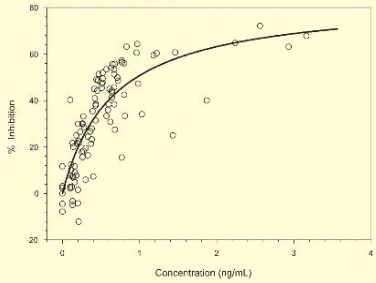
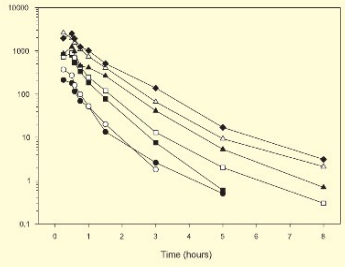
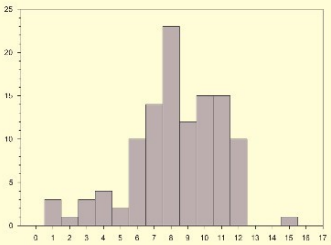
Pharmacokinetics in Drug Development: Advances and Applications

Volume 3







Edited by
Peter L. Bonate, Ph. D.
Danny R. Howard, Ph. D.

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Pharmacokinetics in Drug Development

Peter L. Bonate • Danny R. Howard
Editors

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Editors
Peter L. Bonate, Ph.D.
Clinical Pharmacology,
Modeling, and Simulation
GlaxoSmithKline
Research Triangle Park, NC, USA
peter.l.bonate@gsk.com

Danny R. Howard, Ph.D.
Translational Sciences
Novartis
East Hanover, NJ, USA
dan.howard@novartis.com

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Preface

The primary objective of this book series is to provide readers with practical guidance on the application of pharmacokinetics as a drug development science. Our goal has been, and continues to be, to provide the link between the theoretical and the applied. We ask every author to write their chapter with this question in the back of their mind: "If you were training someone new to industry, what about this topic should they know?" In the first two volumes, topics were chosen specifically for their relative "stability" and they represented the core what we do as a profession. Though the approaches and technologies may have advanced, the practical considerations for topics like bioavailability study designs, analysis procedures for absorption data or dose-proportionality, or the role of pharmacokinetics in early development have remained relatively consistent over time. Some of the topics, however, have changed and some become more prominent over time. With this volume, we begin to address the more "adaptable" issues facing pharmacokineticists and pharmacologists supporting new compound development.

The topics chosen for this volume were selected because they are some of the current development or technological issues facing drug development project teams. They regard the practical considerations for the assessment of selected special development populations. For example, they include characterization of drug disposition in pregnant subjects, for measuring arrhythmic potential, for analysis of tumor growth modeling, and for disease progression modeling. Practical considerations for metabolite safety testing, transporter assessments, Phase 0 testing, and development and execution of drug interaction programs reflect current regulatory topics meant to address enhancement of both safety assessment and early decision-making during new candidate selection. Important technologies like whole body autoradiography, digital imaging and dried blood spot sample collection methods are introduced, as both have begun to take a more visible role in pharmacokinetic departments throughout the industry.

We are very pleased to extend the goals of the series to this newest volume. We remain committed to the aim of publishing material to fill the gap between the academic sciences and the practical application of that knowledge in drug development. Our grateful thanks goes out to the authors who contributed their time (and more importantly) their opinions, thoughts, authorship, and most of all, *patience* to this project. Without their hard work, expertise, and keen knowledge of the subjects presented, it would not be possible to have reached our shared goal.

We would like to dedicate this book to the editors and authors' families – whose love for us and understanding for our obsession make it possible for us to happily wander through the maze of our scientific dreams.

Research Triangle Park, NC — Peter L. Bonate
East Hanover, NJ — Danny R. Howard

About the Editors

Peter Bonate has 16 years industrial experience, 13 years as a clinical pharmacologist/pharmacokineticist and three years in drug metabolism and bioanalysis. He is currently a Director in the Clinical Pharmacology, Modeling, and Simulation department at GlaxoSmithKline in the oncology therapeutic area. He has also worked at Genzyme, Hoechst Marion Roussel, Eli Lilly, and Quintiles. He received his PhD in 1996 from Indiana University in Medical Neurobiology with an emphasis on the pharmacokinetics of drugs of abuse. He received an MS in Statistics from the University of Idaho and an MS in Pharmacology from Washington State University both in 1990. In 2003, he was elected a Fellow of the American College of Clinical Pharmacology and in 2007 was elected a Fellow of the American Association of Pharmaceutical Scientists (AAPS). He was founder of the Modeling and Simulation focus group, has served as chair of the population pharmacokinetics focus group, and was section leader for the Clinical Pharmacology and Translational Research Section within AAPS. He has served or currently serves on the editorial boards for the *Journal of Clinical Pharmacology*, *Pharmaceutical Research, Journal of Pharmacokinetics and Pharmacodynamics*, and *the AAPS Journal*. He has more than 40 publications in the field of pharmacokinetics and clinical pharmacology, is co-editor of the series *Pharmacokinetics in Drug Development* published by AAPS Press in 2004, and is author of the book *Pharmacokinetic–Pharmacodynamic Modeling and Simulation* published by Springer in 2006.

Danny Howard received his Bachelor of Science degree in Pharmacy, and PhD from the University of Missouri in Kansas City. He began working in the pharmaceutical industry in 1991, first as a biopharmaceutics consultant and then as pharmaceutical scientist for Marion Merrell Dow, Hoechst Marion Roussel, Aventis, and Quintiles. He is currently the Vice President of Global Pharmacokinetics and Pharmacodynamics for Novartis. His career has included responsibilities in both clinical and nonclinical pharmacokinetics and pharmacodynamics, bioanalytics, and pharmaceutical business operations. He has worked with numerous drug submissions supporting both large and small molecules worldwide. He was a charter member of the Missouri Biotech Association and served as its first Board Chairman. With Peter Bonate, he is the co-editor of the series *Pharmacokinetics in Drug Development* published by AAPS Press in 2004.

Contents

Contributors

Robyn P. Araujo Center for Applied Proteomics and Molecular Medicine, George Mason University, Manassas, VA, USA

Carlo L. Bello Pfizer, Oncology, Clinical Pharmacology, La Jolla, CA, USA

Peter L. Bonate GlaxoSmithKline, Clinical Pharmacology, Modeling, and Simulation, Research Triangle Park, NC, USA

Jack Cook Pfizer, Clinical Pharmacology, Specialty Care Business Unit New London, CT, USA

Stephen B. Duffull School of Pharmacy, University of Otago, Dunedin, New Zealand

Joseph C. Fleishaker Pfizer, St. Louis Laboratories, Clinical Research, St. Louis, MO, USA

Lee-Kien Foo School of Pharmacy, University of Otago, Dunedin, New Zealand

David M. Haas Indiana University School of Medicine, Indianapolis, IN, USA

Brett E. Houk Pfizer, Oncology, Clinical Pharmacology, La Jolla, CA, USA

Danny R. Howard Novartis, Drug Metabolism and Pharmacokinetics Translational Sciences, East Hanover, NJ, USA

J. Matthew Hutzler Boehringer Ingelheim, Ridgefield, CT, USA

Caroline H. Johnson Laboratory of Metabolism, Center for Cancer Research, National Institutes of Health, National Cancer Institute, Bethesda, MD, USA

David J. Kazierad Cardiovascular, Metabolic & Endocrine Disease Research Unit, Pfizer, Groton, CT, USA

Graham Lappin Xceleron, The BioCentre, York, UK

John C. Lindon Department of Biomolecular Medicine, Faculty of Medicine, Imperial College London, South Kensington Campus, London, UK

Tapan K. Majumdar Novartis, Drug Metabolism and Pharmacokinetics, Translational Sciences, East Hanover, NJ, USA

Majid Y. Moridani Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University HSC, Amarillo, TX, USA; Department of Pediatrics, School of Medicine, Texas Tech University HSC, Amarillo, TX, USA

Diane R. Mould Projections Research Inc., Phoenixville, PA, USA

Angus N.R. Nedderman Pfizer, Department of Pharmacokinetics, Dynamics and Metabolism, Sandwich, Kent, UK

Jamie L. Renbarger Indiana University School of Medicine, Indianapolis, IN, USA

Tanya Russell Pfizer, Oncology Clinical Pharmacology, San Diego, CA, USA

Alain Schweitzer Novartis, Drug Metabolism and Pharmacokinetics, Translational Sciences, Basel, Switzerland

Daniel S. Stein Novartis, Translational Medicine, Translational Sciences, East Hanover, NJ, USA

Thomas N. Thompson R&D Services Pharma Consulting, Omaha, NE, USA

Don K. Walker Pfizer, Department of Pharmacokinetics, Dynamics and Metabolism, Sandwich, Kent, UK

Modeling Tumor Growth in Oncology

1

Peter L. Bonate

Abstract

In cancer drug development, measurement of tumor growth is necessary for preclinical assessment of anticancer activity and clinical assessment of efficacy. This chapter reviews mathematical models of preclinical and clinical tumor growth. Issues and models with regards to mouse xenograft data will be highlighted.

1.1 Introduction

Cancer is one of the leading causes of death worldwide. It is expected that in 2010, 1.5 MM new cases of cancer will be diagnosed in the USA and more than a half-million people will die from their illness (1,500 persons each day), with prostate, breast, lung, and colon having the greatest incidence (American Cancer Society 2010). Vast amounts of money, time, and effort are spent every year to develop new drugs to treat cancer. Unfortunately, the approval rating for new cancer drugs is dismal; around 5% of drugs that enter the clinic will be approved for use by doctors and patients (Kola and Landis 2004). Certainly, one way companies can improve their success rates for achieving new drugs is to better leverage their preclinical and clinical data and reduce attrition via application of mathematical models of disease. Prospective modeling of tumor growth is an example of how pharmaceutical companies are working to reach this goal.

As part of the drug development process for cancer drugs, particularly with regards to solid tumors, measurement of tumor burden and size, both before and after therapy, is common at different points in the development process to assess the effectiveness of a drug. Preclinically, mice are injected with tumor fragments that are allowed to grow and are then administered the new chemical entity (NCE) to determine whether the NCE can retard or shrink tumor growth. Tumor size or volume are later assessed in humans to determine whether the NCE is effective and can prolong survival. Recent attention has focused on modeling tumor growth to better understand the exposure–response relationship for NCEs. This chapter will review tumor growth kinetics in both preclinical and clinical models used to characterize the growth of tumors over time. Tumor growth models are also described by Mould in the chapter on Modeling the Progression of Disease elsewhere in this book.

P.L. Bonate
Clinical Pharmacology, Modeling, and Simulation, GlaxoSmithKline, 5 Moore Drive, 17.2259, Research Triangle Park, Durham, NC 27709, USA
e-mail: Peter.l.bonate@gsk.com

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1.2 Xenograft Models

The preclinical models for measuring antitumor activity are relatively straightforward. As part of the drug discovery process, researchers will subcutaneously implant human tumor fragments into the flank of nude or severe combined immunodeficient (SCID) mice and allow the tumors to grow. Once the tumors have reached a predefined size (usually 100–300 mm^3), the mice are randomized to different treatment groups: these usually include a placebo, some dose of the NCE, and a positive control of a drug already known to have an antitumor effect at the given dose. The doses are given and tumor size is measured over a period of time defined by the protocol, usually weeks. The effect of the NCE relative to the placebo and active control is determined. Effective cancer agents are assumed to be those that will reduce or shrink tumors. Such models are referred to as xenograft models and are meant as a model for human tumor growth. Most every drug approved in cancer was first tested in a xenograft model to determine its anticancer activity.

There are often two types of measurements reported in these studies, tumor volume and tumor weight, both of which are derived from the same set of measurements. Because the volume or weight of the tumors cannot be actually measured, their length (the longest axis) and width (in mm) is measured using calipers and then weight or volume is estimated using one of several formulas based on these values. Assuming the tumor is a prolate ellipsoid (which has a shape like a monolithic dome or an egg cut along its shortest axis at the middle, see http://www.monolithic.com/stories/shapes-prolate-ellipsoid-vertical for example, accessed July 2010), tumor volume (in mm^3) is estimated as $0.5 \times \text{length} \times \text{width}^2$. If it is assumed that the tumor has unit volume, then tumor weight (in mg) is equal to tumor volume assuming a density of 1 mg/mm^3 for tumor tissue. For nonspherical tumors other equations are used to estimate the volume. The reader is referred to Clarke (1997) and Rygaard and Spang-Thomsen (1997) for details. Plots of tumor weight or volume over time are often used to show the effect of the drugs on the tumors.

Figure 1.1 presents an example of a xenograft study for ABT-263, a small molecule inhibitor of Bcl-2, which has shown activity in cell-cultured tumors. ABT-263 showed activity in a variety of tumors under a once-daily dosing schedule (Shoemaker et al. 2008). Figure 1.1 shows that ABT-263 has similar or better activity than etoposide, cyclophosphamide, and carboplatin in SCLC H146 xenografts and had activity in paclitaxel-resistant H146 xenografts. AVT-263 also did not exhibit resistance with multiple cycles of therapy. ABT-263 is now currently in Phase 1/2a under a daily dosing schedule (14 days on/7 days off or continuous dosing) in patients with SCLC and non-hematologic malignancies.

Although xenografts are relatively easy to perform, there are problems (Kelland 2004). First, these are human tumors grown in mice and so the mice must be immunocompromised for the tumors to grow in order to prevent a severe transplant reaction from occurring in the host animal. Second, since these tumors are implanted in the flank, they do not mimic tumors of other origins, e.g., a lung cancer tumor grown in the flank of mice may not be representative of a lung cancer tumor in the lung. Recent interest has focused on so-called orthotopic models, wherein tumors of particular origin are grown at the origin of interest (Garber 2010), and in transgenic mice, which are thought to more faithfully mimic the human cancer process (Sharpless and DePinho 2006). There are problems and criticisms associated with these models as well, the foremost being that there is no proof that these models perform any better at predicting human activity than conventional approaches. There is also the question of the relevance of the xenograft models with targeted therapeutics. Last, xenograft models never metastasize.

Xenografts have been criticized for their low predictive value. A retrospective analysis done by the National Cancer Institute showed that only 15 of 33 compounds that were in Phase 2 of drug development had activity in more than one-third of the xenograft models tested ($p = 0.04$). Also, activity in a particular tumor line did not generally predict human activity in that cancer, e.g., activity in breast cancer xenograft models

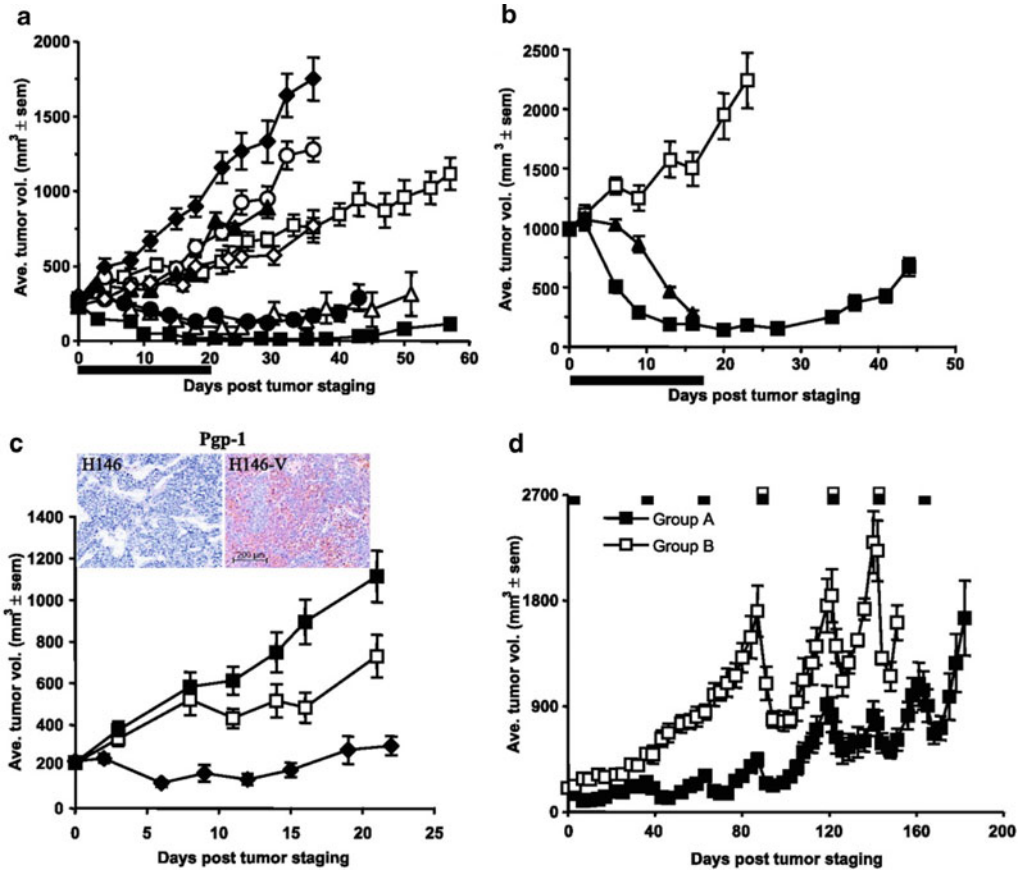

Fig. 1.1 Example of a xenograft study. (**a**) Efficacy of ABT-263 in the H146 SCLC xenograft model relative to several standard cytotoxic agents. Shown is data compiled from seven independent experiments. In each trial, tumors were size matched to 240–300 mm^3 (day 0) and therapy was initiated the following day. *Open circles*, cisplatin given at 3 mg/kg, IP, thrice every 4 days; *closed triangles*, etoposide given at 25 mg/kg, IP, q4d × 3; *open squares*, carboplatin given at 50 mg/kg, IP, q4d × 4; *open diamonds*, cyclophosphamide given at 100 mg/kg, IP, q4d × 3; *closed circles*, vincristine given at 0.5 mg/kg, IV, q7d × 4; *open triangles*, paclitaxel given at 30 mg/kg, IP, q4d × 3; *closed squares*, ABT-263 given at 100 mg/kg, po, 21 doses daily (*black bar*); *closed diamonds*, cisplatin vehicle. For simplicity, only one vehicle group has been plotted. However, all statistics and analyses of efficacy were conducted by comparing to the vehicle control specific for each agent. All cytotoxic agents were given at or near their maximum tolerated doses. All drugs exhibited a statistically significant inhibition of tumor growth throughout the study except for cyclophosphamide, which was significant only on days 4, 8, and 16 postdose initiation ($p < 0.05$, Wilcoxon rank sum test). (**b**) Treatment with ABT-263 causes regression of large, established H146 xenograft tumors. Tumors were allowed to reach an average tumor volume of ∼1,000 mm^3 before initiation of therapy. *Closed squares*, ABT-263 was given at 100 mg/kg, po, 17 doses daily (*black bar*); *closed triangles*, docetaxel given at 30 mg/kg, IV, q7d × 2; *open squares*, vehicle. ABT-263 treatment resulted in 92% TGI at the end of therapy with all tumors showing at least an 80% reduction in tumor volume relative to starting size ($n = 10$ mice per group). (**c**) Analysis of paclitaxel-resistant variant of H146. Parental H146 tumors were initially treated with four doses of paclitaxel at 30 mg/kg/day. Tumors that relapsed after treatment were propagated into new hosts and expanded into new lines. The H146 variant line (H146-V) shown here was significantly more resistant to paclitaxel treatment of 30 mg/kg/day compared with the parental line. *Closed diamonds*, ABT-263 given at 100 mg/kg, po, 21 doses daily; *open squares*, paclitaxel given at 30 mg/kg, IP, q4d × 3; *closed squares*, paclitaxel vehicle. Immunohistochemical analysis of parental H146 and H146-V tumors showed that the variant line expresses significantly higher levels of Pgp-1 (*inset*; magnification, ×100). ABT-263 given at 100 mg/kg/day still showed significant efficacy in the H146-V line ($p < 0.01$, Wilcoxon rank sum test). (**d**) Efficacy of ABT-263 in the H146 xenograft model after multiple cycles of therapy. Tumors were randomized into groups of equal tumor volume (∼200 mm^3) on day 0 with group A receiving ABT-263 at 100 mg/kg/day, po, from day 0 to day 4 and group B receiving vehicle. Additional 5-day cycles of treatment with ABT-263 at 100 mg/kg/day were administered as follows: group A, days 36–40, 63–67, 87–91, 119–123, 140–145, and 161–165; group B, days 87–91,

did not predict activity in breast cancer in humans, the exception being non-small cell lung cancer which had a 45% predictive rate (Johnson et al. 2001). What is interesting about this argument about the predictive value of xenografts is the perceived need for a high prediction rate. In toxicology, the overall concordance rate between toxicity in man and similar toxicity in animals is only 70%, with 30% of human toxicities not predicted at all by animal studies (Greaves et al. 2004), and yet few would suggest we should not do toxicology studies prior to first time in man. Although xenograft are not completely predictive of activity, they are much better at weeding out failures, as drugs that fail to show efficacy in xenograft models very likely will not be active clinically.

It has been argued that the predictive value of xenograft models can be significantly improved when the doses administered to mice produce exposures similar to the exposures seen in the clinic (Kerbel 2003; Inaba et al. 1988) since often the doses given to mice are four- to fivefold higher than the maximum tolerated dose (MTD) seen in humans (Maruo et al. 1990; Inaba et al. 1989; Tashiro et al. 1989). The difficulty with this approach is that prior to first time in man, the MTD in humans is not known so the doses studied in mice are often the MTD in mice. Later, after the MTD has been established in man, the dose in mice can be adjusted to produce pharmacokinetically equivalent exposures. Further testing of this hypothesis needs to be performed.

1.3 Preclinical Models for Tumor Growth

Modeling of tumor growth kinetics began in the 1960s with Anna Kane Laird (1964) who showed that unperturbed tumor growth in a test tube followed Gompertzian kinetics, which look similar to the profiles produced by the sigmoid E_{max} model familiar to most pharmacokineticists. The proposed equation for cell growth was

$$Y(t) = Y(0)\exp\left[\frac{A}{\alpha}(1-\exp(-\alpha t))\right] \qquad (1.1)$$

where, $Y(t)$ is tumor size at time t, $Y(0)$ is the baseline tumor size, and A and α are constants. For small values of αt or when $\alpha = 0$, tumor growth becomes exponential. Since Laird's initial report, Gompertzian growth has been shown for a variety of tumors in different unperturbed situations both in vitro and in vivo. The first paper to show that a Gompertz equation best described tumor growth in animals was by Simpson-Herren and Lloyd (1976) in a C3H mouse mammary tumor and L1210 ascites tumor (often used as a model for leukemia). The first paper to show that a Gompertz equation applies to human tumor growth was Sullivan and Salmon (1972).

It was a series of papers by Norton and Simon (1976a,b) that really called attention to the use of the Gompertz equation in describing tumor growth (Norton 1988). Based on their studies, they predicted that for chemotherapy, one could increase cell kill by delivering treatments at higher doses (increased dose intensity) through minimization of tumor regrowth between cycles. This hypothesis, referred to as the Norton–Simon hypothesis, was confirmed in clinical trials (Citron et al. 2003). Norton et al. (2005) later showed how a Gompertz equation could be modified to account for perturbation in the presence of an active treatment and how to optimize chemotherapeutic dose regimens under Gompertzian growth. In the unperturbed state, tumor volume could be modeled by

$$\frac{dY}{dt} = \alpha Y(t) - \alpha \times Ln(Y(t)) \times Y(t) \qquad (1.2)$$

Fig. 1.1 (continued) 119–123, and 140–144. Group B was also treated with vehicle on days 36–40 and 63–67. *Black boxes*, dosing periods for group A; *white boxes*, dosing periods for group B. ABT-263 treatment resulted in significant tumor regression, even after six previous cycles of therapy. Regression of large (>2,000 mm^3) tumors was also seen after multiple therapy cycles. Reprinted with permission from Shoemaker et al. (2008). Copyright American Association of Cancer Research, 2008

but in the presence of drug effect the equation is modified to

$$\frac{dY}{dt} = \alpha Y(t) - \alpha \times Ln(Y(t)) \times Y(t) \times (1 - DE) \tag{1.3}$$

where, DE is a drug effect function whose domain is on the interval (0, 1). When the model was applied to capecitabine, the point of maximal drug effect was approximately 7 days of treatment. The model predicts that dosing after 7 days diminishes anticancer benefit but increases the risk of toxicity. Preclinical studies in xenograft models confirmed that a 7 day-on/7 day-off regimen achieved a maximum tolerated dose 1.5 times higher than the conventional schedule (Traina et al. 2006). Based on these preclinical results, a clinical trial was started testing the safety of a 7 day-on/7 day-off schedule for capecitabine and was found to be safe and well tolerated (Traina et al. 2008). A Phase 2 study to determine the efficacy under this dosing schedule is on-going.

Miklavcic et al. (1995) modeled the effects of bleomycin and electrotherapy in xenografts. Four different models were tested: exponential, Gompertz, Bertalanffy, and logisitic. Untreated mice were modeled as

$$\begin{aligned}
&\frac{dY}{dt} = \lambda Y && \text{Exponential}\\
&\frac{dY}{dt} = Y\left(\alpha - \beta Ln\left(\frac{Y}{Y_0}\right)\right) && \text{Gompertz}\\
&\frac{dY}{dt} = \alpha Y^{2/3} - \beta Y && \text{Bertalanffy}\\
&\frac{dY}{dt} = \alpha Y - \beta Y^2 && \text{Logistic}
\end{aligned} \tag{1.4}$$

with initial conditions $Y(0) = Y_0$. Based on goodness of fit measures, the Gompertz model was chosen as best. Mice treated with bleomycin were modeled as

$$\frac{dY}{dt} = Y\left(\alpha - \beta Ln\left(\frac{Y}{Y_0}\right) - \gamma C_t\right) \tag{1.5}$$

where γ was a measure of drug effect and C_t was the predicted tissue concentration based on a three-compartment model.

Jackson et al. (2010) used a Gompertz model to describe the tumor growth rate for A2780 mice xenografts and the interaction between a targeted therapeutic and cytotoxic chemotherapeutic agent. Since only concentration data were available for the targeted therapeutic, a kinetic–dynamic model was used to model the temporal relationship with the cytotoxic agent. The authors also included a biomarker model linking the pharmacokinetic model for the targeted therapeutic and its effect on tumor growth. The model was able to discriminate between the effects of the two agents and showed that the two agents had an additive effect on tumor growth inhibition.

Although there has been some debate as to whether Gompertz or logistic growth rates have a biological basis (Xu 1987), their original use was purely empirical. Marusic (1995) showed that Gompertz, logistic, and Bertalanffy models are in fact special cases of the generalized two parameter model

$$\frac{dY}{dt} = aY^{\alpha} - bY^{\beta}. \tag{1.6}$$

For example, in a logistic equation $\alpha = 1$ and $\beta = 2$. Other types of empirical models to explain tumor growth include the nonlinear mixed effects model proposed by Liang and Sha (2004) wherein tumor growth was modeled using a biexponential equation

$$Y_i(t_{ij}) = \exp(p_{i1} - d_{i1}t_{ij}) - \exp(p_{i2} - d_{i2}t_{ij}) + \varepsilon_{ij} \tag{1.7}$$

where, the subscript i refers to the ith subject at the jth timepoint. While useful to explain a particular set of data, such empirical models are difficult to extrapolate beyond the conditions originally studied. Gompertzian models also suffer from the fact that the plateau is difficult to estimate because the mice are often killed for ethical reasons when tumor sizes exceed

a certain size (usually >1,000 mm^3), which often occurs prior to the plateau occurring.

More recent models attempt to account for treatment effects through the use of mechanistic or semi-mechanistic models. Yamazaki et al. (2008) used a modified indirect response model where tumor growth was described by

$$\frac{dY}{dt} = K_{in}\left(1 - \frac{Y(t)}{TG_{50} + Y(t)}\right) \times \left(1 - \frac{E_{\max} \times C^n}{EC_{50}^n + C^n}\right)Y(t) - K_{out}Y(t) \quad (1.8)$$

where, the additional $Y(t)$ on Kin-side of the equation allows for tumor growth and the term $\left(1 - \frac{Y(t)}{TG_{50} + Y(t)}\right)$ allows tumor growth to plateau. Using this model, the authors predicted the tumor growth profiles for GTL16 gastric carcinoma and U87MG glioblastoma xenografts following treatment at five different dose levels with PF-02341066, a cMET tyrosine kinase inhibitor. Interestingly, although they modeled cMET phosphorylation levels in tumors, they did not test whether cMET phosphorylation could be a driver of (1.8) instead of plasma concentrations. Also, such a model implies that the drug inhibits tumor growth with no effect on cell death. It may be that in such a case, the model needs to be modified to

$$\frac{dY}{dt} = K_{in}\left(1 - \frac{E_{\max} \times C^n}{EC_{50}^n + C^n}\right)Y(t) - K_{out}\left(1 + \frac{E_{\max death} \times C^n}{EC_{50,death}^n + C^n}\right)Y(t) \quad (1.9)$$

where a term is added to the Kout-side of the equation to account for cell death.

A model that has seen rapid acceptance within the pharmacometrics community is the Simeoni tumor growth model. Using paclitaxel and 5-fluorouracil (5-FU) as probes, Simeoni et al. (2004a) reported on a semi-mechanistic model of tumor growth. In the unperturbed state, tumor growth is expected to occur exponentially, at least initially, followed by a linear growth phase that eventually plateaus. Such tumor growth can be modeled using a Gompertz or logistic model. In their data, a plateau phase was never achieved and to account for this detail, a model was developed to explain the exponential and linear growth components. The authors used a change point differential equation to account for the two different phases. In terms of differential equations, tumor size Y was modeled as

$$\begin{aligned} \frac{dY}{dt} &= \lambda_0 Y(t), Y(t) \le Y_t \\ \frac{dY}{dt} &= \lambda_1, Y(t) > Y_t \\ Y(0) &= Y_0 \end{aligned} \quad (1.10)$$

where λ_0 and λ_1 are the parameters characterizing the exponential and linear rate of growth, and Y_t is the tumor size at which growth changes from exponential to linear. Y_t can be expressed as a function of λ_0 and λ_1 where $\lambda_0 Y_t = \lambda_1$. The parameters λ_0 and λ_1 are considered an indication of the aggressiveness of the tumor. The change point model in (1.10) can be simplified to

$$\frac{dY}{dt} = \frac{\lambda_0 Y(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1}Y(t)\right)^{\Psi}\right]^{1/\Psi}}, Y(0) = Y_0 \quad (1.11)$$

For large values of Ψ, (1.11) is a good representation of (1.10) and for this reason Ψ is fixed to 20. When $Y(t) < Y_t$, the system behaves exponentially because the term $(\lambda_0/\lambda_1)Y(t)^{\Psi}$ is negligible. On the other hand, when $Y(t) > Y_t$, the term of 1 in the denominator becomes negligible and the system switches to linear growth.

In the perturbed state when animals are treated with cancer drugs, the model needs to account for the cells that are killed by the drug. To do this, the proliferating cells are modeled as a set of damaged cells and dead cells in a transit compartment manner (top of Fig. 1.2). This represents the semi-mechanistic part of the model. Three transit compartments are used to account for the damaged cells, representing the

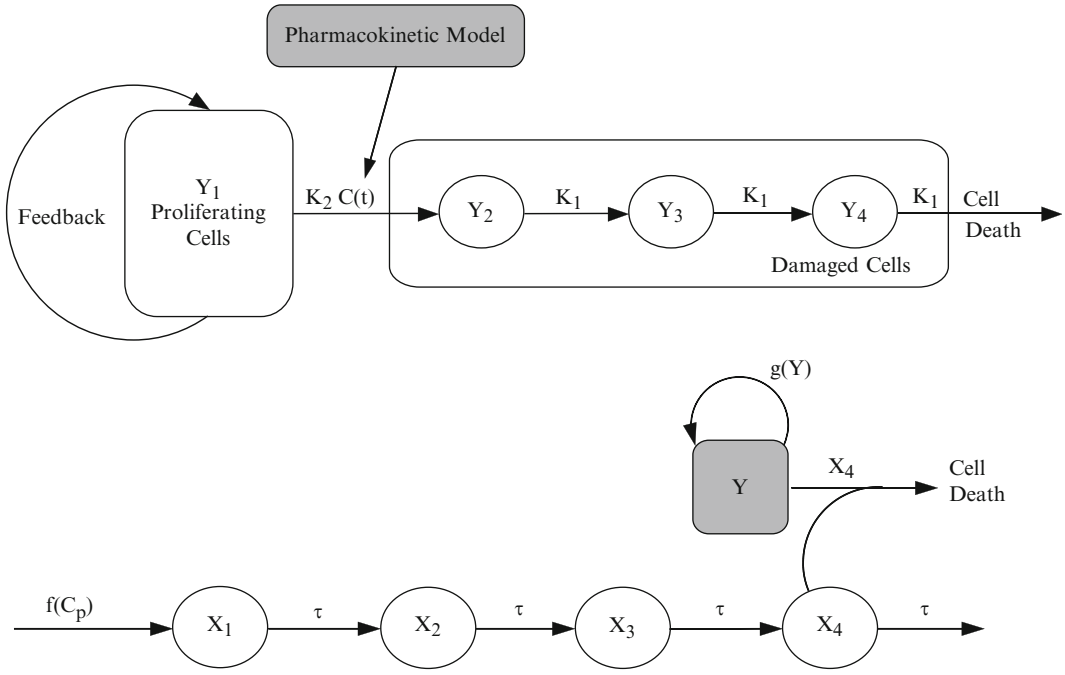

Fig. 1.2 Schematic of the semi-mechanistic tumor growth model proposed by Simeoni et al. (2004a) (*top*) and the cell transit model proposed by Lobo and Balthasar (2010) (*bottom*)

three degrees of damage. Mathematically, the differential equations for the model become

$$\begin{aligned}
\frac{dY_1}{dt} &= \frac{\lambda_0 Y_1(t)}{\left[1+\left(\frac{\lambda_0}{\lambda_1}Y_1(t)\right)^{\Psi}\right]^{1/\Psi}} - K_2 C(t) Y_1(t) \\
\frac{dY_2}{dt} &= K_2 C(t) Y_1(t) - K_1 Y_2(t) \\
\frac{dY_3}{dt} &= K_1 Y_2(t) - K_1 Y_3(t) \\
\frac{dY_4}{dt} &= K_1 Y_3(t) - K_1 Y_4(t) \\
w(t) &= Y_1(t) + Y_2(t) + Y_3(t) + Y_4(t) \\
Y_1(0) &= w(0), Y_2(0) = Y_3(0) = Y_4(0) = 0 \\
C(t) &= 0, t \le t_0
\end{aligned} \tag{1.12}$$

where K_2 is a parameter that represents the efficacy of the drug at killing the tumor, K_1 is the rate of death of the drug, $w(t)$ is the total tumor weight and $C(t)$ is the drug concentration at time t, and t_0 is the start of drug administration. The number of transit compartments between cell proliferation and cell death is empirical and can in fact be changed depending on the tumor type. The top of Fig. 1.3 shows a theoretical tumor growth curve assuming a single intravenous bolus of drug on day 9. Depending of the value of K_2, the drug can transiently retard growth or completely shrink the tumor.

A number of secondary parameters can be defined from the primary model parameters. The average time to cell death is equal to n/K_1. A Time Efficacy Index (TEI), which can be interpreted as the time interval required to achieve a predefined tumor weight animals during linear growth, can be defined as

$$TEI = \frac{K_2 \times AUC}{\lambda_0} \tag{1.13}$$

where, AUC is the total area under the curve following a single dose administration. If animals are exposed to a constant drug concentration C_{ss}, the threshold concentration for tumor eradication (C_{TE}) can be estimated as λ_0/K_2 such

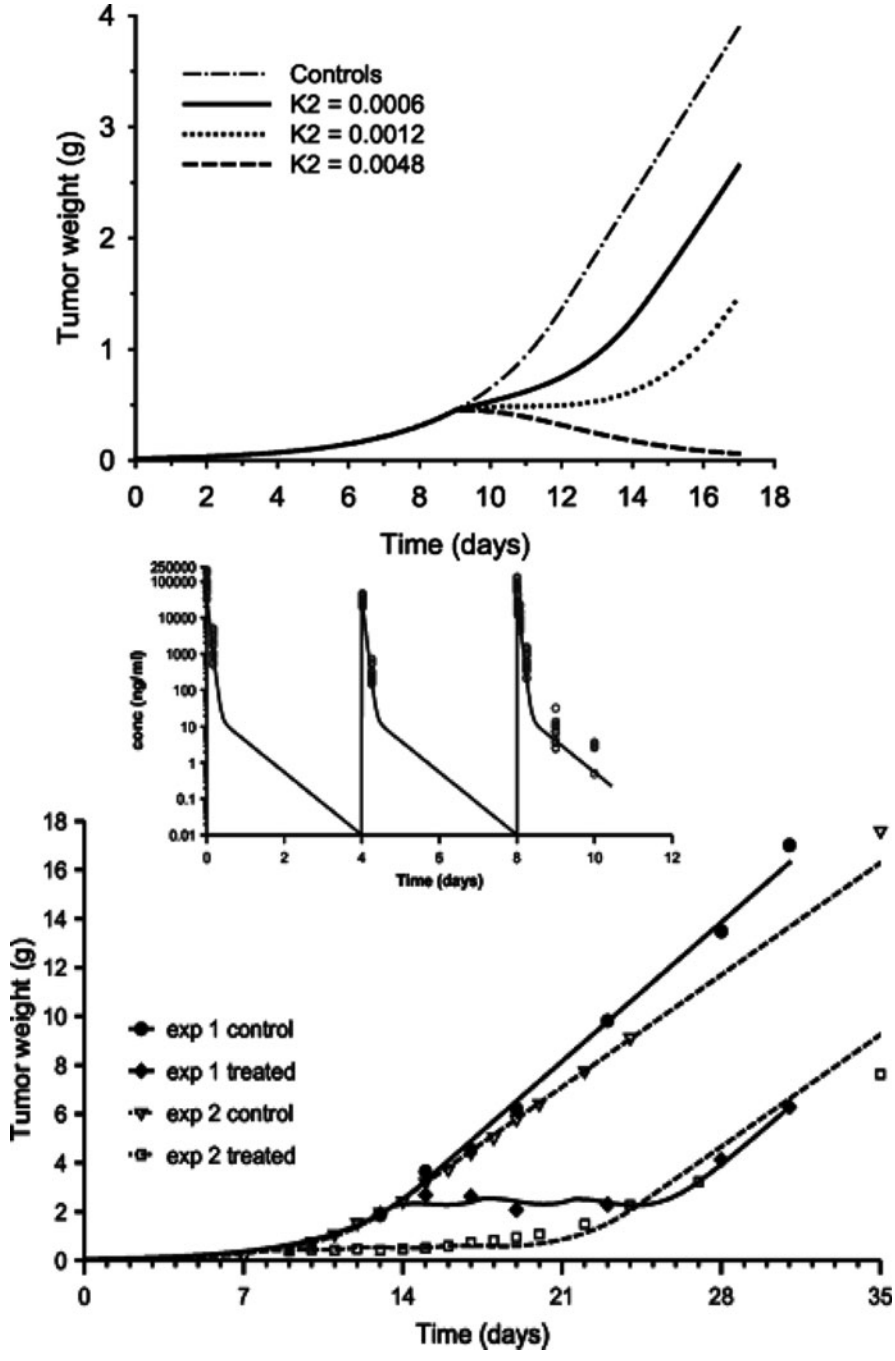

Fig. 1.3 Top plot shows the theoretical effect of K_2 on simulated tumor growth curves: the simulations were performed assuming a single intravenous bolus given on day 9; $\lambda_0 = 0.0154$/day; $\lambda_1 = 0.0211$ g/day; $w(0) = 0.0162$ g; $K_1 = 0.0265$/day. λ_0, first-order rate constant of tumor growth; λ_0, zero-order rate constant of tumor growth; $w(0)$, tumor weight at the inoculation time; K_1, first-order rate constant of transit; K_2, measure of drug potency. Bottom two plots show the observed and model-fitted tumor growth curves obtained in two different experiments in nude mice given intravenously either the vehicle or paclitaxel [experiment 1 (*exp* 1), 30 mg/kg every 4 days for 3 days from day 8; experiment 2 (*exp* 2), 30 mg/kg every 4 days for 3 days from day 13]. Middle plot shows the fitting of the pharmacokinetic data of paclitaxel given as repeated intravenous bolus doses at 30 mg/kg dose level; *Conc.*, concentration. Reprinted with permission from Simeoni et al. (2004a). Copyright American Association of Cancer Research, 2004

that if $C_{ss} < C_{TE}$ then the tumor will grow to the asymptotic weight of $\lambda_1/(K_2 \times C_{ss})$. If $C_{ss} > C_{TE}$, then the tumor size will decrease. In examining the product of CTE and human total systemic clearance, a linear relationship on a log–log scale was noted for ten different drugs and further when K_2 was plotted against the maximum tolerated dose, a linear log–log relationship was again seen (Rochetti et al. 2007).

Using this model, Simeoni et al. modeled a variety of tumor growth curves for paclitaxel, 5-FU, and a NCE. The bottom of Fig. 1.3 shows the observed and predicted growth curves for two different experiments in mice bearing A2780 tumors following paclitaxel administration. From this initial report, a number of further examinations of the usefulness of the model have been reported by the authors (Magni et al. 2006; Rocchetti et al. 2005; Simeoni et al. 2004b; Poggesi et al. 2004), and by others outside the group (Goteti et al. 2010).

It should be pointed out, however, that the Simeoni model is not without its flaws. First, unlike the Gompertz model, the Simeoni model has no plateau and continues linear growth to infinity. In reality, tumors have a self-limiting size and when the animal does not die before that limit is reached, a plateau is evident in tumor size and/or weight. The Simeoni model cannot account for a plateau. Second, although the model is touted as a semi-mechanistic model, the actual growth function is empirical based on observation. Also, the model is new to pharmacologists who perform the xenograft studies. Gompertzian growth has 40 years of experience behind it; pharmacologists are comfortable with it. The Simeoni model is new and untested and the comfort level is not the same when it is used. Despite these, however, the model still has its advantages and good modeling practice would be to compare a variety of models (Simeoni, Gompertz, logistic, etc.) before choosing an appropriate form.

Since these initial reports, the basic Simeoni model has been expanded to other situations. Stuyckens et al. (2007) extend the basic model by allowing for drug resistance to occur either through an empirical resistance function or through a semi-mechanistic approach and further show how the model can be expanded in a kinetic–dynamic model through which concentration measurements are not necessary.

Koch et al. (2009) modified the Simeoni model to allow a smooth transition between exponential and linear growth by changing dY_1/dt in (1.12) to

$$\frac{dY_1}{dt} = \frac{2\lambda_0\lambda_1 Y_1(t)^2}{(\lambda_1 + 2\lambda_0 Y_1(t))w(t)} - K_2 C(t) Y_1(t) \quad (1.14)$$

All other equations remain the same. In the studies is reported by Simeoni, none the drugs examined were given in combination. Koch et al. extend their model to account for combination therapy when two drugs are getting together. They replace K_2 in (1.14) with a term they refer to as the "total influence" function and change the first two differential equations in the model to

$$\begin{aligned}\frac{dY_1}{dt} &= \frac{2\lambda_0\lambda_1 Y_1(t)^2}{(\lambda_1 + 2\lambda_0 Y_1(t))w(t)} \\ &\quad - \left(K_2^a C_a(t) + K_2^b C_b(t)\Phi\right) Y_1(t) \\ \frac{dY_2}{dt} &= \left(K_2^a C_a(t) + K_2^b C_b(t)\right) Y_1(t) - K_1 Y_2(t)\end{aligned} \quad (1.15)$$

where, K_2^a and K_2^b are the K_2 values for Drug A and Drug B and Φ is a synergy term such that $\Phi > 1$ implies synergy, $\Phi = 1$ implies additive, and $\Phi < 1$ implies antagonism. It should be noted that unless many different dose combinations of Drug A and Drug B are given, Φ may be unestimable.

Bueno et al. (2008) reported a model which characterized the pharmacokinetics of LY2157299, a novel Type I receptor TGF-β kinase antagonist, and tumor growth kinetics in Calu6 and MX1 tumor types. The pharmacokinetic model consisted of a two compartment model with first-order absorption and first-order elimination. Since tumor size did not plateau, the tumor model used was the Simeoni growth model where the change in tumor size (dY/dt) was characterized by

$$\frac{dY}{dt} = \frac{\lambda_0(1 - \mathrm{INH2})Y(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} Y(t)\right)^{\psi}\right]^{1/\psi}}. \quad (1.16)$$

INH2 was a zero to one time-delayed, normalized inhibition effect related to the degree of phosphorylated Smad, proteins that modulate the activity of TGF-β agonists (Fig. 1.4). The authors then used simulation to understand the relationship of tumor growth inhibition and tumor growth delay with steady-state concentrations of LY2157299 and different dosing schedule.

A competing model to the Simeoni model is the proposed transit model approach by Lobo and Balthasar (2010), which they developed to account for the delay in tumor growth inhibition versus methotrexate plasma concentrations. The transit model they proposed is shown in the bottom of Fig. 1.2. Mathematically, the model proposed was

$$\begin{aligned}
\frac{dY}{dt} &= g(Y) - K_4 Y(t), Y(0) = w(0) \\
\frac{dX_1}{dt} &= \tau\left(\frac{K_{max} C_p}{IC_{50} + C_p} - X_1(t)\right) \\
\frac{dX_2}{dt} &= \tau(X_1 - X_2) \\
\frac{dX_3}{dt} &= \tau(X_2 - X_3) \\
\frac{dX_4}{dt} &= \tau(X_3 - X_4) \\
X_1(0) &= X_2(0) = X_3(0) = X_4(0) = 0
\end{aligned} \tag{1.17}$$

where Y is the tumor size, τ is the transit rate constant (similar to K_1 in the Simeoni model), and $g(.)$ is a tumor growth function. Sample growth functions include a exponential growth

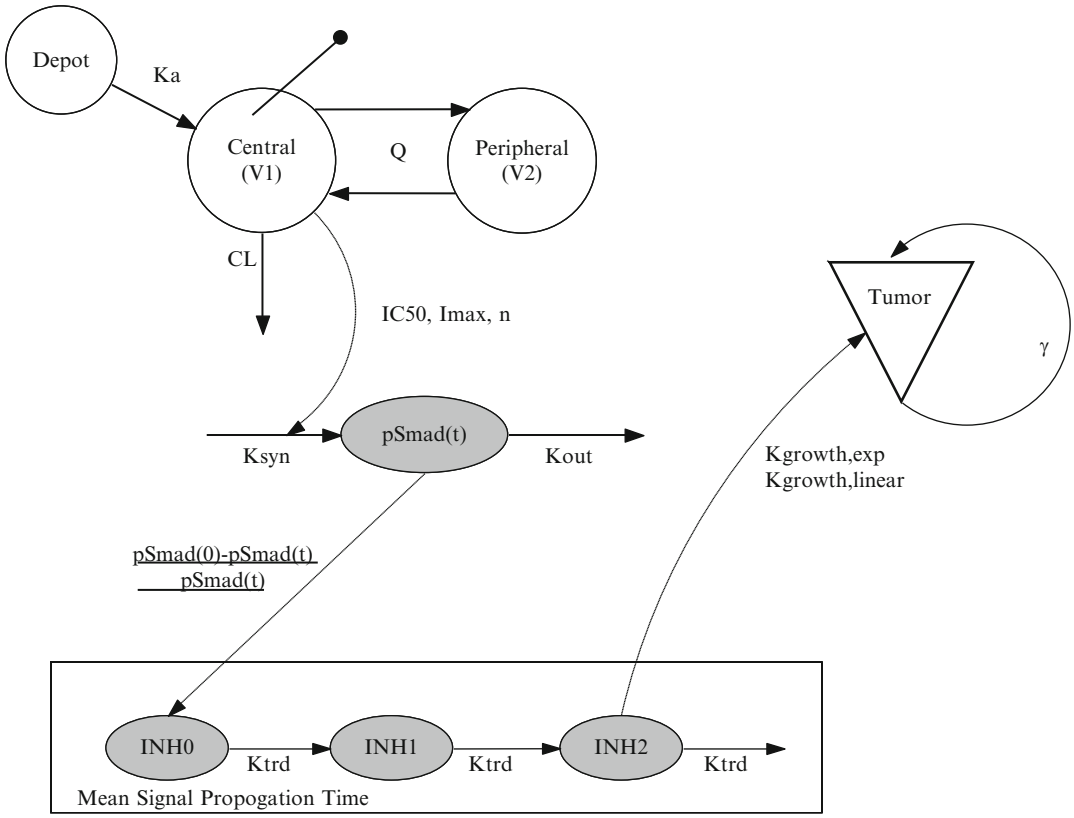

Fig. 1.4 Schematic model for the tumor growth kinetics following treatment with LY2157299 as presented by Bueno et al. (2008). *Gray circles* denote biomarkers. Best lines denote negative influence functions, e.g., plasma concentrations of LY2157299 inhibit phosphorylation of pSmad

$$g(.) = K_g Y(t), \tag{1.18}$$

exponential growth that plateaus

$$g(.) = K_g Y(t)\left(1 - \frac{Y(t)}{Y_{\max}}\right), \tag{1.19}$$

or even a Simeoni type function

$$g(.) = \left[1 + \left(\frac{\lambda_0}{\lambda_1} Y(t)\right)^{\Psi}\right]^{1/\Psi}. \tag{1.20}$$

Lobo and Balthasar compared the transit model to two established models for chemotherapeutic effects, a phase-specific and phase-nonspecific model. The transit model was found to provide a superior goodness of fit compared to the established models. Yang et al. (2010) simulated data from the Simeoni model (which they call the cell distribution model) and the transit model (which they call the signal distribution model) and compared the simulated data using the alternative model. Their analysis revealed that the signal distribution model was more flexible in fitting data derived from the cell distribution model than vice versa. They concluded that although the models appear similar, they are in fact mechanistically distinct, are not interchangeable, and that the cell transit model is more robust, particularly when data are sparse.

Jumbe et al. (2010) recently reported a modified transit compartment model wherein tumor cells were divided into two groups, those that were insensitive to the drug and grow a constant rate and those that were sensitive to the drug and eventually die. The sensitive cells were modeled as a progressive process of cell damage whereby the cells stop replicating and then eventually die. The total volume of the tumor was the sum of the insensitive cells and sensitive cells at the progressive stages of death. Using this model, the authors were able to characterize the effects of trastuzumab-DM1, an antibody–drug conjugate under development for the treatment of breast cancer, in two different mice xenograft models of HER2-positive breast cancer specifically designed to be trastuzumab resistant. The effect of trastuzumab was shown to be cell-cycle-phase nonspecific in its mechanism of action.

A new model has recently been reported to model the antitumor effect of antiangiogenic agents. Ribba et al. (2010) used four ordinary differential equations to describe the temporal changes of non-hypoxic (P), hypoxic (Q), and necrotic (N) tissue within a tumor. A latent variable K, which they call the carrying capacity, accounts for the process of angiogenesis. Using sunitinib as a probe, the authors modeled the tumor growth kinetics of HT29 lung and HCT116 colon xenografts in mice using a kinetic–dynamic model to account for temporal changes in sunitinib concentrations. It is too early at this point to determine the value of the model in drug development but its mechanistic nature holds promise.

1.4 Measuring Tumor Size in Cancer Patients

There are many different ways to measure tumor size, the most common being radiologic measurement. Usually, the cross product measurement of the two longest perpendicular diameters seen on a cross-sectional image, like an X-ray, ultrasound, CT, or MRI scan, is taken as the size of the tumor. With new imaging techniques, actual tumor volume can now be assessed, but this is not often done (yet). For X-ray measurement, diameter may be measured manually with a caliper, but for imaging and digital X-rays, computerized measurements can be made. The difficulty with measuring perpendicular diameters is when the legion of interest is not well defined or is asymmetrical. For this reason, measurment of tumor size in many pivotal trials is done by a standardized review, sometimes using just a single reviewer, to reduce intersubject variability and increase reproducibility.

Being able to accurately measure tumor size is important for many reasons. A patient's initial tumor size is used to stage the patient for many types of cancers. For example, breast cancer patients having a tumor size of 2–5 cm are classified as T-2. Tumors >5 cm are classified as T-3.

How a patient is treated depends upon their staging. Once a patient initiates therapy, treatment is dependent on how the tumor shrinks in response to a therapy. A tumor may show initial shrinkage with a drug but then may start to grow again, a process known as disease progression, at which point the physician may change the course of treatment. Without an accurate tumor size measurement physicians are treating blind. Tumor size is also an important indicator for survival. For example, patients with lung tumors <2 cm in size have a higher survival rate than patients with larger sized tumors.

In most cases, multiple lesions are measured and the sum of these lesions is returned as a composite measure of tumor burden; this is often called the sum of longest diameters. Nearly 30 years ago, the World Health Organization (WHO) (Miller et al. 1981) reported on guidelines to standardized tumor measurements across studies. Under the WHO criteria, patients can be defined into one of five response types: "complete response" (CR), "partial response" (PR), "stable disease" (SD), "progressive disease" (PD), or "not evaluable."

While a huge step forward there were still problems with the WHO guidelines, like lack of specification of the number of lesions to be reviewed, definitions for what constitutes progressive disease, and how to handle new imaging modalities. In 2000, several research groups updated the WHO guidelines and created the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Therasse et al. 2000). The core of RECIST is standardized tumor size measurement. In 2009, RECIST Version 1.1 was released as a means to further improve consistency and standardization across clinical trials (Eisenhauer et al. 2009). RECIST 1.1 has a few changes to version 1. These include reducing the number of measured lesions to be assessed from a maximum of ten to five, reducing the number of measured lesions from a maximum of five to two in a particular organ, new guidelines for assessment of measuring the lymph nodes, guidelines on defining disease progression, and new guidelines on imaging (interestingly, in the first version of RECIST no radiologists were included in developing the guidelines). Table 1.1 presents definitions for the response criteria under RECIST 1.1.

The overall response rate (ORR) for a trial is the proportion of patients that achieve a specified reduction in tumor size for a predefined period of time (at least 4 weeks) that includes both CR and PR (McKee et al. 2010). Stable disease is not included in ORR, but is included in the Disease Control Rate, which is the proportion of patients achieving a PR, CR, or SD. Response duration is defined as the time from initial response to the time of documented disease progression. In considering a drug's ORR, the FDA considers magnitude, percent of CRs, and duration of response.

Table 1.1 Summary of response criteria under RECIST 1.1

Response	Definition
Complete response	Complete disappearance of all lesions lasting at least 4 weeks; lymph nodes must be non-pathological in size
Partial response	A 30% decrease in sum of longest diameters lasting at least 4 weeks taking as a reference the baseline tumor size
Stable disease	Neither partial response or progressive disease criteria met taking as a reference the smallest sum of diameters as the reference
Progressive disease	20% increase in tumor size using the smallest sum of diameters as the reference (which may be the baseline) with no complete response, partial response, or stable disease documented before increased disease and a minimum increase of at least 5 mm or appearance of new lesions
Not evaluable	When no measurement is available or incomplete measurements are done

Tumor measurements are often made every few weeks, usually 4–8 weeks, depending on the cancer type. From these, the best overall response is determined (which in itself is complicated, see Eisenhauer et al. (2009) Tables 1–3 for details) and then based on when, and if, progression occurs, time to progression (TTP) is determined, which is formally defined as the time from randomization to documented, objective disease progression (McKee et al. 2010). TTP is related to progression-free survival (PFS), which is defined as the time from randomization to disease progression or death. Should a patient die during study, TTP is censored. TTP can be used as a primary endpoint in a clinical trial in which the majority of patients who die on the study are not expected to be to the cancer itself, although PFS is preferred since it is expected to better correlate with overall survival, the gold standard of primary endpoints in oncology.

While standardized criteria certainly have their advantages, there are still unresolved issues with regards to standardization. Examples include when there are more than five lesions, radiologists do not consistently choose the same five lesions to assess. Reproducibility is still an issue, with interobserver and intraobserver variabilities of 15% and 6% for measurements of tumor size in three dimensions using CT (Schwartz et al. 2000). And, there are some questions as to whether RECIST applies to pediatric oncology (McHugh and Kao 2003).

1.5 Clinical Models for Tumor Growth

There have been few published models that have examined the relationship between exposure and tumor growth over time in humans. The goals of these studies have been to relate short-term changes in tumor size to long-term changes in outcome or to confirm the presence of a concentration-effect relationship. Both of these goals have utility. The success rate in Phase 3 oncology studies is not as large as one would think, about 50%. Being able to leverage the information from Phase 2 may increase the probability of success in Phase 3. Being able to establish a concentration-tumor size relationship may be useful as supporting data in a registration dossier with only a single well-controlled study.

Tham et al. (2008) presented a model for tumor growth in non-small cell lung cancer (NSCLC) patients using a kinetic–dynamic model. Under this empirical model, an effect compartment was used to transduce dose into an "effect concentration" which was then used as an input into an indirect response type-model. Using this model, the authors were able to predict tumor size following treatment with gemcitabine.

Wang et al. (2009) modeled four randomized clinical trials for NSCLC. Tumor size Y was modeled using a mixed exponential decay and linear growth function

$$Y(t) = Y(0)\exp(-St) + kt \tag{1.21}$$

where, $Y(0)$ is the baseline tumor size, S is the exponential tumor rate shrinkage constant, and k is the linear growth rate constant. The exponential portion of the model explains the rate of tumor shrinkage, while the linear growth function explains the rate of tumor growth after tumors have ceased shrinking. Random effects were added to the model by allowing the baseline, S, and k to be log normally distributed. An exponential error model was used to account for unexplained residual variability. Figure 1.5 presents a goodness of fit plots for six representative patients. The model appears to capture the general tendencies of the observed data.

Simply modeling tumor size was not the goal of the Wang et al. paper. The goal was to incorporate changes in tumor size as a predictor of survival and to determine whether short-term changes in tumor size could be used to predict long-term overall survival. The authors found that overall survival could be modeled using a parametric lognormal survival model in which the mean survival time was a function of ECOG (Eastern Cooperative Oncology Group) performance status, baseline tumor size, and percent

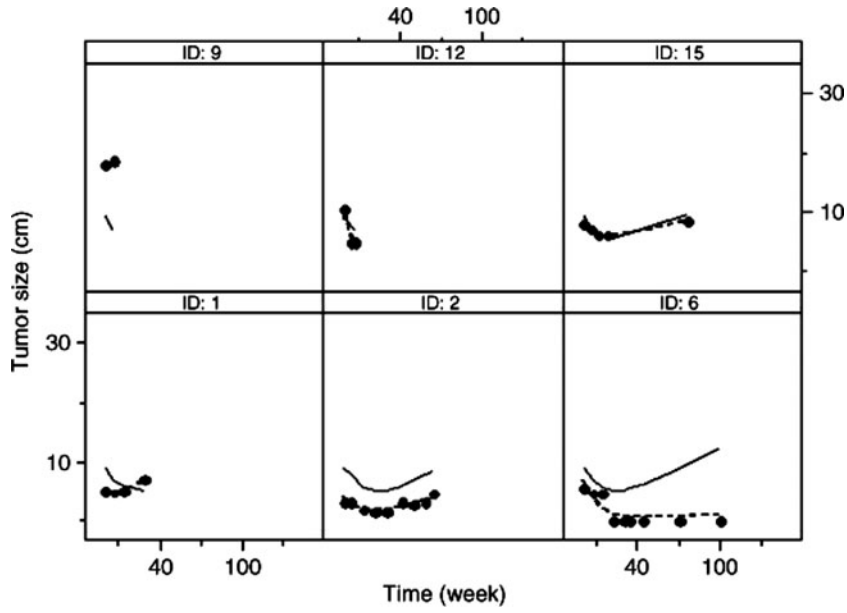

Fig. 1.5 The time course of NSCLC tumor size change for representative individual patients. The *symbols* represent the observed tumor sizes, the *solid line* represents the mean tumor size for the overall population, and the *broken line* represents the individual predicted tumor size. Figure reprinted from Wang et al. (2009). Reprinted by permission from Nature Publishing Group [Clinical Pharmacology and Therapeutics, 2004]

change from baseline 8 weeks after initiating therapy. Wang et al. did not link the tumor size model to a particular pharmacokinetic model because the studies used to develop the model were different drugs. But future analyses could link a pharmacokinetic model with a tumor model. Similarly, for NCEs being developed for NSCLC, a model could be developed explaining change in tumor size as a function of that drug's pharmacokinetics, which could then be linked to the Wang et al. survival model to predict overall survival based on short-term efficacy studies, thus leveraging information.

Claret et al. (2009) developed a kinetic–pharmacodynamic model linking capecitabine exposure to tumor growth inhibition in patients with colorectal cancer. Using data from Phase II and Phase III data, the authors modeled tumor size Y at time t using the equation

$$\frac{dY}{dt} = K_{\text{growth}} \times Y(t) - K_{\text{death}} \times \text{Dose} \times \exp(-\lambda t) \times Y(t) \quad (1.22)$$

where, K_{growth} is the tumor growth rate, K_{death} is the tumor death rate, Dose is the daily dose administered, and $\exp(-\lambda t)$ is the progression rate at time t, where λ is the estimated progression appearance factor. Because no pharmacokinetic data were available, dose was used as the exposure measure affecting tumor death. Between-subject variability was accounted for by allowing K_{growth}, K_{death}, and λ to be treated as log normally distributed random effects. Similar to the Wang et al. paper, the authors then developed a survival model linking percent change in tumor size 7 weeks after treatment to overall survival but with a twist. The twist was that they did not have a survival data with capecitabine, but they did have survival data with 5-FU so they developed their survival model using the 5-FU data and then piggybacked the models together (Fig. 1.6). Hence, one part of their model was drug-specific while the other part of their model was disease-specific. Using simulation, the authors validated their model using an independent Phase 3 study. Based on these

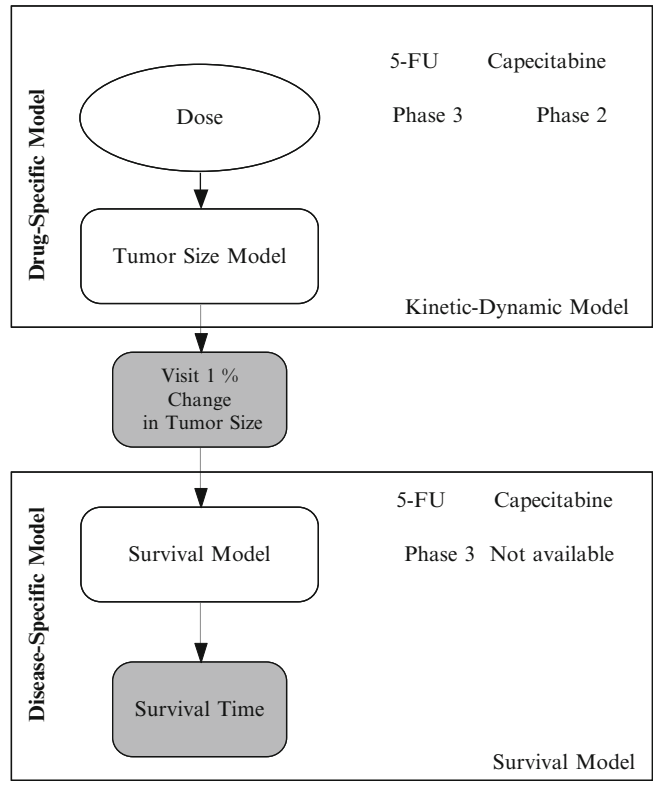

Fig. 1.6 Schematic of the kinetic–dynamic-survival model of Claret et al. (2009). *Gray boxes* are model outputs

results the authors have developed a framework for predicting the Phase 3 survival based on Phase 2 data which might be useful when deciding whether to pursue further development of the compound.

Houk et al. (2009) expanded on the Claret et al. model and reported on the tumor growth kinetics in patients with metastatic renal cell cancer (mRCC) and gastrointestinal stromal tumors (GIST) following treatment with sunitinib.[1] Tumor growth kinetics (dY/dt), as measured by the sum of longest diameters, for each tumor type was described by

$$\frac{dY}{dt} = K_{\text{growth}} \times Y(t) - K_{\text{death}} \times C(t) \times \exp(-\lambda t) \times Y(t) \quad (1.23)$$

where, $C(t)$ is the plasma concentration of sunitinib. This time, exposure was modeled as a function of drug concentration. Their models showed a different rate of growth and death for mRCC and GIST. Patients with mRCC had a K_{growth} twofold higher than patients with GIST and threefold higher K_{death}. The rate of progression was 1.5-times faster in mRCC than in GIST. Simulations showed that 38% more of mRCC patients and 23% more of GIST patients would show a partial response (at the least a 30% decrease from baseline in tumor size) when sunitinib was administered 50 mg once-daily compared to 25 mg once-daily. Combining this efficacy model with a variety of different adverse event models, the authors generated a composite efficacy – adverse event profile for sunitinib. It should be noted that one difficulty with this model is the estimation of K_{growth}. Since most patients, once they start to show signs of disease progression, are taken off the study drug, an estimate of K_{growth} is often unavailable or imprecisely estimated.

[1] Houk et al. discussed this model in another chapter in this book.

1.6 Modeling Response in Humans

Under RECIST criteria, patients are assigned a best overall response. It is often of interest to model best overall tumor response as a function of exposure. The usual method is to treat the responses as an ordinal variable such that CR > PR > SD > PD and then use ordinal logistic regression to model response as a function of exposure. An example of this approach is the exposure–response analysis reported for sunitinib in mRCC patients as reported by Houk et al. (2009) in which there was a significant relationship between sunitinib exposure and the probability of either a CR or PR ($p < 0.0001$). In GIST patients a trend toward significance was observed but did not reach statistical significance. In both cases there was a trend towards decreasing tumor size with increasing sunitinib exposure.

There are pros and cons to this approach. The pros are that the results have direct interpretation and is relevant, e.g., increasing exposure increases the probability of a complete response. The con is that RECIST collapses a dynamic measure (tumor growth) into a single endpoint, which always results in loss of information and decreased statistical power at detecting covariate effects. Further research is needed in the link between dynamic models of tumor growth and logistic regression of best overall response.

1.7 Mathematical Models of Cancer

A handful of reports have been published on theoretical models of cancer growth and progression, some of which were reviewed in Sanga et al. (2006). Araujo and McElwain (2004) present a history of these type of mathematical models. These models do not use the traditional ordinary differential equation framework familiar to most pharmacokineticists and instead use partial differential equations, which take into account both time and space. For example, Sinek et al. (2009) reported on the effect of doxorubicin and cisplatin using a partial differential multicompartment model of concentrations in the extracellular, cytosolic, and nuclear compartments. From this they were able to predict DNA-bound drug concentrations, drug concentrations at various cell depths, cell inhibition, and cell survival. Sanga et al. argue that "*the multifaceted nature of cancer requires sophisticated, nonlinear mathematical models to capture more realistic growth dynamics and morphologies*". Although none of these models have yet to show utility in drug development, with the rise of systems biology it is only a matter of time before these nonlinear time- and space-models of cellular dynamics link with pharmacokinetic–pharmacodynamic models to lead to an integrative holistic model of drug response and effect.

Conclusions

The difficulties and challenges associated with understanding the dynamics of cancer may benefit from mathematical modeling. Indeed, the role of mathematical modeling in drug development is becoming more mainstream and accepted. In the March 2010 issue of Forbes magazine, there was a cover item that said "Can Math Cure Cancer?" and inside was a story called "The Mathematics of Cancer". The main focus of the article was on Larry Norton, of the Norton–Simon hypothesis, and how he thinks that "*adding more mathematics to the crude science of cancer therapy will help*". Forbes is not a scientific magazine, it is not even oriented towards professional economists. The target audience for Forbes is the everyday investor and yet here is a story discussing the role of modeling in drug development and how it could help cure cancer.

Modeling tumor growth may prove to be an advantageous tool in cancer drug development since modeling allows for greater understanding of mechanisms and allow for predictions outside the domain of the studies used to develop the model. And yet, there are still many limitations to the models we use. The linear ordinary differential equations used to characterize tumor growth are a gross simplification and have only a small face validity in their use. True tumor growth is nonlinear

and stochastic and requires much more complex models involving partial differential equations. Still, modeling provides a means to understand data from a variety of complex sources and across many different data types. Early leveraging of preclinical information (even if the model is a simplification of the true underlying data generating process) and later application of modeling in drug development will allow companies make better decisions, hopefully earlier. The use of mathematical modeling in oncology is relatively new and is ripe for research with a need for new innovative modeling methods, techniques, and applications.

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