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Practical Treatment Guide for Dose Individualisation in Cancer Chemotherapy

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Abstract

Dosages of anticancer drugs are usually calculated on the basis of a uniform standard, the body surface area (BSA). Although many physiological functions are proportionate to BSA, overall drug clearance is only partially related to this parameter. Consequently, following administration of equivalent drug dosages based on BSA, a wide variability in plasma drug concentrations can be found between patients, as a result of which some patients experience little toxicity while others may show severe toxic symptoms. A clear pharmacokinetic/pharmacodynamic correlation has been demonstrated for some anticancer drugs, and this relationship provides a background against which rational dose optimisation can be implemented for individual patients. The 3 strategies that can be employed for optimising dosage regimens, none based on BSA, are described and criticised.

A priori adaptive dosage determination is based on the relative contribution of identifiable characteristics of patient, drug therapy and disease state that influence plasma drug concentrations; the dosage regimen is based on each patient's profile with regard to these characteristics. Although this approach is most successful with drugs whose clearance is closely tied to renal function, patient characteristics such age, obesity, serum albumin or hepatic function may be useful. The anticancer drug most closely identified with this approach is carboplatin, although dosage reduction strategies for etoposide, taxanes, anthracyclines, topotecan, oxazaphosphorines, vinca alkaloids or melphalan are advocated for patients with renal or hepatic dysfunction. The importance of pharmacogenetics for fluorouracil and mercaptopurine is also briefly discussed.

The second approach consists of adaptive dosage adjustments during repetitive or continuous administration of a drug. It has been used for several years to

administer methotrexate therapy and, more recently, it has been developed more fully and applied to continuous infusion of fluorouracil or etoposide. It was based, after determination of a target plasma concentration or area under the plasma drug concentration-time curve (AUC), on modification of the drug dosage during the cycle of chemotherapy or for the next cycle.

Finally, the third approach of adaptive dosage adjustment with feedback control, based on population pharmacokinetics, with limited sampling strategy, may allow a feedback revision of the dosage following measurement of plasma drug concentration and comparison with the population previously studied. This approach is a theoretical strategy which has not, until now, been used prospectively in clinical oncology.

For drugs such as anticancer agents with a very narrow therapeutic index, every effort should be made to minimise interpatient variability in drug exposure in order to maximise the benefit while keeping the risk of serious adverse effects at an acceptable level. This is particularly important when treatment is being given with curative intent.

The need for dose individualisation of drugs with a narrow therapeutic index is now well accepted. For drugs that do not produce toxicity at dosages or plasma concentrations close to those required for therapeutic effects, there is little interest in or need for dose optimisation or individualisation. In these circumstances, patients are treated with dosages high enough to ensure that therapeutic concentrations are achieved. In contrast, some drugs, such as antineoplastic chemotherapeutic agents, which frequently produce toxicity at dosages close to those required for a therapeutic effect, provide considerable scope for dose optimisation in individual patients.

When considering candidate drugs for pharmacokinetically guided dose adaptation in clinical oncology, 2 major criteria must be identified.[1] First, a relationship must be established between plasma drug concentration and response: the response must be optimal in the majority of patients when plasma drug concentrations are maintained within a therapeutic range. Secondly, large interpatient variability in distribution and/or elimination of the drug is observed as a result of genetic and/or pathophysiological conditions. There may also be large differences in the sensitivity of patients to a given plasma drug concentration.

Finally, another criterion may be added concerning the technical feasibility of dose adaptation.

The obvious goal of considering dose adaptation for individual patients is to maximise the probability of producing a desired therapeutic effect while minimising the probability of a toxic event. With anticancer drugs, this goal is often modified to seek the maximum probability of producing a desired therapeutic effect while producing acceptable toxicity.[2] So, dose adaptation in clinical oncology requires us to define relationships between the pharmacokinetics of the drug and its pharmacodynamic effects, i.e. antitumour activity and/or toxicity.

1. Rationale for Pharmacokinetically Guided Dose Adaptation

Because the pharmacokinetics of any one drug are known to be quite variable from one patient to another, both toxic and therapeutic responses to drug administration are frequently better correlated with plasma drug concentrations or the exposure of the patient to the drug [e.g. area under the plasma drug concentration-time curve (AUC)] than with the administered dose.[3]

On the basis of these criteria, anticancer drugs are clear candidates for pharmacokinetically guided dosage regimens, but specific problems arise.

By contrast with other drugs, pharmacodynamic effects are delayed in clinical oncology: the main

toxicities (neutropenia, mucositis) are observed 1 or 2 weeks after completion of treatment and tumour response or cumulative toxicities may be seen after multiple courses of therapy.

The other important point for anticancer drugs concerns the relevance of pharmacokinetic/pharmacodynamic relationships. The relevance of the relationships between pharmacokinetics and toxicity and between pharmacokinetics and activity should be viewed in the context of the use of the drugs:[2] for palliative treatment, manageable and predictable toxicity is a primary requirement. Therefore, pharmacokinetic/pharmacodynamic relationships are valuable if they can be exploited in order to achieve this. In contrast, if curative therapy is being attempted, more severe toxicity may be accepted, provided that the drug is being used to optimal therapeutic effect, and to achieve this, pharmacokinetic/activity relationships may be useful.

For anticancer drugs, the relevant pharmacokinetic parameters for use in pharmacokinetic/pharmacodynamic relationships are generally AUC or plasma drug concentration at steady state (C^{ss}). Other parameters are peak plasma drug concentration (C_{max}), duration of concentration above a threshold or AUC intensity.

Pharmacodynamics is here described by either discontinuous parameters (response, no response) or continuous parameters such as time to progression or survival. For toxicity, 2 types of parameters may also be considered: quantitative parameters such as percentage reduction in leucocyte, granulocyte or platelet counts, or semi-quantitative parameters defined by World Health Organization (WHO) grading.[4]

Mathematical models [e.g. modified Hill (i.e. the coefficient defining the steepneses of the concentration-effect curve) linear, exponential] have been used to describe pharmacodynamic effects and to relate them to pharmacokinetics.[5]

2. Pharmacokinetic-Pharmacodynamic Relationships in Clinical Oncology

Relationships between the pharmacokinetics and pharmacodynamics of anticancer drugs have been extensively reviewed.[5-9] Table I illustrates relationships between pharmacokinetics and clinical outcome. Encouraging examples of relationships between AUC and response have mainly been reported in paediatric oncology[16-22] and different strategies of pharmacokinetically guided protocols have been proposed by the Saint-Jude Hospital team in Memphis, Tennessee in the US.[22-30] Moreover, examples of relationships between clinical outcome and pharmacokinetics have also been described in adults treated for solid tumours.[10-15]

Table I. Pharmacokinetic/response relationships for drugs in clinical oncology

Drug	Tumour type	Pharmacokinetic parameter	Reference
Carboplatin	Teratoma	AUC	10
Carboplatin	Ovarian	AUC	11
Cyclophosphamide	Breast	AUC	12
Cytarabine	Relapsed leukaemia	Blast Ara CTP	13
Etoposide	Lung	C^{ss}	14
Fluorouracil	Head/neck	AUC	15
Mercaptopurine	ALL	RBC AUC	16
	ALL	RBC AUC	17
Methotrexate	ALL	C^{ss}	18
	ALL	AUC	19
	ALL	Blast MTX PG	19
	Osteosarcoma	C_{max}	20
Teniposide	Paediatric solid tumour	AUC	21

ALL = acute lymphocytic leukaemia; **AUC** = area under the plasma drug concentration-time curve; **Blast Ara CTP** = concentrations of aracytine triphosphate in blast cells; **Blast MTX PG** = concentrations of methotrexate polyglutamates in blast cells; **C_{max}** = peak plasma drug concentration; **C^{ss}** = plasma drug concentration at steady-state; **RBC AUC** = AUC of drug in red blood cells.

Very many examples have been reported of the pharmacokinetic/toxicity relationships for established agents used in cancer chemotherapy. They principally concern relationships between haematological toxicity and pharmacokinetic parameters,[31-64] but relationships between discontinuous parameters and pharmacokinetics have also been reported (table II).[12,65-70]

3. Methods of Drug Dosage Adjustment in Clinical Oncology

3.1 Conventional Method

Traditionally, anticancer drugs have been standardised to body surface area (BSA) or bodyweight.[71,72] This practice is based on the relationship that exists between body size (e.g. total bodyweight and BSA) and physiological functions (e.g. cardiac output, liver or renal blood flow and glomerular filtration rate (GFR).[73,74] The BSA is particularly useful for scaling between species or between infants and adults. The goal of dose standardisation is to produce consistent systemic drug exposure. The nomogram most commonly used in clinical practice to estimate BSA was derived in 1916 by DuBois and DuBois[75] from only 9 non-obese individuals of varying age, shape and size. This formula remains the most appropriate method of estimating BSA. It was challenged in 1970 by Gehan and George[76] who directly measured the skin-surface area of 401 individuals and confirmed the validity of the nomogram. The usefulness of normalising anticancer drug dose to BSA in adults has been questioned[71,77-80] and recently, Dobbs and Twelves[81] and Gurney et al.[82] questioned the use of BSA for epirubicin dose calculation. A retrospective analysis of more than 300 patients and 9 anticancer agents showed that normalisation of doses to BSA was of minimal clinical value in achieving consistent drug exposure. Since the letter by Grochow,[77] the number of drugs for which clearance has been poorly correlated with BSA (or not correlated at all) has grown (see table II in Gurney[83]). Despite this clear demonstration, the practice of dosage ad-

Table II. Pharmacokinetic/toxicity relationships for drugs in clinical oncology

Drug	Toxicity	Pharmacokinetic parameter	Reference
Busulfan	Hepatotoxicity	AUC	65
Carboplatin	Thrombocytopenia	AUC	31
	Myelosuppression	AUC	33,34,38,51,63,64
Cisplatin	Nephrotoxicity	C_{max}	66
	Neurotoxicity	C_{max}	67
Cyclophosphamide	Cardiotoxicity	AUC	12
Docetaxel	Myelosuppression	AUC	58
Doxorubicin	Myelosuppression	AUC	47
Epirubicin	Myelosuppression	AUC	40
Etoposide	Myelosuppression	AUC,C^{ss}	36,37,41,44-46,49,55,60-62
Fluorouracil	Mucositis	AUC	68
	Myelosuppression	AUC	50
Irinotecan	Myelosuppression	AUC	56,57
	Diarrhoea	Biliary index	69
Melphalan	Myelosuppression	AUC	35,43
Paclitaxel	Myelosuppression	AUC	48,52,53
Teniposide	Myelosuppression	AUC	42
Thiotepa	Myelosuppression	AUC	39
Topotecan	Myelosuppression	AUC	54
Vinblastine	Myelosuppression	C^{ss}	32
Vincristine	Neurotoxicity	AUC	70

AUC = area under the plasma drug concentration-time curve; $\mathbf{C_{max}}$ = peak plasma drug concentration; $\mathbf{C^{ss}}$ = plasma drug concentration at steady-state.

Table III. Practical methods of drug adjustment in clinical oncology

Drug	Method of dose adjustment	Criteria	Objectives
Anthracyclines	*A priori*	Liver function (bilirubin)	Risk of major toxicity
Carboplatin	*A priori*	Renal function: GFR	Target AUC with maximum likelihood of efficacy and minimum likelihood of toxicity
Docetaxel	*A priori*	BSA	
	A priori	Liver function (enzymes)	Risk of major neutropenia
Etoposide	*A priori*	Renal function and/or hypoalbuminaemia	Limit major toxicity
	During continuous infusion	C^{ss}	Obtain maximum likelihood of efficacy and minimum likelihood of toxicity
Fluorouracil	*A priori*	DPD deficiency	Avoid life-threatening toxicity
	During continuous infusion	AUC at mid-cycle	Obtain maximum likelihood of efficacy and minimum likelihood of toxicity
	During repeated administration	C^{ss}	Obtain maximum likelihood of efficacy and minimum likelihood of toxicity
Mercaptopurine	*A priori*	TPMT deficiency	Avoid life-threatening toxicity
	During repeated administration	Erythrocyte thioguanine nucleotides	Control treatment compliance
Methotrexate	Adaptive rescue	C_{min} 24h and 48h after infusion	Avoid life-threatening toxicity or minimise likelihood of toxicity

AUC = area under the plasma drug concentration-time curve; **BSA** = body surface area; $\mathbf{C_{min}}$ = trough plasma drug concentration; $\mathbf{C^{ss}}$ = plasma drug concentration at steady-state; **DPD** = dihydropyrimidine dehydrogenase; **TPMT** = thiopurine methyltransferase.

justment to BSA is so widespread that it may be difficult to change it to a more rational approach. It is necessary to consider that heavy and tall people, with a large BSA, do not necessarily have a larger liver or kidneys.

In practice, most agents were used in a mg/m^2 or mg/kg dose recommended for phase II trials. This recommended dose is based on the results of phase I clinical trials and its recommendation may involve no pharmacokinetic consideration at all. Dose reductions or delays are implemented in the face of unacceptable toxicity, but doses are seldom escalated in the absence of toxicity. As a result of the poor therapeutic indexes of anticancer drugs, this means that patients not showing signs of toxicity are receiving too small a dose.

3.2 *A Priori* Dosage Determination Based on Patient Characteristics

Dose adaptation attempts to take into account the pretreatment patient characteristics known to affect the pharmacokinetics or pharmacodynamics of a drug. As with other agents, hepatic and renal function must be explored before administration of anticancer drugs. While renal dysfunction is easily evaluated by measuring serum creatinine, calculating creatinine clearance (CL_{CR}) or determining GFR by the isotopic method,[84] the impact of hepatic dysfunction on drug elimination or metabolism is more difficult to determine. The major problem is that hepatic enzymes and/or serum bilirubin levels are not good indicators of metabolising activity.[85,86] Moreover, alternating hepatic function tests, such as indocyanine green (a marker of hepatic blood flow), phenazone (antipyrine) [a substrate marker for cytochrome P450 (CYP) activity] or lorazepam (a substrate marker of hepatic glucuronidation) have limited value in predicting the pharmacokinetics of chemotherapeutic drugs.

Different guidelines should be proposed according to the pharmacokinetic characteristics of the drug (table III).

3.2.1 Dose Adaptation According to Renal or Liver Function

Carboplatin

Carboplatin is mainly eliminated by the kidneys, as indicated by the fact that about 65% of the administered dose is recovered in the urine, mostly

as unchanged carboplatin, 24 hours after administration. As demonstrated by Egorin et al.[31] and Calvert et al,[87] the renal clearance of carboplatin is related directly to the GFR, but poorly to the BSA. The nonrenal clearance consisting of protein and tissue binding represents one-quarter of the total body clearance when renal function is normal. The total body clearance of carboplatin is highly variable from one individual to another (range between 20 and 200 ml/min.)[88]

Moreover, the carboplatin AUC to which a patient is exposed correlates with carboplatin-induced thrombocytopenia, both when the drug is given as a single agent and when it is given in combination with cyclophosphamide, etoposide or paclitaxel. Differences were observed between patients previously treated with chemotherapy and those who were not.[31] A correlation between duration of leucocyte nadir and carboplatin AUC has also been demonstrated in high dose regimens[89-91] and in combination therapy with either etoposide, fluorouracil or paclitaxel, or with both vinblastine and methotrexate.[33,34,38,51,63,64] In different studies, authors have not been able to demonstrate relationships between carboplatin dose and the degree of thrombocytopenia, although a good correlation with carboplatin AUC was described.[33,38,51] All these data suggest that the AUC in the individual patient is the most important factor in predicting the degree of thrombocytopenia and leucopenia with carboplatin.

AUC is indeed an important determinant of the therapeutic effect of carboplatin. Horwich et al.[10] studied 78 patients with germ cell tumours of the testis. These patients were treated with a combination of carboplatin, bleomycin and etoposide. The AUC for all patients was estimated retrospectively. Relapses occurred in 5 of 8 patients who had an AUC of <4 mg/ml · min. No relapses occurred in patients whose AUCs were >4 mg/ml · min.

The retrospective calculation of AUC has also been used to study its effect on myelosuppression and response rate in ovarian cancer. Jodrell et al.[11] studied a database of 1028 patients with ovarian cancer treated in phase II studies with carboplatin. In these patients, GFR was either retrospectively estimated by the Cockcroft-Gault equation or prospectively determined by ^{51}Cr-ethylene diamine tetraacetic acid (^{51}Cr-EDTA) clearance. AUC was then estimated from the total dose of carboplatin given. This study demonstrated that, for both untreated and previously treated patients, the response rate increased as the AUC increased up to 5 mg/ml · min. A further increase in the AUC beyond this point resulted in little further increase in the response rate, suggesting that there was a plateau in the AUC-response effect. However, further studies did not confirm the existence of this plateau: in a prospective randomised trial in ovarian cancer, the administration of chemotherapy to achieve an AUC of 12 mg/ml · min every 4 weeks (for 4 cycles) was associated with a complete response rate of 58%, whereas an AUC of 6 mg/ml · min every 4 weeks for 6 courses produced a response rate of only 32%.[92-94]

Different approaches to the determination of carboplatin dosage include the following.

Thrombocyte nadir directed dosage: During phase I clinical trials, Egorin et al.[31] developed an approach to individualising carboplatin dosage. They demonstrated first that the clearance of carboplatin was related to the GFR determined by CL_{CR}, and secondly that the degree of thrombocytopenia was related to the carboplatin AUC. They derived from these observations a formula by which the dose of carboplatin could be calculated on the basis of the measured pretreatment CL_{CR}, the patient's BSA and the desired thrombocyte nadir. A separate formula was derived for patients previously exposed to myelosuppressive therapy.

In non-pretreated patients,

$$\text{Dosage } (\text{mg/m}^2) = (0.091)\,\frac{CL_{CR}}{BSA}\left[\frac{PPC - PND}{PPC} \times 100\right] + 86 \quad \text{(Eq. 1)}$$

where BSA = body surface area, CL_{CR} = measured creatinine clearance, PND = platelet nadir desired and PPC = pretreatment platelet count.

In pretreated patients,

$$\text{Dosage } (\text{mg/m}^2) = (0.091)\,\frac{CL_{CR}}{BSA} \cdot \left[\left(\frac{PPC - PND}{PPC} \times 100\right) - 17\right] + 86 \quad \text{(Eq. 2)}$$

This formula was prospectively validated in a study which confirmed that the observed thrombocyte nadirs correlated closely with the desired values.[95]

This formula allows the clinician to calculate the dose on the basis of a clinical end-point: thrombocytopenia. However, in some combination regimens, thrombocytopenia may not be the pharmacodynamic end-point that is of interest, since neutropenia may have become the dose-limiting toxicity.

AUC-directed dosage: Calvert et al.[87] have developed a formula to allow a dose of carboplatin to be calculated in order to achieve a targeted AUC:

$$\text{Dose (mg carboplatin)} = \text{AUC (mg/ml} \cdot \text{min)} \times (\text{GFR} + 25)\text{(ml/min)} \quad \text{(Eq. 3)}$$

The formula has been validated in a prospective study.[87] In these studies, GFR was determined by isotopic measurement of ^{51}Cr-EDTA clearance. The feasibility of obtaining rapid and reliable estimates of GFR is indeed a problem, particularly when isotopic determination is not in current clinical use.

In clinical practice, estimation of GFR might be done from plasma creatinine levels using the Cockcroft-Gault or Jeliffe equations. Both formulas correlate with the ^{51}Cr-EDTA method, but both are biased: they underpredict the GFR for high carboplatin clearances and overpredict it for low CL_{CR}. These biases result in patients being exposed to a lower AUC than expected when their GFR exceeds 60 ml/min, or to a higher AUC when their GFR is below that figure. The degree of underprediction increases as the GFR increases.[88,96]

Another possibility for estimating GFR consists of 24-hour urinary creatinine. This biochemical determination results in some discrepancies due to the difficulty of obtaining the 24-hour urinary collection accurately.

Finally, the approach of using population pharmacokinetics of carboplatin has been attempted, investigating the relationship between carboplatin clearance and a number of factors including the plasma creatinine level. Age, weight, sex and serum creatinine level were significant independent variables in determining carboplatin clearance and the so-called Chatelut formula permitted carboplatin clearance to be calculated directly:[88]

$$CL_{carbo}\text{(ml/min)} = 0.134 \cdot BW + \frac{218 \cdot BW \cdot (1 - 0.00457 \cdot age) \cdot [1 - (0.314 \cdot gender)]}{\text{serum creatinine}(\mu\text{mol/L})} \quad \text{(Eq. 4)}$$

where CL_{carbo} = carboplatin clearance and BW = bodyweight and gender = 0 if male and 1 if female.

This formula showed a little bias and a precision similar to that of the ^{51}Cr-EDTA method. This approach has been validated prospectively.[97] However, it seems that *a priori* estimation of carboplatin clearance is highly dependent on the biochemical method for determination of serum creatinine level.[98,99]

Target AUC of carboplatin in monotherapy and in combined regimens: Target AUC must be defined as a function of the combination of drugs used. When carboplatin was used as a single agent, an AUC of 7 mg/ml · min could be targeted when the patient has never received any chemotherapy. In combination with etoposide, cyclophosphamide or vinorelbine, this AUC must be reduced to 5. Because of a pharmacodynamic interaction between paclitaxel and carboplatin (decrease of carboplatin-induced thrombocytopenia), an AUC of 7 mg/ml · min for carboplatin could be reached.[96,100,101] Finally, when the patient has been previously treated, AUCs of 5 and 4 mg/ml · min were recommended in monochemotherapy and in combination, respectively.[102] The use of these different approaches for dose determination was not valid for low AUC values (<2 mg/ml · min) which were targeted when carboplatin was combined with radiotherapy.[103]

Etoposide

Etoposide, a semi-synthetic epipodophyllotoxin, is one of the more commonly used anticancer drugs. The toxicity of this drug has been shown to be regimen-dependent. Its pharmacokinetics have been intensively studied in a wide variety of patient groups given different regimens alone or in combination with other chemotherapeutic agents.[62,104]

The pharmacokinetics of etoposide are linear over a large range of doses. The drug is extensively bound to plasma protein and elimination is by both renal and biliary pathways, mainly as unchanged etoposide. Relationships have been established between total or free etoposide AUC and neutropenia, which represents the dose-limiting toxicity in monochemotherapy or in combination.[44,45,105,106] Some considerations have been published concerning the dose individualisation of etoposide based on patient characteristics:

(1) It is clear that patients with impaired renal function as measured by serum creatinine levels greater than the normal range experienced significantly worse haematological toxicity than patients with normal renal function.[107] A dose reduction of approximately one-third would correct this increase in AUC and result in a drug exposure similar to that in patients with normal renal function.[84] This figure was based on a cut-off of serum creatinine (i.e. 130 μmol/L). Moreover, a population pharmacokinetic study performed in 100 patients proposed a formula to determine the decrease in renal clearance as a function of serum creatinine levels. This population approach proposed a relationship between serum creatinine levels and etoposide clearance. Consequently, a more rational adaptation of etoposide dosage was proposed in the case of renal dysfunction.[108]

(2) In the case of liver impairment, different types of patients must to be considered: the role of the liver in etoposide clearance may actually be as important as renal clearance, with the recent observation that approximately 50% of an intravenous dose of ^{14}C-labelled etoposide was recovered in the faeces of cancer patients.[109] Moreover, it is important to take into account the impact of liver dysfunction on serum albumin levels. In patients with hyperbilirubinaemia, Stewart et al.[110-112] have reported that serum bilirubin influences protein binding, probably by displacing etoposide: free etoposide is increased in patients with raised bilirubin or liver enzymes due to decreased hepatic clearance, and in patients with decreased serum albumin due to reduced binding. Dose reduction in these patients by at least 30% is essential to avoid increased toxicity.[113]

Taxanes

Paclitaxel is a diterpenoid taxane derivative. Its dose-limiting toxicity is neutropenia.[52,53,114,115] It displays nonlinear pharmacokinetics, especially at shorter infusion times and at high doses.[116] Hepatic metabolism and biliary excretion are the most important elimination routes of this drug and its metabolites. In humans, the total faecal excretion is approximately 70% of the paclitaxel dose, with 6α-hydroxy-paclitaxel being the major component in most patients.[53,117] Thus, it can be expected that the pharmacokinetics and pharmacodynamics of paclitaxel differ in patients with altered hepatic function. Some fragmentary reports have demonstrated that paclitaxel can be safely given at normal doses to patients with mild liver dysfunction (normal bilirubin and transaminases less than 10 times normal values). In patients with abnormal bilirubin levels, no guideline has been proposed in the literature.[118-120]

Docetaxel is another new semisynthetic taxoid with a high activity in different solid tumours. Its limiting toxicities consist of neutropenia, peripheral neurotoxicity and oedema.[121] Docetaxel exhibits linear pharmacokinetics characterised by a 3-compartmental model. It is mainly eliminated by metabolism and biliary excretion and the proportion of the dose excreted in urine is only 10%. Therefore, the pharmacokinetics of this drug are not affected by renal impairment. Moreover, in phase I and II clinical trials, a good correlation was found between docetaxel AUC and neutropenia.[58,122] Population pharmacokinetic/pharmacodynamic studies of single agent docetaxel were prospectively performed in 547 patients entered in several phase II clinical trials. They demonstrated that docetaxel clearance was highly correlated with BSA, justifying a dosage for that drug calculated in mg/m^2. Moreover, the population studies have identified 5 covariables (age >70 years, hypoalbuminaemia, elevation of α_1-acid glycoprotein, low α1-acid glycoprotein levels and elevated levels of the liver enzymes ALT and AST which are predictive

for a reduced clearance. As a correlation was found between docetaxel clearance and the risk of severe neutropenia, these parameters allow us to identify patients with high risk of severe neutropenia and consequently a rational dosage reduction has been proposed.[59]

Anthracyclines

The anthracycline antibiotics, daunorubicin, doxorubicin, epirubicin and idarubicin are rapidly and extensively metabolised following systemic administration. The primary metabolites include daunorubicinol, doxorubicinol, epirubicinol and idarubicinol and various glucuroconjugated or aglycone metabolites.[123-125] The urinary excretion of these compounds and their metabolites, measured for 4 or 5 days following drug administration, accounted for less than 20% of the dose. Consequently, there is no pharmacokinetic basis for the dosage adjustment of the anthracycline antibiotics in the presence of impaired renal function.[84]

In the case of impaired hepatic function, Reich[126] proposed guidelines for doxorubicin dosage reduction as a function of serum bilirubin level and serum liver enzyme level: when bilirubin levels exceeded 12, 30 or 50 mg/L, respectively, it was recommended to reduce the doxorubicin dose by 50 or 75% or to stop altogether.

A recent article by Twelves et al.[127] disagreed with these guidelines: if a systematic relationship exists between raised biochemistry liver tests and reduced doxorubicin clearance, the authors recommend a dose reduction to 50% in patients with a raised level of bilirubin and a dose reduction to 75% in patients with both elevated aspartate aminotransferase (AST) and bilirubin levels. Concerning epirubicin, a study by Twelves et al.[128] demonstrated a relationship between liver biochemistry, in particular serum aspartate transaminase (AST) levels, and epirubicin pharmacokinetics. Serum AST may be the best indicator rather than bilirubin levels for dosage adjustment: when the level is above the upper limit of normal with a normal bilirubin level, a dose reduction of approximately one-third would correct this decrease in epirubicin clearance; when AST and bilirubin levels are above the upper limit of normal, the epirubicin dosage must be reduced by approximately half.

Topotecan

Topotecan, an analogue of camptothecin, is an inhibitor of DNA topoisomerase I. The urinary recovery of topotecan ranges from 40 to 70%, suggesting that renal excretion is the primary clearance pathway.[129-131] A recent study was performed in patients with normal and impaired renal function. A significant correlation was observed between systemic plasma clearance of topotecan and CL_{CR}. In patients with mild renal dysfunction (CL_{CR} ranging from 40 to 59 ml/min), no dose adjustment is required. By contrast, in patients with moderate renal impairment (CL_{CR} of <40 ml/min), a dose reduction of one-half of the dose is necessary.[132] In patients with hepatic dysfunction, the nature and severity of treatment-induced toxic effects and the pharmacokinetics of topotecan were similar to those observed in patients with normal hepatic function. Cancer patients with hepatic injury can be treated with topotecan without dose modification.[133]

Oxazophosphorines

Oxazophosphorines are alkylating agents that need to be metabolised to active compounds.[134-138] Since the enzymatic activation of cyclophosphamide and ifosfamide occur mainly in the liver, hepatic dysfunction may, in theory, disturb the metabolism of these drugs and consequently diminish the cytotoxic efficacy of the drug.[139] However, as a result of low renal clearance of cyclophosphamide and activated cyclophosphamide, more than 80% of the drug is metabolised even in patients with hepatic dysfunction, and the exposure of patients to activated cyclophosphamide was unchanged in these patients. While no specific studies have been done with ifosfamide, it is reasonable to assume that the metabolism of ifosfamide will be similarly affected.

Dosage adjustment of ifosfamide in the presence of impaired renal function is indicated because of the increased risk of CNS toxicity and significant renal excretion of alkylating activity fol-

lowing ifosfamide administration. Dosage reduction was also recommended in patients with renal failure receiving cyclophosphamide.[84]

Vinca Alkaloids

Vinca alkaloid derivatives (vincristine, vinblastine, vindesine, vinorelbine) are not excreted significantly in the urine.[140] No dosage adjustment is necessary for vinca alkaloids in patients with renal impairment. Different studies have shown the impact of liver disorders on the pharmacokinetics of vincristine. Reduced clearance was associated with raised serum alkaline phosphatase, but no guidelines for dosage adjustment have been proposed. This decrease in clearance was associated with the development of neurotoxicity.[70,141]

Vinorelbine is a vinca alkaloid extensively used in metastatic breast cancer.[142] Its pharmacokinetics have been studied in breast cancer patients with liver metastases. Vinorelbine clearance was significantly reduced in patients with massive metastatic liver involvement (>75% of liver volume replaced by tumour) and high levels of bilirubin, transaminases and γ-glutamyl transferase. Moreover, its clearance is significantly correlated with the monoethylglycinexylidide test ($r^2 = 0.7$; $p < 0.0001$) which might be useful for individualisation of the vinorelbine dosage. In any case, these patients with large metastatic liver involvement should receive reduced doses.[143]

Melphalan

Melphalan is an alkylating agent used in the treatment of multiple myeloma.[144] Renal dysfunction during the course of the disease occurs in the majority of patients. The drug is both secreted and reabsorbed by the renal tubules. The mean urinary excretion of unchanged melphalan ranges from 15 to 98%. Some studies have recommended a dose reduction in patients with renal impairment, and a positive correlation of melphalan clearance with GFR has been reported;[145] however, in other studies, no such correlation was found.[146] A careful follow-up of haematological toxicity and possibly a dose reduction of melphalan are proposed for myeloma patients with renal impairment.[145,146]

3.2.2 Dose Adaptation in the Elderly

The question whether age is a cause of modification of pharmacokinetic parameters has received no clear and general answer.[147] 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: hypoalbuminaemia due to poor nutrition, reduction of hepatic or renal blood flow, comedications, etc.[148] Recently, age was identified as the patient feature which had the greatest impact on fluorouracil clearance compared with other covariables.[149] Only relatively few specific studies[107,150-154] have been performed concerning the pharmacokinetics of anticancer drugs in elderly patients. It therefore appears that dose adaptation as a function of individual physiology is better than adaptation as a function of chronological age.[155]

3.2.3 Dose Adaptation in the Obese Patient

As mentioned in section 3.1, anticancer doses have been standardised to BSA. Selecting drug doses can be a challenging decision for the clinician when treating a patient with cancer who is significantly overweight. If total bodyweight is used to determine BSA, calculated doses can be as much as 25 to 30% higher than if ideal bodyweight is used, with the potential for severe toxicity. No dosage guidelines have been established for obese patients receiving cancer chemotherapy.[156] However, a limitation of calculated BSA at a level of $2.2m^2$ is usually recommended. The physiological changes that occur in obese individuals and their effects on drug disposition have been reviewed.[79,157] They include increases in blood volume, cardiac output, lean body mass, organ size and adipose tissue mass. A few studies[158-160] have reported the influence of body fatness on the pharmacokinetics of antineoplastic drugs. These studies collectively suggest that differences exist in the pharmacokinetics of anticancer agents between patients with normal bodyweight and obese patients but these differences may be difficult to identify and characterise adequately, given that 5- to 10-fold ranges in anticancer drug clearance are commonly reported in the absence of obesity. Finally,

obesity must be taken into account when predicting the clearance of drugs such as carboplatin. Benezet et al.[161] demonstrated that actual bodyweight must be balanced by ideal bodyweight to estimate clearance using the Chatelut formula.

3.2.4 Pharmacogenetics

Recent developments in the field of pharmacogenetics should also be noted in the context of dose adaptation. Some drugs require metabolism to be activated or inactivated. Some enzymes involved in the biotransformation have polymorphic expression. Therefore, assessing enzyme activity (i.e. phenotype) or gene mutations (i.e. genotype) could help to predict optimal dose regimens.

Fluorouracil is catabolised into dihydrofluorouracil ($5FUH_2$) by dihydropyrimidine dehydrogenase (DPD). Patients who are genetically deficient in this enzyme are at particular risk of life-threatening toxicity.[162] The gene for DPD has recently been localised to chromosome 1p22, and at least one mutation has been identified.[163-165] For all other patients who are not genetically deficient, there seems to be no case for adjusting doses on the basis of the variations in the normal levels of this enzyme.[166-168]

Mercaptopurine is used in conjunction with methotrexate as maintenance therapy in childhood acute lymphocytic leukaemia. The influence of pharmacogenetics and variability in metabolism of the pharmacology of mercaptopurine is now well documented.[169] This drug is inactivated by *S*-methylation, a reaction catalysed by the enzyme thiopurine methyltransferase (TPMT). A polymorphic variation in the activity of this enzyme has been described and 3 populations can be defined.[16,169-174] Deficiency in TPMT, owing to homozygosity for low TPMT, is quite rare (1 in 300), but can lead to pronounced toxicity. TPMT activity varies widely in the subpopulation who have intermediate TPMT activity and can be related inversely to formation of the active 6-thioguanine nucleotide (6-TGN) metabolites and therapeutic response. Finally, homozygotes for high TPMT activity may be resistant to mercaptopurine therapy and can tolerate high doses of the drug, without experiencing myelosuppression. Individualisation of mercaptopurine dose, based on TPMT activity, is a good example of the use of a patient characteristic to optimise drug administration.

Many anticancer drugs are extensively metabolised by CYP enzymes, specially the isoenzymes CYP3A4 and CYP2C8: cyclophosphamide, ifosfamide,[35] taxol,[175] docetaxel,[176] irinotecan,[177] epipodophyllotoxins[178] and vinca alkaloids.[140] Even though there is no evidence of polymorphism in these enzymes, large variability has been observed in humans. Moreover, significant clinical interactions have been described due to inhibitors or activators of these enzymes in clinical oncology.[179] For example, the concomitant use of anticonvulsant drugs with paclitaxel led to an increase of the maximum tolerated use of paclitaxel because of a modification in the metabolism profile.[180]

The UDP glycosyltransferases (UGTs) represent a superfamily of enzymes that catalyse addition of the glycosyl group from a nucleotide sugar to a hydrophobic molecule.[181] This is the case for irinotecan, an anticancer agent used in the treatment of colon cancer, which is activated by a carboxylesterase to form the active metabolite SN-38, a potent inhibitor of topoisomerase. SN-38 is further conjugated by UGT.[182] Recently, Iyer et al.[183] revealed that the UGT 1A1 isoform is responsible for the glucuronidation of SN-38. This same isoform conjugates bilirubin or several endogenous substrates. Moreover, when hepatic microsomes from patients who have Criggler-Najjar type I syndrome were incubated with SN-38, a very important deficit in glucuronidation was observed, suggesting a genetic predisposition to the metabolism of irinotecan and an increased risk of irinotecan toxicity. This was confirmed by the study by Wasserman et al.[184] which showed that patients with Gilbert syndrome treated with irinotecan experienced a severe toxicity. These authors suggest that unconjugated serum bilirubin could be a predictive parameter for irinotecan toxicity. Other authors[185] supported the idea that individualisation of irinotecan dose by gene diagnosis would be

better than phenotyping of UGT 1A1 by determination of bilirubin.

3.3 Dose Adaptation During Repeated or Continuous Administration

Protracted infusion offers a very simple method of dose adaptation. The time to reach C^{ss} depends on the drug under consideration. For drugs with 1-compartment pharmacokinetics, 90% of the C^{ss} is reached within 3.3 half-lives. 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 if a relationship has been established between this C^{ss} and a pharmacodynamic end-point. This methodology has been used for continuous intravenous infusions of fluorouracil and etoposide. However, it is also applicable to repeated oral administration of drugs such as etoposide or to repeated weekly intravenous administration of fluorouracil or cisplatin.

Another possibility for dose adaptation consists of administering a low test dose of an anticancer drug to determine exactly the pharmacokinetic parameter for the individual patient, and then modifying the dose to obtain a target AUC. Such a method has been used for methotrexate[186] and melphalan.[43]

3.3.1 Fluorouracil

Fluorouracil is one of the oldest drugs used in cancer chemotherapy. Despite its extensive use in the treatment of breast cancer and gastrointestinal tumours, its pharmacokinetics remain complex because of the existence of both dose and time dependence. A relationship was demonstrated between toxicity and the exposure of patients to the drug when it was administered by continuous infusion for 3 to 5 days in association with cisplatin in patients with head and neck cancer.[68] Thyss et al.[187] have shown that the AUC obtained at mid-cycle predicts the incidence of fluorouracil-induced stomatitis. Consequently, nomograms have been developed to adjust the dose of fluorouracil based on its plasma concentrations. Adaptation of the dose at mid-cycle resulted in a decrease in the incidence of stomatitis from 20 to 12%. In addition, a better response was observed in patients with dosage adjustments even though no upward adjustment was made. A subsequent study showed that response rate and patient survival are highly correlated with fluorouracil AUC but not with the dose.[15] In another study, patients with metastatic colon cancer were treated with fluorouracil by continuous infusion with or without semustine and responses to chemotherapy were found to be related to the extent of systemic exposure.[188] Finally, in a randomised prospective study which compared conventional dosage versus pharmacokinetically guided dosage, Fety et al.[50] demonstrated that patients with advanced head and neck cancer treated with a combination of fluorouracil plus cisplatin by continuous infusion benefit from individual pharmacokinetic monitoring.

This approach could not be used in patients who received the drug by intravenous bolus because of the nonlinearity of the pharmacokinetics. However, a dosage-adjustment strategy has been established by Gamelin et al.[189] for treating patients with metastatic colorectal cancer with intravenous bolus doses of fluorouracil. In a prospective phase II study, they showed that a weekly 8-hour intravenous infusion of high dose fluorouracil (1.3 g/m^2) with folinic acid produced the best response rates with acceptable toxicity when plasma concentrations were between 2 and 3 mg/L. The acute toxicity, whatever the type, was correlated with plasma fluorouracil concentrations higher than 3 mg/L and not with the dose. This dosage adjustment led to an increase in dose intensity of flurouracil in metastatic colorectal cancer.

In a multicentre phase II prospective trial, the same author confirms that individual dose adjustment with pharmacokinetic monitoring (dose ranging from 950 to 3400 mg/m^2/week) provided high survival and response rates with good tolerability.[190]

3.3.2 Etoposide

The phase-specific nature of etoposide cytotoxicity is now well documented and its regimen-dependence in the clinical setting has been clearly demonstrated.[191,192] Pharmacokinetic studies per-

formed during these clinical trials also suggested that plasma etoposide concentrations associated with haematological toxicities (2 to 3 mg/L) were higher than those associated with antitumour activity (1 to 2 mg/L). Despite the limited stability of etoposide in aqueous solution, several groups have investigated the use of continuous infusion of etoposide. Stewart et al.[41] demonstrated that the dose-limiting toxicity of etoposide (neutropenia) is highly correlated with the degree of systemic exposure of unbound drug. Hence, they described the use of adaptive control to optimise dosage in individual patients by targeting specific white blood cell counts using the patients' own plasma etoposide concentration 24 hours in a 72-hour infusion.[106,193] Hence, etoposide dosage regimens were optimised on the basis of plasma etoposide concentrations measured after 24 hours of a 72-hour infusion and the correlation between plasma etoposide concentrations and neutropenia. Using this approach, patients with individualised dosage received, on average, 32% more drug but with no more toxicity than patients with standard dosage.

Recently, Joel et al.[61] have developed another strategy based on a target C^{ss} of etoposide after a loading dose administered prior to a 5-day continuous infusion. Haematological toxicity was higher in patients with a C^{ss} reaching 3 mg/L than in patients with a figure of 2 mg/L. Equally important was the demonstration that tumour response was similar in the 2 cohorts of patients with small-cell lung cancer. Moreover, the target C^{ss} was reached with a very low confidence limit. Such differences between toxicity and tumour response as a function of plasma concentrations have been reported by Kunitoh et al.[194] and Minami et al.[49] when they used a 14-day infusion of etoposide. Therapeutic monitoring of infused etoposide is feasible and helps to overcome problems associated with pharmacokinetic variability. The difference between the doses required for obtaining maximum antitumour response and toxicity suggest that these 2 pharmacodynamic effects may be associated with the maintenance of target plasma concentrations.

Another alternative for continuous exposure to etoposide was the use of the oral formulation.[45,55] However, the inter- and intrapatient variability in bioavailability with oral etoposide is likely to contribute to the unpredictable toxicity seen in some patients.[195] This makes the estimating of total systemic exposure over a course of treatment, or dose optimisation in individual patients based on AUC or a specific plasma concentration, difficult to achieve.[196,197]

3.3.3 Methotrexate

Methotrexate is an antifolate that has been used for many years in the treatment of solid tumours and childhood leukaemia. Plasma drug concentrations have been shown to be the best predictor for methotrexate toxicity. Consequently, the monitoring of methotrexate concentrations in plasma is now routinely performed to predict which patients will require folinic acid rescue and to adapt the dose of this antidote.[198-200] The use of very high doses of methotrexate in children with osteosarcoma has stimulated the development of a test dose for determining the dosage necessary to reach a plasma concentration of 10^{-5} mol/L for a 36-hour infusion or of 10^{-3} mol/L for an 8-hour infusion.[186,201]

Patients with acute lymphoblastic leukaemia who had a C^{ss} of less than 16×10^{-3} mol/L were at higher risk of relapse but this appeared to be most relevant in patients with poor prognoses,[18] and other authors have reported an association between plasma pharmacokinetics and event-free survival.[202,203] More recently, cellular levels of methotrexate and its polyglutamated derivatives have been measured and related to clinical effect. Polyglutamated intracellular metabolites of methotrexate are more active inhibitors of the target enzyme dihydrofolate reductase than the parent compound. Large inter- and intra-patient variation in the concentrations of these polyglutamates has been reported, but there is some indication that this relates to tumour response in patients with leukaemia.[19,204,205]

3.3.4 Melphalan

The pharmacokinetics of this alkylating agent have been studied in depth. The use of a test dose,

with or without a Bayesian estimate of pharmacokinetic parameters, permitted the individualisation of dosages for subsequent courses of therapy. Moreover, a correlation was demonstrated between myelosuppression and melphalan AUC, providing some justification for the use of a pharmacokinetically guided dosage for this drug.[35,43]

3.3.5 Busulfan

High dose busulfan is used in conditioning regimens before allogenic or autologous bone marrow transplantation (BMT) in adults and children. Several studies have established the wide inter- and intra-patient variabilities in high dose busulfan disposition.[65,206-208] Some factors of variability have been identified: age, alteration in hepatic functions, disease, circadian rhythm and drug interactions. Hepatic veno-occlusive disease (HVOD)[65,206-208] is a frequent life-threatening toxicity in patients undergoing BMT after the administration of a regimen containing high dose busulfan. In adults, a pharmacodynamic relationship has been established between a high systemic busulfan exposure and the occurrence of HVOD. Moreover, Slattery et al.[209] demonstrated that busulfan C^{ss} (<900 μg/L) was the only statistically significant determinant of relapse in patients treated by BMT for chronic myeloid leukaemia. By contrast, in children, before the prospective evaluation of busulfan dosage adjustment, further studies are required to demonstrate firmly the existence of a pharmacodynamic relationship in terms of toxicity and allogeneic engraftment, especially when busulfan is combined with cyclophosphamide. The maximum tolerated and minimum effective AUCs in children undergoing BMT are likely to depend mainly upon the disease, the nature of the combined high dose regimen and the type of BMT.[210-215]

3.4 Dose Adaptation with Feedback Control

The approach of adaptive dosage with feedback control is the most complicated and complex method. In this approach, population-based predictive models are used initially, but allow the possibility of dosage alteration based on feedback revision. Patients are initially treated with a standard dose and during treatment the pharmacokinetics of the drug being used are estimated by a limited sampling strategy and compared with those predicted from the population model with which dosage was initiated. On the basis of the comparison, more patient-specific pharmacokinetic parameters are calculated and dosage is adjusted accordingly to maintain the target C^{ss} or exposure of the drug to produce the desired pharmacodynamic effect. Despite its mathematical complexity, this approach may be the only way to deliver the desired precise exposure of an anticancer drug.[1,216]

4. Conclusions

A knowledge of drug pharmacokinetics and pharmacodynamics has contributed to the optimisation of drug development and to the treatment of patients in several non-oncological therapeutic areas. The routine use of pharmacokinetic methods in determining the dosage of carboplatin, methotrexate, fluorouracil or etoposide indicated that such optimisation is also possible with chemotherapeutic agents. For these drugs, the concept of AUC-based dosage has been validated since toxicities are clearly related to the AUC. Moreover, it seems likely that therapeutic efficacy is also related to AUC although further clinical trials are necessary to clearly establish this point. The use of AUC-based dosage to compensate for variations in elimination and/or distribution between and within individual patients is a desirable practice. Whereas therapeutic drug monitoring in all patients is impractical, the routine use of BSA for calculating the dosage should be avoided and other methods investigated which are based on the pharmacological characteristics of the drug but also mainly on the characteristics of the patient. In these conditions, the proposal from Gurney[83] concerning a non–BSA-based dosage calculation method defined by 3 mandatory steps (prime dose, modified dose and toxicity-adjusted dose) should be evaluated prospectively. This dosage adjustment approach does not necessarily require pharmacokinetic considerations. But the identification of patients' features predictive of drug pharmacokinetics would

allow the clinician to rationally choose the dosage of the first treatment cycle. Moreover, by following these features, it will be possible to anticipate intrapatient pharmacokinetic variabilities which should be taken into account with the observed toxicity in the calculation of subsequent dosage. Moreover, if the principle of increasing doses to the point of toxicity in the curative situation should be widely accepted, determination of the actual exposure of a patient to a drug would facilitate the incrementation for the next cycle.

Finally, for drugs such as anticancer agents with a very narrow therapeutic index, every effort should be made to minimise interpatient variability in drug exposure in order to maximise the benefit while keeping the risk of serious adverse effects at an acceptable level. This is particularly important when treatment is being given with curative intent. The use of adaptive dosage may offer the best way to achieve this goal. What is now required is further prospective validation of these approaches in a controlled manner.

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