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Tumor Growth Rates Derived from Data for Patients in a Clinical Trial Correlate Strongly with Patient Survival: A Novel Strategy for Evaluation of Clinical Trial Data

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Abstract

Purpose—The slow progress in developing new cancer therapies can be attributed in part to the long time spent in clinical development. To hasten development, new paradigms especially applicable to patients with metastatic disease are needed.

Patients and Methods—We present a new method to predict survival using tumor measurement data gathered while a patient with cancer is receiving therapy in a clinical trial. We developed a two-phase equation to estimate the concomitant rates of tumor regression (regression rate constant d) and tumor growth (growth rate constant g).

Results—We evaluated the model against serial levels of prostate-specific antigen (PSA) in 112 patients undergoing treatment for prostate cancer. Survival was strongly correlated with the log of the growth rate constant, $\log(g)$ (Pearson $r=-0.72$) but not with the log of the regression rate constants, $\log(d)$ ($r=-0.218$). Values of $\log(g)$ exhibited a bimodal distribution. Patients with $\log(g)$ values *above the median* had a mortality hazard of 5.14 (95% confidence interval, 3.10–8.52) when compared with those with $\log(g)$ values *below the median*. Mathematically, the

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minimum PSA value (nadir) and the time to this minimum are determined by the kinetic parameters d and g , and can be viewed as surrogates.

Conclusions—This mathematical model has applications to many tumor types and may aid in evaluating patient outcomes. Modeling tumor progression using data gathered while patients are on study, may help evaluate the ability of therapies to prolong survival and assist in drug development.

Introduction

The therapy of cancer continues to challenge oncologists. The pace of progress has often been slow, in part because of the time required to evaluate new therapies. With a few notable exceptions, such as the proteasome inhibitor bortezomib, the time from conception to approval for most new cancer therapeutics is at least 10 years, with a large part of this time spent in clinical development [1]. To reduce the time to approval, new paradigms to assess therapeutic efficacy are needed. Furthermore, because most new therapies are initially tried and approved in patients with metastatic disease, such novel paradigms must be especially applicable to this patient population.

For patients with advanced prostate cancer, androgen deprivation remains the first therapeutic option, and usually results in a prompt and often sustained clinical response [2]. However, the disease can eventually evolve to androgen-independent prostate cancer (AIPC), and it is at this stage that current therapeutic efforts are increasingly focused [3–5]. Metastatic prostate cancer, and especially AIPC, behaves like other drug-resistant cancers and together with the tumor marker PSA is an excellent model for metastatic cancer, and for evaluating new strategies for disease assessment.

The present study was undertaken to develop a rational basis for evaluating drug efficacy in patients participating in clinical trials using data gathered while the patient is enrolled in the study. We describe a novel paradigm for predicting drug efficacy using prostate cancer and PSA values as a model that may also be applicable to most cancers where tumor load can be assessed by serum or radiographic measurements.

Materials and Methods

Patient Characteristics

The data for this analysis came from two clinical trials approved by the institutional review board of the National Cancer Institute. The primary objective of both trials was to determine whether novel combinations of chemotherapy produced sufficiently high clinical responses to warrant further investigation in patients with AIPC [6, 7]. All patients had metastatic AIPC and had failed to benefit from combined androgen blockade, as well as antiandrogen withdrawal. Therapies consisted of either thalidomide plus docetaxel (docetaxel as the control arm) or ketoconazole plus hydrocortisone and alendronate (ketoconazole plus hydrocortisone as the control arm). The overall survival time was calculated from the on-study date until the date of death.

In total, 112 patients were included in the mathematical analysis, comprising all patients enrolled in the two studies. Thirty-two patients who enrolled in both studies are only included in the analysis once with the start date as the date of enrollment in their first protocol. All datapoints were obtained from patients during enrollment in clinical trials. None of the datapoints were obtained after patients were removed from clinical trials.

Mathematical Analysis

The Regression–Growth Equation—We developed an equation based on the model that the PSA level decreases exponentially (i.e., as a first-order process) but that there is also independent exponential regrowth of the tumor reflected in the measured PSA level. This equation is:

$$f = \exp(-d \cdot t) + \exp(g \cdot t) - 1 \quad (1)$$

where $\exp$ is the base of the natural logarithm, $e = 2.7182 \dots$, and f is the PSA signal at time t , normalized to the value at day 0, the time at which treatment is commenced. The rate constant d (decay, in days^{-1}) accounts for the exponential decrease in the PSA signal, whereas the rate constant g (growth, also in days^{-1}) represents the exponential regrowth of the tumor following treatment. Figure 1 depicts a set of theoretical lines derived on the basis of this model.

We note that, for individuals in whom the data show a continuous decrease from the time of treatment, equation (1) can be replaced by the reduced form

$$f = \exp(-d \cdot t), \quad (2)$$

while for individuals whose PSA values showed a continuous increase the resulting reduced-form equation is:

$$f = \exp(g \cdot t). \quad (3)$$

We also considered a model in which regrowth appears substantially after the start of treatment:

$$f = \exp(-d \cdot (t - \tau)) + \exp(-g \cdot t) - 1 \quad (4)$$

where τ is the time until regrowth reached the pretreatment value.

Relation Between g , d , and the Nadir and Time to Nadir—It is also possible to estimate g and d from two parameters readily available from patients undergoing therapy, namely, the nadir (the minimal level of f), for which we use the symbol $\min$, and the time since treatment initiation at which this minimum was reached, for which we use the symbol $t_{\min}$. The values of $\min$ and $t_{\min}$ are related to g and d as follows:

Differentiating equation (1) with respect to t , and setting the value of df/dt equal to zero, gives the time taken to reach the minimum as:

$$t_{\min} = \ln(d/g) / (d+g) \quad (5)$$

This can also be written as:

$$t_{\min} = \ln(r) / (g \cdot (1+r)) \quad (5A)$$

where r is the ratio of the regression and growth rate constants, namely, $r = d/g$.

Substituting $t_{\min}$ for t in equation (1), one obtains

$$\min = \exp(g \cdot t_{\min}) / \exp(-d \cdot t_{\min}) - 1 \quad (6)$$

This can also be written in terms of r by substituting the equivalent value from equation (5A), as

$$\min = \exp(g \cdot (\ln(r) / (g \cdot (1+r)))) + \exp(-d \cdot (\ln(r) / (g \cdot (1+r)))) - 1$$

This in turn simplifies to:

$$\min = \exp(\ln(r) / (1+r)) + \exp(-r \cdot (\ln(r) / (1+r))) - 1 \quad (6A)$$

Because equation (5) and equation (6) both contain the unknown rate constants d and g , and each is linked to the directly observable values $\min$ and $t_{\min}$, d and g can be estimated directly from measurements of $\min$ and $t_{\min}$. Unfortunately, equation (6) is a so-called transcendental equation, that is, one that cannot be put into a form in which g and d can be extracted directly from $\min$ and $t_{\min}$. A solution can be obtained, however, by noting (equation (6A)) that $\min$, the minimum value of the PSA signal, is dependent only on r , the ratio of the regression to growth rate constants. Online supplementary Table 1 lists values of $\min$ from which one can obtain values for r and $\ln(r)/(1+r)$ that can be used to calculate g using equation (5A). Then, together with the known value of $t_{\min}$, one can find g from equation (5A), and with r evaluated, d . This procedure cannot be used for patients in whom the PSA signal increases continuously from the beginning of treatment, for whom equation (3) can be used to obtain the growth rate constant g .

Data Analysis

We fitted equation (1) to each of the 109 datasets for which there were at least three datapoints. Curve fitting was performed using Sigmaplot (Systat Software, Inc., San Jose, CA).

Statistical Analyses

Data were analyzed in Excel (Microsoft, Redmond, CA) and in Sigmaplot 9.0. Linear regressions were implemented using the polynomial linear routine of Sigmaplot 9.0. Cox regression analyses were performed using the Interactive Statistical Pages at <http://statpages.org/prophaz.html> [7]. Sample comparisons were performed by Student's t -test using <http://statpages.org/index.html> [8], with p set at .05 for significance. The distribution of the logarithms of patients' readings around the model was overall normal, and independent of time (except for the initial time where the value was normalized to 1). The standard error of the parameter estimates was evaluated by the standard asymptotic method using the inverse of the Hessian.

Results

The median number of datapoints was 10 per patient and the median time over which data were collected was 227 days. Following the curve-fitting analysis of each patient dataset, we identified five groups among the 109 patients for which we had more than two time points as shown in Figure 2 and online supplementary Figure S1. The growth rate constants varied over a nearly 1,500-fold range, while the regression rate constants varied over a 50-fold range (Fig. 3A). Furthermore, the regression rate constants were consistently larger than the growth rate constants, with median values of $10^{-1.7} \text{ day}^{-1}$ versus $10^{-2.5} \text{ day}^{-1}$, respectively.

Correlations with Survival Time

Figure 3B depicts the distributions of patient survival times and the two rate constants for the 99 patients in whom the PSA time courses had a g or d (or both) with an associated $p < .05$. Survival was more strongly correlated with the logarithm of the growth rate constant than with the logarithm of the regression rate constant. This result suggests that, while a given therapy may result in tumor reduction, the critical determinant in survival is whether or not the therapy alters the inherent growth rate of the tumor. Figure 3C depicts the correlations between patient survival times and the initial PSA level, the minimum PSA level, and the time to the PSA minimum.

Figure 4 depicts Kaplan–Meier plots of fractional survival against time of survival for the upper and lower 50% of cases, in each case stratified by $\log(g)$, $\min$, $t_{\min}$, and the initial PSA value. Patients whose tumor growth rate constants were in the upper 50% had shorter survival times than patients with tumor growth rate constants in the lower 50%. The time to the minimum PSA level also had a strong impact on survival, comparing the upper 50% with the lower 50%, as did the nadir or minimum. An initial PSA signal in the upper 50% had a small, but statistically significant, impact on survival. These results are best understood when one recognizes the dependence of time to minimum and minimum on the growth rate constant (equation (5) and equation (6A), respectively), so that these values are surrogates of the growth rate constant. This is underscored by the results in online supplementary Figure S2.

Patient-to-Patient Variability in the Kinetic Parameters

Figure 5A depicts the distribution of the growth rate constants (g) in the form of a histogram. Interestingly, when the clinical outcome was evaluated, we found that, among the 46 patients with the highest growth rate constants, 28 experienced progressive disease (PD), only four had a partial regression (PR), one had a PSA response, ten were scored as stable disease (SD), and three were not evaluable. In contrast, among the 46 patients with the lowest growth rate constants, there were only two patients with PD, 26 patients who experienced a PR, one who had a minimal response, an additional 11 with a PSA response, five demonstrating SD, and one that was not evaluable. The shaded columns depict the validation dataset (see below).

Validation Study

The approach used in the present study was validated using data from an independent trial conducted by the Southwest Oncology Group, as depicted in Figure 5. The shorter lower line depicts the regression through the data obtained from the validation set. Neither the slope of this line nor its intercept is statistically different from the line above it representing the study group, supporting the validity of our analysis.

Discussion

Clinicians and regulators have an interest in early prediction of treatment outcomes. Regulatory agencies often seek improved survival in the approval of a new cancer therapeutic. However, the effect of a therapeutic agent on survival has become much more difficult to define, especially as patients increasingly enroll in successive treatment regimens. The current study underscores the obvious: the growth of *treatment-refractory cancer cells* is responsible for the death of a patient. We show that survival predictions can be made in patients with metastatic disease using data gathered while a patient is enrolled in a clinical trial and undergoing treatment. While in the present study we have used prostate cancer as a model, the biology described is likely applicable to many cancers wherein measures of tumor load, including values such as radiographic measurements, are available.

It has long been recognized that, at least during part of their growth, tumors follow exponential kinetics. Gompertzian tumor growth has been debated, and some have argued that it cannot apply to tumors over their entire life span [10, 11]. In our dataset (see online supplementary Fig. S1), only three cases of 112 (11, 47, and 77) show even a suggestion of the limited terminal plateau that the Gompertzian equation describes. While it may still be true that a Gompertzian equation might describe the entire growth history of a tumor, our results clearly demonstrate that, during the window of observation that our datasets comprise, the tumors that grow appear to be growing exponentially. One might consider the total course of growth of a tumor as consisting of *a series of intervals* each with a different growth rate constant. After all, why should the growth rate constant be fixed over the years during which a tumor grows? Patients with advanced disease may be in the *final interval*, such that during the brief period of a clinical trial we are able to measure a growth rate constant that in turn predicts survival. Furthermore, most models consider tumor growth in the absence of treatment. The mathematical equation used in this work recognizes that, especially during therapy, both tumor growth and regression occur simultaneously, and discerns their independent contributions to the measured growth. To our surprise, however, the regression portion of the curve, while needed to accurately describe the data, does not predict survival in these patients with prostate cancer. It is the growing (surviving) fraction that determines survival.

The use of mathematics to describe tumor kinetics has been widely explored in prostate cancer because of the sensitivity and specificity of the tumor marker PSA. Two derivations, PSA doubling time (PSA-DT) and PSA velocity (PSAV), have received special attention [12–22]. The PSA-DT rests on the assumption that increases in PSA follow first-order kinetics and hence an exponential growth curve, so that a plot of the log of the PSA versus time produces a slope that should remain constant provided the patient is *not receiving an effective therapy*. PSA-DT has been advanced as a method to discern disease aggressiveness [13, 16, 17, 19]. Others have described its usefulness in predicting cancer-specific mortality [21]. Similar results have been reported for PSAV, the change in PSA over time [12, 20].

Like the growth rate constant described in this study, PSA-DT is a mathematical estimate of the rate of tumor growth. With three or more PSA measurements, the PSA slope, PSA-DT, is calculated using a least-squares regression formula and the natural log of PSA values in order to make the kinetic pattern more linear. But in most cases, even this natural log transformation does not conform to a purely linear kinetic pattern. We would argue that one explanation for the poor fit is the failure to model the two concurrent processes of regression and growth. The mathematical calculations used here discern these two independent variables.

Our observations, correlating overall survival with a calculated growth rate constant, have precedence in the literature both in patients who have received definitive local therapy and are followed without treatment and in patients with metastatic disease receiving generally ineffective therapies. In both of these scenarios, tumor growth unopposed by any regression results in a PSA-DT that is comparable with the growth rate constant g described in the current study [21–24]. Precedence can also be found in patients with metastatic hormone-refractory prostate cancer, in whom PSAV has been shown to be associated with the time to death after treatment [25]. However, with the advent of more effective therapies, models that account for simultaneous tumor regression and growth are needed, because net growth is a complex interplay of cellular proliferation and necrosis/apoptosis/senescence.

The small sample size and patient enrolment in clinical trials at a single institution are limitations of the present study. Positive attributes include the fact that all but six of the 1,369 available PSA values were used in the calculations, avoiding arbitrary selection of

PSA measurements within an interval of time. Another positive attribute is that the growth rate constant is a continuum and survival correlates very highly across this continuum. We would also note that because patients with metastatic disease usually die from their cancer, the analysis in this study was likely not biased by death from causes other than cancer. We also recognize that the value of this approach will need larger trials for validation.

For a therapy to alter survival it must fully eradicate the tumor, reset the pace by selecting for a clone with a slower growth rate constant, or alter the pretherapy growth rate constant by affecting the biology of all cells without killing them. Because the Response Evaluation Criteria in Solid Tumors define disease progression as an increase in a single dimension of 20% (a volumetric increase of 72.8% if one assumes a sphere), the tumor volume can nearly double before disease is scored as progressive. As depicted in online supplementary Figure S3, if our dataset was limited to PSA values that had risen no more than 72.8% above the starting value or the nadir, this limited dataset could also reliably predict survival. We note, however, that we cannot exclude in every case that therapy might alter the growth rate without “resetting it,” and that the measured change in the growth rate might require continued therapy. We would also caution that the conclusions and their potential relevance to other cancers apply only to patients with metastatic disease who are treatable and for whom therapeutic interventions have limited efficacy. Finally we recognize that the therapies used in these patients included conventional cytotoxic agents. Similar studies will have to be conducted with novel targeted agents to determine whether the same principles apply.

Examining the derived growth and regression rate constants leads one to several observations that match clinical intuition. First, the self-evident observation that patient survival relates inversely to the tumor growth rate. Second, the relationship between the minimal value of PSA and the growth rate constant implies that the rate of tumor growth determines the quality of the response to therapy. The minimum is lower if the growth rate constant is lower, in the face of at least modestly effective therapy. Nearly all of the partial and complete responses—as judged by the depth of tumor reduction—occurred in patients with slower growth rates. Another observation relative to the clinical heuristic is that the regression rate is faster than the growth rate. We can agree that, generally, tumors respond faster than they grow over time. Further, the regression rate has a much narrower range across the patient population than the growth rate. This implies that the biology of tumor regression may be more similar across patients than that of tumor growth—there are very few pathways for cell death, but a myriad of growth factors and signal transduction pathways to facilitate/encourage growth. A final implication of these studies is that a higher risk patient population with a more rapid growth rate and a higher hazard of earlier death (hazard ratio, 5.14) can be identified early on in the course of treatment.

The analysis presented here underscores the obvious: a successful therapy must either eradicate the tumor in its entirety or significantly alter the growth rate constant. But the analysis here also demonstrates clearly that, given a reliable measure of tumor load, the growth rate constant can be estimated from data gathered while a patient is on study. We believe that this approach will not be limited to analyses where serum markers are measured. In an accompanying manuscript [26], we have applied the same methodology to analyze data obtained by radiographic measurement of renal cell carcinoma and have obtained similar results. For a homogenous patient population, it ought to be possible to generate a “mean” growth rate constant for a given disease after, for example, failure of second-line therapy. This in turn should allow more rapid discernment of those therapies that can prolong survival. Because the growth rate constant is a validated surrogate for survival, investigators should be able to predict the effect an experimental intervention will have on

survival by examining the data harvested during the study. This information might streamline drug development and drug approval.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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For the convenience of future users of this approach, a file in Excel into which data on tumor sizes at given times can be uploaded and the parameters g and d extracted is available in the Supplementary Material as an Excel File.

REFERENCES

1. Adams J. The development of proteasome inhibitors as anticancer drugs. *Cancer Cell*. 2004; 5:417–421. [PubMed: 15144949]
2. Sharifi N, Gulley JL, Dahut WL. Androgen deprivation therapy for prostate cancer. *JAMA*. 2005; 294:238–244. [PubMed: 16014598]
3. Petrylak D. Therapeutic options in androgen-independent prostate cancer: Building on docetaxel. *BJU Int*. 2005; 96(suppl 2):41–46. [PubMed: 16359438]
4. Pienta KJ, Bradley D. Mechanisms underlying the development of androgen-independent prostate cancer. *Clin Cancer Res*. 2006; 12:1665–1671. [PubMed: 16551847]
5. Silvestris N, Leone B, Numico G, et al. Present status and perspectives in the treatment of hormone-refractory prostate cancer. *Oncology*. 2005; 69:273–282. [PubMed: 16282706]
6. Dahut WL, Gulley JL, Arlen PM, et al. Randomized phase II trial of docetaxel plus thalidomide in androgen-independent prostate cancer. *J Clin Oncol*. 2004; 22:2532–2539. [PubMed: 15226321]
7. Pezzullo, JC.; Chulyadyo, R. [Revised October 24, 2007; accessed September 22, 2008] Cox Proportional Hazards Survival Regression. Available at <http://statpages.org/prophaz.html>
8. Pezzullo, JC. [Updated May 17, 2008; accessed September 22, 2008] Web Pages that Perform Statistical Calculations!. Available at <http://statpages.org/index.html>
9. Figg WD, Liu Y, Arlen P, et al. A randomized, phase II trial of ketoconazole plus alendronate versus ketoconazole alone in patients with androgen independent prostate cancer and bone metastases. *J Urol*. 2005; 173:790–796. [PubMed: 15711271]
10. Retsky MW, Swartzendruber DE, Wardwell RH, et al. Is Gompertzian or exponential kinetics a valid description of individual human cancer growth? *Med Hypotheses*. 1990; 33:95–106. [PubMed: 2259298]
11. Siler W. Parameters of mortality in human populations with widely varying life spans. *Stat Med*. 1983; 2:373–380. [PubMed: 6648150]
12. D'Amico AV, Chen MH, Roehl KA, et al. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. *N Engl J Med*. 2004; 351:125–135. [PubMed: 15247353]
13. Hanks GE, Hanlon AL, Lee WR, et al. Pretreatment prostate-specific antigen doubling times: Clinical utility of this predictor of prostate cancer behavior. *Int J Radiat Oncol Biol Phys*. 1996; 34:549–553. [PubMed: 8621277]
14. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999; 281:1591–1597. [PubMed: 10235151]
15. Laufer M, Pound CR, Carducci MA, et al. Management of patients with rising prostate-specific antigen after radical prostatectomy. *Urology*. 2000; 55:309–315. [PubMed: 10699599]

16. Egawa S, Arai Y, Tobisu K, et al. Use of pretreatment prostate-specific antigen doubling time to predict outcome after radical prostatectomy. *Prostate Cancer Prostatic Dis.* 2000; 3:269–274. [PubMed: 12497076]
17. Stephenson AJ, Aprikian AG, Souhami L, et al. Utility of PSA doubling time in follow-up of untreated patients with localized prostate cancer. *Urology.* 2002; 59:652–656. [PubMed: 11992834]
18. Ward JF, Blute ML, Slezak J, et al. The long-term clinical impact of biochemical recurrence of prostate cancer 5 or more years after radical prostatectomy. *J Urol.* 2003; 170:1872–1876. [PubMed: 14532796]
19. D'Amico AV, Moul J, Carroll PR, et al. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. *J Urol.* 2004; 172:S42–S46. discussion S46–S47. [PubMed: 15535442]
20. Rozhansky F, Chen MH, Cox MC, et al. Prostate-specific antigen velocity and survival for patients with hormone-refractory metastatic prostate carcinoma. *Cancer.* 2006; 106:63–67. [PubMed: 16333854]
21. D'Amico AV, Cote K, Loffredo M, et al. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol.* 2002; 20:4567–4573. [PubMed: 12454114]
22. D'Amico AV, Moul JW, Carroll PR, et al. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst.* 2003; 95:1376–1383. [PubMed: 13130113]
23. Zhou P, Chen MH, McLeod D, et al. Predictors of prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Clin Oncol.* 2005; 23:6992–6998. [PubMed: 16192586]
24. D'Amico AV, Chen MH, Roehl KA, et al. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. *J Clin Oncol.* 2005; 23:4975–4979. [PubMed: 16051949]
25. Crawford ED, Pauler DK, Tangen CM, et al. Three month change in PSA as a surrogate endpoint for mortality in advanced hormone refractory prostate cancer (HRPC): data from Southwest Oncology Group study S9916. *Proc Am Soc Clin Oncol.* 2004; 23:382.
26. Stein WD, Yang J, Bates SE, et al. Bevacizumab reduces the growth rate constants of renal carcinomas: A novel algorithm suggests early discontinuation of bevacizumab resulted in a lack of survival advantage. *The Oncologist.* 2008; 13:1055–1062. [PubMed: 18827177]

Figure 1.

Theoretical plots for the regression– growth model. The dotted line labeled “regression” describes that fraction of the tumor that is regressing (decaying) during treatment. The line depicted is the prediction of this equation with parameter g set to zero (i.e., regression only). The dashed line labeled “growth” describes that fraction that begins at a negligible amount but grows continuously. The line depicted is the prediction of this equation with parameter d set to 0 (i.e., growth only). The solid line labeled “sum of regression and growth” gives the (net) sum of these two processes. The line depicted is the prediction of the full regression–growth model of equation (1) of the text, with rate constant g set at 100 per day and d set at 10 per day.

Figure 2.

Prostate-specific antigen (PSA) level (as a fraction of the value at the start of treatment) against time in days for six patients of the 109 for whom sufficient data were available to attempt a full analysis. We excluded three patients for whom data from two or fewer time points were available, leaving 109 datasets to be analyzed. After inspection of the scatterplots for all 109 patients, we omitted six datapoints (one point from each of the six patient datasets, numbers 40, 44, 68, 93, 109, and 111) that were obvious outliers. The full set can be found in the supplementary material as online supplementary Figure S1. All patient data were normalized by dividing each PSA reading by the baseline PSA reading obtained at, or just before, the start of treatment. For 99, either g or d (or both) had an associated $p < .05$. Most of these 99 patients ($n = 68$) were characterized by a pattern of both regression and subsequent regrowth and fit equation (1). (A) and (B) are two cases in which the full equation (1) was applicable. Seven of the 99 showed no evidence of regrowth and their data fit equation (2), regression only (C), while 24 did not show a nadir and their data fit equation (3), growth only (D). Six patients (of the 68 patients whose PSA curve was characterized by a pattern of both regression and subsequent regrowth) showed evidence of delayed regrowth requiring application of equation (4) (E). For 10 individuals, the data showed much scatter and the model did not fit the observed data well (F). The lines drawn are the best-fit theoretical predictions of the appropriate equations. The derived parameters for g and d are provided in online supplementary Table 2.

Figure 3.

Distribution of regression and growth rate constants and their correlations with survival. **(A):** Dotplots of the distribution of the best-fit regression rate constants (d , left panel) or growth rate constants (g , right panel). The horizontal line in each set is the median value. The ordinate is the logarithm of the derived rate constant. The abscissa has an arbitrary scale. We extracted the parameters g and d and their associated Student's t -values and p -values. We declared significance at $p < .05$. When either g or d was not significant at this level, we used the respective reduced form of equation (1), namely, equation (2) or equation (3). For those cases in which the data obviously increased after the minimum and yet the derived value of g , using equation (1), was not significant, we tested whether application of equation (4) resulted in significant values for both g and d . **(B and C):** Dependence of patient survival (ordinates, in days) on five parameters that characterize the time course of the prostate-specific antigen (PSA) level. All abscissas are logarithmic scales. **(B):** Distributions of patient survival times and the two rate constants for the 99 patients in whom the PSA time courses had a g or d (or both) with an associated $p < .05$. Growth rate constants (g , per day) were derived using equation (1) or equation (3) and regression rate constants (d , per day) were derived using equation (1) or equation (2). Survival was more strongly correlated (Pearson's $r = -0.72$; $p < .0001$; d.f. = 84) with the logarithm of the growth rate constant than with the logarithm of the regression rate constant ($r = -0.218$; $p = .074$; d.f. = 66). **(C):** Correlations between patient survival times and the initial PSA level in ng/ml ($r = -0.22$; $p = .0257$; d.f. = 98), the minimum value of the PSA signal (min , nadir, as a fraction of the initial signal) ($r = -0.54$; $p < .0001$; d.f. = 62), and the time to reach the minimum PSA value (t_{min} , in days) ($r = 0.62$; $p < .0001$; d.f. = 62). The lines drawn are the linear regressions with parameters as listed in the text. For those patients in whom the data demonstrated regression, we calculated min and t_{min} . For patients for whom g and d were both significant, min was determined by noting the point at which the PSA value first began to increase and then continued to do so for two subsequent time points, and t_{min} was the time of this minimum, or

the mean of two time points if the minimum value was identical at two time points. For those cases in which the signal decreased continuously, *min* was the lowest value reached during the study and t_{min} was the first time this value was reached.

Figure 4.

Kaplan–Meier plots of fractional survival against survival time for the upper and lower 50% of cases, in each case stratified by $\log(g)$, $\min$, $t_{\min}$, and the initial PSA value. The ordinate is the fraction of patients in each group still surviving, while the abscissa is days. **(A):** Patients whose tumor growth rate constants were in the upper 50% had shorter survival times (hazard ratio [HR], 5.14; 95% confidence interval [CI], 3.10–8.52) than patients whose tumor growth rate constants were in the lower 50%. **(B):** The nadir or minimum ($\min$, nadir) had a strong impact on survival (HR, 2.59; 95% CI, 1.54 – 4.380, comparing the upper 50% with the lower 50%). **(C):** The time to the minimum ($t_{\min}$) PSA level also had a strong impact on survival (HR, 3.17; 95% CI, 1.83–5.48, comparing the upper 50% with the lower 50%). **(D):** An initial PSA signal in the upper 50% had a small, but statistically significant, impact on survival (HR, 1.74; 95% CI, 1.19–2.64, as compared to the lower 50%). See note in Figure 3 regarding $\min$ and $t_{\min}$.

Figure 5.

Histograms of growth rate constants. The validation set consists of data from 42 patients with metastatic prostate cancer treated with ixabepilone (BMS-247550, an epothilone B analogue). **(A):** Histogram of the distribution of values of the derived growth rate constant g (92 of the 99 patients are depicted because in seven no growth was observed and only the regression rate constant, d , could be calculated). The red-shaded columns depict the distribution for the growth rate constants derived for the validation set. **(B):** The dependence of patient survival (ordinate, in days) on the values of the derived growth rate constants (abscissa, g , per day) for the full dataset of our study group (black solid symbols) and the validation set (red symbols). The lines drawn are the linear regressions for each set separately. The shorter lower line depicts the regression through the data obtained from the validation set. A second line superimposed on the upper longer line represents the line obtained when data from both groups were analyzed together. Neither the slope of these lines nor their intercepts are statistically different from the line above representing the study group. As in the study group, 13 patients in the validation group whose prostate-specific antigen values only fell *during the period of observation*, and hence had only “regression curves,” were excluded because (as discussed in the methods section) there was no possibility of calculating a meaningful growth rate constant from the available data. Among the remaining 29 patients, six had too few datapoints or a too scattered dataset for analysis. The remaining 23 had data that yielded growth rate constants with a p -value $< .05$ in 21 and $< .075$ in two.