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STI571 trials are expanding

By Lora Wilson RN, BSN, OCN

Much is happening in the world of STI571 (Glivek) and GIST. Many of you are already well informed thanks to the Life Raft and your excellent internet research skills.

Initial results, as you know, are promising. Statistical data is not yet available to the public at present due to the need for thorough review of the data, scientific peer review and analysis. Anecdotal information, however, abounds. By and large, patients are responding clinically and are having significant improvement in their quality of life.

One of the difficult aspects of this study has been the limited access for patients. The three participating sites are working...
Glivec resistance a concern; optimism prevails

By Peter Rowbotham

As Charles Sawyers said when opening the session on STI at the ASH meeting, there is a "buzz in the air". Frederick Appelbaum (director of clinical research at Fred Hutchinson Cancer Center in Seattle, Wash) set the tone when he said "... The development of STI571 is, without question, one of the most exciting advances in clinical oncology in the last decade ..."

... In my reports over the course of more than a year, I have mentioned the interesting development of farnesyltransferase inhibitors (FTIs – after STI it should be easy to remember!). It now looks as though these are getting to a very significant stage of development, with considerable promise for chronic myeloid leukemia (CML) therapy. Schering Plough has an FTI drug, SCH66336 which has had very promising early results and should be in a Phase II trial by early summer next year. ... SCH66336 is a remarkable inhibitor of leukemia in the murine (mice) model, and also of bcr-abl in human cell lines.

The graphs that I saw, looked as though they were showing results similar to those of STI571. But even if that is not so, this FTI inhibitor knocks out cell lines that are resistant to Glivec. It is a truly exciting development, and apparently this FTI is not toxic. We should enjoy this advance, while knowing at the same time that not every such advance works its way through to fruition.

It was exciting to hear that this agent seems to overcome resistance to STI. More work needs to be done, but it is an important potential addition to current CML therapies. If it works out as expected, it could perhaps be used with STI in a future trial.

On Sunday morning, Dec. 3, Dr. Brian Druker of Oregon Health Sciences University, the developer and primary investigator of Glivec, gave a very nice paper at a National Cancer Institute special session, in which he talked about some of the challenges with Glivec, including the mechanism of relapse (presumably in the context of the blast phase trial of CML in particular), and the issue of optimizing therapy for patients on an individual basis. He spoke quietly but effectively, in what I thought was a visionary way, about the broader potential of molecular pathogenetic targeting of the sort achieved by Glivec, and conveyed his hope that Glivec would be the first of many examples of molecular targeted therapy.

... The rapidly growing and very positive data on STI (Glivec) has been extensively reported in newspapers throughout the USA and the UK, and much of that information has been made available on this list. It would be redundant to repeat it, but it is worth noting that each new batch of information about STI seems to be more positive than the last.

One of the few concerns at this stage, is the potential for the development of resistance to STI. ... I personally think that it would be very prudent to keep a watchful eye on what can be done if resistance does develop. The commonest form of resistance in the research work seems to be an over-expression of the bcr-abl gene, which I think means something like the bcr-abl protein (nearly everything seems to be proteins in biology) has become (through an evolutionary and selective process) bigger and stronger, so that normal doses of STI don't work any more.

But, as I understand the evidence, if a patient was to go off STI for, say, four months, the over-expressed protein would disappear. STI then works again, and obviously that would have treatment (clinical) implications. It might also be possible to increase the STI dose sufficiently to overcome this stronger pro-

See ASH conference report, Page 3
tein, although Sawyers it was said that, anecdotally, that he hadn’t seen that happen, perhaps because the STI increase wasn’t large enough.

There is a great deal more to be learnt about this whole question of resistance, but as far as I can see the present threat is relatively small, and largely manageable, and likely to be increasingly so as the research data increases. So for the moment, it is perhaps a matter of watching but not worrying.

While resistance to STI is always a possibility, the thrust of many of the comments was to the effect that this may not be an overly significant threat, and that there are ways to deal with some forms of potential resistance, and much research on other ways to overcome it.

New NCI-sponsored clinic trial of STI571 for GIST

Editor’s note: Dr. George Demetri, principal investigator at Dana Farber Cancer Institute in Boston, posted the following to Jerry Mayfield’s Unoficial STI571 Web site, www.newcmldrug.com, on Jan. 2

By George D. Demetri

I would like to call attention to the fact that the U.S. National Cancer Institute (NCI), in concert with the NCI-Canada Clinical Trials Group and Novartis Oncology, have agreed to move quickly to expand our initial group’s promising studies in GIST (please recall that the original group of investigators included the Dana-Farber Cancer Institute in Boston, Oregon Health Sciences University in Portland Oregon, Fox Chase Cancer Center in Philadelphia, and the University of Helsinki in Finland ). I refer interested readers to the link http://cancertrials.nci.nih.gov/types/leuk/sti571/sti1100.html for more information.

NCI has very successfully put this project on a “fast track,” and the result is that an international (U.S.A. and Canada) North American Intergroup study has already begun to enter patients. This trial (known by the unassuming title of Intergroup Study S0033) will test two different doses of STI571 in patients with GIST who have disease that is not amenable to curative surgery. The study will be conducted under the auspices of the U.S. cooperative group mechanism which will effectively make this agent available for appropriate GIST patients through most of the larger cancer centers in North America. We have developed this trial in close collaboration with our colleagues in Europe (the EORTC), and European cancer centers will be conducting essentially the same trial through their own mechanisms.

With this clinical trial, patients with GIST will have access to this promising agent (there is no "placebo" - all eligible patients will receive active drug), while we are studying whether the dose of this drug is an important variable in the clinical outcomes of patients. I wish to reassure you that our collaborative research group is working very hard to get accurate information disseminated as quickly and as responsibly as possible concerning the use of STI571 ("Glivec") for the treatment of GIST patients. I would encourage interested patients and patients to speak with their physicians about this important new trial.
The Life Raft Group

Who are we and what do we do? We are a group of patients and caregivers (spouses and others) in the STI-571 (Glivec) GIST trials who have come together to share our experiences and to provide each other with support. Persons not in the trial are encouraged to seek support from the broader LMS community. We try to emphasize side effects, symptoms, and other drug-related issues. Members are encouraged to correspond privately to each other or to the wider group as appropriate to the specific issue.

Privacy: Privacy is of paramount concern. We have all pledged to respect the privacy of members of our group, and agreed not to send information that might be considered private to anyone outside of the group. We try to err on the side of privacy. To assist in that goal, we don’t include in professional members of the various study sites.

Method: Our primary means of communication is through an email group maintained by each member on their own computer. Occasional updates of general interest are provided to all members.

Disclaimer: We are patients and caregivers, not doctors. Any information shared among the group should be used with caution, and is not a substitute for careful discussion with your doctor.

Newsletter note: Read at your own risk! Every effort to achieve accuracy is made, but we are human and errors occur. Please advise the newsletter editor of any errors you may find.

Do you know what the “STI” in STI-571 stands for?
It’s signal transduction inhibitor, an agent that interferes with the cellular pathways that prompt the growth of gastrointestinal stromal tumors.

From the front page

Druker
these stories.” I thank each and every one of you for sharing your stories, traveling to Oregon, and becoming part of our family.

This year promises to bring more successes. Over 3,000 CML patients have been treated with STI571 worldwide and STI571 should be on the market by the third quarter of 2001.

The early results in the gastrointestinal stromal tumors gives us all great hope that the success in CML will be one of many success stories for STI571 and other drugs that target the specific abnormalities that drive the growth of cancer cells.

Best wishes for the holidays and a happy and healthy New Year.

Wilson
hard to accommodate all of the patients wanting to be treated, but there is a time-lag between initial contact and the start of treatment.

Fortunately, this should be alleviated in the near future through a cooperative agreement between Novartis and the National Cancer Institute. STI571 is soon to be offered to eligible patients through an NCI-sponsored Phase III trial.

The study inclusion criteria is similar to the Novartis-sponsored trial. The Phase III trial involves a randomization between 400mg and 800mg, versus 400mg and 600mg as in the current trial. Approximately 600 patients will participate at multiple sites nationwide. We are hoping that many of these study sites will be up and running by mid to late February.

Many patients are wondering what will happen to them when the study is over in 2 years. Because there is no current alternative treatment for GIST, it is anticipated that STI571 will continue to be available to patients who are responding. The actual mechanism for this (how it will be dispensed, etc) is not yet known.

I continue to be impressed by the level of knowledge of our patients. There is so much yet to learn about this disease. I’m certain we will see more and more GIST information available as news about STI571 spreads.

The very best to all of you (and don’t forget to keep up those diaries!)