Effective Strategies for Tumors Affecting Chemopreventive Metabolism

Commentary on Charles et al., p. 7492

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In this issue, Charles et al. (1) showed in vivo that cytokines secreted by tumors, such as interleukin-6, down-regulate the transcription of cytochrome P450 CYP3A4 in liver and consequently the metabolism of CYP3A4 substrates. Reduced metabolism of chemotherapeutic agents could be responsible for side effects observed for these agents. The investigators postulate that treatment of the inflammation evoked by the tumor could normalize the expression of CYP3A4 and perhaps other cytochromes P450 and hence reduce the side effects of drugs used for the treatment of cancers.

Chemotherapeutic treatment of cancers has a narrow therapeutic window and can be accompanied by life-threatening side effects. It would be desirable to dose patients individually with a dose high enough to kill tumor cells but below a concentration that yields life-threatening side effects. In cancer chemotherapies, dosing is commonly done according to body surface area for lack of a better variable and dosing is reduced when leukocyte counts decline (i.e., patients are dosed to the maximum tolerable dose under the axiom “more is better”). Dosing to body surface area is understandable as it gives an exact dimension to the intuitive notion that one size dosing does not fit all and that larger patients require a higher dose than smaller patients do. This is based on an allometric approach that size predicts the speed of physiologic processes, including the rate of elimination of drugs. Although this approach is applicable for drugs that are excreted unchanged, it does not apply for drugs where metabolism determines the rate of excretion. Many chemotherapeutic agents are detoxified by metabolism, and the activities of metabolizing enzymes vary between individuals. This explains why a standard allometric approach, such as dosing according to body surface area, is not very suited for drugs that are detoxified by metabolism (2). Variations in activity of metabolizing enzymes and thus the pharmacokinetics of the drugs they metabolize are influenced genetically but also environmentally and, as shown by Charles et al., possibly by the presence of inflammation caused by tumor cells.

Predicting deviating pharmacokinetics in individuals from their genome has required years of intense research, and success has been slow. Nevertheless, polymorphisms in thiopurine methyltransferase (TPMT*2; 3A; 3C) for 6-mercaptopurine, UDP-glucuronyltransferase (UGT1A1*28 and *6) for irinotecan, and dihydropyrimidinidemehydrogenase (DPYD*2A) for 5-fluorouracil predict slow detoxifying capacity and consequently more side effects when individuals carrying these mutations receive standard doses (3). These examples represent the extremes of the spectrum: absent catalytic activity of the major metabolizing enzyme.

For many drugs, a single enzyme does not govern metabolism, and slow metabolism by one major enzyme stays unnoticed because the other enzymes involved in the metabolism of a compound are active enough to guarantee elimination within the reference range. Pharmaceutical companies deliberately try to avoid, if possible, bringing compounds to the market in which a single enzyme dominates elimination because of the possibility of unexpected side effects in a subpopulation of poor metabolizers. To date, however, sufficient clinically used chemotherapeutics remain in which a single enzyme dominates the major detoxifying or activating pathway.

On top of the genetic variation, environmental factors play a dominant role in the metabolic variation between individuals. Inducers and inhibitors in food, concomitant viral infections (4), inflammation evoked by tumors, and inhibitory and inducing drugs ensure that metabolic enzymes are not a static unity, but vary according to the situation. These environmental factors influence the farnesoid X-activated receptor, constitutive androstane receptor, and nuclear factor-κB pathways of CYP3A4 regulation (5).

Because of the many factors influencing absorption and metabolism, measuring blood levels of a chemotherapeutic would be ideal. This needs expensive equipment, however, and in addition to technical complexity, we lack defined concentrations at which therapy will be effective and also concentrations at which side effects will occur. Despite these difficulties, Yamamoto et al. (6) have shown that using a probe for CYP3A4 activity to aid dosing reduced side effects in patients receiving docetaxel. The hunt for probes representing metabolic capacity, parallel to creatinine for kidney clearance, has been on for decades. CYP3A4 is the main liver and intestinal cytochrome P450 and is involved in the metabolism of a large number of drugs (7), including chemotherapeutics, such as paclitaxel, docetaxel, vincristine, vinblastine, imatinib, gefitinib, etoposide, and ifosfamide. The activity of CYP3A4 shows a 20-fold interpatient variation (8). The activity of CYP3A4 can be predicted by the specific probes midazolam (elimination from blood), [14C-N-methyl]erythromycin breath test (a radioactive-labeled methyl group is cleaved of erythromycin by CYP3A4 and appears in exhaled air as carbon dioxide), or 6β-hydroxycortisol to cortisol ratio in urine. All
these tests have drawbacks, such as timed blood sampling and expensive gas chromatography-mass spectroscopy analysis for midazolam, a radioactive dose of 3 μCi [14C]erythromycin or low turnover of cortisol, and consequent inaccuracy for 6β-hydroxycortisol to cortisol ratio as a measure for catalytic CYP3A4 activity. CYP3A4 has a large active site fitting multiple substrates simultaneously, and a single probe may not reliably predict all clearances (9, 10). This lack of an easy, accurate, specific, and simple test for catalytic activity hampers studies investigating the correlation between CYP3A4 activity and therapeutic success or side effects. The search for suitable probes is constantly ongoing, however; perhaps, the ratio 4-hydroxycholesterol to cholesterol could fill the gap (11).

We know that one dose does not suit all. We know that having a specific genotype predisposed for more side effects for some chemotherapeutics. We know that a patient’s metabolic capacity can be used to adjust the dose to reduce side effects. The bottleneck is that this can be done in a research setting, but easy testing and proof that this testing helps in maintaining therapeutic outcome while reducing side effects has not been accomplished. Adjusting the dose of a chemotherapeutic has simply been easier. Progress is stepwise and the usefulness of predicting deviating metabolic capacity to avoid serious side effects must now also be proven for chemotherapeutics.

Charles et al. showed us that metabolic capacity does vary not only between individuals but also within an individual in time, depending on his or her inflammatory status caused by a tumor we intend to eradicate. Treating inflammation provoked by tumors is an area of intense debate (12), and it should be recognized that, even if treated, the natural variation in CYP3A4 expression will remain.

It is necessary to reach the stage in chemotherapies that we have already accomplished for toxic antibiotics: treat with high enough blood levels to eliminate cancer cells but low enough to prevent serious side effects. To do that, we need probes that are good surrogate markers for the pharmacokinetics of the agent in use and proof of efficacy of tumor therapies using probe-based dose adjustments. The possibility to treat patients effectively while reducing life-threatening side effects before they appear is a possibility we owe to our patients.

References
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