. There was, however, a significant correlation between the length of survival and the pretreatment enzyme level. Patients with normal levels survived over twice as long as those with elevated levels. When Cox's proportional hazards regression analysis was used to compare the prognostic potential of galactosyltransferase with a number of known clinical indicators of prognosis, the variable most related to survival was performance status ($P < 10^{-4}$) followed by galactosyltransferase ($P = 0.01$) and then the extent of disease ($P = 0.03$). The other variables, such as previous therapy, the type, site, and size of primary tumor, did not contribute significantly to the relationship with survival. The pretreatment level of galactosyltransferase is therefore a relatively independent prognosticator of survival and, as such, could be potentially useful in patient management by increasing the accuracy of the initial assessment of prognosis.

INTRODUCTION

The accurate initial assessment of prognosis is very important in the management of patients with solid tumors. However, much of the research into the development of tumor markers has been aimed at diagnosis or monitoring response, and less attention has been paid to their prognostic potential. For a marker to be clinically useful in establishing initial prognosis, it must act relatively independently of existing clinical prognosticators.

One such marker is carcinoembryonic antigen. Its pretreatment or preoperative serum level was reported to be prognostic of survival in patients with gastric cancer (1), squamous cell cancer of the cervix (2), colorectal cancer (3), and early breast cancer (4). Pretreatment levels of several acute phase reactants have also been reported as prognosticators of survival for patients with invasive bladder cancer (5) and gastrointestinal cancer (6). Other markers, such as serum $\beta$-human chorionic gonadotropin and $\alpha$-fetoprotein, while reflecting the length of survival, are actually related to the extent of disease rather than being independent prognosticators of survival (7). There are other reports of markers being prognostic, but in most cases, the extent of disease has not been considered.

The serum level of galactosyltransferase has been extensively investigated as a possible tumor marker (8). It has been reported to have diagnostic (9) and monitoring (10) potential in ovarian cancer, and similar potential has been shown for breast cancer (11). There has been much interest in the "isoenzymes" of serum galactosyltransferase (12,13).

Despite this level of interest, little is known about the prognostic potential of serum galactosyltransferase. We report here a preliminary study of 218 patients with a variety of solid tumors, to determine whether the pretreatment level of serum galactosyltransferase has any general prognostic potential.

MATERIALS AND METHODS

Patients and Samples. Blood samples were taken by venipuncture from 218 adult patients with malignant disease prior to the commencement of their chemotherapy and at follow-up during therapy and assessment. There were 116 males and 102 females with ages from 18 to 82 (mean, 56 yr) of which 78 had had prior therapy including surgery for 52 patients, radiotherapy for 13 patients, chemotherapy for 2 patients, and a combination of these for 11 patients. Twenty-one patients with no overt disease were referred for adjuvant therapy, and the majority of the remainder had advanced disease. No patient had any active intercurrent illness, and all patients had creatinine clearance of greater than 60 ml/min. Patients were followed for up to 170 wk (mean follow-up, 41 ± 32 wk). Standard WHO response criteria (14) and the Eastern Cooperative Oncology Group scale of performance status were used in patient assessment. The control population comprised 60 normal healthy volunteers. The serum was collected by centrifugation and stored at -70°C.

Galactosyltransferase Assay. The level of galactosyltransferase activity in serum was determined by incubating 2 ml of serum in a total reaction volume of 0.1 ml containing 18 $\mu$Ci of uridine diphosphogalactose (Sigma Chemical Company), 1 $\mu$Ci of uridine diphospho-$[^3H]$galactose (Amersham), 1 $\mu$m of MnCl$_2$, 0.05% Triton X 100, 1.2 mg of ovalbumin (Sigma) as the acceptor, and 0.05% imidazole buffer, pH 7.3, as previously described (15). After 1-h incubation at 37°C, the amount of $[^3H]$galactose transferred to ovalbumin was determined as previously described (16). The upper limit of the normal range for serum galactosyltransferase activity (mean ± 2 SD) was 47.2 nmol of galactose transferred per ml of serum per h.

Statistical Analysis. The distribution of enzyme activity in the various patient groups was compared to that of the control group using the $t$ test, while the paired $t$ test was used to analyze the significance of the change in enzyme level associated with response. Log-rank life table analysis was performed essentially as described by Peto et al. (17), and the proportional hazards regression analysis was that described by Cox (18) using the BMDP Program-2L.

RESULTS

Table 1 shows that, although there was a highly significant difference between the control and patient group, only 76 of the 218 patients (35%) had elevated serum levels of galactosyltransferase prior to the start of treatment. The distribution of enzyme activity for each disease site was also significantly different from the control group with the exception of those with head and neck cancer. The group with unknown primary site had the highest proportion (69%) of patients with elevated enzyme levels.

The relationship between the extent of disease and pretreatment galactosyltransferase is given in Table 2. The distribution of enzyme activity in both groups with local disease and presenting for adjuvant therapy was not significantly different from
GALACTOSYLTRANSFERASE AND PROGNOSIS

Table 1 Serum galactosyltransferase levels and site of primary

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Mean ± SD (nmol/ml serum/h)</th>
<th>Elevated galactosyltransferase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>60</td>
<td>32.8 ± 7.2</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>34</td>
<td>45.0 ± 24.9*</td>
<td>26</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>26</td>
<td>48.7 ± 17.8*</td>
<td>38</td>
</tr>
<tr>
<td>Colorectal</td>
<td>31</td>
<td>48.4 ± 28.9*</td>
<td>35</td>
</tr>
<tr>
<td>Lung</td>
<td>37</td>
<td>49.3 ± 25.3*</td>
<td>41</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>39</td>
<td>50.0 ± 22.6*</td>
<td>44</td>
</tr>
<tr>
<td>Head and neck</td>
<td>25</td>
<td>30.9 ± 8.9</td>
<td>4</td>
</tr>
<tr>
<td>Unknown primary</td>
<td>13</td>
<td>55.8 ± 19.1*</td>
<td>69</td>
</tr>
<tr>
<td>Other</td>
<td>13</td>
<td>42.9 ± 16.5*</td>
<td>38</td>
</tr>
<tr>
<td>Total</td>
<td>218</td>
<td>46.4 ± 22.9*</td>
<td>35</td>
</tr>
</tbody>
</table>

* Significantly different from controls (P < 0.001; t test).

Table 2 Galactosyltransferase levels and the extent of disease

The conditions are the same as for Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Mean ± SD (nmol/ml serum/h)</th>
<th>Elevated galactosyltransferase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>21</td>
<td>34.0 ± 8.2</td>
<td>14</td>
</tr>
<tr>
<td>Local</td>
<td>43</td>
<td>36.9 ± 13.9</td>
<td>16</td>
</tr>
<tr>
<td>Metastatic (nonliver)</td>
<td>109</td>
<td>44.4 ± 17.4*</td>
<td>33</td>
</tr>
<tr>
<td>Metastatic (liver)</td>
<td>45</td>
<td>66.3 ± 32.4*</td>
<td>69</td>
</tr>
</tbody>
</table>

* See Table 1, Footnote a.

Fig. 1. Changes in serum galactosyltransferase with the initial response to therapy. Serum galactosyltransferase was measured prior to the start of therapy and at approximately 12 wk after therapy was started. The upper limit of the normal range is represented by the dashed line.

Fig. 2. The log-rank life table analysis of survival of: 142 patients with normal compared to 76 patients with elevated levels of galactosyltransferase (A); 64 patients with local disease compared to 154 patients with metastatic disease (B); 54 with normal compared to 10 with elevated galactosyltransferase for patients with local disease (C); 86 with normal compared to 68 with elevated galactosyltransferase for patients with metastatic disease (D); 113 patients who initially responded compared to 99 who did not initially respond (E); 86 with normal compared to 27 with elevated galactosyltransferase for responding patients (F); and 53 with normal compared to 46 with elevated galactosyltransferase for nonresponding patients (G). The level of significance (P) is included in each analysis.

Table 3 Relationship between length of survival, galactosyltransferase, and other clinical prognosticators assessed by Cox's proportional hazards regression analysis (BMDP Program-2L)

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Galactosyltransferase</td>
<td>0.012</td>
</tr>
<tr>
<td>Extent of disease</td>
<td>0.028</td>
</tr>
<tr>
<td>Tumor type</td>
<td>Not significant</td>
</tr>
<tr>
<td>Tumor size</td>
<td>Not significant</td>
</tr>
<tr>
<td>Tumor site</td>
<td>Not significant</td>
</tr>
<tr>
<td>Previous therapy</td>
<td>Not significant</td>
</tr>
<tr>
<td>Smoking</td>
<td>Not significant</td>
</tr>
<tr>
<td>Age</td>
<td>Not significant</td>
</tr>
<tr>
<td>Sex</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

level, the extent of disease, and the initial response to therapy. There was a highly significant difference between the survival probability of patients with normal and elevated enzyme levels. The mean length of 50% survival was 57 wk for those with normal enzyme levels compared to 27 wk for those with elevated levels (Fig. 2A).

Since the extent of disease was also related to the length of survival (Fig. 2B), patients with local disease were analyzed separately from those with metastatic disease. Patients with localized disease who have normal enzyme levels survive significantly longer than those with elevated levels (Fig. 2C). Fig. 2D shows that the same was also true for patients with metastatic disease.

Although the initial response to therapy is a powerful prognosticator of survival (Fig. 2E), galactosyltransferase levels further subdivided the survival curves of both the responders (Fig. 2F) and nonresponders (Fig. 2G).

The prognostic potential of galactosyltransferase was compared to a number of known clinical indicators of prognosis using the Cox proportional hazards regression analysis, and the results are summarized in Table 3. The variable most related to the length of survival was patient performance status with a $P < 10^{-4}$. This was followed by the pretreatment level of galactosyltransferase with a $P = 0.012$ and then the extent of
disease with a \( P = 0.028 \). All the other variables did not contribute significantly to the relationship with the length of survival.

**DISCUSSION**

The 35% of cancer patients with elevated pretreatment serum galactosyltransferase given in Table 1 is similar to that reported by others (8, 19). Even though there was a significant difference between the galactosyltransferase levels of the controls and all patient groups except those with head and neck cancer, the lack of site specificity and the small proportion of patients with elevated enzyme levels suggest that galactosyltransferase has little potential as a general diagnostic marker.

Only patients with metastatic disease had enzyme levels significantly different from the control group (Table 2), and we have previously shown that there are also significant differences in the enzyme levels between those with local, non-liver metastatic, and liver metastatic disease (20). It is doubtful, however, that this relationship between galactosyltransferase and disease spread would be of any clinical use.

Galactosyltransferase has been reported as a potential monitor of response in patients with advanced breast cancer (21) and in ovarian cancer (10). We were unable to demonstrate that changes in the level of galactosyltransferase were related to response in our group of patients, and therefore the potential of galactosyltransferase as a response monitor may be limited to breast and ovarian cancer and may not have general application as a response monitor for other tumors.

Therefore the clinically useful potential of serum galactosyltransferase is as a prognostic indicator (Fig. 2) rather than a diagnostic or monitoring tumor marker. The relationship between the length of survival and the pretreatment serum level of galactosyltransferase is relatively independent of the usual pretreatment clinical indicators (Table 3) and the patient's initial response to therapy (Fig. 2, F and G). This degree of independence means the pretreatment level of galactosyltransferase is a potential marker for other tumors.

If its prognostic potential is corroborated, galactosyltransferase could allow a more accurate assessment of prognosis and influence therapeutic decision making. It may provide greater insights into the nature of response to therapy and aid identification of those patients who might benefit from intensive therapy compared to those who would not. It has an exciting potential to improve the quality of management of cancer patients.

**REFERENCES**

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