Cancer Chemother Pharmacol (1993) 32: 99–102

Cancer Chemotherapy and Pharmacology

Review

Use of pharmacokinetic-pharmacodynamic relationships in the development of new anthracyclines

Jacques Robert

Fondation Bergonié, 180 rue de Saint-Genès, F-33076 Bordeaux Cedex, France

Received 5 November 1992/Accepted 9 November 1992

Introduction

Because of the delay between drug administration and response evaluation, relationships between the behavior of a drug in the body and the positive effects of the drug are very difficult to establish in oncology in comparison with other medical fields. For any drug, there are numerous sources of interpatient variability concerning both pharmacokinetics (drug distribution and elimination) and pharmacodynamics (drug efficacy and toxicity). The occurrence of a >2-month delay between the evaluation of pharmacokinetic parameters and that of the pharmacodynamic properties of a drug makes difficult any prediction of drug efficacy in individual patients on the basis of pharmacokinetic estimations. Oncologists have therefore tried to circumvent this difficulty by the use of the *toxicity* of the drug as a pharmacodynamic endpoint. Most anticancer drugs are active against all rapidly dividing normal cells, especially blood cells. Thus, using reductions in blood cell counts as a measure of drug effects provides a useful tool for the understanding of pharmacokinetic-pharmacodynamic relationships in oncology. Blood cell counts can easily be obtained several times before and after drug administration and provide reliable and quantitative evaluations of drug effects.

In this short commentary, we summarize the parameters to be used for establishing pharmacokinetic-pharmacodynamic relationships, the results that have been obtained for anthracyclines, and the possibilities offered by such evaluations for the development of new anthracyclines. The reader is also referred to the work of Ratain et al. [16], who have developed the essential concepts and strategies of pharmacodynamics in cancer therapy, and to that of Newell [14], who has recently reviewed this field extensively.

Paper presented at the 4th International ARTAC Workshop on Therapeutic Trials in Cancer and AIDS, Paris 1991

Correspondence to: J. Robert

Pharmacokinetic and pharmacodynamic parameters

The fate of a drug in the body can be characterized by several parameters that are obtained from the study of the plasma concentrations achieved after drug administration. Of course, the plasma concentrations concern only the most easily accessible compartment. Measurements of the tumor concentration and of protein binding, among other parameters, provide a more detailed picture of the drug in the body. The most widely used pharmacokinetic parameter is the total exposure to the drug, represented by the integral of the curve plotted for plasma drug concentration versus time and usually referred to as the area under the curve (AUC). The AUC can easily be obtained from most pharmacokinetics studies and is a model-independent parameter. It is analogous to the "c x t" used to evaluate drug exposure in in vitro cell-culture models. Less frequently, other parameters can be tentatively used for the establishment of pharmacokinetic-pharmacodynamic relationships: C_{max} (plasma peak concentration after bolus drug administration); C_{ss} (steady-state plasma drug concentration during infusion therapy); C_x (plasma concentration at a given time after administration); elimination half-life, which often contributes heavily to the AUC; or volume of distribution, which is representative of tissue fixation of the drug. The metabolism of the drug can also be taken into account; some drugs have active metabolites or, in contrast, can be detoxified. The absolute or relative amounts of metabolite(s) must therefore be considered as relevant pharmacokinetic parameters.

We have mentioned that acute toxicity, especially myelosuppression, is a more readily obtainable indicator of a drug's "activity" than is its true efficacy in terms of the tumor-response rate. Myelotoxicity and tumor-cell death may depend on the same biochemical mechanism. Absolute blood cell counts at the nadir have also been used in several studies [3, 11]. However, the nadir values have proved to be dependent on pretreatment counts as well as on drug dosage or pharmacokinetics [1]. Because of this, the *relative* drop in the blood cell count is recommended as a more direct measure of drug action for correlation with pharmacokinetic parameters. The effect can be expressed either as a percentage of change [(initial – nadir) × 100/initial] or as a surviving fraction (nadir/initial). Plotting of percentages of change versus AUC was initially carried out by Egorin et al. [6] for an anthracycline. The fitting of the data could correspond either to an exponential curve derived from the log cell-kill law [25] as calculated using the equation

$$\text{Survival fraction} = e^{-kAUC} \quad (1)$$

or to a sigmoidal relationship derived from the model of Chou [4]:

$$\text{Survival fraction} = \frac{(AUC_m)^b}{(AUC)^b + (AUC_m)^b}, \quad (2)$$

where AUC_m is the AUC providing half of the maximal effect and b is the Hill coefficient.

The different blood cell populations can be analyzed in this way: total white blood cells (WBCs), granulocytes, platelets (all quantified as the number of cells $\times 10^9$/l), or erythrocytes (quantified as grams of hemoglobin per 100 ml blood). It must be stressed that similar relative drops in blood cell counts may not provide the same clinical toxicity; a 50% decrease from 7 to 3.5 $\times 10^9$ WBCs/l is not considered as being toxic, whereas the same relative decline from 2 to 1 $\times 10^9$ WBCs/l represents grade 3 toxicity according to the WHO scale.

Pharmacokinetic-pharmacodynamic relationships of anthracyclines: literature data

Until recently, few studies have been devoted to anthracyclines in this respect. Preisler et al. [15] were capable of showing that a pharmacokinetic parameter (doxorubicin plasma concentration at 3 h after administration) was significantly correlated with the outcome of remission induction therapy in 45 patients treated for acute nonlymphocytic leukemia. Similarly, we showed in 12 patients suffering from a locally advanced breast cancer primarily treated with doxorubicin that the peak plasma concentration of the drug was significantly related to the reduction in the tumor mass at 3 weeks [19]. In both studies, the importance of the distribution phase of doxorubicin was stressed as a possible determinant of drug activity. It could be speculated that improved tumor penetration might be dependent on very high initial plasma levels. More recently, Hu et al. [11] also observed a significant correlation between the plasma AUC of epirubicin and a complete response to treatment in nasopharyngeal carcinoma patients. The results presented above, although statistically significant, involved small numbers of patients and might not be reproducible in larger studies.

The metabolic transformations of anthracyclines have also been the subject of several investigations concerning their role in drug pharmacodynamics. Greene et al. [9] showed that daunorubicin reductase activity in WBCs was higher in leukemic patiens who responded to therapy; this result suggests that the reduced metabolite daunorubicinol has better intracellular activity than does the parent drug despite the relatively low cell penetration of the former, which prevents its clinical use [24]. Gessner et al. [7] observed that daunorubicin aglycones were present in higher quantities in the plasma of nonresponding leukemic patients. In a series of patients treated with doxorubicin, Cummings et al. [5] noticed that the two patients who developed early cardiotoxicity (below a cumulative dose of 300 mg/m^2) had the highest plasma levels of 7-deoxyaglycones; this observation is consistent with the view that doxorubicin cardiotoxicity is dependent on the free-radical formation from the doxorubicin redox cycle, which leads to the cleavage of the molecule and to the formation of 7-deoxyaglycones. Robert et al. [21] observed in 48 patients with various malignancies that a low rate of epirubicin glucuronidation was correlated with lower percentages of change in granulocytes and with a better tumor response to the course of treatment studied. None of these results has yet been confirmed by other teams, and our present knowledge of anthracycline metabolism does not allow a clear interpretation of these findings.

Egorin et al. [6] were the first authors to show a correlation between the total AUC of an anthracycline (menogaril) and the relative drop in WBCs at the nadir. Such a correlation had not been observed for doxorubicin by Chang et al. [3], who had used the absolute WBC nadir instead of the relative drop; this is not surprising, since an important determinant of the nadir is, in fact, the pretreatment count [1, 16]. Similarly, Hu et al. [11] failed to observe a correlation between the granulocyte nadir and the epirubicin AUC. In studying doxorubicin infusions (median duration, 3 months), Ackland et al. [1] found a correlation between the plasma C_{ss} of the drug and the relative drop in WBCs. Since for long-term infusions the AUC = C_{ss} x infusion time, the use of C_{ss} or AUC yields equivalent results. This correlation is the only one concerning the parent drug of the anthracycline family, doxorubicin. No data are available to identify the best parameter to predict for doxorubicin myelosuppression after bolus administration, e.g., C_{max} or AUC. This question must remain open, particularly in view of the conflicting results obtained in in vitro studies [18]. In a recent study on epirubicin, Jakobsen et al. [12] showed that the only parameter to be significantly related to the relative drop in WBCs was the AUC of epirubicin itself or of the sum epirubicin + epirubicinol. The change in thrombocyte counts, however, was not significantly related to any pharmacokinetic parameter.

Establishment of pharmacokinetic-pharmacodynamic relationships for new anthracyclines

Several new anthracyclines have recently been introduced into clinical trials. It is essential to find out as quickly as possible how these new agents behave in comparison with the classic anthracyclines, i.e., to determine their fate after administration and to establish which major toxic features might be expected. Pharmacokinetic evaluation has been regularly performed for every new anthracycline for many years, but pharmacodynamic parameters, although easy to obtain as described above, are generally not determined simultaneously. However, during the early clinical development of three new anthracyclines, 4′-*O*-tetrahydropyranyldoxorubicin (pirarubicin), 4′-iodo-4′-deoxydoxorubicin (iododoxorubicin), and *N*-L-leucyldoxorubicin (leurubicin), we managed to obtain original data concerning both pharmacokinetics and pharmacodynamics. These results may shed some light on the pharmacologic and toxicologic properties of the new agents and may accelerate their clinical development by a better understanding of their behavior.

Pirarubicin is characterized [21] by a relatively short terminal elimination half-life as compared with that of doxorubicin (16.6 vs 30 h) and an increased plasma clearance (140 vs 30 l h^{-1} m^{-2}). Among its metabolites, doxorubicin may play a positive role due to its own cytotoxic activity. Pirarubicin causes significant hematologic toxicity, which requires a careful estimation of the dose to be given at each course of treatment. We found [22] a signifi-

cant negative correlation between the pirarubicin AUC and platelet survival ($r = -0.60$, $P < 0.02$), whereas the correlation with granulocyte survival ($r = -0.40$) was not significant. In contrast, the AUC of the metabolite doxorubicin was significantly negatively correlated with the granulocyte survival fraction ($r = -0.54$, $P < 0.05$) but not with the platelet survival fraction ($r = -0.37$). These results might indicate a difference in the toxic properties of pirarubicin as compared with doxorubicin; it can be suggested that pirarubicin itself is mainly responsible for the thrombocytopenia, whereas the metabolite doxorubicin causes the granulocytopenia. Another explanation would be that platelets may be more sensitive to the drug that presents a high peak plasma concentration (pirarubicin) than to the metabolite, which is present at lower but more sustained levels (doxorubicin). These suggestions are of interest for the subsequent development of the drug and raise specific questions whose answers should improve its management. We had shown, for instance, that the repetitive administration of pirarubicin over 3 consecutive days favored the relative importance of doxorubicin because of its protracted half-life [20]. A return to the classic 3-week delay between injections minimizes doxorubicin exposure with respect to that of pirarubicin.

We have recently shown during a phase I study of iododoxorubicin [23] that the AUCs of both the unchanged drug and its 13-dihydro derivative were closely related to the granulocyte and platelet surviving fractions. The most significant correlations were found between the granulocyte survival fraction and the metabolite AUC, suggesting that the metabolite is primarily responsible for drug activity, as previously deduced from preclinical studies [24]. This must be due to the finding that the AUCs of the metabolite are much higher than those of the parent drug [8]. Our results were obtained across the whole range of the phase I doses tested (6–90 mg/m^2), and one might suspect that the relationships observed represent only the classic dose-dependent toxicity. However, when only the nine patients treated at the dose of 80 mg/m^2 (close to the maximum tolerated dose) were taken into account, the same significant correlations were obtained between the AUCs of iododoxorubicin or iododoxorubicinol and the granulocyte or platelet surviving fractions. This finding strongly supports the view that the AUC itself is a major determinant of cytotoxicity in vivo.

A third example comes from the work of Canal et al. [2] using leurubicin. This new anthracycline is suspected to be a prodrug of doxorubicin. Canal et al. [2] showed that the correlation between the leurubicin AUC and the leukocyte surviving fraction was rather poor ($r = -0.51$, $P < 0.05$), whereas the correlation between the AUC of the metabolite doxorubicin and the leukocyte surviving fraction was much more significant ($r = -0.74$, $P < 0.001$). This was heavily influenced by the observation that one patient in their study barely transformed leurubicin into doxorubicin; this patient showed a very high leurubicin AUC, a very low doxorubicin AUC, and no leukocyte killing by the drug. Doxorubicin therefore appears to be the major active compound after leurubicin administration. This study provides evidence that leurubicin is a prodrug of doxorubicin and suggests that metabolic tests of prodrug activation should be performed before drug administration in each patient. Since the metabolic transformation of leurubicin into doxorubicin occurs especially in red blood cells, their in vitro ability can easily be tested. Such information will be important for the clinical handling of the drug.

Potential uses of pharmacokinetic-pharmacodynamic modeling

At present, the possible uses of clearly established pharmacokinetic-pharmacodynamic relationships involve both the design of treatment protocols and individual drug monitoring. In the first case, the clinician can choose the dose to be given so as not to exceed acceptable hematologic toxicity. For instance, in the case of iododoxorubicin [23], we observed that below a dose of 60 mg/m^2 the platelet toxicity was negligible; if clinicians want to avoid this risk in a special type of patient, they should select this dose level for therapeutic purposes.

In the second case, prediction of myelosuppression in individual patients can also be very helpful to the clinician and is made possible despite the wide individual variation in pharmacokinetic parameters. The use of a test dose prior to the injection of the therapeutic dose may help determine the optimal dose in each individual patient. It is obvious that all patients cannot be subjected to a complete pharmacokinetic evaluation, but the development of limited sampling models for doxorubicin [13, 17] and, more recently, epirubicin [12, 26] allows a good prediction of the AUC from two blood samples obtained at selected times after administration. Such evaluations have been made possible by the refinement of Bayesian approaches to population pharmacokinetics. Prediction of myelosuppression can also be improved by incorporating parameters of the patient's clinical status in refined models, as has been stated by Hande [10] in a recent editorial. The recent development of granulocyte or granulocyte-macrophage colony-stimulating factors (G-CSF, GM-CSF) can also be integrated into the process of dose individualization; the AUC of the drug in a patient can be determined and known at 1 week before the occurrence of the blood cell drop. The use of CSF might therefore be restricted to patients who are expected to develop severe neutropenia.

There is no doubt that in the future clinical pharmacology will continue its development as a routine aid to the oncologist for the optimal handling of anticancer drugs. There is a need in all cancer-treatment centres to establish clinical pharmacology units devoted to the routine monitoring of individual patients at special risk of developing toxicity. In this respect, anthracyclines constitute a paradigm because of the (relatively) long experience with these agents and their considerable therapeutic value.

We have shown in this review that performing precise pharmacodynamic evaluations during the pharmacokinetics study of a new anthracycline provides important clues concerning the cytotoxicity of the drug and the role of its metabolites or of the schedule of its administration. Of course, basic mechanistic explanations cannot be obtained in this way, but the early establishment of clear pharmaco-

kinetic-pharmacodynamic relationships can play a positive role in the development of a new anthracycline and can help clinicians use the drug in an optimal way. It is unfortunate that such pharmacokinetic parameters were not clearly established for the reference molecules of the anthracycline series, daunorubicin and doxorubicin, and were determined only very recently for epirubicin [12]; since these drugs cannot presently be used as single agents, important comparisons with the new derivatives cannot be carried out. It must be kept in mind that the actually most relevant pharmacodynamic parameter would be the efficacy of the drug rather than its toxicity, since the former is the expected end point of chemotherapy. The development of methods for the quantitative early evaluation of response to treatment could help in this respect. It must be added that toxicologic drug monitoring could also lead to increasing doses for patients having unusually low AUCs; this would improve response rates, as has been pointed out by Hande [10], and is presently under investigation for several anticancer drugs.

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