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Current Perspective

At the right dose: personalised (N-of-1) dosing for precision oncology

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Abstract The objective of oncology therapeutics, especially in the age of precision medicine, is to give the right drug(s) to the right patient at the right time. Yet, a major challenge is finding the right dose for each patient. Determining safe and efficacious doses of oncology treatments, especially for novel combination therapies, can be challenging. Moreover, traditionally, dosing cancer drugs is based on giving each patient the same dose (a flat dose) or a dose based on surface area/weight. But patients' ability to tolerate drugs is influenced by additional factors including, but not limited to age, gender, race, comorbidities, organ function, and metabolism. Herein, we present evidence that, in the era of targeted drugs, individualised drug dosing determined by starting at reduced doses and using intrapatient dose escalation can yield safe and effective personalised dosing of novel combinations of approved drugs that have not previously undergone formal phase I trials and can also optimise dosing of tested drug regimens.

1. Introduction

The aim of precision cancer medicine is to provide the right treatments to the right patient at the right time. A critical component of this aim is to optimise dosing for each patient. Typically, dosing is standardised for

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patients based on relatively small numbers of participants in early-phase clinical trials. However, these doses do not take into consideration the wide variability in tolerance that may be due to patient frailty, comorbidities, organ compromise, coadministered drugs, gender, age, race, and pharmacologic metabolism. We therefore discuss how some of these challenges can be resolved by exploiting intrapatient dose escalation for both novel combinations of approved agents that have not been previously tested in early-phase trials as well as for dosing known drug regimens.

Historically, dosing of cancer treatments has been guided by information from phase 1 clinical trials that determine the maximum tolerable dose (MTD) and recommended phase 2 dose (RP2D). The traditional 3 + 3 study design enrols three patients in a given dose cohort to assess dose-limiting toxicity (DLT), generally defined as a ≥ grade 3 clinically relevant toxicity. The MTD is achieved if there are one or fewer DLTs in an expanded cohort of six patients [1]. Hence, dosing is determined on very small numbers of patients and often over only the first 1-month therapy cycle.

Some low-grade toxicities (e.g., chronic diarrhoea) that are tolerable over the usual 4-week MTD evaluation period, may not be bearable over a longer period; thus, an RP2D lower than the MTD may also be ascertained from the clinical trial. The RP2D is often defined as the dose level that optimises multiple parameters across enroled patients: safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics.

Alternative phase 1 clinical trial designs utilise accelerated escalation, which aim to further decrease the number of patients in the trial and hence minimise the number of participants on lower doses and to find the therapeutic, tolerable dose faster; accelerated designs may have as few as one patient per cohort [2,3]. While a number of other phase 1 trial designs have been attempted, the classical 3 + 3 study design remains the most commonly used model. Regardless of the design used, 'optimal' dosing is ascertained on small cohorts that do not reflect cancer population diversity, especially considering standard clinical trial eligibility criteria that exclude real-world comorbidities.

Phase 1 clinical trials were developed in the cytotoxic era wherein administering the highest dose possible was critical to maximise efficacy. However, these principles likely do not apply to novel targeted therapies. The highest tolerated dose in a phase 1 trial may be higher than needed for optimal target engagement/efficacy of a targeted therapeutic. Indeed, less drug is sometimes better, especially if the target is impacted and the patient can continue therapy with a good quality of life [4,5]. Optimal dosing for targeted therapies in oncology initiatives such as Project Optimus (from the Food and Drug Administration) [6] aim to refine dose selection to incorporate additional information such as dose-response and exposure-response relationships [4,7–10].

Overall, there are at least two major categories of phase I studies—trials of first-in-human agents and trials that combine approved agents. Herein, we will address issues with the dosing of novel combinations of approved agents, though many of the discussion points also apply to investigational new drugs and to established drug regimens.

2. Challenges of novel drug combinations

Administering approved drugs in new combinations in order to increase efficacy is a mainstay of oncology clinical trials. The MTD and RP2D for these combinations are derived from phase I trials (as described above), with limited numbers of patients and with the same dosing recommended for all future patients. However, this paradigm poses several challenges. First, it results in oncologists prescribing a flat dose or a dose based on an individual patient's weight or surface area, even though patients differ in numerous ways, and these differences impact both toxicity and efficacy: age, gender, muscularity/frailty, renal and hepatic function, and metabolic variations, including in minority populations as well as due to coadministration of non-oncologic therapeutics [11–16].

The second major challenge associated with the derivation of dosing of combinations of approved drugs from phase I trials is due to insights from next-generation sequencing (NGS) in the precision/personalised oncology era. Advanced/metastatic cancers are complex and have distinct molecular profiles [17]. A personalised or precision medicine approach requires treating patients based on the tumour molecular landscape, which means many individualised combinations. If there are 300 drugs available in oncology, there are ~45,000 two-drug combinations and ~4.5 million three-drug combination. Performing phase I trials for all these combinations or even a large part of them could take over 1000 years. Another solution is needed.

3. N-of-1 strategies with intrapatient dose optimisation for novel drug combinations

The University of California San Diego investigation of profile-related evidence determining individualised cancer therapy (I-PREDICT) [18,19] clinical trial aimed to treat patients with advanced and metastatic cancers through an N-of-1 customised approach, with each patient receiving a unique set of therapeutics tailored to the molecular profile of their tumour. Recommended therapeutic combinations had single-agent dosing from United States Food and Drug Administration (FDA) approval labelling, but often the exact combination of drugs had never been given together in a phase I clinical trial. In order to provide safe and tolerable starting doses in the trial, the study used evidence from ~100,000 patients reported in several large analyses of phase I–III

clinical trials of ≥ 2 drugs as a general template for dosing *de novo* combinations of gene- and immune-targeted therapeutics, hormonal therapy, biologics, and chemotherapy [20–24]. These literature studies suggested that antibodies were better tolerated than small molecular inhibitors or cytotoxic chemotherapy in combinations. In general, a starting dose that was approximately 50% of the single-agent FDA-approved dose should be considered for combination therapy. Combinations with antibodies could be started at higher doses in many cases, given their improved tolerability. Certain therapeutics (e.g., mTOR inhibitors, PARP inhibitors, histone deacetylase inhibitors, cytotoxic drugs, and the immunotherapy agent ipilimumab) had increased toxicity, requiring more significant dose reductions and enhanced monitoring. In the I-PREDICT trial, patients were seen in clinic weekly to start, with blood counts and follow-up of renal and liver function, and doses were titrated up or down to tolerance. With this guidance, patients on the I-PREDICT study were able to receive *de novo* novel combinations of two-, three-, and four-drug combinations with a trend to less serious toxicity than that experienced by patients who received conventional multiagent therapy on study. Indeed, serious adverse events deemed at least possibly related to drug occurred in 3.6% of highly matched patients versus 15.6% of patients with lesser degrees of matching of molecular findings to drugs ($P = 0.14$ with higher degrees of matching often reflecting novel drug combinations). There were no treatment-related deaths in the study. The rate of serious adverse events was unrelated to the number of drugs administered. Moreover, patients whose molecular profiles were well matched to their individualised drug combinations showed significantly better outcomes (response rate, progression-free, and overall survival) than patients whose tumours were poorly or not at all matched to their drug regimen [18,19].

In the I-PREDICT trial, we had no choice but to start at lower doses and escalate within a patient given the number (~4.5 million) of possible unique drug combinations. Initially, the intrapatient dose escalation was used out of necessity since many of the combinations that matched a tumours' NGS profile had not previously been tested in phase I studies. However, once the analysis revealed equivalent or reduced toxicity in the presence of better outcomes in spite of initial administration of drugs at reduced doses, it became apparent that intrapatient dose escalation might be an optimised methodology for giving drugs, especially for targeted or immunotherapeutic drugs, and including for regimens with established or approved doses. Indeed, most therapies are started at the same FDA-approved doses, regardless of whether the patient is a muscular 20-year-old or a frail 75-year-old. Furthermore, toxicity diminishes quality of life and may result in the patient refusing further therapy or the oncologist being hesitant to continue therapy if the side-effects are serious. Most oncologists will start a therapy at the standard FDA-approved single-agent or combination dose and later evaluate a patient to determine if a dose reduction is required. The I-PREDICT methodology lowered doses for *de novo* combinations from the outset, and since doses were titrated upwards with careful monitoring of patient tolerance, many older patients or patients with poorer performance status, or even younger patients who experienced low-grade chronic toxicities at lower doses, remained on the lower doses.

Clinical trials attempt to 'cherry pick' the ideal oncology patient, with numerous inclusion and exclusion criteria, in order to protect patient safety and to provide the best chance of identifying a therapeutic signal. Indeed, patients enroled on clinical trials require intensive screening for enrolment, and they must have excellent performance status, normal or near-normal organ function, not be on potentially interacting drugs, and have no major comorbidities. Hence, a clinical trial cohort does not represent the standard oncology patient population, which tends to be older, frailer, have more medical issues, be on multiple interacting drugs, and often have organ dysfunction (Fig. 1). Individual variations in drug metabolism can also affect drug levels; therefore, pharmacogenomic evaluations may alter dosing recommendations [25]. Real-world data analyses postapproval of outcomes and tolerability can provide some guidance on the non-trial population; however, for most approved therapies, this information often lags significantly behind the approval. Even in patients who represent the clinical trial population, the standard 3 + 3 study design to determine the MTD and RP2D represents only a small number of patients, and it is unclear if these few patients are characteristic of even a young, otherwise healthy cancer patient. As such, we contend that it is critical to provide an individualised approach to dosing for even approved oncology therapeutics.

Model-informed precision dosing combines patient factors affecting pharmacokinetics, precision dosing software, and therapeutic drug monitoring (i.e., quantifying drug levels in an individual patient) to determine optimal

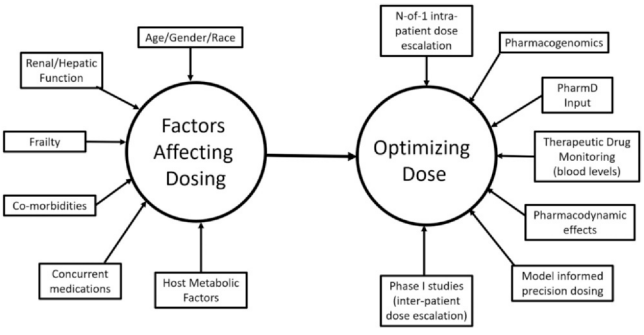

Fig. 1. Personalised/precision dosing. A number of factors can affect dosing in oncology patients and multiple considerations are required to provide an optimised, personalised dose.

dosing regimens for each person and may be useful for combination therapy dosing as part of a precision medicine approach [26,27]. In addition, input from oncology pharmacists and adjustment based on pharmacodynamic effects (e.g., toxicity, biomarker, and imaging responses) may also play an important role in determining individually safe and efficacious doses (Fig. 1).

4. Future directions: intrapatient dose optimisation for oncology drugs

Phase I studies are crucial for evaluating a starting point for later-phase clinical trials and guidance for starting doses of an experimental therapeutic in the clinic. However, the adage to 'start low and go slow' should apply to all oncology patients being treated with non-cytotoxic drugs, since the data suggest that, for non-cytotoxic compounds, patients on lower doses do not fare worse [5]. Therefore, starting at lower doses with intrapatient dose escalation can be exploited for *de novo* combinations of approved drugs as well as for established drug combinations or even for single drugs with customary dosing. Intrapatient dose escalation is important to achieving efficacious doses while maintaining tolerability. Toxicity from starting at too high of a dose can limit the ability to achieve ongoing exposure to effective components of a combination regimen or even of single drugs due to dose interruptions. The ability to tolerate side-effects varies considerably between patients. For some targeted therapies that are continued until progression, patients may be on them for months to years if an excellent response is achieved. Low-grade toxicities such as rash, fatigue, or diarrhoea that are not well assessed in a phase 1 clinical trial may be intolerable for prolonged periods and result in poor adherence or drug discontinuation. These considerations further emphasise the importance of starting at lower doses and intrapatient dose escalation as a generalised model for finding the best individualised dose for each person. In conclusion, precision/personalised therapy necessitates identifying not only the right drug(s) for each patient but also the right dose.

Author Contributions

Razelle Kurzrock conceptualized the project, helped write the original draft, reviewed, and edited. Mina Nikanjam wrote the original draft, reviewed, and edited. Jason Sicklick and Shumei Kato reviewed and edited the manuscript.

Declaration of Competing Interest

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