INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.16415

ORIGINAL ARTICLE

Therapeutic drug monitoring in anticancer agents: perspectives of Australian medical oncologists

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Key words
therapeutic drug monitoring, medical oncology, implementation tools, clinical pharmacology.

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Received 22 September 2023; accepted 20 April 2024.

Abstract

Background: In the development of anticancer agents for solid tumours, body surface area continues to be used to personalise dosing despite minimal evidence for its use over other dosing strategies. With the development of tyrosine kinase inhibitors and other oral targeted anticancer agents, dosing using therapeutic drug monitoring (TDM) is now utilised in many health systems but has had limited uptake in Australia.
Aim: To determine attitudes and barriers to the implementation of TDM among Australian oncologists.
Methods: A comprehensive questionnaire was developed by the Dutch Pharmacology Oncology Group from semistructured interviews of stakeholders. Seventy-nine questions across seven domains were developed with three free-text responses. This was rationalised to 17 questions with three free-text responses for Australian medical oncologists who identified limited experience with TDM.
Results: Fifty-seven responses were received, with 49 clinicians (86%) identifying limited experience of performing TDM in daily practice. Clinicians were positive (62–91% agree/strongly agree across seven questions) about the advantages of TDM. There was a mixed response for cost-effectiveness and scientific evidence being a barrier to implementation, but strong agreement that prospective studies were needed (75% agreed or strongly agreed); that national treatment guidelines would enable practice (80%) and that a 'pharmacology of oncolytics' education programme would be useful (96%) to provide knowledge for dose individualisation.
Conclusion: Despite the limited experience of TDM in oncology in Australia, medical oncologists appear positive about the potential benefit to their patients. We have identified three barriers to implementation that could be targeted for increased adoption of TDM in oncology in Australia.

Introduction

The widespread adoption of therapeutic drug monitoring (TDM) of anticancer agents has had piecemeal implementation despite its common acceptance in the dosing of antibiotics, psychotropics, antiseizure medicines, immunosuppressants and digoxin.[1] The aim of TDM is to individualise a patient's dose of medicine to achieve a target exposure thereby maximising efficacy and avoiding toxicity. This is particularly important in many anticancer agents with a narrow therapeutic window, where an exposure-response or exposure-toxicity relationship has been demonstrated.

Body surface area-guided dosing, where larger patients are given a larger dose and smaller patients a smaller dose, became the default dosing strategy for almost all chemotherapeutic agents. This is despite limited evidence of its effectiveness for individual agents[2] and no consideration of the variable and different metabolic pathways of each agent or individual variability in pharmacokinetics and pharmacodynamics. Only two traditional chemotherapeutics are routinely dosed with other strategies: Carboplatin, using the Calvert formula to determine

Funding: None.
Conflict of interest: None.

exposure (area under the curve) based on renal function[3] and mitotane, which uses TDM, but is used so rarely that only one research laboratory performs drug levels in Australia.[4] TDM dosing was successfully established for methotrexate,[5,6] busulfan[7] and 6-merceptopurine[8] in haematological malignancies and sarcoma, but was never adopted in methotrexate dosing for breast or bladder cancer.

As combination chemotherapy regimens evolved in many tumour types, dosing research became more complicated, and regimens often evolved before dosing optimisation could be established. This was demonstrated in a phase 3 randomised controlled trial of 5-fluorouracil (5FU) dosed using TDM in metastatic colorectal cancer, which confirmed a significant improvement in response rate and survival benefit.[9] At the time of its publication, however, the treatment of metastatic colorectal cancer had evolved to include a combination bolus and infusion 5FU regimen with the addition of a second chemotherapeutic agent and a targeted agent,[10] so that the gains demonstrated in the trial by titrating the dose to a target area under the curve exposure were never adopted in multiagent regimens as standard of care. There have been multiple subsequent observational and single-arm phase 2 studies showing the feasibility and benefit of using TDM for 5FU in combination regimens,[11,12] with a consensus guideline from the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT) endorsing in a strong recommendation for TDM of 5FU in colorectal cancer and squamous cell carcinoma of the head and neck.[13] There are similar small studies with paclitaxel.[14]

The development of tyrosine kinase inhibitors has been accompanied by new pharmacologic research in imatinib, sunitinib, pazopanib and erlotinib demonstrating large interpatient exposure variability at standard doses, with a substantial number of patients below the target level and at risk of treatment failure.[15] Defined therapeutic ranges for imatinib, sunitinib and pazopanib were established with evidence of improved outcomes[16] and a review of all oral anticancer agents confirmed the wide-reaching potential benefit from TDM and identified multiple agents still to be evaluated.[17] The IATDMCT published a second guideline endorsing TDM for imatinib for gastrointestinal stromal tumours.[18]

While there has been some adoption of TDM in isolated centres, mainly in Europe,[19] research and implementation in the United States and Australia has been scarce. Despite many reviewers calling for TDM in oncology to become more mainstream,[20,21] it has remained a secondary consideration with the common misperception that the optimal dosing strategy is confirmed in the drug development phase.[22] To address the lack of implementation of TDM in oncology in Australia, a questionnaire was sent to Australian medical oncologists to determine the attitudes and barriers to the use of TDM.

Methods

Study design

The survey tool was developed by a Dutch Medical Oncology research group in collaboration with the Dutch Pharmacology Oncology Group (DPOG).[23] To identify attitudes to TDM and barriers to its implementation, semistructured individual interviews and a focus group were conducted for patients, healthcare professionals, health insurance and pharmaceutical companies. Seventy-two barriers and 90 facilitators to implementation were identified across six domains, which were adapted into a survey for medical oncologists and oncology pharmacists. The survey contained six free-text introductory demographic questions, 79 check-box responses using a Likert scale and three free-text responses (Appendix B).

Many of the 79 questions related to the direct clinical experience of using TDM for antineoplastics and the effect of this on patient care. For Australian medical oncologists with limited practical experience of TDM in oncology, the Australian questionnaire used branched logic for question 5: 'I have experience in performing TDM of oral oncolytics in daily practice'. If the oncologist answered 'Yes', they were asked to complete the full 79 questions and three free-text responses. If they answered 'No', they were asked to complete a further 17 questions and three free-text responses. These 17 questions were selected from the following themes: evidence (four), beliefs about advantages and disadvantages of TDM (seven), Knowledge and experience (four), Daily clinical setting (1) and Tools/Possible improvements (1) (Appendix A).

A testing phase with the PREDICT (Pathway of Research to Evaluation of Dose-Individualised Cancer Therapy) executive committee and five external medical oncologists was conducted and a consensus of the selected questions for oncologists with limited experience in TDM was obtained. A literal English translation of Dutch questions was preserved for direct comparison.

Study population

The Australian questionnaire was administered electronically through the REDCap system with an email link to participate. The email link was sent to all members of the Medical Oncology Group of Australia (MOGA), which includes approximately 600 medical oncologists

and trainees. An initial email was sent on 28 March 2022, with a reminder email on 11 April 2022, and the survey closed on 11 May 2022. This project was authorised as a negligible risk research activity (AU202112-01) on 7 December 2021.

Results

Fifty-seven responses were received: 45 complete and 12 incomplete. This represents participation from 9.5% of the membership.

Demographics (four questions)

Forty-eight were medical oncologists (84%) and nine were advanced trainees in medical oncology (within 3 years of qualifying as medical oncologists). Thirty-five participants (61%) had 10 years or less experience in medical oncology with a median age bracket of 41–50 years. Male to female ratio was 33:24. These results are demonstrated in Figure 1.

Experience (one branched logic question)

Forty-nine (86%) participants responded 'No' to 'I have experience in performing TDM or oral oncolytics in daily practice' with 39 of these participants completing the following 17 questions. Ten participants had incomplete responses. Eight (14%) participants responded 'Yes', with six participants completing all 84 questions.

Evidence (four questions)

Responses to the four questions of evidence for TDM are demonstrated in Figure 2. The majority of participants thought that there was added value in the routine use of TDM (56%). There was a mixed response to the need for further scientific evidence and evidence of cost-effectiveness. The majority of participants (75% agreed + strongly agree) that prospective studies are needed.

Advantages of TDM (seven questions)

Responses to the seven questions outlining the advantages of TDM are demonstrated in Figure 3. The majority

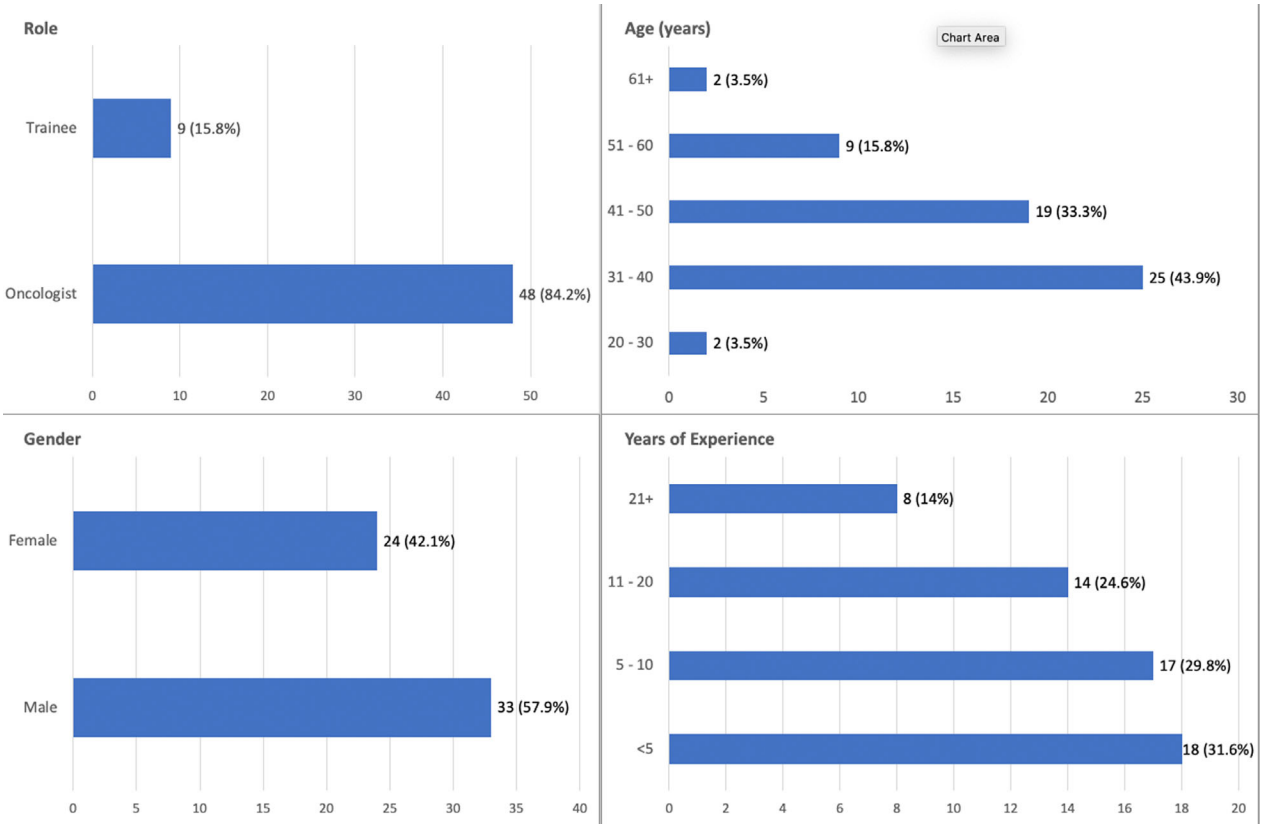

Figure 1 Participant demographics.

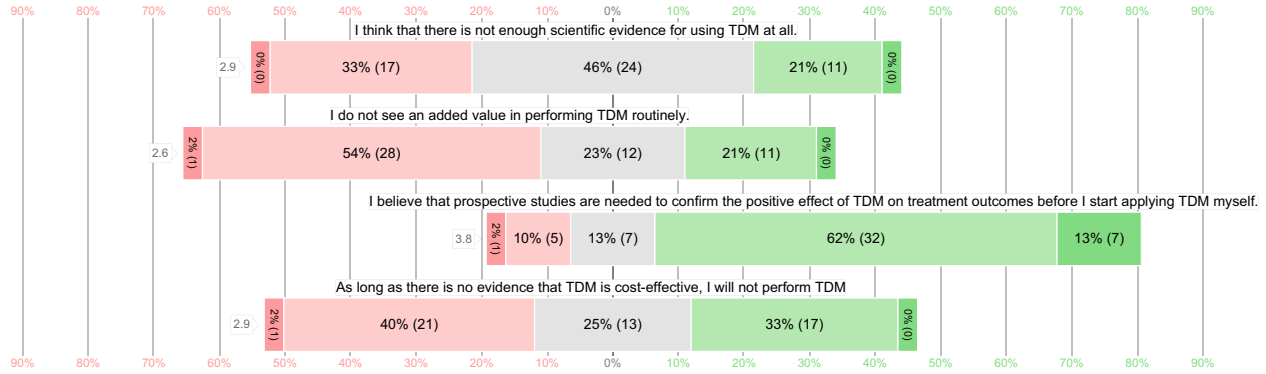

Figure 2 Evidence for therapeutic drug monitoring (TDM) (four questions). Scale: dark red = strongly disagree, light red = disagree, grey = neutral, light green = agree, dark green = strongly agree.

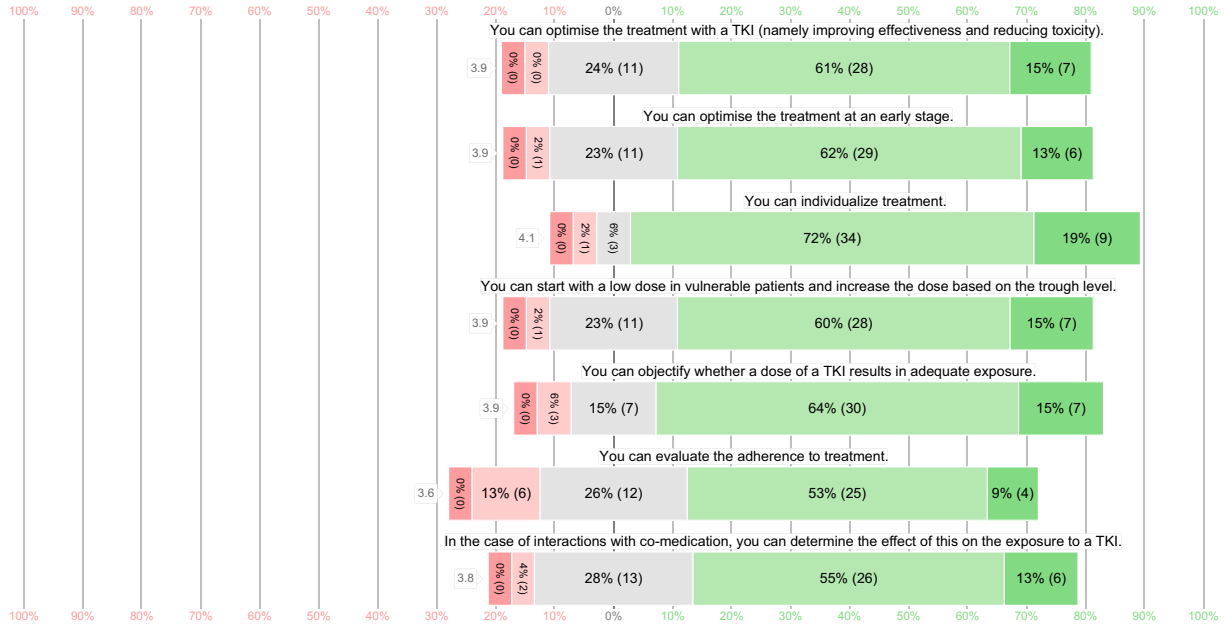

Figure 3 Advantages of therapeutic drug monitoring (TDM) (seven questions). Scale: dark red = strongly disagree, light red = disagree, grey = neutral, light green = agree, dark green = strongly agree.

of responses agreed or strongly agreed with each advantage (62–91%) across seven questions.

Knowledge/experience (four questions)

Responses to the four questions about knowledge and experience are demonstrated in Figure 4.

As reflected in the initial branched logic question, most participants (68%) felt a lack of awareness about TDM, a lack of experience (91%), too little knowledge about performing TDM (87%) and difficulty in finding background information (76%).

Possible improvements (two questions)

Responses to the two questions about possible improvements are demonstrated in Figure 5. Eighty per cent of participants would not perform TDM as it is not yet in national or local treatment guidelines. Ninety-six per cent of participants would support an education programme.

Subgroups

We analysed the subgroup of clinicians ($n = 8$) who responded 'Yes' to the question, 'I have experience

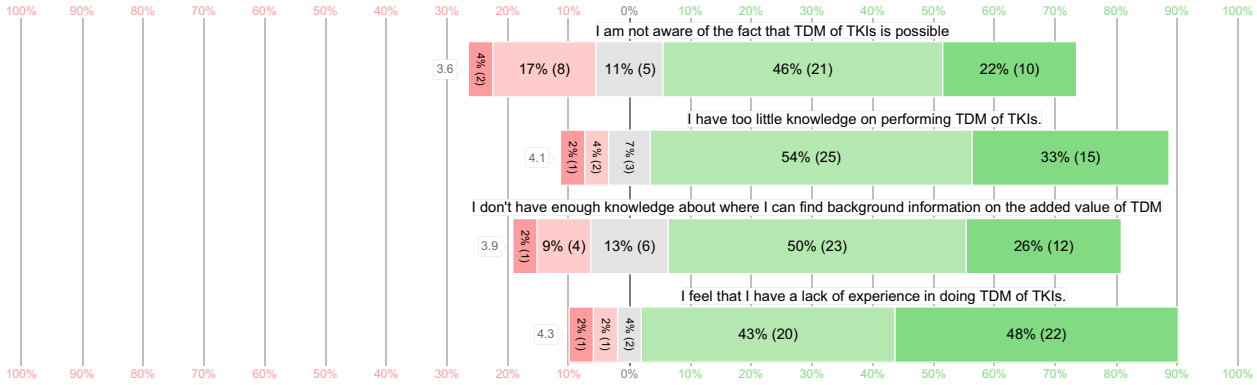

Figure 4 Knowledge and experience (four questions). Scale: dark red = strongly disagree, light red = disagree, grey = neutral, light green = agree, dark green = strongly agree.

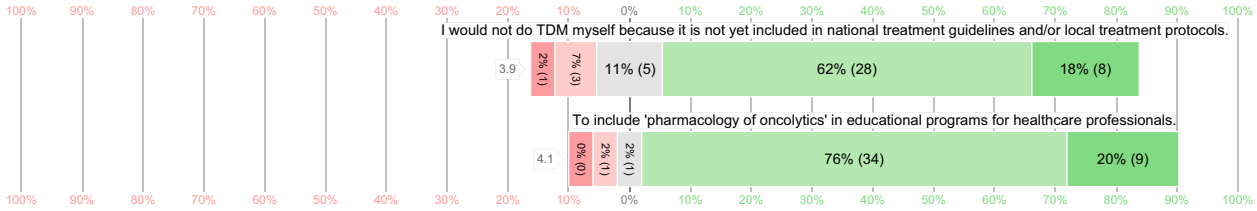

Figure 5 Tools and possible improvements (two questions). Scale: dark red = strongly disagree, light red = disagree, grey = neutral, light green = agree, dark green = strongly agree.

performing TDM of oral oncolytics in daily practice'. The responses of this group reflected the responses of the group as a whole and did not skew the results reported above. Six participants completed all 84 questions, with a heterogeneity of responses (see Appendix C).

We also analysed the subset of participants who had 10 years or less experience in oncology and similarly found that the responses of this group reflected the responses of the whole (see Appendix D).

Free-text responses – barriers and facilitators of TDM in oncology

Thirty-three of the 57 (58%) participants made contributions to the three free-text questions. Many comments covered multiple themes. For barriers to the use of TDM in daily practice themes, there were 32 mentions of issues concerning the practical implementation of the test: cost, access, availability, staff resources, time, turnaround time and difficulty in interpreting the result. There were eight mentions related to concerns for patients: time to explain the test, an extra blood test and delays to the patient. There were 10 mentions of scientific evidence as a barrier to implementation and one mention of the need for guidelines. For facilitators in the implementation of TDM, 11 participants mentioned guidelines, six mentioned an education programme, six mentioned evidence and four mentioned cost and access.

Discussion

The results of this questionnaire indicate the limited awareness, knowledge and use of TDM for antineoplastic agents by Australian medical oncologists. The level of engagement with our survey was less than 10% of those emailed. MOGA[24] is the national specialist professional society for medical oncologists with a membership of roughly 600 medical oncologists and senior trainees, providing excellent representation of the workforce in Australia. The low number of respondents, even amid waning participation in the MOGA selective survey programme, suggests TDM is of low priority in the clinical practice of medical oncologists in Australia.

For those who completed the survey, the majority of clinicians had limited experience using TDM in daily practice, with most confirming that they were not aware that TDM of tyrosine kinase inhibitors was

possible, despite its implementation in several health systems around the world. This may partly be explained by the experience level of the cohort, with the majority having 10 or less years of clinical experience in a time that has seen an eruption of new agents with novel antineoplastic mechanisms.[25] More than three-quarters of clinicians agreed they had too little knowledge, felt a lack of experience and did not know where they could find background information reflecting the paucity of pharmacological education in oncology training and continuing medical education. This is in direct contrast to the experience level seen with this survey among Dutch medical oncologists[22] and confirms the considerable deficit in education and experience that is required to implement dosing research into mainstream practice in oncology in Australia.

Despite the lack of experience, there was strong recognition of the advantages of TDM. Between 62% and 91% of clinicians agreed or strongly agreed with each of the seven advantages of TDM, with the strongest response for the potential to 'individualise treatment'. This result could inform future engagement with clinicians who already aim to personalise treatment by stratifying tumours according to mutation status. Utilising TDM to individualise doses could offer medical oncologists an additional level of personalised treatment for their patients and a useful strategy for clinician engagement.

The issue of cost-effectiveness drew a mixed response from the cohort, suggesting that clinical utility is a greater driver for implementation than cost, as is currently seen in the DPYD genotyping Medicare Benefits Schedule funding debate in Australia.[26] There was a mixed response as to whether there was enough scientific evidence. This may reflect disparate views of the level of evidence needed to implement pharmacokinetic research and whether observational and phase II research can drive a change in dosing method. Even so, there was a strong response (75%) supporting the need for prospective studies to confirm the positive effect of TDM on treatment outcomes. Project Optimus aims to address this by embedding robust dose-related efficacy and toxicity research into the Food and Drug Administration approval for new oral agents.[27]

The strongest responses to tools for implementation were inclusion in the national treatment guidelines (80%) and a 'pharmacology of oncolytics' education programme (96%), both of which are being addressed by the PREDICT research platform.[28]

The main limitation of our study was the low participation rate among Australian medical oncologists, which may skew the results if a larger and less engaged cohort were sampled.

Conclusion

For the successful implementation of TDM in oncology in Australia, it is valuable to understand the facilitators and barriers to the uptake of this dosing strategy by medical oncologists. Despite the lack of experience with TDM, Australian medical oncologists are positive about the potential benefit to patients. The need for prospective evidence, inclusion in national treatment guidelines and an education programme are three surmountable barriers that might be targeted for future implementation.

Acknowledgements

The authors thank the MOGA for facilitating this survey to their members, with particular thanks to Dr Deme Karikos and Kay Francis. This survey was developed by the DPOG with particular thanks to Kim Westerdijk, Ingrid Desar and Nielka van Erp. The Australian adaption of the survey tool was developed and evaluated by members of the PREDICT executive committee with particular thanks to Christine Ashcroft, Professor Paul Scuffham and Professor Ian Olver. This project was funded by the NSW Cancer Council Grant: PW 18-01 PREDICT – Pathway of Research to Evaluation of Dose-Individualised Cancer Therapy.

References

1 Ghiculescu R. Therapeutic drug monitoring: which drugs, why, when and how to do it. *Aust Prescr* 2008; **31**: 42–4.

2 Baker SD, Verweij J, Rowinsky EK, Donehower RC, Schellens JH, Grochow LB *et al*. Role of body surface area in dosing of investigational anticancer agents in adults, 1991-2001. *J Natl Cancer Inst* 2002; **94**: 1883–8.

3 Jodrell DI, Egorin MJ, Canetta RM, Langenberg P, Goldbloom EP, Burroughs JN *et al*. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol* 1992; **10**: 520–8.

4 Baudin E, Pellegriti G, Bonnay M, Penfornis A, Laplanche A, Vassal G *et al*. Impact of monitoring plasma 1,1-dichlorodiphenildichloroethane (o,p'DDD) levels on the treatment of patients with adrenocortical carcinoma. *Cancer* 2001; **92**: 1385–92.

5 Evans WE, Crom WR, Abromowitch M, Dodge R, Look AT, Bowman WP *et al*. Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia. Identification of a relation between concentration and effect. *N Engl J Med* 1986; **314**: 471–7.

6 Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with

individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med* 1998; **338**: 499–505.
7 Grochow LB. Busulfan disposition: the role of therapeutic monitoring in bone marrow transplantation induction regimens. *Semin Oncol* 1993 Aug; **20**: 18–25 quiz 26.
8 Erb N, Harms DO, Janka-Schaub G. Pharmacokinetics and metabolism of thiopurines in children with acute lymphoblastic leukemia receiving 6-thioguanine versus 6-mercaptopurine. *Cancer Chemother Pharmacol* 1998; **42**: 266–72.
9 Gamelin E, Delva R, Jacob J, Merrouche Y, Raoul JL, Pezet D *et al*. Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. *J Clin Oncol* 2008; **26**: 2099–105.
10 Saltz LB, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R *et al*. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008; **26**: 2013–9.
11 Li M, Mindt S, Lück A, Hutzschenreuter U, Kollendt M, Lathan B *et al*. Drug monitoring detects under- and overdosing in patients receiving 5-fluorouracil-containing chemotherapy-results of a prospective, multicenter German observational study. *ESMO Open* 2023; **8**: 101201.
12 Denda T, Kanda M, Morita Y, Kim HM, Kashiwada T, Matsuda C *et al*. Pharmacokinetic dose adjustment of 5-FU in modified FOLFOX7 plus bevacizumab for metastatic colorectal cancer in Japanese patients: a-JUST phase II clinical trial. *Cancer Chemother Pharmacol* 2016; **78**: 1253–61.
13 Beumer JH, Chu E, Allegra C, Tanigawara Y, Milano G, Diasio R *et al*. Therapeutic drug monitoring in oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology Recommendations for 5-fluorouracil therapy. *Clin Pharmacol Ther* 2019; **105**: 598–613.
14 Zhang J, Zhou F, Qi H, Ni H, Hu Q, Zhou C *et al*. Randomized study of individualized pharmacokinetically-guided dosing of paclitaxel compared with body-surface area dosing in Chinese patients with advanced non-small cell lung cancer. *Br J Clin Pharmacol* 2019; **85**: 2292–301.
15 Lankheet NA, Knapen LM, Schellens JH, Beijnen JH, Steeghs N, Huitema AD. Plasma concentrations of tyrosine kinase inhibitors imatinib, erlotinib, and sunitinib in routine clinical outpatient cancer care. *Ther Drug Monit* 2014; **36**: 326–34.
16 Westerdijk K, Desar IM, Steeghs N, van der Graaf WT, van Erp NP, Dutch Pharmacology and Oncology Group (DPOG). Imatinib, sunitinib and pazopanib: from flat-fixed dosing towards a pharmacokinetically guided personalized dose. *Br J Clin Pharmacol* 2020; **86**: 258–73.
17 Widmer N, Bardin C, Chatelut E, Paci A, Beijnen J, Levêque D *et al*. Review of therapeutic drug monitoring of anticancer drugs part two – targeted therapies. *Eur J Cancer* 2014; **50**: 2020–36.
18 Clarke WA, Chatelut E, Fotoohi AK, Larson RA, Martin JH, Mathijssen RH *et al*. Therapeutic drug monitoring in oncology: International Association of Therapeutic Drug Monitoring and Clinical Toxicology consensus guidelines for imatinib therapy. *Eur J Cancer* 2021; **157**: 428–40.
19 Yu H, Steeghs N, Nijenhuis CM, Schellens JH, Beijnen JH, Huitema AD. Practical guidelines for therapeutic drug monitoring of anticancer tyrosine kinase inhibitors: focus on the pharmacokinetic targets. *Clin Pharmacokinet* 2014; **53**: 305–25.
20 Groenland SL, Mathijssen RH, Beijnen JH, Huitema AD, Steeghs N. Individualized dosing of oral targeted therapies in oncology is crucial in the era of precision medicine. *Eur J Clin Pharmacol* 2019; **75**: 1309–18.
21 Beumer JH. Without therapeutic drug monitoring, there is no personalized cancer care. *Clin Pharmacol Ther* 2013; **93**: 228–30.
22 Papachristos A, Patel J, Vasileiou M, Patrinos GP. Dose optimization in oncology drug development: the emerging role of pharmacogenomics, pharmacokinetics, and pharmacodynamics. *Cancers (Basel)* 2023; **15**: 3233.
23 Westerdijk K, Steeghs N, Tacke CS, van der Graaf WT, van Erp NP, van Oortmerssen G *et al*. Therapeutic drug monitoring to personalize dosing of imatinib, sunitinib, and pazopanib: a mixed methods study on barriers and facilitators. *Cancer Med* 2023; **12**: 21041–56.
24 Available from URL: https://www.moga.org.au/.
25 Available from URL: https://ascopost.com/news/september-2019/cancer-drugs-account-for-over-a-quarter-of-all-new-drug-approvals-in-the-us/.
26 White C, Scott RJ, Paul C, Ziolkowski A, Mossman D, Fox SB *et al*. Dihydropyrimidine dehydrogenase deficiency and implementation of upfront *DPYD* genotyping. *Clin Pharmacol Ther* 2022; **112**: 791–802.
27 Murphy R, Halford S, Symeonides SN. Project Optimus, an FDA initiative: considerations for cancer drug development internationally, from an academic perspective. *Front Oncol* 2023; **13**: 1144056.
28 Available from URL: https://www.newcastle.edu.au/research/centre/cdrmr/research/predict.

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix A. Australian questionnaire.
Appendix B. Dutch questionnaire.
Appendix C. Results for clinicians with experience performing TDM (79 questions with 3 free-text responses).
Appendix D. Subgroup analysis.