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Chemotherapy dose adaptations

Dosing of chemotherapy drugs is complicated due to their extreme toxic nature and variable pharmacokinetic and pharmacodynamic characteristics. Also, data on dose modifications in specific patient groups are often sparse

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In the treatment of cancer it is almost impossible to achieve tumour remission without adverse effects, some of which may be very serious and life-threatening. However in those cancers where there is the potential for a curative effect, for example some malignant lymphomas and breast cancers, toxic effects that would be considered unacceptable in the treatment of non-malignant disease can be clinically justified. In other cancers, or in the adjuvant and palliative settings, benefits need to be carefully weighed up against risks.

The dosing of traditional chemotherapy drugs is complicated by therapeutic indices which are generally lower than for any other drugs in use, and also by large intra- and inter-patient variability in pharmacokinetics (PK) and pharmacodynamics (PD). Dose individualisation based on body surface area (BSA) has been practised for many years based on studies which indicated that "effective" and maximum tolerated doses were similar for animals and humans when normalised to BSA.[1,2] Current research indicates that BSA-based doses fail to reduce the variability in PK and PD for the majority of drugs in adults, and it is widely known that the BSA method fails to account for several factors known to be relevant for drug disposition.[3] These include, for example, hepatic and renal function, body composition, nutritional status, specific enzyme expression/activity, drug resistance, drug-binding proteins, gender, age and prior or concomitant medication and disease.

However, alternative dosing strategies are generally lacking and approaches to manage chemotherapy toxicity and/or therapeutic effects include alterations of dosage, dosage intervals and/or administration duration, the use of different drug formulations (eg, liposomal formulations of doxorubicin) or analogue drugs (eg, cisplatin versus carboplatin), and the use of supportive care (eg, mesna with cyclophosphamide). For example, the common 3-week cycle length was mainly based on the time an average patient needs to recover from the myelosuppressive effect from the previous course of chemotherapy to be able to manage the next course.

Dose modifications according to organ impairment

Renal and hepatic dysfunction

Renal and hepatic dysfunction in cancer patients can have multiple causes. Examples that apply to both include metastases, co-administered medication, organ damage caused by drugs and/or radiotherapy, or pre-existing intrinsic disease. Electrolyte disorders associated with malignancy or tumour lysis syndrome may also affect the kidneys, while renal hypoperfusion may be caused by dehydration or bleeding, and obstruction to outflow by blood clots, stones or tumour invasion of the kidney, ureters or bladder. Hepatic conditions may include cirrhosis in patients who misuse alcohol, or viral hepatitis. However, there are no standardised approaches for defining organ dysfunction in patients with cancer and there is no evidence on whether patients with tumour related organ dysfunction should be treated differently than those with pre-existing organ dysfunction. In addition, the information on chemotherapy drug PK and PD in patients with hepatic or renal dysfunction is usually limited. Chemotherapy doses are therefore most commonly reduced by fractions, for instance 25% or 50%, based on the degree of organ impairment and extent of hepatic or renal clearance, and as recommended by local guidelines or the drug Summary of Product Characteristics. There is little evidence for individualised dose adjustments, although two examples will be discussed below.

Routine tests

Routine tests used for assessing hepatic and renal function are not exact measures of organ function and not necessarily accurate predictors of how the clearance of specific drugs will be affected. Hepatic function is commonly assessed by measurement of the serum bilirubin level and standard liver function tests (LFTs). In terms of drug clearance, this can be seen as an oversimplified strategy because although these biochemical indicators reflect liver integrity and to some extent metabolic function, they do not necessarily reflect drug metabolising capacity of liver enzymes. In the absence of more accurate measures abnormal LFTs may still be sufficient to determine when large dose reductions may be appropriate and when hepatotoxic drugs should be completely avoided. There are examples of studies which have aimed to develop specific dose modification schemes for patients with liver dysfunction. Dobbs et al.[4] observed a relationship between raised asparate aminotransferase (AST) and epirubicin clearance in women with breast

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cancer. This relationship was used in a dosage formula in which the target area under the plasma concentration–time curve (AUC) was defined as the average AUC measured in a group of women with normal liver tests, and a prospective evaluation indicated that dosing based on AST may reduce PK variability.

In the assessment of renal function, the glomerular filtration rate (GFR) is often estimated using creatinine clearance prediction equations rather than being measured with gold standard tests such as isotopic or inulin clearance, which may be unavailable or considered too expensive. The disadvantage with methods based on creatinine clearance is that the estimated GFR can be inaccurate in many patients because creatinine levels may be affected by factors such as diet, drugs, age, obesity, cachexia and diseases, for example malignancies.[5] Serum creatinine is also insensitive to small changes in GFR and there are inter-laboratory differences in the calibration, precision and accuracy of assays used to measure serum creatinine levels. The various prediction equations have consequently been reported to have suboptimal predictive capabilities for ideal patient care and estimated GFR may need to be used with caution when calculating dosage adjustments.[5] A well known example of dosage modification based on renal function is the case of carboplatin, which will be discussed below.

In view of the limited data to support more individualised dose modifications for patients with organ dysfunction in general, the actual determination of PK could be considered the most accurate approach. Sub-therapeutic test doses could guide the selection of therapeutic doses for drugs with linear PK in order to obtain similar drug exposure to that obtained in patients with "normal" organ function. However, as discussed below, this approach may not be practically feasible and a correlation between exposure and clinical effects may not exist.

Dose modifications according to PK

The clinical effects of cancer chemotherapy drugs can, in most cases, not be directly measured. Levels of toxicity or PK measures for drugs and/or metabolites may therefore be used as surrogate markers, and the monitoring of these is often mentioned as one approach to improve chemotherapy dosing. Although these surrogate markers have the advantage of being clinically measurable, their relationships with clinical effects are however limited to specific drugs and tumour types.[3] In cases where PK–PD relationships exist, these may be further confounded by patient and disease specific factors such as age, concomitant medication, differences in intra-tumour PK and drug resistance. For example, elderly patients may have PD alterations which are not reflected by any changes in PK.[6]

Examples of drugs for which the monitoring of plasma drug concentrations (therapeutic drug monitoring; TDM) and PK-guided dosing are commonly used in clinical practice include methotrexate and carboplatin. The TDM of methotrexate is used to determine the dosage of folinic acid, which is given to diminish the toxicity of methotrexate, while carboplatin is dosed to achieve a pre-defined AUC. The widely adopted Calvert-formula uses the correlation between renal and total body clearance of carboplatin and GFR to calculate the dose required to achieve this AUC (Dose = AUC x (GFR+25)).[7] Target AUC's are normally recommended as 5 and 7mg/mL x min for previously treated and untreated individuals, respectively, based on the relationship for AUC with therapeutic and toxic effects.[7] Actual PK modelling is therefore not necessary on a routine basis.

For most drugs real-time measurements and PK data analyses would be required for PK-guided dosing, and although this is achievable with advances in analytical methods, this may not be practically and economically viable. The monitoring of PK measures such as AUC requires a number of blood samples, and to be feasible in clinical practice, the approach is essentially dependent on the development of limited sampling models. The monitoring of PK measures may also have little benefit if the optimal target PK measure is unknown, although it still may be useful in some settings. For example, obese patients frequently receive doses which are "capped" at a BSA of 2–2.2 m^2. Doses are therefore reduced without any evidence suggesting an increased exposure compared with that in normal weight subjects. Recent studies have shown that the clearance of several chemotherapy drugs is not reduced in obese patients and that capping may result in suboptimal treatment outcomes.[8] The comparison of drug disposition in obese and normal weight patients could therefore help inform dosage recommendations even when the target exposure is unknown.

In some cases possible changes in PK and/or PD can be predicted by measuring or estimating the activity of critical enzymes involved in the metabolism of particular drugs, and this can be used in attempts to manage treatment toxicity. For example, dihydropyrimidine dehydrogenase (DPD) and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) deficiencies can be measured or detected with genotyping prior to 5-fluorouracil (5-FU) and irinotecan treatment, respectively. Genetic polymorphism of DPD, the enzyme which catalyses the oxidation of 5-FU, can result in varying degrees of deficiency and complete DPD-deficiency can be lethal. Different tests have been developed to identify patients with DPD-deficiency before treatment, including the measurement of DPD-activity in peripheral mononuclear cells, the determination of the dihydrouracil-uracil (UH2-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.[9]

Genetic polymorphisms in genes coding for other drug metabolising enzymes, including the cytochrome P450 (CYP) enzymes, also cause large differences in drug metabolism and PK.

For example, when phenotyping hepatic CYP3A4 with the ^{14}C-N-methyl-erythromycin breath test in patients receiving docetaxel, enzyme activity was found to vary more than twenty-fold while docetaxel clearance varied nearly sixfold.[10] However, alternative dosing approaches based on such findings have yet to be developed for routine use.

Conclusions

Dosing of chemotherapy drugs is complicated due to their extreme toxic nature and variable PK and PD characteristics. Also, data on dose modifications in specific patient groups are often sparse.

Patients receiving chemotherapy require careful assessment of organ function prior to, during and following therapy. However, there is no common system to define organ dysfunction in patients with cancer and the commonly used estimates of hepatic and renal functions have limitations. As a consequence, these need to be considered with reference to the full clinical picture. If treatment is tolerated following routine empiric dose reductions, the escalation of subsequent doses should also be considered. Toxicity is commonly regarded as the most important effect to control, but the risk of under-dosing and reduced efficacy should be given equal attention. In clinical practice it appears to be more common to reduce doses or delay treatment in response to toxic effects than it is to increase the dose-intensity when treatment is well tolerated. Trials on adjuvant cyclophosphamide, doxorubicin and 5-FU in breast cancer have shown that under-dosing may lead to an almost 20% relative reduction in disease-free survival.[11] Bonadonna et al.[12] observed an even larger survival reduction in patients receiving less than 85% of the target doses of the cyclophosphamide, methotrexate and 5-FU regimen.

PK-guided adaptive dosing methods can be useful to standardise drug exposure within or between patients, but the correlations between cancer chemotherapy drug PK and PD are often poor or absent and may be affected by many confounding factors. The determination of "target" exposures to cancer medicines is therefore not straightforward. For some chemotherapy drugs the PK and PD are directly affected by the activity of certain drug metabolising enzymes which exhibit genetic variability, and the genotyping or phenotyping of these enzymes have the potential to contribute to more reliable and robust systems for dose modifications. ■

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