Preface to Precision Dosing of Targeted Anti-Cancer Drugs

Small molecule protein kinase inhibitors (KIs) and anti-neoplastic monoclonal antibodies (mAbs) are rapidly expanding classes of non-cytotoxic or 'targeted' antineoplastic drugs that are effective at treating numerous malignancies, including previously difficult to treat forms of cancers. However, variability in disposition causes inter-individual variability in drug exposure that is inadequately addressed by the standard fixed-dose schedule of administration (1). Accordingly, precision dosing has great potential to maximise therapeutic response, minimise adverse drug reactions (ADRs), and improve cost-effectiveness of these expensive drugs.

Multiple studies have demonstrated the benefit of using therapeutic drug monitoring (TDM) to individualise KI dosing on the basis of plasma-KI concentration and therapeutic concentration ranges have been established for erlotinib, gefitinib, imatinib, nilotinib, pazopanib and sunitinib (2-4). However, a major barrier to the routine clinical translation of TDM is the preclusive cost and logistical complexity required to develop high quality prospective studies to confirm clinical utility (5,6).

Given these limitations, novel and practical complementary strategies are required to facilitate the clinical application of precision dosing for targeted anti-cancer drugs. Such strategies, which may include the application of population pharmacokinetic (PopPK) and physiological-based pharmacokinetic (PBPK) modelling and simulation (7,8), development of clinical prediction models based on routinely available clinical data (9), or the tracking of early novel markers of response or toxicity in diagnostically amenable tissues (10), may facilitate earlier dose optimisation and identify patients for whom TDM is most critical. However, such strategies rely on a sound understanding of the physiological and molecular characteristics driving variability in exposure. As such, fundamental clarification of the importance of factors known to contribute to between subject variability (BSV) such as genotype (11) and ethnicity (12) remains critical.

Notably, given the major role of cytochrome P450 (CYP) 3A4 in KI elimination (13), and limited capacity of existing strategies, such as genetic testing, to account for variability in CYP3A4 activity, novel diagnostic approaches are required to provide clinically actionable insights regarding the activity of this enzyme. Such insights may facilitate the more rational use of these drugs, and re-open the potential for applications such as combination with certain cytotoxic chemotherapies (14) that were previously considered unfeasibly due to unacceptable toxicities.

The manuscripts included in this Precision Dosing of Targeted Anti-Cancer Drugs focussed issue of *Translational Cancer Research* evaluate the evidence for precision dosing in this field, describe some of the key challenges to clinical translation, and describe novel strategies to facilitate the clinical translation of precision dosing for targeted anti-cancer drugs.

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References

1. Rowland A, Van Dyk M, Mangoni A, et al. Kinase inhibitor pharmacokinetics: Comprehensive summary and roadmap for addressing inter-individual variability in exposure. Expert Opin Drug Metab Toxicol 2017;13:31-49.
2. de Wit D, Guchelaar HJ, den Hartigh J, et al. Individualized dosing of tyrosine kinase inhibitors: are we there yet? Drug Discov Today 2015;20:18-36.
3. Verheijen RB, Yu H, Schellens JHM, et al. Practical Recommendations for Therapeutic Drug Monitoring of Kinase Inhibitors in Oncology. Clin Pharmacol Ther 2017;102:765-76.
4. van Dyk M, Miners J, Kichenadasse G, et al. A novel approach for the simultaneous quantification of 18 small molecule kinase inhibitors in human plasma: a platform for optimised KI dosing. J Chromatogr B Analyt Technol Biomed Life Sci 2016;1033:17-26.
5. Goulooze SC, Galettis P, Boddy AV, et al. Monte Carlo simulations of the clinical benefits from therapeutic drug monitoring of sunitinib in patients with gastrointestinal stromal tumours. Cancer Chemother Pharmacol 2016;78:209-16.
6. Kim HY, Martin JH, Mclachlan AJ, et al. Precision dosing of targeted anticancer drugs—challenges in the real world. Transl Cancer Res 2017;6:S1500-11.

7. Darwich AS, Ogungbenro K, Hatley OJ, et al. Role of pharmacokinetic modeling and simulation in precision dosing of anticancer drugs. Transl Cancer Res 2017;6:S1512-29.
8. van Dyk M, Rowland A. Physiologically-based pharmacokinetic modeling as an approach to evaluate the effect of covariates and drug-drug interactions on variability in epidermal growth factor receptor kinase inhibitor exposure. Transl Cancer Res 2017;6:S1600-12.
9. Hopkins AM, Rowland A, Kichenadasse G, et al. Predicting response and toxicity to immune checkpoint inhibitors using routinely available blood and clinical markers. Br J Cancer 2017;117:913-20.
10. Rathod A, Hopkins A, Rowland A, et al. Circulating cell free DNA for tracking early treatment response and disease progression in advanced cancers. Transl Cancer Res 2017;6:S1530-40.
11. Barratt DT, Somogyi AA. Role of pharmacogenetics in personalised imatinib dosing. Transl Cancer Res 2017;6:S1541-57.
12. Touma JA, McLachlan AJ, Gross AS. The role of ethnicity in personalized dosing of small molecule tyrosine kinase inhibitors used in oncology. Transl Cancer Res 2017;6:S1558-91.
13. Mikus G, Foerster KI. Role of CYP3A4 in kinase inhibitor metabolism and assessment of CYP3A4 activity. Transl Cancer Res 2017;6:S1592-9.
14. Kichenadasse G, Mangoni A, Miners J. Combination of small-molecule kinase inhibitors and irinotecan in cancer clinical trials: efficacy and safety considerations. Transl Cancer Res 2017;6:S1613-23.

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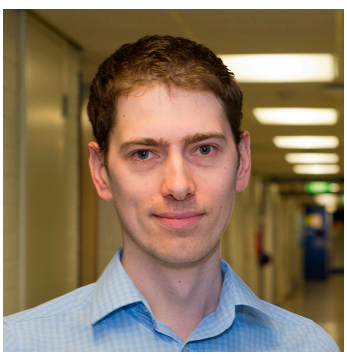

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