**Sugen drug an option if Gleevec fails**

Researchers at ASCO say SU11248 worked in 11 of 18 trial patients.

CHICAGO — Patients with the rare digestive-tract cancer known as gastrointestinal stromal tumor (GIST) who develop resistance to the frontline drug Gleevec may benefit from a novel compound that targets specific genetic mutations in GIST cells.

At the American Society of Clinical Oncology’s annual meeting in Chicago, scientists from Dana-Farber Cancer Institute presented data from an early stage clinical trial of a new drug called SU11248 in patients with Gleevec-resistant GIST. The study, headed by Dr. George Demetri, demonstrated that 11 of the 18 patients (61 percent) with progressive metastatic GIST experienced disease shrinkage or stabilization with no further progression when treated with SU11248. Like Gleevec, SU11248 target specific enzyme switches, called kinases, that keep cancer cells growing. The findings were presented June 1.

An estimated 5,000-10,000 cases of GIST are diagnosed in the United States each year. Surgery has been effective in treating some patients when the disease has not spread, but there are few treatment options for those patients in whom the tumor spread beyond the original site of surgery. Last year, the FDA approved the use of Gleevec as the first effective treatment.

**By Richard Palmer**

Do you need an 800-pound Gleevec gorilla in your corner or will a 400-pound one thrash GIST just as well?

Well, for the moment, the answer depends on which side of the Atlantic you happen to be sitting.

European researchers and U.S. researchers both gave presentations at the annual meeting of the American Society of Clinical Oncology held May 31-June 3 in Chicago. Both presentations were on the phase III study of Gleevec for GIST, where patients were given daily doses of either 400 mg. or 800 mg. of Gleevec. One key question researchers aimed to answer is whether a high dose of Gleevec is better for patients’ survival.
for GIST. Gleevec has proven to be highly beneficial therapy for metastatic GIST, but not all patients can tolerate it and some develop resistance to the drug over time.

“Approximately 85 percent of GIST patients benefit from treatment with Gleevec, but, over time, they tend to develop resistance to it and the disease once again begins to grow,” says Demetri. “Two-and-a-half years after starting treatment with Gleevec, approximately three-quarters of patients will show some level of resistance to Gleevec. There is no other effective treatment for these patients, and that is why we need new treatment options for them.”

Last year, Demetri and his colleagues, including Dr. Jonathan Fletcher of Dana-Farber and Dr. Michael Heinrich of Oregon Health & Science University, sought to identify what those additional mutations are and to design a counterattack with a new targeting strategy. They screened a variety of compounds known to act against abnormal enzymes. The results with SU11248, which is now made by Pfizer Oncology of La Jolla, CA, were particularly promising.

“SU11248 is a small molecule that inhibits the production of four enzyme switches: KIT, PDGF-R, VEGF-R, and FLT-3,” explains Demetri, who is also an associate professor of medicine at Harvard Medical School.

“Laboratory and animal studies showed it could be effective in GIST cells that had become resistant to Gleevec. The VEGF-R blockage is particularly interesting, too, since this drug is a powerful anti-angiogenesis drug, blocking the growth of new blood vessels to feed tumors, as well as shutting down other overactive enzyme switches inside the cancer cells.”

Based on the results of those pre-clinical studies, Demetri and his colleagues began a Phase I clinical trial of SU11248 in patients with Gleevec-resistant GIST. (The main purpose of a Phase I trial is to determine the safe dose for administration of new medications.) Successive groups of patients were treated with SU11248 at starting daily doses of 25, 50, or 75 mg. for 14 days, followed by a 14-day rest period per cycle. The maximum safe dose was determined to be 50 mg. after some patients at the 75-mg. dose level experienced unpleasant, but temporary, side effects (fatigue, nausea and vomiting).

The development of SU11248 as a potential treatment for Gleevec-resistant GIST “is an exciting example of the new world of targeted therapy,” Demetri remarks. “We can analyze cancer cells to identify mutations, then screen drugs in the laboratory that target those specific mutations. The resulting therapies should be more effective and less toxic than traditional chemotherapy, which tends to attack normal cells as well as cancerous ones.”

In addition to Fletcher and Heinrich, the study’s other contributor were Dr. Annick Van den Abbeele of Dana-Farber, Dr. Christopher Fletcher of Brigham and Women’s Hospital, and collaborators at Pfizer Oncology (the biotechnology company formerly known as Sugen).
Editorial

Life Raft raises research questions

By Norman J. Scherzer
Executive Director, Life Raft Group

The different results of the European and American studies on whether progression is linked to dosage level will likely generate an attempt by the two groups to reconcile their findings. The Americans found that progression was not related to dosage level; the Europeans found that it was. Both groups used intent to treat (starting dosage) as their statistical model. Neither looked at the actual dosage delivered (changed dosage).

Given their conflicting results, the researchers will likely investigate whether they had a somewhat different distribution of molecular mutations or a different percentage of patients with changes in dosage. Unfortunately, that will miss the point that we need to look at the actual dosage delivered in addition to the initial dosage (intent to treat).

We recognize that intent to treat is the statistical gold standard of cancer research protocols. But, GIST patients want to know what dose will keep them from relapsing. It is disturbing that even though the Gleevec trials started nearly three years ago, we are aware of no group of medical researchers that have analyzed the actual dose patients were taking when they relapsed.

It is just hard to understand why, for example, a patient with an initial starting dosage of 800 mg. a day who is switched to 400 mg. a day after two weeks and then relapses after two years would be counted by both the American and European group as if he/she was still on 800 mg. per day.

Given the fact that the Life Raft Group has found that about 50 percent of GIST patients have a change in dosage — and that one could speculate that these changes were disproportionately due to higher dosage levels having to be lowered because of side effects — the current inattention to actual dosage seems shortsighted. More important, it is potentially dangerous to those GIST patients struggling to survive the lethal time gaps of research protocols.

The fact that there is yet no consistent procedure to measure the actual drug concentration level of Gleevec in GIST patients over time further compounds this situation. Imagine that the patient in the example above began at 800 mg. per day, decreased to 400 mg. per day and, when evaluated, only had a drug concentration level equivalent to 300 mg. per day.

This editorial comment represents the personal views of this reporter and is not intended to be confrontational nor disrespectful of the many competent and caring physicians involved in this research. The team of LRG members who contributed to this editorial was concerned that we might alienate the very physicians we depend upon for the care of GIST patients. Although our points are sometimes strong our confidence in the ability of the physician community to handle constructive criticism is even stronger.

It is time, however, for a wake-up call. If it is possible that higher actual dosages can prevent relapses we must move quickly to evaluate that by looking at actual dosage delivered. At the same time we should evaluate drug concentration levels.

In the interim, if one takes the perspective of good preventive care it seems reasonable that if a higher dosage turns out to prevent relapse it would be much more useful to be at that higher dose rather than take a lower dose until relapse occurs, and then hope that the higher dose can catch up with progressing disease.

Learning Experience

ASCO proved to be a valuable learning experience for the Life Raft Group. We have learned that abstracts may be preliminary and may be superceded by more current data at the actual meeting. We have learned that things are not always as they appear, not even “scientific data.” We have learned that it is extremely valuable to have direct access to individual researchers to glean information and observations that are not part of a formal paper. We have learned that the research community is made up of distinct parts and interests and that they function within a set of rules and guidelines that do not always produce the maximum level of coordination. We have learned that the perspective of patients is not always the same as that of the research community, regardless of the best of intentions and skills.

We recognize that we do not have all the answers and that those we provide are subject to human error. Accordingly we invite those with points of view different from those expressed in this editorial to contribute them to future newsletter editions.
400 vs. 800: European, U.S. study findings differed

With many of the 25,000 cancer professionals in attendance, the U.S. group took the podium the afternoon of Saturday, May 31. With results from 746 patients from 57 institutions, the study’s authors said they’d found “no significant differences to date (median: 14 months on Gleevec) between the two dose levels.”

Fifteen minutes later, the European group took the podium and presented their findings from 946 patients at 56 centers in 13 countries. They estimated that “progression-free survival was significantly better” at 800 mg. per day. How much better? The group calculated that 58 percent of patients on 800 mg. would be progression-free as of a 17-month median, compared to 50 percent of patients on 400 mg. — a difference of 8 percent.

Two studies, opposing conclusions. What’s a GIST patient to do?

For starters, both studies were interim and that means the conclusions are subject to change. Indeed, the abstract of the European study originally submitted to ASCO weeks in advance of the convention largely agreed with the U.S. group’s findings, saying the “small observed advantage of the high dose arm is not statistically significant.” But abstracts often contain “immature data,” researchers say, which can and do change over time.

The Europeans had an opportunity to gather more up-to-date results shortly before ASCO convened, did an actuarial estimate on the findings, and presented updated results. This illustrates that a difference of a couple of months can change the outcome of a study.

Another factor may come into play, and it involves the way the clinical trials are set up. In these studies, half the patients were started on 400 mg./day, half on 800 mg./day. If a patient’s dose is lowered due to severe side effects, or increased due to disease progression, it doesn’t matter to the researchers — patients are still counted as if they stayed on their starting dose. This is called “intent to treat” in clinical trial lingo.

While “intent to treat” is a statistically proven way of summarizing the results of a trial, it may not reflect reality. In an informal survey of Life Raft Group members, nearly half of those who started on 800 mg. Gleevec had to reduce their dose. Some were only on 800 mg. for a few weeks before side effects forced them to drop to 400 mg. Yet for trial purposes, they are counted as if they’re still on 800 mg.

So the European study’s preliminary findings that 800 mg. is “significantly better” than 400 mg. may be, if anything, an understatement.

If many of those patients reported as being 800 mg. are, as the Life Raft Group’s experience shows, really on 400 mg., the effectiveness of 800 mg. is being discounted.

While U.S. researchers say their data so far is inconclusive, the media department of M.D. Anderson Cancer Center in Houston, Texas, wasted no time in jumping to a conclusion: Two days after the ASCO presentation, a press release was put out by MDA, titled “Doubling Dose of Gleevec to Treat GIST is Not Any More Beneficial,” beginning with this statement: “Less is perhaps more when it comes to using Gleevec to treat advanced gastrointestinal stromal tumors (GIST). . .”

If the European findings are any indication, oncologists treating GIST patients with Gleevec may want to hold off discounting an increase in dose for patients who experience disease progression.

Also of interest

Gleevec may be the “magic cancer bullet” but it’s far from a cure. Of the 946 patients in the European study, 322 experienced disease progression as of the 17-month median, and 185 had died. Of the 746 patients on the U.S. study, 260 were off the trial at the 14-month median, and 190 had died.

Nonetheless, the U.S. study did confirm the “extraordinary anti-tumor activity (of Gleevec) in patients with metastatic GIST.”
Growing tumors share similarities, reveal likely targets for chemotherapy

While Gleevec is the most effective treatments of an uncommon leukemia and soft tissue sarcoma, it doesn’t work for everyone. U.S. researchers attending the May 31-June 3 meeting of the American Society of Clinical Oncology in Chicago reported finding four ways that GIST gets around Gleevec.

In an abstract titled “Mechanisms of resistance to imatinib mesylate [Gleevec] in advanced gastrointestinal stromal tumor (GIST)” the authors reported the following:

Based upon 16 patients resistant to Gleevec (three with initial resistance and 13 who relapsed after an initial response), the authors identified four mechanisms of Gleevec resistance:

1. Target resistance due to mutation (four relapses) evidenced by acquisition of a new KIT or PDGFRA point mutation superimposed on the pretreatment mutation in that gene, and with KIT or PDGFRA protein activation. Apparently the second (new) mutation caused the tumors to become less sensitive to Gleevec.

2. Target resistance by over expression (two relapses) evidenced by KIT genomic amplification, accompanied by over expression of the KIT oncoprotein and without acquisition of a new point mutation in the KIT gene. In these cases, no new gene mutations were found, however the cells produced more KIT protein (~4-fold over expression of KIT protein) than Gleevec was able to inhibit.

3. Target modulation (two relapses) evidenced by activation or an alternate receptor tyrosine kinase protein, accompanied by loss of KIT oncoprotein expression. In these cases, signaling from another receptor provided a new growth signal to the tumor(s) even though KIT signaling was no longer active.

4. Functional resistance (five relapses and three with initial resistance) evidenced by KIT or PDGFRA activation, in absence of a secondary genomic mutation, and with pretreatment KIT or PDGFRA mutations in six tumors (three relapse and all three with initial resistance) being outside of the juxtamembrane hot spot regions. In these cases, the gene mutations were apparently outside the exons that respond best to Gleevec (exon 11 for KIT and exon 12 for PDGFRA).

Most important, all tumors at progression demonstrated activation of similar essential downstream signaling pathways/kinases, including the AKT/mTOR pathway, which therefore may be targeted.

The study authors were J.A. Fletcher, C.L. Corless, S. Dimitrijevic, M. Von Mehren, B. Eisenberg, H. Joensuu, C.D. M. Fletcher, C. Blanke, G.D. Demetri, M.C. Heinrich, for the GIST Working Group; Brigham and Women’s Hospital, Boston, Mass.; Oregon Health Sciences University, Portland, Ore.; Novartis Oncology, Basel, Switzerland; Fox Chase Cancer Center, Philadelphia, Penn.; University of Helsinki, Helsinki, Finland; Dana-Farber Cancer Institute, Boston, Mass.
Test reveals who’ll respond to Gleevec

Mutational analysis of gastrointestinal tumors gives clinicians new tool to predict outcomes

PORTLAND, Ore. — An international team of researchers has concluded that lab testing can predict just how well patients with gastrointestinal stromal tumor will respond to Gleevec, according to a study presented at the annual meeting of the American Society of Clinical Oncology.

Patients with a favorable lab result had an 84 percent chance of a partial remission in response to Gleevec. Only 10 percent of patients with an unfavorable lab result had a partial remission.

“These results demonstrate that the most important predictor of tumor shrinkage during Gleevec therapy is not age or tumor size but rather the specific type of mutation causing the tumor,” said Dr. Michael Heinrich of the Oregon Health & Science University Cancer Institute, an associate professor of medicine at the Portland VA Medical Center and co-principal investigator of the study.

Gleevec inhibits a mutant tyrosine kinase called KIT. The presence of mutant KIT protein in GISTs led researchers to suspect that Gleevec would be an effective treatment for this cancer.

“The majority of GI stromal tumors have a mutant form of KIT that acts like a gas pedal stuck to the floor, providing a constant stimulus for GIST cells to grow,” Heinrich said.

“Treatment with Gleevec inhibited KIT activity much like turning off this engine driving tumor cell growth.”

While the majority of the GIST patients treated in the Gleevec trial benefited from the drug, some did not, so research done to find out why.

The researchers analyzed DNA samples of the GIST tumors from 127 patients enrolled in the trial to determine whether a KIT tyrosine kinase mutation was present and whether the specific type of mutation had an impact on drug response.

The results revealed three distinct subsets of GIST. Those with “exon 11” mutations of KIT responded well to Gleevec; 84 percent of patients with such tumors had a partial remission (greater than 50 percent shrinkage of their tumors), and half of these people were still benefiting from the drug after 22 months.

GISTs that lacked a KIT mutation, however, did not respond well to Gleevec. Only 10 percent of patients in this group had a partial remission, and Gleevec failed them all in less than a year.

GIST with an “exon 9” mutation of KIT responded in an intermediate fashion in the trial, with half of the patients failing treatment after 187 days.

“KIT mutation status not only predicted the likelihood of Gleevec response, it was also the most important predictor of duration of response and overall patient survival in the trial,” Heinrich said.

Further studies by Heinrich and his colleagues also revealed a new wrinkle in the GIST story. Among the tumors that lacked a KIT mutation, some had a mutation in a different (but closely related) tyrosine kinase called PDGFRA. While mutations in this kinase were found in only 4.7 percent of GIST cases in the Gleevec clinical trial, the drug was effective against some of these PDGFRA mutations.

“We are in the process of studying the PDGFRA mutations, but so far preliminary data suggest that there are parallels with KIT — that is, if a PDGFRA mutation is present, then Gleevec response can be predicted by the exact type of mutation,” Heinrich said.

The study results suggest that clinical testing for specific mutation type may help clinicians treat patients with GIST. KIT mutational testing is now available at OHSU and testing for the newly identified PDGFRA mutations will be available soon.

“Mutational testing can be helpful in confirming the diagnosis of GIST and in defining the prognosis for patients who need Gleevec therapy,” said Dr. Christopher Corless, associate professor of pathology in the OHSU School of Medicine and co-investigator in the GIST research.

“As Gleevec is used more and more in combination with surgery, we believe that testing for mutations in GIST will be important in deciding whether Gleevec therapy should be used before and/or after surgery for GIST,” Heinrich said.
Story of Gleevec told in ‘Magic Cancer Bullet’

Head of Novartis tells how an orange pill is making medical history

When the first results from patient trials appeared on Dr. Daniel Vasella’s desk in April 1999, the chairman and CEO of Novartis sensed that an important chapter of medical history was about to be rewritten.

The results indicated that Gleevec, the tiny orange capsule — the development of which he had spearheaded — was working wonders to arrest a life-threatening form of leukemia. In his book, “Magic Cancer Bullet,” Vasella recounts the step-by-step challenges of bringing this revolutionary medicine to market and producing it in large enough quantities to make a difference in the lives of patients and their families everywhere in the world.

The book, reports Life Raft Executive Director Norman Scherzer, “has a significant amount of coverage of the Life Raft Group and a number of patients, including Life Raft Group members Anita Scherzer and Darlene Vaughan.”

The Scherzers attended a June 12 dinner put on by the group Cancer Care at the New York Hilton. More than 600 people attended; one of the honorees was Vasella, who greeted the Scherzers at the door.

“After greeting us he handed us a copy of his new book, the ‘Magic Cancer Bullet,’ which was being released that day,” relates Norman. “He then walked over to a side table, and carefully wrote the following inscription: ‘To Anita and Norman. With deep gratitude for not only the support and help they gave me and the book, but especially for everything they are doing for patients around the world! Dan, New York City, June 12, 2003.’”

The leaders of major pharmaceutical companies rarely speak out so candidly and comprehensively about their businesses, but Vasella takes readers behind the scenes and reveals the enormous pressures, the heavy costs, and the high risks involved in betting heavily on a drug like Gleevec — regarded by many as the most exciting cancer breakthrough discovery yet — while staying focused on the ultimate goal of saving lives.

There have been 25 deaths in the Life Raft Group to date:

Jim Ackerman, 49, Jan. 16, 2001, husband to Betsy, father of Jill and Tom.
Amy Barney, 25, June 10, 2001, wife to Reed, mother of Joshua.
Jeff Prichard, 52, July 11, 2001, husband to Joyce, father of Gregory and Scott.
Ron Martinez, 60, July 25, 2001, husband to Jo Ann, father of Run, Wendy, Natalie.
Bruce Gunn, 43, Nov. 8, 2001, husband to Raisin, father of Seamus, Liam, Brendan and Aislinn.
Mary Golnik, 50, April 18, 2002, wife to Gary, mother to Timothy.
Ana Maria Baldor-Bunn, 30, April 19, 2002, wife to Stan, mother to William.
Stewart “George” Wolf, 51, April 19, 2002, husband to Maggy, father to Thomas.
Jerry Pat Rylant, 61, May 5, 2002, husband to Pamela, father of four, grandfather to 10.
Todd Hendrickson, 44, June 29, 2002, husband to Janet, father to Max, Tyler and T.J.
Nora Shaulis, 42, Nov. 4, 2002, wife to David, mother to Griffin.
Kathy Colwell, 45, Jan. 5, 2003, wife to Tom, mother of Katherine, Mary and Tom.
Cynthia G. Whitson, 64, Jan. 19, 2003, wife to Jerry, mother to Steve, Jill, Randy and Donna.
Who are we and what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization providing support through education and research to patients with a rare cancer called GIST (gastrointestinal stromal tumor). The Association of Cancer Online Resources provides the group with several listservs that permit members to communicate via secure e-mail. Most members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy inhibits the growth of cancer cells in a majority of patients. It represents a new category of drugs known as signal transduction inhibitors and has been described by the scientific community as the medical model for the treatment of cancer.

How to join

GIST patients and their caregivers may apply for membership free of charge at the Life Raft Group’s Web site, www.liferaftgroup.org or by contacting our office directly.

Privacy

Privacy is of paramount concern, and we try to err on the side of privacy. We do not send information that might be considered private to anyone outside the group, including medical professionals. However, this newsletter serves as an outreach and is widely distributed. Hence, all newsletter items are edited to maintain the anonymity of members unless they have granted publication of more information.

How to help

Donations to The Life Raft Group, which is incorporated in New Jersey, U.S.A., as a 501-c-3 nonprofit organization, are tax deductible in the United States.

Donations, payable to The Life Raft Group, should be mailed to:

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