

## **INQUIRY INTO OFF-PROTOCOL PRESCRIBING OF CHEMOTHERAPY IN NSW**

**Name:** Professor Stephen Ackland & Professor Jennifer Martin,  
University of Newcastle

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## **Chemotherapy dosing – urgent need for evidence to guide practice**

Our submission is on behalf of a team of cancer physicians and clinical pharmacologists in New South Wales public hospitals and Universities. It is co-written by Professor Stephen Ackland (SA), a medical oncologist who has worked in the area of dose individualisation for cancer patients for over 25 years, and Professor Jennifer Martin (JM) a clinical pharmacologist who has researched, educated and practiced dose individualisation of other classes of drugs such as cardiovascular medications and infectious diseases for the last 20 years. They are leading a NSW-wide Consortium planning to develop research into dose individualization.

Both authors are members of the College of Physicians and employed by the University of Newcastle and HNE Health. Both have recently submitted an application to the Cancer Institute NSW requesting funds to research how to dose safely and effectively for individual patients with cancer. They are writing this submission in their academic capacity, without speaking on behalf the University. JM was a member of the recent CI NSW Inquiry into under-dosing chemotherapy.

*Jennifer H. Martin MBChB, MA (Oxon.), FRACP, PhD*

*Chair of Clinical Pharmacology*

*University of Newcastle School of Medicine*

*New South Wales*

*Stephen Ackland MBBS, FRACP*

*Director, Hunter Cancer Research Alliance*

*University of Newcastle*

*New South Wales*

## **STATEMENT**

It is a factual statement to say that currently, good-quality evidence-based guidelines are not generally available for tailored dosing of cancer medications in today's complex patient cohort. It is also reasonable to state that calculating the dose of a cancer drug is a challenging and complex process and no amount of Guidelines is ever going to enable best practice for an individual patient. Rather these seek to guide a dosing decision, which must be made by taking into account clinical factors, phenotype, demographics, patients preference, body size, and genetics. Additional factors must also be considered that affect how much cancer drug gets to the tumour. These include how well the chemotherapy is cleared through the kidneys and other standard pharmacological rules that hold for similar types of medications, knowledge of cancer biology and patient physiology across ages, gender and comorbidity. Guidelines struggle to incorporate such a complex mix of factors so that there are many scenarios where adherence to guidelines is not sensible.

To that end we need high quality evidence about how to individualise the dose, followed by a method of measuring drug 'exposure' during dosing to ensure we have a large enough amount of drug in the body and for long enough without causing side effects. Recent reports about underdosing in oncology clinics in Australia have brought this critical issue into new light. In an attempt to fix this, an urge to publish more Guidelines often occurs in health systems. It is easy to request more Guidelines. But these are not necessarily the answer as patients are complex and cancer variable, as highlighted above.

In drug development, identification of an "ideal" dose is often performed in early phase trials using a small number of highly selected cases that typically do not represent the population in which the treatment will be applied. Clinical trials typically exclude people with kidney and liver problems, the organs central to eliminating drugs from the body. Thus the evidence helps understand how a drug works in a carefully controlled environment, but doesn't prepare us for how to use the drug in real life.

Each individual has a different ability to handle drugs. For most areas of medicine this is not a big problem since the drugs used are safe at the effective dose.

However, anticancer drugs tend to have a narrow therapeutic index; that is to say that the dose that can kill a cancer is very close to the one that can cause terrible side effects. This means that careful dose calculation is paramount in the care of our cancer patients.

Oncologists do have some dosing information on specific doses that were used for specific patients with specific body sizes, ages and ethnicity from well-designed and rigorous industry clinical trials, and for whom food and other variables (such as comorbidity and other medications) are tightly controlled. However, it is also known that most of our patients are very dissimilar to those patients in clinical trials. Some studies for example are undertaken in Japan or East Asia, some in Black Americans. Therefore we do not know how that highly controlled clinical trial data applies to our particular patient make up in New South Wales. This means there can be uncertainty when choosing a dose of a drug, particularly in any patient over 80kg or over 70 years of age, which is a great majority of current cancer patients.

Further, despite local evidence we have continued to use very old dosing regimens, based on little or no evidence to support better dosing regimens for new medications, and often unchanged since the 1970s. These include 'flat dosing' (i.e. one dose fits all as with many older and almost all new oral biologic cancer drugs). However the evidence to support this is either unavailable or of low quality. From a pharmacology perspective for example, dosing on a body surface area calculation (what is currently in the Guidelines for many drugs) is known to be quite inexact in the majority of cases (Gurney, 1996). Body size (height and weight) only accounts for around 20% of variation between people. Even in established chemotherapy protocols about 20% will be overdosed causing bad side effects, and about 20% will be underdosed, also leading to unacceptable outcomes (lower than anticipated

probability of benefit). In other words, the published protocols are a reasonable starting point but should not be seen as the law.

Further, even simple things like food intake is relevant, as is the gut microbiome, which is defined by diet, ethnicity and other environmental factors. For example, widely variable dietary intakes alone are known to affect exposure of many of the new, expensive oral chemotherapies by several fold; this variation is likely to affect survival or relapse (Lucas et al, 2016). Dosing Guidelines for such circumstances thus have very limited value; the dose must instead be individualised for each patient and each cancer.

In contradistinction to the lack of evidence for protocolised dosing and even for dosing on a BSA basis, it is well known that measurement of blood levels of drug (known as therapeutic drug monitoring) provides information regarding whether a patient's drug exposure is adequate for cancer response and risk of side effects. Systems for TDM in oncology have generally not been implemented in the past, apart from a few automated drug level measurements such as methotrexate and busulfan in selected circumstances for childhood cancers. Although in the past the logistics of implementing a TDM program in oncology have been considered prohibitive, we suggest that technological advances in the last few years now allows such programs to be cost-effective in developed countries, allowing prevention of severe side effects and its consequences to the health system, as well as avoidance of underdosing and its adverse consequences on cancer control. This is especially the case for newer, very expensive targeted therapies, but also for standard older agents such as anthracyclines, fluoropyrimidines, taxanes and platinum-based drugs. To effectively implement such a Statewide service involves the need for integrated research funding for the appropriate research, research implementation, leadership within the Guidelines groups, and appropriate pathology support and reimbursement.

*We hypothesise that changing a patient's exposure by increasing or decreasing the dose of chemotherapy (including immune therapies) during their first treatment cycle will improve cancer survival.*

In light of recent events in NSW however, we are seeking support to investigate the practice more widely this using rigorous research plans, transparent documentation and governance, appropriate ethics approval and inclusion of behavioural specialists to support implementation of evidenced based practice.

We value the opportunity to make a statement for the Inquiry based on what we believe is needed in NSW - a platform for individualised cancer dosing, based on developing knowledge of the effect of patient variables on outcome that can be implemented initially NSW-wide and eventually nationally into clinical practice. Both pharmacological variables (measurements of drug exposure), and biological factors known to affect cancer outcome (such as amount of mismatch repair gene activation) need to be included.

### **What is not needed:**

The NSW government plans to allocate \$6 million over three years to roll out new software with the aim of delivering evidence-based treatment. While this is a welcome move, a concern held by many oncologists is that a rigid adherence to published protocols and software-based prescriptions may prevent proper dose individualization and lead to reduced efficiency and effectiveness and to harm. Additionally, while EviQ has been a fantastic repository of guidelines for initial chemotherapy dosing, it simplifies a very complex system to a point where trainees and young oncologists do not intuitively learn the fundamental pharmacological principles of dosing. The risk is that the future oncology workforce will be less able to make critical judgements, leading to suboptimal healthcare. Specialist training programs will need appropriate emphasis on the pharmacological basis of cancer drug treatment, including mechanisms of action, pharmacokinetics and pharmacodynamics. Overall this Inquiry is a great opportunity to support the research and science behind evidenced based dosing and support for cancer dosing in NSW and beyond.

## REFERENCES:

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