

Short Communication

How to calculate the dose of chemotherapy

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Body surface area-dosing does not account for the complex processes of cytotoxic drug elimination. This leads to an unpredictable variation in effect. Overdosing is easily recognised but it is possible that unrecognised underdosing is more common and may occur in 30% or more of patients receiving standard regimen. Those patients who are inadvertently underdosed are at risk of a significantly reduced anticancer effect. Using published data, it can be calculated that there is an almost 20% relative reduction in survival for women receiving adjuvant chemotherapy for breast cancer as a result of unrecognised underdosing. Similarly, the cure rate of cisplatin-based chemotherapy for advanced testicular cancer may be reduced by as much as 10%. The inaccuracy of body surface area-dosing is more than an inconvenience and it is important that methods for more accurate dose calculation are determined, based on the known drug elimination processes for cytotoxic chemotherapy. Twelve rules for dose calculation of chemotherapy are given that can be used as a guideline until better dose-calculation methods become available. Consideration should be given to using fixed dose guidelines independent of body surface area and based on drug elimination capability, both as a starting dose and for dose adjustment, which may have accuracy, safety and financial advantages.

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Despite the recent advances in anticancer treatment and the promise of novel targeted therapies, it is likely that cytotoxic chemotherapy will continue to be used for the next few decades. It is now recognised that our current method of dose calculation for chemotherapy using body surface area (BSA) is inaccurate (Gurney, 1996, 1998; Ratain, 1998). This method does not account for the marked inter-patient variation in drug handling that is known to exist for these drugs so that drug effects such as toxicity are also highly variable and therefore unpredictable. One consequence is unexpected underdosing which leads to reduced effectiveness of chemotherapy. However, until there is a better method, BSA-dosing will prevail since there has been over 40 years of experience with this method and 'old habits die hard'. The following discussion will remind the clinician of the inaccuracies of this system and will suggest guidelines for dose calculation that encourages consideration of important parameters other than BSA alone.

To calculate dose accurately drug elimination needs to be understood. Typically there is a 4–10-fold variation in cytotoxic drug clearance between individuals due to differing activity of drug elimination processes related to genetic and environmental factors (Gurney, 1996). For example, the activity of cytochrome P450 (CYP) 3A4/5, the major oxidising enzymes for many cytotoxic drugs varies by as much as 50-fold (Wrighton *et al*, 1996). A common single-nucleotide polymorphism (SNP) or CYP3A5 has recently been identified and others are being searched for (Kuehl *et al*, 2001). In addition many drugs and disease states are known to inhibit or induce CYP activity further adding to this variation (George *et al*, 1996). Another example is the eight-fold variation in dihydropyrimidine dehydrogenase (DPD) activity, the enzyme

that catabolises 5FU (Etienne *et al*, 1994). Less is known about the variation in other critical hepatic elimination processes such as active biliary excretion by multidrug resistance gene 1 (MDR1), multidrug resistance-associated protein 2 (MRP2) and the other ATP binding cassette (ABC) family of efflux pumps, although some polymorphisms have been identified (Tanabe *et al*, 2001). A number of SNPs have also recently been identified for the steroid and xenobiotic receptor (SXR), a common-pathway receptor which transcriptionally activates a number of the drug elimination genes such as CYP3A4, MRP2 and MDR1 (Zhang *et al*, 2001). Variation in renal function is more easily identified but none of these complex processes are accounted for when BSA alone is used to calculate drug dose.

THE PROBLEM OF UNDERDOSING

It is clear that for most cancers there is a plateau in the dose–response curve for cytotoxic chemotherapy. Increasing the dose above a standard dose will increase toxicity, but does not improve anti-tumour effect (Gurney *et al*, 1993; Stadtmauer *et al*, 2000). High-dose chemotherapy is now largely reserved for acute leukaemia and aggressive lymphomas in relapse. However, the dose intensity studies from the last two decades have shown that anti cancer effect is substantially reduced if the dose of drug is intentionally decreased below the standard. What has not been recognised is that a significant proportion of patients may be *inadvertently* underdosed because of our inaccurate dose–calculation methods, which may cause a reduced cure or other effect.

The dose of a new drug is conventionally determined in a phase I study and then adjusted after more widespread use. The end point of this process is prevention of toxicity rather than identifying the dose for best anti-tumour effect. One consequence of this, coupled with the inaccuracy of BSA-dosing, is that significant underdosing becomes intrinsic to our system of dose determina-

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tion. Figure 1 illustrates the scheme of a phase I study for a drug with linear pharmacokinetics. The horizontal lines represent the variation in systemic exposure at various dose levels. At dose level 3, those patients with lower drug elimination capability develop dose-limiting toxicity and subsequently that dose level is defined as the maximum tolerated dose. Dose level 2 is recommended for phase II studies since it causes tolerable toxicity in all patients. However, due to the variation in drug handling, a proportion of patients will be relatively underdosed since they are more capable of eliminating the drug. This means the wide distribution of systemic exposure is skewed towards the ineffective range when dose is calculated using BSA. Evidence for this effect can be found in a recent study by Gaemelin *et al* (1999). This group had defined the optimum 5FU plasma concentration with a regimen using 5FU in a dose of 1300 mg m² infused over 8 h every week. For a group of 81 patients treated with dose calculated using BSA, 80% of patients were found to have an ineffective 5FU plasma concentration after the first dose.

What other evidence is available to indicate that underdosing occurs with the current dose calculation method? Here the problem is in defining and identifying underdosing. Can the lack of effect on normal tissue (i.e. toxicity) be used to identify a lack of effect in neoplastic tissue? For this to be tenable a toxicity-response relationship must be shown for cytotoxic chemotherapy. There is a wealth of information regarding dose-toxicity and dose-response relationships but very little information is available in the literature examining the relationship between toxicity and response (Gurney *et al*, 1993). Three studies from the 1970s and 80s purport a relationship between lack of myelosuppression and lack of anti-tumour effect in osteosarcoma and multiple myeloma (Cortes *et al*, 1974;

McIntyre *et al*, 1978; Carpenter *et al*, 1982). However, a firm relationship cannot be claimed given the low patient numbers and the technique of analysis of these studies.

More recently, some studies have illustrated a toxicity-response relationship for breast cancer, testis cancer, ovarian cancer and lymphoma (Table 1) (Rankin *et al*, 1992; Horwich *et al*, 1997; Poikonen *et al*, 1999). A randomised MRC study of combination chemotherapy in advanced testicular cancer showed a significantly higher relapse rate in patients receiving carboplatin who failed to develop myelosuppression. There was a similar relationship shown for patients receiving cisplatin. Relapse rate for the cisplatin containing regimen was 11% for patients with a nadir white cell count (WCC) of over 2.0×10^9 per litre compared with 4% for patients whose WCC fell below 2.0×10^9 per litre after chemotherapy. Although this difference was not statistically significant, inadvertent underdosing may be an issue for cisplatin as well as carboplatin-containing regimen in the treatment of testicular cancer. These studies show a significantly worse anti-tumour effect for those patients who failed to develop myelosuppression after treatment compared to those who did. It is important that this relationship is examined more fully in other cancer types. This can be done by re-analysis of previous studies where nadir blood counts have been recorded in the majority of patients. A recent randomised study by the Australian Lymphoma and Leukaemia Group comparing high dose cyclophosphamide, epirubicin, vincristine and prednisolone (CEOP) with standard dose CEOP, showed that those patients who did not experience a nadir neutrophil count of $< 1.0 \times 10^9$ per litre, had a statistically inferior progression free survival (Gurney *et al*, manuscript in preparation).

If lack of myelosuppression is accepted as an indication of underdosing, the frequency of this event can then be determined. Table 2 is a selection of trials where the frequency and timing of nadir blood counts have been adequately recorded. A substantial percentage of patients (30 to 75%) receiving commonly used chemotherapy regimen have 'inadequate' myelosuppression and may be underdosed.

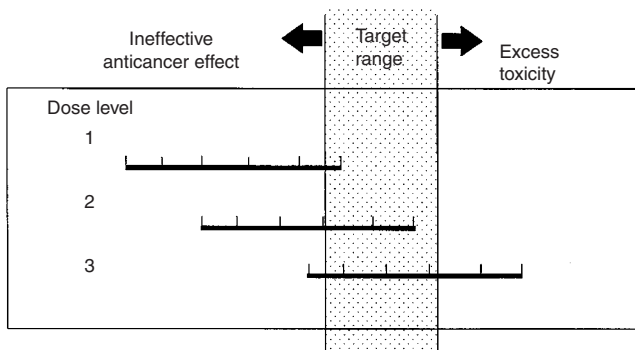


Figure 1 Hypothetical phase I study of a drug with linear pharmacokinetics. Horizontal bars represent interpatient variation in systemic exposure. Each vertical tick mark represents an individual patient on the study. Dose level 3 would be considered the MTD and dose level 2 would be recommended for phase II study despite the majority of patients on that dose level having a systemic exposure in the sub-therapeutic range.

THE SIGNIFICANCE OF UNDERDOSING

The possible significance of the underdosing is outlined in Table 3. Calculation of published data from studies using adjuvant cyclophosphamide, doxorubicin and 5FU (CAF) for node positive breast cancer show that BSA-based dosing may lead to almost a 20% relative reduction in survival in this setting (Budman *et al*, 1998; Early Breast Cancer Trialists' Collaborative Group, 1998; Silber *et al*, 1998). This impact is equivalent to the benefit from the use of adjuvant chemotherapy in node negative breast cancer, or the addition of paclitaxel to the CAF regimen in node positive breast cancer. Similarly, BSA-based dosing may reduce the cure rate of intermediate prognosis testis cancer by almost 10% compared to a dosing method that prevents underdosing (Samson *et al*, 1984; Horwich *et al*, 1997). Clearly, if these calculations are

Table 1 Relationship between myelosuppression and anticancer effect

Reference	Tumour type	Outcome
Carpenter <i>et al</i> , 1982	Stage 2 breast cancer randomised between melphalan or CMF	In patients with 1 to 3 nodes, a nadir WCC of $< 3 \times 10^9$ per litre was significant predictor of disease free survival in multivariate analysis
Poikonen <i>et al</i> , 1999	Stage 2 breast cancer treated with CMF	Low nadir leukocyte associated with longer distant disease free survival.
Horwich <i>et al</i> , 1997	Testis cancer treated with carboplatin, etoposide and bleomycin	Patients with nadir WCC $< 2 \times 10^9$ per litre and or platelets $< 90 \times 10^9$ per litre had lower relapse rate. 14% vs 28%, $P=0.04$
Rankin <i>et al</i> , 1992	Advanced ovarian cancer. Carboplatin plus chlorambucil vs carboplatin	Worse progression-free survival for patients who had grade 0 WCC nadir ($P<0.001$)
Gurney <i>et al</i> , (unpublished)	Aggressive lymphoma treated with CEOP	Worse progression free survival for patients with neutrophil count nadir of $> 1 \times 10^9$ per litre ($P=0.04$)

CMF=cyclophosphamide, methotrexate, 5FU. CAF=cyclophosphamide, doxorubicin, 5FU. CEOP=cyclophosphamide, epirubicin, vincristine, prednisolone.

Table 2 Lack of myelosuppression from standard chemotherapy regimen

Reference	Tumour type	Nadir myelosuppression
Horwich <i>et al</i> , 1997	Testis cancer treated with carboplatin or cisplatin and etoposide, bleomycin	7% of BEP and 65 % of CEB had nadir WCC > 2.0×10^9 per litre
Rankin <i>et al</i> , 1992	Carboplatin (dosed on BSA) with or without chlorambucil for advanced ovarian cancer	29.4% of patients had nadir WCC > 4×10^9 per litre
Budman <i>et al</i> , 1998	Adjuvant CAF for breast cancer	44% of patients had nadir WCC > 2.0×10^9 per litre
Silber <i>et al</i> , 1998	Adjuvant CAF or CMF for breast cancer	50% had nadir neutrophil count > 1.0×10^9 per litre
Bishop <i>et al</i> , 1999	Advanced breast cancer treated with CMF or paclitaxel	37% had nadir neutrophil count > 1.5×10^9 per litre
Ratain <i>et al</i> , 1991	Randomised study of standard vs individualised dose of etoposide by 72 h infusion	60% of patients on standard arm had nadir WCC of > 2.0×10^9 per litre
Hovgaard and Nissen, 1992	CHOP for lymphoma. 127 historical controls.	50% of patients had nadir WCC > 2.0×10^9 per litre

CMF=cyclophosphamide, methotrexate, 5FU. CAF=cyclophosphamide, doxorubicin, 5FU. BEP= bleomycin, etoposide, cisplatin. CEB=carboplatin, etoposide, bleomycin. CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone.

Table 3

Impact of inadvertent underdosing on adjuvant chemotherapy for stage 2 breast cancer

1. Halving the dose of CAF causes a reduction in the 5-year survival from 79 to 72% (absolute reduction=7%) (Budman *et al*, 1998)
2. In 50% of patients receiving CAF as adjuvant treatment for breast cancer, the nadir neutrophil count will not fall below 1.0×10^9 per litre. (Silber *et al*, 1998)
3. There is an absolute survival benefit of 12% for patients less than age of 50 years receiving chemotherapy for node positive breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1998)

If (conservatively) 30% of patients receiving CAF for stage 2 breast cancer are underdosed because of conventional dosing, absolute reduction in 5-year survival may be 30 of 7%=2.1%, which is a 17.5% relative reduction in survival.

Impact of inadvertent underdosing on chemotherapy for advanced testis cancer

1. A significant reduction in the cisplatin dose (120 to 75 mg m^{-2}) in the PVB regimen causes a reduction in the 3-year survival from 84 to 60% (absolute reduction=24%) (Samson *et al*, 1984)
2. In 75% of patients receiving BEP for treatment of advanced testis cancer, the nadir white cell will not fall below 2.0×10^9 per litre. (Horwich *et al*, 1997)
3. The disease-free survival for BEP is 80% at 5 year (intermediate prognosis) (International Germ Cell Consensus Classification, 1997)

If (conservatively) 30% of patients receiving chemotherapy for advanced testis cancer are underdosed because of conventional dosing, reduction in long term disease free survival may be 30 of 24%=7.2%, which is a 9% relative reduction in cure rate.

accurate, we can no longer tolerate the inaccuracies of BSA dosing as of minor consequence. It is important that more accurate calculation methods are developed. Another obvious bonus of an accurate dose calculation scheme is prevention of toxicity from overdosing.

PREVENTION OF UNDERDOSING

One popular method of dose individualisation is to adjust subsequent doses of chemotherapy based on the level of myelosuppression eventually avoiding overdosing and underdosing – so called 'toxicity-adjusting dosing' (Gurney, 1996). A Swedish group has adopted this approach in the adjuvant treatment of breast cancer (Berch *et al*, 2000). Using the 5FU, epirubicin and cyclophosphamide (FEC) regimen, dose adjustments were made on each cycle to ensure a target level of myelosuppression. After a number of dose adjustments this method of individualising dose gave a three-fold interpatient range of cyclophosphamide dose (450 to 1800 mg m^2) and a four-fold range for epirubicin (38 to 120 mg m^2). This is more in keeping with the known interpatient variation in drug clearance for these drugs. However, it would be better to achieve an individualised dose variation from the first dose rather than the third, fourth or fifth dose. To achieve this, the dose calculation method must take into account the activity of the elimination processes for the drug(s) in question before the first treatment is given.

FIXED DOSE?

Until better dose calculation methods are determined most clinicians will continue with the traditional method using BSA. However, clinicians

should be mindful of the inaccuracies of this system and should not be duped by its pseudo-scientific use of formulas and slide rules. Doses should be rounded liberally. Fractional doses are irrelevant and unnecessary. Furthermore they are expensive and possibly unsafe. It is unreasonable to use a small portion of an extra vial of chemotherapy if the dose prescribe is inaccurate 40% of the time. Ask your pharmacist whether he/she can really draw up 215 mg of DTIC (instead of 200 or 220 mg), 85 mg of docetaxel (instead of 80 or 90 mg) or 63 mg of methotrexate. What is the additional cost of prescribing 305 mg of paclitaxel instead of 300 mg?

Consideration should be given to using a range of 'fixed doses' for a particular drug that could be used as the starting dose and for dose adjustments. Remember that drug elimination varies by at least four-fold between individuals. Can a clinically significant different pharmacodynamic effect be expected between 650 and 700 mg of 5FU? This probably holds true even for carboplatin where doses are determined as a function of glomerular filtration rate. There is still a margin of error in these calculations so dose rounding is also tenable in this situation. The alternative of using a fixed dose for chemotherapy has recently been suggested for cisplatin and irinotecan after investigators found no relationship between BSA and clearance for both of these drugs (de Jongh *et al*, 2001; Mathijssen *et al*, 2002).

GUIDELINES

Guidelines for dose calculation are listed in Table 4 and an example in Table 5. These are not comprehensive and should be used in conjunction with clinical experience and good clinical practice. Some of them are subjective and based on opinion and derived

Table 4 Twelve rules for dose calculation of cytotoxic chemotherapy

1. **BSA-calculated dose is inaccurate.** Do not use this as the **sole** parameter for dose calculation.
2. Do not use **extremes of BSA** to calculate dose (e.g. < 1.5 and > 2.0). The use of ideal body weight has no scientific basis. However, the presence of cachexia or obesity both affect drug handling.
3. Use BSA as a means to learn the **typical absolute dose range** of drugs for a particular protocol (e.g. a typical doxorubicin dose is 80 to 120 mg, not 60 mg m^{-2}). The best dose is likely to be in that range and independent of BSA
4. **Round the calculated dose liberally.** Do not order 'fractional' dose size. e.g. 102 mg of doxorubicin should be 100, 67 mg of methotrexate should be 65 or 70 mg. This has safety, compounding and financial implication.
5. Always take **parameters other than BSA** into consideration when calculating dose (see points 6–9).
6. **Know how the drug is eliminated.** If you do not know, don't order the drug. Adjust the dose based on the appropriate tests of **drug elimination** e.g. serum creatinine, GFR, bilirubin, transaminases, or other specific tests of drug elimination as they become available (genotype, phenotype).
7. Check for other medications that may inhibit or enhance cytotoxic drug elimination (see Table 6).
8. Check for other parameters that affect **drug disposition** e.g. serum albumin, presence of ascites, cachexia, obesity, performance status.
9. Check for other factors that affect **normal tissue sensitivity** that may require dose reduction e.g. prior chemotherapy and radiotherapy, performance status, cachexia.
10. **Know that this dose will be incorrect in up to 40% of the time.** Approximately 10% of patients will be overdosed and 30% of patients will be underdosed.
11. **Measure a biological endpoint** such as myelosuppression to check affect of the administered dose. Adjust the subsequent dose **UP** as well as down accordingly. A suggested minimal neutrophil count nadir for myelosuppressive drugs is 1.5×10^9 per litre. Adjust all drugs in a regimen that have similar elimination routes (e.g. doxorubicin, vinca alkaloids, podophyllotoxins, irinotecan, taxanes).
12. Always have your dose calculation **checked** by someone else e.g. pharmacist or nurse.

Table 5 Case example

A 45 year old woman with metastatic breast cancer to liver and bone presents for chemotherapy and you are asked to order the treatment. It has been decided that a combination of doxorubicin and cyclophosphamide will be used. Her height is 160 cm and weight 92 kg. Using the Dubois formula, her body surface area is 1.95 m^2 . The protocol dose is doxorubicin 60 mg m^{-2} and cyclophosphamide 600 mg m^{-2} . Her FBC is normal.

How will you calculate the dose of chemotherapy? Is there any further information you need?

1. Both drugs are eliminated by the liver. You want to know that the liver functions tests are not grossly abnormal
2. You want to know whether she is taking any other medications that may interfere with drug elimination (see Table 6).
3. You want to know whether she has previously received chemotherapy or extensive radiotherapy since this may affect the bone marrow response to treatment. This is the patient's first dose of chemotherapy and she had radiotherapy to the breast after lumpectomy 2 years ago. Her liver functions tests are only mildly abnormal. She is on no other medications.

Initial calculation according to the protocol gives a doxorubicin dose of 117 mg and cyclophosphamide 1170 mg. What dose will you give? What factors affect your decision?

1. This patient is probably obese given her height and weight. It is known that drug clearance of both drugs is reduced in obese patients.
 2. You know that BSA-dose calculation is inaccurate.
 3. You know that doxorubicin comes in 50 mg ampoules and cyclophosphamide comes in 200 mg ampoule.
 4. You know that giving fractional doses are difficult to compound accurately and can lead to unnecessary costs.
- You decide to give a dose of doxorubicin 100 mg and cyclophosphamide 1000 mg.

What about subsequent doses?

You monitor the toxicity of the patient using neutropenia as a surrogate pharmacodynamic marker. You dose-reduce according to standard practice in the case of excessive toxicity. However, you also check for the absence of toxicity since you do not want the patient to be underdosed.

The patient has minimal toxicity. A nadir FBC shows a neutrophil count of 2.5×10^9 per litre and platelets of 180×10^9 per litre (no significant drop from pre-treatment level). You increase the dose for cycle 2 by 15–20% with appropriate rounding of dose (doxorubicin 120 mg, cyclophosphamide 1200 mg). You plan to check the nadir blood count after cycle 2.

from clinical practice while others are based on best evidence as reviewed in Gurney (1996). The guidelines allow a framework in which to work, in an area currently fraught with uncertainty. As other methods of dose calculation become available, they can be tested against these guidelines and adopted into clinical practice if found to be superior.

As yet there are no useful *in vivo* measures of drug elimination that can be used for dose calculation. Efforts have been aimed at predicting alteration in drug elimination in those with grossly abnormal liver or renal function with limited success. Carboplatin can be fairly accurately dosed by measuring the GFR. Guidelines exist for dose adjustment of other cytotoxic drugs that are predominantly renally excreted (Kintzel and Dorr, 1995). However, most cytotoxic drugs are largely hepatically eliminated. Attempts at using elevation of serum transaminases and alkaline phosphatase as a guide to dose adjustment have largely failed except perhaps for docetaxel (Alexandre *et al*, 2000).

Potential drug interactions is an extensive problem and warrants a separate review. Drug elimination can be enhanced by activation of the steroid xenobiotic receptor (SXR) and other nuclear receptors (Synold *et al*, 2001; Kast *et al*, 2002). SXR has multiple ligands including rifampicin, dexamethasone, cyproterone acetate, spirinolactone, St John's wort and others. SXR activation leads to upregulation of transcription of many elimination pathways including CYP3A4/5, 2B6, 2C8, MDR1, MRP2 and glutathione-s-transferase. Inhibition of CYP enzymes and MDR1 and probably other efflux pumps can occur with drugs such as cyclosporin, HMGCoA reductase inhibitors, verapamil, omeprazole and cimetidine. However, few clinically significant interactions have been documented or examined for cytotoxic chemotherapy. Anti-convulsant induction of CYP3A4 (phenytoin, phenobarbitone, carbamazepine) has been shown to affect the pharmacodynamics of paclitaxel, irinotecan and teniposide and concomitant administration of anti-convulsants with chemother-

Table 6 Commonly used drugs that affect CYP3A4/MDR1 elimination routes**Drugs that inhibit CYP3A4/MDR1** (decrease drug elimination)

Macrolide antibiotics (erythromycin, clarithromycin)
 Azole antifungal agents (fluconazole, ketoconazole, itraconazole)
 Antidepressants (nefazodone, fluvoxamine)
 HIV protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir)
 HMC-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin)
 Cimetidine
 Verapamil
 Diltiazem
 Cisapride
 Cyclosporin

Drugs that induce CYP3A4/MDR1 (increase drug elimination)

Rifampicin
 Dexamethasone
 Cyproterone acetate
 Spirinolactone
 Phenytoin
 Carbamazepine
 Phenobarbitone
 St. John's wort (hyperforin)

Cytotoxic drugs that are eliminated by CYP3A4/MDR1

(competitive inhibition)

Anthracyclines
 Vinca alkaloids
 Taxanes
 Irinotecan
 Podophylotoxins
 Ifosfamide
 Cyclophosphamide

apy has been associated with a worse disease-free survival in children with acute lymphoblastic leukaemia (Chang *et al*, 1998;

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