Serum Tumor Marker Half-Life during Chemotherapy Allows Early Prediction of Complete Response and Survival in Nonseminomatous Germ Cell Tumors

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ABSTRACT

The prognostic value and therapeutic utility of monitoring the decay of a-fetoprotein (AFP) and human chorionic gonadotropin (HCG) after chemotherapy for nonseminomatous germ cell tumors was assessed. Patients treated on successive front-line chemotherapy protocols at Memorial Hospital between 1979 and 1988 were studied. Marker values taken within the first 90 days of treatment were reviewed for the 198 patients who had initially abnormal values and serial measurements at Memorial Hospital. Since markers frequently increased in an unpredictable fashion in the first week after chemotherapy, prechemotherapy values would be inaccurate for assessment of subsequent half-life. Therefore, the first two values measured >7 days after the start of treatment were used for all calculations of half-life. Among 38 patients who had the two successive AFP measurements elevated, those who later achieved a complete response (CR) had a median AFP half-life of 6.1 days (n = 20), whereas those not achieving CR had a median AFP half-life of 13.3 days (P = 0.02). Among 37 patients with the two successive HCG values elevated, those who later achieved CR had a median HCG half-life of 4.2 days (n = 10), whereas those not achieving CR had a median HCG half-life of 18.4 days (P = 0.04). Forty-two patients who had an AFP half-life >7 days or an HCG half-life >3 days had significantly shorter overall survival (median, 8 months) than the other 156 patients (median not reached) (P < 0.0001). These 42 patients also achieved CR in lower proportion (29%) than the other 156 patients (89%) (P < 0.001). Cox regression identified prolonged marker half-life as the most significant independent predictor of survival. Lack of appropriate decay of serum tumor markers can identify patients unlikely to achieve CR or prolonged survival and thus can be used to select patients during treatment who may benefit from an early change to more aggressive therapy.

INTRODUCTION

Identification of the 20–30% of patients with advanced NSGCT1 who are destined to fail conventional therapy (and ultimately die from malignancy) remains an important objective of clinical research. Most studies have concentrated on pretreatment clinical characteristics as prognostic variables. Pretreatment features have been used to predict the probability of attaining CR (1) and relapsing after CR (2), demonstrate potential prognostic features within risk strata (3), and provide evidence of stage migration (4). Despite their use, as many as 10% of “good risk” patients fail to achieve CR in current trials (5, 6). Almost all patients with refractory disease subsequently die (7). A proportion of “poor risk” patients will achieve long-term survival with conventional therapy (3, 8, 9), making the use of very intensive initial therapy inappropriate. Clarification of new clinical characteristics permitting more accurate recognition of patients likely to fail therapy is therefore valuable.

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1 The abbreviations used are: NSGCT, nonseminomatous germ cell tumor; AFP, a-fetoprotein; CR, complete response; d.f., degrees of freedom; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.

The introduction of novel treatment strategies may allow an improvement in survival for patients with a poor prognosis, particularly if introduced early during management.

The management of NSGCT has been distinguished not only by the frequency with which patients can be cured but also by the availability of accurate serum tumor markers. AFP and HCG are glycoproteins that are present at elevated levels in the serum of most patients with metastatic NSGCT (10, 11). These markers aid in management by reducing errors in diagnosis and staging, providing prognostic information at the time of presentation of patients with metastatic disease and furnishing an accurate and objective means of monitoring response to therapy and detecting recurrent disease (10, 12–14).

Each marker is elevated in approximately 50–70% of patients and 70–85% of patients with disseminated disease will have one or both markers elevated at presentation (10, 11). The kinetics of both markers have been studied after complete surgical resection of disease and the biological half-life was 5–7 days for AFP and 18–48 h for HCG (15). This is the same as the half-life in normal subjects (16, 17). While clearance from the serum after chemotherapy has been less well studied, one group reported mean half-lives of 5.7 days for AFP and 3.1 days for HCG (18).

In the setting of advanced disease, elevated pretreatment marker values have been associated with a worse prognosis (1, 19). Therefore, a higher proportion of patients likely to fail conventional therapy will have elevated marker levels prior to the commencement of chemotherapy. Studies of markers after chemotherapy have identified an increase immediately after initiation of treatment in some patients (18, 20). This has been postulated to be due to release of these substances after tumor cell death.

The aim of this study was to analyze the prognostic value of monitoring the decay of AFP and HCG after the commencement of chemotherapy. Prior studies of prognostic features have emphasized pretreatment clinical characteristics. Marker regression is a posttreatment characteristic which may be able to identify early treatment failure (21) regardless of pretreatment risk stratification.

PATIENTS AND METHODS

All patients with NSGCT treated on Memorial Hospital front-line chemotherapy protocols designed for good risk and poor risk patients between 1979 and 1988 who had elevated AFP or HCG levels were considered. To assure comparability of laboratory measurements, patients who did not have an adequate number of serial measurements at Memorial Hospital were excluded. The numbers of patients studied and inclusion criteria are detailed in Table 1. All patients received chemotherapy regimens containing high doses of cisplatin ($\geq$100 mg/m$^2$/cycle) or carboplatin. The details of treatment and response have been described previously (5, 8, 22, 23).

Complete resolution of all biochemical and radiographic abnormalities or the resection of only teratoma or necrotic debris after chemotherapy was classified as CR to chemotherapy. Complete resection of residual malignancy after chemotherapy was classified as CR to chemo-

References:

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2. To whom requests for reprints should be addressed, at Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

3. The abbreviations used are: NSGCT, nonseminomatous germ cell tumor; AFP, a-fetoprotein; CR, complete response; d.f., degrees of freedom; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase.
therapy plus surgery. Any response less than CR was considered to be an incomplete response. Patients were classified as good or poor risk according to their predicted probability of achieving CR calculated by a logistic regression model using pretreatment HCG, LDH, and number of metastatic sites (1). Patients with an NSGCT and either a predicted probability of CR < 0.50 or an extragonadal primary site were considered poor risk. Patients with an NSGCT arising in the testis and a predicted probability of CR ≥ 0.50 were considered good risk.

HCG was assayed using a modification of the highly sensitive and specific double antibody radioimmunoassay procedure of Vaitukaitis et al. (24). The standard HCG for this assay was obtained from National Laboratories, a division of Carter Wallace. A specific antiserum to purified HCG from pooled human fetal serum was prepared in rabbits. The antiserum against the purified \( \beta \) subunit of HCG was used. (24). The standard HCG for this assay was obtained from National Institute of Arthritis, Metabolism and Digestive Diseases (standard CR117). The antiserum against the purified \( \beta \) subunit of HCG was prepared in rabbits. A value of \( \geq 2 \) ng/ml was considered normal. Two assays were used to quantitate serum AFP. Prior to June 1984, a radioimmunoassay was used with reagents kindly provided by Wampole Laboratories, a division of Carter Wallace. A specific antiserum to purified AFP from pooled human fetal serum was prepared in rabbits. After June 1984, a sandwich enzyme immunoassay method from Hybritech (San Diego, CA) was used. Both the capture and signal antibodies were monoclonal. Both methods provide equivalent quantitative results, but the enzyme immunoassay has an improved sensitivity of 15 ng/ml. All values for AFP > 15 ng/ml were considered abnormal.

The first 10 values for HCG and AFP recorded in the clinical chemistry department at Memorial Hospital were collected for 231 patients. Marker values were plotted semilogarithmically, and the half-life of marker decline was calculated between each point using a computer spreadsheet program. Marker values frequently increased in an unpredictable manner during the first 7 days after the initiation of chemotherapy. This is consistent with release from treated, dying tumor (18). Therefore, no pretreatment values or values measured during the first week of therapy were used for assessment of marker half-life. The first two values measured more than 7 days after the start of treatment were used for all calculations of the half-life of marker decline. In order to limit the time span under study, only values measured in the first 90 days after the start of chemotherapy were considered.

Patients were classified as having prolonged marker half-life if the first 2 values after the seventh day of treatment were abnormal and the half-life for AFP was > 7 days or for HCG was > 3 days. Marker decline was deemed to be satisfactory if the half-life of AFP was < 7 days or HCG was < 3 days or if either of the first 2 values after day 7 was normal. Patients who had elevations of both markers were considered to have prolonged marker half-life if either HCG or AFP half-life was prolonged.

Hypotheses concerning differences in proportions were tested using \( \chi^2 \) and Fisher's exact tests and those concerning differences in medians of continuous data using the Wilcoxon test (25). Survival distributions were estimated by the method of Kaplan and Meier (26), and univariate comparisons were made using the log rank test (27).

Two analyses were performed. In the first analysis of 198 patients, survival was calculated from the time the patient was deemed to have satisfactory markers or a prolonged half-life. This was at the date of the first marker value after day 7 if this value was normal or at the date of the second marker value otherwise. Comparisons of survival in this analysis were made with the log rank test (27). In the second analysis utilizing Cox regression (28), survival was always calculated from the date of the second marker value after day 7. This analysis included 176 patients, since the remaining 22 patients did not have a second marker value prior to day 90. If both AFP and HCG were elevated, survival was calculated from the latter of the 2 dates. Survival was always calculated from a date within 90 days from the start of chemotherapy.

Cox regression analysis (28) was used to assess whether prolonged marker half-life was a prognostic factor for survival. A variable, NORMALIZE, was defined to indicate whether markers were decaying at the proper rate or not. NORMALIZE took the value 1 if marker half-life was prolonged and 0 if markers were decreasing satisfactorily, as defined above. Along with known prognostic variables (see below), we considered whether NORMALIZE was an independent prognostic variable for survival.

Cox regression considers the logarithm (base e) of the relative risk of death, \( \log \left( \frac{\lambda(t)}{\lambda_0(t)} \right) \), to be a linear function of k prognostic variables \( Z_i \), where \( i = 1, 2, \ldots, k \):

\[
\log \left( \frac{\lambda(t)}{\lambda_0(t)} \right) = a_1 Z_1 + a_2 Z_2 + \ldots + a_k Z_k. \tag{A}
\]

In Equation A, \( \lambda(t) \) is the hazard function (relative rate of death) at time \( t \), \( \lambda_0(t) \) is a baseline hazard function (corresponding to \( Z_1 = Z_2 = \ldots = Z_k = 0 \)), \( Z_i \) is a value of the ith prognostic variable, and the coefficients \( a_i \) are estimated from the data. The variables considered as potential prognostic factors were NORMALIZE and the known prognostic factors (1, 19, 29): pretreatment HCG (or log [HCG + 1]), pretreatment LDH (or log [LDH + 1]), the total number of metastatic sites (coded as 0 for elevated markers only, 1 for one site of metastasis, or 2 for two or more sites of metastasis), AFP (or log [AFP + 1]), site of primary tumor, and a variable termed RISK (coded as 0 for good risk patients and 1 for poor risk patients). RISK took the value 1 if the probability of CR (1) was calculated to be < 0.5 or the primary site was extragonadal. Otherwise, RISK took the value 0. Procedures of the Statistical Analysis System were used for all computation (30).

**RESULTS**

**Patient Characteristics.** AFP baseline values were elevated in 151 patients, HCG values in 134 patients, and both markers in 87 patients. Patient characteristics for the 198 patients studied are shown in Table 2.

Since marker values increased unpredictably in the first 7 days after the initiation of chemotherapy, only values measured after the seventh day of treatment were used to calculate the half-life of marker decay. For patients with 2 elevated marker values after the seventh day, the half-life between the first 2 values was calculated and results are shown in Table 3. Both AFP and HCG half-lives were significantly prolonged in those patients not achieving a CR.

Half-life values were calculated in this way; patients whose AFP half-life was > 7 days or whose HCG half-life was > 3 days had significantly shorter survival and achieved CR less frequently. The cutoff values of 7 days and 3 days were chosen prospectively, based on the expected biological half-lives. Even though the median half-life of HCG decline in patients achieving CR with chemotherapy was 3.5 days, a cutoff of 3 days was used, because only 2 patients had a half-life for HCG between 3 and 4 days and neither achieved a prolonged CR.

**Response Proportions and Relapse.** Proportions of CR according to prolonged or satisfactory decline of serum markers are shown in Table 4. If prolonged half-life of either AFP or HCG were considered separately, each was capable of identifying a group of patients less likely to achieve CR. If patients with a prolonged half-life of either marker were included in a single group, a larger, more clinically useful group of 42 patients was identified. Only 12 of these 42 patients (29%) achieved a
HALF-LIFE OF SERUM TUMOR MARKER DECLINE IN NSGCT

Table 2 Characteristics of 198 patients with elevated AFP or HCG

<table>
<thead>
<tr>
<th>Patients</th>
<th>All</th>
<th>Good risk</th>
<th>Poor risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>28</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Median</td>
<td>13-54</td>
<td>13-54</td>
<td>15-51</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testis</td>
<td>173 (87%)</td>
<td>118 (100%)</td>
<td>55 (69%)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>14 (7%)</td>
<td>0</td>
<td>14 (17%)</td>
</tr>
<tr>
<td>Retroperitoneum</td>
<td>11 (6%)</td>
<td>0</td>
<td>11 (14%)</td>
</tr>
<tr>
<td>No. of metastatic sites*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Markers elevated only</td>
<td>18 (9%)</td>
<td>18 (16%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>≥2</td>
<td>117 (60%)</td>
<td>47 (40%)</td>
<td>70 (88%)</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAB-6* /</td>
<td>75</td>
<td>54</td>
<td>21</td>
</tr>
<tr>
<td>VAB-6 + EP</td>
<td>64</td>
<td>64</td>
<td>0</td>
</tr>
<tr>
<td>CBE*</td>
<td>29</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>AFP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>151 (76%)</td>
<td>91 (77%)</td>
<td>60 (75%)</td>
</tr>
<tr>
<td>Median value (ng/ml)</td>
<td>256</td>
<td>165</td>
<td>453</td>
</tr>
<tr>
<td>Range (ng/ml)</td>
<td>16-139,600</td>
<td>18-10,400</td>
<td>16-139,600</td>
</tr>
<tr>
<td>HCG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>134 (68%)</td>
<td>71 (60%)</td>
<td>63 (79%)</td>
</tr>
<tr>
<td>Median value (ng/ml)</td>
<td>64</td>
<td>19</td>
<td>1,492</td>
</tr>
<tr>
<td>Range (ng/ml)</td>
<td>2.2-44,500</td>
<td>2.5-3,800</td>
<td>2.2-44,500</td>
</tr>
<tr>
<td>LDH°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>141 (72%)</td>
<td>63 (54%)</td>
<td>78 (98%)</td>
</tr>
<tr>
<td>Median value (units/liter)</td>
<td>493</td>
<td>347</td>
<td>771</td>
</tr>
<tr>
<td>Range (units/liter)</td>
<td>239-16,629</td>
<td>239-1,440</td>
<td>240-16,629</td>
</tr>
</tbody>
</table>

* Adequate data available in 196 patients.
* Ref. 22.
° Ref. 5.
" Ref. 23.
' Ref. 8.
VAB-6. cyclophosphamide + vincristine + bleomycin + dactinomycin + cisplatin; EP, etoposide + cisplatin; CBE, carboplatin + bleomycin + etoposide.

Table 3 Correlation of response and marker half-life calculated between the first and second marker values measured after day 7 of chemotherapy, for 66 patients in whom both the first and second values were abnormal

<table>
<thead>
<tr>
<th>Response</th>
<th>CR-chemo*</th>
<th>All CR</th>
<th>IR</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP half-life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>17</td>
<td>20</td>
<td>18</td>
<td>0.017</td>
</tr>
<tr>
<td>Median (days)</td>
<td>5.9</td>
<td>6.1</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td>Range (days)</td>
<td>3.3-35.7</td>
<td>3.3-100</td>
<td>3.2-100</td>
<td></td>
</tr>
<tr>
<td>HCG half-life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>8</td>
<td>10</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Median (days)</td>
<td>3.5</td>
<td>4.2</td>
<td>18.3</td>
<td>0.037</td>
</tr>
<tr>
<td>Range (days)</td>
<td>2.5-62.4</td>
<td>2.5-62.4</td>
<td>0.9-19.0</td>
<td></td>
</tr>
</tbody>
</table>

* CR-chemo, complete response to chemotherapy alone; All CR, all complete responses, including CR-chemo; IR, incomplete response; Inc, increasing marker value, half-life not valid.
* Wilcoxon test comparing all CR with incomplete responses.

CR, compared with 139 of 156 patients (89%) with satisfactory marker values ($\chi^2 = 63.67, 1 $d.f., $P < 0.0001$).

Twelve patients who had prolonged marker half-life achieved a CR. Residual viable malignancy was resected after chemotherapy more frequently in this group of patients. Four of the 12 patients (33%) had residual malignancy resected compared to 13 of 139 patients (9%) who were found to have satisfactory marker decay (Fisher's exact test, $P = 0.03$). Relapse also occurred more frequently; 8 of the 12 patients (67%) with abnormal marker half-life relapsed after CR compared to 18 of 139 patients (13%) with satisfactory markers (Fisher's exact test, $P = 0.0001$). The 13% relapse rate is slightly higher than expected for an overall group of patients with germ cell tumors, but this was probably due to the worse prognosis of patients who were selected for this analysis because they had an NSGCT and elevated markers.

Proportions of CR are shown in Table 4 for Memorial Hospital good and poor risk patient groups. Prolonged marker half-life identified patients within each group who achieved a CR less frequently.

Survival Analysis. Survival for all patients is shown in Fig. 1.

Patients with prolonged marker half-life had dramatically shorter survival compared to the other patients (log rank $\chi^2 = 66.4, 1 $d.f., $P < 0.0001$). Only 6 patients with prolonged marker half-life were alive >24 months from the start of treatment. Three of these 6 patients had viable malignancy resected after chemotherapy; 1 additional patient relapsed 13 months after starting chemotherapy and has remained alive with disease at 35+ months. Only 2 patients with prolonged marker half-life achieved a CR with chemotherapy alone and remained alive after 24 months (32+ and 69+ months) after starting treatment.

Prolonged half-life of both AFP and HCG could be used individually to identify a group of patients with shorter survival.
HALF-LIFE OF SERUM TUMOR MARKER DECLINE IN NSGCT

Fig. 1. Survival for 198 patients according to abnormal or satisfactory decay of AFP and HCG after initiation of chemotherapy (log rank test, $\chi^2 = 66.37$, 1 d.f., $P < 0.0001$).

(Fig. 2). Fourteen patients had prolonged half-life of one marker but satisfactory values for the other. Seven of these 14 patients (50%) achieved a CR, but only 4 remained continuously alive and free of disease after therapy. Thus, patients who had only one abnormal marker, while the other was satisfactory, had a poor prognosis. Therefore, analyses of marker half-lives of both HCG and AFP should be considered complementary. In addition, prolonged marker half-life identified a group of patients with shorter survival within both the good risk and poor risk (Fig. 3) patient subgroups.

Seventy-five patients with NSGCT, who were otherwise excluded from this analysis because they had normal pretreatment AFP and HCG values (Table 1), had longer survival compared to all of the 266 patients (Table 1) with initial marker elevation (log rank $\chi^2 = 4.5$, $P = 0.03$). This supports the notion that patients selected for inclusion in the analysis because they had initially elevated AFP or HCG values had a worse prognosis.

Cox regression analysis was used to derive independent prognostic variables for survival. In this analysis, survival was always measured from the date of the second marker value after the seventh day of treatment. Twenty-two of the 198 patients studied were excluded from the Cox regression. All of these patients had a normal value for the first marker assay after the seventh day but did not have a second marker assay before the 90th day. CR proportions for the 176 patients included in the Cox regression are shown in Table 4.

The Cox model yielded NORMALIZE as the most significant prognostic factor among the variables considered and RISK as a second independent prognostic factor. None of the other variables entered the Cox model, and these 2 prognostic variables did not have a significant interaction. The final model was

$$\log \left( \frac{S(t)}{S_0(t)} \right) = 1.29 \text{NORMALIZE} + 1.41 \text{RISK} \quad (B)$$

This model has an overall $\chi^2$ (score statistic) of 76.15, 2 d.f., and a $P < 0.0001$.

The model yields four prognostic groups of patients. Kaplan-Meier plots of survival for these groups are displayed in Fig. 4. The survival curves are very similar to those for the original
The aims of trials for patients with a poor prognosis for survival. The relative risk of dying for those with prolonged marker half-life compared to those with satisfactory markers was 3.63. This means that there was >3-fold risk of death for those whose elevated markers did not decline appropriately. For patients in the same NORMALIZE group, the risk of dying for poor risk patients relative to good risk patients was 4.10. This implies approximately a 4-fold risk of death for poor risk patients compared to good risk patients.

After inspection of the coefficients in Equation B, the hypothesis that the two coefficients were equal was generated. This hypothesis was tested and confirmed. This meant that a Cox model could be generated with a single independent variable taking the value 0 for good risk patients with markers normalizing appropriately, the value 1 for good risk patients with markers not normalizing appropriately or poor risk patients with markers normalizing appropriately, and the value 2 for poor risk patients whose markers were not normalizing appropriately. There was then a relative risk of dying of 3.82 for one of these groups relative to the adjacent better one. This model is not reported in more detail because it was suggested only by the results of the first Cox regression analysis and lacks clinical applicability.

Similar results were found when Cox regression was undertaken separately in the good and poor risk patient subgroups. These analyses were limited by small numbers of patients. NORMALIZE was the only variable to enter the model for poor risk patients and NORMALIZE and LDH were the only variables for good risk patients.

**DISCUSSION**

This study shows that assessment of the decline of serum tumor markers after the initiation of chemotherapy is a powerful prognostic tool. The identification and utilization of prognostic factors has made possible the rational development of treatment programs for germ cell tumors. Clinical trials for patients with a good prognosis have demonstrated that fewer cycles of treatment (6, 31) and fewer cytotoxic agents (5) can be used without jeopardizing response proportions and survival outlook. The aims of trials for patients with a poor prognosis have been to increase the frequency of CR without intolerable toxicity (23, 32). Although disagreement exists over the weight of individual prognostic variables, decision algorithms used internationally to classify good and poor risk patients have generally recognized baseline tumor marker levels and bulk of disease as the most important predictive factors for response (19). These pretreatment prognostic factors have been used to decide what treatment program should be recommended for an individual patient.

Exploration of possible prognostic features evident only after the initiation of chemotherapy has been limited. Almost all current treatment programs await assessment of response after the completion of 3 or 4 cycles of chemotherapy before decisions regarding further treatment are considered. Assessment of response frequently involves surgical exploration and resection of residual disease in the retroperitoneum and chest.

Several studies of fewer patients have suggested that a prolonged half-life of marker decline may have prognostic implications (15, 18, 21, 33). The therapeutic usefulness of this information has, however, remained ill defined. The data in this report demonstrate that prolonged decay of markers compared to expected biological half-life is a powerful predictor of failure to respond and poor survival. Patients in whom a prolonged marker half-life was identified had a CR proportion of 31% and most patients achieving CR subsequently relapsed. Only 5 of 42 patients (12%) remained alive and free of disease >24 months from the start of treatment. It is possible that some of the long-term survivors were salvaged from chemotherapy-resistant malignancy by complete resection of residual malignancy after chemotherapy. Abnormal marker decline identified a poor prognosis subset of patients within both good and poor risk patient groups.

Cox regression analysis selected prolonged marker decay as the most significant predictor of limited survival. The only other independent prognostic factor for survival was good or poor risk patient category. The risk categorization was in turn derived from the primary site (all extragonadal tumors considered poor risk) and a mathematical formula which uses pretreatment HCG, LDH, and the number of sites of metastatic disease to predict the chance of achieving a CR. No other potential prognostic factor entered the model. This result indicates the importance of prolonged marker half-life as a predictor of poor survival. It also confirms that our existing risk stratification, which was derived from a logistic regression analysis of response, also predicts survival more powerfully than individual pretreatment variables and independently of the analysis of marker half-life. This substantiates the hypothesis that post-treatment clinical variables can complement pretreatment risk stratification.

Can the prognostic implications of marker half-life analysis be used to the patients' advantage? Once a treatment program has been initiated, why not wait until response is assessed at the completion of therapy? While these questions require evaluation in prospective studies, there are strong theoretical reasons to suggest that an early change of chemotherapy regimen may be of benefit to those patients identified with a poor prognosis. The median time to classification of patients according to marker half-life in this study was 33 days after the start of treatment. This is much briefer than the 3–6 months usually required to assess response. An early change to a more intensive regimen may avoid the problem of cumulative toxicities from chemotherapy and the potential development of chemotherapy resistance. For example, good risk patients may benefit from a change to a more intensive chemotherapy combination containing ifosfamide. Poor risk patients with abnormal marker half-life may benefit from a change to therapy such as high dose.
chemotherapy with autologous stem cell support. The latter option is currently the subject of prospective evaluation in a clinical trial at Memorial Hospital.

Previous reports have suggested the value of monitoring tumor marker half-life (15, 18, 21, 33-35). The majority of these studies have compared the marker levels prior to chemotherapy with the level at the time of the second cycle of treatment. Some studies have found this to be useful (21), while others have not (34). The likely reason for this discrepancy, and the potential flaw in this methodology, is that such an analysis fails to consider an initial increase in serum tumor marker levels which may occur at the initiation of chemotherapy. This phenomenon has been well described and is unpredictable, in that some patients have no increase while others may have elevations up to 600% of baseline (18, 20). This elevation makes it difficult to determine whether a decline in marker values after initiation of chemotherapy provides powerful prognostic information. It is likely that the most accurate method of assessing marker decline would be by measurement of multiple elevated values after the first week of treatment, with measurement of a best fit half-life applied to the data. This does not require excessively complicated analysis, because the calculations can be easily performed in a number of currently available personal computer programs. These results have led us to consider the more complex decline in LDH. It is possible that further prognostic information may be discerned from the decline in LDH, particularly in patients with initially normal AFP and HCG values.

This study demonstrates that prolonged decay of AFP or HCG after chemotherapy identifies patients unlikely to achieve CR or long-term survival. These patients may benefit from an early change in treatment. We recommend that all patients with NSGCT receiving chemotherapy be monitored with weekly assays for AFP and HCG until these markers have normalized. Patients enrolled in clinical trials should be prospectively monitored to confirm the significance of prolonged marker half-life. Patients who are not receiving treatment in a clinical trial and who are found to have an abnormal decay of markers should be referred to a major treatment center so that a change to more intensive therapy can be considered.

REFERENCES


Serum Tumor Marker Half-Life during Chemotherapy Allows Early Prediction of Complete Response and Survival in Nonseminomatous Germ Cell Tumors

Guy C. Toner, Nancy L. Geller, Claire Tan, et al.


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