Targeted Therapy Thwarts Tumor Progression

Sunitinib, a drug that binds to multiple enzymes, offers new hope for patients resistant to imatinib.

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. Among the 105 patients who were receiving placebo, the time was just 6.4 weeks.

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 drug both blocks enzymes that permit uncontrolled cell growth and cuts off growth factors to blood vessels.

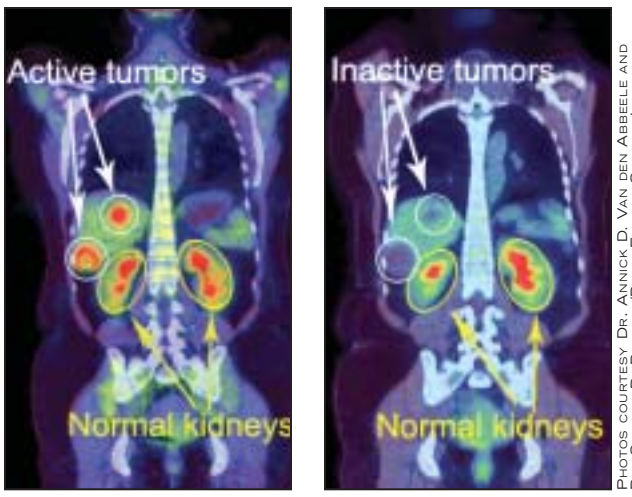
DR. DEMETRI

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 receiving 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.



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 the marked ability of multitargeted biologic therapy to halt growth.

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. 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," Dr. Demetri said.

Sunitinib was generally well tolerated, even among those patients who were not able to tolerate imatinib because of that agent's side effects, which can include a life-threatening rash. The most common side effects observed with sunitinib treatment 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. ■

Alcohol Intervention Helps Hepatitis C Patients Start Treatment

BY JANE SALODOF MACNEIL
Southwest Bureau

SANTA ANA PUEBLO, N.M. — A hepatitis C virus clinic in Minnesota helped alcoholic patients become eligible for antiviral therapy by integrating alcohol screening and a behavioral intervention into medical care.

Nearly half (47%) of 47 new patients who were flagged for "severe alcohol use" reduced their drinking after physicians warned that it could make them ineligible for antiviral treatment, according to a poster presented by Dr. Eric W. Dieperink at the annual meeting of the Academy of Psychosomatic Medicine.

Some of the patients relapsed after this initial brief intervention. But nearly two-thirds (62%) subsequently reduced their alcohol use by participating in an onsite program with a psychiatric clinical nurse-specialist. And 17 patients (36%) achieved long-term abstinence and were offered antiviral therapy.

"There was a big effect of just having the [clinic staff] address alcohol use at the initial visit," Dr. Dieperink, a psychiatrist at the University of Minnesota, said in an interview at the meeting.

"It's a cost-effective way to help people start treatment," he added.

Standard practice is to refer patients to a substance abuse program and tell them to "come back in 6 months when you're sober," Dr. Dieperink said. He and his colleagues reasoned that people who are facing medical consequences would be more likely to respond to an alcohol intervention than would a general population. They decided, therefore, to engage patients medically and psychiatrically at the clinic.

Gastroenterologists at the Veterans Affairs Medical Center in Minneapolis invited psychiatrists into the clinic about 6 years ago, Dr. Dieperink said, citing concerns about depression as a side effect of interferon treatment.

Over time, the collaboration between the two groups took on other psychiatric disorders in an ongoing attempt to address barriers to treatment.

"Alcohol is considered a barrier to treatment for hepatitis C and also hastens the fibrosis related to liver disease. So there were two reasons to address it," Dr. Dieperink said.

The intervention began with all patients being screened for psychiatric problems at their initial clinic visit.

Instruments used for screening included the Alcohol Use Disorders Identification Test-C (AUDIT-C), which the psychiatric clinical nurse-specialist reviewed. The nurse-specialist subsequently met with patients who scored above 4 on the AUDIT-C or were referred by staff members for alcohol problems.

Nearly half (47%) of 47 new patients flagged for 'severe alcohol use' reduced their drinking after physicians warned that it could make them ineligible for antiviral treatment.

A cornerstone of the program was having gastroenterologists discuss alcohol each time they saw the patients. "At every visit, the hepatology folks continued to address alcohol," said Dr. Dieperink.

"That was the synergistic—constantly attending to the alcohol use at every visit—which we think made a big difference," he explained.

He described the approach as matter of fact. Physicians would compare the patients' drinking with standards and norms for their age groups, recommend that they cut back, and offer to arrange follow-up visits with the nurse.

The nurse intervention also was brief, he said, lasting 4-10 sessions, during which the nurse would "flexibly engage" the patients. Most patients had received some alcohol treatment in the past, according to Dr. Dieperink, and many did not want to be referred to another treatment program.

The poster described the 47 veterans as 51 years old on average. Of the 47 patients, 32 were diagnosed with alcohol dependence and 15 with alcohol abuse. Most (82%) were hepatitis C genotype 1. Nearly two-thirds had stage II or higher liver fibrosis. The mean AUDIT-C score was 6.5. In addition, 24 patients (51%) self-reported use of cannabis, cocaine, or methamphetamine during the previous 6 months.

The patients had consumed alcohol for an average of 17.3 days during the 30-day period before they came to the clinic, consuming a mean of 9.5 drinks per day.

After the initial brief intervention, the average number of drinking days per month fell to 10.6 and the average number of drinks consumed per day declined to 5.5.

Ten patients refused referral to the nurse-specialist. Among those who participated in the follow-up program, the average number of drinking days fell to 8.8 after 3-18 months and the number of drinks per day to 3.8 after 5-22 months.

Of 37 patients who participated in the follow-up program with the clinical nurse-specialist and/or a mental health practitioner, only 3 were excluded from antiviral therapy because of continued alcohol use. Seventeen were offered retroviral therapy, and 13 started treatment.

The investigators said the treatment rate, 28% of patients with serious alcohol use, compared favorably with the 21% treatment rate reported for consecutive hepatitis C patients in Veterans Affairs clinics nationwide. ■

Pages 62a—62f〉