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Nine Steps to Personalised Therapy: The Art and Science of Anti-Cancer Drug Dosing.

(a Guidance Statement of the Medical Oncology Group of Australia)

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Summary

Cancer medicine has undergone considerable development in recent decades, with many more agents with diverse mechanisms of action and toxicities. However, drugs still have a narrow therapeutic index, and significant interpatient variability in pharmacokinetics and metabolism, so getting the dose right for each patient remains a critical issue in attaining the best individual patient benefit-cost ratio. Published guidelines and trial evidence provide a solid foundation for guiding drug selection but, especially for personalised dosing, are only a starting point. We summarise issues in interpreting evidence about appropriate personalised dosing. We provide 8 steps to guide clinicians in decision-making, based on: pharmacology of each agent (absorption, distribution, metabolism, elimination and mechanism of action); scientific evidence for recommended doses; professional knowledge of patient's unique phenotype; previous drug tolerance; individual dose adjustment in combination therapy; communication and documentation, with the added need for ongoing monitoring and adjustment. This process uses a mixture of scientific evidence and professional judgement. We suggest professional education and future research towards refined dosing.

Introduction

Cancer medicine is an exciting yet challenging discipline, especially with the advent of a range of new targeted therapies and immune active agents that have great promise to increase survival or possibly cure some patients. Substantial advances in identifying active agents, more effective combinations, and using pre- or post-operative chemotherapy combined with radiation, have led to longer survival and improved quality of life.

Oncology clinical trials focus on determining appropriate drug selection for a particular cancer and stage of disease. However, an often-overlooked aspect of cancer medicine is ensuring precision in dosing. Getting the dose right is important to maximise the benefit for both individual patients and the health system to ensure cost-effectiveness and to reduce the burden of care. To maximise benefits and minimise adverse effects, anti-cancer drug dosing needs to be individualised. Every patient is a unique blend of genetic and environmental influences, so using a single flat dose for all patients is unlikely to provide the best possible outcomes for all circumstances.

Here we review the issues around decision-making processes by an oncology physician to arrive at the most appropriate dose for each patient. This information is valuable to a range of health professionals, including nurses, pharmacists and administrators, as well as patients, to allow them to understand medical oncologists' decisions and support them where appropriate. Then we provide 9 principles that should guide cancer physicians in determining the most appropriate individual dose to provide the best possible outcomes. Lastly, we suggest future improvements towards optimal cancer drug dosing, and education and training recommendations.

Dose for a population vs. dose for an individual

Appropriate drug *selection* for each cancer is a central, well-understood, tenet in medical oncology. Cancer clinical trials provide evidence of absolute and relative benefits and side-effects of treatment regimens. Evidence-based tools are readily available, including NCCN guidelines, ESMO guidelines, and EviQ protocols to facilitate clinical decision-making and drug/regimen selection.[1] However, dose recommendations in such protocols are not personalised for an individual.
Most conventional anti-cancer drugs have a narrow therapeutic index (**figure 1**). Too low a concentration at its target leads to sub-optimal or no benefit (but likely minimal toxicity); too high a concentration can lead to unacceptable or life-threatening toxicity (but possibly maximal benefit). Studies from the 1980s and 1990s showed that most anti-cancer drugs have a plateau in the dose-response curves, such that significant overdosing does not increase therapeutic benefit.[2,3] However, dose-intensity studies from the same period showed that the anticancer effect is substantially reduced if the dose of drug is intentionally reduced below the "standard" dose (summarised in[4]).

A misunderstood area of dose calculation of anticancer drugs is the concept of dose determination for a population versus dose determination for an individual. Protocol doses that have been determined from phase 1 and 2 studies are based on trial populations and can thus be seen as an 'averaging' process to determine an approximate dose. Substantial differences have been noted between study populations and a general cancer population, and are listed in **Table 1**. It is estimated that at least 10 to 20% of the normal population of cancer patients are not eligible for a clinical trial due to one or more of these factors[5,6]. In one Australian cancer centre only 35% of local lung cancer patients would have been eligible for practice-determining phase 3 trials and a similar proportion for novel targeted therapy trials. [7] Consequently, dose finding studies involving a restricted population are not always transferrable to patients seen in the clinic. Thus, using a 'protocol' dose in **all** cancer patients may lead to excessive, potentially life-threatening toxicity in a

significant proportion, or alternately under-dosing, and cannot afford a blanket recommendation.

The protocol dose determined in a trial does not take individual variation into account. Humans have a four to ten-fold variation in drug elimination processes so the same dose will lead to large variations in systemic exposure. [8-10] In cancer patients, additional factors are at play which lead to further variation in drug handling and tolerance, including renal and hepatic function, cachexia, and concomitant proprietary and complementary medications. For many drugs, such variations are inestimable but can be substantial. Such variations are not adequately accounted for by BSA-based or weight-based dosing alone.[9,11] Carboplatin is an exception where, due to its simple elimination by glomerular filtration, it is possible to predict exposure and platelet nadir using a formula based on renal function, weight and gender. However, even this has inaccuracies and a margin of error, especially at the extremes of body size.[12]

As a consequence, medical oncologists in normal day-to-day practice must extrapolate from published evidence to achieve an optimal dose for each patient. While authorities have made recommendations about enhancing phase 2, 3 and 4 trials to provide more information about dosing in real practice, these recommendations are yet to be adopted. [13]

Drug dosing philosophy

An under-appreciated aspect of patient management is the treating philosophy of the oncologist. Some are more conservative, others more aggressive in their strategy to achieve the best outcomes for patients; this is the result of an unknowable amalgam of training, experience, and influence from peers. This variable philosophy is evident in conferences with audience response systems, where standardised case presentations invariably draw a range of responses. Although not formally studied in oncologists, this suggests that there is no “ideal” or “perfect” management, despite extensive evidence for a particular treatment. One study in pharmacy students observed that convergence (defined as a single response in >75% of participants) occurred in only 60% of conferences and teaching occasions. [14] Anecdotally, we have observed similar variation in audience response in oncology meetings. Presumably, this variation in medical opinion reflects the personal philosophy of the treating oncologist, accompanied by their interpretation of the available data.

Oncologists treatment philosophy also varies between scenarios. For example, most oncologists would be more aggressive (accept higher doses and more toxicity) in patients with a reasonable chance of cure (eg. germ cell tumour, high grade lymphoma) or in an adjuvant setting, compared to symptomatic control in patients with non-curable advanced disease. A lower threshold for dose reduction, for example, might operate in patients where the aim is quality of life, or where the evidence for life-prolongation is not strong.

To protocol or not to protocol?

Strictly speaking, any deviation from the original published clinical trial protocol is an “off protocol” deviation without supporting evidence. However, common sense should prevail when deciding to apply a protocol in full. For example, the studies demonstrating superiority of palonosetron over ondansetron as anti-emesis included only 13 highly- or moderately-emetogenic anticancer drugs.[15,16] Since these antiemetics are supportive care, few oncologists would think substitution of one for the other in conjunction with other anticancer drugs has any influence on cancer-related outcomes. Yet this small variation is unquestionably a protocol deviation, a departure

from the published evidence. That being the case, how far a deviation from any published protocol is considered reasonable? Clearly, there is no easy answer to this question, and whilst the extreme positions would be recognisable to most practitioners, the subtle variations may not.

The published dose-reduction or discontinuation rate in a clinical trial is one indication of protocol deliverability to an eligible population. Of the patients recruited for a study, what proportion were able to be treated at 100% dose intensity over the expected planned treatment time? What is the discontinuation rate, and what proportion of this was due to toxicity? Sometimes, this data is not published, and oncologists need to be sufficiently familiar with the drug protocols to infer, and to extrapolate if necessary. Consequently, adjusting drug doses within a protocol, or otherwise varying a protocol may be necessary.

Adjusting drug doses

Typically, medical oncologists personalise drug dose using a number of strategies. Examples include:

1. **Give the dose that is specified in the clinical trial protocol**, and then individualise the dose in subsequent cycles, based on toxicity (or lack of) and the response in the cancer. It is standard practice, for example, to reduce dose in the face of excessive toxicity. However, it is uncommon ot increase the dose if no toxicity is observed.

2. **Adjust a protocol dose before it is given**. This implies that the oncologist perceives a patient as not typical in their drug-handling ability or other characteristics, so that a standard protocol dose may either cause more harm than anticipated, or be less effective. Some examples include body surface area (BSA) capping or dose capping for large patients (ie, using a maximum dose regardless of patient size, based on weight or BSA), limiting doses in the elderly, or of renally cleared drugs in patient with renal diseases, or intentionally giving lower doses to patients in isolated environments where support for severe toxicity is limited. Typically, further dose adjustment is undertaken based on tolerance of the initial dose, including dose increase if no toxicity develops.

3. **Modify a protocol for all patients**. This has usually occurred when there is widespread realisation that the published trial protocol dose does not fit the typical patient in clinical practice.

One example of this is capecitabine in advanced colorectal cancer which was initially assessed at a dose of 1250 mg/m^2 twice daily for the first 14 days of a 21-day cycle. These initial trials reported that 30%–50% of patients required capecitabine dose reductions while on study. [17,18] In wider clinical practice, it became apparent that many physicians used capecitabine monotherapy at a starting dose of 1000 mg/m^2 twice daily, especially in elderly or frail patients, without a demonstration of efficacy at that starting dose in formal trials. [19,20] It took almost a decade for a 'lower dose' protocol to be formally shown to be the more acceptable starting dose, especially in the elderly or less fit population, where dose escalation to the 'standard dose' was found to be unacceptably toxic. [21] In this case, adherence to the 'protocol' dose by physicians would have led to a decade of intolerable and dangerous toxicity in patients with advanced colorectal cancer.

Another example is cabazitaxel in metastatic castrate-resistant prostate cancer where the initial studies that showed a survival benefit used a dose of 25 mg/m^2. [22] Initially, a dose of 20 mg/m^2 was

determined in a phase I study in patients with advanced solid tumours but was later escalated to 25 mg/m^2 when a small phase II study showed that about 1/3 of breast cancer patients could tolerate that dose.[23] In the prostate cancer registration study (TROPIC), the febrile neutropenia rate was 8% with a number of early deaths.[24] In the Australian expanded access program where prophylactic use of G-CSF was not available, the febrile neutropenia rate was 11.5%. [25] Based on clinical experience, many Australian clinicians reduced the starting dose to 20 mg/m^2 in frail or elderly patients. Recently, it was shown in a randomised trial that the lower starting dose was equally effective and less toxic than the initial protocol dose, validating the Australian clinicians' decision to use a non-protocol dose based on their initial 'off-trial' experience with the drug. [26]

4. **Use a protocol that has not been extensively examined** in this patient group or disease state. In this case either a single or few published studies support the use of the agent(s) but there is limited data on the appropriate dose, particularly for patients who might have different drug pharmacological parameters. In this case, a starting dose may be selected with the intention to adjust doses after observing the effects (single study of a new combination that has been reported in abstract form). An example is the use of AUC2 as the basis for dosing weekly carboplatin when used with radiation in head and neck cancer – this dose is well below the maximum tolerated dose in an often-overlooked dose-finding study in this scenario. [27]

5. **Construct a new protocol for an individual** and not on a trial. Rare cancers are underrepresented in clinical trials so evidence for therapy may not be available. However, it is not always reasonable to withhold all treatment due to the 'lack of evidence'. In this case, absence of information is not the same as having studies that fail to show a benefit. In this case oncologists may construct a treatment regimen by extrapolating data from cancers with a similar phenotype or molecular profile.[28]

Oncologists are commonly faced with this type of clinical scenario in more common cancers which have not been studied in formal clinical trials. For example, there is no trial data to guide treatment for a patient requiring neo-adjuvant chemotherapy for bladder cancer and who has diabetic sensory neuropathy or hearing impairment. All the evidence for a survival advantage uses cisplatin. However, few would argue against a substitution using carboplatin in this setting (as it is not neurotoxic), despite the lack of trial evidence for a survival advantage. Similarly, very rare cancers present a treatment challenge, when there may only be case studies published in the literature to guide therapy. For these patients, it is unlikely that there will ever be a randomized study or clinical trial, and the oncologist may consider fabricating a protocol, based on experience, expert opinion, and discussions.

Electronic chemotherapy prescribing

Compared to handwritten chemotherapy orders, electronic health records (EHRs) and chemotherapy ordering can potentially increase use of evidence-based regimens, optimise use of supportive care medications, reduce errors and improve patient safety, maintain or improve practice efficiency, and create and monitor measures of adherence with evidence-based practice. [29]

However, EHRs have not been shown to improve quality and may actually significantly increase the time to access clinical data and reduce the doctor's free time, leading to increased cost. [30,31] Worryingly, a recent study showed that more than 70% of clinicians override e-prescribing alerts for potential drug–drug interactions when using electronic medication ordering. [32]

A fundamental issue regarding the use of electronic chemotherapy prescribing is the potential disconnect between the knowledge of a regimen and its automated prescription. Users can order a complex chemotherapy regimen with insufficient awareness of its evidence-based indication or limitations. Automated dose calculation obviates the imperative for oncologists-in-training to grasp the intricacies of dose individualisation. Computers can take away the critical reasoning inherent in the steps of chemotherapy prescription: examination (and learning) of a drug dose in a regimen; the manual dose calculation process; the appropriate rounding of dose; review to ascertain that the dose *seems* correct (how much does the dose deviate from that used in my other patients?); will the dose suit *my* patient (how does my patient differ from those on the original clinical study?). Moreover, there is a possibility that a computer-calculated dose might be perceived as being more correct than a dose estimated by an oncologist with years of clinical experience.

Although there are many potential advantages for electronic prescribing including safety, efficiency and maintenance of standards, the complexity of chemotherapy dose calculation should not be 'dumbed down' by over-reliance on automated systems. It is critical that such computer systems be recognised for what they are – a tool to be used by well-trained clinicians and not accepted as the 'source of truth'; or worse – as a method to relegate chemotherapy prescription to less experienced staff. [33] We must develop strategies to educate junior staff about the intricacies of dose calculation.

8 Practical Steps to Chemotherapy Dosing

Here we summarise the guiding principles underpinning decisions towards personalised drug dosing in cancer into 8 practical themes.

1. **Know the pharmacology of each drug**
   - The clinician should consider the pharmacological parameters for the anticancer agent including absorption, distribution, metabolism, elimination, as well as dose-response relationships, if they exist.
   - It should be understood that these parameters usually relate to an average, otherwise well, person in a fasting state; often the data is based on small patient numbers.
   - Most drugs have a sigmoidal concentration-response curve (figure 1); for drugs with a steep concentration-response curve, there may be disadvantage in significantly reducing dose.
   - Most drugs, when used for solid tumours, have a ceiling concentration beyond which no further therapeutic effect is derived, and where further dose increase is likely to lead to toxicity.
   - Sometimes the shape of the concentration-effect curve is not known, especially for newer agents (linear is assumed but not proven).

2. **Know the trials that led to the definition of recommended doses and schedules** -
   - Early phase trials define drug dose for use in later phase trials. These studies are usually done in reasonably fit individuals and are often too small to define the extent of interpatient variability.
   - Later phase trials often do not include further pharmacokinetic studies to quantify and investigate interpatient variability.
   - Most trials recruit patients with a carefully defined phenotype; extrapolating the experience of trial patients to the real world can be a challenge.

3. **Know your patient**
   - Each patient is unique; gain an understanding of how the patient differs from a typical clinical

trial patient.

- Factors such as coexisting disease states, concomitant medicationss, other clinical parameters (eg. serum albumin, ascites, cachexia, obesity) and previous bowel or gastric surgery are some factors that may affect drug handling.
- Hepatic and renal dysfunction may affect drug metabolism and elimination.

4. **Understand the patient's unique circumstances**
   - Patients living in rural and remote locations may have tenuous access to high level care for acute life-threatening toxicities, such as neutropenic sepsis.
   - Chemotherapy dosing may need modification to prevent serious risks when endemic or epidemic infections (such as COVID-19) are in play.

5. **Be aware of other factors that might affect normal tissue sensitivity**
   - Previous radiotherapy or chemotherapy may affect normal tissue sensitivity.
   - Radiosensitivity can be an issue; many chemotherapy drugs and targeted agents interact with and enhance radiation, including radiation given many months or years prior. Common examples include fluoropyrimidines, gemcitabine and taxanes.

6. **Consider using toxicity as a surrogate for drug exposure**
   - Consider measuring a biological endpoint such as myelosuppression, rash or other toxicities and use this as a surrogate for drug exposure.
   - Make appropriate dose reductions for unacceptable toxicity.
   - Consider dose escalation in the absence of toxicity, especially for drugs with a narrow therapeutic window.
   - Therapeutic drug monitoring (TDM) is not a standard practice for most cytotoxic agents. Mitotane is an exception. TDM remains the subject of research for anticancer drugs.

7. **Make appropriate dose modifications for drug combinations**
   - Drugs do not contribute equally to all side effects or anticancer effect.
   - Be prepared to adjust the dose and schedule of drugs individually according to known contribution to clinical effect.
   - Most anticancer drugs are metabolised by hepatic enzymes. Knowledge of each drug elimination route will help determine whether some or all drugs should be modified, especially if one drug in a combination is predominantly renally eliminated.

8. **Communicate about any variance from a standard protocol**
   - If you plan to start treatment with a dose or combination not used in literature, discuss the reasons for variation with your patient, oncology pharmacist and other team members. Consider getting further opinions from your peers and experts in the area.
   - Be prepared to adjust doses and schedule individually according to known contribution to clinical effect.

9. Consider conducting a clinical trial to answer dosing or scheduling questions
   - Observation in the "real world" is helpful in changing practice. As noted previously, schedules or doses can sometimes be too toxic for the average patient; this is an opportunity to study drug dosing and scheduling changes formally
   - Sometimes, biomarkers or assays become available after the introduction of drugs into clinical practice. This is an ideal opportunity to utilise biomarkers or drug concentration assays, for

example, to improve personalised medicine

Future research

With personalised chemotherapy dosing as a goal, opportunities for research include therapeutic drug monitoring (TDM), pharmacogenomics, and identification of other biomarkers of drug metabolism or effect. In the past, TDM of anticancer drugs was slow and resource intensive and so not widely used. Now this approach has great capacity; recent advances in techniques for remote blood collection (dried blood spot (DBS)), rapid and precise analysis using technologies such as LC-MS/MS, population-based predictive pharmacokinetic/pharmacodynamic (PK/PD) modelling, and the ability to communicate dosing recommendations to doctors in real time over large distances now make this approach feasible and attractive. In the modern era when drugs are given daily or weekly, TDM offers promise to maximise anticancer effect and minimise adverse effects by estimating the ideal dose early during treatment. Analysing individual genes to predict dosing in oncology has shown limited benefits in the clinic; TPMT genotyping is used routinely to adjust mercaptopurine dose in paediatric ALL with significant cost savings, and UGT1A1 genotyping can identify variants at high risk of irinotecan toxicity but is not in widespread use. [34,35]

Pharmacogenomic techniques such as global SNP analysis can now quickly identify variants in several hundred genes involved in drug metabolism and effect, potentially allowing clinicians to recognise outliers and adjust starting dose of treatments accordingly. Research to identify multi-gene pharmacogenomic signatures that could benefit cancer patients is now required. Proteomic approaches, or identification of other individual biomarkers are research areas in their infancy. Clinical trials could be designed to explore novel biological surrogates for efficacy, including functional imaging and novel toxicity biomarkers. Population data regarding drug dosing in the community could be extracted from available databases to inform relevant changes to guidelines.

Training and Education Recommendations

As pointed out above, the practice of medical oncology is complex, with now a large number of anticancer agents and supportive medications available. For best quality medical management clinicians need to be knowledgeable about not only the indications for each agent, but also the clinical pharmacology (mechanism of action, absorption, distribution, metabolism and elimination) and possible drug interactions. We recommend that professional colleges and other organisations responsible for training, education and professional development include anticancer drug pharmacology as a component of their curricula; it should be a significant component of the medical oncology training curriculum. A masters course in cancer pharmacology and therapeutics should be considered.

Conclusions

This paper is a practical guideline for the dose calculation of anticancer drugs for practising clinicians. It is a call for clinicians to be vigilant, to be familiar with expert guidelines and wherever possible apply evidence-based medicine. It is acknowledged that the published guidelines and protocols determined from clinical trials should be regarded as a solid foundation for guiding patient care. However, especially for the *dose* of anticancer drugs, such protocols are the starting point for dose determination, not rigid laws which should never be broken. Moreover, it is incumbent on practicing oncologists to fine-tune doses for individual patients, both for the initial and subsequent dose. Appropriate and safe dose calculation is not a static, set-and-forget action but

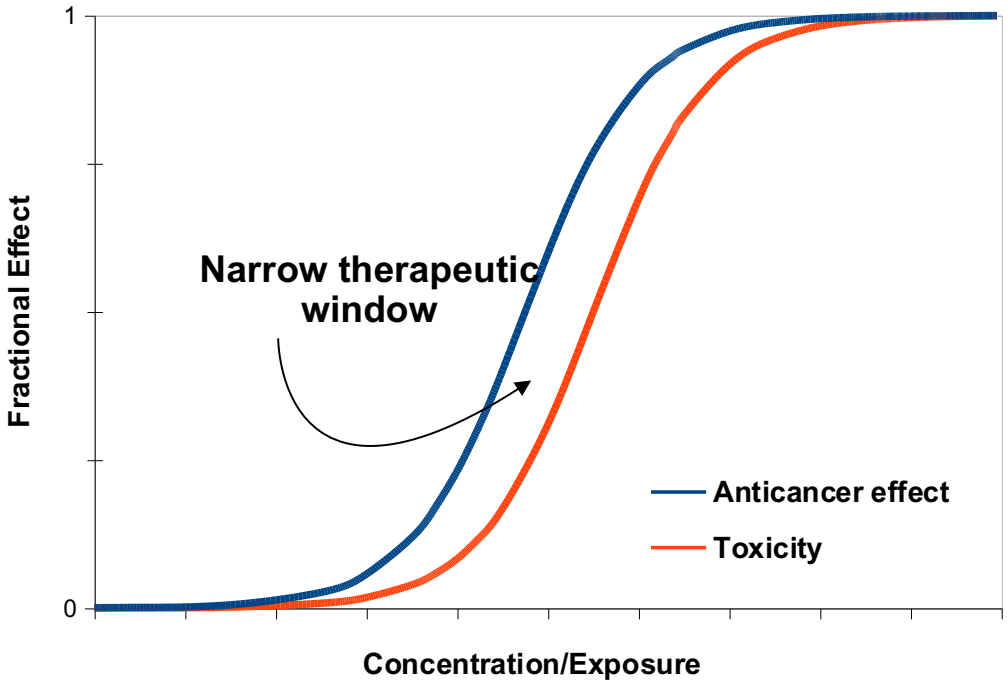
one that requires knowledge of the agent that is to be administered, taking into account a patient's unique circumstance. This philosophy is even more important in the current environment where drug protocols are loaded onto electronic prescribing software so that it is possible to order a chemotherapy regimen without significant attention given to the complex interplay between the drug, the patient and the disease. [1,36]

Table 1

Characteristics of a trial population versus the normal cancer patient population

1. Restricted performance status, usually ECOG 2 or better
2. Moderate organ impairment is not eligible
    - **a.** Low blood counts
    - **b.** Creatinine > 1.5 x upper limit of normal
    - **c.** Liver transaminases > 2.5 x upper limit of normal
3. Restrictions are placed on previous systemic therapy
4. Usually a 4 week wash-out from previous therapy which precludes patients with rapidly progressive cancer
5. Recent surgery excluded
6. Co-morbidities – often restricted in presence of
    - **a.** Recent ischaemic events
    - **b.** Recent pulmonary embolism or DVT
    - **c.** Cardiac failure
    - **d.** Uncontrolled diabetes
    - **e.** Patients with risk of GI bleeding or active peptic ulceration
    - **f.** Recent or active infections
    - **g.** Prolonged QT interval on ECG
    - **h.** Previous other malignancy within 5 years
7. Concomitant medication exclusions
    - **a.** CYP enzyme inducers (dexamethasone, phenytoin, carbamazepine, rifampicin, St John's Wort)
    - **b.** CYP enzyme inhibitors (ketoconazole, itraconazole, clarithromycin, anti-retrovirus medications such as indinavir, nelfinavir, ritonavir)
    - **c.** Anticoagulants
    - **d.** Steroid use restricted

Figure 1: Typical Concentration-Effect Curves for Anticancer Drugs



Most therapeutic drugs typically have a sigmoidal relationship between exposure/concentration at the target (for which plasma concentration is a clinical surrogate) and effect. The therapeutic window for some drugs is wide (eg. penicillin, tamoxifen, anti-PD1 agents) so that there is a wide concentration range over which efficacy without significant toxicity can be achieved. Some drugs have an intermediate therapeutic window (eg. antihypertensives). For many anticancer drugs (eg. most classical cytotoxic agents, capecitabine, oral targeted therapies) there is a narrow therapeutic window, so that there is a limited ideal concentration range to provide the highest chance of therapeutic benefit at acceptable risk of side effects. In these cases, getting the dose (plasma concentration) right is very important.

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