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REVIEW

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Overview of recent topics in clinical pharmacology of anticancer agents

Abstract The rationale for studying the clinical pharmacology of antineoplastic agents is that the information obtained will result in enhanced drug development and enhanced or improved clinical use. A great deal of effort has been expended in studying the pharmacokinetics and pharmacodynamics of investigational and noninvestigational antineoplastic agents. More recently, a deeper appreciation has developed regarding the importance of the metabolism of antineoplastic agents and the potential role of metabolites in their activity or toxicity, as well as the potential for drugdrug interactions. Investigators studying the clinical pharmacology of antineoplastic agents face an increasingly challenging task as new agents continue to be developed. Some of these challenges arise from the enhanced potency of new agents, resulting in increased difficulty in measuring such agents in biological matrices. Furthermore, as agents have been developed to affect specific biological targets, the necessity of assessing pharmacodynamics at the biochemical or molecular level has become increasingly important. In addition, development of agents with cytostatic, as opposed to cytotoxic, properties poses a further challenge to assessment of pharmacologic effect. In addressing these challenges, a great deal of effort has been expended to develop increasingly sensitive analytical chemical techniques, in evaluating alternative biological matrices, such as saliva, in which to monitor drug concentrations in a less invasive fashion, and in developing limited sampling strategies to assess both the pharmacokinetics and pharmacodynamics of antineoplastic agents. Similarly, a great deal of effort has been expended in providing suitable means for assessing the numerous novel targets for which antineoplastic agents are being developed. These include the assessment of cell cycle kinetics and specific oncoproteins, definition of cell damage such as cleavable complexes, and formation of drug-macromolecular adducts in suitable target cells. Additional effort is being expended to explore nontraditional means of drug delivery. In this regard, the increasing importance of orally administered agents reflects a fundamental change in the approach to antineoplastic drug delivery. Finally, the increased computational power made available by faster personal computers has facilitated a number of innovative modeling techniques involving population modeling, modeling of combination chemotherapy, and assessment of drug-drug interactions.

Key words Clinical pharmacology · Anticancer agents

Introduction

One of the difficulties in producing a review such as this is that it is impossible to be familiar with all the research that is being or has been performed and the people doing it. Thus it is guaranteed that someone's important work will be overlooked and that colleagues will be unintentionally insulted. With these assumptions and consequences in mind, I would like to set forth a framework that I believe is relevant to the clinical pharmacology of antineoplastic agents. I hope that it might provide some guidelines for future studies in the area and also a framework with which to view studies on the clinical pharmacology of antineoplastic agents.

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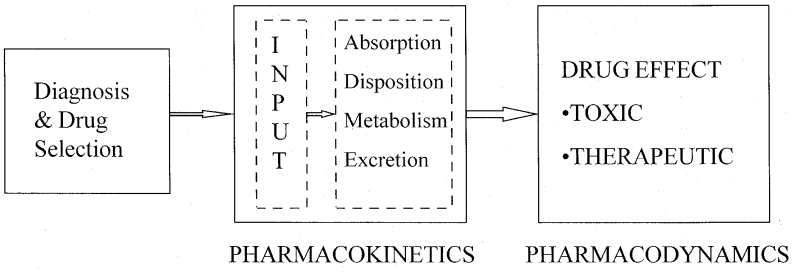

Fig. 1 Schematic representation of "the system" addressed in clinical pharmacology studies of antineoplastic agents

Framework for clinical pharmacological studies of antineoplastic agents

A basic question that should be borne in mind is, "Why do clinical pharmacological studies of antineoplastic agents?" Two good reasons are that the information generated will facilitate development of the drug under study and that it will allow more intelligent use of the agent, or agents, under study. It should be understood that in the latter case, the more intelligent use may be in patients in general, in individual patients, or in special subpopulations of patients.

A key concept in clinical pharmacological studies of antineoplastic agents is generation of information. This requires sampling the system. The question then arises as to what the system is. As indicated in Fig. 1, the system can be envisioned as a patient in whom a diagnosis is made, and the drug, or drugs, selected to treat the problem. Treatment requires input of drug into the system; this is followed by absorption, metabolism, distribution, and elimination of the drug or drugs that are administered, and subsequent target organ effects, both therapeutic and toxic. The process of input followed by absorption, distribution, metabolism, and elimination is referred to as "pharmacokinetics," a process that is commonly represented by a mathematical description of the behavior of a drug, and possibly its metabolites, in the system. Pharmacokinetics is frequently described as "what the body does to the drug." Drug effects at the molecular, biochemical, cellular, or clinical level are referred to as "pharmacodynamics" and often described as "what the drug does to the body." A major goal of clinical pharmacology is to integrate pharmacokinetics and pharmacodynamics so that their relationships can be understood, and so that drug treatment can be optimized based upon such an understanding.

The pharmacokinetics of antineoplastic agents are frequently represented as concentration × time profiles, the definition of which may require frequent sampling of the system and measurement of drug concentrations at those times sampled. A less frequently articulated, although implicitly understood, phenomenon is that there is also a time course of drug effect, which can be described by parameters such as peak effect, time to peak effect, and duration of drug effect. The relationship between relevant pharmacokinetic parameters such as plasma concentration or area under the concentration × time curve and drug effect is often modeled using a Sigmoid E_{max} model, as described by the Hill equation [67, 69]. The flexibility of this model is such that it can fit the wide variety of theoretical relationships that exist between pharmacokinetics and pharmacodynamics.

In performing pharmacokinetic and pharmacodynamic studies, it must be understood that two basic relationships need to be defined. The first of these is the relationship between a pharmacokinetic parameter and the likelihood of achieving a therapeutic response. The second is the relationship between a pharmacokinetic parameter and the likelihood of producing a toxic response. Furthermore, it must be understood that these relationships deal with probabilities rather than absolutes: there is no guarantee that the achievement of a specific pharmacokinetic value will produce the desired therapeutic effect or avoid an undesired, toxic consequence. With the understanding that achieving any given value of a relevant pharmacokinetic parameter can be associated with the presence or absence of positive and negative pharmacodynamic consequences, it is obvious that there are only four potential outcomes of drug therapy: 1) efficacy without toxicity; 2) efficacy with toxicity; 3) toxicity without efficacy; and 4) neither efficacy nor toxicity. With antineoplastic chemotherapy, as with any drug treatment, the goals of therapy are to maximize the likelihood of a favorable response while simultaneously minimizing the likelihood of unacceptable toxicity. It is well understood in medical oncology that some toxicity may be obligatory, and that avoidance of toxicity may do patients a disservice by reducing their likelihood of achieving a favorable therapeutic response.

New considerations regarding input into the system

A number of new factors regarding input into the system need to be considered. These include issues of whether dose should be normalized on a mg/m^2 basis, as is commonly done in current medical oncology practice [30], and the realization that prolonged infusions of antineoplastic agents can produce very low drug concentrations, which may be below the limit of quantitation using available technology. This latter concern has obvious implications for defining pharmacokinetic/pharmacodynamic relationships because it may mean that concentrations of the agent under study cannot be measured in the required biological matrix. Furthermore, the development of newer, but insoluble agents and classes of drug continues to raise formulation issues, and the increasing interest in orally administered agents carries with it a number of real problems. We continue to be challenged by how to address pharmacolo-

gical studies of combinations of agents, and finally the increasing interest in high-dose chemotherapy presents unique challenges for clinical pharmacological studies.

As a consequence of the method of antineoplastic drug development, in which preclinical in vivo studies form the basis for subsequent clinical studies, the strategy of normalizing dose for body surface area has become an accepted practice. Recently, this concept has undergone closer inspection and its scientific rationale has been questioned [30]. In current practice, the recognition that carboplatin clearance is related to renal function [19, 31] rather than body surface area has resulted in a change in standard practice such that carboplatin is rarely administered on a mg/m^2 basis, but is dose adjusted based on renal function [9, 10, 18].

The concept of fixed rather than body surface area-normalized dosing should be an area for fruitful clinical pharmacological studies of antineoplastic agents. One such study is CALGB 9763 (A prospective evaluation of body surface area as a determinant of paclitaxel pharmacokinetics/pharmacodynamics in women with solid tumors). This study is prospectively evaluating the feasibility of delivering a fixed total dose of 360 mg of paclitaxel as a 3-h infusion every 3 weeks, rather than following the standard practice of administering the drug on a mg/m^2 basis. The study, which includes an obligatory pharmacokinetic component, has significant economic implications. The ability to manufacture a unit dose of an agent has obvious benefits for the pharmaceutical company involved. Similarly, reconstituting a fixed dose without subsequent individualization for different patients is more efficient and cost-effective than preparing individualized doses. It would not be surprising to see additional studies of this type as new antineoplastic agents become available, and to see similar studies performed to evaluate objectively the standard practice of mg/m^2 dosing used for established and noninvestigational agents currently in clinical use.

Hydrophobic compounds are frequently administered to patients in vehicles containing potentially bioactive, although not necessarily cytotoxic, excipients. The use of diluent 12, a 1:1 mixture of cremophor and ethanol, is associated with well-documented, as well as other underappreciated, pharmacodynamic consequences. Specifically, the allergic phenomena associated with administration of cremophor, which is polyethoxylated castor oil, is not only well recognized, but in the case of paclitaxel has resulted in a standard practice in which concomitant medication, consisting of steroids and histamine type 1 and type 2 antagonists, is obligatorily delivered along with paclitaxel [57, 73]. More recently, the concentrations of cremophor produced in plasma by shorter infusions of therapeutic doses of paclitaxel have been shown to be sufficient to modulate P-glycoprotein and are likely to have measurable consequences for the pharmacokinetics of paclitaxel [56] and possibly other agents. Less well appreciated is the fact that delivery of 200–225 mg/m^2 of paclitaxel over 3 h also results in delivery of 30–35 ml of intravenous ethanol [72].

As with diluent 12, the reliance on other nonaqueous formulation vehicles must be considered when hydrophobic antineoplastic agents such as 9-aminocamptothecin [46] are administered to patients. One other example in this area involves the potential use of dimethylsulfoxide (DMSO) as a vehicle for solubilizing certain agents. Although not specifically a chemotherapeutic agent, peripheral blood stem cells are routinely cryopreserved in 10% DMSO. Recent studies from our laboratory have documented production of DMSO concentrations in the range of 30 mM when peripheral blood stem cell preparations are reinfused into patients following high-dose chemotherapy [17]. That such a procedure is not associated with obvious DMSO-related toxicity raises the question of whether this agent will see increased use in drug formulation studies. If this is the case, the potential pharmacodynamic consequences of DMSO in patients will require further elaboration. Similar comments could be made regarding a number of polar-planar or lipophilic compounds such as dimethylacetamide, polyethylene glycol, and Tween 80 that are used in pharmaceutical formulations.

In addition to the above formulation issues, the entire field of liposomal encapsulation of antineoplastic agents remains an area of active investigation [38, 40]. At least one agent formulated in this fashion has been approved for noninvestigational use [32], and many trials are evaluating the potential utility of others. Integrating the pharmacodynamics of these agents with their pharmacokinetics, which are often strikingly different from those of the agents in nonliposomal form, remains an interesting and important challenge.

The use of oral administration for input into the system is not a new concept. Oral delivery of agents such as hydroxyurea, etoposide, busulfan, and cyclophosphamide is a well-established clinical practice. However, increasing use of oral agents requires that certain implicit assumptions be addressed. These include less precise dosing because tablets come in a limited number of sizes and increased variability in the amount delivered to the system as a result of the variability in absorption and first-pass metabolism in the gastrointestinal tract and liver. In contrast, oral administration of an agent facilitates the prolonged exposure, or administration, that may be required for some newer classes of drug. One overriding consideration associated with the increased facility of drug delivery, but reduced precision of dosing, associated with oral agents is whether the goal of therapy is palliation or cure. If it is understood that cure is not a realistic expectation, the advantages of oral delivery may well override the concern for less precision in dosing, which might be a major concern in the treatment of diseases such as testicular cancer.

There is currently great interest in understanding the clinical pharmacology of antineoplastic agents when given in combination with other drugs. Some of these combinations are intentional, as with traditional combination chemotherapy involving $\geq$2 cytotoxic agents. However, several newer types of combinations have also attracted attention. There is great activity in the area of combining cytotoxic agents with modulators of drug resistance. Representative of this type of work is that involving SDZ PSC833 [22, 63], cylcosporine A [6, 77], and dexverapamil [47, 75].

In addition to these agents, which are designed to enhance the activity of cytotoxic agents, there are at least three currently available compounds that are administered with antineoplastic agents due to their ability to mitigate specific antineoplastic drug-related toxicities. Although mesna [70] has been shown not to alter the plasma pharmacokinetics and antitumor activity of oxazophosphorines, the potential drug-drug interactions associated with the use of amifostine [8] and dexrazoxane [35] continue to be explored. Furthermore, there is increasing realization of the potential for drug-drug interactions, on either a pharmacokinetic or pharmacodynamic basis, when agents such as antiemetics, steroids, and histamine blockers are administered prophylactically to prevent chemotherapy-associated toxicities. Just as these intentional combinations of agents are being recognized as highly relevant areas for study, the realization has developed that unintentional combinations of antineoplastic agents with a variety of other classes of drug are relatively common occurrences in oncologic practice. The potential drug-drug interactions resulting from coadministration of chemotherapeutic agents with analgesics, antimicrobials, and total parental nutrition are a relatively unexplored area of the clinical pharmacology of antineoplastic agents. Furthermore, the increasing recognition that cancer is a disease of the elderly [23] and that such patients are frequently taking concomitant therapy for other diseases such as hypertension, cardiovascular disease, and pulmonary disease will require that the potential drug-drug interactions occurring in such patients be addressed.

Administration of high-dose chemotherapy to patients requires a somewhat different philosophical approach to dose-response and pharmacokinetic/pharmacodynamic relationships. Although it is common to think and extrapolate linearly, biological systems may not be linear and the clinical pharmacology of high-dose chemotherapy may involve such nonlinear behavior. Thus although some of the "new" toxicities associated with high-dose chemotherapy may simply reflect linear extrapolation of pharmacokinetic/pharmacodynamic relationships of the system such that toxicities encountered at low frequency at standard doses of drug become detectable at higher doses, new or unexpected toxicities encountered with high-dose chemotherapy may reflect saturation of a clearance process [11]. In the latter case, an increase in dose results in a greater than proportional exposure-to-drug period. Alternatively, high doses of an agent may deplete some critical protective mechanism so that a new drug effect becomes manifest, eg, the hepatotoxicity produced by acetaminophen overdoses.

Questions related to sampling the system

Having previously stated that a key concept in clinical pharmacological studies involves generation of information and that this requires sampling the system, a number of relevant questions related to sampling the system remain. One basic question is what should be measured. Should we measure the drug itself or its metabolites? Should we assess patient physiology, homeostasis, or tumor size? Should we put greater emphasis on sampling cells as opposed to biological fluids? Are there specific biochemical markers of drug action or cell death that are appropriate for assessment, or should we find some practical means of measuring perturbation of the cell cycle resulting from chemotherapeutic agent administration?

Although measurement of drug may sound simple, a number of caveats are associated with it. The quest for increasingly potent agents has resulted in an increasing number of drugs that produce very low plasma drug concentrations. Recent examples of such compounds introduced into clinical practice include dolastatin [53], flavopiridol [5], 9-aminocamptothecin [46], and bryostatin [51]. The requirement for expensive and complex analytical methodologies, such as liquid chromatography/mass spectrometry, means that measurement of such compounds is not feasible at a large number of institutions. Furthermore, for some important classes of drug, such as camptothecins [14], that exist in several forms in equilibrium and that can interconvert depending upon handling, there is still active debate as to what is the appropriate form of drug to measure [71]. Specifically, whether it is sufficient to measure total drug as opposed to measuring lactone and/or ring-opened forms of the drug has not been resolved. Preventing interconversion of such species can be complicated, impractical, and expensive.

We must continually question whether it makes sense to measure the parent compound, particularly if that compound is a prodrug, or whether it is essential to measure active metabolites. As one example, the relevance of measuring cyclophosphamide or ifosfamide, instead of their activated hydroxy or mustard forms, can be considered [13]. Until recently, suitable analytical methodology did not exist to investigate this question easily. More recently, a gas chromatography/mass spectrometry method for measuring active metabolites of these oxazophosphorines has been published [3] and initial studies investigating this issue have been undertaken [4]. However, the availability of reagents for such studies is limited and sample handling is currently such that widespread application of this potentially important methodology is precluded.

Sharing the logistic difficulties of this method are the means for measuring activated forms of antimetabolites. Although measurements of antimetabolites such as gemcitabine [2, 28] and cytosine arabinoside [61] are relatively straightforward, the active forms of these compounds are nucleocide triphosphates formed intracellularly [24, 27] and assessment of these pharmacologic entities requires sampling of cells, rather than plasma, and application of more complicated analytical chemical methodology. As a result, generation of data in this area has been slow and infrequent. Furthermore, institutions undertaking studies of such active metabolites must generate data that will substantiate the utility of such measurements. Should that be that case, it is likely that means will be found to facilitate broader application and implementation of such measurements.

Whether measurements of parent compound or metabolites are undertaken, such measurements must involve a validated method [58]. Method validation includes all of the procedures required to demonstrate that a particular method for the quantitative determination of the concentration of an analyte or series of analytes in a particular biological matrix is reliable for the intended application. It is essential to employ well-characterized and fully validated analytical methods to yield reliable results that can be satisfactorily interpreted. Specific validation criteria are needed for methods intended for analysis of each analyte, ie, drug and/or metabolite. Furthermore, when sample analysis is conducted at more than one site, it is necessary to validate the analytical method or methods at each site and provide appropriate validation information for different sites to establish interlaboratory reliability. Finally, unless a method is used regularly, thus generating confidence in its continued validity, it is essential to document that the method is still valid prior to analysis of samples in a new study.

Another issue related to measurement of drugs or metabolites is whether it is sufficient to measure total drug concentrations or whether the free or nonprotein-bound fraction is the important pharmacologic parameter to assess. It is common for the protein binding of an antineoplastic agent to be characterized in vitro before the drug is introduced into clinical trials. This is done far less frequently for drug metabolites than for the parent compound. Furthermore, it is relatively uncommon for free as opposed to bound drug to be determined in clinical samples.

Certain practical issues must be confronted when the free fraction of drug is to be determined. A small free fraction of a low or moderate total plasma concentration of drug may not be quantifiable using the analytical methodology available. Therefore it may be impossible to measure the free fraction. Furthermore, the precision of the analytical methodology available may not be sufficient to define a relevant difference in free fraction. The difference between a 1% and 2% free fraction may be quantitatively small, but represents a 100% difference in free fraction.

The field of drug metabolism has been relatively neglected in antineoplastic pharmacology. There are several reasons for this. Failure to define all the metabolites of a drug before it enters clinical trials is one. Furthermore, preclinical metabolism studies involving mouse or rat enzyme preparations do not always reflect the metabolic profile encountered in humans [37, 44]. The recent availability of human hepatic preparations from sources such as the Washington Regional Transplant Consortium (Washington, DC, USA) [37] and of cloned human drug-metabolizing enzymes from commercial sources such as Gentest Corp. (Woburn, MA, USA) has been associated with an increase in attempts at in vitro definition of the human metabolism of antineoplastic agents during preclinical development or early in clinical development.

It is useful to consider examples of each of these issues regarding metabolism. The difference between rat and human metabolic profiles of an antineoplastic agent is well illustrated by paclitaxel [37, 44]: the two major metabolites produced by rat liver preparations are not only different to the major human metabolite but are only minor human metabolites. The utility of measuring the appropriate metabolites of an antineoplastic compound may be well illustrated by studies with irinotecan, for which definition of plasma concentrations of not one but two metabolites may be relevant to explaining the drug's dose-limiting diarrhea [29].

In contrast, gemcitabine may be an example of a case in which relevant metabolites are measured but the data are inappropriately ignored in clinical practice. It is well established that cellular accumulation and phosphorylation of gemcitabine is a saturable process [27]. Irrespective of these data, standard practice for gemcitabine use involves administration by 30-min infusions, which produce plasma gemcitabine concentrations in excess of those required to saturate production of its active metabolite [27]. As a consequence, the vast majority of drug administered is inactivated by cytidine deaminase without producing a pharmacodynamic effect. Whether a change in administration schedule would increase the activity or therapeutic index of gemcitabine is a pharmacologically rational question to raise, and one that requires examination.

Development of many new classes of antineoplastic agent will require us to be smarter when sampling the system. Examples of such drugs include antiangiogenesis agents [25], telomerase-targeting drugs [59], antisense oligonucleotides [66], matrix metalloproteinase inhibitors [76], farnesyl transferase inhibitors [49], differentiating agents [55], and potentially antineoplastic viruses [34]. Each of these classes of drug has a proposed target that could be monitored if the correct samples can be obtained. Correct sampling involves determination not only of the appropriate matrix, but also the correct times at which to sample the system. Again, this may sound easier than it will be to do. Many of these new classes of compounds represent challenges with respect to measurement of their amounts or concentrations in biological systems or matrices. Furthermore, not all of them kill cells and some may need to be present continuously. In this regard, it may be relevant to refer to lessons learned and practices commonly employed in areas of clinical pharmacology other than cancer chemotherapy.

What to sample

A basic question involved in sampling the system is "What should be sampled?" Is sampling plasma sufficient? The rationale for measuring drug concentrations in plasma is that: 1) it is the means by which we usually introduce drugs into the system; 2) it is presumably what carries the drug to its site of action; and 3) it is relatively accessible. Despite this, sampling plasma involves a certain degree of patient inconvenience and risk. The potential for sampling alternative fluids, such as saliva [62, 65] or urine, warrants consideration. Similarly, noninvasive means of assessing drug are an active area of ongoing research [74]. In

contrast, there is an equally great interest in sampling interstitial fluid from the index tissue in which pharmacodynamic effect is monitored. The basis for the use of microdialysis in this regard is that transfer of drug from a blood capillary to either a normal or tumor cell involves transfer across extracellular fluid. Such studies been performed in mice [78] and rats [21], and instrumentation is also available for clinical application [20, 48].

In addition to the question of what to sample to measure drugs or metabolites, the question of what to sample to monitor pharmacodynamic effect can be raised. Normal tissue may be useful for sampling to monitor toxicity in an index tissue or, potentially, as a surrogate for antitumor response. It may also serve as a means of assessing perturbation in cell function related to the perceived means of action of the drug under study or as a means to assess timing for optimum application of a drug or combination of drugs. Although sampling of the tumor itself may seem the easiest way because it is, after all, the target of therapy, the realities of obtaining tumor specimens currently preclude this from becoming common practice. Furthermore, even for tumors such as melanoma, wherein location might allow sampling, tumor heterogeneity among metastases and the contribution of normal tissue within a tumor biopsy must be recognized as potential complicating factors if such sampling strategies are proposed or undertaken.

When considering sampling the system, the question of when to sample is as important as what to sample

The obvious candidates for when to sample a system are before treatment, during treatment, or after treatment. The frequency or intensity of sampling the system is another variable to consider. Practical constraints on frequent and intensive sampling include patient discomfort and risk, patient inconvenience, and the expense involved. Each of these issues has fostered interest in developing limited sampling strategies for assessing the system. To date, two strategies have been commonly employed [15, 52], each of which has relative advantages and disadvantages. The stepwise regression approach to limited-sampling strategy development [52] has the advantages of being easy to develop and involving user-friendly software. However, it also has the disadvantage of being inflexible. Samples must be drawn at precise times, and the methodology defines only one pharmacokinetic or pharmacodynamic parameter.

Alternatively, limited-sampling strategies based on optimal-sampling theory [15] have the advantage of being extremely flexible. They can use samples drawn at less-than-optimal times and have the potential to define multiple pharmacokinetic parameters. However, optimal-sampling theory-based limited-sampling strategies have the disadvantages of involving complex theory, requiring a population pharmacokinetic model, and involving software that is less than user-friendly.

The rationale behind developing limited-sampling strategies is to allow easy investigation in an individual patient or to facilitate collection of data in a sufficient number of patients to allow pharmacokinetic/pharmacodynamic relationships to be determined, for which large populations are necessary. One particularly innovative approach that has recently been published is that using measurement of total plasma platinum at 24 h after treatment to assess the AUC of carboplatin produced in patients treated with that drug [26]. As stated earlier in this paper, common practice is to administer a desired AUC of carboplatin, rather than a mg/m^2 dose. Even with this potential refinement in dosing strategy, it is helpful to have a means to assess whether the AUC intended for delivery was delivered. Moreover, the ability to obtain measurements on a stable, easily handled drug sample at a single time point in a large number of patients should allow exploration of relationships between drug exposure and therapeutic intent in a variety of tumor types. These data would augment our understanding of the known relationships between drug exposure and toxicity [39, 54].

Modeling the system

Although appropriate sampling and measurement of the system are critical to successful clinical pharmacological studies of antineoplastic agents, they are not sufficient by themselves. The information and data generated must be integrated. This is most commonly done through modeling the system. A wide variety of tools is available for pharmacokinetic and pharmacodynamic modeling. In applying these tools, it is helpful to remember that the tool selected should fit the need. Use of an inappropriately simple modeling approach may generate information; however, such information may not be applicable for the needs of the study. Conversely, attempts to apply overly complex modeling methodology may frustrate or inhibit generation of information that could be useful for the purposes intended.

One common theme in pharmacokinetic/pharmacodynamic modeling is the benefit resulting from the continued development of faster and cheaper computers. To some extent, the increased interest in clinical pharmacology of antineoplastic chemotherapeutic agents reflects the fact that faster and cheaper computers have brought the ability to perform such studies within the means of most investigators.

When modeling the pharmacokinetic information sampled from the system, there is no one universal pharmacokinetic parameter that must be employed. Potential candidates for use as pharmacokinetic parameters include the area under the concentration $\times$ time curve, peak plasma drug concentration, duration that plasma drug concentration remains above a given threshold concentration, free or total drug concentration, the cumulative dose or cumulative AUC delivered, and possibly dose or AUC intensity. This list of potential candidates is not all-inclusive, and part of the challenge and pleasure to be derived from such modeling exercises involves exploration and definition of appropriate pharmacokinetic parameters for use.

Similarly, there is not a universal pharmacodynamic parameter for use in pharmacokinetic/pharmacodynamic modeling. Two approaches have been commonly employed [45]. The first of these assesses the change from baseline in some variable within an individual patient. Examples include percentage reduction in white blood cell or platelet counts. Alternatively, when large numbers of patients are available and the pharmacodynamic consequence to be assessed is not precisely quantifiable, the definition of the probability of a toxic consequence occurring within a cohort of patients sharing a restricted or defined pharmacokinetic parameter has been used.

With increased interest in high-dose chemotherapy, patients can be expected to have a 100% change in myeloid elements or a 100% likelihood of experiencing significant toxicity. Therefore the two previously described approaches do not provide useful measurements and newer approaches, such as consideration of duration of drug effect, are likely to be required in defining meaningful relationships between pharmacokinetics and pharmacodynamics in high-dose chemotherapy studies. Furthermore, the myeloid elements that recover in patients undergoing autologous or allogeneic blood stem cell transplants are not derived from cells that have been exposed to drug introduced into the system. Rather, they have been stored outside the system during the time that drug was in the system.

Finally, the challenge of relating pharmacokinetic measurements to therapeutic drug outcome remains an area for active study. Whether traditional criteria of response, either partial or complete, are relevant remains to be seen. Furthermore, whether a clinical response is as relevant a parameter as a pathologically documented response may be a question to consider. It remains to be seen whether the pharmacodynamic parameters of time to progression or overall patient survival are more meaningful for use in clinical pharmacological studies than are the more commonly employed criteria for response. Additionally, the ability to use surrogate markers, such as carcinoembryonic antigen, CA125, and prostate serum antigen, as criteria for response remains an area of active and potentially fruitful research.

Even when appropriate pharmacokinetic and pharmacodynamic parameters are known, the development of innovative approaches to model such data continues. Application of population modeling concepts to clinical pharmacological studies of antineoplastic agents continues to grow. Such population studies have most commonly employed one of two approaches [60, 64]. The first of these is nonlinear mixed-effects modeling [65], most commonly implemented using the program NONMEM [7]. Alternatively, the iterative, two-stage approach [64] has also gained acceptance and has been implemented using proprietary software and the program ADAPT II, among others [16, 33].

Increased emphasis has also been placed on developing integrated pharmacokinetic/pharmacodynamic models. Some of these linked models are available as standard in certain software packages [16]. More innovative approaches to this concept are represented by the recent publication of a population model for the leukopenic effect of etoposide [41].

Even with the emphasis on and activity applied to modeling the pharmacokinetic and pharmacodynamic relationships of antineoplastic agents, in reality such agents are rarely used individually. As a result, the significant challenge of developing appropriate models to describe the behavior of combinations of agents remains. Despite the publication of mathematical models for describing agents that have either 1) a common receptor and common mechanism, 2) separate receptors but a common mechanism, or 3) separate receptors and separate mechanisms [36], practical constraints in antineoplastic pharmacology remain. These constraints are that: 1) the Hill equations describing the pharmacokinetic/pharmacodynamic relationships for the individual agents in a combination are rarely available; and 2) the precise receptors and/or mechanisms of action of the individual agents have not been well defined. As a result, application of the published models has proven difficult.

Special systems

One final consideration regarding the systems studied in the clinical pharmacology of antineoplastic agents is that not all systems are the same. An area of great current activity is studies of special systems. These include: 1) the elderly [43], and gender- [42, 43] and ethnicity-related differences in pharmacology [1]; and 2) definition of the pharmacology of antineoplastic agents in patients with impaired hepatic [68] or renal function [50]. Although the general principles of sampling and modeling the system may be applicable to these systems, the parameters defining pharmacokinetics and pharmacodynamics in the general population may be different in these special systems. In addition, there is also interest in systems with special input. Specifically, the subset of antineoplastic chemotherapy involving regional delivery [12], such as intraperitoneal, intraarterial, intrathecal, and intravesical chemotherapy, carries with it special mathematical and practical considerations.

Conclusions

This paper began with an admission of ignorance and the recognition that it is impossible within a constrained space to provide an encyclopedic overview of the current state of the clinical pharmacology of antineoplastic chemotherapy. What I have attempted to do is provide an overview and framework for pursuing such studies in the laboratory or following them in the literature. This approach reflects my personal bias, research interests, and weaknesses. I hope that it has fulfilled my intended function and that failure to cite or recognize the work of any individual scientist or group is understood to be unintentional.

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References

1. Albin N, Massade L, Gouyette A (1997) Value and applications of pharmacogenetics in oncology and hematology. Bull Cancer 84:643
2. Allerheiligen S, Johnson R, Hatcher B, Freeman K, Tarassoff P, Voi M, Dorr A (1994) Gemcitabine pharmacokinetics are influenced by gender, body surface area (BSA), and duration of infusion. Proc Am Soc Clin Oncol 12:136
3. Anderson LW, Ludeman SM, Colvin OM, Grochow LB, Strong JM (1995) Quantitation of 4-hydroxycyclophosphamide/aldophosphamide, an activated metabolite of cyclophosphamide. J Chromatogr B Biomed Appl 667:247
4. Anderson LW, Chen TL, Colvin OM, Grochow LB, Collins JM, Kennedy MJ, Strong JM (1996) Cyclophosphamide and 4-hydroxycyclophosphamide/aldophosphamide kinetics in patients receiving high-dose cyclophosphamide chemotherapy. Clin Cancer Res 2:1481
5. Arneson D, Evans E, Kovatch R, Moore R, Morton T, Tomaszewski J, Smith AC (1995) Preclinical toxicology and pharmacology of flavopiridol (NSC-649890) in rats and dogs. Proc Am Assoc Cancer Res 36:366
6. Bartlett NL, Lum BL, Fisher GA, Brophy NA, Ehsan MN, Halsey J, Sikic BI (1994) Phase I trial of doxorubicin with cyclosporine as a modulator of multidrug resistance. J Clin Oncol 12:835
7. Beal SL, Sheiner LB (1989) NONMEM User's Guides. NONMEM Project Group, University of California, San Francisco
8. Bukowski RM (1996) Amifostine (Ethyol): dosing, administration and patient management guidelines. Eur J Cancer 4:S46
9. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E (1989) Carboplatin dosage: prospective evaluation of a simple formulation based on renal function. J Clin Oncol 7:1748
10. Chatelut E, Canal P, Brunner V, Chevreau C, Pujol A, Boneu A, Roché H, Houin G, Bugat R (1995) Prediction of carbolatin clearance from standard morphological and biological patient characteristics. J Natl Cancer Inst 87:573
11. Chen TL, Passos-Coelho JL, Noe DA, Kennedy MJ, Black KC, Colven OM, Grochow LB (1995) Nonlinear pharmacokinetics of cyclophosphamide in patients with metastatic breast cancer receiving high-dose chemotherapy followed by autologous bone marrow transplantation. Cancer Res 55:810
12. Collins JM (1996) Pharmacokinetics and clinical monitoring. In: Chabner BA, Longo DL (eds) Cancer chemotherapy and biotherapy, 2nd edn. Lippincott-Raven, Philadelphia, p 17
13. Colvin M (1982) The comparative pharmacology of cyclophosphamide and ifosfamide. Semin Oncol 9:2
14. Constin D, Potmesil M (1994) Preclinical and clinical development of camptothecins. Adv Pharmacol 29B:51
15. D'Argenio DZ (1981) Optimal sampling times for pharmacokinetic experiments. J Pharmacokinet Biopharm 9:739
16. D'Argenio DZ, Schumitsky A (1990) ADAPT II User's Guide. Los Angeles, CA, Biomedical Simulation Resource, University of Southern California
17. Egorin MJ, Rosen MD, Sridhara R, Sensenbrenner L, Cottler-Fox M (1997) Plasma concentrations and pharmacokinetics of dimethylsufoxide and its metabolites in patients undergoing peripheral stem cell transplant. J Clin Oncol (in press)
18. Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J (1985) Prospective validation of a pharmacologically based dosing scheme for the cis-diamminedichloroplatinum (II) analogue diamminecyclobutanedicarboxylatoplatinum[1]. Cancer Res 45:6502
19. Egorin MJ, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J (1984) Pharmacokinetics and dosage reduction of carboplatin in patients with impaired renal function. Cancer Res 44:5432
20. Ekstrom PO, Andersen A, Saeter G, Giercksky KE, Sirdal L (1997) Continuous intratumoral microdialysis during high-dose methotrexate therapy in a patient with malignant fibrous histiocytoma of the femur: a case report. Cancer Chemother Pharmacol 39:267
21. Ekstrom PO, Andersen A, Warren DJ, Giercksky KE, Sirdal L (1996) Determination of extracellular methorexate tissue levels by microdialysis in a rat model. Cancer Chemother Pharmacol 37:394
22. Erlichman C, Moore M, Thiessen J, DeAngelis C, Goodman P, Manzo J (1994) A phase I trial of doxorubicin (D) and PSC833: a modulator of multidrug resistance (MDR). Proc Am Soc Clin Oncol 13:134
23. Ershler WB, Longo DL (1997) Aging and cancer: issues of basic and clinical science. J Natl Cancer Inst 89:1489
24. Estey EH, Keating MJ, McCredie KB, Freireich EJ, Plunkett W (1990) Cellular ARA-CTP pharmacokinetics, response, and karyotype in newly diagnosed acute myelogenous leukemia. Leukemia 4:95
25. Folkman J (1996) Fighting cancer by attacking its blood supply. Sci Am 275:150
26. Ghazal-Aswad S, Calvert AH, Newell DR (1996) A single-sample assay for the estimation of the area under the free carboplatin plasma concentration versus time curve. Cancer Chemother Pharmacol 37:429
27. Grunewald R, Abbruzzese JL, Tarassaff P, Plunkett W (1991) Saturation of 2′, 2′-difluorodeoxycytidine 5′-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. Cancer Chemother Pharmacol 27:258
28. Grunewald R, Kantarjian H, Du M, Faucher K, Tarassoff P, Plunkett W (1992) Gemcitabine in leukemia: a phase I clinical, plasma, and cellular pharmacology study. J Clin Oncol 10:406
29. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ (1994) Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. Cancer Res 54:3723
30. Gurney H (1996) Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. J Clin Oncol 14:2590
31. Harland SJ, Newell DR, Siddik ZH, Chadwick R, Calvert AH, Harrap KR (1984) Pharmacokinetic of cis-diammine-1,1-cyclobutane dicarboxylate platinum (II) in patients with normal and impaired renal function. Cancer Res 44:1693
32. Harrison M, Tomlinson D, Stewart S (1995) Liposomal-entrapped doxorubicin: an active agent in AIDS-related Kaposi's sarcoma. J Clin Oncol 13:914
33. Hawtof FA, Egorin MJ (1991) Evaluation of a new program for population of PK/PD analysis applied to simulated phase I data (abstract). Clin Pharmacol Ther 49:153
34. Heise C, Sampson-Johannes A, Williams A, McCormick F, Von Hoff DD, Kirn DH (1997) ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumor efficacy that can be augmented by standard chemotherapeutic agents. Nat Med 3:639
35. Hellman K (1996) Cardioprotection by dexrazoxane (Cardioxane; CRF 187): progress in supportive care. Support Care Cancer 4:305
36. Holford NHG, Sheiner LB (1982) Kinetics of pharmacologic response. Pharmacol Ther 16:143
37. Jamis-Dow CA, Klecker RW, Katki AG, Collins JM (1995) Metabolism of taxol by human and rat liver in vitro: a screen for drug interactions and interspecies differences. Cancer Chemother Pharmacol 36:107
38. Janknegt R (1996) Liposomal formulations of cytotoxic drugs. Support Care Cancer 4:298

39. Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN, Goodlow JL, Tan S, Wiltshaw E (1992) Relationship between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10:520
40. Juliano RL, Akhtar S (1992) Liposomes as a drug delivery system for antisense oligonucleotides. Antisense Res Dev 2:165
41. Karlsson MO, Port RE, Ratain MJ, Sheiner LB (1995) A population model for the leukopenic effect of etoposide. Clin Pharmacol Ther 57:325
42. Kaul S, Srinival NR, Mummaneni V, Igwemezie LN, Barbhaiya RH (1996) Effects of gender, age, and race on the pharmacokinetics of etoposide after intravenous administration of etoposide phosphate in cancer patients. Semin Oncol 23 (6 Suppl 13):23
43. Kinirons MT, Crome P (1997) Clinical pharmacokinetic considerations in the elderly: an update. Clin Pharmacokinet 33:302
44. Klecker RW, Jamis-Dow CA, Egorin MJ, Erkmen K, Parker RJ, Stevens R, Collins JM (1994) Effect of cimetidine, probenecid and ketoconazole on the distribution, biliary secretion and metabolism of ^{3}H-Taxol in the Sprague-Dawley rat. Drug Metab Dispos 22:254
45. Kobayashi K, Jodrell DI, Ratain MJ (1993) Pharmacodynamic-pharmacokinetic relationships and therapeutic drug monitoring. In: Workman P, Graham MA (ed) Pharmacokinetics and cancer chemotherapy. Imperial Cancer Research Fund Cold Spring Harbor Laboratory Press, p 51
46. Liang MD, Dahut W, Quinn MF, Harold N, Arbuck SG, Chen A, Hamilton JM, Sorensen JM, Allegra CJ, Grem JL, Takimoto CH (1996) Preclinical and clinical studies of a new colloidal dispersion formulation of 9-amino-camptothecin. Proc Am Assoc Cancer Res 37:432
47. Motzer RJ, Lyn P, Fischer P, Lianes P, Ngo RL, Cordon-Cardo C, O'Brien JP (1995) Phase I/II trial of dexverapamil plus vinblastine for patients with advanced renal cell carcinoma. J Clin Oncol 13:1958
48. Muller M, Mader RM, Steiner B, Steger GG, Jansen B, Gnant M, Helbich T, Jakesz R, Eichler HG, Blochl-Daum B (1997) 5-fluorouracil kinetics in the interstitial tumor space: clinical response in breast cancer patients. Cancer Res 57:2598
49. O'Reilly S, Rowinsky EK, Slichenmyer W, Donehower RC, Forastiere AA, Ettinger DS, Chen TL, Sartorius S, Grochow LB (1996) Phase I and pharmacologic study of topotecan in patients with impaired renal function. J Clin Oncol 14:3062
50. Omer CA, Anthony NJ, Buser-Doepner CA, Burkhardt AL, deSolms SJ, Dinsmore CJ, Gibbs JB, Hartman GD, Koblan KS, Lobell RB, Oliff A, Williams TM, Kohl NE (1997) Farnesyl: proteintransferase inhibitors as agents to inhibit tumor growth. Biofactors 6:359
51. Parkinson DR, Arbuck SG, Moore T, Pluda JM, Christian MC (1994) Clinical development of anticancer agents from natural products. Stem Cells 12:30
52. Ratain MJ, Vogelzang NJ (1987) Limited sampling model for vinblastine pharmacokinetics. Cancer Treat Rep 71:935
53. Reeves HW, Newman RA, Hutto T, Madden T (1997) High-performance capillary electrophoresis measurement of dolastatin-10. J Chromatogr B Biomed Appl 693:451
54. Reyno LM, Egorin MJ, Canetta RM, Jodrell DI, Swenerton KD, Pater JI, Burroughs JN, Novak MJ, Sridhara R (1993) Impact of cyclophosphamide on relationships between carboplatin exposure and response or toxicity when used in the treatment of advanced ovarian cancer. J Clin Oncol 11:1156
55. Rifkind RA, Richon VM, Marks PA (1996) Induced differentiation, the cell cycle, and the treatment of cancer. Pharmacol Ther 69:97
56. Rislchin D, Webster LK, Millward MJ, Linahan BM, Toner GC, Woollett AM, Morton CG, Bishop JF (1996) Cremophor pharmacokinetics in patients receiving 3-, 6-, and 24-hour infusions of paclitaxel. J Natl Cancer Inst 88:1297
57. Rowinsky EK, Donehower RC (1995) Paclitaxel (Taxol). N Engl J Med 332:1004
58. Shah VP, Midha KK, Dighe S, McGilveray IJ, Skelly JP, Yacobi A, Layloff T, Viswanathan CT, Cook CE, McDowell RD, Pittman KA, Spector S (1992) Analytical methods validation: bioavailability, bioequivalence, and pharmacokinetic studies. J Pharm Sci 81:309
59. Shay JW, Wright WE (1996) Telomerase activity in human cancer. Curr Opin Oncol 8:66
60. Sheiner LB (1984) The population approach to pharmacokinetic data analysis: rationale and standard data analysis methods. Drug Metab Rev 15:153
61. Sinkule JA, Evans WE (1983) High-performance liquid chromatographic assay for cytosine arabinoside, uracil arabinoside, and some related nucleosides. J Chromatogr 274:87
62. Slavik M, Wu J, Riley C (1993) Salivary excretion of anticancer drugs. Ann NY Acad Sci 694:319
63. Sonneveld SP, Marie JP, Laburte C, Schoester M (1994) Phase I study of SDZ PSC833, a multidrug resistance modulating agent, in refractory multiple myeloma. Proc Am Assoc Cancer Res 35:359
64. Steimer JL, Mallet A, Golmard JL, Boisvieux JF (1984) Alternative approaches to estimation of population pharmacokinetic parameters: comparison with the nonlinear mixed-effect model. Drug Metab Rev 15:265
65. Takahashi T, Fujiwara Y, Sumiyoshi H, Isobe T, Yamaoka N, Yamakido M (1997) Salivary drug monitoring of irinotecan and its active metabolite in cancer patients. Cancer Chemother Pharmacol 40:449
66. Tonkinson JL, Stein CA (1996) Antisense oligodeoxynucleotides as clinical therapeutic agents. Cancer Invest 14:54
67. Venitz J (1995) Pharmacokinetic-pharmacodynamic modeling of reversible drug effects. In: Derendorf H, Hochhaus G (eds) Handbook of pharmacokinetic/ pharmacodynamic correlation. CRC Press, Boca Raton, London, Tokyo, p 1
68. Venook AP, Egorin MJ, Brown TD, Batist G, Budman DR, Rosner GL, Jahan TM, Schilsky RL (1994) Paclitaxel (Taxol) in patients with liver dysfunction (CALGB 9264). Proc Am Soc Clin Oncol 13:139
69. Wagner JG (1968) Kinetics of pharmacologic response. I. Proposed relationships between response and drug concentrations in the intact animal and man. J Theor Biol 20:171
70. Wagner T (1994) Ifosfamide clinical pharmacokinetics. Clin Pharmacokinet 26:439
71. Warner DL, Burke TG (1997) Simple and versatile high-performance liquid chromatographic method for the simultaneous quantitation of the lactone and carboxylate forms of campothecin anticancer drugs. J Chromatogr B Biomed Appl 691:161
72. Webster LK, Crinis NA, Morton CG, Millward MJ (1996) Plasma alcohol concentrations in patients following paclitaxel infusion. Cancer Chemother Pharmacol 37:499
73. Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, Baker JR, Van Echo DA, Von Hoff DD, Leyland-Jones B (1990) Hypersensitivity reactions from Taxol. J Clin Oncol 8:1263
74. Wells P, Harte RJ, Price P (1996) Positron emission tomography: a new investigational area for cancer research. Clin Oncol (R Coll Radiol) 8:7
75. Wilson WH, Jamis-Dow C, Bryant G, Balis FM, Klecker RW, Bates SE, Chabner BA, Steinberg SM, Kohler DR, Wittes RE (1995) Phase I and pharmacokinetic study of the multidrug resistance modulator dexverapamil with EPOCH chemotherapy. J Clin Oncol 13:1985
76. Wojtowicz-Praga SM, Dickson RB, Hawkins MJ (1997) Matrix metalloproteinase inhibitors. Invest New Drugs 15:61
77. Yahanda AM, Alder KM, Fisher GA, Brophy NA, Halsey J, Hardy RI, Gosland MP, Lum BL, Sikic BI (1992) Phase I trial of etoposide with cyclosporine as a modulator of multidrug resistance. J Clin Oncol 10:1624
78. Zamboni W, Houghton P, Hulstein J, Crom W, Thompson J, Cheshire P, Stewart C (1997) Relationship between tumor extracellular fluid (ECF) exposure to topotecan (TPT) and tumor response in human neuroblastoma xenografts. Proc Am Assoc Cancer Res 38:305