Genome Medicine

COMMENT

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Patient rights in precision oncology: right treatment, right time, right dose, right order, right place

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Abstract

Precision oncology has facilitated a transition from a one-size-fits-all to a precise individualized approach. This Comment discusses the broader challenges in the implementation of personalized treatments to further improve patients' outcomes, towards comprehensive strategies that address tumor complexity and patients' molecular portfolios, as well as quality of life and diversity considerations.

Keywords Precision oncology, Biomarkers, Targeted treatments, Dose, Sequence, Trial decentralization

Precision oncology has facilitated a transition from a one-size-fits-all to a precise individualized approach, with the potential to offer more effective and less toxic treatments to patients [1]. Even so, precision oncology is often narrowly defined as matching of a single tumor biomarker with a cognate monotherapy. Yet, based on the complexity of tumor and host molecular portfolios, as well as quality-of-life and diversity considerations, precision management strategies should also consider the best drug combinations, the timing of precision matched drug administration, the optimum order of administration, in addition to the well-being of patients, with host-related factors such as individualized dosing and quality-of-life issues (e.g., keeping the patient close to home) requiring attention.

Our aim is to address the broader challenges in the implementation of precision oncology in the context of patient "rights"—right treatment, right time, right dose, right order, and right place (Fig. 1).

Right treatment

Selecting the right treatment for each patient is of fundamental importance. Multiple biomarker-matched treatments are now approved by several international regulatory agencies. Some of the best examples wherein biomarker-based treatment selection led to transformative changes in oncology include the use of the BCR-ABL inhibitor imatinib in patients with *BCR-ABL*-rearranged chronic myelogenous leukemia (CML), the HER2 antibody trastuzumab in patients with HER2-positive breast cancer, and immune checkpoint inhibitors (ICIs) in patients with microsatellite (MSI)-high tumors [2]. These successes were fueled by remarkable advances in clinical-grade tumor molecular profiling that now incorporates technologies almost unimaginable just a couple of decades ago, including genomic sequencing performed on both tissue and blood samples. Clinical trial designs have also evolved at a breathtaking pace, from traditional

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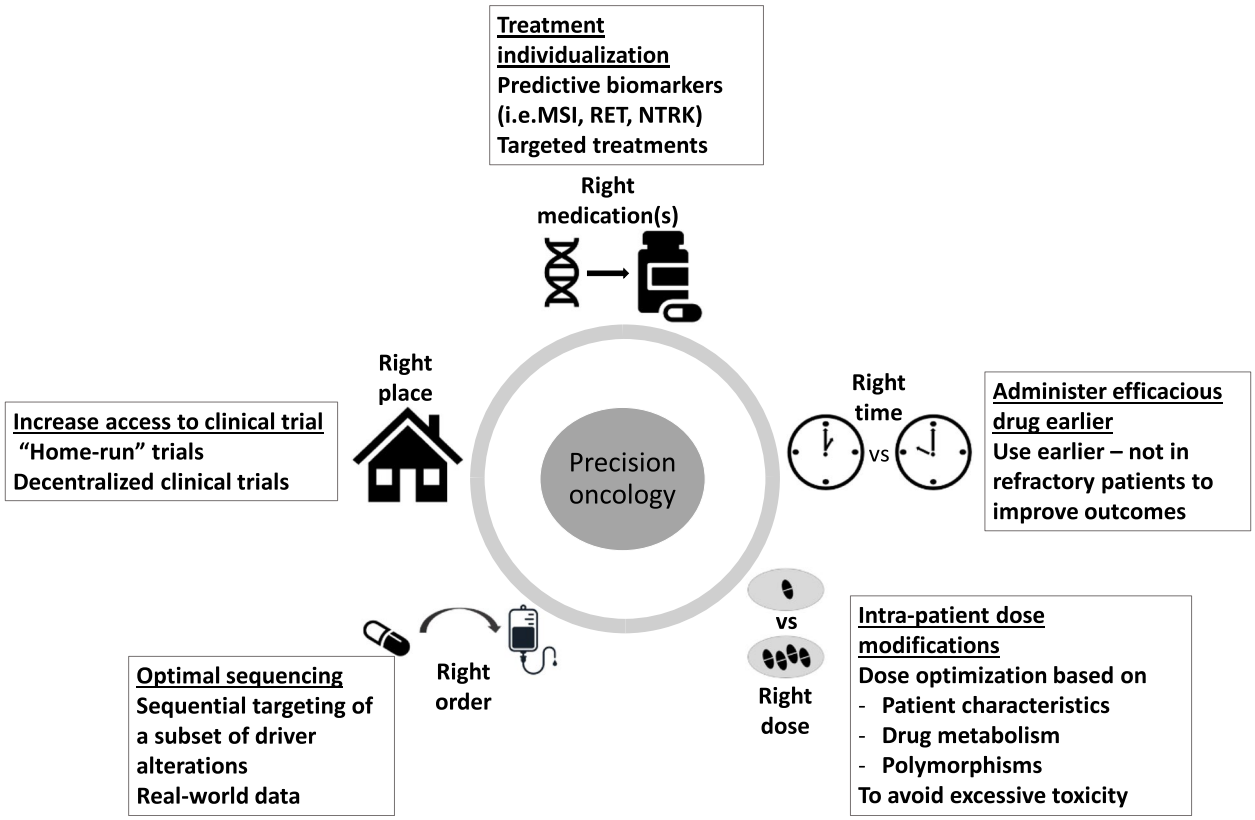

Fig. 1 Patient "rights"—right medication(s), right time, right dose, right order, and right place—in implementing precision/personalized oncology

tumor-based, biomarker-agnostic trials to tumor-agnostic, biomarker-specific designs and, with the more recent advance to N-of-1 trials, wherein every patient is treated with a unique drug or combination of drugs matched to their molecular profile [3].

Right time

Biomarker-matched drugs that show some activity in heavily pretreated patients with late-stage refractory cancer need to be advanced to earlier treatment lines, where their activity may be remarkably amplified. The poster-child for the success of such a strategy is imatinib. When administered to late-stage BCR-ABL-positive CML, imatinib has activity, but response rates and survival impact are low; in contrast, imatinib in newly diagnosed CML patients results in near-universal responses and a near-normal life expectancy, probably because of the absence of secondary molecular aberrations in frontline disease [4]. Despite this observation, the vast majority of studies of biomarker-matched therapies for solid cancers have been conducted in the advanced treatment-refractory disease setting. In this late-stage setting, responses occur, but in only a subset of patients and are often brief. Immunotherapy may be an exception, wherein selected patients with advanced/refractory MSI-high or tumor mutational burden (TMB)-high tumors can achieve durable complete remissions. Yet, giving treatment early may be more beneficial, as evidenced in the study wherein an ICI resulted in lasting complete responses in all 12 patients with MSI-high locally advanced rectal cancers, mitigating the need for surgery, radiation, or chemotherapy [2]. In conclusion, the evaluation of gene- and immune-targeted treatments at the right time, which may be earlier in the disease course, is imperative in order to increase efficacy.

Right dose

One of the aims of precision oncology should be to administer the right dose to each patient. Yet, this aspect of personalized medicine is often neglected. Historically, chemotherapy is administered at the highest tolerable doses. Doses are adjusted only minimally per patient characteristics such as body surface area or, in some cases, creatinine clearance. However, selected patients with specific genetic backgrounds may demonstrate excessive toxicity or fatal events post-chemotherapy. For instance, toxicity risks are significantly higher in patients with *DPYD* polymorphisms causing lower enzymatic

metabolic activity for fluoropyrimidines [5]. Other factors associated with differences in drug metabolism, efficacy, or toxicity include gender, age, race, frailty, or lack thereof, host organ function, and drug-drug interactions in patients receiving more than one drug or with co-morbidities. For the most part, these factors are not taken into major consideration when dosing patients for cytotoxics or for newer drugs. Indeed, targeted agents and ICIs are mainly approved at fixed doses. Moreover, the doses are often determined in early-phase clinical trials based on the maximum tolerated dose, which is assessed on a very small patient group followed for a short period of time.

A one-size-fits-all dose/schedule is sub-optimal and may lead to toxicity, often resulting in treatment interruptions/discontinuation. Moreover, approved doses may be higher than the ones required to achieve antitumor effects. The FDA now recognizes that, in the era of targeted therapeutics, "less may be more" [6]. Indeed, once a specific small molecule inhibitor is given at a dose adequate to suppress the target enzyme, any increase in dose may only amplify side effects. Individualized dosing could be facilitated by intra-patient dose modifications according to tolerance with or without individualized pharmacokinetic monitoring [7].

Right order

As a greater number of therapeutic options become available for patients, the optimal sequence of drug administration becomes more important. It is not known if patients fare better by being given combinations of drugs to co-target co-drivers or if the drugs are given in sequence. However, there is long-established evidence that combination therapy overcomes tumor heterogeneity. For instance, progress in the treatment of pediatric acute lymphocytic leukemia, in which increasingly intensive combination regimens ultimately achieved high cure rates, suggested that overcoming resistance requires eliminating tumor clones. Hence, if the goal is cure, eradicating the disease with combination therapy appears necessary [8]. Sequentially targeting a subset of driver alterations may result in the emergence of new clones promoting progressive resistance. Still, if cure is not possible, the impact of sequential therapy rather than combination therapy requires assessment, as does the optimal sequence of therapeutic interventions. Randomized trials as well as real-world data may be exploitable to begin to answer these challenging questions [9].

Right place

Clinical trial access, as well as expert medical care, needs to be equitable for all patients with cancer. The best place for a cancer patient, from a quality-of-life perspective, may be at home with family. Patients with cancer often have to travel far from home in order to access clinical trials of novel agents. This is difficult for patients and families. Importantly, decentralized trials—"home-run" trials [10]—permit patients to stay at home and hence also enable trial access for underserved groups, including those who live in rural areas.

Decentralization of clinical trials implies performance of a proportion or all clinical trial activities at locations other than a central site [10]. Decentralized clinical trials can involve digital health technologies, including portable devices (sensors) and online platforms for reporting adverse events in real time. They can be site-less (fully remote), with care provided by the home oncologist, or take the tack of the US National Cancer Institute and cooperative groups using platform designs with multiple cohorts and opening at > 1000 sites, or they may also use extensive community site networks, since, for example, ~ 85% of cancer patients in the USA are treated in the community and not in large academic centers.

Conclusions

Advancing to next-generation precision oncology means moving beyond the current narrow matching of a single biomarker to a single agent. First, because metastatic tumors are both complex and distinct from each other, the right treatments, that is, tailored combinations of matched therapies, may be needed for optimized outcomes. Second, based on the CML model, wherein biomarker-matched treatment in the newly diagnosed setting yields transformative, rather than incremental survival gains, perhaps because genomic evolution and hence resistance has not occurred, treatment at the right time is necessary in solid cancers, and that right time may be at diagnosis rather than in advanced/metastatic refractory disease. Third, multiple differences between patients mean that tolerance to drugs is likely to differ. Therefore, the right dose for each patient, rather than a one-size-fits-all approach, is needed and can be achievable via intra-patient dose finding as well as pharmacokinetic/pharmacodynamic monitoring. Fourth, when many therapeutic options are available, the question as to the right order of administration is relevant. Fifth, quality of life and increasing access to therapeutic trials means that receiving therapy in the right place—that is, at home rather than via travel to a distant center—is critical. We envision a future where technological advancements can reshape the definition of precision oncology. For instance high-throughput computing may be used to assist multi-omic analysis of tumors, identifying potential pharmacological targets, followed by the artificial intelligence-informed customized drug-design for the patient.

Abbreviations

CAR	Chimeric antigen receptor
CML	Chronic myelogenous leukemia
FDA	Food and Drug Administration
ICI	Immune checkpoint inhibitor
MSI-high	High microsatellite instability
NSCLC	Non-small cell lung cancer
PD- 1	Programmed death-1
TMB	Tumor mutation burden

Acknowledgements
Not applicable.

Authors' contributions
E.F.: Investigation, Writing original draft A.M.T.: Supervision, Writing – review & editing R.K.: Conceptualization, Project administration, Supervision, Writing – review & editing All authors reviewed the manuscript.

Funding
RK is funded in part by National Institutes of Health/National Cancer Institute award number 5U01 CA180888 - 08 and 5UG1 CA233198 - 05. AMT is supported by Mr. and Mrs. Steven Mckenzie's Endowment, Katherine Russell Dixie's Distinguished Professorship Endowment, and don or funds from Jamie's Hope and Mrs. and Mr. James Ritter for Dr. Tsimberidou's Personalized Medicine Program and by the National Institutes of Health/National Cancer Institute award number P30 CA016672 (University of Texas MD Anderson Cancer Center).

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 20 October 2024 Accepted: 8 April 2025
Published online: 12 May 2025

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