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Commentary

Delivered Dose: A Drug-centric Phenotype for Chemotherapy Dose Individualization

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Abstract. It is pointed out that genotype-based approaches are unlikely to be effective at dose individualization. Delivered dose, which refers to the amount of drug delivered to the point of action to be measured by quantitative imaging techniques, is a drug-centric phenotype that separates pharmacokinetic effects from pharmacodynamic effects. Delivered dose serves as a midway measurable numeric parameter between drug administration and therapy outcome. One potential way to reduce chemotherapy outcome variation is to individualize prescribed drug so that uniform delivered dose is achieved across the patient population.

KEY WORDS: chemotherapy; delivered dose; dose individualization; genotype; imaging; phenotype.

Cancer chemotherapy is a delicate balance between response and toxicity: while under-dosing undermines response, over-dosing results in excessive toxicity. Therefore, dose is a critical factor in cancer chemotherapy (1) and misdosing can happen to a significant portion of cancer patients (2). One way to improve cancer chemotherapy, and drug therapy in general, is to optimize drug dose for each patient (dose individualization), an issue attracting increasing attention from both the research community and regulatory agencies (3).

Conventionally, the prescribed dose of cancer drugs is individualized according to patients' body surface area (BSA). However, BSA-based dosing is not effective at reducing therapy outcome variation and this practice has been put into question by recent studies (4). In light of this, there is an urgent need to develop new approaches for chemotherapy dose individualization.

One approach to dose individualization is genotype-based. The underlying rationale is that variation in response to drug therapy has both pharmacokinetic (PK) and pharmacodynamic (PD) components, which are regulated, in part, by genes that vary from patient to patient (5,6). In practice, a few PK/PD-related genes are screened and recommendations on drug dose are made based on the screening results (7).

There is no denying that genes play important roles in shaping up the PK/PD profiles in patients and that a genotype-based approach can indeed achieve patient *stratification*: responders *vs*. non-responders, poor *vs*. extensive metabolizers, etc. However, a genotype-based approach is unlikely achieve dose *individualization* for the following reasons.

First, generally speaking, genes are static while tumor growth is dynamic. This dynamic feature leads to variation in PK/PD profiles in the same patient at different disease stages. Therefore, the optimal dose for a patient may vary with time, depending on disease progression and treatment outcome. For example, tumor vasculature is an important factor affecting cancer chemotherapy and it changes as tumor grows (8). Such intra-patient variation cannot be accounted for by static DNA sequences.

Second, the PK/PD profiles of many anticancer drugs are determined by a multitude of genes. For example, about 30 genes are involved in the metabolic pathway of 5-fluorouracil (9). Keep in mind that this is just the metabolic aspect of the pharmacokinetics of this drug, which includes absorption, distribution, metabolism and excretion (ADME). On top of this melee of PK-related genes, there are also PD-related genes (e.g., the thymidylate synthase gene (6)). Further confounding the picture is that tumor DNA can be different from germline DNA (10,11). Considering that these genes perhaps do not operate independently of each other, the situation becomes hardly tractable.

Third, genotype is not numeric by nature, while drug dose is numeric by nature. The translation of non-numeric DNA sequences (e.g., A→G mutation in a specific gene) into numeric dose recommendations (e.g., 200 mg/day→100 mg/day) inevitably involves assumption and simplification. There is nothing wrong with assumption and simplification, which are part of the scientific process. But assumption and simplification need to be verified and validated. Current practice in genotype-based dose adjustment seems to be long on testing and recommendation but short on verification and validation (7). For example, enzymes encoded by CYP450

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genes (e.g., *CYP2D6* and *CYP2C19*) are involved in drug metabolism and CYP450 genotyping has been advertised as a guidance for drug dose individualization (7). However, a recent study commissioned by the Centers for Disease Control and Prevention concluded that "it is not known if potential benefits from CYP450 testing will outweigh potential harms" (12).

Finally, there are non-genetic factors affecting a patient's PK/PD profile, such as renal function, tumor vasculature, co-existing illness and co-administered drugs, diet, to name a few. It is unlikely these non-genetic factors can be fully defined, let alone fully controlled. Without complete control of these non-genetic factors, it is doubtful that two patients with identical PK/PD-related genetic makeup will have identical PK/PD profile. The implication is that the optimal dose for patients with identical PK/PD genes may still vary from person to person and from time to time. Hence, even if all the first three concerns are addressed, a purely genotype-based approach can only go so far in drug dose individualization.

Taking these issues into consideration, it is hard to see how genotype alone, especially single nucleotide polymorphisms (SNPs), can translate into specific recommendations on optimal drug dose for each patient at each treatment stage. What genotyping can achieve is patient stratification. To move beyond stratification and achieve true individualization, a phenotype-based approach is needed.

There are different levels of phenotypes. The question is: what is the most effective phenotype in facilitating drug dose individualization? At one extreme of the spectrum of phenotypes is therapy outcome, measured by (patho)physiological parameters of the patient (tumor size, organ functions, etc.). While outcome is the true end-point of drug therapy, it lags behind treatment procedure, making it hard to provide timely feedback on dose adjustment. At the other extreme of the spectrum of phenotypes is the bioactivities of enzymes encoded by PK/PD-related genes (13), which are biochemical parameters of the patient. For the purpose of drug dose individualization, biochemical parameters suffer similar shortcomings as DNA sequences, albeit one step closer to drug reality.

A common feature of therapy outcome ((patho)physiological parameters) and enzyme bioactivity (biochemical parameters) is that they describe the state of the patient, which of course is important for therapy planning and assessment. However, it is necessary to have an intermediate phenotype between these two extremes that describes the state of the drug, not the state of the patient. The role of such a drug-centric phenotype is to complement, not to replace, patient-centric phenotypes such as therapy outcome and enzyme bioactivity.

Here, we suggest that the actual amount of drug delivered to tumor tissues (= tumor drug concentration × tumor volume), called delivered dose, serves as a useful drug-centric phenotype for dose individualization. Delivered dose overcomes the aforementioned shortcomings of genotype-based approaches: it is a numeric parameter that is affected by disease progression, multiple enzymes and non-genetic factors. More broadly, delivered dose refers to the amount of drug delivered to points of action. The essence of delivered dose is that by achieving the same delivered dose in different patients, PK differences, regardless of origin and complexity, are eliminated. The hypothesis is that by eliminating PK differences, therapy outcome variation will be reduced.

Delivered dose serves as a midway measurable numeric parameter between drug administration and therapy outcome. It provides timely feedback for dose adjustment. To this end, the patient needs to go through a dose-establishing

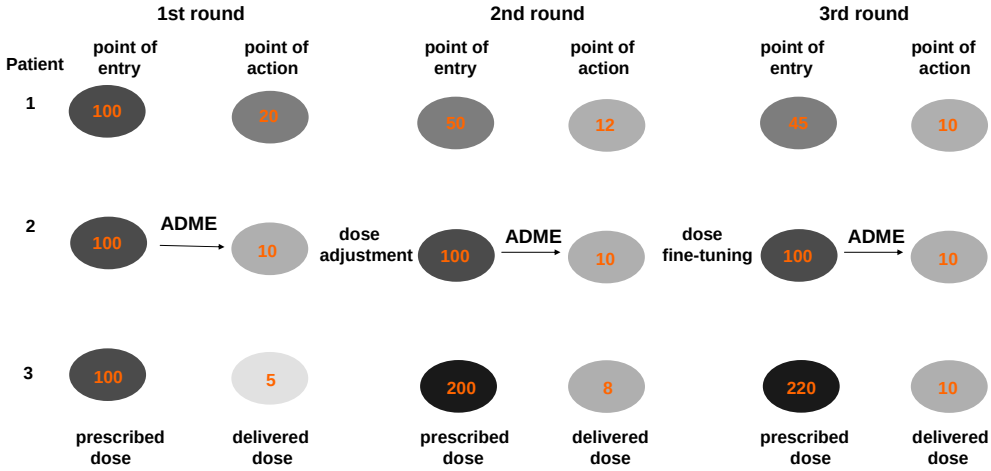

Fig. 1. Proposed chemotherapy dose individualization procedure. ADME stands for Absorption, Distribution, Metabolism and Excretion. The numbers denote drug dose in arbitrary unit. Delivered dose is determined non-invasively using quantitative imaging technologies such as ^{19}F MRI. In the 1st round, patients are given the same prescribed dose. In the 2nd – 3rd rounds, the prescribed dose is adjusted/fine-tuned for each patient so that uniform delivered dose is achieved across the patient population. The dose adjustment process may be purely trial-and-error or may be aided by genotyping. The patient will go through such a dose-establishing procedure at the beginning of each treatment stage. Dose individualization using nuclear imaging is currently used in the delivery of Bexxar®, a radioimmunotherapy drug for treating non-Hodgkin's lymphoma (20).

procedure (Fig. 1). In this process, all patients receive the same initial prescribed dose. The delivered dose in each patient is then determined. Based on the delivered dose, the prescribed dose is adjusted for each patient, with the aim of achieving the same delivered dose across the patient population. After receiving the adjusted prescribed dose, the delivered dose is measured again for each patient, and if needed, the prescribed dose will be fine-tuned. This dose-establishing procedure will be conducted at the beginning of each treatment stage. The target delivered dose may vary from one treatment stage to the next, depending on treatment results. By going through the dose-establishing procedure for each patient at each treatment stage, both inter- and intra-patient variations can be taken into account, thus truly individualize drug dose.

Determining delivered dose requires quantifying drug concentration in tumor and other tissues, the importance of which was pointed out 10 years ago (14). In order to gain wide acceptance in clinical practice, delivered dose has to be measured non-invasively using quantitative imaging techniques. Non-invasive determination of delivered dose poses tremendous technical challenges. Of the two imaging modalities capable of *in vivo* drug tracking and quantification, each has its own limitations. Positron emission tomography (PET) has high sensitivity but radio-labeled drugs cannot be administered at therapeutic dose. To determine delivered dose at the therapeutic level, a radio-labeled drug needs to be co-administered with its non-radio-labeled counterpart, which bring a range of complications (15). The production and handling of radio-labeled drugs has its own complications. Also, PET cannot distinguish a parent drug from its metabolites. In practice, PET has been used to determine receptor occupancy for certain CNS drugs (16). Although receptor occupancy is different from delivered dose, it nonetheless can help with drug dose optimization.

In contrast to PET, magnetic resonance imaging (MRI) does not require radio-labeling of drugs and hence avoids complications related to radioactivity. Also, magnetic resonance spectroscopy (MRS) can detect drug metabolites. However, the sensitivity of MRI is much lower than that of PET. Also, a dilemma for MRI is that it is extremely difficult to use the ^{1}H signal for drug tracking and quantification due to huge endogenous ^{1}H background. However, if a drug is labeled by fluorocarbons for ^{19}F MRI, which has no endogenous background, then the drug might lose its pharmacological activity. A potential solution to this dilemma is to make the fluorocarbon-labeled drug a prodrug which will be converted into the active form at the tumor sites, with the prodrug→drug conversion process monitored by ^{19}F MRS. This, however, will limit the applicability of this method as prodrug development is a challenging issue in its own right.

These technical difficulties notwithstanding, the determination of delivered dose is an achievable goal because technical difficulties can be resolved through research. In contrast, intrinsic limitations of the genotype-based approach do not go away. In the meantime, the combination of existing experimental methods and mathematically modeling may provide reasonable estimate of local drug concentration in certain cases (17).

In summary, the determination of delivered dose makes it possible to individualize prescribed dose on the basis of achieving uniform delivered dose across the patient population, under the premise that eliminating PK differences will reduce therapy outcome variation. Ideally, delivered dose should also be individualized to account for PD variation in patients. This would require the identification and determination of proper PD biomarkers, an issue that is outside the scope of this article (18,19).

Finally, we wish to point out that genotype and phenotype are the two sides of the same coin. They complement each other rather than compete against each other. In the context of personalized medicine, genotyping is probably more suited for patient stratification while phenotyping is probably more suited for therapy individualization. Phenotyping, such as the determination of delivered dose, can also help to verify and validate genotype-based dose recommendations.

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REFERENCES

1. Frei E, Canellos GP. Dose: a critical factor in cancer chemotherapy. Am J Med. 1980;69:585–94. doi:10.1016/0002-9343(80)90472-6.
2. Gurney H. How to calculate the dose of chemotherapy. Brit J Cancer. 2002;86:1297–302. doi:10.1038/sj.bjc.6600139.
3. Peck CC, Cross JT. "Getting the dose right": facts, a blueprint, and encouragements. Clin Pharmacol Ther. 2007;82:12–4. doi:10.1038/sj.clpt.6100215.
4. Baker SD, Verweij J, Rowinsky EK, Donehower RC, Schellens JHM, 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.
5. Lin JH. Pharmacokinetic and pharmacodynamic variability: a daunting challenge in drug therapy. Curr Drug Metab. 2007;8:109–36. doi:10.2174/138920007779816002.
6. Hoskins JM, McLeod HL. Cancer pharmacogenetics: the move from pharmacokinetics to pharmacodynamics. Curr Pharmacogenomics. 2006;4:39–46. doi:10.2174/157016006776055400.
7. Katsanis SH, Hudson GJ. A case study of personalized medicine. Science. 2008;320:53–4. doi:10.1126/science.1156604.
8. Jain RK. Delivery of molecular and cellular medicine to solid tumors. Adv Drug Del Rev. 2001;46:149–68. doi:10.1016/S0169-409X(00)00131-9.
9. Marsh S, McLeod HL. Cancer pharmacogenetics. Brit J Cancer. 2004;90:8–11. doi:10.1038/sj.bjc.6601487.
10. Cerri E, Falcone A, Innocenti F. Cancer pharmacogenomics: germline DNA, tumor DNA, or both? Curr Pharmacogenomics. 2007;5:87–101. doi:10.2174/157016007780831781.
11. Ikediobi O. Somatic pharmacogenomics in cancer. Pharmacogenomics J. 2008;8:305–14. doi:10.1038/tpj.2008.8.
12. EGAPP. Recommendation from the EGAPP working group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med. 2007;9:819–25. doi:10.1097/GIM.0b013e31815bf9a3.
13. Shi MM, Bleavins MR, de la Iglesia FA. Technologies for detecting genetic polymorphisms in pharmacogenomics. Mol Diagn. 1999;4:343–51. doi:10.1016/S1084-8592(99)80011-3.
14. Eichler H-G, Müller M. Drug distribution, the forgotten relative of clinical pharmacokinetics. Clin Pharmacokinet. 1998;34:95–9. doi:10.2165/00003088-199834020-00001.

15. Lappin G, Garner RC. The utility of microdosing over the past 5 years. Expert Opin Drug Metab Toxicol. 2008;41:1499–506. doi:10.1517/17425250802531767.
16. van Waarde A. Measuring receptor occupancy with PET. Curr Pharmaceuti Des. 2000;6:1593–610. doi:10.2174/1381612003398951.
17. Pelkonen O, Kapitulnik J, Gundert-Remy U, Boobis AR, Stockis A. Local kinetics and dynamics of xenobiotics. Crit Rev Toxicol. 2008;38:697–720. doi:10.1080/10408440802194931.
18. Sadee W. Drug therapy and personalized health care: pharmacogenomics in perspective. Pharma Res. 2008;25:2713–9. doi:10.1007/s11095-008-9702-4.
19. Glassman RH, Ratain MJ. Biomarkers in early cancer drug development: limited utility. Clin Pharmacol Ther. 2009;85:134–5. doi:10.1038/clpt.2008.231.
20. Dillman RO. Radioimmunotherapy of B-cell lymphoma with radiolabelled anti-CD20 monoclonal antibodies. Clin Exp Med. 2006;6:1–12. doi:10.1007/s10238-006-0087-6.