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Feature Articles

Individual Dose Adaptation of Anticancer Drugs

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The dose of anticancer drugs is currently adjusted to the patient body surface area, although patients have different abilities to clear anticancer drugs. The dose adjustment to physiological functions permits major toxic accidents to be avoided. The adjustment to tumour drug content is considered, but for ethical or technical reasons, it cannot be used routinely The best criterion for the dose adjustment seems to be drug plasma concentration. The relationship between plasma concentration and efficacy may not be excellent, since it depends on the presence of resistant cells and on the blood flow through the tumour. A relationship between plasma concentration and/or the area under the curve (AUC) with toxicity has been reported with all major anticancer drugs. Different methods of dose adjustment to the drug plasma concentration are reported. In conclusion, dose adjustment to the drug plasma concentration or to the AUC can improve the chemotherapy efficacy, while reducing toxicity.

Key words: anticancer drugs, dose adjustment, new therapeutic strategy, pharmacokinetic, pharmacology
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INTRODUCTION

ONE IMPORTANT limitation in clinical pharmacology is the diversity which exists between individuals, and this variability is often enhanced in patients with disease. Furthermore, in cancer therapy, there is a very narrow interval between therapeutic doses and those causing toxicity, this interval generally being called the therapeutic window. Taken together, the idiosyncratic variability and the narrowness of the therapeutic window make it essential to try to adapt doses administered to individual patients.

However, criteria for this individual dose adaptation have to be determined, and no definitive agreement has emerged which could be of general use for avoiding toxicity while maintaining the optimal efficacy of each drug. The most simple criteria are age, body weight, size or surface area, which do not require any laboratory-based investigations. These can be supplemented with estimates of the general excretory functions of the body through standard blood tests, such as creatinine clearance and serum bilirubin for renal and hepatic functions, respectively. Another alternative is the study of the behaviour of the drug in individuals, using previously established pharmacokinetic–pharmacodynamic relationships.

This paper critically reviews the major criteria presently used in routine anticancer chemotherapy, and the modern means of pharmacologically-guided dose adaptation which provide a rational approach for the optimisation of the use of anticancer drugs. Comprehensive reviews on the problem of pharmacokinetic dose monitoring have been published by Kobayaschi and Ratain [1], Liliemark and Peterson [2], Moore and Erlichman [3] and Galplin and Evans [4]. It must be emphasised at the beginning of this review that the 'optimal dose' is a concept which cannot be easily defined in oncology, since toxicities which would be considered as unacceptable in the treatment of other diseases are produced by therapeutic doses of anticancer agents.

DOSE ADAPTATION TO BODY WEIGHT AND SURFACE AREA

The use of body weight as a reference for drug dosing is a general procedure, both in clinical medicine and in experimental pharmacology. This infers a homogenous drug distribution in the body, so that an equal proportion of targets will be reached by the drug. This is, of course, never the case, but helps the prescriber and generally allows reproducible pharmacodynamics of the drug within individuals with similar morphological features. It can be used, for instance, to standardise a drug dose in a laboratory animal species or in an age-defined group of humans. This is, however, insufficient to standardise doses in different animals species or in different age groups of humans. In 1940, Dawson [5] proposed to adapt the drug dosage in pediatrics as a function of body surface area rather than of body weight. It was later shown that this was a good criterion for standardisation of drug administration from the neonate to the young adult [6] and from one animal species to another [7].

Without any theoretical or experimental rationale, this

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method of individual dose adaptation has been transferred to oncology and is now in general use. Some recent papers have, however, pointed out that this reference to body surface area had shown its usefulness only in pediatrics and in experimental pharmacology, and is not appropriate in adult therapy [8–10]. It has even been shown that this 'adaptation' has a result opposite to that required, e.g. for cyclophosphamide [11] and doxorubicin in the obese [12]. Gilles [8] has recently pointed out that the diversities of individual total plasma clearances of doxorubicin, epirubicin and cytarabine were less when expressed as crude values than when referred to body surface area: this shows that the same doses, when administered to adults, give closer plasma levels than doses related to body surface areas. Despite this clear demonstration, the habit of dose adjustment to body surface area is so widespread that it could be difficult to change it to a more rational practice. It is necessary to consider that heavy and tall people, with a large body surface area, do not necessarily have larger liver or kidneys or other internal organs than people with smaller body surface area, the increase of mass being not exclusively related to organs in drug processing. Indeed, the total body clearance of a drug has never been shown to be correlated to body surface area as it should be if dose adaptation according to this criterion is appropriate. There is always a large, individual variability of drug plasma or tumour levels [13–15] which is unrelated to body surface area, and cannot be taken into account by this simple anatomical feature.

DOSE ADAPTATION TO PHYSIOLOGICAL FUNCTIONS

Anticancer drugs generally have a preferential route of elimination, either in urine (methotrexate, cytarabine, cisplatin, carboplatin, bleomycin) or in bile and faeces (doxorubicin, vinca alkaloids, fluorouracil). In consequence, the hepatic and renal elimination functions have to be explored before drug administration, serum creatinine or creatinine clearance for renal function, and bilirubin or transaminases levels for hepatic function. A detailed review of the effect of renal and hepatic disease on the pharmacokinetics of anticancer drugs was published in 1982 [16]. In case of renal failure, the course of treatment is generally postponed or the doses of drugs like methotrexate, melphalan, bleomycin or cisplatin reduced by 50% [17–19]; in the case of impaired hepatic function, the dose of drugs like doxorubicin or fluorouracil is often reduced as a function of bilirubin levels. Reich [20] has proposed guidelines for doxorubicin dosage reduction as a function of serum bilirubin concentration (and serum liver enzyme levels): dose reductions by 50, 75 or 100% were recommended when bilirubinaemia exceeded 12, 30 or 50 mg/l. However, there is still a controversy concerning the role of bilirubinaemia as a predictor of doxorubicin elimination, and liver enzyme levels may be more useful in dosage reduction than bilirubin levels [21, 22].

This type of approach founded on physiological functions is not a true adaptation; it just avoids major toxic accidents by large-scale dosage reduction. A special mention must be made for carboplatin, whose pharmacokinetics have been shown to be strictly dependent upon glomerular filtration rate, so that its area under the concentration versus time curve (AUC) is entirely predictable from renal function [23]. It is, therefore, possible for this drug to adapt precisely to the dose to be administered in order to achieve the same AUC exposure in all patients. Liver tissue is also involved in the activation of some anticancer drugs, such as cyclophosphamide, and its dysfunction can, in this case, be responsible for insufficient production of active drug species [24]. In addition, it must be recalled that most drugs bind to serum albumin and that a hypoalbuminaemia due to liver dysfunction may increase the absolute amount of active free drug in plasma [25]. However, no simple dose adaptation has been proposed in such circumstances which can explain some unpredicted toxic events.

The question of whether age is a cause of modification of pharmacokinetic parameters has received no clear and general answer. It has been shown that some drugs have a reduced clearance in elderly patients [18], but it is generally possible to give the full doses of a chemotherapy regimen to elderly patients in order to optimise their therapy [26–28]. In fact, aging cannot be considered as an independent feature, and is characterised by a conjunction of physiological alterations that may or may not occur together [29–31]. For example, decreasing plasma albumin concentrations are frequent, and the consequence is worsened by the overall use of co-medications that compete with anticancer drugs on albumin sites. Also seen in elderly patients are decreases of the intracellular water mass; decreases in liver volume and hepatic blood flow; decreases in kidney glomerular filtration rate, etc. It therefore appears that dose adaptation as a function of individual physiology is better than adaptation as a function of chronological age. Adjusting cyclophosphamide and methotrexate according to creatinine clearance in older women allowed Gelman and Taylor [32] to reduce myelotoxicity. The case of children has been extensively studied by Evans' group [36]. Maturation of drug metabolism and elimination is progressive and justifies special attention in drug administration in children. It has been observed for several drugs, including methotrexate, cyclophosphamide and teniposide, that total plasma clearance is higher in adolescent children than in adults: the maximum tolerated dose of several drugs for children was about 1.3 times more than for adults [34].

Another physiological function to consider is the capacity for drug metabolism, either for activation or for detoxification. The liver enzyme which activates cyclophosphamide is inducible by several drugs including cyclophosphamide itself, which could lead to a progressive decrease of the doses administered in order to avoid an increase of toxicity from one course of treatment to the other. Several enzymes involved in drug detoxification may also be genetically deficient. This is the case for the thiopurine methyltransferase [35], which catabolises 6-mercaptopurine; low levels of the enzyme (measured, for instance, in erythrocytes) being associated with a higher toxicity and possibly a lower efficiency of the drug [36]. A genetic polymorphism has also been characterised for fluorouracil detoxification by dihydropyrimidine dehydrogenase. An enzyme deficiency has been shown to be associated with a lethal toxicity of the drug in several reports [37]. This could lead to a selection of patients able to receive fluorouracil on the basis of their phenotype. Another example is the acetylation of a still experimental anticancer drug, amonafide [38]. The acetylator phenotype has been extensively studied in other fields of pharmacology and the so-called 'slow acetylators' seem to tolerate much higher amonafide doses than 'fast acetylators', allowing the development of a prospective test for dose adaptation.

DOSE ADAPTATION TO INTRATUMORAL DRUG CONCENTRATION

The targets of anticancer drugs are localised in the tumour cells; therefore it appears rational to try to adapt the dose to the drug concentration to be reached in the tumour. However, this is rather difficult, both for practical and ethical reasons.

Sampling tumour tissue is not easy, especially if several samples are needed, or if the tumour or its metastases are not readily accessible. Even if sampling is possible, tumour heterogeneity introduces a limitation for interpreting the results [39]. Tumour samples can comprise a mixture of viable and dead cells of blood, stromal and other tissues, but it would be necessary to measure drug levels only in the viable tumour cells, and most methods require an overall drug extraction and assay. Flow cytometry offers an interesting alternative for the quantification of fluorescent drugs, such as anthracyclines, in viable tumour cells. However, an important quenching of fluorescence occurs when anthracyclines are intercalated in DNA, which is precisely their ultimate target.

Tumour concentration mainly depends on three parameters, the dose of drug administered, blood flow through the tumour tissue, and transport of the drug through the tumour cell plasma membrane. Tumours are generaly poorly perfused, whereas the tissues subject to drug toxicity, such as bone marrow, kidney or heart, receive a much higher blood flow. Tumour drug concentration cannot, therefore, reflect drug concentration in such organs, and gives no information on the potential toxicity of the chemotherapy performed.

In contrast, several studies have shown that the concentration of a drug (or of a metabolite) can be a good predictor of drug efficacy. This is especially the case for cytarabine [40, 41] and 6-thioguanine [42]. However, the correlation observed cannot be used for dose monitoring, but rather for prediction of resistance to treatment. Cummings and McArdle [43] have shown that the tumour accumulation of doxorubicin was statistically higher in those tumours which were sensitive to this drug (breast and gastric carcinomas) than in tumours usually resistant, such as colon adenocarcinomas. It has been shown that anthracycline accumulation in leukaemic cells was well correlated to P-glycoprotein expression, and was, therefore, a good indicator of multidrug resistance [44]. This correlation can be better used for predicting drug resistance than for indicating an optimal drug dose. In other malignancies, such a relationship between tumour anthracycline concentration and treatment outcome has never been observed [13, 45]. Cisplatin accumulation in tumours has also been studied by several authors; no correlation between platinum accumulation in squamous cell cancer and drug efficiency has been observed [14, 46–48], and this parameter cannot even be used as a predictor of treatment outcome. However, a correlation between cisplatin efficacy and DNA adduct formation in white blood cells has been observed [49]. It is tempting to hypothesise that the number of these cisplatin–DNA adducts in white blood cells reflects the number in tumour cells, and could currently be used as a predictor of drug activity.

In conclusion, it appears that the determination of tumour drug concentration cannot help the clinician in dose adaptation; at best, it can show that a certain amount of the drug has been able to reach the tumour, or that a certain amount of active metabolite has been formed to support drug activity. However, dose monitoring cannot rely on such measurements, which are both difficult to obtain and insufficiently informative.

DOSE ADAPTATION TO PLASMA DRUG CONCENTRATION

Evaluating drug concentrations in plasma appears more realistic than in tumour tissue. Blood samples can be obtained before, during and after chemotherapy without practical or ethical problems. Plasma is a homogeneous compartment which directly receives the drug in most cases, and from which it is either distributed to other compartments or eliminated.

The relationship between drug concentrations in plasma and tumour has not been studied extensively. In the case of doxorubicin, there is a good correlation between these two parameters [13, 15], although the modalities of administration may strongly influence this correlation [50]. In the case of cisplatin, no relationship between plasma and tumour concentration has ever been observed [14, 46, 48]. Several factors may influence drug transport from the plasma to the tumour compartments: drug diffusibility through cell membranes depends on their lipophilicity, special mechanisms of transport may operate, especially for antimetabolites, and efflux pumps such as P-glycoprotein may prevent natural products from accumulating in tumour cells. Despite the variability of these mechanisms of drug transport in tumours, numerous studies have clearly established the close relationship between drug plasma concentration and its efficacy.

Such a relationship between pharmacokinetic parameters and drug efficacy has been shown for several antimetabolites, as well as for anthracyclines, cisplatin, epipodophyllotoxins and vinca alkaloids [51, 55]. The pharmacokinetic parameter most generally involved is plasma concentration itself or its time integral, the AUC. Total plasma clearance, which is inversely proportional to the AUC, is also often considered as the most relevant pharmacokinetic parameter in this respect. Table 1 presents the main results that have been published in the literature concerning the relationship between drug pharmacokinetics and efficacy. It is clear that drug pharmacokinetics cannot be the only determinant of drug efficacy; in general, the coefficient of correlation between a pharmacokinetic parameter and efficacy does not exceed 0.7, which means that not more than one half of the variability of tumour response can be explained by drug distribution and elimination, the other half depending predominantly on the cellular and molecular determinants of drug sensitivity.

More and more investigators are reporting the existence of a correlation between a pharmacokinetic parameter of an anticancer drug and its toxicity. This is especially true for new drugs which benefit from pharmacokinetic studies to a larger extent than older drugs have done. Table 2 presents the main results from the recent literature. Drug toxicity is generally better correlated to plasma concentration or AUC than to the dose administered. The toxicity endpoint generally considered is the decrease in blood cell counts, either absolute (granulocyte or platelet nadirs) or relative to the pretreatment counts (per cent cell death).

However, there are only very few indications that cumulative toxicities, which occur with drugs like doxorubicin, bleomycin or cisplatin, depend on individual pharmacokinetic parameters. The pharmacokinetic parameters which are most often considered are drug plasma concentration and/or the AUC. With most anticancer drugs having linear kinetics (in other words, their clearance is constant over a major dose range), the AUC does not depend on the duration of drug administration (bolus or slow infusion).

The bolus injection is followed by very high peak plasma drug levels, which may have important consequences both for drug efficacy and toxicity. The slow infusions of antimetabolites, which are phase-dependent and have short half-lives, have been shown to strongly improve their efficacy while their toxicity is unchanged or decreased [56]. This led to the idea that the AUC could be mostly responsible for antitumour activity, while peak

Table 1. Pharmacokinetic–pharmacodynamic relationships established for anticancer agents: drug efficacy data

Drug	Pharmacodynamic parameter	Reference
Platinum complexes		
Cisplatin: total	PlC, AUC	75,77
ultrafiltrable	AUC	82
	WBCC of adducts	55
Antimetabolites		
Cytarabine	PlC	83,84
Methotrexate	AUC	69,85,86
6-Mercaptopurine	RBCC of metabolite	42
5-Fluorouracil	AUC	76,87
Anthracyclines		
Doxorubicin	PlC, AUC	88,89
Epirubicin	AUC	90
Epipodophyllotoxins		
Etoposide	AUC	73
Teniposide	AUC	91
Vinca-alkaloids		
Vinblastine	AUC	92

PlC, plasma clearance; AUC, area under the curve; Css, steady state plasma concentration; WBCC, white blood cell count; RBCC, red blood cell count.

Table 2. Pharmacokinetic–pharmacodynamic relationships established for anticancer agents, drug toxicity data

Drug	Pharmacodynamic parameter	Toxicity	Reference
Alkylating agents			
Melphalan	AUC	Renal	17
Busulphan	AUC	Veno-occlusive disease	93
Platinum complexes			
Cisplatin: total	PlC,AUC	Digestive	75
	PlC,AUC	Renal	75,94,95
	PlC	Otological	96
ultrafiltrable	PlC, AUC	Renal	19
Carboplatin	AUC	Haematological	23,97,98
Iproplatin	AUC	Haematological	99
Antimetabolites			
Methotrexate	PlC	Haematological	66,99
Trimetrexate	PlC,AUC	Haematological	100,101
6-Mercaptopurine	RBCC of metabolite	Haematological	42,102
5-Fluorouracil	AUC	Digestive, haematological	103,104,105,106,107
		Cardiac	108
Anthracyclines			
Doxorubicin	Css	Haematological	109
Epirubicin	AUC	Haematological	110
Pirarubicin	AUC	Haematological	104
Iododoxorubicin	AUC	Haematological	111
Leurubicin	AUC	Haematological	112
Epipodophyllotoxins			
Etoposide	Css	Haematological	73,78,113
	AUC	Haematological	78,114
Tenimposide	AUC	Haematological	51
Vinca-alkaloids			
Vinblastine	Css	Haematological	115
Vincristine	AUC	Neurotoxicity	116

See legend in Table 1 for abbreviations.

plasma concentrations were responsible for adverse effects [57]. This is, however, not true for all drugs; protracted infusions of doxorubicin have been shown to be less toxic than bolus injections [58, 59], but the high efficacy of doxorubicin might be comprised when the infusions are prolonged in important proportions [60–63]. A similar schedule dependence of etoposide efficiency has been shown by Slevin and colleagues [64], and warrants a strict evaluation of any change of scheduling of even well-known anticancer drugs.

Drug plasma concentration has a great predictive value since it is the result of the patient's own physiological characteristics, such as hepatic and renal functions, level of body fat and bioavailability, also of its genetic characteristics, for example, isoenzymes of drug metabolism.

METHODS FOR DOSE ADAPTATION

Several methods have been developed for dose monitoring of anticancer drugs. They all rely on a good knowledge of the pharmacokinetics of the drugs and on the pharmacokinetic–pharmacodynamic relationships [65].

The test-dose method

The use of high-dose methotrexate in the treatment of children's osteosarcoma has stimulated the development of a method able to adjust the dose administered to an optimum, avoiding lethal toxicities as well as insufficient treatments [66]. Cano's group in Marseille, France, in particular, has developed a test-dose method [50, 67]. The administration of 50 mg of drug, followed by nine blood samplings from 0.25 to 30 h post-injection allows the determination of the clearance of the drug. Knowing that a plasma concentration of 10^{-5} mol/l for 36 h is optimal, a single equation allows the calculation of the dose to be administered. A measurement of plasma drug concentration is performed at the fifth and 23rd hours of infusion; folinic acid rescue is also monitored as a function of residual methotrexate plasma concentrations, measured at 47, 53 and 71 h after the beginning of the infusion. Due to this precise dose adaptation, the toxic events occurring during or after high-dose methotrexate therapy have become very infrequent, despite a dose range between 1 and 2 g/m^2 always providing a plasma concentration of 10^{-5} mol/l. Other authors have also developed test-dose techniques for predicting methotrexate toxicity [66, 68], and Evans and colleagues [69] have even shown that it was possible to optimise high-dose methotrexate therapy by pharmacokinetic monitoring to attain a good efficacy. Similar test-dose methodologies have been proposed by Tranchand and associates [70] for high-dose melphalan treatment.

Dose adaptation during a continuous infusion

Protracted infusion offers a very simple method of dose adaptation. It is first necessary to use constant rate pumps in order to achieve a regular flow. The time to reach a steady-state plasma level (Css) depends on the drug used. For a drug which distributes into only one compartment, 90% of the Css is reached within 3.3 half-lives; since most anticancer drugs are distributed in several compartments, the time to reach Css depends upon the relative contribution of the successive phases to drug elimination. For fluorouracil, Css is reached within a few hours [71], whereas it is reached between 16 and 24 h for etoposide and doxorubicin [72–74], and is not reached even in 5 days for cisplatin [75]. When a stable plasma concentration is reached and determined, it is possible to modify the infusion rate for the remainder of the course of treatment. For instance, Santini and colleagues [76] measured plasma fluorouracil concentration during the first half of a 5-day infusion, and then adapted the dose during the second half of the infusion in order to obtain a given total AUC. Similarly, Collery and colleagues [77] have applied this method for cisplatin and etoposide 5-day infusions; Ratain and colleagues [78] have also proposed a dose adaptation of etoposide for a 3-day infusion.

Dose adaptation from population studies

When the drug is not administered as a continuous infusion, there is no chance for dose adaptation during the first cycle of treatment, which will be used to establish the patient's characteristics. A number of recent reports for several anticancer drugs have established a limited sampling strategy, which allows a good prediction of the total plasma clearance of the drug from only two blood samples, provided that complete population pharmacokinetic studies have been performed before. Table 3 presents some results that have been obtained by various investigators. The statistical distribution of the parameters in the population can be used not only for the estimation of the clearance in a given patient with only two time points, but also for the calculation of the dose which must be administered in the subsequent courses of treatment in order to reach a desired AUC. Several software programmes have been developed for this purpose as a complement to pharmacokinetic identification programs. Bayesian estimations of population kinetics have been obtained for methotrexate [79], doxorubicin [80] and cisplatin [81], but to date their use has been uncommon.

CONCLUSIONS

The discovery and development of new anticancer drugs, which are more active and less toxic than those presently available, is needed for cancer treatment, especially for metastatic disease. However, we need more effective use of the very potent drugs already available. The difference between an effective and a toxic dose is small, and all modalities which tend to increase it are welcome. Route of administration, duration of infusion, dose fractionation and circadian timing of administration are among the numerous strategies that are regularly used. Administration of an optimal dose, taking into account the individual characteristics of drug distribution and elimination in

Table 3. Drugs for which a limited sampling protocol or a Bayesian population estimation have been determined

Drug	Reference
Alkylating agents	
Cyclophosphamide	117
Thiotepa	118
Platinum complexes	
Cisplatin	67,81
Carboplatin	119
Antimetabolites	
Methotrexate	79
Fluorouracil	76,120
Anthracyclines	
Doxorubicin	121,122
Epirubicin	110, 123
Epipodophyllotoxins	
Etoposide	124,125,126
Vinca-alkaloids	
Vinblastine	127

each patient, is probably one of the best approaches and positive results have been obtained, especially for fluorouracil.

Dose adaptation obviously involves higher costs but the decrease of toxic events probably compensates for the cost of pharmacologically-guided dose adaptation. A general benefit that can also be obtained from such studies is a better knowledge of population pharmacodynamics of anticancer drugs, a domain yet unexplored, which might give some clues to the understanding of variability of drug effects among patients.

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