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Crowdsourcing Clinical Trial Protocols

BY ROBERT H. CARLSON

The design of a clinical trial protocol typically has input from a small research team—rarely more than 10 reviewers and usually far fewer.

And the number of patients who review a protocol in detail and offer input is typically… zero.

Now, though, a different kind of clinical trial is about to begin enrolling patients, a trial that used crowdsourcing to develop the protocol. The trial will evaluate the use of metformin in men with rising prostate-specific antigen after localized treatment for prostate cancer.

Faster trial development and increased patient accrual are among the goals.

Crowdsourcing is a phenomenon of the Internet age, a collaboration of many people in an online community who are asked to contribute services, ideas, or content to an enterprise for little or no financial cost.

Continued on page 31

Best Gastrointestinal Cancer Papers, 2013

BY GAURI VARADHACHARY, MD

What have we learned about advances in GI cancers from the 2013 publications? The literature in the past year suggests a continued emphasis on evaluating the role of predictive markers and understanding cancer biology/heterogeneity.

A brief review cannot do justice to the vast number of important publications, so I highlight here five significant papers from 2013—I have chosen one (or more with a similar theme) for each gastrointestinal disease site that signifies the advances, drawbacks, and additional work planned ahead.

RAS Mutations and Management of Colorectal Cancer—Looking beyond *KRAS* Exon 2 Mutation; Updated PRIME Study (*Douillard et al: Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. NEJM 2013;369:1023-1034*)

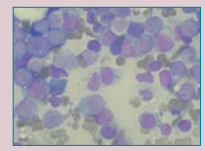
The original report from the PRIME study (*JCO 2010;28:4697-4705*) concluded that panitumumab-FOLFOX4 was well tolerated and significantly improved progression-free survival (PFS) in patients with wild-type (WT) *KRAS* tumors. Consistent with the results from other studies, patients with *KRAS* mutations in exon 2 (codons 12, 13) did not benefit from the addition of anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) therapy in the PRIME study.

Continued on page 9

New AML Score Improves Risk Evaluation

BY HEATHER LINDSEY

A new prognostic score for acute myeloid leukemia (AML) based on information about seven mutated genes and associated epigenetic changes may one day help guide treatment for a subset of patients, according to new research now available online ahead of print in the *Journal of Clinical Oncology* (***doi: 10.1200/JCO.2013.50.6337***).



The researchers evaluated gene mutations and expression, as well as epigenetic changes, in which the chemical modification methylation impacts DNA expression without altering the DNA sequence.

Continued on page 36

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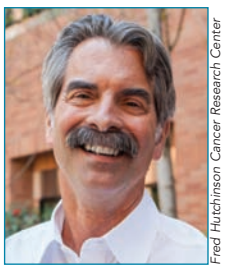
NEW AML SCORE SHOWS IMPROVED RISK EVALUATION

Continued from page 1

Guido Marcucci, MD, Professor of Medicine and Associate Director for Translational Research at Ohio State University Comprehensive Cancer Center–Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC-James), co-led the study with OSU colleagues Clara Bloomfield, MD, and Kati Maharry, MAS.

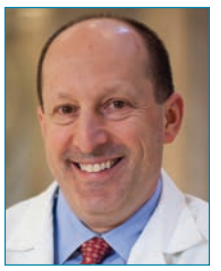
"We wanted to integrate genetic and epigenetic information in order to find a unique gene-expression signature that allows us to identify AML patients who will or will not do well with chemotherapy," Marcucci said. "Individuals predicted not to do well could then be considered for a stem cell transplant or investigational drugs.



Fred Hutchinson Cancer Research Center

This scoring system was studied in an intermediate-risk group of AML patients with normal cytogenetics and could potentially provide added prognostic value to the traditional genetic tests for AML, commented **Jerald Radich, MD,** a member of the Clinical Research Division at Fred Hutchinson Cancer Research Center, who was not involved with the study.

Once the scoring system is validated and being used in the clinic, it could provide an assessment of which patients might experience good outcomes with chemotherapy and which ones might do better receiving more aggressive therapy, he said.



Also asked for his opinion for this article, **Steven Libutti, MD,** Director of the Montefiore-Einstein Center for Cancer Care, noted that by evaluating mutations, methylation changes, and gene expression, the strategy is potentially a "more robust and complete fingerprint of prognosis for cytogenetically normal AML."

Another potential implication of this new AML score is at the clinical trial research level, where it could allow investigators to better design studies, said Radich. For example, "we could offer new agents to patients with a higher risk score."

> The seven-gene score encompassing epigenetic and genetic prognostic information was able to identify novel AML subsets that are meaningful for treatment guidance.

Study Details

Marcucci and his colleagues used next-generation sequencing to analyze the regions of methylated DNA associated with prognostically important gene mutations in cytogenetically normal (CN) AML cells from 134 patients age 60 and older who had been treated on Cancer and Leukemia Group B (CALGB)/Alliance clinical trials.

The seven genes identified by the researchers were *CD34*, *RHOC*, *SCRN1*, *F2RL1*, *FAM92A1*, *MIR155HG*, and *VWA8*. Lower expression and higher DNA methylation were associated with a better outcome for each of these genes.

Notably, he said, five of the genes are relatively unknown as being associated with AML. Additionally, while CD34 is a protein expressed in the majority of patients with AML, MIR155HG RNA transcript does not code for any protein but is important in malignant transformation, both in leukemia and other types

continued on page 37

AML SCORE

Continued from page 36

of cancer: "This was a surprise to us," he said.

Once the seven genes were identified, the team developed a weighted summary score and evaluated it in a validation set of four independent groups, totaling 355 patients—i.e.:

- Patients aged 60 and older with primary AML;
- Patients 59 and younger with primary AML;
- Patients 60 and older with CN-AML; and
- Patients 59 and younger with CN-AML.

A low score was found to be significantly associated with a higher rate of complete remission and longer disease-free survival (DFS) and overall survival (OS) than a high score.

Because the weights in the expression-weighted score were nearly identical for all the genes, the investigators also tested an unweighted summary score, which they describe as simpler to compute for risk stratification, using the number of individual genes with high expression.

When the unweighted score was applied to the initial group of 134 older patients, those with no or one highly expressed gene had a 96 percent complete response rate, 32 percent three-year disease-free survival rate, and 39 percent rate of three-year overall survival.

In comparison, these rates in patients with six to seven highly expressed genes were 25, zero, and four percent, respectively.

Older patients in the validation sets with no or only one highly expressed gene had CR rates ranging from 69 to 89 percent compared with 50 percent in individuals with six or seven highly expressed genes. Low-risk older patients had a three-year OS rate ranging from 44 to 46 percent compared with 10 to 12 percent in the high-risk group. Disease-free survival rates were not available in all patients because of the small sample sizes.

Younger patients in the validation sets with no or only one highly expressed gene had CR rates ranging from 91 to 100 percent, while those in the group with six to seven highly expressed genes had CR rates of 53 to 71 percent. Three-year OS in the low-risk group ranged from 76 to 82 percent, while those in the high-risk group had rates of seven to 24 percent.

Using Akaike Information Criterion, the researchers determined that the unweighted-summary score is a better model compared with all other prognostic markers and previously reported gene-expression profiles.

Use in the Clinic

Still, Marcucci cautioned, although a lot of prognostic data are being gained with new technology, the clinician has to determine how to use this information in a way that benefits patients. "We need to integrate and synthesize information in a way that can be implemented in the clinic," he said.

Overall, the test is relatively easy to use and takes about 24 to 48 hours for results. "It could be integrated as part of a diagnostic work-up of patients, if adequately validated," Marcucci said.

Also asked for his opinion for this article, **Jean-Pierre Issa, MD,** Director of the Fels Institute for Cancer Research and Molecular Biology at Temple University School of Medicine, said he considered that the scoring system would be fairly easy and straightforward to use in the clinic as a gene-based disease classification. In addition, he noted, the approach is already being used clinically for breast cancer with MammaPrint to help physicians make decisions about the use of hormonal therapy alone, or in conjunction with chemotherapy. However, the AML score needs to be done in a central laboratory with attendant complexities and delays, he cautioned.

"I have a bias toward DNA diagnostics, instead of RNA, which the study largely focuses on." DNA extraction is easier and more stable than RNA and can be done on paraffin. A score based on DNA analysis for epigenetic changes and mutations may be more practical, he added.

Libutti also said that the actual generation of the data from patient samples would require molecular biology expertise that may not be available at most pathology labs. While this type of data generation would need to be done at a central lab, as with other current genomic-based tests, the process could probably be refined into an assay that could be used more universally, he said.

Next Steps

The scoring system needs to undergo further evaluation in validation studies and clinical protocols to determine how helpful it is in patients, Marcucci said.

Added Libutti: "It would be good to see [a trial] done as a head-to-head comparison with other gene-expression prediction assays for AML. This really needs to be tested in a clinical trial that integrates more measurements than what's used in this particular study. But this is a first step toward a comprehensive characterization of AML."

Radich said he would like to see further evaluation of why specific genes are associated with poor outcomes in patients. "Once we understand the biology, those pathways may be treatable, so we can turn someone who has a bad risk into a good risk."

The unweighted-summary score was found to be a better model compared with all other prognostic markers and previously reported gene-expression profiles.