Short Communication

Evaluation of Biomarkers of Survival Response in Hormone-refractory Prostate Cancer Patients Treated with Suramin

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Abstract

Hormone-refractory prostate cancer (HRPC) patients often have nonmeasurable disease. In such patients, predictive biomarkers other than tumor response may be required to compare therapeutic effects. We examined the predictive value for survival of various clinical and laboratory parameters, including prostate-specific antigen (PSA), in HRPC patients treated with suramin. Data from 103 HRPC patients were analyzed using various survival analyses, the likelihood ratio approach, and logistic regression analyses. When pretreatment factors, survival analyses, the likelihood ratio approach, and laboratory parameters, including prostate-specific antigen were significant variables. However, in view of the complexities involving the relationship between PSA expression and prostate cancer growth and possible selective effect of treatment on PSA, further prospective testing is necessary. Therefore, ΔPSA cannot necessarily be used as a biomarker for survival response in individual patients during the evaluation of the therapeutic response of HRPC to new antineoplastic drugs.

Materials and Methods

Data. Data on the following pretreatment factors: age; performance status; weight; Hb; alkaline phosphatase; ACP; LDH; plasma PSA concentrations; platelet, WBC, and lymphocyte counts;

Received 4/28/97; revised 4/9/98; accepted 4/16/98.

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1 Supported by National Cancer Institute Contract NO1-CM57734 (NIH, Department of Health and Human Services, Bethesda, MD). L. M. R. was the recipient of a Gordon Richards Fellowship of the Canadian Cancer Society, Ontario Division, and a McEachen Fellowship of the Canadian Cancer Society, National Division.

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albumin; creatinine clearance; cholesterol; exposure to flutamide prior to suramin; time from first diagnosis of the disease to suramin treatment; and sites of metastases were collected in 103 patients enrolled into two Phase I trials of suramin (1-3). The current analysis excluded patients with pretreatment PSA concentrations of <4 ng/ml. At every clinic visit during treatment (approximately weekly) and after treatment (approximately monthly), serum PSA concentrations, ACP; and lymphocyte counts were performed, in addition to routine laboratory studies.

**Statistical Methods.** First, univariate analyses using Kaplan-Meier estimation (7) and the log-rank test (8) were conducted to identify pretreatment and other variables that could potentially reflect survival. These variables included, among others, percentage decrease in PSA from the start of therapy to 4 weeks of treatment (ΔPSA), percentage decrease in ACP from the start of therapy to 4 weeks of treatment, and percentage decrease in lymphocyte counts from baseline to nadir count. Continuous variables were dichotomized at their respective observed median values because there were no other previously established prognostic cutoff values. A Cox proportional hazards model (9) was further developed using stepwise regression with predictive variables that were significant at $P < 0.2$ in the univariate analyses.

Patients were categorized by their ΔPSA values as: ≤0%, 0.1-24.9%, 25-49.9%, 50-74.9%, and 75-100%. Within each of the ΔPSA categories, patients were further divided into two groups: survival of <1 year and survival of ≥1 year. For each of the ΔPSA ranges, LR (5) was calculated as the proportion of patients having ΔPSA in a range $R$ and survival of <1 year to the proportion of patients having ΔPSA in the same range $R$ and survival of ≥1 year, defined above. Furthermore, a multivariate predictive model for the probability of <1 year survival was developed using logistic regression analysis (10) with pretreatment variables and ΔPSA as predictor variables. A 1-year survival time was considered a reasonable cutoff point for assessing response in individual patients in a Phase II clinical trial setting (6).

Analyses were conducted using SAS software (SAS Institute Inc., Cary, NC) and STATA 3.1 software (Stata Corp., College Station, TX). All hypotheses-testing procedures and development of models were conducted under the assumption that the study patients constituted a representative group of the population of HRPC patients. It was also assumed that these groups of patients represented a homogeneously selected group, who fulfilled predefined eligibility criteria, received the same treatment, and were evaluated and monitored in the same fashion. However, it was understood that the hypotheses generated in this study would require further testing in a prospective randomized study before these results could be extended to the population at large.

**Results**

Pretreatment patient characteristics are presented in Table 1. The estimated median survival time was 16.9 months (95% Greenwood CI, 14.8-18.1 months). Table 2 lists the results of univariate analyses using the log-rank test for each of the variables with $P < 0.2$. Variables that were not found to be significant using the log-rank test ($P \geq 0.2$) were: treatment cohort; baseline performance status; weight; lymphocyte, WBC, and platelet counts; creatinine clearance; cholesterol; time of withdrawal of flutamide before suramin; prior flutamide treatment; percentage decrease in ACP from baseline to 4 weeks from the start of the therapy; and percentage decrease in lymphocyte count from baseline to nadir count. All other variables, including age, alkaline phosphatase, ACP, PSA, LDH, Hb, albumin, time from diagnosis to start of suramin treatment, and ΔPSA, which were significant at $P < 0.2$, were entered into a Cox proportional hazards model, and a backward stepwise selection procedure was adopted. ACP, LDH, and ΔPSA were found to be significant predictors ($P = 0.0003, 0.0003, and 0.003$, respectively) of the hazard, and their RR were $1.001 (CI, 1-1.002), 1.001 (CI, 1-1.001)$, respectively.
Table 3 Percentage decrease in PSA (ΔPSA) in patients (n = 95) with <1 year of survival and their LRs

<table>
<thead>
<tr>
<th>ΔPSA</th>
<th>&lt;1-yr survival, n* (proportion)</th>
<th>≥1-yr survival, n (proportion)</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0%</td>
<td>10 (0.26)</td>
<td>2 (0.03)</td>
<td>8.7</td>
</tr>
<tr>
<td>0.1–24%</td>
<td>7 (0.18)</td>
<td>6 (0.11)</td>
<td>1.6</td>
</tr>
<tr>
<td>25–49%</td>
<td>11 (0.29)</td>
<td>10 (0.18)</td>
<td>1.6</td>
</tr>
<tr>
<td>50–74%</td>
<td>7 (0.18)</td>
<td>16 (0.28)</td>
<td>0.6</td>
</tr>
<tr>
<td>75–100%</td>
<td>3 (0.09)</td>
<td>23 (0.40)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*In some patients, PSA at 4 weeks was not available.

and 0.988 (CI, 0.982–0.994), respectively. Therefore, the risk of death increased marginally with every unit increase in ACP or LDH and decreased marginally with every unit increase in ΔPSA. However, a value of 50% ΔPSA, with no changes in ACP or LDH measurements, would result in a relative risk of 0.55. With the categories for the variables defined as in Table 2, proportional hazards assumption was not met by any variable, except LDH (categorized as LDH = 1 if LDH levels were >608 units and as LDH = 0 if LDH levels were ≤608 units) and ΔPSA (categorized as ΔPSA = 1 if ΔPSA levels were <50% and as ΔPSA = 0 if ΔPSA levels were ≥50%). When these two categorized variables, LDH and ΔPSA, were fit by a Cox proportional hazards model, both were significant (P = 0.009 and 0.0019, respectively), and the corresponding RRs were 1.81 (CI, 1.16–2.82) and 2.006 (CI, 1.293–3.114). However, it should be noted that these categories were classified using arbitrarily selected cutoff points and that other cutoff points could result in different results. It is notable that the RR using ΔPSA as a continuous variable and assuming ΔPSA = 50% is 0.55, which is very close to the RR of 0.50 (= 1/2.006) obtained when ΔPSA was categorized with 50% as the cutoff point. In this study, 50 patients had ≥50% ΔPSA at 4 weeks; 45 of these 50 patients had PSA measurements beyond 4 weeks, and the majority of these patients (42 of 45 patients) had ≥50% ΔPSA for ≥4 weeks.

Because treatment evaluation in a Phase II trial setting is time bound and because response criteria are typically evaluated at predefined times after the initiation of the treatment, we examined ΔPSA for use as a possible response criterion. We considered survival at 1 year from start of therapy as the primary end point of interest because the historical median survival in a similar group of patients is reported to be 10–12 months (6). We used the LR concept to evaluate the relationship between ΔPSA and the likelihood of the survival at 1 year (Table 3). The LR decreases with the increasing range of ΔPSA (from 8.7 for the range of ≤0% ΔPSA to 0.2 for the range of >75–100% ΔPSA). Therefore, the likelihood of <1 year of survival decreases with increasing ΔPSA.

We also conducted logistic regression analyses with a stepwise selection procedure to identify variables predicting the probability of <1 year of survival. ΔPSA (odds ratio = 0.97; CI, 0.96–0.99; P < 0.0004) and Hb (odds ratio = 0.67; CI, 0.48–0.94; P = 0.019) were found to be significant variables in this model. Fig. 1 illustrates the predicted probability of <1 year of survival versus the observed ΔPSA. For a 50% ΔPSA, the model predicts the probability of <1 year of survival to be between ~0.2 and ~0.7. Furthermore, for a predicted probability of <1 year of survival of 0.5, ΔPSA could be anywhere between 10 and 70%. Thus, a single threshold ΔPSA value cannot be selected as a response criterion.

Discussion

We have examined the prognostic value of various factors as possible predictive biomarkers for survival in HRPC patients treated with suramin. We attempted to define a specific response criteria based on laboratory parameters that might complement conventional response criteria in HRPC patients. In an earlier study (4), we reported that pretreatment Hb, platelet count, and PSA and ΔPSA were significant predictors of survival in a Cox proportional hazards model, with RRs in each of these factors, except for Hb, being close to 1. In this study with a more mature data set (90 of 103 patients dead, 8 of 103 patients alive, and 5 of 103 patients lost to follow-up), we found that ACP, LDH, and ΔPSA were significant predictors of survival in the Cox proportional hazards model, although the RR for each factor was close to 1. Furthermore, some pretreatment characteristics found to be significant in earlier studies were not significant predictors of survival when longer follow-up data were available. When a time-variant Cox proportional hazards model was fit with PSA as the time-variant factor and with updated survival data, we found, as in our previous study (4), PSA to be a significant factor, but with a RR of 1.001.

The aim of our study was to identify a factor that could be used as a response criterion and allow therapeutic efficacy to be evaluated at an earlier point in a trial. Using previously reported survival data of HRPC patients (6), we selected 1-year survival as an appropriate inference end point. In this regard, our earlier study (4) conducted exploratory analyses such as tree-based modeling and sensitivity analyses to assess ΔPSA as a potential response criterion. The sensitivity analyses (4) indicated that, although sensitivity increased with 75% ΔPSA compared to 50% ΔPSA, specificity was poor. The disadvantage of this sensitivity analysis was that we had to dichotomize the outcome at an arbitrary cutoff point (example: 75% or 50%), which meant loss of information due to aggregating outcome categories. Also, sensitivity and specificity are usually established in retrospect in a group of patients (5), whereas physicians would like to assess the odds of survival, say at 1 year, given the observed ΔPSA for a given patient. In this regard, the LR approach (5) is more informative. It is interesting to note that the likelihood of survival of <1 year decreases with increasing ΔPSA (Table 3). Although further modeling using multivariate logistic regression analysis failed to define one specific threshold value of ΔPSA that could be used as a response criteria in
evaluating individual patients (Fig. 1), any reduction in PSA may be associated with improved survival.

It could be asked whether traditional response criteria are related to survival. No studies in HRPC have been reported wherein a sensitivity analysis has been conducted to evaluate how sensitive and specific are standard tumor response criteria (reduction of tumor burden by ≥50%). More conclusive evidence that tumor response is equal to survival benefit would require a prospective, randomized study in patients with measurable disease. The limitation of such studies in prostate cancer as related to the unusual incidence of bidimensionally measurable disease and whether changes in this smaller subset of patients is representative of the HRPC patient population as a whole.

Suramin has recently been evaluated in a prospective randomized, placebo-controlled, multi-institutional study (11). In this trial, pain, analgesic consumption, quality of life, and serial changes in PSA concentrations were all evaluated. The results of this trial should provide insight into the relationships among various clinical and laboratory parameters (including serial PSA measurements), quality of life indices, time to progression, and survival for patients treated with suramin.

In conclusion, our results indicate that more study is necessary on serial measurements of serum PSA in patients with HRPC before PSA can be used in Phase II efficacy clinical trials as a marker to evaluate therapeutic effects of new antineoplastic drugs. Ideally, prospective randomized studies will address this issue.

References
Evaluation of biomarkers of survival response in hormone-refractory prostate cancer patients treated with suramin.


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