Targeted Therapy Thwarts Tumor Progression

BY BETSY BATES
Los Angeles Bureau

SAN FRANCISCO — A new, multitargeted biologic therapy halted gastrointestinal tumor progression so dramatically, a phase III study was unblinded early so that patients assigned to placebo could immediately receive the drug, researchers reported at a symposium sponsored by the American Society of Clinical Oncology.

The drug, sunitinib, underwent expedited review at the Food and Drug Administration and received approval during the meeting for the treatment of gastrointestinal stromal tumors (GIST) resistant to the first-line drug imatinib, and for treatment of advanced kidney cancer.

Dr. George D. Demetri used a Certs analogy of "two mints in one" to describe the multipronged way in which sunitinib targets tumors: blocking mutated signaling enzymes that permit uncontrolled cell growth, while cutting off growth factors to blood vessels that feed tumors.

An interim analysis of an international study found that sunitinib made a "truly dramatic difference" in the time it took tumors to progress in patients with GIST. Among 207 patients randomly assigned to receive sunitinib, time to progression was 27.3 weeks, compared with 6.4 weeks in 105 patients receiving placebo.

The difference equated to a 70% reduction in the risk of progression in the study patients, all of whom had developed either intolerance or resistance to imatinib (Gleevec), which Dr. Demetri called the "poster child drug for selectively inhibiting … kinase signaling enzymes."

The study also found a 51% reduction in the relative risk of death among patients taking sunitinib, reported Dr. Demetri, director of the Center for Sarcoma and Bone Oncology at the Dana-Farber Cancer Institute, Boston.

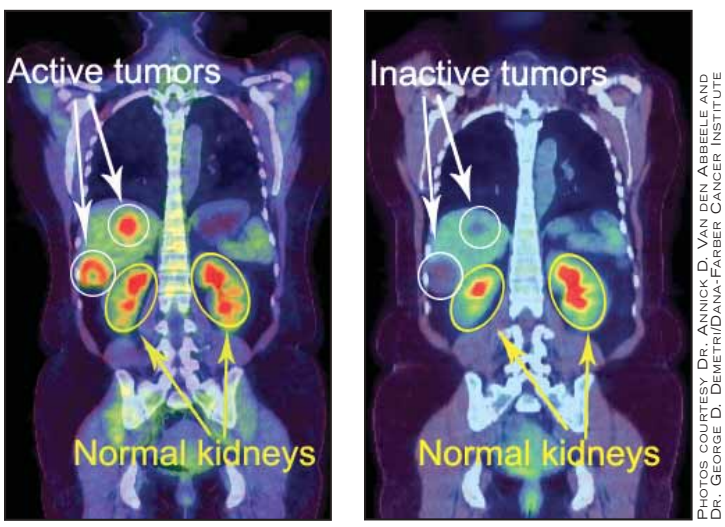
The trial was unblinded after patients had been on the drug for 6-8 months, when an interim analysis demonstrated "strongly positive" efficacy. At the time of the American Society of Clinical Oncology's gastrointestinal symposium, median survival had not been reached in either treatment group.

Beyond offering hope for patients with imatinib-resistant GIST tumors, sunitinib's success may offer a blueprint for how to develop drugs quickly based on customized genetic tumor profiles.

Dr. Demetri described an analysis of how well compounds selectively bind to signaling enzymes—kinases—that are known to spur the growth of cancer cells. In this case, sunitinib was shown to potently bind not only to KIT—a tyrosine kinase and an imatinib target—but also to many other signaling enzymes.

"We can [now] look for mutations that cause resistance, much as you would analyze bacteria for resistance to antibiotics," he explained. "This gives us a tool to move very quickly from laboratory compounds to new effective things that can be tested for helping patients in the clinic.

Sunitinib was generally well tolerated, even among patients who could not tolerate imatinib due to that agent's side effects, which can include a life-threatening rash.



PHOTOS COURTESY DR. ANNICK D. VAN DEN ABBEELE AND DR. GEORGE D. DEMETRI/DANA-FARBER CANCER INSTITUTE

PET images of gastrointestinal stromal tumors in the liver show how multitargeted biologic therapy can halt growth.

The most common side effects associated with sunitinib were fatigue, diarrhea, nausea, mouth sores, and skin discoloration.

Dr. Demetri said the new agent will provide oncologists with a therapeutic option for patients whose tumors become resistant to imatinib, a problem that generally develops after 18 months to 2 years of therapy.

The symposium was also sponsored by the American Gastroenterological Association, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology. ■

Lower Ca Risk if Hepatitis C Patients Respond to Interferon

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Patients with hepatitis C and cirrhosis who had a sustained response to interferon monotherapy were less likely to develop hepatocellular carcinoma or die of liver-related causes than were patients without a sustained response in a large Italian study, Dr. Savino Bruno reported.

Newer regimens using pegylated interferon plus ribavirin have been shown in separate studies to increase the likelihood of a sustained virologic response, so all patients with hepatitis C virus (HCV) who are candidates for treatment should be given the newer combination therapy—even patients with established cirrhosis, Dr. Bruno said at the annual meeting of the American Association for the Study of Liver Diseases.

Several previous clinical trials of the efficacy of interferon-based therapies in clearing HCV, conducted mostly in Japan, hinted at a slight protective effect from sustained virologic response. This is the first study in a large Western population-based cohort designed to study the protection conferred by sustained virologic response. Such response is defined as undetectable serum HCV-RNA levels 24 weeks after stopping interferon.

In the current study, investigators reviewed data on 1,214 consecutive patients with HCV and Child's class A cirrhosis who were treated with interferon at 23 Italian medical centers from 1992 through 1997. Patients had a mean age of 60 years, 62% were male, and 55% were infected with HCV genotype 1.

The available records showed a sustained virologic response in 16%, and 6% of these developed hepatocellular carcinoma over a mean follow-up period of nearly 8 years.

Among the 84% of patients without a sustained virologic response, 17% developed hepatocellular carcinoma, said Dr. Bruno, head of the liver unit at Fatebenefratelli and Oftalmico Hospital, Milan, and his associates. Dr. Bruno has no relationships with the company that makes interferon.

Only 2% of patients in the sustained virologic response group died of liver-related causes, compared with 12% of patients who did not have a sustained virologic response.

Factors that increased the risk for hepatocellular carcinoma were older age (58 years and up), being male, and not having a sustained virologic response, according to a multivariate analysis.

Lack of a sustained response to treatment doubled the risk of developing cancer and quadrupled the risk for liver-related death. Older age quadrupled the risk for cancer.

Because a sustained response to treatment didn't completely eliminate the risk of hepatocellular carcinoma, especially in older patients, cancer surveillance in these patients must continue, Dr. Bruno said.

The study excluded patients who were coinfected with hepatitis B or HIV. ■

Novel Biomarker Can Provide Early Warning of Liver Cancer

BY BRUCE JANCIN
Denver Bureau

HONOLULU — Measurement of the L3 glycoform of serum α-fetoprotein provides a unique early warning of the presence of hepatocellular carcinoma in patients at high risk due to chronic liver disease, Dr. Young Y. Wang reported at the annual meeting of the American College of Gastroenterology.

Indeed, the ratio of serum α-fetoprotein (AFP)-L3 to total AFP provides a substantial improvement in predictive power for this purpose over the conventional use of total AFP. This conclusion was reached on the basis of findings from a seven-center, double-blind, prospective comparative study involving 440 patients at high risk for hepatocellular carcinoma (HCC) because of liver cirrhosis and/or chronic hepatitis, according to Dr. Wang of Wako Pure Chemical Industries Ltd., Richmond, Va.

An assay that determines the AFP-L3/total AFP ratio using an automated analyzer—the Wako liquid-phase binding assay system, or LiBASys—gained Food and Drug Administration approval last July as a risk assessment test in patients at elevated risk for HCC, the fourth most common type of cancer and the No. 3 cause of cancer mortality worldwide.

Of the 440 patients, 39 were diagnosed with HCC using generally accepted criteria during the multiyear Wako-sponsored study. Patients with an elevated AFP-L3/total AFP ratio of 10% or more had a 40% chance of developing radiologically confirmed HCC within the next 21 months. Follow-up lasted about 2.5 years.

This translated into an 8.2-fold increased relative risk of HCC, compared with that in patients with a ratio of less than 10%. An elevated ratio had 51% sensitivity and 93% specificity for the detection of HCC.

In contrast, a total AFP above the cutoff point of 10 ng/mL was associated with only a 5.3-fold increased relative risk, along with 80% sensitivity and 62% specificity. A total AFP above the alternative threshold of 100 ng/mL conferred a 4.1-fold increased relative risk of HCC with 26% sensitivity and 94% specificity.

The mean time between development of an elevated AFP-L3/total AFP ratio and radiologic evidence of HCC was 205 days. A positive assay warrants stepped-up evaluation for the malignancy, Dr. Wang suggested.

The reason total serum AFP has proved suboptimal for early detection of HCC is that it consists of three glycoforms. AFP-L1 is generated mainly by inflammatory cells in the liver, hence this AFP subfraction is elevated in patients with chronic liver disease without HCC. AFP-L2 comes from testicular carcinoma and other germ cell tumors. AFP-L3 is the glycoform generated by malignant hepatocytes.