To Test *OR* Not to Test

An update on UGT1A1 testing

Oncology Issues recently interviewed Howard McLeod, PharmD, about Genzyme's in-vitro diagnostic test that helps identify patients with a greater risk for irinotecan toxicity. McLeod, who is Fred N. Eshelman Distinguished Professor and director of the UNC Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina, Chapel Hill, N.C., and Lineberger Cancer Center, had this to say about the FDA-approved genetic test.

Q. *How does the UGT1A1 genetic test work? What is the test's significance in terms of identifying risk of irinotecan toxicity in colorectal cancer patients?*

A. Unfortunately most anticancer drugs are associated with some type of adverse event. These events are usually unpredictable and undesirable and interfere with the therapeutic intent of the treatment. Irinotecan is certainly a drug that has those features. We have been able to manage some of irinotecan's side effects, such as acute diarrhea, through changing the drug infusion or through the use of other medications, such as Lomotil. Other aspects of irinotecan have been difficult to predict. Neutropenia, for example, is a common blood disorder that occurs in many patients undergoing chemotherapy. While this condition is not a big deal for many individuals, patients with more severe neutropenia can require hospitalization and run the risk of sepsis.

Early in the development of irinotecan, researchers observed that the active metabolite of the drug, SN-38, was cleared from the body through a process called glucuronidation. A gene called UGT1A1 was responsible for sticking that glucoronide group onto the drug. Once glucoronide was on a compound, it was easily excreted by the bile. So, for example, bilirubin and a number of estrogen molecules in the body are glucuronidated. Irinotecan is one of several anticancer drugs that also undergo this process.

Researchers found that a subset of the population, about 10 percent, have a genetic change in the UGT1A1 gene that hinders their ability to perform this glucuronidation process. This change does not have an apparent phenotype; it is not something that can be detected by the usual bilirubin test or by some outward manifestation of the patient. However, when patients with the genetic change in UGT1A1, called UGT1A1*28, receive a standard dose of irinotecan, they have a very high risk of severe, or in some cases fatal, neutropenia.

In late 2004, the U.S. Food and Drug Administration (FDA) reviewed the data on UGT1A1*28 and decided that this genetic change should be included in the FDA packet insert for irinotecan as a risk factor for severe toxicity to the drug alongside the other standard risk factors: pelvic irradiation, performance status of 2 or greater, and age greater than 70 years. Thus, UGT1A1*28 is one of the first examples of genetics identifying a patient population that would be predisposed to a risk of toxicity.

Q. *What is the current status of the UGT1A1 test? Is the test available for use in the community care setting?*

A. The package insert for irinotecan was changed in June 2005, and the FDA-approved UG1A1 test was released in August 2005, by Third Wave Technologies. Today, the UGT1A1 test is widely available from most reference labs, including Genzyme, Quest Diagostics, and LabCorp, as well as several local labs. Many hospitals and major medical centers are offering UGT1A1 testing; the genetic test often takes a day or two to get the results.

Q. *What does the test cost? Is the cost covered by insurance?*

A. The test costs about $250, depending on the particular laboratory's overhead. The test is currently covered by most public and private insurers because it is an FDA-identified risk factor.

Q. *Should every patient with colorectal cancer be offered this test?*

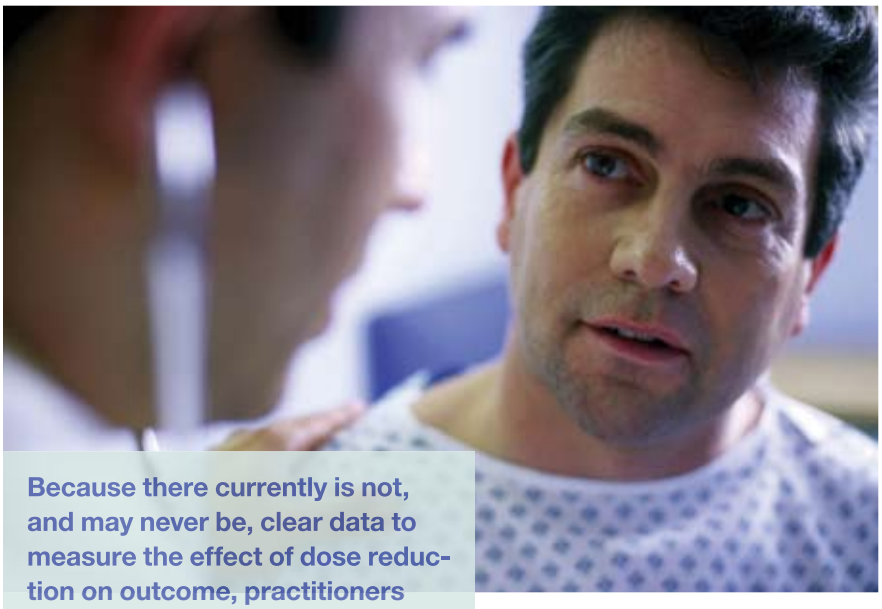
A. I can offer you my opinion based on the literature. In November 2004, the FDA considered the dosing of irinotecan as part of its deliberations. At that time the FDA-approved dose of irinotecan was 300-350mg/m^2 every 28 days. Today many people are receiving several lower regimens, 180-200mg/m^2 every 2 weeks or 100-125mg/m^2 weekly for four out of six weeks, and other regimens as well.

Since November 2004, the literature has grown. Data are now available on a number of different dose levels, including studies that were presented at the June 2006 ASCO meeting.[1] Looking across the spectrum of data—ranging from extremely low doses at 20mg/m^2 all the way up to 350mg/m^2 over different regimens—here's what I recommend to my clinical colleagues when asked:

- For patients receiving single agent irinotecan or irinotecan combined with a nonmyelotoxic drug, for example irinotecan plus cetuximab, if the patient is getting a dose greater than 150mg/m^2, the UGT1A1 test is useful for identifying patients at risk for severe neutropenia.
- For patients receiving a combination of irinotecan with another marrow-toxic agent, for example irinotecan plus oxaliplatin (the IROX regimen), then I suggest using

100 mg/m^2 as the threshold for when testing would be useful. My opinion is based on about 10 literature publications to date over a range of dosing regimens that seem to define a conservative but useful threshold for testing.[2]

- For patients receiving doses below those levels, the relative impact of UGT1A1 appears to be very small. So, even though patients with the UGT1A1 genetic variant—the so-called 7/7 genotype or *28—might have an increased risk, it is neither statistically nor clinically significant.



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It is also my opinion that we will never have clear data (e.g., prospectively designed randomized trial data) to tell practitioners exactly when testing should and should not be conducted. Simply put: there is not enough desire in the clinical community nor is there enough funding through either the National Institutes of Health or any other interested body to conduct studies to define exactly the right dosing based on genotype for this drug.

That being said, prospective studies are being conducted to try and help. The CALGB cooperative group has a study gearing up in which different doses of irinotecan will be given based on UGT1A1 genotype. When completed, this study data should offer some guidance for practitioners. But the real level of evidence that most clinicians would like to know, that is, exactly when and when not to use this test, in my mind, will never be produced. This situation is unfortunate and less than ideal, but it is reality.

Q. *Is there any downside to offering a patient this test?*

A. The UGT1A1 test was designed to avoid toxicity, so we don't really know whether the test has a downside.

One theoretical downside exists: too much of a dose reduction, while it certainly could mean that the dose is safe, may also mean that the dose is no longer as effective. And this theoretical scenario is the main concern of practitioners. For clinicians at community cancer centers, the balance of trying to make the drug safe for patients yet still effective can be tricky. The decision comes down to a true risk/benefit analysis. Right now, data are available on the risk side, but not a great deal of data can be found on the benefit side. Data from the N9741 clinical trial and some of the other trials suggest that when practitioners dose reduce for other reasons, they do not see a big diminishing in the drug's effectiveness. (In the N9741 trial, irinotecan was dose reduced because of an observed high mortality rate in the first 60 days of therapy. And the paper that was recently published in the *Journal of Clinical Oncology* clearly showed that that dose reduction did not result in an inferior outcome.[3])

Because there currently is not, and may never be, clear data to measure the effect of dose reduction on outcome, practitioners should discuss with their patient what level of side effect risk he or she is willing to assume. For patients who want full-press therapy, regardless of toxicity risk, genotyping does not really serve a purpose. If, however, a patient is on the fence about the issue, testing might be quite useful. Additionally, if a patient wants therapy that has low toxicity risk regardless of the efficacy, testing might be useful to dial in a therapy with a low risk of toxicity. Certainly, patients in all of those categories are routinely seen in the clinic setting.

Q. *For community-based clinicians, is there a particular learning curve for working with the UGT1A1 test or with the test results?*

A. In my mind this test is very similar to many other tests that are used in oncology care today. If a patient has poor renal function and a clinician wants to give a drug that is excreted by the kidneys, then the practitioner either knows what to do or looks up what to do.

Genetic testing for side effects is similar in nature. The decision is not a case of choosing to treat or not to treat with irinotecan. If a practitioner has selected irinotecan as the right drug for a patient, he or she is not going to change that choice based on UGT1A1 genotype. The practitioner may, however, change the dose or the particular regimen based on the genetic test.

In my opinion, the community-based oncologist with a busy clinical practice is not going to have to become a

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molecular biologist or a genetics counselor. Instead he or she will have to know *how* to respond to the results of genetic tests. And practitioners will respond the same way they have responded to most of the other lab results they order. Just as with patients with low white counts and patients with low kidney functions, the clinician will gather the information that a patient has a UGT1A1 mutation and factor it into the patient's treatment algorithm.

Q. *How has the status of the UGT1A1 test changed since your 2004 editorial in the* Journal of Clinical Oncology?[4] *Is there any new evidence in terms of the test retaining its predictive power when irinotecan is administered as part of combination therapy?*

A. I want to highlight several points. First, the data for the test being associated with severe diarrhea have really come out in favor of a lack of prediction for that particular endpoint. So, severe diarrhea does not appear to be predicted in most patients by this test.

The data for irinotecan and neutropenia have expanded, however. Data can now be put together from different dose levels and used to come up with some guidelines for when testing is going to most useful and when it appears to be of less value.

Another point that I want to emphasize is that many clinicians may suggest simply measuring bilirubin. If a practitioner is ordering fasting bilirubin (where the patient fasts and then takes the bilirubin challenge assessment), the data for UGT1A1 function is fairly reasonably defined and, in some cases, might even be more useful than genotype because it's a functional readout. Fasting bilirubin is rarely done in routine practice, however, and most clinicians do not plan for a long enough visit to do fasting bilirubin. The standard bilirubin test that is typically ordered has been shown now in several trials *not* to be a useful predictor of irinotecan toxicity.[5] While I would support a functional analysis over a genetic analysis, a bilirubin test, in the way clinicians typically order the test, does not meet that criteria. Bottom line: even though some clinicians may want to forgo to genotype and use the standard bilirubin test, a more high-powered test (fasting bilirubin or the UGT1A1 test) is the better choice.

Q. *When in the treatment process would the UGT1A1 test be offered?*

A. The test is most useful in a patient-centered orientation. Clinicians should first decide if irinotecan is the best drug for the patient and then talk to the patient about the level of side effect risk he or she is willing to endure. If, as mentioned previously, a patient wants aggressive therapy, and he or she is willing to endure whatever side effects may occur, practitioners probably don't need to order the test. In patients who are a little more nuanced, the test may help tailor a specific regimen based on the patients' level of toxicity tolerance.

Additionally, for oncologists that prescribe only one regimen of irinotecan and for patients receiving doses less than 150mg/m^2 as a single agent, the test is probably not going to be all that valuable. On the other hand, if a practitioner is using several different regimens, depending on the patient's wishes, the test could be quite useful.

Q. *Does the data on UGT1A1 testing apply only to colorectal cancer?*

A. To date, data are primarily from colon cancer and non-small cell lung cancer and suggest that the dosing guidance that I mentioned earlier are relevant regardless of the tumor type. It's really a patient bone marrow issue as opposed to a tumor type issue.

Q. *In conclusion, what's your take home message on UGT1A1 testing for the community-based program?*

Almost everything in life is a gene/environment interaction. Genetics is most important when there is lots of environment—in this case, when there's a large dose of an anticancer drug. With UGT1A1 testing, clinicians should think beyond "testing" or "not testing" in patients and focus in on the drug dose and which dose is most appropriate for each patient.

References

[1]McLeod HL, Parodi L, Sargent DJ, et al. UGT1A1*28, toxicity and outcome in advanced colorectal cancer: Results from Trial N9741. *J Clin Oncol.* 2006 ASCO Annual Meeting Proceedings Part I, Vol. 24, No. 18S (June 20 Supplement), 2006: 3520.

[2]Hoskins JM and McLeod HL. UGT1A1*28 and irinotecan-induced neutropenia: dose matters. (Submitted for publication.)

[3]Goldberg RM, Sargent DJ, Morton RF, et al. Randomized controlled trial of reduced-dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: a North American Intergroup Trial. *J. Clin Oncol.* 2006;24(21):3347-53.

[4]McLeod HL, Watters JW: Irinotecan pharmacogenetics: is it time to intervene? *J Clin Oncol.* 2004;22(8):1356-1359.

[5]Meyerhardt JA, Kwok A, Ratain MJ, et al. Relationship of baseline serum bilirubin to efficacy and toxicity of single-agent irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol.* 2004;22(8):1439-46.