Review Article

Modeling NSCLC Progression: Recent Advances and Opportunities Available

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Abstract. Non-small cell lung cancer (NSCLC) is one of the leading causes of death around the world with an estimated 5-year relative survival rate of 16% at diagnosis. Development of drugs treating NSCLC is not easy, and the success rate for an anticancer treatment to pass through the whole clinical development process is as low as 5%. Modeling and simulation lend themselves as tools which can potentially streamline drug development. A critical component of the models developed is a description of how the disease progresses over time and how a treatment would affect its trajectory. Our aim was to review the literature to present the models and growth functions which have been used for describing NSCLC dynamics, and how anticancer treatments can affect such dynamics, both in animals and in humans. Only a limited set of models were identified for such a purpose. Most of the models which have been used were descriptive of tumor growth, yet there were attempts to account for the underlying processes, especially in animals where it is more feasible to collect data needed for developing such models. Moreover, we discuss how modeling and simulation can aid in decision making across the different stages of drug development. Based on some encouraging results from trials of other cancer types where modeling tumor dynamics has played an important role, we propose further exploration of NSCLC using model-based techniques and further use of these techniques in designing and evaluating NSCLC trials.

KEY WORDS: disease progression; drug development; lung cancer; modeling; tumor growth.

INTRODUCTION

Lung cancer is one of the major causes of death around the world. It was estimated to be the most commonly diagnosed type of cancer worldwide in 2008 (12.7% of the total cases newly diagnosed with cancer) and the most common cause of cancer death (18.2% of the total deaths related to cancer) (1). It was also estimated that the 5-year relative survival rate at diagnosis in patients suffering from lung cancer in the USA was only 16% (2). Non-small cell lung cancer (NSCLC), a subtype of lung cancer, accounts for approximately 85% of the lung cancer cases (3).

Despite the high incidence and mortality rates of cancer, the medical needs of cancer patients are unmet. Developing novel therapies for treating cancer is becoming increasingly difficult, and the success rate for an anticancer treatment to pass through the whole clinical development process is as low as 5% (4). Disappointing success rates encountered in oncology and in other specialties urged a paradigm shift from the conventional, mostly empirical, and arbitrary decision making in developing drugs, to more efficient means. Model-

based drug development (MBDD) is among the tools that have been suggested for this purpose (4–7).

Pharmacometrics, a strongly emerging discipline concerned with building mathematical and statistical descriptions of the interactions between patients and their drugs, is an appropriate tool for MBDD (8,9). Modeling and simulation which represent the essential elements of pharmacometrics can be used in oncological drug development in selecting appropriate doses for clinical trials, optimizing trial designs, interpreting outcome data, or even predicting outcomes in settings which have not been explicitly studied (10). Pharmacometrics was also proven to be useful in individualizing clinical therapy in oncology and has been advocated for such a purpose (11–14). This could be achieved based on the different covariates (such as gender, weight, mutational status of the patients, and/or others) which were found to significantly affect the outcome.

Understanding the course of NSCLC and incorporating it within models describing the different aspects of NSCLC and those of its therapies is critical. This article reviews the current understanding of NSCLC progression achieved through modeling and how models developed may contribute to enhancing drug development through informed decision making. Preclinical and clinical applications will be discussed.

DISEASE PROGRESSION MODELING

A disease progression model describes the status of a disease over time in the absence of a treatment or at least in

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the absence of the treatment under investigation. The disease status is usually reflected by the patient's status which in turn can be evaluated by disease biomarkers, clinically relevant endpoints, or even the probabilities of the occurrence or avoidance of an event (15,16).

Some pharmacometric models have the assumption that the baseline disease status does not change over the period of study. This may hold true for most studies which are conducted for a relatively short period of time, yet may not hold for rapidly progressing or chronic progressive diseases requiring a long-term therapy (17). Therefore, disease progression models are necessary to increase the statistical power of detecting a drug effect (18).

Disease progression models can help in revealing whether a drug has a symptomatic effect, where patients would reverse to their original disease condition once the drug is withdrawn after experiencing an improvement, or a disease-modifying effect, where an improvement would persist even after stopping the drug. Disease progression models may also be used to understand the relationships between different biomarkers (which are closer to the drug effect when compared with plasma concentrations) and disease progression or survival (15,18).

Disease progression modeling can also provide a reasonable approach for handling missing data in the case of subjects dropout where the application of last observation carried forward (LOCF) is a common approach. LOCF implies that patients dropping out from a study would stay stable at their last observed disease status, yet in reality the patients could have dropped out because their conditions have worsened or improved, and thus bias would be introduced (19). Accounting for disease progression and dropout should take care of such changes and minimize the bias (20).

Models used to describe the natural progress of different diseases can be broadly classified into linear and asymptotic models, both of which can also be used in describing the growth kinetics of bacteria and tumors (15,18). A linear model assumes that a disease status deteriorates at a constant rate over time. It was used for example in describing the natural course of Alzheimer's disease (21) and the glycemic deterioration associated with type II diabetes mellitus (22). In cases where there is a natural limit for disease progression, an asymptotic model is used. Asymptotic models were used in describing the trajectory of Crohn's disease (20) and in describing the changes in bone mineral density in osteoporosis (23). Modeling the trajectory of a disease can also be done using growth functions where growth depends on the number of actively dividing cells (15). Such functions have been commonly used in describing the growth kinetics of tumors.

PRECLINICAL APPLICATIONS

Preclinical experiments usually evaluate and predict the effect of potential anticancer drugs by measuring the percentage of tumor growth inhibition, and one of the common approaches to do this is by using xenograft models (24). In these models, tumor cells from human immortalized cell lines are implanted in immunosuppressed mice which are either given a placebo or an active drug afterwards. Tumor sizes are then measured and the effectiveness of the drug is evaluated

by comparing the tumor size reduction in the placebo and active drug groups by the end of the experiment. However, valuable information about the tumor growth trajectory is neglected this way and developing a model describing its temporal course would capture more information. Preclinical tumor growth models can provide further insight into the underlying processes because of the relatively more invasive nature of the procedures used for data collection and hence the ability to collect information from sites closer to the "site of action" as compared with data collection procedures used in humans. Moreover, ethical considerations which restrict studying the progress of cancer in untreated patients can favor preclinical models in understanding the natural progression of cancer.

Although some of the models discussed later were developed from data collected from xenograft models which were not necessarily inoculated with tumor grafts of NSCLC origin, yet they could still be useful in studying NSCLC. According to Johnson *et al.* (25), drugs which showed activity against a certain tumor type in humans did not necessarily show exclusive activity against the corresponding tumor line in xenograft models.

Empirical Models

Empirical models are mathematical expressions which are used merely in describing a process. Different empirical models can be used to describe the tumor growth kinetics (26), and usually the effect of a drug is evaluated by testing how it would change the parameters describing the tumor growth. One of the first models used was the exponential model which can be represented as follows

$$\frac{dS}{dt} = \alpha * S \quad (1)$$

where S is the tumor size, dS/dt is the tumor growth rate, and α is a first-order rate constant for tumor growth. The model assumes that the growth rate is dependent on the tumor size, and the time needed for a tumor to double in size is constant. However, this model would hold true until a limit where a tumor cannot grow at the same rate anymore as discussed later. When a treatment is administered, a cell-kill model (27) which can take the following form can be used

$$\frac{dS}{dt} = \alpha * S - k * \text{exposure} * S \quad (2)$$

where k is a constant dependent on drug potency, and exposure represents the exposure to the treatment. Harashima *et al.* (28) managed to link a physiologically based pharmacokinetic model capable of predicting the concentration of free doxorubicin in the extracellular compartment to a cell-kill model (27,29) to quantify the antitumor effect of liposomal doxorubicin. Simulations using the model showed that the longer the circulation of the liposomes the greater the antitumor effect of doxorubicin. This was in agreement with the results which showed a greater activity of doxorubicin encapsulated within liposomes against NSCLC tumors in xenograft models (30).

Another function commonly used in describing the growth kinetics of solid tumors is the Gompertzian model

(31,32). The following differential equation represents the Gompertzian growth kinetics, in one of its formulations, of an untreated tumor (33)

$$\frac{dS}{dt} = \alpha * S - \beta * S * \ln S \quad (3)$$

where S is the tumor size, α is the maximal growth rate, and β is a parameter such that $e^{\alpha/\beta}$ represents the maximal tumor size. In contrast to the exponential model, the growth rate is initially rapid, then gets slower when the tumor mass exceeds a certain limit, and finally a finite limit of growth is reached. In other words, the time needed for doubling the size of the tumor increases as the tumor grows. This is more realistic from a biological point of view considering that the tumor outstrips its blood and nutrient supplies and releases excess excretory products (34). The drug effect can be added as follows

$$\frac{dS}{dt} = (\alpha * S - \beta * S * \ln S) * (1 - DE) \quad (4)$$

where DE is a drug effect function taking a value between 0 and 1.

Gompertzian kinetics was successfully used to describe the dynamics of NSCLC in mice implanted with human NSCLC primary tumors and treated with erlotinib. A pharmacokinetic model describing the erlotinib concentration was used to drive the Gompertz model which in turn accounted for the tumor volume changes. Tumor volume was measured before and after erlotinib administration, and thus allowed for the distinction between parameters relevant to the unperturbed growth and efficacy parameters (35). The Gompertzian kinetics has also shown its usefulness for other types of tumors in xenograft models (36,37). Variants of this model have been developed and used in more mechanism-based modeling as will be discussed later.

In general, empirical models can adequately describe the data yet lack the ability to improve the understanding of the underlying processes and may have a limited predictive capacity in evaluating dose regimens that were not used in model development. This urges the need for developing models capable of capturing more information (38).

Semi-Mechanistic Models

Complex mechanistic models which describe the underlying biological processes may have the potential of providing further insight into these processes and predicting outcomes in simulated conditions which have not been studied before. However, development of such models can be time consuming and can face problems such as over-parameterization and difficulties in parameter identification. Although running extra investigations can help, cost limitations and the fact that carcinogenesis is not fully understood can make it difficult to design or even decide on the experiments required to generate the relevant data. A compromise would be developing models relying on a minimal number of biologically relevant parameters estimated using data typically available in preclinical settings, yet in the same time capable of accounting for phenomena such as delays in drug action, or

the presence of different tumor populations; hence called semi-mechanistic.

Simeoni *et al.* (39) developed a semi-mechanistic model using data from xenograft models with tumors of different origins. The growth of the tumors did not reach a plateau as would have been observed with Gompertzian kinetics. Therefore the Gompertz model was modified and allowed to switch from an initial exponential expression to a linear one after a threshold tumor mass

$$\frac{dS}{dt} = \frac{\lambda_0 * S(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} * S(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} \quad (5)$$

where dS/dt is the growth rate of an unperturbed tumor, S is the tumor weight, t is time, and λ_0 and λ_1 characterize the rates of exponential and linear growths, respectively, and can give an indication about the aggressiveness of the tumor. It was suggested that when ψ is equal to 20 a sharp switch from the first-order exponential growth to a zero-order linear growth can take place after the threshold mass.

The semi-mechanistic part of the model comes into play in describing the drug effect after its administration. It was assumed that a treatment would stop the proliferation of some cells and eventually kills them. As a result of the delay observed before a drug produces its effect, a three-compartment transit model was used to model the cell death process (Fig. 1). This was represented by a set of differential equations, each of which representing a compartment and corresponding to a progressive degree of damage.

$$\begin{aligned} \frac{dS_1}{dt} &= \frac{\lambda_0 * S_1(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} * S(t)\right)^{\psi}\right]^{\frac{1}{\psi}}} - k_2 * c(t) * S_1(t) \\ \frac{dS_2}{dt} &= k_2 * c(t) * S_1(t) - k_1 * S_2(t) \\ \frac{dS_3}{dt} &= k_1 * S_2(t) - k_1 * S_3(t) \\ \frac{dS_4}{dt} &= k_1 * S_3(t) - k_1 * S_4(t) \\ S(t) &= S_1(t) + S_2(t) + S_3(t) + S_4(t) \end{aligned} \quad (6)$$

k_1 is a rate constant of cell death, k_2 is an index of drug efficacy, and $S(t)$ represents the total perturbed tumor weight. The inclusion of a drug-specific parameter (k_2), independent of the growth observed in controls, allows for more specific evaluation of the drugs.

Since its development, the Simeoni model gained a wide acceptance and it has been used for modeling the progression of different tumor types in xenograft models including NSCLC. Bueno *et al.* (40) developed a semi-mechanistic pharmacokinetic/pharmacodynamic model for an inhibitor of type-I receptor transforming growth factor- β kinase, a tumor cell growth regulator (41), which was administered to mice implanted with NSCLC and breast cancer human xenografts. They used a two-compartment model to describe the pharmacokinetics of the drug which in turn was related to the phosphorylated Smad 2,3 (pSmad, a tumor biomarker) through an indirect response model. The Simeoni model (39) was used to describe the growth of the tumor compartment in the control and active treatment groups where the tumor growth was

Fig. 1. A scheme showing the PK/PD model developed by Simeoni *et al.* (39). S_1 proliferating cells, S_2 , S_3 , and S_4 damaged cells, PK pharmacokinetic model, $c(t)$ plasma concentration of the anticancer agent, k_1 transit rate constant, k_2 drug potency. Adapted from (39)

assumed to be inhibited by the decrease in pSmad. The drug induced decrease in pSmad was assumed to drive the inhibitory effect on the tumor compartment after propagating through two transduction (transit) compartments. This allowed for a quantitative description of the signal transduction time course before drug-induced tumor growth inhibition occurs. Such an evaluation can give a hint about the drug onset and offset, further elaborate the mechanism of action, and can also be used for other drugs with the same mechanism of action since transduction is drug independent.

CLINICAL APPLICATIONS

It is worthy to mention that models, especially empirical ones, described previously are not exclusive for preclinical uses and they can be used in describing NSCLC progression clinically. In general, physiologically based models have not been used extensively since they can be complex in development and NSCLC, as with any other type of cancer, is full of black boxes, while less sophisticated models can still be efficient for different purposes.

Tham *et al.* (42) developed a tumor growth inhibition model linking the tumor size measured on a continuous scale to gemcitabine doses administered in patients suffering from NSCLC (Fig. 2). An exposure driven Gompertzian function

was used to describe the tumor growth after gemcitabine administration as follows

$$\frac{dS}{dt} = \left(\text{rateIN} * \text{effect} - \frac{1}{T_{\text{turnover}}} * S \right) * S \quad (7)$$

where S is the tumor size, rateIN is the tumor growth rate at baseline, effect is the inhibitory effect of the drug on the tumor growth rate, and T_{turnover} is a second-order time constant for the tumor turnover. The drug effect was best described by an E_{max} model as follows

$$\text{Effect} = 1 - \frac{E_{\text{max}} * \text{Dose}}{\text{Amt}_{50} + \text{Dose}} \quad (8)$$

where E_{max} is the maximum inhibition of tumor growth (fixed to 1), Dose is the gemcitabine dose administered, and Amt_{50} is a measure of potency where 50% of the maximal drug effect is achieved. The dose as an exposure measure was found to be as good as the area under the concentration-time curve (AUC) of gemcitabine and the AUC of gemcitabine's metabolites in predicting tumor size changes. A tumor effect compartment into which gemcitabine is introduced was included in the model to account for the delay between the drug administration and tumor response.

One of the limitations of this model is that it assumes that there is no change in tumor size at baseline. The authors

Fig. 2. A schematic representation of the model developed by Tham *et al.* (42). E_{max} the maximum inhibition of tumor growth (fixed to 1), dose the dose of gemcitabine administered, Amt_{50} the potency where 50% of the maximal drug effect has been achieved, S the tumor size, rateIN tumor growth rate at baseline, effect the inhibitory effect of the drug on the tumor growth rate, T_{turnover} second-order time constant for the tumor turnover. Adapted from (42)

had no tumor size measurements before commencing the therapy so they were unable to determine the tumor growth rate at baseline. Moreover, patients were given a combination of gemcitabine and carboplatin, which left the tumor responses resulting from gemcitabine administration indistinguishable from that of carboplatin. It is worthy to mention that the authors tested a model driven by carboplatin alone, however this resulted in a worse fit, and an insignificant improvement of fit was seen when the doses of both gemcitabine and carboplatin were included. It would have also been more interesting to link the model to a survival function since survival remains the most clinically relevant endpoint when assessing the efficacy of anticancer therapies.

More recently, Wang *et al.* linked the treatment used to changes in tumor size, which was subsequently linked to survival (43). This was based on an extensive database (3,398 patients) from four registration trials with nine different treatments. The time course of the change in tumor size was described by a mixed dynamic tumor size model. It composed of an exponential-decay component describing the tumor shrinkage as a result of treatment administration, and a linear-growth component to account for the tumor growth under a specific treatment as shown

$$TS_i(t) = BASE_i * e^{-SR_i * t} + PR_i * t \quad (9)$$

where $TS_i(t)$ is the tumor size at time t for the i th individual, $BASE_i$ is the baseline tumor size, SR_i is the tumor shrinkage rate constant which is specific for the treatment used, and PR_i is the linear tumor progression rate describing the tumor growth when a specific treatment is administered. Tumor size changes were then linked to a survival model to account for the time to death. A log-normal distribution was used for the survival model and it was found that the tumor size at baseline (centered at 8.5 cm), percentage reduction in tumor size from the baseline at the 8th week ($PTR_{week\ 8}$), and the performance status scores of the patients (as measured according to the Eastern Cooperative Oncology Group (ECOG) scoring system) were the best predictors of time to death (T)

$$\log(T) = \alpha_0 + \alpha_1 * ECOG + \alpha_2 * (Baseline - 8.5) + \alpha_3 * PTR_{week\ 8} \quad (10)$$

where α_0 is the intercept, and α_1 , α_2 , and α_3 are the slopes for ECOG, centered baseline and $PTR_{week\ 8}$, respectively. The model suggests that measuring the tumor size at the 8th week would allow for an early assessment of an experimental NSCLC treatment. Although only one of the treatment groups was used in developing the survival model, the model was capable of predicting the survival of the eight other groups despite the use of different treatments in different trials.

The usefulness of this model comes from the fact that it links a biomarker of the drug effect on a continuous scale (change in tumor size) to a clinically relevant outcome (survival). This allows comparing between the expected clinical outcomes from trials using different treatments or dosing regimens. Therefore, such a model would provide a more precise and informative tool for clinical screening of novel compounds and for taking pivotal go/no-go decisions

where the less informative categorical objective response rate (ORR) or progression-free survival (PFS) are commonly used (44). Using a continuous measure rather than categorical measures increases the statistical power of the analysis and hence allow for using smaller sample sizes and conducting trials where classical comparative trials are less feasible (45). However, this model does not account for the drug exposure. Including exposure in the model can give a better insight into the potency of the drug used. It also allows carrying out dose-response simulations and thus investigating how changing the drug exposure or the regimen can affect the response and survival (43,46).

WHERE DO WE STAND AND WHAT OPPORTUNITIES DO WE HAVE?

Modeling and simulation have been prospering over the last two decades, and their concepts are now considered to be invaluable in drug development (47,48). An important component of the models developed is a description of the disease progress in order to properly detect the drug signal from the total effect.

Different opportunities for modeling the different aspects of NSCLC, tumor dynamics being an important component of which, exist (Table 1). Such models can help in further elaborating the biology of the disease and if developed with sufficient complexity, they can suggest the level at which a drug produces its effect. They can play a role in the translational phase and the movement of a drug from the preclinical to the clinical phase, and can also help in designing clinical trials, evaluating them and predicting their outcomes. Linking NSCLC biomarkers which have been introduced recently to survival (49) can help in evaluating and validating the adequacy of such metrics for early prediction of outcome.

Modeling and simulation can also play a role in personalized therapy. Including and quantifying covariate relationships for different genetic variations and mutations which were found to be related with positive or negative responses of NSCLC patients to different treatments (50–52) can help in tailoring individualized regimens.

Tumor Self-Seeding

“Tumor self-seeding” is a hypothesis recently proposed in cancer biology which could significantly change our perspective towards tumor growth (53). Metastasis has traditionally been thought of as a unidirectional process in which cancer cells break out of a primary tumor and move to a distant site initiating a metastatic cancerous growth. However, recent data from tumor xenograft models in mice has shown that this could be a multidirectional process where malignant cells migrate to distant sites as well as migrate back to the primary tumor from which they have originated and seed it (54). If this holds true, then a primary tumor should be looked at as a conglomerate of contiguous masses rather than a single mass. Tumor growth modeling can serve as a tool among others to further investigate this hypothesis. Developing a mechanistic model accounting for both the mitotic cell division and self-seeding might help us in detecting and discriminating an anti-seeding effect which should correspond to an anti-metastatic effect (54), an effect which is not evaluated in preclinical studies. This can eventually help in

Table I. Models Used for Describing the Growth Kinetics of NSCLC in Preclinical and Clinical Applications

Tumor growth model	Drug(s)	Tumor origin	Species	Reference
Gompertz	Erlotinib	NSCLC	Mice	(35)
Gompertz	Gemcitabine	NSCLC	Humans	(42)
Simeoni	LY2157299 ^a	NSCLC and breast	Mice	(40)
Mixed (exponential and linear)	Cisplatin, carboplatin, docetaxil, erlotinib, paclitaxel, bevacizumab, pemetrexed, vinorelbine, and placebo	NSCLC	Humans	(43)

NSCLC non-small cell lung cancer

^aLY2157299: a transforming growth factor- β kinase antagonist

classifying drugs into anti-mitotic (causing shrinkage) or anti-metastatic (anti-seeding) allowing the use of a combination of both in an ideal regimen to treat a cancer (55).

Translational Uses

Models capable of discriminating between compound-specific, system-specific, and experiment parameters can be used to improve the design of preclinical experiments and thus reduce the costs and number of animals used (56,57). They have also been recently advocated for translational drug research and for quantitatively predicting the pharmacokinetics and pharmacodynamics of drugs in humans (58). Therefore they can be used in analyzing the efficacy, comparing between the potencies of different candidates, and assist in determining the optimal doses and dosing schedules to start with in humans (59).

Rocchetti *et al.* (60) presented a regression equation to predict the clinically active dose of a new anticancer drug based on estimating its drug potency parameter in a preclinical tumor growth inhibition model. In another experiment based on a model derived from the Gompertz function and data from breast cancer xenograft models treated with capecitabine, it was shown that a 7-day treatment followed by 7-day rest would be superior to the conventional 14-day treatment and 7-day rest schedule. This was confirmed by further preclinical studies which showed a lower toxicity and an improved survival in the mice (36).

Despite their imperfect ability to accurately predict the clinical response, xenograft animal models are widely used within preclinical oncology investigations. Their limited predictive capability could be attributed to their inability to represent the true environment in which a tumor grows in humans, and the inability of implanted tumors to metastasize or to develop drug resistance. Genetically engineered mice mimicking the pathophysiological and molecular features of human malignancies have been introduced recently to overcome these limitations (57,61,62), but they still need further validation. Until then, xenograft models remain to be widely used due to the experience with them and the relatively limited resources required. However care needs to be given to the experimental conditions if conclusions were to be extrapolated to humans.

NSCLC Progress Models in Clinical Trials: Challenges and Prospects

Despite the facts that pharmacokinetic/pharmacodynamic (PK/PD) modeling has been used extensively to assess the drug effect in xenograft tumor models where more mechanistic models have been developed to model the tumor growth

dynamics, the use of disease progression modeling has been comparatively limited in clinical drug development of anticancer drugs, especially for NSCLC. It has to be emphasized though that disease progression modeling of NSCLC, and cancer in general does not come without its complexities and limitations in human settings. An ideal description of any disease requires data collected from patients where the disease progresses naturally without any external interference; however, this is limited for ethical reasons in oncology where the administration of placebo is generally not allowed. It also requires data to be collected for a considerably long period of time to adequately study the trajectory of the disease, yet clinical studies in oncology suffer from relatively high dropout rates because of death or the intolerable adverse events usually associated with anticancer agents.

Attempts have been made to overcome the abovementioned obstacles. Pooling data and meta-modeling present themselves as an option (20) which have been used by Wang *et al.* in their model for NSCLC (43). There is also a general consensus to build cancer progression models in the presence of a treatment, and to include a component specific for the drug in the model. However, this requires data provided from groups with different treatments or with a wide range of exposure for a single treatment to adequately distinguish the disease component in a comparative fashion.

Despite the mentioned difficulties, including a description of NSCLC progression comes with clinical benefits that cannot be ignored. Conventionally, the dose level and schedule for the use of anticancer drugs is determined by assuming that the maximum anticancer effect is achieved by administering the maximum dose limited by toxicity, or the notion known as “more is better” (63). However, some doubt has been cast on this assumption and recently proposed hypotheses argue that there could be doses which are optimal for treatment yet not necessarily the highest possible doses (64,65). Models based on tumor growth data obtained from patients can help in deciding on the optimal dose and dosing algorithms. This benefit is not exclusive to drug development and can come into play in clinical practice.

Antitumor activity in early NSCLC trials is typically evaluated by ORR or PFS, both of which are recorded on categorical scales (66). However, these estimates are generally imprecise in small phase I and phase II trials and are uninformative for taking go/no-go decisions or designing phase III trials. Therefore, exposure-driven relationships relating tumor sizes on a continuous scale (serving as a biomarker) to survival (serving as a clinical endpoint) have been proposed (67). Such full relationships starting from exposure, linking it to tumor dynamics, and ending at survival are still lacking for NSCLC although they have shown their usefulness in other

settings. They were capable of predicting survival in a phase III trial based on phase II data for capecitabine used for treating colorectal cancer (68) and metastatic breast cancer (69). Attempts to use metrics other than tumor size which showed a limited ability of predicting survival are discussed later.

Models developed can help in simulating NSCLC trials, and thus can help in optimizing their designs or even predicting their outcomes (46,70). Claret *et al.* (71) fitted the model developed by Wang *et al.* (43) to tumor size data generated from a phase II clinical trial evaluating the use of carboplatin and paclitaxel (C/P) in addition to motesanib or bevacizumab in treating advanced non-squamous NSCLC (72). They estimated the individual parameters and predicted the tumor sizes at baseline and week 8 which were inputted together with ECOG into the survival model. Their objective was to simulate the overall survival (OS) for NSCLC patients receiving C/P plus motesanib or bevacizumab and C/P alone. The simulated results were compared with the results of an actual phase III trial (MONET1) comparing the use of motesanib or placebo in addition to C/P (73). The hazard ratios were comparable yet the model underestimated the OS. It was suggested to investigate other prognostic factors as covariates and refine the model to account for the difference in mode of action between the cytotoxic chemotherapeutic agents and the antiangiogenic agents to resolve this disparity (74). Despite the improvement of OS by 2 months when motesanib was added to C/P compared with the addition of placebo in MONET1, statistical significance was not reached (73) suggesting that the trial was underpowered. This finding was implied by the results of the simulation study, suggesting that a simulation-based power calculation could have improved the trial design before launching it (74).

Surrogate Metrics

Therapies for NSCLC are generally non-curative as they merely prolong the survival by a couple of weeks or months in average. Developing new treatments for NSCLC usually aim at prolonging the survival significantly or at least producing less adverse events when compared with their counterparts. However, assessing the survival of patients in a clinical trial costs money and time, can unacceptably delay the movement of potentially effective therapies to later stages of development and can be confounded by nonmalignant comorbidities often present in NSCLC patients (49). Therefore interest has grown in introducing surrogate metrics which can predict survival. As discussed previously, the use of continuous metrics are often more informative compared with categorical measures (46,67). The use of tumor size on a continuous scale has been encouraged (75), and it was linked to survival in NSCLC (43) and in other types of cancer (68). However, positive survival outcomes were not always associated with a significant tumor shrinkage especially with novel targeted cytostatic therapies which are expected to result in tumor growth inhibition rather than regression (20,44,76). This was seen with bevacizumab (77) and sorafenib (78) while on the other hand promising tumor regression seen in phase II trials for gefitinib against NSCLC (79,80) was then followed by disappointing survival outcomes in phase III trials (81,82).

Nuclear imaging has been advocated recently to serve as an endpoint to efficiently predict survival as early as possible (49). Positron emission tomography with ^{18}F -fluorodeoxyglucose

(FDG-PET) has shown its ability to predict survival in NSCLC patients as early as 2 weeks after treatment initiation (83), and after 4 weeks in patients with gastrointestinal stromal tumors (84) for which a survival model has been linked to changes in FDG-PET (85). Such metrics can enable early modification of ineffective treatments in clinical therapy and improve the efficiency of decision making as early as possible during development.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893–917.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10–29.
3. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med*. 2008;359(13):1367–80.
4. Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov*. 2004;3(8):711–5.
5. Sheiner LB. Learning *versus* confirming in clinical drug development. *Clin Pharmacol Ther*. 1997;61(3):275–91.
6. FDA. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. 2004. <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm>. Accessed 10 December 2012.
7. Gutierrez ME, Kummar S, Giaccone G. Next generation oncology drug development: opportunities and challenges. *Nat Rev Clin Oncol*. 2009;6(5):259–65.
8. Barrett JS, Fossler MJ, Cadieu KD, Gastonguay MR. Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. *J Clin Pharmacol*. 2008;48(5):632–49.
9. Miller R, Ewy W, Corrigan BW, Ouellet D, Hermann D, Kowalski KG, *et al.* How modeling and simulation have enhanced decision making in new drug development. *J Pharmacokinet Pharmacodyn*. 2005;32(2):185–97.
10. Rombout F, Aarons L, Karlsson M, Man A, Mentre F, Nygren P, *et al.* Modelling and simulation in the development and use of anti-cancer agents: an underused tool? *J Pharmacokinet Pharmacodyn*. 2004;31(6):419–40.
11. Barrett JS, Mondick JT, Narayan M, Vijayakumar K, Vijayakumar S. Integration of modeling and simulation into hospital-based decision support systems guiding pediatric pharmacotherapy. *BMC Med Inform Decis Mak*. 2008;8:6.
12. Noble SL, Sherer E, Hannemann RE, Ramkrishna D, Vik T, Rundell AE. Using adaptive model predictive control to customize maintenance therapy chemotherapeutic dosing for childhood acute lymphoblastic leukemia. *J Theor Biol*. 2010;264(3):990–1002.
13. Dombrowsky E, Jayaraman B, Narayan M, Barrett JS. Evaluating performance of a decision support system to improve methotrexate pharmacotherapy in children and young adults with cancer. *Ther Drug Monit*. 2011;33(1):99–107.
14. Maitland ML, Schilsky RL. Clinical trials in the era of personalized oncology. *CA Cancer J Clin*. 2011;61(6):365–81.
15. Mould DR. Developing models of disease progression. In: Ette E, Williams P, editors. *Pharmacometrics: the science of quantitative pharmacology*. Hoboken: Wiley; 2007. p. 547–82.
16. Holford NH, Mould DR, Peck CC. Disease progress models. In: Atkinson AJ, Abernethy DR, Daniels CE, Dedrick RL, Markey SP, editors. *Principles of clinical pharmacology*. 2nd ed. Burlington: Academic; 2007. p. 313–21.
17. Al-Sallami HS, Pavan Kumar VV, Landersdorfer CB, Bulitta JB, Duffull SB. The time course of drug effects. *Pharm Stat*. 2009;8(3):176–85.
18. Chan PL, Holford NH. Drug treatment effects on disease progression. *Annu Rev Pharmacol Toxicol*. 2001;41:625–59.
19. Sheiner LB. Is intent-to-treat analysis always (ever) enough? *Br J Clin Pharmacol*. 2002;54(2):203–11.

20. Mould DR. Models for disease progression: new approaches and uses. *Clin Pharmacol Ther.* 2012;92(1):125–31.
21. Holford NH, Peace KE. Methodologic aspects of a population pharmacodynamic model for cognitive effects in Alzheimer patients treated with tacrine. *Proc Natl Acad Sci U S A.* 1992;89(23):11466–70.
22. Frey N, Laveille C, Paraire M, Francillard M, Holford NH, Jochemsen R. Population PKPD modelling of the long-term hypoglycaemic effect of gliclazide given as a once-a-day modified release (MR) formulation. *Br J Clin Pharmacol.* 2003;55(2):147–57.
23. Pors Nielsen S, Barenholdt O, Hermansen F, Munk-Jensen N. Magnitude and pattern of skeletal response to long term continuous and cyclic sequential oestrogen/progestin treatment. *Br J Obstet Gynaecol.* 1994;101(4):319–24.
24. Voskoglou-Nomikos T, Pater JL, Seymour L. Clinical predictive value of the *in vitro* cell line, human xenograft, and mouse allograft preclinical cancer models. *Clin Cancer Res.* 2003;9(11):4227–39.
25. Johnson JI, Decker S, Zaharevitz D, Rubinstein LV, Venditti JM, Schepartz S, *et al.* Relationships between drug activity in NCI preclinical *in vitro* and *in vivo* models and early clinical trials. *Br J Cancer.* 2001;84(10):1424–31.
26. Bajzer Z, Marušić M, Vuk-Pavlović S. Conceptual frameworks for mathematical modeling of tumor growth dynamics. *Math Comput Model.* 1996;23(6):31–46.
27. Jusko WJ. Pharmacodynamics of chemotherapeutic effects: dose–time–response relationships for phase-nonspecific agents. *J Pharm Sci.* 1971;60(6):892–5.
28. Harashima H, Iida S, Urakami Y, Tsuchihashi M, Kiwada H. Optimization of antitumor effect of liposomally encapsulated doxorubicin based on simulations by pharmacokinetic/pharmacodynamic modeling. *J Control Release.* 1999;61(1–2):93–106.
29. Ozawa S, Sugiyama Y, Mitsuhashi Y, Kobayashi T, Inaba M. Cell killing action of cell cycle phase-non-specific antitumor agents is dependent on concentration–time product. *Cancer Chemother Pharmacol.* 1988;21(3):185–90.
30. Williams SS, Alosco TR, Mayhew E, Lasic DD, Martin FJ, Bankert RB. Arrest of human lung tumor xenograft growth in severe combined immunodeficient mice using doxorubicin encapsulated in sterically stabilized liposomes. *Cancer Res.* 1993;53(17):3964–7.
31. Norton L, Simon R, Brereton HD, Bogden AE. Predicting the course of Gompertzian growth. *Nature.* 1976;264(5586):542–5.
32. Norton L. A Gompertzian model of human breast cancer growth. *Cancer Res.* 1988;48(24 Pt 1):7067–71.
33. Bernard A, Kimko H, Mital D, Poggesi I. Mathematical modeling of tumor growth and tumor growth inhibition in oncology drug development. *Expert Opin Drug Metab Toxicol.* 2012;8(9):1057–69.
34. Schabel Jr FM. Concepts for systemic treatment of micrometastases. *Cancer.* 1975;35(1):15–24.
35. Frances N, Meille C, Hoffman G, Lave T, Walz A. Integrating distribution to tumor tissue into a dynamic PK/PD model to evaluate the anticancer effect of erlotinib in patient-derived LXFA677 tumor xenograft mice. *PAGE Meeting 2011. Abstract 2174.*
36. Traina TA, Dugan U, Higgins B, Kolinsky K, Theodoulou M, Hudis CA, *et al.* Optimizing chemotherapy dose and schedule by Norton–Simon mathematical modeling. *Breast Dis.* 2010;31(1):7–18.
37. Glatt S, Pitou C, Yingling J, Bueno L, Alwis Dd, Troconiz IF. Preclinical Population PK/PD of TGF beta RI Kinase Inhibitor for Cancer. *PAGE Meeting 2005. Abstract 771.*
38. Danhof M, de Jongh J, De Lange EC, Della Pasqua O, Ploeger BA, Voskuyl RA. Mechanism-based pharmacokinetic–pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. *Annu Rev Pharmacol Toxicol.* 2007;47:357–400.
39. Simeoni M, Magni P, Cammia C, De Nicolao G, Croci V, Pesenti E, *et al.* Predictive pharmacokinetic–pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. *Cancer Res.* 2004;64(3):1094–101.
40. Bueno L, de Alwis DP, Pitou C, Yingling J, Lahn M, Glatt S, *et al.* Semi-mechanistic modelling of the tumour growth inhibitory effects of LY2157299, a new type I receptor TGF-beta kinase antagonist, in mice. *Eur J Cancer.* 2008;44(1):142–50.
41. Massague J. TGF-beta signal transduction. *Annu Rev Biochem.* 1998;67:753–91.
42. Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, *et al.* A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine+carboplatin in non-small cell lung cancer patients. *Clin Cancer Res.* 2008;14(13):4213–8.
43. Wang Y, Sung C, Dartois C, Ramchandani R, Booth BP, Rock E, *et al.* Elucidation of relationship between tumor size and survival in non-small-cell lung cancer patients can aid early decision making in clinical drug development. *Clin Pharmacol Ther.* 2009;86(2):167–74.
44. Michaelis LC, Ratain MJ. Measuring response in a post-RECIST world: from black and white to shades of grey. *Nat Rev Cancer.* 2006;6(5):409–14.
45. Lavin PT. An alternative model for the evaluation of antitumor activity. *Cancer Clin Trials.* 1981;4(4):451–7.
46. Bruno R, Claret L. On the use of change in tumor size to predict survival in clinical oncology studies: toward a new paradigm to design and evaluate phase II studies. *Clin Pharmacol Ther.* 2009;86(2):136–8.
47. Lesko LJ, Rowland M, Peck CC, Blaschke TF. Optimizing the science of drug development: opportunities for better candidate selection and accelerated evaluation in humans. *Pharm Res.* 2000;17(11):1335–44.
48. Chien JY, Friedrich S, Heathman MA, de Alwis DP, Sinha V. Pharmacokinetics/pharmacodynamics and the stages of drug development: role of modeling and simulation. *AAPS J.* 2005;7(3):E544–59.
49. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50 Suppl 1:122S–50.
50. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2010;363(18):1693–703.
51. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2004;350(21):2129–39.
52. Pao W, Wang TY, Riely GJ, Miller VA, Pan Q, Ladanyi M, *et al.* KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med.* 2005;2(1):e17.
53. Norton L, Massague J. Is cancer a disease of self-seeding? *Nat Med.* 2006;12(8):875–8.
54. Kim MY, Oskarsson T, Acharyya S, Nguyen DX, Zhang XH, Norton L, *et al.* Tumor self-seeding by circulating cancer cells. *Cell.* 2009;139(7):1315–26.
55. Comen E, Norton L, Massague J. Clinical implications of cancer self-seeding. *Nat Rev Clin Oncol.* 2011;8(6):369–77.
56. Poggesi I, de Nicolao G, Germani M, Rocchetti M. Re: Antitumor efficacy testing in rodents. *J Natl Cancer Inst.* 2009;101(22):1592–3. author reply 3–4.
57. Simeoni M, De Nicolao G, Magni P, Rocchetti M, Poggesi I. Modeling of human tumor xenografts and dose rationale in oncology. *Drug Discov Today Technol.* 2012. doi:10.1016/j.ddtec.2012.07.004.
58. Danhof M, de Lange EC, Della Pasqua OE, Ploeger BA, Voskuyl RA. Mechanism-based pharmacokinetic–pharmacodynamic (PK–PD) modeling in translational drug research. *Trends Pharmacol Sci.* 2008;29(4):186–91.
59. Barrett JS, Gupta M, Mondick JT. Model-based drug development applied to oncology. *Expert Opin Drug Discov.* 2007;2(2):185–209.
60. Rocchetti M, Simeoni M, Pesenti E, De Nicolao G, Poggesi I. Predicting the active doses in humans from animal studies: a novel approach in oncology. *Eur J Cancer.* 2007;43(12):1862–8.
61. Sharpless NE, Depinho RA. The mighty mouse: genetically engineered mouse models in cancer drug development. *Nat Rev Drug Discov.* 2006;5(9):741–54.
62. Becher OJ, Holland EC. Genetically engineered models have advantages over xenografts for preclinical studies. *Cancer Res.* 2006;66(7):3355–8. discussion 8–9.
63. Hryniuk WM. More is better. *J Clin Oncol.* 1988;6(9):1365–7.

64. Fisher B, Anderson S, Wickerham DL, DeCillis A, Dimitrov N, Mamounas E, *et al.* Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. *J Clin Oncol.* 1997;15(5):1858–69.
65. Cannistra SA. Challenges and pitfalls of combining targeted agents in phase I studies. *J Clin Oncol.* 2008;26(22):3665–7.
66. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92(3):205–16.
67. Bruno R, Lu JF, Sun YN, Claret L. A modeling and simulation framework to support early clinical drug development decisions in oncology. *J Clin Pharmacol.* 2011;51(1):6–8.
68. Claret L, Girard P, O'shaughnessy J, Hoff P, Van Cutsem E, Jorga K, *et al.* Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. *J Clin Oncol.* 2009;27(25):4103–8.
69. Claret L, Girard P, O'shaughnessy J, Hoff P, Van Cutsem E, Blum J, *et al.* Model-based predictions of expected anti-tumor response and survival in phase III studies based on phase II data of an investigational agent. *ASCO Meeting Abstracts.* 2006;24(18_suppl):6025.
70. Gobburu JV, Lesko LJ. Quantitative disease, drug, and trial models. *Annu Rev Pharmacol Toxicol.* 2009;49:291–301.
71. Claret L, Lu JF, Bruno R, Hsu CP, Hei YJ, Sun YN. Simulations Using a Drug-Disease Modeling Framework and Phase II Data Predict Phase III Survival Outcome in First-Line Non-Small-Cell Lung Cancer. *Clin Pharmacol Ther.* 2012;92(5):631–4.
72. Blumenschein Jr GR, Kabbinar F, Menon H, Mok TS, Stephenson J, Beck JT, *et al.* A phase II, multicenter, open-label randomized study of motesanib or bevacizumab in combination with paclitaxel and carboplatin for advanced nonsquamous non-small-cell lung cancer. *Ann Oncol.* 2011;22(9):2057–67.
73. Scagliotti GV, Vynnychenko I, Park K, Ichinose Y, Kubota K, Blackhall F, *et al.* International, randomized, placebo-controlled, double-blind phase III study of motesanib plus carboplatin/paclitaxel in patients with advanced nonsquamous non-small-cell lung cancer: MONET1. *J Clin Oncol.* 2012;30(23):2829–36.
74. Sharma MR, Maitland ML, Ratain MJ. Models of excellence: improving oncology drug development. *Clin Pharmacol Ther.* 2012;92(5):548–50.
75. Karrison TG, Maitland ML, Stadler WM, Ratain MJ. Design of phase II cancer trials using a continuous endpoint of change in tumor size: application to a study of sorafenib and erlotinib in non small-cell lung cancer. *J Natl Cancer Inst.* 2007;99(19):1455–61.
76. Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. *J Clin Oncol.* 2004;22(22):4442–5.
77. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, *et al.* A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med.* 2003;349(5):427–34.
78. Ratain MJ, Eisen T, Stadler WM, Flaherty KT, Kaye SB, Rosner GL, *et al.* Phase II placebo-controlled randomized discontinuation trial of sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2004;22(16):2505–12.
79. Kris MG, Natale RB, Herbst RS, Lynch Jr TJ, Prager D, Belani CP, *et al.* Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA.* 2003;290(16):2149–58.
80. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, *et al.* Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial) [corrected]. *J Clin Oncol.* 2003;21(12):2237–46.
81. Giaccone G, Herbst RS, Manegold C, Scagliotti G, Rosell R, Miller V, *et al.* Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 1. *J Clin Oncol.* 2004;22(5):777–84.
82. Herbst RS, Giaccone G, Schiller JH, Natale RB, Miller V, Manegold C, *et al.* Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial—INTACT 2. *J Clin Oncol.* 2004;22(5):785–94.
83. Zander T, Scheffler M, Nogova L, Kobe C, Engel-Riedel W, Hellmich M, *et al.* Early prediction of nonprogression in advanced non-small-cell lung cancer treated with erlotinib by using [(18)F]fluorodeoxyglucose and [(18)F]fluorothymidine positron emission tomography. *J Clin Oncol.* 2011;29(13):1701–8.
84. Prior JO, Montemurro M, Örcurto MV, Michielin O, Luthi F, Benhattar J, *et al.* Early prediction of response to sunitinib after imatinib failure by 18F-fluorodeoxyglucose positron emission tomography in patients with gastrointestinal stromal tumor. *J Clin Oncol.* 2009;27(3):439–45.
85. Schindler E, Westwood P, Amantea M, Hansson EK, Milligan PA, Karlsson MO, *et al.* PKPD-Modeling of Standard Uptake Value (SUV) in Gastro-Intestinal Stromal Tumors (GIST) patients treated with sunitinib. *PAGE Meeting 2012.* Abstract 2595.