Ackland Stephen (Orcid ID: 0000-0001-5303-0017)
Karapetis Christos (Orcid ID: 0000-0003-1741-996X)

The Science and Art of Anti-Cancer Drug Dosing: 9 Steps to Personalised Therapy: (a position paper of the Medical Oncology Group of Australia)

Authors

Stephen P Ackland (1,2)
Michael Michael (3)
Paul de Souza (4)
Jennifer H Martin (5, 6)
Stephen J Clarke (7, 8)
Kay Francis (9)
Christos S Karapetis (9, 10)
Howard Gurney (11, 12)

Affiliations:

1. Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, 2308
2. Department of Medical Oncology, Calvary Mater Newcastle, Waratah, NSW, 2298
3. Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, 3000
4. School of Medicine, University of Wollongong, Wollongong, NSW, 2500
5. Centre for Human Drug Research, School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, 2308
6. Hunter Medical Research Institute, Kookaburra Crt, New Lambton, NSW, 2305
7. Department of Medical Oncology, Royal North Shore Hospital, St Leonards, NSW
8. Sydney Medical School, University of Sydney, Camperdown, NSW
9. Medical Oncology Group of Australia, Sydney NSW
10. Flinders Centre for Innovation in Cancer, Flinders University and Flinders Medical Centre, Bedford Park, SA
11. Crown Princess Mary Cancer Centre, Westmead Hospital, NSW
12. Faculty of Medicine and Health Sciences, Macquarie University, NS

Corresponding author:

Stephen P Ackland stephen.ackland@newcastle.edu.au

Introduction

Ensuring precision in drug dosing is often-overlooked in cancer medicine. Oncology clinical trials focus on determining appropriate drug selection, and defining the best average dose for the specific trial population, but not for individual patients. Getting the dose right is important to maximise the benefit for both individual patients and the health system. Optimal dose selection improves cost-effectiveness. Since every patient is a unique blend of genetic and environmental influences, the chemotherapy dose requires fine-tuning to maximise benefits and minimise adverse effects.

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The clinical decision-making of Australian medical oncologists about chemotherapy dosing was recently called into question with allegations of underdosing in some cases, and a NSW Upper House enquiry was undertaken. The enquiry indicated that the medical and lay public were unclear about how medical oncologists use scientific data together with individual patient health data to make decisions about personalised dosing.¹

A position paper about this issue, published on the MOGA website at <https://moga.org.au/uploads/files/TTkcZrPZ77-sqNAw.pdf> is summarised here. The paper clarifies the approach taken by medical oncologists to determining the optimal dose of anti-cancer therapy. The position paper also supports education and future research. The information therein may be valuable to various health professionals, including healthcare administrators as well as to patients, in understanding medical oncologists' treatment decisions.

Dose for a Population vs. Dose for an Individual

The evidence for drug *selection* for each cancer comes from clinical trials and is well-understood; trials provide evidence of benefits and side-effects and have limitations including the use of restricted populations (**Table 1**). Evidence-based tools to facilitate clinical decision-making, including NCCN guidelines, ESMO guidelines, and EviQ protocols are based mainly on trials.² However, dose recommendations in such protocols are averaged for a population, not personalised for the individual, and often imprecise. The well-known narrow therapeutic index (**figure 1**) of most anti-cancer drugs makes personalised dosing an imperative – too low a concentration at its target leads to sub-optimal or no benefit (but likely minimal toxicity); too high a concentration can result in unacceptable or life-threatening toxicity (but possibly greater anticancer effect).^{3,4}(summarised in ⁵).

In the absence of personalised evidence, medical oncologists in normal day-to-day practice must extrapolate from published evidence to achieve the optimal dose for each patient. While authorities have made recommendations about enhancing phase 2, 3 and 4 trials to provide more dosing information in real practice, these recommendations are yet to be taken up.⁶

Approaches to Personalised Drug Dosing

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

1. **Give the dose that is specified in a clinical trial protocol**, then individualise dose in subsequent cycles
2. **Adjust a protocol dose before it is given, based on knowledge of patient's individual characteristics and circumstances.**

3. **Modify a protocol for all patients when the clinical trial regimen does not ‘fit’ a more general cancer population.** There are many examples in routine clinical practice, including capecitabine⁷⁻¹¹ and cabazitaxel.¹²⁻¹⁶
4. **Use a protocol** that has not refined the dose for use in a patient group or disease state. An example is the common use of area under the plasma concentration-time curve (AUC) of 2 as the basis for dosing weekly carboplatin 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.¹⁷
5. **Construct a new protocol for an individual when published protocols do not fit.** This may apply to rare tumours, or exceptional patients with more common tumours (eg. bladder cancer with diabetic sensory neuropathy).

Electronic chemotherapy prescribing

Electronic chemotherapy prescribing has advantages and disadvantages and does not always improve quality and efficiency.¹⁸ Automated dose calculation obviates the imperative for the prescriber to grasp the intricacies of dose calculation and provides a false impression of accuracy especially where dose selection is concerned. A recent study showed the >70% of clinicians override e-prescribing alerts for potential drug-drug interactions using such tools.¹⁹

9 Practical Steps to Chemotherapy Dosing

Experienced medical oncologists must consider a variety of inputs in making dosing decisions for each patient.

1. **Know the pharmacology of each drug**
 - Humans normally have a 4-10-fold variation in drug elimination processes so the same dose for each patient can lead to large variations in systemic exposure despite using protocol doses.²⁰⁻²²
 - Understand that these parameters usually relate to an average, otherwise well, person in a fasting state; often the data is based on small patient numbers.
 - Understand the dose-response relationship (if known) and the size of the therapeutic window.
2. **Know the studies that led to the definition of recommended doses and schedules**
 - Late phase trials often do not include pharmacokinetic studies to define interpatient variability.
 - Most trials recruit patients with a carefully defined phenotype so extrapolating this data to real-world patients may be inaccurate (table 1).
3. **Know your patient**
 - Co-morbidities, relevant genetic variations, liver and renal function
 - Environmental exposures such as alcohol or smoking

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 of infection 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 surgery, radiotherapy or chemotherapy.
6. **Consider using toxicity as a surrogate for drug exposure.**
- Biological endpoints (eg. myelosuppression, rash or other toxicities) may be surrogates for drug exposure.
 - Consider dose escalation in the absence of toxicity, especially for drugs with a narrow therapeutic window. This is the principle of pharmacodynamic dosing
 - Consider therapeutic drug monitoring (TDM), although this is still not standard practice for most cytotoxic agents: mitotane is an exception. Therapeutic levels are being defined for other agents such as imatinib, everolimus and other targeted agents.
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.
8. **Communicate and document about any variance from a standard protocol**
- discuss and document the reasons for variation with your patient, oncology pharmacist and other team members.
9. **Consider conducting a clinical trial or registry to answer dosing or scheduling questions**
- Clinical trials provide an opportunity to utilise newer strategies such as biomarkers or drug concentration assays, to improve personalised medicine. ⁶

Future research

With personalised chemotherapy dosing as a goal, opportunities for research include TDM, pharmacogenomics, and identification of new biomarkers of drug metabolism or effect. Modern techniques for blood collection, rapid and precise analysis, population-based predictive pharmacokinetic/ pharmacodynamic (PK/PD) modelling, and the ability to communicate dosing recommendations to clinicians in realtime over large distances now make TDM 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 refine dosing in oncology has shown limited benefits to date and is not in widespread use.^{23,24} 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 novel biomarkers are research areas in their infancy. Clinical trials designed to explore novel biological surrogates for efficacy, including functional imaging and novel toxicity biomarkers will inform and guide future practice. Population data regarding drug dosing in the community could be extracted from available databases to inform relevant changes to guidelines.

Training and Education Recommendations

Professional colleges and other organisations responsible for training, education and professional development of specialists involved in the administration or management of chemotherapy should include anticancer drug pharmacology as an essential mandatory component of their curricula; it should be a significant component of the medical oncology training curriculum. Postgraduate courses in cancer pharmacology and therapeutics should be promoted.

Conclusions

The position paper provides practical guidelines to facilitate personalised dose calculation of anticancer drugs. We encourage clinicians to be vigilant, to be familiar with guidelines and, wherever possible, apply evidence-based medicine. Published guidelines and protocols determined from clinical trials are a solid foundation for guiding patient care but, especially for the *dose* of anticancer drugs, are a starting point, not rigid unbreakable laws. Oncologists must fine-tune doses for individual patients, both initially and as treatment progresses, and communicate reasons for change with all stakeholders, especially patients. Appropriate and safe dose calculation is not a static, “set-and-forget” action but requires keen pharmacological knowledge of the agent, taking into account a patient’s unique circumstance. This approach is even more important in the current environment where electronic software facilitates prescribing without significant attention given to the complex interplay between the drug, the patient and the disease.^{2,25}

Table 1

Characteristics of a “typical” trial population vs the normal cancer patient population

1. Restricted performance status, usually ECOG 2 * or better
2. Moderate organ impairment is not eligible:
 - a. Low blood cell counts
 - b. Creatinine > 1.5 x upper limit of normal
 - c. Liver transaminases > 2.5 x upper limit of normal, unless hepatic metastases
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 excluded:
 - a. Recent ischaemic events
 - b. Recent thromboembolism
 - 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 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

*ECOG - Eastern Cooperative Oncology Group; CYP – cytochrome P450

References:

1. NSW Legislative Council Select Committee. Off-protocol prescribing of chemotherapy in New South Wales. ISBN 9781920788179; 2017.
2. EviQ: Cancer Treatments Online. www.eviq.org.au (accessed 11/11/2018).
3. Jodrell DI, Egorin MJ, Canetta RM, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol* 1992; **10**(4): 520-8.
4. Gurney H, Dodwell D, Thatcher N, Tattersall MH. Escalating drug delivery in cancer chemotherapy: a review of concepts and practice--Part 1. *Ann Oncol* 1993; **4**(1): 23-34.
5. Gurney H. How to calculate the dose of chemotherapy. *Br J Cancer* 2002; **86**(8): 1297-302.
6. Minasian L, Rosen O, Auclair D, Rahman A, Pazdur R, Schilsky RL. Optimizing dosing of oncology drugs. *Clin Pharmacol Ther* 2014; **96**(5): 572-9.
7. Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; **19**(8): 2282-92.
8. Cassidy J, Twelves C, Van Cutsem E, et al. First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. *Ann Oncol* 2002; **13**(4): 566-75.
9. Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. *Lancet* 2011; **377**(9779): 1749-59.
10. Price TJ, Zannino D, Wilson K, et al. Bevacizumab is equally effective and no more toxic in elderly patients with advanced colorectal cancer: a subgroup analysis from the AGITG MAX trial: an international randomised controlled trial of Capecitabine, Bevacizumab and Mitomycin C. *Ann Oncol* 2012; **23**(6): 1531-6.
11. Chang HJ, Lee KW, Kim JH, et al. Adjuvant capecitabine chemotherapy using a tailored-dose strategy in elderly patients with colon cancer. *Ann Oncol* 2012; **23**(4): 911-8.
12. Mita AC, Denis LJ, Rowinsky EK, et al. Phase I and pharmacokinetic study of XRP6258 (RPR 116258A), a novel taxane, administered as a 1-hour infusion every 3 weeks in patients with advanced solid tumors. *Clin Cancer Res* 2009; **15**(2): 723-30.
13. Pivot X, Koralewski P, Hidalgo JL, et al. A multicenter phase II study of XRP6258 administered as a 1-h i.v. infusion every 3 weeks in taxane-resistant metastatic breast cancer patients. *Ann Oncol* 2008; **19**(9): 1547-52.
14. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 2010; **376**(9747): 1147-54.
15. Parente P, Gurney H, Ng S, Bahre M. Clinical perspectives: practical insights from clinical experience with cabazitaxel in Australia. *Asia Pac J Clin Oncol* 2015; **11**(3): 199-207.
16. Eisenberger M, Hardy-Bessard AC, Kim CS, et al. Phase III Study Comparing a Reduced Dose of Cabazitaxel (20 mg/m²) and the Currently Approved Dose (25 mg/m²) in Postdocetaxel Patients With Metastatic Castration-Resistant Prostate Cancer-PROSELICA. *J Clin Oncol* 2017; **35**(28): 3198-206.
17. Ackland SP, Hamilton CS, Joseph DJ, Denham JW. Phase I/II study of concurrent weekly carboplatin and radiation therapy in advanced head and neck cancer. *Clin Oncol (R Coll Radiol)* 1993; **5**(3): 133-8.
18. Adelson KB, Qiu YC, Evangelista M, Spencer-Cisek P, Whipple C, Holcombe RF. Implementation of electronic chemotherapy ordering: an opportunity to improve evidence-based oncology care. *J Oncol Pract* 2014; **10**(2): e113-9.
19. Nanji KC, Seger DL, Slight SP, et al. Medication-related clinical decision support alert overrides in inpatients. *J Am Med Inform Assoc* 2017.

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20. Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *J Clin Oncol* 1996; **14**(9): 2590-611.
21. Klumpen HJ, Samer CF, Mathijssen RH, Schellens JH, Gurney H. Moving towards dose individualization of tyrosine kinase inhibitors. *Cancer Treat Rev* 2011; **37**(4): 251-60.
22. Gao B, Yeap S, Clements A, Balakrishnar B, Wong M, Gurney H. Evidence for therapeutic drug monitoring of targeted anticancer therapies. *J Clin Oncol* 2012; **30**(32): 4017-25.
23. van den Akker-van Marle ME, Gurwitz D, Detmar SB, et al. Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lymphoblastic leukemia in Europe. *Pharmacogenomics* 2006; **7**(5): 783-92.
24. Ratain MJ. From bedside to bench to bedside to clinical practice: an odyssey with irinotecan. *Clin Cancer Res* 2006; **12**(6): 1658-60.
25. The Lancet OE. Clinical decision making: more than just an algorithm. *The Lancet Oncology* 2017; **18**(12): 1553.

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Cancer medicine is a challenging field with an increasing range of promising therapies and combinations. Increasingly, personalised medicine shows promise to improve cancer outcomes – response, symptom control, survival and cure. However, optimal dosing is an underappreciated aspect of personalised anticancer therapy, with few clinical trials addressing this specific issue. This position paper aims to inform various health professionals about the principles that guide anti-cancer drug dose selection and modifications. We discuss the available evidence base for personalised dosing, as well as the professional judgement required by experienced oncology physicians to determine the most appropriate dose for each patient. We provide 9 steps to guide clinicians and trainees in this process, 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 (adiposity, co-morbidities, etc.); previous drug tolerance; individual dose adjustment in combination therapy; communication and documentation, with the added need for ongoing monitoring and adjustment. We strongly propose professional education and future research towards optimal dosing.

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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2. Department of Medical Oncology, Calvary Mater Newcastle, Waratah, NSW, 2298
3. Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, 3000
4. School of Medicine, University of Wollongong, Wollongong, NSW, 2500
5. Centre for Human Drug Research, School of Medicine and Public Health, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, 2308
6. Hunter Medical Research Institute, Kookaburra Crt, New Lambton, NSW, 2305
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Corresponding author:

Stephen P Ackland stephen.ackland@newcastle.edu.au

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Author/s:

Ackland, SP;Michael, M;de Souza, P;Martin, JH;Clarke, SJ;Francis, K;Karapetis, CS;Gurney, H

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