Further Refinement of Carboplatin Dosing

Merrill J. Egorin*

Administration of a drug to a patient carries with it the implicit assumption that the drug will produce some beneficial effect in that patient although there is no guarantee that the dose selected will actually produce any observable effect. In reality, the consequences of drug administration can be either favorable, and defined clinically as therapeutic, or unfavorable, and defined clinically as toxic. From a quantitative standpoint, there is a tacit assumption that the amount of drug delivered will, in some way, be related to either the magnitude of the effect produced or the likelihood of an effect occurring. Stated simply, up to a point, more drug will give more result. Obviously, the goal of treating each patient is to maximize the likelihood of producing the desired therapeutic response while, at the same time, minimizing the likelihood of causing unacceptable toxicity. Again, in a simplistic sense, the issue is to give enough but not too much. For a number of drugs, for which the doses required to produce a therapeutic response are much less than those that result in toxic consequences, this very simple approach is quite realistic. Unfortunately, antineoplastic chemotherapeutic agents represent the class of clinically applied drugs with the a narrow line of separation between effective and toxic doses, and in the case of high-dose chemotherapy, toxicity is guaranteed.

What then are the options for selecting an acceptable dose for any given patient? In the most common case, the dose delivered is empirically derived on the basis of phase I and II clinical trials, wherein a supposedly representative patient population has been treated with the agent in question. In reality, such clinical trials usually exclude patients with significant metabolic or excretory organ dysfunction. Moreover, the definition of a maximally tolerated dose as a dose that produces significant but reversible toxicity in 50% of a cohort of patients means that the dose for general application is set by the most sensitive one half of the population, and if more is better, it means that one half of the patients treated with such a dose might actually be undertreated. Thereby, their likelihood of achieving a response or their degree of response may be reduced unnecessarily.

The inherent variability among patients due to factors such as age, gender, genetic constitution, concomitant disease, and concomitant therapy is a major reason the response to a drug is usually more closely related to the amount of drug in the patient at a specific time, or over a span of time, than it is to the dose of drug administered. It is in this regard that measurements of drug concentrations in patient plasma or tissues can have a role. However, defining the pharmacokinetics of an agent is only one half of the task. For pharmacokinetics to be translated into meaningful clinical dosing, the relationship between such mathematical descriptions of drug concentrations and the toxic and therapeutic clinical consequences related to them must be defined. Unfortunately, well-defined pharmacokinetic/pharmacodynamic relationships do not exist for many, if not most, antineoplastic agents currently used in clinical practice. However, if available, such relationships may facilitate development of two dosing strategies that are more precise, and certainly more intellectually pleasing, than mere empiric dosing on a milligram per square meter or milligram per kilogram basis. In the most complex strategy, adaptive control with feedback, drug doses are adjusted on the basis of measurements of drug concentrations in plasma or, possibly, some more relevant tissue sample. However, this approach to increased precision in dosing has the logistical and financial drawbacks inherent in blood sampling, analytical procedures for measuring drug, and computer modeling of patient data.

In the less complex strategy, known as adaptive dosing, the dose of drug delivered is adjusted on the basis of some pretreatment characteristic of the patient that is known to be closely related to the pharmacokinetics of, and possibly the response to, the drug in question. Carboplatin is an ideal example in this regard. First, it is a drug that actually produces significant response rates in a number of tumor types; therefore, there is a reason to want to use it in an optimal fashion. Second, the clearance of carboplatin has been convincingly demonstrated to be intimately related to renal function—specifically, glomerular filtration rate (1,2). Furthermore, well-defined relationships have been demonstrated for the dose-limiting thrombocytopenia of the drug and drug exposure, expressed as the area under the curve (AUC) of plasma concentration versus time (1,3). Retrospective studies in women with advanced ovarian cancer (3) have provided evidence for relationships between carboplatin exposure and the likelihood of achieving a therapeutic response, and other prospective and retrospective studies (4-6) have used...
these relationships to examine the quantitative effects of other agents on carboplatin-related pharmacodynamic effects.

At present, two approaches have been suggested as ways to utilize and integrate the physiologic/pharmacokinetic and pharmacokinetic/pharmacodynamic relationships of carboplatin in delivering optimal doses of the drug to individual patients (1,2,7). Each of these approaches has logistic, if not theoretical, drawbacks.

The dosing approach originally proposed by investigators at the University of Maryland (1,7) requires the reliable collection of a 24-hour creatinine clearance to assess glomerular filtration rate. Although this test is inexpensive, every practicing physician knows that such collections have multiple potential pitfalls related to nursing, patient compliance, and the availability of indoor plumbing. Furthermore, the increased adaptability of the University of Maryland dosing formula, through its ability to aim for a desired platelet count nadir in individual patients (each of whom had a different pretreatment platelet count), means that the calculation of a carboplatin dose requires a calculator.

Currently, calculation of patient-specific carboplatin doses is most commonly done with the formula published by Calvert et al. (2). Although easy to apply, the limited availability of chromium 51-edathamil (51Cr-EDTA) clearances and the previously described issues related to collection of its potential surrogate—a 24-hour creatinine clearance—have dimmed the enthusiasm of practicing clinicians for this alternative approach to patient-specific dosing of carboplatin.

In view of the issues related to collection of a creatinine clearance, there has been, and continues to be, much discussion as to the suitability of a creatinine clearance calculated with one of the two formulas (8,9) that use patient characteristics such as age, weight, gender, and serum creatinine as surrogates for a 51Cr-EDTA clearance-defined glomerular filtration rate or a measured creatinine clearance. Unfortunately, such calculated creatinine clearances are not adequate for the purpose of carboplatin dosing. Therefore, acceptance by physicians of patient-specific, optimal dosing of carboplatin has been retarded by the limited access to 51Cr-EDTA, resistance to collecting creatinine clearances, poor results related to inadequately collected creatinine clearances, or poor performance of dosing based on imprecise creatinine clearances collected from either the Cockcroft and Gault (8) or the Jelliffe (9) formula.

The article by Chatelut et al. in this issue of the Journal (10) should be a major impetus to acceptance of adaptively dosed carboplatin. Using the nonlinear, mixed effects approach to population pharmacokinetic modeling (11), the authors have developed a simple and precise means of estimating carboplatin clearance in individual patients. Unlike the University of Maryland (1,7) or Calvert et al. (2) dosing strategies, which require the addition of a nonrenal clearance component to a patient’s glomerular filtration rate, the French group provides an overall estimate of carboplatin clearance without separation into renal and nonrenal components. In doing so, they remove the necessity of collecting a creatinine clearance and overcome the problems related to inadequate estimation of creatinine clearance by the Cockcroft and Gault (8) or the Jelliffe (9) formula.

The implications of the article by Chatelut et al. are more profound and far-reaching than simply facilitating more intelligent dosing of individual patients with carboplatin. As stated previously, pharmacokinetic/pharmacodynamic relationships are usually more precise than simple dose–response relationships and may actually be defined when no dose–response relationships are apparent. This, in fact, has been shown to be the case for therapeutic response of advanced ovarian cancer to carboplatin therapy (3). The attempt to extend this concept to other tumor types has been frustrated by the lack of data on collected creatinine clearances for patients entered into large phase III clinical trials or for patients with diseases for which large numbers of patients have been treated because multiple phase II trials have been performed. However, these large databases do include the information necessary to calculate a carboplatin clearance with the formula of Chatelut et al. With this value and the relationship: AUC = dose/clearance, it should now be possible to analyze the large databases for patients with diseases such as small-cell lung cancer, non–small-cell lung cancer, and head and neck cancer and who were treated with single-agent carboplatin so that potential exposure-response relationships, such as that proposed for ovarian cancer (3), might be defined. Subsequently, the quantitative effects of other agents combined with carboplatin can be assessed. This type of analysis has been described for a few agents (4-6) and in a limited spectrum of disease, but the potential exists for greatly expanding such work. The ultimate goal of such exercises is the definition of relationships between carboplatin exposure and the likelihood of response as well as toxicity, so that each patient given the drug can receive a dose most likely to achieve the goal of maximizing the likelihood of response and minimizing the likelihood of unacceptable toxicity.

References

Interleukin 12: Newest Member of the Antiangiogenesis Club

Robert S. Kerbel, Robert G. Hawley*

In experimental or clinical oncology circles, the term "magic bullet" has come to acquire a predictable meaning. It refers to drugs that will kill or retard the growth of tumor cell populations while miraculously sparing normal cells and tissues. Such "penicillin-like" antitumor drugs have yet to be discovered, although advances in our understanding of the genetic and biochemical bases of cancer are, hopefully, getting us a little closer to achieving this exalted goal (1,2). For the time being, it remains an unfortunate fact that the toxic side effects mediated by anticancer chemotherapeutic drugs are some of the more important reasons limiting their effectiveness in the clinic. There is, however, one obvious circumstance where the destruction of normal cells and tissues during or after cancer therapy could actually have a significant beneficial effect in cancer treatment, namely, when the tumor vasculature is affected.

As previously shown by Folkman (3), the progressive growth of solid tumors beyond clinically occult sizes (about 1-2 mm in diameter) requires the continuous formation of new blood vessels from existing vessels, a process known as tumor angiogenesis. Hence, it follows that the selective destruction of a tumor’s existing vasculature, or the prevention of further tumor angiogenesis, would represent a possible, potentially effective strategy for the treatment of solid tumors (4-7). The notion of targeting the vasculature of solid tumors and inhibiting angiogenesis as anti-cancer treatment strategies is attractive for several reasons (8). First, either one or both may represent a means of circumventing the problem of acquired drug resistance (8). The rationale is that the genetic instability of tumor cells provides them with the means to generate easily and rapidly drug-resistant mutants. Presumably, genetically stable, normal diploid cells—such as vascular endothelial cells—would be far less adept at generating such variants (8). Second, the "physiologic barrier" of getting high-molecular-weight drugs to sufficiently penetrate into solid tumors could be circumvented if a tumor’s blood vessels, rather than the surrounding malignant parenchyma, were the actual targets of a therapeutic drug (9,10).

Clearly, selective inhibition of tumor angiogenesis and vascular targeting require that the endothelial cells of newly forming or existing tumor-associated blood vessels readily present molecular "targets" that mature blood vessels in normal tissues do not.

In this regard, a fairly large number of molecular changes have been described in activated endothelial cells during angiogenesis; these molecular changes encompass significantly elevated expression of various receptor protein kinases, adhesion molecules, integrins, and proteases, as well as various other molecules (10-13). In some cases, enhanced expression of such molecules may be necessary for the survival of vascular endothelial cells during the proliferative and migratory phases of the angiogenic process. For example, immunologic or pharmacologic interference of the αvβ3 integrin receptor with its extracellular matrix-associated ligands can profoundly inhibit embryonic or solid tumor angiogenesis (14,15). This inhibition of angiogenesis occurs as a result of induction of apoptosis in endothelial cells associated with newly forming microvessel sprouts (15). Remarkably, normal mature vasculature adjacent to the tumor is left unscathed by this type of therapeutic assault, since activated endothelium can express high levels of the αvβ3 integrin, whereas normal quiescent endothelium does not (14,15).

The altered physiologic, metabolic, biochemical, and antigenic status of endothelial cells associated with newly forming vessels raises an interesting question: Is it possible that agents that were ostensibly designed to treat cancer by directly killing tumor cells, or indirectly by boosting antitumor immune responses, exert their antitumor effects by inadvertently inhibiting tumor angiogenesis? Denekamp (7) has reviewed a number of experimental examples where the evidence would appear to provide an affirmative answer to this question. Perhaps one of the best examples is the interferons. Their development as antitumor agents was based primarily on their capacity to stimulate antitumor cytotoxic immunity or to act as direct inducers of tumor cell differentiation and inhibitors of tumor cell proliferation.

Nevertheless, there are instances where sublines of tumors

*Affiliations of authors. Division of Cancer Biology Research, Sunnybrook Health Science Centre and Toronto-Sunnybrook Regional Cancer Centre; and Department of Medical Biophysics, University of Toronto, Ontario, Canada.

Correspondence to: Robert S. Kerbel, Ph.D., Division of Cancer Biology Research, Sunnybrook Health Science Centre, Reichmann Research Bldg., S-218, 2075 Bayview Ave., Toronto, ON M4N 3M5, Canada.