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REVIEW

Nuances to precision dosing strategies of targeted cancer medicines

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Abstract

Selecting the dose of a targeted cancer medicine that is most appropriate for a specific individual is a rational approach to maximize therapeutic outcomes and minimize toxicity. There are many different options for optimizing the dose of targeted cancer medicines and the purpose of this review is to provide a comprehensive comparison of the main options explored in prospective studies. Precision initial dose selection of targeted cancer therapies has been minimally explored to date; however, concentration, toxicity, and therapeutic outcome markers are used to guide on-therapy dose adaption of targeted cancer therapies across several medicines and cancers. While a specific concentration, toxicity, or therapeutic outcome marker commonly dominates an investigated precision on-therapy dose adaption strategy, greater attention to simultaneously account for exposure, toxicity, therapeutic outcomes, disease status, time since treatment initiation and patient preferences are required for optimal patient outcomes. To enable successful implementation of precision dosing strategies for targeted cancer medicines into clinical practice, future prospective studies aiming to develop strategies should consider these elements in their design.

KEYWORDS

initial dose selection, on-therapy dose adaptation, precision dosing, prospective studies, targeted cancer medicines

1 | INTRODUCTION

Targeted cancer medicines target specific molecules involved in the growth, progression, and metastatic dissemination of cancers. Monoclonal antibodies and small molecule kinase inhibitors are two major classes of targeted cancer medicines. Many targeted cancer medicines have well-established tumor biomarkers (gene mutations or expression profiles) that guide medication selection, yet disease progression, survival, and toxicity vary substantially between individuals. Precision dosing is a complementary approach for achieving precision

Abbreviations: HER2, human epidermal growth factor receptor 2; P-gp, P-glycoprotein; OATP1B1, organic anion transporter polypeptide 1B1.

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medicine, the focus being on selecting the drug dose that optimizes therapeutic outcomes (eg, response, progression free survival, overall survival) through strategies that account for intra-patient heterogeneity in pharmacokinetics and pharmacodynamics. Other than dose reduction guidelines for severe toxicity and adjustment of monoclonal antibody dose according to body size,[1] precision dosing is rarely used in routine clinical practice for targeted cancer medicines.

Several potential pharmacokinetic and pharmacodynamic biomarkers have been associated with therapeutic outcomes and toxicity to targeted cancer medicines in observational studies.[2-8] In particular, associations between drug concentration and therapeutic outcomes have been well summarized in a number of recent reviews.[4,5,7,9,10] These concentration-response relationships suggest that for specific drugs, precision dosing strategies may significantly improve outcomes in a subset of patients. However, prior to clinical translation, prospective interventional studies are important to confirm that the precision dosing strategy translates into improved therapeutic outcomes and/or reduced toxicity. For many targeted cancer medicines, there are likely multiple different precision dosing strategies conceivable and the relative benefits, costs, and harms need to be evaluated in order to decide upon the strategy that is best to implement clinically. This manuscript firstly aims to outline the potential for precision dosing of targeted cancer medicines and is followed by a comprehensive comparison of the nuances between precision dosing strategies which have been explored in prospective studies to date.

2 | PRECISION MEDICINE

Precision medicine considers the heterogeneity of a patient's disease, genetics, and demographics to implement an individualized treatment strategy that improves treatment outcomes. The use of patient characteristics and tumor biomarkers to guide the selection of specific targeted cancer medicines in the pursuit of optimized benefit is a common example of precision medicine. For example, genetic targets such as BCR-ABL, Philadelphia chromosome (Ph+) in acute lymphoblastic leukemia, and human epidermal growth factor receptor 2 (HER2) in breast cancer historically represent biomarkers of poor prognosis.[11,12] However, with the development of targeted therapeutics, they have evolved to be actionable drug target pathways for kinase inhibitors (eg, BCR-ABL tyrosine kinase inhibitors) and monoclonal antibodies (eg, trastuzumab/pertuzumab) alike.[11,12] While targeted cancer medicines demonstrate considerable benefits over traditional therapies, their use does not preclude assessment of patient progress: as therapeutic outcomes (eg, response) and toxicity from therapy still vary between individuals.[13]

3 | PRECISION DOSING

Precision dosing can be broken down into strategies guiding initial dose selection and strategies for on-therapy dose adaption (Figure 1). While these strategies are often evaluated separately, since targeted cancer medicines are often narrow therapeutic index drugs, appropriate initial dose selection and on-therapy dose adaption are complementary strategies to reduce the significant inter-individual variability in pharmacokinetics and pharmacodynamics.

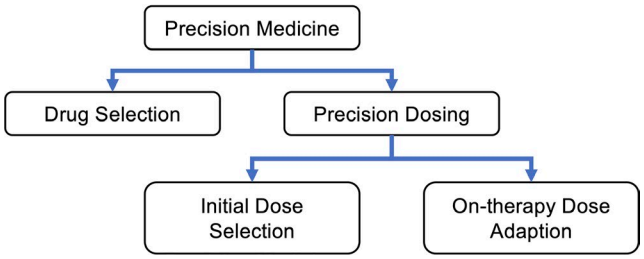

FIGURE 1 Precision dosing strategies

4 | INITIAL DOSE SELECTION

The concept of precision initial dose selection is that if pretreatment biomarkers accurately predict likely therapeutic outcomes, toxicity, or exposure to therapy, these markers can be used to guide the most appropriate initial drug dose (Figure 2).

For small molecule kinase inhibitors, inter-individual differences in clearance are a major driving factor of variability in drug exposure. The main clearance pathway for most small molecule kinase inhibitors is the metabolic enzyme cytochrome P450 (CYP) 3A4.[14] Influx and efflux transporters P-glycoprotein (P-gp) and organic anion transporter polypeptide 1B1 (OATP1B1) also affect clearance, as well as distribution and absorption. For many classes of medicines, attempts to explain variability in the metabolic activity of CYP have largely focused on the assessment of genotype differences via a pharmacogenomics (PGx) approach. While there are several examples where genetic variants account for a large proportion of observed variability in activity, including CYP2C9, CYP2C19, and CYP2D6, there are many cases in which genotype alone is insufficient to predict patient exposure to a drug.[15] Notably, CYP3A4 is the drug-metabolizing enzyme of greatest clinical importance in terms of targeted small molecule anticancer medicine metabolism, and variability is primarily driven by differences in protein expression that are poorly described by a PGx approach.[16-18] It is acknowledged that the *CYP3A4*22* genotype is associated with a significant reduction in CYP3A4 activity,[19] although the frequency of this allele is very low in Caucasian populations. Similarly, expression of active CYP3A5 protein via the CYP3A5 *1 confers additional metabolic activity toward many CYP3A4 substrates; however, again the frequency of this genotype is only approximately 15% in Caucasian populations. The *CYP3A4*22* and *CYP3A5*1* genotypes may alter capacity to clear targeted small molecule anticancer medicines in affected individuals.[20] Such is reported with sunitinib, where patients expressing *CYP3A5*1* (rs776746) showed increased risk of toxicity due to high metabolism and over exposure of the active metabolite.[21] However, their low frequency is such that they are not considered a significant factor in contributing to inter-individual variability

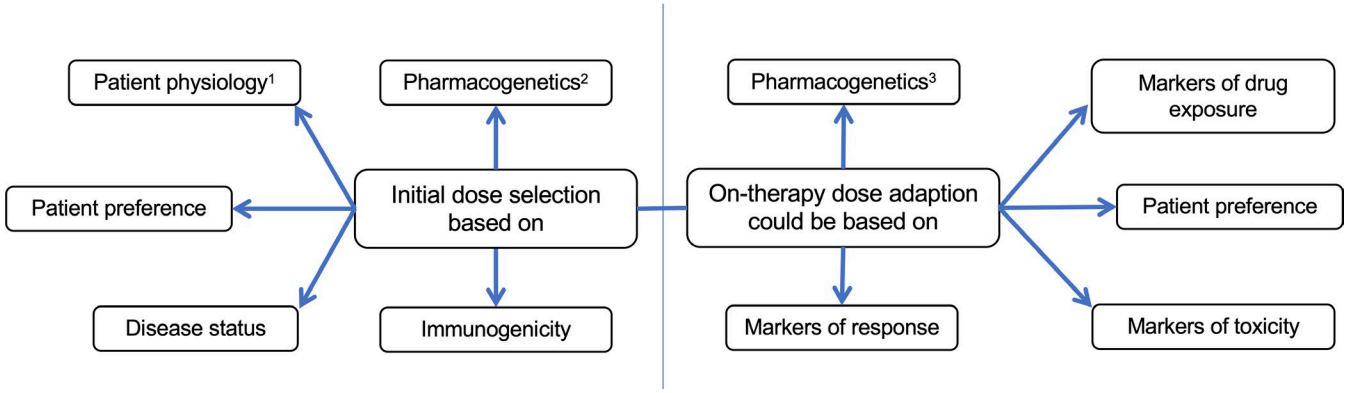

FIGURE 2 Factors Affecting initial dose selection and on-therapy dose adaptation strategies. [1]Patient physology includes: body composition (height/weight), biochemistry, renal function and age. [2]Pharmacogenetics in initial dose selection makers include: presence of target genetic mutations and prognostic makers. [3]Pharmacogenetics in on-therapy include: genetic makers of resistance to targeted therapy.

at a population level. To date, the ability to predict the population level inter-individual variability in the activity of CYP3A4, P-gp, OATP1B1, and the pharmacokinetics of small molecule kinase inhibitors has been poor. There is currently no pharmacogenomic variable that is useful in predict inter-individual differences in drug exposure.[14]

Significant inter-individual differences in drug exposure have also been reported for monoclonal antibodies.[3] Monoclonal antibodies are not typically cleared by metabolism, but instead are prone to gradual clearance at the liver, spleen, and kidneys by phagocytic cells or by their target antigen-containing cells.[22] Most monoclonal antibodies are dosed based on body composition, as these parameters are related to drug clearance,[22,23] although accounting for body size only marginally reduces inter-individual variability in exposure.[22-24] Disease status may also affect the clearance of monoclonal antibodies; for example, trastuzumab clearance was 22% higher in HER2-positive metastatic breast cancer patients with four or more metastatic sites, presumably due to increased drug utilization at target sites.[25] The implication of this is that patients at greatest need of effective treatment achieve lower drug exposure.[25] Similar associations between clearance and disease status have been observed with rituximab, ofatumumab, and obinutuzumab.[26-28] Circulating concentrations of albumin and alkaline phosphatase, gender, antidrug antibodies, and concomitantly administered drugs (eg, immunosuppressive or cytostatic drugs) have also been correlated with monoclonal antibody clearance,[3,24,29,30] so an optimal initial dose of a monoclonal antibody could be calculated using a more refined approach based on multiple covariates including body size, gender, disease status, immunogenicity, blood chemistry, and concomitantly administered drugs.[3]

5 | ON-THERAPY DOSE ADAPTION

In contrast to precision initial dose selection, on-therapy dose adaption takes place after initiation of therapy. Changes in biomarkers could be used to inform on-therapy dose adaption strategies, with most strategies using chemical, clinical/biological markers of therapeutic outcomes, toxicity, genetic markers of resistance, and drug exposure to guide dosing decisions (Figure 2). Thus, on-therapy dose adaption strategies are most easily categorized as response, toxicity, or concentration-guided approaches. However, prior to initiating on-therapy dose adaptation strategies, full consideration of pharmacogenetic markers of drug resistance should be appreciated. For example, first-generation TKIs erlotinib and gefitinib are ineffective in over expressors of the *EGFR* T790M mutation and emerging evidence indicates that tumor mutation burden can change over the course of cancer, indicating that pretreatment status does not always reflect current status.[31,32]

Important factors to consider in the development of on-therapy dose adaption strategies include the disease status, time since drug initiation and prior evidence of successful/unsuccessful strategies, which as a result, may affect the likelihood of benefit or harm from a new approach (Figure 3). First explorations of on-therapy dose adaption strategies for targeted therapeutics are often conducted in patient cohorts who are not responding to standard dosing of the medicine but have exhausted all other available options. Where the strategy demonstrates improved patient outcomes, using the on-therapy dose adaption strategy across additional patient cohorts (eg, prior to demonstrating resistance) may be considered.

Toxicity and response-guided on-therapy dose adaption use the presence or absence of clinical or laboratory markers of therapeutic improvement or toxicity to provide insight into strategies to achieve optimal clinical outcomes to therapy. Therefore, a lack of therapeutic improvement or toxicity may be a sign of under dosing, while the presence of toxicity may reflect overdosing. Optimal toxicity and response-guided dosing utilize clinical or laboratory markers of therapeutic improvement or toxicity that are correlated to longer term clinical outcomes. Proposed toxicity markers include skin rash for cetuximab and hypertension for sunitinib/axitinib.[2,33-35] In such situations, the mechanism of action of the drug resulting in the development of both efficacy and toxicity is likely related.

The fundamental premise of toxicity-guided dosing is that efficacy is likely to be optimized by achieving a dose that produces some

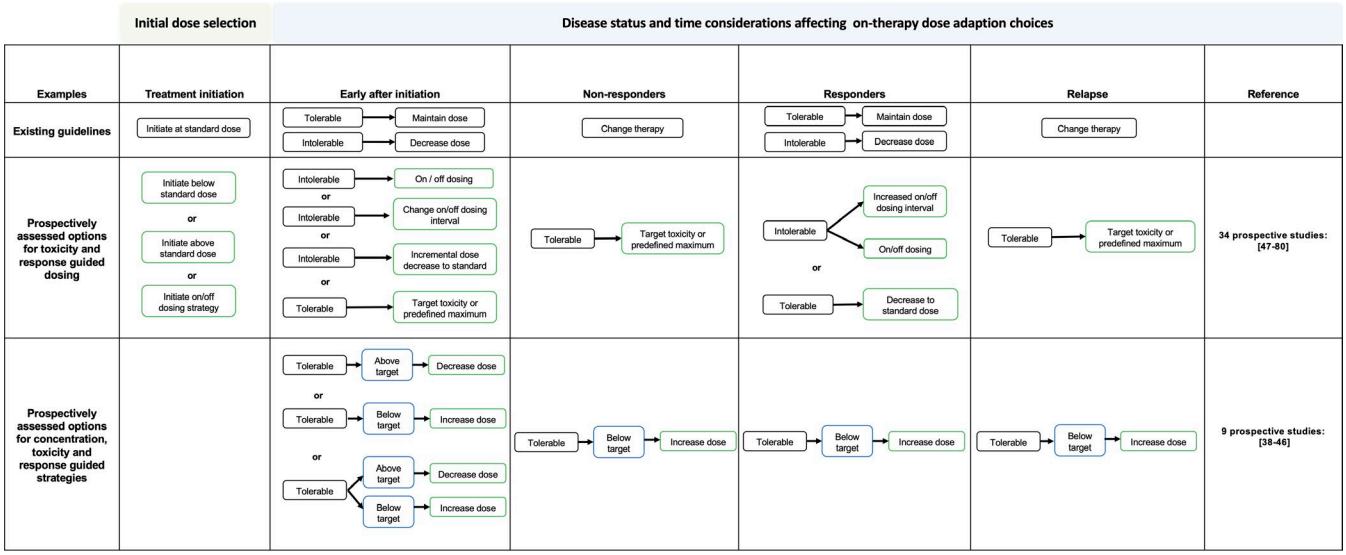

FIGURE 3 Summary of on-therapy dose adaption strategies which have been prospectively assessed for targeted cancer medicines

toxicity. Toxicity-guided dosing builds upon the theory of no toxicity being a sign of under dosing, noting some patients may require doses higher or lower than standard recommendations.[36] Ideally, toxicity-guided dosing strategies are based on mild non-life impacting toxicity markers that occur at lower doses than serious toxicities. Regardless, such a strategy may have a negative influence upon medication compliance.[37] As many targeted cancer medicines are used in patients with advanced disease where few, if any, alternate treatments are available, increased toxicity may be more acceptable, but this may not be the case in treatment naïve individuals were alternate treatment options may be available.

Concentration-guided dosing, also known as therapeutic drug monitoring, involves the measurement and interpretation of drug concentrations in the blood, and is a complementary approach to toxicity and response-guided dosing. Typically, this involves measurement of a steady-state trough concentration which is compared to a predefined optimal target concentration or threshold. Such comparisons allow rational dose adaption to be made, aiming for fewer individuals with excessively high drug exposure that increase the risk of toxicity, or excessively low exposures which increases the risk of therapeutic failure.[2] Such an approach aims to minimize pharmacokinetic variability; however, it does not account for inter-individual differences in pharmacodynamics. Numerous retrospective studies have indicated exposure-response relationships and possible response thresholds for targeted cancer medicines [2,3,5-7]; although the identified target concentrations have varied between studies, possibly due to the relatively short observation time, mixed diagnoses, and small cohort numbers. However, if such obstacles can be overcome and cost-effectiveness can be established, concentration-guided dosing of targeted cancer medicines could be used clinically.

At its simplest, concentration-guided dosing considers the total trough blood concentration of the parent drug. However, some medications have active metabolites that have therapeutic or toxic effects, for this has been suggested for tamoxifen and sunitinib.[38-40] Additionally, many small molecule kinase inhibitors are highly lipophilic compounds, which commonly translate into extensive plasma protein binding (ie, fraction bound to plasma proteins > 0.9).[14] For drugs that are highly protein bound, small variability in the proportion of drug that is bound to plasma proteins results in disproportionately large variability in the fraction unbound. This is important, as the free (unbound) drug is responsible for exerting the drug effects. Thus, free trough plasma concentrations may be a superior exposure marker than total trough blood concentrations for some small molecule kinase inhibitors. In the context of advanced disease, this is important, with patients often having low serum albumin, therefore affecting the active free drug concentration.

Each method of dose adaption has advantages and limitations—for example, toxicity and response-guided on-therapy dose adaption require observation of toxicities which may be easily observable within the clinic, whereas concentration-guided on-therapy dose adaption is reliant on accurate documentation of sampling and dosing times and potentially expensive assay requirements. Toxicity and response-guided on-therapy dose adaption also account for pharmacokinetic and pharmacodynamic variability, and as such have the potential to be a superior guide to efficacy than plasma concentrations. A significant disadvantage of toxicity-guided dosing is that it is reactive and likely more useful for effects that develop quickly after drug initiation, it can also be difficult to track modest changes in toxicity and toxicity assessment has a degree of subjectivity.

6 | PROSPECTIVE STUDIES OF PRECISION DOSING

6.1 | Search process

Prospective studies investigating precision dosing strategies of targeted cancer medicines were identified through a search of Embase,

Scopus, ProQuest, and Google Scholar. Search terms were the name of FDA-approved targeted cancer medicines in addition to the phrases "dose modification","dose adaption", "therapeutic drug monitoring", "dose personalization," and "dose individualization". Upon reading the abstract, studies were considered if the primary purpose was to assess a dosing strategy which differed from current practice standards. Upon reading the full text, studies were excluded if they did not select the initial dose or adapted the dose based on a marker of therapeutic outcomes, toxicity, or drug exposure. Such an example would be a study assessing therapeutic outcomes and toxicity to front-line high dosing without guidelines on what to do in the event of toxicity. Studies included assessment of a dosing strategy which differed from the current practice standard and included initial dose selection or on-therapy dose adaption based on a marker of response, toxicity, or drug exposure.

6.2 | Prospective studies identified

Several potential therapeutic outcome, toxicity, and exposure biomarkers were identified for small molecule kinase inhibitors and monoclonal antibodies in retrospective analyses. Despite this, no prospective interventional studies evaluating initial dose selection strategies for targeted cancer medicines were identified. The major focus of prospective studies to date has been the use of therapeutic outcome, toxicity, and exposure markers to guide on-therapy dose adaption.[38-80]

6.2.1 | On-therapy Dose Adaption Strategies

Figure 3 presents a summary of the on-therapy dose adaption strategies which have been prospectively assessed for targeted cancer medicines. Investigated strategies incorporated the use of exposure, toxicity, or therapeutic outcome markers. When formulating study design, it is important to consider disease status, time since drug initiation, and prior evidence of successful/unsuccessful strategies. While identified strategies were categorized as concentration, toxicity or response-guided strategies based on the dominating biomarker of the studies, patient care is a holistic balance. Thus, successful precision dosing accommodates all clinical requirements to obtain optimal patient outcomes, the hierarchy of which will vary depending on the study, targeted cancer medicine, disease status, time since drug initiation, and patient. Figure S1 presents a study-by-study breakdown of the specific on-therapy dose adaption strategies prospectively assessed for targeted cancer medicines.

Targeted cancer medicines generally have dosage reduction guidelines in response to toxicity listed within the drug label. These guidelines are established during the drug development process and are an important toxicity-guided dosing strategy. Post-marketing investigations of toxicity and response-guided dosing have typically focused upon strategies that adopt an underlying assumption that increasing drug exposure to the maximum tolerated by an individual will increase therapeutic benefit. There have been multiple toxicity and response-guided dosing strategies investigated in prospective studies, each with subtle differences (Figure S1).[47-79] For example, 'front-line high dosing' is where a medication is initiated at a dose above the current practice standard, and if toxicity occurs, the dose is reduced.[48-51] Reducing the dose when toxicity occurs may also be known as a toxicity avoidance strategy. A second strategy is "ramp-dosing", where a medicine is initiated at the standard dose, and then increased until either toxicity or a predefined maximum. To date, ramp dosing has been assessed early after initiation and in those who have failed to respond to initial doses (Figure 3). Ramp dosing in those who have failed to respond or relapsed to standard dosing is a form of response-guided dosing, and typically these are the first precision dosing strategies to be studied for a medicine to extend or achieve efficacy.[52,54-59] Alternatively, ramp dosing with a clear toxicity target is also termed "toxicity targeted dosing" or "toxicity adjusted dosing".[60-70,74] With respect to ramp dosing, if it is shown to benefit those who have failed/relapsed to therapy, it may be logical to investigate the strategy early after initiation or in responders, with the aim to achieve superior outcomes. The rationale behind ramp dosing early after initiation is to achieve high doses quickly yet improve tolerability compared to a front-line high dose strategy. Ramp dosing early after initiation or in responders is considerably more aggressive than ramp-dosing in those who have failed therapy, as the strategy aims to maximize benefit by maximizing the dose to the highest tolerated. Conversely, the standard lower dose may still be more beneficial for the individual compared to other treatment options, but the potential benefit has not been maximized in lieu of maximizing tolerability.

Figure 3 presents a summary of the concentration-guided on-therapy dose adaption strategies identified in prospective studies.[38-46] Given the numerous retrospective studies which have indicated exposure-response relationships and possible response thresholds/targets for targeted cancer medicines,[2,3,5-7] using drug concentrations is a rational approach to optimize efficacy and minimize toxicity. A complexity to concentration-guided dosing is that toxicity and therapeutic outcomes cannot be ignored, which was evident in the identified studies. For example, concentration-guided dosing of imatinib has been explored in randomized control trials using response threshold dosing and intervention strategies where drug dose is modified to target a specific concentration.[42,43] In these studies, a parent drug threshold/target concentration was aimed for in those not experiencing toxicity,[42,43] and as such uses an exposure biomarker yet also considers toxicity and therapeutic outcomes. Furthermore, concentration-guided dosing strategies are not limited to dose escalation; in a toxicity threshold study with dasatinib, patients with a concentration ≥ 1.5 ng/ml were randomized to a dose decrease arm or to continue at a standard dose. Such a strategy was assessed as dasatinib is associated with a high incidence of pleural effusion, and a concentration < 1.5 ng/ml was hypothesized to be associated with less toxicity and maintained efficacy.[41] However, if response was lost after dose reduction, it is unclear if a higher dose and thus concentration would induce response, exemplifying

a need to consider exposure, toxicity, and therapeutic outcomes simultaneously.

7 | FUTURE PERSPECTIVE

In order to implement precision dosing strategies of targeted cancer medicine into clinical practice, the relative benefits, costs, phase of treatment, and harms will need to be evaluated in adequately powered, well-designed randomized prospective studies. A recent randomized study assessed concentration-guided dosing vs standard dosing of imatinib,[42] and while the results of this study were non-significant, protocol deviations limited the ability to detect statistically significant differences, with a sensitivity analysis of the small number of patients adhering to the protocol showing a significant absolute risk reduction of 48%, (P = .033). This highlights the importance of developing precision dosing protocols that clinicians can or will follow, such as incorporating strategies that appreciate exposure, toxicity, therapeutic outcomes, and patient preferences. At present, many of the dosing strategies assessed in prospective studies appear structured, which has pros and cons, and focussed upon the most novel marker; however, this may affect clinical applicability which was indicated in this imatinib study.[42] Furthermore, in many of the precision dosing protocols identified, either patient preferences were not considered or not mentioned in the protocol, which deviates from normal patient care. Thus, precision dosing strategies of targeted cancer medicines should continue to be explored; however, improving the protocols assessed may improve study findings and clinical uptake.

This manuscript focusses on providing examples of potential precision initial dose selection and concentration, toxicity, and response-guided on-therapy dose adaption strategies for targeted cancer medicines. In doing so, it has become clear that it is unlikely that one strategy will fit all medicines and all patients, and future research will have a role in combing these techniques into clinically relevant precision dosing strategies. Sunitinib is a prime example of where a combined approach may work. It is known that metastatic renal cell carcinoma patients experience improved therapeutic outcomes with sunitinib when hypertension, neutropenia, hand-foot syndrome, asthenia, or fatigue occur on-treatment,[81-83] a strong indication that toxicity-guided dosing could improve therapeutic outcomes. However, toxicity-guided dosing alone does not remove all interpatient concentration variability,[84,85] and those who experience toxicity may still have insufficient sunitinib exposure to respond. Thus, toxicity-guided dosing could be used to target toxicity; however, once this is achieved, drug concentrations can be assessed to determine whether improved therapeutic outcomes with sunitinib is likely, and if it is not, an alternate treatment could be trialled more quickly.[84,86] The merits of a combined concentration, toxicity, and response approach to precision dosing can be made for several other targeted cancer medicines, highlighting the importance of future research exploring its potential.

8 | CONCLUSION

Given the increasing evidence from retrospective studies and reviews that pharmacokinetic and pharmacodynamic biomarkers for targeted cancer medicines may affect therapeutic outcomes and toxicity, precision dosing through either precision initial dose selection or on-therapy dose adaption appears rational approaches to improve therapeutic outcomes and minimize toxicity to targeted cancer medicines. To date, multiple concentration, toxicity, or therapeutic outcome markers have been used to guide on-therapy dose adaption of targeted cancer medicines; however, for precision dosing strategies to be successfully integrated within the clinic, they need to be more flexible to simultaneously considering exposure, toxicity, therapeutic outcomes, and patient preferences.

PRINCIPLE INVESTIGATOR

This project did not involve human subjects/individuals and as such, does not have an associated principle investigator.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

All authors were involved in manuscript preparation for this project.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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