

Can Chemotherapy Dosing Be Individualized?

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Myth: Individualized dosing exists in the administration of chemotherapy agents.

Answer: Accurate and appropriate administration of antineoplastic agents based on pharmacogenetics can reduce the morbidity and mortality associated with cancer therapy. With the exception of a few targeted therapies, current antineoplastic drug dosing is based on a trial-and-error approach with either a standard drug dosage protocol or dosage determined by weight, age, kidney function, or body surface area (Meadows, 2005). Starting doses traditionally have been based on the maximum tolerated doses identified during clinical trials. Dose reductions are initiated as a result of side-effect toxicity in individual patients. Knowledge of personalized genetic factors, including cytochrome analyses, would remove much of the trial-and-error approach to initial drug dosage and modification and allow for personalized dosing at treatment onset (Meadows). Pharmacogenomics and pharmacogenetics are helping to identify those factors.

Pharmacogenomics is the study of variations of expression of individual genomes related to disease susceptibility and drug response at the cellular and tissue levels. *Pharmacogenetics*, a closely aligned and often interchangeable concept, is more specific to interindividual DNA-sequencing effects on drug response (Guttmacher & Collins, 2002). Vogel first described pharmacogenetics in 1959 as “the study of the role of genetics in drug response” (Ma, Woo, & McLeod, 2002). Differences in genetic structure dictate how individuals and genetically related populations respond to antineoplastic drugs and their dosages. Advances in the fields are producing

population-based knowledge that can lead to more efficient and effective personalized medicine in the treatment regimens of patients with cancer.

A draft of the human genome sequence was announced in June 2002 by the Human Genome Project and Celera Genomics Corporation (Abramowitz, 2006). By September 2002, 90% of the genome had been mapped (Guttmacher & Collins, 2002); final mapping was announced and available to the scientific community in April 2003.

Human genome mapping led to the recognition of single nucleotide polymorphisms, individual changes in DNA sequences responsible for the interindividual responses to drug and clearance metabolism. Single nucleotide polymorphisms are markers of biologic diversity that occur in the DNA base pairing of adenine, guanine, thymine, and cytosine. Two unrelated people who share 99.9% of the DNA sequencing may vary at more than three million base pairs (Guttmacher & Collins, 2002).

Single nucleotide polymorphisms determine the differences in cytochrome P-450 (CYP) activity in individuals. CYP represents a family of isoenzymes primarily located in the liver and, to a lesser extent, in the small intestine and other organs that metabolize drugs and chemicals (Ma et al., 2002). Fifty-seven known CYP genes are active within the human genome, but only three are responsible for 70%–80%

of the metabolism of clinically used drugs (Ingelman-Sundberg & Rodriguez-Antona, 2005). Individuals can be categorized to one of four major phenotypes of CYP activity that occur in humans: poor metabolizers who lack a functional enzyme, intermediate metabolizers who carry one effective and one dysfunctional gene, efficient metabolizers who carry two efficient genes, and ultrarapid metabolizers who carry two or more functional genes (Ingelman-Sundberg & Rodriguez-Antona).

CYP status indicates differing levels of toxicity within populations. People with ultrarapid metabolizers require larger drug doses for a therapeutic effect. However, drugs remain in the systems of poor or intermediate metabolizers for longer time periods, resulting in increased drug retention and toxicity. Smaller doses or longer intervals between doses are required in CYP inhibitors (Ingelman-Sundberg & Rodriguez-Antona, 2005; Ma et al., 2002). Truly individualized therapy would provide personalization of chemotherapy doses based on CYP status.

Personalized medication is being tested and used in targeted therapies with monoclonal antibodies, vaccines, tyrosine kinase inhibitors, and other medications that affect dysregulated tumor pathways (see Table 1). Rituximab was the first monoclonal antibody approved by the U.S. Food and Drug Administration (FDA). Rituximab is specific to CD-20 molecules on lymphoid cells of the B lineage (Rotea

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