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Other Paradigms: Growth Rate Constants and Tumor Burden Determined Using Computed Tomography Data Correlate Strongly With the Overall Survival of Patients With Renal Cell Carcinoma

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Abstract

In solid tumors, where curative therapies still elude oncologists, novel paradigms are needed to assess the efficacy of new therapies and those already approved. We used radiologic measurements obtained in patients with metastatic renal cell carcinoma enrolled in a phase II study of the epothilone B analog, ixabepilone (Ixemptra), to address this issue. Using a novel 2-phase mathematical equation, we used the radiologic measurements to estimate the concomitant rates of tumor regression and growth (regression and growth rate constants). Eighty-one patients were enrolled on the ixabepilone trial at the time of this analysis. Growth rate constants were determined using computed tomography measurements obtained exclusively while a patient was enrolled on study. The growth rate constants of renal cell carcinomas treated with ixabepilone were significantly reduced compared with those of tumors in patients who received placebo in a previous trial. Furthermore, a correlation with overall survival was found for both the growth rate constant and the initial tumor burden; and this correlation was even stronger when both the growth rate constant and the initial tumor burden were combined. The readily amenable mathematical model described herein has potential applications to many tumor types that can be assessed with imaging modalities. Because the growth rate constant seems to be a surrogate for survival, assessment could aid in the evaluation of relative efficacies of different therapies and perhaps in assessing the potential individual benefit of an experimental therapy.

Keywords

RECIST; chemotherapy efficacy; cancer clinical trials; phase II studies; chemotherapy assessment; chemotherapy evaluation

In the United States, approximately 562,340 deaths due to cancer are projected for 2009, and the majority of these will succumb to chemotherapy-refractory solid tumors.¹ The advent and proliferation of targeted therapies has brought the hope that cancer survival data will improve in larger increments than observed in the past. Along with this advance, there has come the added problem of determining which therapies provide true patient benefit. The 2009 annual report by the Pharmaceutical Research and Manufacturers of America identifies 861 different agents currently in clinical development for cancer.² This is more than double the number of agents reported by Pharmaceutical Research and Manufacturers of America in 2001, when 402 drugs were identified.³ With only a fraction of drugs tested in phase I ultimately achieving regulatory approval, there is an urgent need to identify better methods of selecting active agents. Herein, we present a novel paradigm for assessing the efficacy of anticancer therapy—measurement of tumor growth rate while a patient is receiving therapy. We have used data from a phase II trial of ixabepilone in renal cell cancer, a disease in which the activity of sunitinib and, in particular, sorafenib illuminated the problem of relying on traditional response measures.^{4,5}

Metastatic renal cell carcinoma (mRCC) is a tumor that exemplifies our continued inability to cure solid tumors that have metastasized. Although the incidence of RCC has increased over time, no single “cytotoxic” agent or combination consistently produces responses justifying their routine use in patients with mRCC.^{6–10} For the 2 decades before the approval of “targeted” therapies, interleukin-2 and interferon-alpha were the main treatments for mRCC despite their low response rates (5%–20%) and modest effects on median OS.^{10–16} A shift in outcomes began with the demonstration of an effect of sorafenib (Nexavar) on mRCC, followed by reports of the effectiveness of sunitinib (Sutent) and then temsirolimus (Torisel).^{17–19}

One interesting outcome of the sorafenib trial was the observation that a response rate that would traditionally be considered insignificant could be accompanied by an improvement in progression-free survival.¹⁷ Visually, this was demonstrated in a “waterfall plot,” which demonstrated the magnitude of tumor shrinkage in each patient, and included those with shrinkage that, while insufficient to qualify for a partial response, could confer clinical benefit.^{5,20} This led us to ask whether an impact on tumor growth rate could be measured as an alternate efficacy end point. We used a mathematical analysis of tumor growth using kinetic parameters and in RCCs observed that radiologic tumor measurements could be fitted to an equation that incorporates both exponential growth and decay.^{21,22} The equation provides both a regression (decay) rate constant that defines tumor regression and a growth rate constant that describes tumor progression. Data obtained from the National Cancer Institute's (NCI's) bevacizumab (Avastin) versus placebo randomized trial in mRCC not only confirmed an important impact of bevacizumab in reducing growth rate but also suggested that the growth rate returned at least to placebo levels after the drug was discontinued.²² Subsequently, we noted that in prostate cancers, prostate-specific antigen (PSA) values could be fitted to the same equation.²¹ These data could be mined for different biologic insights, some of which concurred with our fundamental understanding of cancer. For example, the growth rate constant correlated with survival, whereas the decay constant did not, implying that the biologic properties of tumor growth were more important for determining when a patient would die of cancer than the rate of response to therapy. Furthermore, in prostate cancer, the depth of PSA decline was mostly determined by the growth rate constant, implying that, to achieve a very low nadir, the drug must result in a profound reduction in cancer cell growth.

In this study, growth rate constants were derived from radiologic data obtained in a single-arm phase II trial of ixabepilone in renal cell cancer. Ixabepilone, a semisynthetic epothilone B analog and nontaxane microtubule stabilizing agent, exerts antiproliferative effects by

binding tubulin and stabilizing microtubules, effecting mitotic arrest and impairing microtubule trafficking.^{23–26} Epothilones are poor substrates for P-glycoprotein and exhibit activity in paclitaxel-resistant cell lines and paclitaxel-resistant tumor models.^{23–27} Because of encouraging results and tolerable toxicity profiles in phase I studies, a phase II trial was initiated to determine the efficacy and safety of ixabepilone in patients with mRCC.^{28,29} Response evaluation criteria in solid tumors (RECIST) guidelines were used as per protocol, and an overall response rate of 12.6% was observed. The growth rate constants calculated using these data again show a striking correlation with survival and suggest a new end point for clinical trial assessment.

PATIENTS AND METHODS

Clinical Trial and Study Design

The data for this analysis came principally from the phase II clinical trial of ixabepilone in RCC.^{28,29} Limited comparisons were made with data obtained from the NCI randomized trial of bevacizumab versus placebo.^{30,31} Both trials were conducted at Warren G. Magnusen Clinical Center and were approved by the Institutional Review Board, Center for Cancer Research, NCI. All patients provided written informed consent. The Cancer Therapy Evaluation Program, NCI, through Cooperative Research and Development Agreements with Bristol-Myers Squibb (Wallingford, CT) and Genentech (South San Francisco, CA) provided ixabepilone and bevacizumab, respectively. All patients had mRCC and most were treated before the approval of sorafenib (Nexavar), sunitinib (Sutent), or temsirolimus (Torisel) for the therapy for mRCC. Overall survival (OS) was calculated from the on-study date until date of death. Ixabepilone was administered at a dose of 6 mg/m² intravenously during a 1-hour infusion daily for 5 consecutive days every 3 weeks. Other details have been previously provided.^{28,29}

Response Assessment

Measurable disease in the ixabepilone trial was assessed by computed tomography using RECIST guidelines,³² with baseline imaging within 4 weeks of enrollment and restaging after every 2 cycles. Responses were scored according to RECIST guidelines with the longest diameter of up to 5 lesions recorded and summated.

Mathematical, Data, and Statistical Analyses

The use of first-order kinetics to derive a tumor growth rate constant, g , and a decay (tumor regression) constant, d , has been previously described^{21,22} and is briefly summarized here, with more detail having been provided in the cited Refs. ²¹ and ²². Those sources provided an Excel spreadsheet into which radiologic measurements can be inserted; the Excel program immediately computing and reporting the appropriate growth rate constants.

Mathematical Analysis

The regression-growth equation: We developed an equation based on the model that tumor quantity decreases exponentially (ie, as a first-order process) but that there is also independent exponential regrowth of the tumor reflected in larger tumor quantities. This equation is as follows:

$$f = \exp(-d \times t) + \exp(g \times t)^{-1} \quad (1)$$

where $\exp$ is the base of the natural logarithm, $e = 2.7182 \dots$, and f is the tumor measurement at time t in days, normalized to the value at day 0, the time at which treatment is commenced. The rate constant d (decay/day) accounts for the exponential decrease in the

sum of tumor measurements and can be considered a regression rate constant. The rate constant g (growth/day) represents the exponential regrowth of the tumor during treatment. Figure 1 depicts a set of tumor measurement data through which lines were fitted on the basis of this model.

When the data showed a continuous decrease from the time of treatment, such that the parameter g could not be extracted with probability P of <0.05 , Eq. (1) was replaced by the reduced form eliminating the growth rate constant:

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

When tumor measurements showed a continuous increase, so that d could not be extracted with a $P < 0.05$, Eq. (1) was replaced eliminating the decay constant:

$$f = \exp(g \times t) \quad (3)$$

Additional variations on Eq. (1) have been previously described.^{21,22}

Data Analysis

We attempted to fit Eq. (1) to the 75 data sets for which more than 1 data point was available. Curve fitting was performed using Sigmaplot (Systat Software). We extracted the parameters g and d and their associated Student's t values and P values. We declared significance at $P < 0.05$. When either g or d was not significant at this level, we used the respective reduced form of Eq. (1), namely, Eqs. (2) or (3). Data from 9 patients could not be fit to any equation at $P < 0.05$ and were not included in subsequent analyses. The ixabepilone data were also compared with measurements obtained from the earlier NCI trial designed to determine whether bevacizumab (Avastin) was superior to placebo in renal cell cancer.³⁰ In the latter trial, bidimensional measurements were obtained, and the data were recorded as the sum of the product of the perpendicular diameters. To compare the data obtained in the ixabepilone trial (longest diameter) with that of patients who received placebo in the bevacizumab trial (product of perpendicular diameters), we used the square of the largest diameter measured for the RECIST assessment in the ixabepilone trial. As noted in the Results section, this method of analyzing the data would likely overestimate the growth rate constant of tumors in the patients receiving ixabepilone.

Statistical Analyses

Data were analyzed in Excel (Microsoft) and in Sigmaplot 9.0. Linear regressions to evaluate the relationship between the growth rate constant or other parameters and survival were implemented using the polynomial linear routine of Sigmaplot 9.0. Sample comparisons, were performed by Student's t test using SigmaStat 3.5 (Systat Software), with P set at 0.05 for significance. We wished to combine an analysis of the effect of the growth rate constant (g) and the initial tumor burden (ITB) on OS. To this end, we developed an autoscale, by first normalizing both sets of data by subtracting a set's median value from each data point in the set. Then, to scale the data, we divided each normalized data point by the standard deviation of the normalized data points for that set. To assess the regression of OS on the combination of g and ITB, we simply added, for each patient, the autoscaled normalized data value for g and for ITB and then regressed OS against this sum.

RESULTS

Between February 2002 and April 2007, 81 patients with mRCC were enrolled on the ixabepilone trial. Clinical trial results are to be published separately.²⁹ Among the 81 patients enrolled on study, the overall response rate was 12.6%. One patient had a complete response, 9 patients experienced partial responses, and a best response of stable disease for at least 4 cycles (at least 12 weeks) per RECIST criteria was confirmed in 33 patients (37.9%).

Patients enrolled on the ixabepilone trial had extensive tumor burden at baseline. Taking the sum of the longest diameter of all measurable tumors (defined as those >1.0 cm), a median value of 21.7 cm of tumor was recorded. Taking the sum of the longest diameters of up to 5 tumors followed as part of the RECIST evaluations, a median value of 10.5 cm of tumor was recorded. The mean number of metastatic sites was 3, with lung, lymph nodes, liver, bones, and soft tissue the most common sites (a site of metastatic disease, such as “lung parenchyma,” counted as 1 site, regardless of the number of nodules).

The equations described in the Patients and Methods section constitute a kinetic analysis that allows one to discern the growth rate constant when both regression and growth are occurring simultaneously. As noted under Patients and Methods section, we used the sum of the tumor diameters measured for the RECIST evaluation while patients were enrolled on study to determine the effect of ixabepilone on the kinetics of tumor growth, with an emphasis on the effect therapy had on the regression (d) and growth rate constants (g). Figure 1 depicts measurement of tumor behavior for 12 patients with mRCC treated with ixabepilone. The appropriate regression (d , dashed curve) and growth (g , dotted curve) curves, derived for each tumor, together model the measurements obtained in the clinical setting (solid line). The solid line here represents the sum of the fraction of tumor that is regressing and the fraction that is growing. Panels A to E depict data from ixabepilone-treated patients whose clinical course was characterized by tumor regression followed by subsequent regrowth and fit Eq. (1). Panel F depicts a case where neither g nor d could be extracted from the scattered data. Panels G to I depict the results obtained in patients who achieved a complete response and during the period on study had no evidence of regrowth and thus fit Eq. (2). Panels J to L depict the results obtained in patients who had no evidence of benefit from ixabepilone and whose disease progression fit Eq. (3). Two or more sets of response measurements were available in 75 patients and are individually plotted in Figure S1. The remaining 6 patients included 5 who did not have a follow-up tumor measurement and 1 patient who was still being treated at the time of study analysis.

As Figure 1 and the derivations described in the Patients and Methods section demonstrate, g represents the growth of the tumor that remains after the regression or disappearance of any drug sensitive cells. In both mRCC and in prostate cancer, we have previously demonstrated that g correlates with OS, whereas d does not,^{21,22} and in this study, we found similar results. Figures 2A, B depict graphs plotting patient survival versus the logarithms of the rate constants g and d , respectively, for the patients treated with ixabepilone. As can be seen, survival was correlated with the logarithm of the growth rate constant (Fig. 2A, $r = 0.32$; $P = 0.023$) but not with the logarithm of the regression rate constant (Fig. 2B, $r = 0.042$; $P = 0.84$). These results confirm and extend our previous observations and lend support to our conclusion that the critical determinant in survival is the effect of therapy on the tumor growth rate constant not its effect on the regression rate constant. Figure 2C shows the correlation between the log g of the fastest growing lesion (among those measured for RECIST evaluation) and survival. Just as the log g of all measured lesions correlated with survival, so too did the log g of the fastest growing lesion correlate with survival (Fig. 2C, $r = 0.46$; $P = 0.0024$).

Gompertz suggested that biologic growth processes should slow with time to a plateau value, a suggestion sometimes thought to be applicable also to tumor growth in vivo [A Gompertz curve or Gompertz function, named after Benjamin Gompertz, is a sigmoid function. It is a type of mathematical model for a time series, where growth is slowest at the start and end of a time period. $Y(t) = ae^{be^{ct}}$, where a is the upper asymptote, c is the growth rate, b , c are negative numbers and e is Euler's Number ($e = 2.71828$).]³³ We wondered whether this concept would, indeed, characterize the tumors in this study. Would the growth rate constant correlate inversely with the tumor burden? Would we find negative correlations between the growth rate constant and either the sum of all measurable lesions (total tumor burden) or the baseline RECIST measurement (the sum of up to 5 lesions)? In actuality, there was total independence between the growth rate constant and the quantity of tumor measured whether it was the amount followed as part of the RECIST assessment of response ($r = 0.03$; $P = 0.84$) or, as shown in Figure 3, the total tumor burden at study entry ($r = 0.047$; $P = 0.74$).

However, not surprisingly, Figure 4 shows that a strong correlation was observed between tumor burden and OS (Fig. 4A, $r = 0.49$; $P < 0.0001$). When both the tumor burden and the growth rate constant were combined mathematically, an even stronger correlation with survival was obtained (Fig. 4B, $r = 0.61$; $P < 0.0001$), indicating that, together, the amount of tumor at presentation and its growth rate constant, both values obtained from radiographic measurements, are excellent predictors of survival. We confirmed this result using multivariate analysis. Figure 4B highlights with different colored symbols the results in 14 patients who received other therapies or underwent surgical resection of residual disease after discontinuing ixabepilone. Interestingly, they represent a disproportionate fraction of the data points above the arc of 99% confidence representing patients who survived longer than predicted by the growth rate constant measured while receiving ixabepilone.

Although the ixabepilone study was a single-arm phase II trial, we had in hand data from a randomized study conducted a few years earlier at the NCI where patients enrolled on 1 arm received a placebo.³⁰ We decided to compare the growth rate constants of renal cell cancers on ixabepilone with that of the growth rate constants observed in renal cancers of patients randomized to bevacizumab or placebo. As noted in the Patients and Methods section, to compare the data obtained in the ixabepilone trial (the longest diameter for each tumor by RECIST) with that obtained in patients randomized to bevacizumab or placebo in the NCI trial (product of perpendicular diameters), we used the squares of the longest diameter measured for the RECIST assessment in the ixabepilone trial. Note that the sum of the products of 2 measured diameters, as in the bevacizumab trial, would be smaller than or, at most, equivalent to the sum of the squares of the longest diameter, as used in the ixabepilone calculation. Thus, this would likely overestimate the growth rate constant of tumors in the patients receiving ixabepilone. Figure 5 shows the individual growth (g) and regression rate (d) constants of the 66 patients treated with ixabepilone for whom g and/or d was extracted with a $P < 0.05$, depicted in dot plots. These results can be compared with the similar values obtained in the high-dose bevacizumab and placebo arms of the previous study. For patients treated with a placebo, the mean g value was $10^{-2.23}$ /day compared with a mean value of $10^{-2.56}$ for bevacizumab and $10^{-2.53}$ /day for patients treated with ixabepilone.²² The difference in growth rate constants between the placebo and the ixabepilone treatment ($10^{-0.3}$ or approximately a 2-fold difference) was statistically significant ($P < 0.001$). Turning to the regression (d , decay) rate constants for the patients on placebo, the mean d value was $10^{-2.34}$ /day, for patients treated with bevacizumab $10^{-2.14}$ /day, compared with a mean value of $10^{-2.49}$ /day for patients on ixabepilone. The regression rate constants for patients receiving therapy were not statistically significantly different from that for the placebo.

DISCUSSION

This study using computed tomography measurements of tumors extends our previous conclusion that the growth of treatment-refractory cancer cells is responsible for the death of a patient with cancer, whereas regression of tumor ultimately has no effect on OS.^{21,22} Although the former is intuitive, the latter underscores the discouraging fact that in a patient with a metastatic solid tumor, such as mRCC, where complete eradication of disease is usually not possible, the rate of tumor reduction is made irrelevant by the rate at which residual tumor regrows. Furthermore, these results again demonstrate that using data gathered while a patient is receiving therapy—and this applies here to data obtained by computed tomography—a growth rate constant can be calculated that can serve as an end point in clinical trials and as a surrogate to predict OS in patients with metastatic cancer.

The observation that the growth rate constants correlate strongly with OS concurs with our previous results where we found similar correlations.^{21,22} Further supporting this conclusion was the observation that the growth rate constant derived from the fastest growing tumor from each data set was correlated with OS. Although the growth rate constant as a tool for clinical trial assessments needs independent validation, we have found a correlation with survival in every data set thus far examined, with the exception of a trial employing vaccine therapy, where the growth rate constant was obtained while the patient was actively receiving vaccine rather than later after an immune response had been established (manuscript in preparation). We have also found that the kinetic analysis is precise enough to see differences between therapies, notably, across a decade of prostate cancer studies (manuscript in preparation), such that we can also envision the growth rate constant being used as a tool for individual patients to confirm whether a new therapy has reduced the growth rate or not.

The biologic inferences that can be made from calculation of the growth rate constant are also worthy of note. The tumor that grows during therapy is the tumor that determines survival—a simple heuristic evident to clinicians but not always quantified in the RECIST-measured response rate. Furthermore, in this study, we found a strong negative correlation between the ITB and the OS (Fig. 4A). Because the growth rate constants are fully independent of the ITB (Fig. 3), we considered the possibility that there would be an additive effect of growth rate and tumor burden in predicting OS. This was, indeed, found (Fig. 4B) where the regression coefficient of 0.61 appeared as the largest of any in this study. Whether these observations would be true for all cancers or for only a subset that includes RCC, we do not know. Data sets in other diseases need to be analyzed.

The finding that tumor growth rate is of critical importance in determining outcome is consistent with other studies that have examined tumor doubling times, albeit in the absence of therapy.^{34–37} It is important to note that there is a fixed ratio between any determined growth rate constant and the doubling time, a fact well known to enzyme kineticists. This value, $dt = 0.693/g$, means that the doubling time can be extrapolated from the growth rate constant. For PSA, for example, the doubling time has been very well accepted as indicative of survival and is often used in the clinical trial setting.^{34–37} The value of Eq. (1) is that the growth rate constant can be determined even in the face of ongoing therapy as long as the nadir value has passed.

Our analysis also suggested that ixabepilone had a significant effect on the growth rate constant when compared with placebo. Even though the placebo group was not a concurrent cohort, we consider it valid for our comparisons for several reasons. First, neither the biology of mRCC nor its surgical management changed in the 5 years between studies (note that the majority of patients had undergone nephrectomy in both studies). Second, entry

criteria in the 2 trials were similar. Further supporting the validity of this placebo group, their survival was nearly identical to that of the placebo group in the randomized sorafenib registration trial: 453 days (or 15.1 months) versus 15.9 months, respectively.^{17,22} Limiting our comparison to the growth rate constants in the 2 settings, we believe that the data show ixabepilone to have a clear impact on slowing tumor growth.

Although we remarked above that a correlation between growth of treatment refractory cancer and survival is intuitive, it is not entirely clear how such a correlation would be preserved in the setting of a clinically effective agent. We would argue that the correlation of the on-study growth rate constants with survival could be explained either by the fact that a substantial portion of the remaining lifespan of these patients was spent receiving ixabepilone (median time on study 117 days) and hence what happened on study impacted OS or by the possibility that the on-study and off-study growth rate constants were related.

During the conduct of the ixabepilone trial, both sorafenib (Nexavar), and sunitinib (Sutent) became available first through clinical trials and, subsequently, by Food and Drug Administration approval. The data in Figure 4B show what happened to patients who went on to receive other therapies. In 7 of the 14 cases, the therapy did not impact their predicted survival, based on their inclusion within or below the 99% confidence intervals around the regression line. However, it is interesting that a few patients did “deviate,” albeit only slightly, from the projected survival and survived longer than would have been predicted. We believe this can be attributed to the therapy administered after ixabepilone.

The analysis here again underscores the obvious to provide true clinical benefit, a therapy must either eradicate tumor in its entirety or significantly alter the growth rate of a tumor. It also demonstrates that the growth rate constant can be calculated from radiologic measurements gathered while a patient is undergoing therapy. We would emphasize here that the measurements used in these analyses were determined as the patients were being treated and were obtained by numerous radiologists—“the radiologist of the day.” They were not remeasured after the study was concluded, which indicates similar valuable information could be generated in practice provided the lesion(s) that are measured are clearly identified so that sequential radiologists can measure the same lesion and transmit the values to the treating physician, who can calculate the growth rate constant. Importantly, the data suggest that tumor growth rate constants may be a valuable measure for determining the benefit of a new agent in the context of a clinical trial and may be added to the list of innovative strategies for assessment in drug development.

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FIGURE 1.

Plots for the regression/growth model using clinical data obtained from 12 patients treated with ixabepilone. Tumor measurements (solid circles) are fitted using Eq. (1), (2), or (3) as described in the Patients and Methods section. Measurements for patients (A) to (E) fit Eq. (1), such that rate constants for both regression and disease progression could be determined. This is displayed as concomitant regression (dashed curve) and growth (dotted curve) kinetically added together (solid line). Data obtained in patient (F) could not be fit by any equation. Measurements for patients (G) to (I) fit only the regression curve [dashed curve, Eq. (2)], whereas measurements (J) to (L) fit only the growth curve [dotted curve, Eq. (3)] without any evidence of disease regression.

FIGURE 2.

Dependence of patient survival (y axis in days) on the log of the growth and regression rate constants. All x axes are logarithmic scales. Growth rate constants (g , per day) were derived using Eq. (1) or (3), and regression rate constants (d , per day) were derived using Eq. (1) or Eq. (2). Panel A: $\log g$ calculated from the sum of linear tumor measurements (sum of RECIST measurements for all lesions assessed) is plotted against survival. The regression has $r = 0.32$; $P = 0.023$. Panel B: $\log d$ against survival. The regression has $r = 0.042$; $P = 0.84$. Panel C: $\log g$ calculated from linear tumor measurements of the fastest growing tumor (lesions) versus survival. The regression has $r = 0.46$; $P = 0.0024$.

FIGURE 3.

Lack of dependence of tumor growth rate constant (g) on initial tumor burden. y axis: $\log g$ as in Figure 2A; x axis: tumor burden as the RECIST sum of the lengths of visible tumors at time of admission (cm). The regression has $r = 0.03$; $P = 0.84$.

FIGURE 4.

Dependence of survival on tumor load (panel A) and on the combination of the growth rate constant and tumor load (panel B). The y axis is the survival in days. In panel A, the x axis is the sum of the linear measurements of all visible tumors in each patient. In panel B, the x axis is the sum of the normalized, autoscaled tumor length and the normalized, autoscaled $\log g$ (see Statistical Analysis section). In both the figures, the regression has a $P < 0.0001$. In (A), the Pearson r is 0.49; in (B), the Pearson r is 0.61. Symbols relating to subsequent therapy: downward pointing red triangle ($n = 7$) = sorafenib (Nexavar); upward pointing blue triangle ($n = 2$) = sunitinib (Sutent); green square ($n = 2$) = gemcitabine (Gemzar); reddish-pink circle ($n = 1$) = anti-CTL4; pink diamond ($n = 1$) = surgical resection of disease; and downward pointing reddish brown triangle ($n = 1$) = multiple therapies.

FIGURE 5.

Dot plots of the distribution of the best-fit regression rate constants (d , left side of each panel, filled circles) or growth rate constants (g , right side of each panel, open circles) for patients with mRCC who received placebo or bevacizumab in the randomized trial^{17,25} (panels A and B, respectively) and patients on the ixabepilone study (panel C), where g was calculated from the sum of the squares of the RECIST linear tumor dimensions. The horizontal lines in each set represent the mean values and standard deviations. The y axis is the logarithm of the derived rate constant. Regression rate constants could be measured in a larger number of patients treated with ixabepilone compared with patients who received a placebo. The values for both d and g varied over at least a 50-fold range. For the patients who received placebo, the mean g value was $10^{-2.23}/\text{day}$ ($\text{SD} = 10^{-0.35}$) compared with mean values of $10^{-2.56}/\text{day}$ for bevacizumab ($\text{SD} = 10^{-0.38}$) and $10^{-2.53}/\text{day}$ ($\text{SD} = 10^{-0.37}$) for patients treated with ixabepilone. For the patients who received placebo, the mean d value was $10^{-2.34}/\text{day}$ ($\text{SD} = 10^{-0.39}$) compared with mean values of $10^{-2.14}/\text{day}$ ($\text{SD} = 10^{-0.35}$) for patients treated with bevacizumab and $10^{-2.49}/\text{day}$ ($\text{SD} = 10^{0.77}$) for patients treated with ixabepilone.