REVIEW

Benefits of Pharmacological Knowledge in the Design and Monitoring of Cancer Chemotherapy

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Prescribing chemotherapy is a difficult task, because of drug resistance, which prevents all tumors to respond to a given protocol and because of drug toxicity, which is generally unavoidable but which must be limited to acceptable levels. The therapeutic window of anticancer drugs is very narrow and clinicians have to try to optimize the individual doses and schedules of the drugs to be administered. They can rely upon simple anthropometric features, such as body weight or surface area; they can also take into account the physiological status of the patient: age, liver and kidney function, genetic characteristics of drug metabolism, etc. The best way for dose adaptation lies in the establishment of pharmacokinetic/pharmacodynamic relationships, i.e., between the behavior of a drug in the body and its efficacy and toxicity. When it is established that the optimal effect of a drug is related to a given parameter, such as the area under the curve plotting plasma concentration vs. time (AUC), it becomes possible to administer the drug with the dose allowing to obtain the target parameter value. Individual dose adaptation can be achieved thanks to the study of the pharmacokinetics of a test dose preceding that of the therapeutic dose, or by the measure of drug plasma levels, either at steady state during a protracted infusion, or from cycle to cycle during repetitive protocols. Population analysis now allows the adaptation of anticancer drug dosing from a minimum knowledge of individual pharmacokinetic features, together with other characteristics of the patients such as age, gender or physiological functions. (Pathology Oncology Research Vol 4, No 3, 171-178 1998)

Key words: anticancer drugs; pharmacokinetics; pharmacodynamics; dose adaptation; chemotherapy

Introduction

The first anticancer drugs were introduced to clinics 50 years ago for the treatment of leukemias. Chemotherapy was originally restricted to some rare indications, but is now a major therapeutic weapon against cancer, generally used in combined strategies with surgery and radiotherapy. It can be also used alone, sometimes when the tumor can be cured by chemotherapy, and more often when the cancer is disseminated and not accessible to

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local treatments. Strong efforts have been made in discovery and development of new anticancer drugs with the hope of obtaining drugs able to cure most solid tumors.

About 50 anticancer drugs are now available to the clinicians. However, prescribing chemotherapy remains a difficult task, because two severe limitations hinder the use of these drugs: 1) drug resistance, which prevents all tumors from responding to a given treatment; a response rate of 30% is considered as satisfactory in colon cancer, but would be regarded as insufficient in breast cancer; 2) drug toxicity, which is generally unavoidable but which must be limited to acceptable levels. The window between drug activity and toxicity is very narrow and the clinicians must find the optimal individual dose and schedule to be administered.

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Whereas the radiation oncologists can measure with precision what they are doing, thanks to dosimetry, the medical oncologists have no such instruments to evaluate the dose of drug actually delivered to the tumor. This is why pharmacologists have developed several tools to improve knowledge of drug/host relationships. Pharmacokinetics describes what happens to a drug in the body, while pharmacodynamics studies what does a drug to the organism, including the tumor. Research of relationships between pharmacokinetics and pharmacodynamics in oncology should result in optimal use of anticancer drugs. We describe in this review the principles of such studies and give some examples of their development.

1. Pharmacokinetic and pharmacodynamic terminology

1.1. Pharmacokinetics

This consists of a mathematical description of the *in vivo* fate of a drug.¹ It concerns the processes of absorption, distribution, metabolism and elimination of the drug. Central to this description is the curve representing drug plasma concentration *versus* time, from which numerous pharmacokinetic parameters are derived, such as:

- The peak plasma concentration, C_{max}, which represents the highest drug concentration reached in plasma after a bolus administration,
- The plasma concentration at steady-state, C_{ss}, when the drug is administered via a constant rate IV infusion,
- The area under the plasma concentration *versus* time curve, AUC, which represents the total exposure of the patient to the drug,
- The half-life, T_{1/2}, which represent the time required for a two-fold decrease of drug plasma concentration. For most drugs, several successive half-lives are obtained, from some minutes to several hours or even days.
- The total plasma clearance, which is related to the AUC through the simple formula :

Dose = *AUC* × *Clearance*

For drugs given via a constant rate IV infusion, the relationship between clearance, plasma concentration and dose rate is as follows, once C_{ss} has been achieved:

$Plasma C_{ss} = Dose rate / Clearance.$

When one knows the plasma clearance of a drug, the dose required for a given AUC or C_{ss} may be readily calculated.

• The total volume of distribution at steady state, Vd_{ss}, which represents the volume of a vessel containing all the drug present in the body at the concentration it has in plasma; it evaluates in fact the degree of tissue binding of the drug.

1.2. Pharmacodynamics

Pharmacodynamics describes the effects of a drug on the body, including both activity and toxicity.¹ The potential pharmacodynamic consequences of the presence of drug in the patient can be described by a graph where intensity of drug effect is plotted against drug dose. For these drugs that do not produce toxicity at doses close to those required for efficacy, there is little interest for dose optimization or individualization. Under these circumstances, patients are treated with doses high enough to ensure the achievement of therapeutic concentrations (*Figure 1A*). In contrast, most drugs used in anticancer chemotherapy frequently produce toxicity at doses close to those required for a therapeutic effect (*Figure 1B*). For these drugs, the therapeutic window between activity and toxicity is quite narrow.

In addition, large interpatient variability in drug distribution and elimination is frequently observed, resulting from genetic and physiopathologic conditions. Both tox-



Figure 1. Graphic representation of the pharmacodynamic effect of a drug. A. The therapeutic effect can be exerted without any significant toxic effect; there is no need for dose adaptation. B. The therapeutic effect cannot be obtained without toxic events; dose optimization is required.

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Figure 2. Definition of the therapeutic window of an anticancer drug: For a dose or an AUC A, there is no activity and no toxicity; For a dose or an AUC D, the toxicity is unacceptable while drug activity plateaus at a maximum; The therapeutic window is between B and C, with acceptable toxicity and drug response close to its maximum likelihood.

icity and efficacy of a drug are frequently better correlated with a given pharmacokinetic parameter, such as AUC, than with the dose administered. As a consequence, there may be wide differences among patients regarding the dose required to achieve an optimal response with acceptable toxicity. In these conditions, there is a need for dose optimization in individual patients: this requires first the establishment of pharmacokinetic-pharmacodynamic relationships.

The theoretical pharmacodynamic response is presented in *Figure 2*: the slope of the efficacy curve and the maximum effect are dependent on the sensitivity of the tumor to the drug. An increase in dose or AUC from A to B will increase efficacy with a moderate increase in toxicity, while an increase from C to D will give an unacceptable toxicity with no increase in probability of response. Thus, therapeutic drug monitoring consists in trying to treat all patients between B and C.

On the basis of these criteria, anticancer drugs are clear candidates for pharmacologically guided dosing, but specific problems arise. Response to treatment is generally observed after several courses of treatment. Thus, it may not be possible to use conventional pharmacodynamic end-points to determine the optimal dose to be administered to an individual patient. Another specific point concerns the benefits of adaptive dosing, which must be viewed in the context of the use of anticancer drugs.

For palliative treatment, keeping toxicity within acceptable limits is a primary requirement. Thus, dose optimization should focus on the management of toxicity. In contrast, for curative therapy, more severe toxic events may be accepted, provided that the drug can reach its maximal therapeutic effect: dose optimization should focus on efficacy endpoints.

1.3. Establishing pharmacokinetic-pharmacodynamic relationships

The best pharmacokinetic parameters to be used for the establishment of pharmacokinetic-pharmacodynamic relationships are generally AUC or C_{ss} . Other parameters are C_{max} , duration of plasma concentration above a threshold, or AUC intensity. Pharmacodynamics will be described by either discontinuous parameters (response, no response) or continuous parameters such as time to progression or survival. When considering toxicity, two types of parameters may also be considered: quantitative parameters such as leukocyte, granulocyte or platelet counts, or semi-quantitative parameters defined by WHO grading.²

Mathematical functions have been used to describe pharmacodynamic effects and the most commonly used function is the modified Hill equation, which describes a sigmoid equation. The mathematical relationship is described by Hill equation where $E_{\rm max}$ represents the maximum possible effect, *C* represents a pharmacokinetic parameter or the dose and C_{50} represents the concentration, the AUC or the dose which induces 50% of $E_{\rm max}$. H is Hill's coefficient which defines the degree of sigmoid shape of the curve.

$$E = E_{\max} \left\{ \frac{C''}{C'' + (C_{50})''} \right\}$$

However, pharmacokinetic-pharmacodynamic relationships may also be represented by linear or exponential models with the following equation:

 C_{j}

in which % survival fraction or SF (which expresses the ratio between nadir and pretreatment cell counts for example) represents the pharmacodynamic parameter which is proportional to the exponential of the drug concentration *C* (or the drug AUC) and of the time *t*. *k* is a constant determining the slope of the dose-response curve. This model is analog to the one allowing the study of the *in vitro* cytotoxicity of a drug.

2. Individual dose adaptation in clinical oncology

Several criteria for dose adaptation of anticancer drugs can be used. The most simple only uses the anthropometric characteristics of the patient: body weight or surface area; taking into consideration the physiological functions of xenobiotic elimination will allow some refinements; but the true dose adaptation should rely on pharmacokinetic estimates of the drug in the body.

2.1. Dose adaptation to body weight and surface area

This is an empiric method which is the most frequently used by oncologists. Anticancer drugs are commonly administered on the basis of the dose recommended after phase I trials and calculated in mg/m² or mg/kg. This recommendation generally involves no pharmacokinetic consideration at all. Dose reductions or delays are prescribed in case of unacceptable toxicity, but doses are not increased in absence of toxicity. Due to the poor therapeutic index of anticancer drugs, this means that patients showing no signs of toxicity may receive suboptimal doses. Reference to body surface area originates from experimental considerations, especially for comparing animals of different species.³ It does not appear to be appropriate in human adult therapy. The variability of drug plasma levels is unrelated to body surface area. The scattering of individual pharmacokinetic parameters may be even lower when expressed as rough levels than related to body surface area. The clearance of a drug has never been shown to be correlated to body surface area as would be the case if this criterion for dose adaptation was appropriate.⁴

2.2. Dose adaptation to physiological functions

This kind of adaptation attempts to take into account the patient characteristics known to affect the pharmacokinetics or pharmacodynamics of a drug. There are many sources of individual variability of pharmacokinetics that may be involved in determining the effects of a given drug. Anticancer drugs have preferential routes of elimination, and the dysfunction of an elimination pathway leads to increased drug plasma levels or AUC that can lead to unexpected toxicity. This is currently taken into account by dosage reductions that are prescribed in case of renal or hepatic disturbances, generally evaluated by creatininemia and bilirubinemia, respectively. For instance, the dose of doxorubicin is generally reduced by 50% when bilirubinemia reaches 25 µmol/l and by 100% when it reaches 35 umol/l. However, other parameters might be better indicators of excretion functions than the simple levels of creatinin or bilirubin in plasma. Liver enzymes have been shown to be fairly well correlated to doxorubicin clearance, and should replace bilirubinemia as a criterion for dose adaptation.⁵ The pharmacokinetics of carboplatin are strictly dependent upon glomerular filtration rate, so that its AUC is entirely predictable from renal function: it becomes possible to adapt precisely the dose of carboplatin to be administered as a function of a desired AUC in plasma.6

Another important factor modulating drug availability to its targets is sometimes the level of albumin in plasma when there is a high degree of binding of the drug to serum albumin. This is the case for etoposide: in case of liver dysfunction lowering albuminemia, unexpected toxicities of this drug have been encountered.⁷

Recent developments in the field of pharmacogenetics should also be noted in the context of adaptive dosing. Several enzymes involved in drug detoxification may be genetically deficient. This is the case for thiopurine methyltransferase, which catabolizes mercaptopurine: constitutionally low levels of enzyme are associated with higher toxicity and lower efficacy of the drug.⁸ This may also be the case for fluorouracil: genetic deficiency in dihydropyridine dehydrogenase, the enzyme responsible for its detoxification, determines a lethal toxicity of the drug.⁹ The metabolism of new drugs, such as irinotecan¹⁰ or amonafide,¹¹ also presents a genetic polymorphism that strongly intervenes in drug disposition. Such observations may lead to the selection of patients able to receive a given drug according to their phenotype of drug metabolism; they may also be used for dose adaptation in order to compensate for the individual features of drug metabolism.

Patient's age is also a physiological variable that can be taken into consideration for dose adaptation. Some drugs have a reduced clearance in elderly patients,¹² although it is generally possible to give full drug doses of most anticancer drugs without considering age: aging is not an independent feature, but is characterized by the summation of physiological alterations that may or may not occur together: decrease in albumin plasma levels, decrease in intracellular water mass, in liver volume and blood flow, in glomerular filtration rate, etc. Therefore, dose adaptation should preferably rely on physiological alterations rather than on age *per se*.

Table 1. Relationship between anticancer drug pharmacokinetics and drug activity: some examples from the literature

Drug parameter	Tumor type	РК	Refe- rence
Aracytine	Relapsed		
2	leukemias	Blast ara-CTP	13
Methotrexate	ALL	C _{ss}	14
	Osteosarcoma	C _{max}	15
Fluorouracil	Head and neck	AUC	16
	Colorectal	Plasma	
		concentration	17
Doxorubicin	Breast	C _{max}	18
	AML	Plasma	
		concentration	19
Epirubicin	Nasopharynx	AUC	20
Cisplatin	Head and neck	Plasma	
		concentration	21
	Ovary	AUC	22
Carboplatin	Ovary	AUC	23
Etoposide	Lung	C _{ss}	24
Teniposide	Pediatric	AUC	25
	tumors		
Cyclophos-			
phamide	Breast	AUC	26
Vinblastine	Breast	AUC	27

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Drug	Toxicity	PK parameter	Reference
Methotrexate	Leucopenia	Plasma concentration	28
Fluorouracil	Leucopenia, mucositis	AUC	29
	-	Plasma concentration	17
Mercaptopurine	Leucopenia	Thioguanine metabolites in red b	lood cells 30
Doxorubicin	Leucopenia	C _{ss}	31
Epirubicin	Leucopenia	Plasma concentration	32
Pirarubicin	Leucopenia	AUC	33
Mitoxantrone	Aplasia duration	AUC	34
Cisplatin	Neurotoxicity	C _{max}	35
-	Mucositis	AUC	22
	Nephrotoxicity	AUC	36
Carboplatin	Thrombopenia	ASC	37
Etoposide	Leucopenia	AUC	38
-	Leucopenia	Css	39
Cyclophosphamide	Cardiotoxicity	AUC	26
Vinblastine	Leucopenia	C _{ss}	40
Vincristine	Neurotoxicity	AUC	41
Paclitaxel	Leucopenia	Time above a threshold	42
	-	plasma concentration	
Docetaxel	Leucopenia	AUC	43
Irinotecan	Leucopenia	AUC	44
Topotecan	Leucopenia	AUC	45

Table 2 Relationship between anticancer drug pharmacokinetics and drug toxicity: some examples from the literature

2.3. Dose adaptation to plasma drug concentrations

This is indeed the most potent method for achieving the optimization of drug administration. Plasma concentrations have a great predictive value because they result from a number of physiologic and genetic characteristics of the patient: hepatic and renal function, importance of body fat, metabolic capacities, etc.

A relationship between pharmacokinetic parameters and drug efficacy has been shown for several antimetabolites,¹³⁻¹⁷ as well as for anthracyclines,¹⁸⁻²⁰ organic platins,²¹⁻²³ epipodophyllotoxins,^{24,25} cyclophosphamide26 and vinca alkaloids²⁷ (*Table 1*). The pharmacokinetic parameter most generally involved is plasma concentration itself or its time integral, AUC. It is obvious that pharmacokinetics cannot be the only determinant of drug efficacy, but is often responsible for most of the variability in tumor response between patients, the remaining part being determined by cellular and molecular tumor determinants.

More frequently, a relationship between a pharmacokinetic parameter, especially AUC, and drug toxicity has been evidenced (*Table 2*).²⁷⁻⁴⁵ Generally, this relationship is much more significant than the one existing between drug dose and toxicity, justifying the use of pharmacokinetics for predicting toxicity. The toxicity endpoint that has been most often considered is the decrease in blood cell counts. However, in some instances, drug toxicity is delayed and dependent upon cumulative administrations: this is the case, for instance, for anthracycline cardiotoxicity; in this case, the use of pharmacokinetics for predicting the level of toxicity does not appear possible.

Bolus injections are followed by high peak plasma concentrations, whereas protracted slow infusions generate moderate and constant plasma levels. In general, the pharmacokinetics are linear and both types of administrations lead to similar AUC values. For several drugs, it has been shown that prolonging the duration of the infusion led to decreased toxicity with a maintained efficacy of the drug. It has been concluded that peak levels were mostly responsible for toxicity and AUC values for efficacy.⁴⁶ This is not true, however, for all drugs, and care should be taken to study the schedule-dependence of drug activity before modifying the schedules of administration.

3. Methods for dose adaptation

Several methods can be used for dose monitoring of anticancer drugs; they all rely on a good knowledge of the pharmacokinetics of the drug and on the pharmacokineticpharmacodynamic relationships.

3.1. Test dose

This method was originally developed for methotrexate in the treatment of childhood osteosarcomas: the very high doses of this drug that are necessary to cure patients are also highly toxic and require good monitoring. In French experience, the administration of a test dose of methotrexate, 50 mg, is followed by a detailed pharmacokinetic study from 0.25 h to 30 h after administration.^{47,48} This allows identification of the pharmacokinetic characteristics of the individual patient. It becomes then possible, assuming that the kinetics of methotrexate are linear, to calculate the therapeutic dose to be delivered over 36-hr infusion in order to reach a given steady-state plasma concentration: this dose ordinarily ranges between 1 and 2 g for a plasma concentration of 10⁻⁵ M. It is possible, during this infusion, to analyze additional blood samples to verify that the plasma levels are within the limits that have been chosen before: if not, dose adjustment can be performed and folinic acid rescue can be implemented. This feed-back control ensures that the treatment will remain far from unacceptable toxicity.

Such test-dose methods have also been developed for other drugs such as melphalan,⁴⁹ but other methods are now preferred, which require less frequent blood samplings.

3.2. Dose adaptation from cycle to cycle or during a continuous infusion

When an important number of courses of treatment is programmed, or when the infusion is administered over a long period, it is possible to adapt the dose as a function of the pharmacokinetic parameters of the patient, as evaluated at the beginning of the treatment. This has been especially developed for fluorouracil. Some protocols of administration of this drug plan a 5-day continuous infusion; it is possible to measure steady-state plasma drug concentrations during the first half of the infusion, and to adapt at this point the dose of the remaining part of the infusion in order to obtain a given total AUC. Such dose monitoring of fluorouracil has been shown to provide increased efficacy and lower toxicity in head-and-neck cancers.^{16,29} Similar approaches have been developed for cisplatin⁵⁰ and etoposide.³⁹

In other protocols, fluorouracil is administered as repetitive weekly short infusions for several months. It is thus possible to analyze drug concentration each week in a given plasma sample, and to adapt the dose to be administered the following week. Such monitoring has been shown to improve both efficacy, tolerance and survival in patients suffering from colorectal cancer, and can easily be performed routinely in the clinical setting.⁵¹

3.3. Dose adaptation from population studies

This approach to dose adaptation of anticancer drugs is the most complex method. In this approach, populationbased predictive models are used. In a first phase, the pharmacokinetics of the drug is studied in a well-defined

population of patients and the pharmacokinetic parameters calculated according to Bayesian procedures. Then, a limited sampling strategy is generated, allowing the estimation of pharmacokinetic parameters from one or two plasma samples obtained at selected times. Once the population kinetics are known, it is possible to estimate these parameters in any patient from similar plasma samples obtained during the first course of treatment or during the first part of a continuous infusion. The doses to be administered during the following courses or the second part of the infusion can then be calculated on the basis of a target C_{ss} or AUC in order to obtain the desired pharmacodynamic effect. The Bayesian approach allows to introduce in the model, in addition to drug plasma concentrations, a variety of independent variables that may contribute to the pharmacokinetics of the drug: sex, age, albuminemia, creatininemia, bilirubinemia for instance. This strongly improves the potency of the method for predicting pharmacokinetic parameters from single points. In addition, the samplings have not to be performed at fixed times but within relatively large limits. Despite its mathematical complexity, this approach may be the only way to deliver a predefined exposure of an anticancer drug to an individual patient. This methodology has been used for several years for methotrexate therapy.⁵² It has also been developed for anthracyclines,^{53,54} carboplatin⁵⁵ and etoposide.⁵⁶

Conclusion

Despite the continuous process of discovery and development of new anticancer drugs, it appears that we are still far from curing cancer by chemotherapy. However, the presently available drugs are not used optimally; it is possible, in many cases, to increase both the proportion of responders and the tolerance to treatment by monitoring the doses as a function of individual characteristics of the patient. Individual dose adaptation obviously involves higher costs, but the decrease of toxic events surely compensates for the cost of pharmacologically-guided dose adaptation, which brings significant benefits to the cancer patient.

References

- Grochow LB, Ames MM: A clinician's guide to chemotherapy. Pharmacokinetics and pharmacodynamics. Williams & Wilkins, Baltimore, 1998.
- Ratain MJ, Schilsky RL, Conley BA, Egorin MJ: Pharmacodynamics in cancer therapy. J Clin Oncol 8:1739-1753, 1990.
- Reilly JJ, Workman P: Normalisation of anticancer drug dosage using body weight and surface area is it worthwhile ? A review of theoretical and practical considerations. Cancer Chemother Pharmacol 32:411-418, 1993.
- Ratain MJ: Body-surface area as a basis for dosing anticancer agents: science, myth, or habit? J Clin Oncol 16:2297-2298, 1998.

- Twelves CJ, Dobbs NA, Gillies HC, et al: Doxorubicin pharmacokinetics: the effect of abnormal liver biochemistry tests. Cancer Chemother Pharmacol 42:229-234, 1998.
- Chatelut E, Canal P, Brunner V et al: Prediction of carboplatin clearance from standard morphological and biological patient characteristics. J Nat Cancer Inst 87:573-580, 1995.
- Stewart LF, Arbuck SG, Fleming RA et al: Changes in the clearance of total and unbound etoposide in patients with liver dysfunction. J Clin Oncol 8:1874-1879, 1990.
- Evans WE, Horner M, Chu YQ et al: Altered mcrcaptopurine metabolism, toxic effects, and dosage requirement in a thiopurine methyltransferase-deficient child with acute lymphocytic leukemia. J Pediat 119:985-989, 1991.
- Diasio RB, Beavers TL, Carpenter JT: Familial deficiency of dihydropyrimidine dehydrogenase: biochemical basis for familial pyrimidinemia and severe 5-fluorouracil-induced toxicity. J Clin Invest 81:47-51, 1988.
- Iyer L, King CD, Whitington PF et al: Genetic predisposition to the metabolism of irinotecan (CPT-11). Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. J Clin Invest 101:847-854, 1998.
- 11. *Ratain MJ*, *Mick R*, *Berezin F et al*: Paradoxical relationship between acetylator phenotype and amonafide toxicity. Clin Pharmacol Ther 50:573-579, 1991.
- 12. Egorin MJ: Cancer pharmacology in the elderly. Semin Oncol 20:43-49, 1993.
- Kantarjian HM, Estey EH, Plunkett W et al: Phase I-II clinical and pharmacologic studies of high-dose cytosine arabinoside in refractory leukemia. Am J Med 81:387-394, 1986.
- Evans WE, Crom WR, Abromowitch M et al.: Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. Identification of a relation between concentration and effect. N Engl J Med 314:471-477, 1986.
- Graf N, Winkler K, Berlemovic M. et al: Methotrexate pharmacokinetics and prognosis in osteosarcoma. J Clin Oncol 12:1443-1451, 1994.
- Milano G, Etienne MC. Renee N et al: Relationship between fluorouracil systemic exposure and tumor response and patient survival. J Clin Oncol 12:1291-1295, 1994.
- Gamelin E, Danquechin-Dorval EM, Dumesnil YF et al: Relationship between 5-fluorouracil dose intensity and therapeutic response in patients with advanced colorectal cancer receiving infusional therapy containing 5-FU. Cancer 77:441-451, 1996.
- Robert J, Iliadis A. Hoerni B, et al: Pharmacokinetics of adriamycin in breast cancer. Eur J Cancer Clin Oncol 18:739-745, 1982.
- Preisler HD, Gessner T, Azarnia N et al: Relationship between plasma adriamycin levels and the outcome of remission induction therapy for acute nonlymphocytic leukemia. Cancer Chemother Pharmacol 12:125-130, 1984.
- Hu OYP, Chang SP, Jame JN, Chen KY: Pharmacokinetic and pharmacodynamic studies with 4⁺-epidoxorubicin in nasopharyngeal carcinoma patients. Cancer Chemother Pharmacol 24:332-337, 1989.
- Vermorken JB. van der Wijgh WJF. Klein I et al: Pharmacokinetics of free and total platinum species after rapid and prolonged infusions of cisplatin. Clin Pharmacol Ther 39:136-144, 1986.
- Desoize B, Maréchal F, Millard H and Cattan A: Correlation of clinical pharmacokinetic parameters of eisplatin with efficacy and toxicity. Biomed Pharmacother 45:203-205, 1991.
- 23. Jodrell DI, Egorin MJ, Canetta RM et al: Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. J Clin Oncol 10:520-528, 1992.

 Roaman JT, Abromowitch M, Stakale JA, et al. Clinical phatmacodynamics of continuous infusion of teniposide. J Clin Oncol 5:1007-1014, 1987.

24. Desoize B, Maréchal F and Cattan A: Clinical pharmacokinet-

- Ayash LJ, Wright JE, Tretyakov O, et al: Cyclophosphamide pharmacokinetics: correlation with cardiac toxicity and tumor response. J Clin Oncol 10:995-1000, 1992.
- Lu K, Yap HY, Loo TL: Clinical pharmacokinetics of vinblastine by continuous intravenous infusion. Cancer Res 43:1405-1408, 1983.
- Stoller RG, Hande KR, Jacobs SA, et al: Use of plasma pharmacokinetics to predict and prevent methotrexate toxicity. N Engl J Med 297:630-634, 1977.
- Santini J, Milano G, Thyss A et al: 5-FU therapeutic monitoring with dose adjustment leads to improved therapeutic index in head and neck cancer. Br J Cancer 59:287-290, 1989.
- Lennard L. Lilleyman JS: Variable mercaptopurine metabolism and treatment outcome in childhood lymphoblastic leukemia. J Clin Oncol 7:1816-1823, 1989.
- Ackland SP, Ratain MJ, Vogelzang NJ, et al: Pharmacokinetics and pharmacodynamics of long-term continuous infusion doxorubicin. Clin Pharmacol Ther 45:340-347, 1989.
- 32. Jakobsen P, Bastolt L, Dalmark M et al: A randomized study of cpirubicin at four different levels in advanced breast cancer. Feasibility of myelotoxicity prediction through single blood sample measurement. Cancer Chemother Pharmacol 28:465-469, 1991.
- 33. Robert J, Monnier A, Poutignat N, et al: A pharmacokinetic and pharmacokinetic study of the new anthracycline pirarubicin in breast cancer patients. Cancer Chemother Pharmacol 29:75-79, 1991.
- 34. Canal P, Attal M, Chatelut E et al.: Plasma and cellular pharmacokinetics of mitoxantronc in high-dose chemotherapeutic regirmen for refractory lymphomas. Cancer Res 53:4850-4854, 1993.
- 35. Gregg RW, Molepo JM, Monpetit VJ, et al.: Cisplatin neurotoxicity: the relationship between dosage, time, and platinum concentration in neurologic tissues and morphologic evidence of toxicity. J Clin Oncol 10:795-803, 1992.
- Kelsen DP, Alcock N and Young CW: Cisplatin nephrotoxicity: correlation with plasma concentrations. Am J Clin Oncol 8:77-80, 1985.
- Newell DR, Siddik ZH, Gumbrell LA, et al: Plasma free platinum pharmacokinetics in patients treated with high-dose carboplatin. Eur J Cancer Clin Oncol 23:1387-1399, 1987.
- Bennett CL, Sinkule JA, Schilsky RL, et al: Phase I clinical and pharmacological study of 72-h continuous infusion of etoposide in patients with advanced cancer. Cancer Res 47:1952-1956, 1987.
- Ratain MJ Mick R, Schilsky RL, et al: Pharmacologically based dosing of etoposide: a means of safety increasing dose intensity. J Clin Oncol 9:1480-1486, 1991.
- Ratain MJ, Vogelzang NJ: Phase 1 and pharmacological study of vinblastine by prolonged continuous infusion. Cancer Res 46:4827-4830, 1986.
- Desai ZR, van den Berg HW, Bridges JM, et al: Can severe vincristine neurotoxicity be prevented Cancer Chemother Pharmacol 8:211-214, 1982.
- 42. Gianni L, Kearns CM, Giani A, et al: Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetics/pharmacodynamics relationships in humans. J Clin Oncol 13:180-190, 1995.

- 43. Bruno R, Hille D, Riva A et al: Population pharmacokinetics/pharmacodynamics of docetaxel in phase II studies in patients with cancer. J Clin Oncol 16:187-196, 1998.
- 44. Chabot GG, Abigerges D, Catimel G, et al: Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. Ann Oncol 6:141-151, 1995.
- 45. van Warmerdam LJ, Verweij J, Schellens JH et al: Pharmacokinetics and pharmacodynamics of topotecan administered daily for 5 days every 3 weeks. Cancer Chemother Pharmacol 35:237-245, 1995.
- 46. *Ratain MJ*, *Vogelzang NJ*: Experimental rationale for continuous infusion therapy. In: Cancer chemotherapy by infusion (Ed: Lokich J) Precept Press, Chicago, 1987, pp. 12-34.
- 47. Monjanel S, Imbert AM, Favre R, et al: High-dose methotrexate: preliminary evaluation of a pharmacokinetic approach. Cancer Chemother Pharmacol 3:189-196, 1979.
- Favre R, Monjanel S, Alfonsi M, et al: High-dose methotrexate: a clinical and pharmacokinetic evaluation. Cancer Chemother Pharmacol 9:156-160, 1982.
- 49. *Tranchand B, Poin YD, Minuit MP, et al*: High-dose melphalan dosage adjustment: possibility of using a test-dose. Cancer Chemother Rep 23:95-100, 1982.

- Desoize B, Dumont P, Manot L, et al: Comparison of two dose prediction models for cisplatin. Anticancer Res 14:2285-2290, 1994.
- 51. Gamelin E, Boisdron-Celle M, Delva R, et al: Long-term weekly treatment of colorectal metastatic cancer with fluorouracil and leucovorin: results of a multicentric prospective trial of fluorouracil dosage optimization by pharmacokinetic monitoring in 152 patients. J Clin Oncol 16:1470-1478, 1998.
- Iliadis A, Bachir-Rao M, Bruno R, Favre R: Bayesian estimation and prediction of clearance in high-dose methotrexate infusions. J Pharmacokin Biopharm 13:101-115, 1985.
- Bressolle F, Ray P, Jacquet JM, et al: Bayesian estimation of doxorubicin pharmacokinetic parameters. Cancer Chemother Pharmacol 29:53-60, 1991.
- Wade JR, Kelman AW, Kerr DJ, et al: Variability in the pharmacokinetics of epirubicin. Cancer Chemother Pharmacol 29:391-395, 1992.
- 55. Guillet P, Monjanel S, Nicoara A, et al: A Bayesian dosing method for carboplatin given by continuous infusion for 120 h. Cancer Chempother Pharmacol 40:143-149, 1997.
- Evène E, Chatelut E, Tranchand B et al: Estimation Bayésienne des paramètres pharmacocinétiques de l'étoposide. Bull Cancer 84:699-703, 1997.