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Overview

Chemotherapy Dosing Part II: Alternative Approaches and Future Prospects

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ABSTRACT:
This overview follows on from part I, which described the current practices used in chemotherapy dosing and the paucity of scientific evidence to support them. In part II, alternative approaches are discussed, both in terms of scientific rationale and practical application. These include therapeutic drug monitoring, the use of pharmacokinetic–pharmacodynamic relationships, flat-fixed dosing, Bayesian modelling and dose banding. Kaestner, S. A., Sewell G. J. (2007). *Clinical Oncology* 19, 99–107

Key words: Body surface area, cancer, chemotherapy, dose, pharmacokinetics

Introduction

This overview considers alternatives to the body surface area (BSA) dosing approach discussed in part I [1]. Alternative dosing strategies, either to individualise dosing, such as therapeutic drug monitoring (TDM), or to rationalise dosing, such as dose banding, are examined, together with the potential application of new technologies, such as gene expression profiling.

Published studies describing alternatives to BSA dosing strategies are critically reviewed to establish whether there is a viable alternative to BSA chemotherapy that could be introduced into clinical practice to optimise therapeutic outcomes and reduce variability. Finally, a concluding section summarises the evolution of chemotherapy dosing, presents a realistic view on whether change is necessary or possible, and identifies the most promising scientific avenues for further research.

Alternative Dosing Approaches

Alternative approaches suggested for dose optimisation of cytotoxic drugs are mainly based on monitoring various pharmacokinetic measures, obtained purely from real-time measurements or partly from pharmacokinetic models. Doses can also be adjusted according to levels of toxicity, or alternatively may be empirically derived. The use of pharmacokinetic and toxicity as surrogate markers for therapeutic effect was discussed in part I [1].

A Priori Pharmacokinetic-guided Dosing of Carboplatin

Carboplatin is a drug for which non-BSA-based dosing has been well established, and several different strategies have been suggested [2–7]. An early dosing scheme proposed for carboplatin was based on the relationship between carboplatin area under the plasma concentration–time curve (AUC) and the percentage platelet decrease at nadir [8,9]. Carboplatin is mainly cleared by renal elimination, and because of the wide range of glomerular filtration rate (GFR) values observed, even for individuals with 'normal' renal function, a large variability in clearance can be expected, unless the dose is adjusted for renal function [2,10–13]. The widely adopted Calvert formula uses the correlation between renal and total body clearance of carboplatin and GFR to obtain a dose from a target AUC (dose = AUC × (GFR + 25)) [2,10,14]. Target AUCs are normally recommended as 5 and 7 mg/ml × min for previously treated and untreated individuals, respectively, based on the relationship for AUC with therapeutic and toxic effects [1,2]. The Calvert formula has even been successfully used in a cancer patient with renal failure, where the GFR was set to zero, and the resulting carboplatin dose was 125 mg [15]. Had BSA-based dosing been used for this particular patient, any empirical adjustments for impaired renal function would have been based on a 609 mg dose (300–400 mg/m^2). Despite the more robust approach of the Calvert formula for dose individualisation, pharmacokinetic variability can still be

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quite large, although reduced in comparison with that for BSA-based dosing [2,16–19]. Variability in exposure following use of the Calvert formula can be expected from variations in non-renal clearance, probably due to irreversible tissue binding [2]. It can also arise as a result of inaccuracies in the methods used for GFR estimation. When developing the formula, Calvert *et al.* [2] used, and subsequently recommended, the isotopic ^{51}Cr-ethylenediamine-tetraacetic acid (^{51}CrEDTA) method to measure GFR [20]. ^{51}CrEDTA and other isotopes, for example ^{125}I-iothalamate or ^{99m}Tc-DTPA, as well as inulin and iohexol, are exogenous markers that have generally been recommended as the preferred choice for obtaining accurate GFR estimates [21–26]. In Europe, ^{51}CrEDTA is widely used in clinical practice, but not in the USA [15,24]. Instead, it is common to use iothalamate clearance, the creatinine clearance method based on 24-h urine collection, GFR or creatinine clearance prediction equations, or the Chatelut formula, which predicts carboplatin clearance [23,27–32]. These equations are based on factors such as age, gender, bodyweight, race, serum creatinine, urea and albumin. Cockcroft–Gault is probably the most frequently used prediction equation, and the Bjornsson, Jeliffe, Wright and Modification of Diet in Renal Disease Study equations (MDRD1 and MDRD2) are other examples [23,33–37]. All of these equations have been reported to have suboptimal predictive capabilities for ideal patient care, and they may be less accurate in overweight or cachectic individuals, or in cancer patients whose creatinine, albumin and urea nitrogen levels may differ from those in healthy people [23,24,27,33,36,38–43]. Serum creatinine, a variable used in all equations, is insensitive to small changes in GFR, and is, for example, affected by diet, total muscle mass, previous nephrotoxic treatment, as well as other medications that may modify creatinine excretion [2,23,24]. Also, there are inter-laboratory differences in the calibration, precision and accuracy of assays used to measure serum creatinine levels [23,24,28,44]. For example, to avoid the overestimation of carboplatin clearance, Ando *et al.* [28] recommended that 0.2 mg/dl is added to the estimated creatinine concentration when creatinine levels are measured by the enzymatic peroxidase-antiperoxidase (PAP-Cr) method. However, in contrast to the lack of support for these formulae, it has also been suggested that their accuracy may be sufficient, considering differences in drug handling at the tumoural and cellular levels [45]. Cystatin C is another less studied protein that can be used as a marker for GFR. This is considered to compare favourably with creatinine, although it is reabsorbed from the renal tubule, which may be a disadvantage [46,47].

Tonkin *et al.* [48] recommended BSA-based dosing in favour of GFR-based AUC individualisation of carboplatin, based on the finding that BSA dosing resulted in a higher dose intensity (DI) than GFR-based dosing, without having a significant effect on toxicity. However, this was a relatively small study that did not have a cross-over design, and the results should therefore be interpreted with caution.

Therapeutic Drug Monitoring

Cytotoxic drugs fulfil one of the prerequisites for TDM, which is a large inter-patient pharmacokinetic variability. However, TDM is often precluded in cytotoxic drug therapy because of tumour heterogeneity, and because drug concentrations and the therapeutic effect in the target tissue are unknown or are not related to the plasma drug concentration. There is also a time-lag between drug measurement and the clinical effect, which can be represented by an anticlockwise hysteresis loop [49]. Another problem is that drugs in combinations frequently have overlapping therapeutic and toxic effects, and the contribution from each drug is unknown. TDM is applicable mainly for drugs with identifiable therapeutic plasma concentrations, which should be similar between individuals [50]. As discussed previously, this is generally not the case for cytotoxic drugs, and it might be more important to look at patient factors rather than to monitor the blood drug concentrations. Similar considerations apply to the monitoring of pharmacokinetic measures other than drug concentration. Additionally, TDM is more complicated for drugs with non-linear pharmacokinetics, drugs that accumulate, and also pro-drugs or drugs with active metabolites [50,51]. TDM has the same economical and practical limitations as those discussed for pharmacokinetic studies (see part I [1]), where the validation of methods is necessary but difficult to carry out, and the appropriate training of staff is required [51–53].

Published reports of TDM in cancer chemotherapy reflect these difficulties with varying levels of success. TDM of plasma drug concentrations has been successfully applied to evaluate a fixed dosing scheme for suramin in patients with hormone refractory prostate cancer, and both AUC and plasma levels have been used to guide etoposide dosing [54–56]. 5-Fluorouracil (5-FU) concentrations and dihydropyrimidine dehydrogenase (DPD) activity (see enzyme expression below) have also been monitored, but this approach is complicated by circadian variation of both measures [57,58]. The monitoring of 5-FU AUC has proved more useful in improving the therapeutic index for the drug [59]. However, TDM in cancer therapy is only commonly used for methotrexate, either to monitor drug clearance or AUC, or to use methotrexate plasma levels for individual dose adjustments of leucovorin [49,58,60–62]. Even for methotrexate it has been questioned whether it is correct to aim for a specific target AUC, without clearly knowing if that AUC is really optimal for each patient [62].

Furthermore, drug monitoring has been advocated for the individualisation of cisplatin doses, based on either AUC or area under the DNA-adduct curve, which seems reasonable based on the relationship with clinical effect [62,63], described in part I [1]. However, the monitoring of pharmacokinetic measures such as AUC requires a number of blood samples, and to be feasible in clinical practice, the approach is more or less dependent on limited sampling models (LSMs). LSMs have been developed to facilitate TDM of etoposide in children, and to simplify drug pharmacokinetic–pharmacodynamic studies for drugs such as 5-FU,

epirubicin and doxorubicin [64–67]. The advantage is that LSMs only need one or a few samples at carefully defined time points (determined by multivariate analysis). However, these are sensitive and can often only be applied to patients treated with the same dose schedule and rate of administration. Sampling times must also be identical to those used in the initial model. Therefore, the prospective validation of these models is essential [3,29,66,68]. An example of these difficulties is an LSM developed for carboplatin by Ghazal-Aswad *et al.* [3], using the 24-h total plasma platinum concentration to calculate the free carboplatin AUC. This model was considered to be flexible, but in a separate prospective evaluation by Panday *et al.* [68], it was shown to systematically overestimate the AUC. This could be the result of using different infusion times in the retrospectively and prospectively studied patient groups in the original study, as well as the use of carboplatin in drug combinations by Panday *et al.* [68].

Enzyme Expression/Activity-based Dosing

As discussed in part I [1], there are several known examples in which the expression and/or activity of drug metabolising enzymes are known to affect drug pharmacokinetics. These could, therefore, be of value in chemotherapy dose determination. For example, hepatic cytochrome P450 (CYP) 3A4 activity accounted for two-thirds of the inter-patient variability in docetaxel clearance in a study by Hirth *et al.* [69], and was consequently considered for docetaxel dose individualisation in combination with alanine aminotransferase, albumin, and α-L-acidic glycoprotein levels. A better known example is to account for DPD activity in treatment with 5-FU [70,71]. Different tests have been developed to identify patients with an increased risk of 5-FU toxicity before treatment [72–74], and these could also be used for identifying individuals with high DPD activity who are at risk of under-dosing. A common technique is to measure DPD activity in peripheral mononuclear cells, which has been correlated with hepatic DPD activity and 5-FU clearance [58,75–77]. However, the strengths of correlations presented have varied, and the technique is time consuming [71,78,79]. Simpler, more rapid, tests are based on the determination of the dihydrouracil–uracil (UH_2–U) ratio in plasma and the 2-^{13}C-uracil breath test, similar to the ^{13}C-urea breath test used to diagnose *Helicobacter pylori* infection [75,80,81]. For example, Gamelin *et al.* [75] created a chart for individual dosage adjustment of 5-FU based on the initial UH_2–U ratio. It must be remembered that neither method will probably determine DPD activity accurately, and, in any case, DPD activity is unlikely to be the only factor causing variability in 5-FU pharmacokinetics, especially in patients where DPD activity is within 'normal' limits.

Other examples of using enzyme expression to predict serious adverse outcomes include 6-mercaptopurine (6-MP) and irinotecan [82–84]. Inheritable enzyme deficiencies in both thiopurine S-methyltransferase (TPMT), one of the enzymes metabolising 6-MP, and uridine diphosphate glucuronyltransferase 1A1 (UGT1A1), which metabolises the irinotecan metabolite SN-38, can be detected with genotyping [83,85]. The importance of introducing this knowledge into clinical practice is shown by the Food and Drug Administration support for both TPMT and UGT1A1 genotyping before treatment with 6-MP or irinotecan, respectively [85]. Enzyme phenotyping and/or gene expression profiling are therefore obvious components of Bayesian models for dose optimisation, as discussed below.

Pharmacokinetic/Pharmacodynamic Modelling

Using Bayes' theorem, past experiences can be used in the care of new patients by combining population pharmacokinetic or pharmacodynamic models with sparse data from the individual patient [62]. The application of these models can be considered as a type of TDM that does not depend on the monitoring of each individual. To be of any value, the prerequisites for this drug dosing strategy are similar, for example being largely dependent on the existence of pharmacokinetic/pharmacodynamic relationships. Population pharmacokinetic and Bayesian models have been developed and applied prospectively for various cytotoxic drugs, including paclitaxel and carboplatin [7,17,86]. A study by de Jonge *et al.* [17] was based on earlier observations of a correlation between plasma paclitaxel levels of at least 0.1 μmol/l >15 h and prolonged survival. Through dose adaptation based on a Bayesian model, this study showed an increase in the percentage of patients achieving this 'target' plasma concentration for a sufficient period of time. Another example of the development and application of a Bayesian model is high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin (CTC) in patients with various cancer types [16]. Total course AUCs obtained following Bayesian dosing were compared with the AUCs patients would have obtained without any dose adjustment during the course. Both these AUCs were compared with a defined target AUC (expressed as median values from a reference population). For all three drugs, adjustment during courses resulted in a higher percentage of exposures within ±25% of the target than conventional dosing, which was BSA based for cyclophosphamide and thiotepa, and Calvert formula based for carboplatin. However, no clear benefit in toxicity profiles was observed for pharmacokinetic-monitored dosing. This latter observation is important to bear in mind, because even if a model reduces pharmacokinetic and/or pharmacodynamic variability, it does not necessarily optimise the therapeutic effect. Pharmacokinetic models are not an exact description of reality, and do not necessarily apply to each individual.

In comparison with TDM using LSMs, Bayesian models are easier to apply clinically because they offer more flexibility in blood sampling times, in addition to making simultaneous estimations of several measures possible [20,60]. However, there are still drawbacks with Bayesian modelling relating to technical feasibility, including access to the right analytical equipment, trained technicians for bioanalysis, and clinical pharmacists/pharmacologists to interpret pharmacokinetic data [16]. Also, as for TDM, it can be

inconvenient and time consuming for the patient if pharmacokinetic studies are done on each treatment course, and the requirement for overnight stays may preclude out-patient treatment. There must be an expectation of substantial clinical benefits for either of these dosing strategies to be adopted in the general clinical setting.

Toxicity-guided Dosing and High-dose Chemotherapy

Because many pharmacokinetic–pharmacodynamic models in cancer chemotherapy use measures of toxicity as the pharmacodynamic outcome, they can be regarded as an indirect form of toxicity-guided dosing, where dose adjustments are based on predictions of levels of toxicity in an individual. In the more direct type of toxicity-guided dosing, the adjustment of doses is based on actual levels of toxicity observed after, for example, BSA-based or empirical starting doses, often with the aim of achieving the maximal tolerated levels of toxicity. Toxicity-based dosing is precluded for drugs that do not have short-term clinical markers for dose-limiting toxicity. For example, with hydration and potassium/magnesium supplementation, the dose-limiting toxicity of cisplatin has changed from nephrotoxicity to neurotoxicity and ototoxicity, which cannot be used to guide dosing of the drug [63]. Toxicity-guided dosing is relatively common, and in the absence of therapeutic guidelines, this approach may be useful for avoiding both under-dosing and lethal or irreversible toxicity. However, in reality, reaching these highly toxic levels is probably not necessary for achieving a therapeutic effect with all drugs, or in all patients, whereas for other drugs, or patients, the levels are insufficient and the selection of a different drug may be the more appropriate choice. To aim for a certain level of toxicity in healthy tissue is questionable, as the actual clinical benefit is unknown. Also, as considered in part I [1], the level of toxicity does not necessarily relate to the duration of toxicity. Toxicity-guided dosing can be exemplified in a retrospective study by Rivera *et al.* [87], where the first cycle neutrophil count was found to be the only significant predictor of subsequent neutropenic events during therapy with 5-FU, cyclophosphamide and doxorubicin. This information was considered useful for targeting individuals who might benefit from treatment with colony-stimulating factors instead of reducing doses, a viewpoint that relies on the assumption that a delivered dose closer to the scheduled dose (a greater dose intensity), and higher doses in general, result in a clinical benefit. The same assumption is relevant for high-dose chemotherapy, which also aims to overcome chemotherapy resistance, and for which the clinical outcomes have varied and obviously depend on the drugs in question [88,89]. For example, a study by Bergh *et al.* [90] compared treatment with 5-FU, epirubicin and cyclophosphamide (FEC) with granulocyte colony-stimulating factor, individually dosed to give a similar degree of toxicity, with standard FEC followed by high-dose CTC with stem cell support, in a total of 525 women with breast cancer. Significantly improved response rates and a lower incidence of toxicities were observed for the individualised FEC regimen, and high-dose therapy was not recommended as suitable for the treatment of breast cancer. In another study on women with breast cancer, who received high-dose chemotherapy with stem cell rescue in the adjuvant setting, an increased relapse-free survival was observed, but the benefits were obscured by an excess number of early toxic deaths [91]. A final important factor to consider for both toxicity-guided dosing and high-dose chemotherapy is that even in cases where maximum tolerated doses are therapeutically beneficial, the benefits may be lost if schedule adherence and compliance decrease (as a result of toxicity), reducing the dose intensity.

Empirically Derived Doses

A further approach for cytotoxic drug dosing involves the use of empirically determined doses as a starting point, with successive arbitrary adjustments to these, according to the presence or absence of clinical effects or toxicity. Empirically based dosing is rare compared with BSA dosing, but has been suggested and used, for example, with carboplatin [4,15]. Given the lack of scientific rigour of BSA-based dosing, empirical, or flat-fixed, dosing seems justifiable. Average fixed doses for drugs could be determined from the common ranges of BSA-based doses given in clinical practice, or alternatively from large trials in a relevant patient population. Clearly, there may be several 'average' doses for a drug, depending on factors such as scheduling, drug combination, and which type of cancer is treated.

Provision of Patient-specific Cytotoxic Drug Doses and Dose Banding

As a consequence of dose individualisation (usually based on BSA), cytotoxic drug infusions are normally prepared for each patient immediately before administration, depending on infusion stability and microbiological issues. This approach has several disadvantages for patients, pharmacy staff and oncology nurses, and also results in economic costs to the healthcare system. From the viewpoint of the patient, out-patient treatment is often delayed because of a high, unplanned, workload on the pharmacy cytotoxic drug service [92–94]. This increases patient waiting times, causing patient distress and increasing costs, particularly if nurse overtime is required to complete drug administration. Preparing individual doses places unpredictable demand on pharmacy cytotoxic drug services, which can exceed their resources and capacity at peak treatment times, placing significant pressure on personnel and equipment. The problem is exacerbated because the handling of cytotoxic drugs is restricted to class II cabinets or isolators [95]. This high workload may, in turn, increase the likelihood of errors in cytotoxic drug preparation and reconstitution [94–98]. Medication errors and oncology

protocol miscalculations have been observed in every type of hospital setting, and these can have tragic outcomes [99]. Healthcare staff handling the drugs are also at risk [100], but unfortunately there is a lack of legislation for national guidelines for this type of work in some countries. A survey by the European Society of Clinical Pharmacy and the International Society of Oncology Pharmacy Practice in 1999 made it clear that centralised pharmacy cytotoxic services are not standard in all European countries [95]. The safe handling of, and occupational exposure to, cytotoxic drugs are therefore key issues in oncology pharmacy [95,101]. From an economic point of view there are significant costs associated with the preparation of cytotoxic agents [95,102,103]. Individual dose preparation precludes the efficient use of resources, resulting in an increased amount of documentation associated with the process, as well as a substantial amount of drug wastage due to discarding partly used vials and deferred doses [92–94].

In view of the issues described above, Plumridge and Sewell [92] suggested 'dose banding' as a first step in rationalising chemotherapy dosing. In dose banding, individually calculated doses of intravenous cytotoxic drugs are placed within defined ranges or bands. A pre-determined standard dose is applied to each band (usually the midpoint of the band) and this standard dose can be given with pre-filled syringes or infusions. For each drug, dose-banding tables are constructed so that the maximum variation between the standard dose given to the patient and the prescribed dose is 5% or less. An example of a dose-banding scheme, showing the bands, standard doses and variance from prescribed dose, is presented in Fig. 1.

In the UK, dose banding is widely used to provide chemotherapy for oncology out-patients, and several drugs have been successfully dose banded, including cyclophosphamide, methotrexate, doxorubicin, epirubicin, vincristine, 5-FU, and folinic acid [92–94,104]. Various benefits have been proposed for dose banding, including decreased patient waiting times, possibilities to treat patients nearer their homes, the facilitation of chemotherapy administration on any weekday, increases in time left for clinical activities for pharmacists, reduced drug wastage, and reduced occupational exposure risk as the drugs can be prepared by centralised units or the pharmaceutical industry [92–94,104,105]. Batch preparation of standard doses can reduce errors related to the preparation of an infinite variety of discrete dose units. Also, prospective end-product testing of batches, including drug assay, is possible and validated, pre-determined shelf lives can be applied to batches of pre-filled syringes [92,106]. Dose banding reduces the number of steps necessary for dose calculation, and the use of pre-printed dose charts could reduce the risk of stress-related errors in the provision of cytotoxic drugs [107]. Drugs suitable for ready to use, pre-made doses must, however, exhibit adequate chemical and physical stability and microbiological integrity of the process [92] to permit batch preparation and storage. A potential disadvantage for dose banding is the need to use a combination of syringes/infusions given to a certain dose. At present, there is a set maximum of two or three syringes per dose, but the clinical feasibility and patient/nurse acceptances of this have not been evaluated [92,93]. Also, it may be that the banding of doses adds to the existing errors in dose calculation, and the approach has yet to be justified in terms of safety and efficacy, although studies on this are in progress [108]. Considering the acceptance of BSA individualisation of oral cytotoxic drug doses, the defined limits of ±5% from the prescribed dose in dose banding does, however, not seem unreasonable. In fact, doses of oral cytotoxic drugs such as capecitabine, are effectively 'banded' because only two different tablet sizes, 150 and 500 mg, are available. For this drug, different tablet combinations are given for different BSA ranges, which is similar to the different combinations of

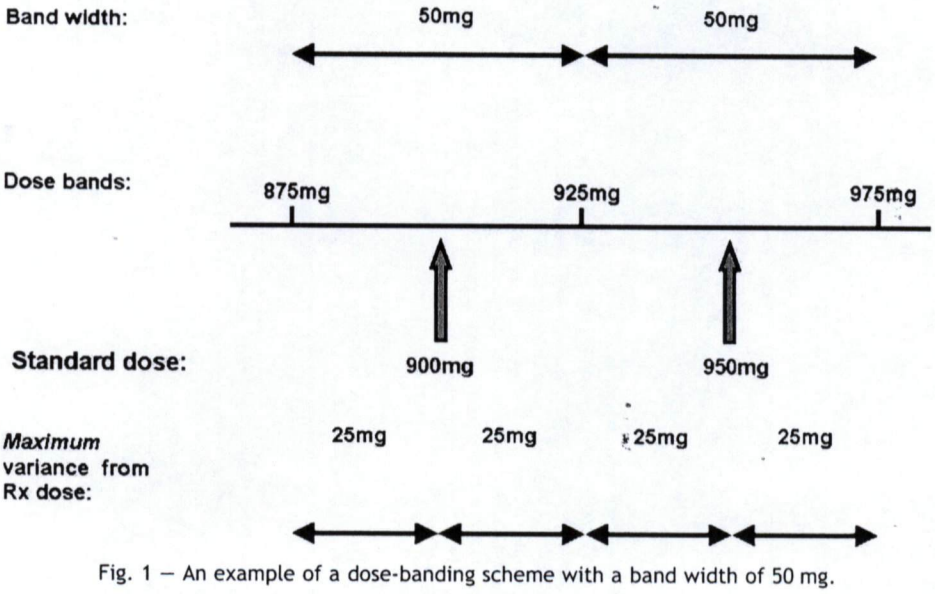

Fig. 1 – An example of a dose-banding scheme with a band width of 50 mg.

pre-filled syringes given in the dose banding of intravenous drugs [109–112].

Further research is needed to study the application of dose banding to more robust, scientifically derived alternatives to BSA-based dosing strategies [92].

Conclusions

Any argument for the replacement of BSA-based dosing (see part I [1]), must propose a better alternative. This is not a trivial matter, but the options discussed in this overview have different merits and are worthy of consideration.

Therapeutic optimisation strategies used in other therapeutic areas, such as asthma, should be considered for cancer chemotherapy. For example, strategies involving a loading/maintenance dose schedule, such as that used in clinical trials for perifosine, based on pre-clinical observations of minimised toxicity and improved efficacy, may be of value for several drugs [113]. Studies on dose magnitude will probably be compromised by ethical and patient safety considerations. However, a possible approach to safely study the therapeutic effect of increased doses could, for example, adopt approaches such as vector targeting, which has been studied in the pre-clinical setting with 5-FU [114]. Considerations of the benefits and drawbacks with this type of treatment, and other genetic combination therapies, are, however, beyond the scope of this overview.

For drugs in clinical use, careful studies using the population approach to identify factors with predictive value for drug pharmacokinetic or therapeutic effect, preferably after the administration of fixed doses, are clearly desirable. There should be clear definitions on which correlations are considered clinically relevant, and it should be clarified which pharmacokinetic deviations are thought to have a clinical effect. As discussed in part I [1], the administration schedule should also be taken into account. For example, the GFR might be relevant for the clearance of a drug after a bolus dose, but not during continuous infusion resulting in a low plasma drug concentration [4]. If relationships are observed between the pharmacokinetic and clinical effect, which is the ultimate measure, they should then be prospectively validated in different populations. Although the implementation of both pharmacokinetic and pharmacogenetic analyses and monitoring in routine clinical practice is complex and associated with practical limitations, knowledge gained in each area would be useful for developing Bayesian models with practical application in cancer chemotherapy. Also, some of these procedures could probably be simplified. For example, phenotyping seems more important than genotyping for predicting CYP3A drug clearance (see part I [1]).

Until Bayesian models can be adopted for individualised chemotherapy dosing in routine care, flat-fixed dosing, with appropriate modifications for abnormal organ function, seems a sensible way forward. This approach could be combined with dose banding to simultaneously improve current chemotherapy and patient handling processes. However, for drugs such as 5-FU, 6-MP and irinotecan, testing/genotyping for the respective DPD, TPMT, and UGT1A1 enzyme variants should be considered before dose selection.

Although BSA dosing has been scrutinised in different reports for the last 15 years, there has been no substantial change in clinical practice. This change will be dependent on education and research efforts from, and communication between, biochemists, pharmacists, medical oncologists, oncology nurses, and patients. The involvement of the pharmaceutical industry is also important, both to review doses for drugs with existing marketing authorisation, and to develop alternative dosage strategies for new drugs at the clinical trial stage.

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