Genomic Profile Points to Recurrence of HCC

BY BRUCE JANCIN

VIIENNA — A large-scale genomic profiling study has identified two gene signatures that are strong independent predictors of disease recurrence in patients with early-stage hepatocellular carcinoma.

These findings will provide physicians with practical genetic tools to gauge patient prognosis and select individuals for secondary chemoprevention. Moreover, the specific genes included in these signatures will be evaluated as potential targets for badly needed adjuvant therapies following surgical resection and other potentially curative therapies, Dr. Augusto Villanueva said at the annual International Liver Congress sponsored by the European Association for the Study of the Liver (EASL).

The U.S.-European study involved 287 patients with surgically resected early hepatocellular carcinoma (HCC) who underwent genomic profiling using whole genome expression platforms to scrutinize roughly 24,000 genes. The investigators evaluated 20 gene signatures that were previously reported in much smaller studies as showing promise for predicting patient survival and/or disease recurrence. Of these, 16 were tumor based, whereas the other 4 came from adjacent cirrhotic tissue, explained Dr. Villanueva of the University of Barcelona.

At a median 46 months of follow-up, 64% of the patients had experienced HCC recurrence, and 34% of patients were dead. The following two signatures were found to be independent predictors of outcome:

- The previously described tumor-based “proliferation-G3” signature (Hepatology 2007;45:42-52), which is marked by overexpression of genes controlling the cell cycle, predicted early recurrence (hazard ratio 1.9) and total recurrences (HR 1.72).

- The “poor-prognosis” G20 gene signature in adjacent nonmalignant cirrhotic tissue previously described by Dr. Villanueva and coworkers (N. Engl. J. Med. 2008;359:1995-2004) also predicted both early recurrence (HR 2.06) and overall recurrence (HR 1.73).

Patients with both the proliferation-G3 and poor-prognosis gene signatures had a 2-year HCC recurrence rate of roughly 70%, compared with 20% for those with neither signature. Patients with either one of the two gene signatures had an intermediate recurrence rate.

The genomic information coming from the tumor and the surrounding tissue is complementary in predicting recurrence, as the tumor arises in a carcinogenic field of cirrhotic liver, Dr. Villanueva explained. Early recurrences represent true metastases, whereas later ones are de novo tumors. In early-stage disease, tumor biology isn’t nearly as important in terms of patient prognosis as is the genomic information provided by the adjacent tissue.

The more advanced the tumor, the greater the importance of the tumor’s genomic signature in terms of patient prognosis.

Dr. Heiner Wedemeyer, EASL secretary general, singled out this genetic signature study as one of the congress highlights. He described it as a major step forward in understanding the mechanism of HCC, a particularly complex malignancy that is the No. 3 cause of cancer-related mortality worldwide.

The immediate clinical implications of the genomic-profiling results are limited by the very few treatment options available today for HCC. The real clinical payoff will come several years from now, when a raft of investigational therapies for HCC that are well along in the developmental pipeline are expected to reach the market, said Dr. Wedemeyer of Hannover (Germany) Medical School.

Dr. Joseph M. Llovet, principal investigator of the gene signature study, agreed. “Only one drug is approved now for HCC—sorafenib—but others are coming,” he noted.

Although Dr. Llovet is principal investigator in three of the phase III HCC trials, he confessed that he has been unable to persuade the sponsoring pharmaceutical companies to engage in what he calls “trial enrichment,” genomic profiling to select the best candidates for a given therapy, in the way that breast cancers are tested for overexpression of HER2 to identify women who are eligible for trastuzumab (Herceptin).

“We are moving toward that in HCC. I think in a reasonable period of time we will see more trial enrichment,” Dr. Llovet predicted.

All of this drug development activity is most welcome. During 1990-2005, deaths from liver and bile duct cancer in the United States increased by 47%, far and away the largest increase for any type of cancer, he said.

Screening Combo Finds HCC in Patients With Cirrhosis

BY MICHELE G. SULLIVAN

NEW ORLEANS — A combination of ultrasound and alpha-fetoprotein testing identified almost all hepatocellular carcinomas in patients with cirrhosis associated primarily with chronic hepatitis C, according to the findings of a retrospective study.

At an alpha-fetoprotein cutoff level of greater than 20 ng/mL, the combination has 100% specificity and 87% sensitivity, making it an accurate and cost-effective screening method for these patients, Dr. Roger Soloway said at the annual Digestive Disease Week.

Because patients with cirrhosis are at significantly increased risk of developing hepatocellular carcinoma (HCC), the American Association for the Study of Liver Diseases recommends that they have liver cancer screening every 6-12 months. Although Dr. Soloway noted that CT and MRI are the “gold standard” in identifying HCC, they are too expensive to employ as a first-line method on a frequent basis.

He and his colleagues examined the medical records of 140 patients with cirrhosis who were screened for HCC with an initial ultrasound liver scan and alpha-fetoprotein (AFP) test, and then had a follow-up CT or MRI within 6 months.

There were 35 cases of HCC in the group. Ultra sound alone detected HCC in 26, for a sensitivity of 77% and a specificity of 99%. There were eight false negatives and one false positive.

In the eight false-negative cases, a subsequent CT scan identified HCC. The mean AFP level in this group of patients was 32,325 ng/mL, only two patients had a level lower than 20 ng/mL.

In the 75 patients with a true negative ultrasound, the mean AFP level was 17 ng/mL.

In all, 9% of the patients in this group had an AFP greater than 20 ng/mL and one patient had a level of more than 400 ng/mL.

“In this series alone, 74 CT or MRI studies could have been avoided with the combined use of ultrasound and AFP for screening,” said Dr. Soloway, the Marie B. Gale Centennial Professor of Medicine at the University of Texas Medical Branch, Galveston. “This would eliminate more expensive imaging studies until confirmation is necessary, thus reducing the overall cost of medical monitoring for patients in HCC screening populations.”

Dr. Jason B. Welch, also of the University of Texas Medical Branch at Galveston, was a co-convener of the study.

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