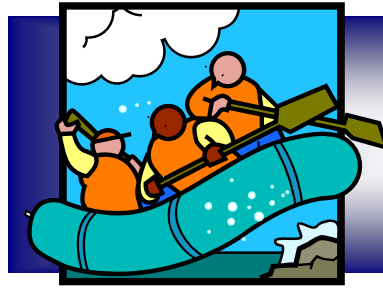




Life Fest 2006 will be held at the Adam's Mark Hotel in Dallas, Texas.

Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

August 2006

In memory of Pastor Paul Isaak and Nellie Stein

Vol. 7, No. 7

Life Fest 2006 agenda now available

All GIST patients and families welcome to attend

By Tricia McAleer

The agenda for Life Fest 2006 is now online at <http://www.liferaftgroup.org/members/lifest.html> (you can also find the agenda in this newsletter on pages 4-5). Posted on the Life Raft Group website are more details about the meeting as well as registration information.

The meeting will begin Friday evening, September 15th and end Sunday, September 17th at 12:30 p.m. at the Adam's Mark Hotel in Dallas, Texas. All GIST patients and caregivers are welcome. The Life Raft Group encourages people to share this invitation with others that may be interested in attending.

The meeting has a growing list of highlights, none of which can surpass the incredible emotional experience of walking into a room filled with people who understand and share the same passion for survival. Any Life Rafters who were in Cambridge, Mass. in 2002 and Orlando, Fla. in 2004 can testify to an overwhelming sense of compassion that makes meetings like these so needed.

Among the highlights on Friday September 15th include:

- A welcoming reception followed by a Texas-style dinner featuring keynote speaker, Dr. Daniel Vasella, Chief Executive Officer of Novartis Pharmaceuticals. An introduction will be followed by the Texas Life Raft Group assisted by

See Life Fest, Page 4

More placebo clinical trials predicted for cancer patients

Patient advocacy concerns presented about potential ethical dilemmas

By Norman J. Scherzer

After the controversy created by the use of a placebo in an early clinical trial for GIST patients, we hoped this issue would have gone away. Last year at the American Society of Clinical Oncology (ASCO) conference, it was raised again by an official of the Food and Drug Administration (FDA) who chose to advocate the use of placebos in clinical trials for cancer patients. This year at ASCO we were greeted by a paper called: *Re-*

*search, Ethical and Regulatory Perspectives Regarding the Use of Placebos for Terminally Ill Patients with Cancer**.

After noting that clinical trials for cancer have not historically involved placebo controls, the authors address whether that precedent should change with the relatively recent development of novel targeted cancer drugs such as Gleevec. They observe that these new drugs are different from more traditional cancer therapies in that they may produce disease stabilization rather than tumor reduction and that they may do so

with comparatively reduced toxicities. They reason that the use of placebos may help tease out the efficacy of these drugs when stability-rather than tumor shrinkage- is the end point and, further, that the lower toxicity of the drug "may allow patients, investigators and involved clinicians to presumably remain blinded to the use of a placebo." They predict that placebo-controlled trials involving patients with terminal disease are expected to become increasingly common.

See PLACEBOS, Page 7

Life Raft Group reexamines the role of drug level testing

By Jerry Call

Clinical trials have given us a lot of information about dosing Gleevec. Unfortunately, however, doctors and researchers do not always reach the same conclusions about what the data is telling them. Measuring Gleevec drug levels in patients may provide a measure of reassurance to patients and doctors that they are on the right course with regards to dosing.

In early CML clinical trials, a large variation in drug levels was noted between patients taking the same dose of Gleevec. Despite this large variation, how a patient responded was found to be more dependent on the dose they were taking compared to their blood levels (C_{max} or C_{min}). These early results may have led many experts in the field to conclude that monitoring blood levels in the clinic was not necessary. Given some of the new and perhaps conflicting research, it may be time to reexamine the need for blood level testing.

Recent data from the GIST reGISTry indicates that 72 percent of patients are prescribed Gleevec at 400 mg/day. A dose of 300 mg/day is generally considered to be at the lower end of the therapeutic range for Gleevec. Research into the pharmacokinetics of Gleevec in GIST patients has suggested that Gleevec blood (or serum) levels drop over time (EORTC study; Judson et al.). In fact, Gleevec levels may drop 30 to 40 percent over the course of the first year on Gleevec. What happens to those patients that start at 400 mg/day and have a 30 to 40 percent reduction in Gleevec levels? In theory, they may receive a dose of Gleevec equivalent to taking 240 mg to 280 mg/day.

What causes the reduction in Gleevec blood levels over time? At least three different theories have been put forth that might explain this phenomenon:

1. Gleevec clearance increases over time—possibly related to improved liver function (Judson et al.); in other words, the body becomes more efficient at removing Gleevec.

2. Multi-drug resistance proteins are induced over time decreasing the transport of Gleevec across the intestinal membrane (Burger et al.).

3. Patient adherence to taking the drug falls off over time (Tsang et al. and Feng et al.).

The first two items are out of the patient's control, but the third is not. The practical problem that patients face is that one, two or all three of these theories could be correct with different implications. If patient adherence was the primary cause of dropping Gleevec levels, then only less adherent patients would have to be concerned; but if Gleevec clearance increased or multi-drug transport was the problem then all patients stand to be affected.

Monitoring Gleevec blood levels over time would remove the question from the realm of the theoretical and place it into the realm of the practical. From the patient's point of view it would not matter which theory was correct; if drug levels were monitored and shown to drop, the Gleevec dose could be raised to compensate.

Increased patient education about the need for patient adherence to taking their medication is needed. This goes hand-in-hand with better side effects management. Better adherence does not totally remove the need for drug testing because, with the present data, patients cannot exclude the other possibilities for reduced drug levels.

Another potential problem that patients face is drug interactions. Gleevec affects and is affected by drugs that inhibit or induce certain liver enzymes. Gleevec is most affected by the liver enzyme CYP3A4, but is also affected by

The Life Raft Group

Who are we, what do we do?

The Life Raft Group is an international, Internet-based, non-profit organization offering 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. Many members are being successfully treated with an oral cancer drug Gleevec (Glivec outside the U.S.A.). This molecularly targeted therapy 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. Several new drugs are now in clinical trials.

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 articles 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, 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:

The Life Raft Group
40 Galesi Dr., Suite 19
Wayne, NJ 07470

Disclaimer

We are patients and caregivers, not doctors. Information shared is not a substitute for discussion with your doctor. As for the newsletter, every effort to achieve accuracy is made but we are human and errors occur. Please advise the newsletter editor of any errors.

Surgery and genotyping studies highlighted at ASCO conference

By Jerry Call

One of the highlights of the American Society of Clinical Oncology (ASCO) conference was the session “Gastrointestinal Stromal Tumors: Multimodal Approach.” George Demetri M.D. began the discussion with a review of the history and biology of GIST. Dr. Demetri reviewed the current status of GIST and brought up some new challenges ahead.

The following are some questions addressed in the GIST session:

- What is the role of surgery in managing GIST patients with kinase inhibitors?
- Is there a role for kinase inhibitor therapy following maximal response?
- Are there genetic predictive factors which can identify GIST patients most likely to benefit from a given kinase inhibitor?

The following four presentations took place during the “Gastrointestinal Stromal Tumors: Multimodal Approach” session.

1. “*Indication and results of surgery*

following imatinib treatment of locally advanced or metastatic GIST.” Hohenberger et al.

Dr. Peter Hohenberger, a surgeon from the University of Mannheim, Germany, gave this presentation titled “Indication and results of surgery following imatinib treatment of locally advanced or metastatic GIST.” Hohenberger noted that while imatinib (Gleevec) is effective to control advanced GIST, patients eventually develop progression. Imatinib provides an opportunity to resect tumors not amenable to resection earlier.

Dr. Hohenberger presented the results of a surgery survey that covered 113

Is surgery the best option?



GIST patients. The indications for doing the resections were grouped as:

1. To convert a partial response (PR) into no evidence of disease (NED) number of patients (n) = 44
2. True neoadjuvant n=14
3. Focal progression n=13
4. Progressive disease n=42
5. Emergency n=11

See ASCO 2006, Page 6

AMG 706 will not get FDA approval for GIST

By Norman J. Scherzer

The Life Raft Group has been following the AMG 706 phase II trial for GIST patients for quite some time. We reported in the last issue of our Newsletter our disappointment that we did not see data about AMG 706 at the ASCO (American Society of Clinical Oncology) conference this year.

On July 20, we had a conference call with Dr. Daniel Stepan, lead clinical scientist for Amgen for this study. Amgen has decided that the phase II data (which they will formally present at a

professional conference in a few months) will not support a filing with the Food and Drug Administration (FDA) for regulatory approval of this drug for GIST.



We have been assured, however, that any GIST patients currently on AMG 706 who continue to derive benefit from it will continue to receive this drug on an indefinite basis.

Clinical trials for AMG 706 are ongo-

ing for other cancers. It is conceivable that if any of these lead to FDA approval, that GIST patients will be able to have this drug prescribed for them on an off-label basis, although that is entirely up to the prescribing physician.

Finally, Amgen will continue to explore other possible trials for AMG 706 and GIST, such as one for GIST patients who develop resistance to both Gleevec and Sutent and one for pediatric GIST patients.

We agreed that the Life Raft Group and Amgen will continue to work together to seek treatments for GIST patients.

LIFE FEST

From Page 1

the mayor of Dallas, Laura Miller.

- A special tribute to Dr. Daniel Vasella by the Kids of the Life Raft Group.
 - The presentation of our Scientist of the Year Award to Dr. Jonathan Fletcher of Dana-Farber Cancer Institute.
- After this great Friday evening, the learning experience begins full blast on Saturday September 16th:
- GIST medical update by Dr. Jonathan Trent, GIST specialist from M.D. Anderson.
 - Research update by Dr. Jonathan Fletcher and some of our key research team members. These include Dr. Chris Corless of Oregon Health & Science University, Dr. Laurie Letvak of Novartis, Dr. Maria Debiec-Rychter of Catholic University, Leuven, Belgium, Dr. Matt van de Rijn of Stanford, and Dr. Brian Rubin of the University of Wash-

ington. This is the LRG team working to find a cure for GIST.

- Other presentations include a cutting edge presentation by Jerry Call, Life Raft Science Coordinator, and Norman Scherzer, Life Raft Executive Director, on every thing you need to know to survive GIST, including unpublished information on navigating clinical trials and finding the best treatments and dosage levels. In addition, a presentation will be given by Dr. Laurie Letvak of Novartis on everything you ever wanted to know about treatment compliance. Dr. Alberto Pappo of the Hospital for Sick Children in Toronto, Canada will give a pediatric GIST update.
- Presentation of our Volunteer of the Year Award to Richard Palmer by Jerry Cudzil, Life Raft Board Member.
- Lunch on Saturday will be keynoted by Dr. David Epstein, President of Novartis Oncology International, and highlighted by the presentation of Survivor Awards given to all those who have officially passed the 5-year mark in their

battle with GIST. These survivor awards will honor the incredible milestones reached by a growing number of GIST patients.

- Following lunch, an expert panel of eight of the world's GIST experts will field questions from the audience.
- Pediatric GISTers will have their own program and pediatric GIST families will have extensive workshops on their own.
- We have planned over 10 interactive workshops dealing with issues such as managing treatment side effects, nutrition, coping, medical insurance and the latest clinical trials update.
- We will pause on Saturday at 5:15 p.m. for a memorable candle ceremony celebrating the lives of those that are no longer with us.
- Saturday night is free to spend the night on the town visiting Dallas.

For any questions about logistics, please contact Trish at tmcaleer@liferaftgroup.org.

See LIFE FEST, Page 5

Life Fest 2006 Agenda	
Friday, September 15, 2006 (Items In Green Are For Private Meetings)	
10:00 a.m. – 1:00 p.m. Life Raft Group Board of Directors Meet	
3:00 p.m. Registration Table Opens	
4:00 p.m. LRG Research Team Meets	
6:00 p.m. Reception	
7:00 p.m. Formal Dinner Greetings, John Poss and Kerry Hammett, Texas Life Raft Group Greetings, Laura Miller, Mayor of Dallas Tribute to Dr. Daniel Vasella by the Kids of the Life Raft Group Keynote Address by Dr. Daniel Vasella, CEO of Novartis Presentation of Scientist of the Year Award to Dr. Jonathan Fletcher by Dr. Daniel Vasella	
Saturday, September 16, 2006	
7:30 a.m. General Breakfast	
7:30 a.m. LRG Research Team Meeting-To Be Joined By Dr. David Epstein, President of Novartis Oncology International	
9:00 a.m. General Session Convenes: Welcome, Stan Bunn, LRG Board of Directors President	
9:00 a.m. Separate Program for Pediatric GIST Kids	
9:15 a.m. LRG Update, Norman Scherzer, LRG Executive Director	
9:50 a.m. Presentation of Volunteer of the Year Award to Richard Palmer by Jerry Cudzil, LRG Board of Directors	
10:00 a.m. Report by LRG Research Team, Dr. Jonathan Fletcher and Team Members	
11:00 a.m. Medical Update, Dr. Jonathan Trent, M.D. Anderson	
12:00 p.m. Lunch Remarks by Dr. David Epstein, President of Novartis Oncology International Presentation of Survivor Awards by Dr. David Epstein	

LIFE FEST

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Saturday, September 16, 2006 Afternoon				
<p>1:30 p.m. Moderator Rodrigo Salas Expert Panel: Dr. Chris Corless, Oregon Health & Science University, Dr. Jonathan Fletcher, Brigham and Women's Hospital, Dr. Laurie Letvak, Novartis, Dr. Alberto Pappo, Hospital for Sick Children, Toronto, Dr. Jonathan Trent, M.D. Anderson, Dr. Maria Debiec-Rychter, Catholic University, Leuven, Belgium, Dr. Matt van de Rijn, Stanford University, Dr. Brian Rubin, University of Washington, and other distinguished experts</p>				
Workshops				
2:30 p.m.	Side Effects Management, Monica Davey, Oncology Nurse, Fox Chase Cancer Center	Medical & Surgical Procedures Explained, Dr. Arnold Kwart, Washington Hospital Center	Clinical Trials Updates, Jerry Call, LRG Science Coordinator	Pediatric GIST Family Workshops, Dr. Alberto Pappo, Dr. Cristina Antonescu (by teleconference) and other experts
3:30 p.m.	Break			Pediatric GIST Kids Special Program
4:00 p.m.	Coping for Caregivers, Jim Hughes	Coping for Patients, Moderator to be named	Nutrition, Moderator to be named	
5:15 p.m. Candle Ceremony Led by Bob Book				
Dinner On Your Own				
Sunday, September 17, 2006				
7:30 a.m. Breakfast				
9:00 a.m. Work-shops	GIST Explained, Jerry Call	Medicare and Other Medical Insurance, Moderator to be named	Local Outreach Forum, Dick Kinzig and Kerry Hammett	Improving the Life Raft Group: Suggestions for the Executive Director
<p>10:00 a.m. General Session-Moderator Chris Carley Surviving GIST: Connecting the Dots: Jerry Call and Norman Scherzer</p>				
<p>11:00 a.m. Moderator Mia Byrne Compliance, Dr. Laurie Letvak, Novartis</p>				
<p>11:30 a.m. Moderator Silvia Steinhilber Pediatric GIST Update, Dr. Alberto Pappo, Hospital for Sick Children, Toronto, Canada</p>				
12:00 p.m. Pediatric GIST Kids Presentation				
12:30 p.m. Adjourn				
Lunch and time in Dallas On Your Own				

ASCO 2006

From Page 3

Operation mortality rates were zero percent for patients with a partial response or focal progression. They were 1.7 percent for patients with progressive disease while in the hospital, but 7.7 percent within 30 days.

Surgery to remove all of the tumors of interest with clear margins was successful in the majority of cases in all of the groups (72% to 86%) except progressive disease (26%).

With a median follow-up of 15.8 months, 14 patients with complete tumor removal from groups 1, 2 and 3 stopped Gleevec. Of these patients, 8 of 14 developed a recurrence.

The median progression-free survivals of the groups were the following:

1. PR to NED = 11 months, but 16 months with clear margins (R0)
2. Neoadjuvant = median not reached, 72 percent disease-free at one year
3. Focal progression = 8 months
4. Generalized progression = 3 months
5. No data was given for the emergency surgery group

Summary:

- R0 resection (clean margins) of PR residual GIST after imatinib yields over one year of progression-free survival (PFS).

- Imatinib should be continued after surgery.

- This series represents a selected group of patients; it is not a prospective trial and may have bias.

- Single focus progressive disease does not necessarily indicate wide spread dissemination.

- If tumors are resectable, do molecular pathology and exon analysis. As Hohenberger states, "...you will get more information about this tumor and you might get some information about which other drug might be effective to control this tumor."

- Patients with multifocal progression (generalized progression) cannot be cured by surgery.

Conclusions from the study:

- Patients with inoperable or locally advanced GIST developing a PR under

imatinib should be evaluated for resection as early as possible.

- Resection of tumor remnants is a safe procedure with a chance for contributing to long-term cure.

- Randomized trial of early resection vs. delayed resection should be feasible.

- Timing of surgical intervention is crucial.

2. "The Role of Surgery in Multimodality Therapy for Advanced GIST." Raut et al.

Expounding on the topic of surgery, Dr. Chandrajit Raut M.D of Dana-Farber Cancer Institute was the discussant that presented on "The Role of Surgery in Multimodality Therapy for Advanced GIST."

Dr. Raut noted that the advent of targeted therapy using kinase inhibitors (like Gleevec) has altered the natural history of advanced disease, but that pathologic complete response is rare. He also noted that response to kinase-directed therapy is not maintained indefinitely (resistance eventually develops) and that surgery of previously unresectable GIST after treatment with imatinib may be feasible (including complete resection); thus the role of surgery needs to be reevaluated throughout the course of a patient's treatment.

Dr. Raut presented the surgery experience that the Dana-Farber team had with 69 patients. In most respects, it was similar to the German data presented by Dr. Hohenberger. One difference between the two studies was that 14 patients in the German study did not resume kinase therapy (due to financial reasons, intolerance, etc.) and only one patient did not resume kinase therapy in the American study.

Progression-free survival data between the two groups was very similar; for focal progression it was 8 months for both studies, for generalized progression it was 3 months for both studies, and for surgery after stable disease it was 11 months for the German study and has not been reached for the American

study.

Dr. Raut addressed the question of what data currently support surgery for advanced GIST, to which he added:

- Surgery is feasible.

- Mortality rates are low.

- Morbidity (frequency of complications following a surgical procedure or other treatment) rates are high, reflecting the complexity of treating this patient population.

- PFS and overall survival are encouraging but are they better than kinase inhibitor therapy alone?

Raut noted that there are stumbling blocks to designing a prospective trial to answer questions about surgery. One of these is whether or not patients would consent to a randomized surgery trial.

The question to ask is who may benefit from surgery?

- Both Hohenberger and Raut studies found that patients who were stable had the best chance of benefit followed by patients with limited (focal) progression.

- Both studies found that patients with generalized progression typically receive little benefit from surgery.

- Survival is better after complete resection when compared to incomplete resection.

Dr. Raut proposed some guidelines for surgery:

- Operate once maximal response (stable disease after maximum shrinkage) is reached on kinase inhibitor therapy

- *En bloc* resection without tumor rupture

- Extent of resection

- Complete resection whenever possible

- Stable disease

- Remove all lesions

- Limited disease progression

- Remove all progressing lesions

- Debulk additional lesions as

much as possible

- Generalized progression

- Resect only if symptomatic or emergency

PLACEBOS

From Page 1



Amongst the criteria they cite for a placebo-based clinical trial to be considered ethical is that the trial must have a methodological justification and must fulfill the following ethical consideration regarding risk: “a patient randomly assigned to placebo should not be substantially more likely than those in active treatment group(s) to: die; suffer irreversible morbidity, disability, or other substantial harms; suffer reversible but serious harms; or suffer severe discomfort.” They further note that for a trial to be ethical, the placebo arm must also include the best supportive care.

The authors consider that the use of historical data as a substitute for randomized placebo-controlled trials is problematic due to differences in patient populations, unrecognized prognostic factors, changes in supportive care and subsequent therapies over time.

They further discuss the differences in various placebo trial designs, the major one being whether the trial protocol permits a cross-over to the treatment arm should the patient on a placebo demonstrate disease progression.

They recommend (“encourage”) that the choice of placebo trial design should

be based upon a “dialogue between investigators, sponsors, and the FDA,” although they also stress “that the FDA does not mandate the use of placebo-controlled trials.”

Comment: Although the authors seem well intentioned, it is striking that all four are physicians and never include within their perspective the participation of patients. Can one imagine in comparison, an article, entitled *Research, Ethical and Regulatory Perspectives Regarding the Reimbursement of Physicians for the Care of Terminally Ill Patients with Cancer*, discussing profound changes in such reimbursement without inviting the point of view of a single physician? It seems to me that whomever decides whether to permit a placebo-based clinical trial for terminally ill cancer patients is as important as the criteria for such a decision. Under current circumstances a person in a criminal trial would receive much more due process, certainly including the right to speak and be represented, than he would in a clinical trial.

Had the authors asked us for our opinion we would have told them the following:

1. You may not make decisions about

us without us, stealing a mantra from our colleagues at ECPC, the European Cancer Patient Coalition. Current FDA procedures not only do not mandate the participation of patients in the development of clinical trial protocols, they will not permit patients to see the proposed protocol unless the pharmaceutical company involved consents, something the company will generally not do unless the patient agrees in advance not to disclose what he/she sees. In other words, the patient must agree not to publicly discuss with other patients what he has seen in order to get permission to see it.

2. The burden of proof for dismissing the use of historical data must be upon those proposing to use a placebo and that burden must pass the objective and transparent review of a panel that does not include those proposing the trial protocol. That has not happened in the past.

3. There must be an objective and transparent assessment of the short and long-term consequences of any placebo-based trial to those that were placed on such a placebo, including a follow-up and careful documentation regarding their survival and well-being. That has not happened in the past. *Particular attention should be paid to the following question: if a drug being tested is likely to produce stability rather than tumor shrinkage, then how could any progression which occurs due to a placebo be reversible?*

4. Patients are not idiots and can figure out whether they are on a placebo. In fact this has happened in the past when patients on a placebo-based clinical trial discovered that not only did they have different side effects than those on the actual drug (a decrease in toxicity does not mean the absence of recognizable side effects) but that when they opened the pill, the placebo was a white powder and the drug was orange. Some of the patients involved began a discussion over the internet regarding how to decipher whether one had been given a placebo, thus affecting the trial blind. When we presented this situation to the drug company we were dismissed with the observation: “so what, the patient has to stay on the placebo anyway in order to

DRUG TESTING

From Page 2

CYP2D6. Drugs that induce these enzymes cause Gleevec levels to drop; drugs that inhibit these enzymes cause Gleevec levels to rise. Monitoring Gleevec blood levels provides a backup to the doctors and pharmacists ability to anticipate and correct these drug interactions.

While testing Gleevec blood levels is not commercially available, it is clinically available. Dr. Merrill Egorin of the University of Pittsburgh is able to provide doctors with Gleevec blood level testing. At the present time there is no charge for this testing. Doctors interested in having their patients' Gleevec levels tested should contact Dr. Egorin at the University of Pittsburgh Cancer Institute.

The Life Raft Group staff has begun talks with Dr. Egorin and other GIST experts about the expanded use of Gleevec blood level testing. We believe this testing might be particularly useful for monitoring blood levels over time and for other situations such as monitoring for potential drug interactions. The results must be interpreted with caution as Gleevec blood levels are not an absolute indicator, especially when looking at a single point in time. In particular, variations in protein binding between patients can produce misleading results.



Dr. Merrill Egorin from the University of Pittsburgh Cancer Institute.

Case scenario of patient treatment adherence

The following theoretical case indicates a representative scenario where monitoring Gleevec blood levels might be helpful. A patient is taking Gleevec on an adjuvant basis to try to prevent a recurrence after surgery. The patient starts at 400 mg/day but is unable to tolerate this dose. The patient is reduced to 300 mg/day and finally to 200 mg/day. The patient is able to tolerate 200 mg/day; but is this a therapeutic dose?

Comment: The patient may have other conditions besides GIST and it is unclear if the patient's side effects are entirely related to Gleevec or partially related to another condition. Also, if the side effects are more Gleevec-related, is the patient not tolerating Gleevec because they metabolize it

poorly (and therefore achieve a therapeutic dose at below normal concentrations) or are they just intolerant to Gleevec even as sub-therapeutic doses? The difference is important. Gleevec doses below 300 mg/day are typically considered to result in either a shorter progression-free survival (at best) or may promote drug resistance (worst-case theory). If the patient had normal drug levels in spite of the below-normal dose, then the doctor might lean towards continuing the adjuvant treatment. But if the patients blood levels were below normal, the doctor might suggest that adjuvant therapy (which is of unknown benefit anyway) should be discontinued in this patient.

Opinion on surgery for metastatic GIST

By Jerry Call

In this issue of the Newsletter we reported on several American Society of Clinical Oncology (ASCO) presentations dealing with surgery. A few comments about this important subject seem appropriate. These comments only apply to surgery for *metastatic disease*.

In the absence of clinical trial data about surgery for metastatic disease, there are 4 or 5 case series that have been published (at least in abstract form). For the most part, the data from these studies seems to be fairly consistent and some conclusions can be reached. One of the most solid conclusions seems to be that surgery is of little benefit for patients with widespread progression of metastatic disease. Surgery for limited progression (one or two tumors) appears to have some benefit. Few patients die as a result of surgery, but

non-fatal complications can arise.

There are also some areas where it is difficult to reach any conclusions. From these studies we know that patients with stable disease do pretty well after surgery; but we do not know how well they would have done with Gleevec alone. It will probably be quite some time before any trial can answer that question (none are in progress).

Given the limited data available, the decision on whether or not to have surgery for metastatic disease after responding to Gleevec is a complex decision. It involves many factors such as:

1. Can all disease be removed?
2. How complicated is the surgery?
3. How likely are complications?

Given the complexity of these decisions and the limited data, it is recommended that patients be seen in a center with recognized GIST expertise. This type of evaluation should include a multidisciplinary review, including an oncologist and a surgeon.

ASCO 2006

From Page 6

- Peritonectomy/omentectomy (excision or resection of the peritoneum or omentum; these are thin layers of connective tissue that line the abdomen)
 - When practical, for peritoneal seeding
- Margins
 - Wide margins not generally necessary
 - No data on improved survival with wider margins
 - Radical resection when appropriate
- Lymphadenectomy (lymph node removal) not necessary
- Resume kinase inhibitor therapy postoperatively (very important)

Dr. Raut listed some questions that still remain unanswered, such as “Do individuals with certain mutations derive a greater benefit from surgery?” Dr. Raut noted that “. . . this is a very interesting question and one that we are trying to answer ourselves and one that may be able to generate some data.” Raut noted that the goal must be for multimodality therapy to be alternated with appropriately planned surgery in an effort to increase the time patients with advanced GIST are maintained on individual drug therapies.

3. “Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correlates with KIT and PDGFRA mutation status.” *Heinrich et al.*

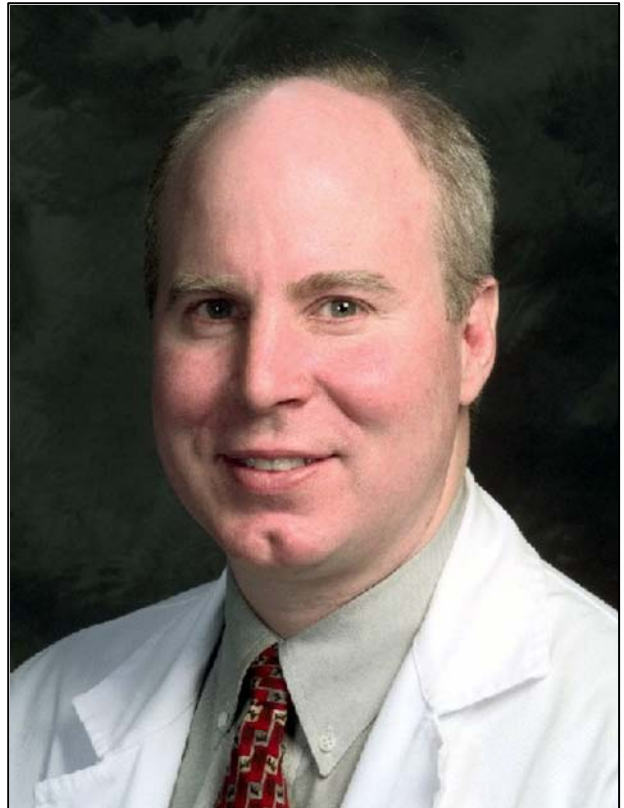
Dr. Michael Heinrich gave a presentation titled “Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correlates with KIT and PDGFRA mutation status.” Sunitinib is the generic name for Sutent. It is approved in the United States and Canada. Sunitinib has direct anti-tumor activity against GIST by inhibition of the KIT and PDGFRA proteins. It also has indirect activity by targeting VEGF receptors and PDGFRB. These are proteins that are important in the formation of the new blood vessels that feed tumors.

This presentation emphasized the importance of genotyping when it comes to GIST.

It has been known since 2001 that genotyping predicts how GIST patients might respond to Gleevec. Recently Dr. Maria Debiec-Rychter and colleagues reported that genotyping can predict which patients benefit the most from higher doses of Gleevec. This current report by Heinrich and colleagues shows that genotyping can also predict which patients are more likely to respond to Sunitinib (Sutent) based not only on their primary mutation but also on their secondary mutations.

Results were based on a Phase I/II study of 97 GIST patients that had failed Gleevec or were unable to tolerate Gleevec. Median PFS and median overall survival for the entire group was 7.8 months and 19.0 months respectively.

The distribution of initial mutations in this study was similar to other studies with 84 percent of patients having a mutation in KIT, 5 percent with PDGFRA mutations and 11 percent with wild-type GIST. Clinical response to Sutent was correlated to the patient’s primary genotype (pre-Gleevec). In this study clinical benefit was defined as stable disease for at least 6 months or a partial response; KIT exon 9 GISTs had the best clinical benefit rate (63%) followed by wild-type (56%), KIT exon 11 (36%) and PDGFRA (25%). Significant tumor shrinkage with Sutent is more common in KIT exon 9 patients (37% had a partial response) compared to KIT exon 11 patients (5%). *Note: The ASCO abstract and presentation incorrectly list the benefit rate for KIT exon 9 as 42 percent. The correct value in this study was 63 percent. A previous study presented by Dr. George Demetri at 2004 ASCO found a benefit rate of 80 percent when*



HEINRICH

looking at 15 patients. This difference might reflect the relatively small sample sizes involved (19 and 15 patients). It should be noted that while 63 percent of exon 9 patients benefited for at least 6 months, a substantial portion, 50 percent of exon 9 patients, benefited for at least 19 months.

In addition to its correlation with primary mutations, Heinrich and colleagues were able to show that Sutent has activity against some secondary mutations but not others. Secondary mutations are the most common cause for resistance to Gleevec. For the first time, Heinrich reported that secondary mutations were more common in Gleevec-resistant patients with primary KIT exon 11 mutations (62%) than in Gleevec-resistant patients with primary KIT exon 9 mutations (16%, P=0.002).

In this study, 29 patients had secondary KIT mutations. These included mutations in exon 13 and exon 14, the por-

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be able to cross-over to the actual drug.” Aside from the fact that this is simply not true (what prevents the patients from just not taking what they know is a placebo, or opting for surgery, or just leaving the trial?), it certainly raises a serious issue regarding being able to maintain a blinded placebo in a clinical trial for savvy and internet connected patients. Finally, I would add the provocative note that a group of patients may be capable of going one step further by creating a mechanism to test whether a pill is real or a placebo. While one might legitimately criticize such a step as a threat to the integrity of the research process, others might understand that terminally ill patients fighting for survival may have competing interests.

5. Finally, we submit that the search for bias free clinical trial protocols for new targeted drugs must also consider that should patients remain on these drugs for some time that changes in actual drug dosage must be considered. Current clinical trials make no attempt to factor this in and instead consider that

the dosage initially prescribed should be exclusively used for analysis regardless of how many patients are no longer on that regimen when they demonstrate disease progression.

Let’s end with a story: A major patient advocacy organization has gathered a clinical trial group consisting of cancer researchers, pharmaceutical company executives and FDA officials on the roof of a 50 story building. At issue is whether a new and novel fast opening parachute would permit the survival of someone falling from such a height. Historical data is deemed by the patient advocacy organization to insufficient to answer this question.

Half the clinical trial group is fitted with the new parachute on their back. The other half is fitted with a placebo parachute on their back. The patient advocacy organization concludes that neither group is smart enough to figure out whether they have the real parachute by temporarily removing what is on their back and carefully examining it.

They then set a fire on the first floor of

the building and, after the flames have reached the 49th floor, they ask the clinical trial group to sign an informed consent form agreeing to participate in the trial. One hundred percent of the group signs, closely matching the consent rates of terminally ill cancer patients being asked to agree to a placebo-based clinical trial. Patients then assemble on the street a safe distance from the building and observe the clinical trial participants leaping off the roof.

Study Conclusions: Of the 50 participants half were randomly assigned to the actual parachute group and half to the placebo group. Thirty-three percent of the actual parachute group survived the fall as compared to zero percent of the placebo group! Publication of the data will be presented at a meeting of PASCO (Patient Advocacy Society Cancer Organization).

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The first pediatric GIST review board: creating a virtual center of excellence

By Norman J. Scherzer

Some time ago we reported that we were creating a center for pediatric GIST clinical excellence at a major U.S. medical center. Our intention was to overcome the lack of practical information on how to manage this important subset of GIST patients by referring enough of them to one location to accumulate the expertise that simply does not exist yet. Although our intentions were noble and our plan looked good on paper, we have not been successful. There were a number of reasons for this but the most important was that we could not get a critical mass of pediatric GIST patients to travel to this one location for ongoing and coordi-

nated care.

Just prior to the recent American Society of Clinical Oncology (ASCO) meeting, a pediatric GIST parent contacted us to ask if we could come up with a standard of practice for managing such patients. That implied gathering a group of physicians to agree upon a best practices protocol and that meant finding some who were truly experts in this area. We could not identify the latter, let alone the former.

While at ASCO and talking to Dr. Lee Helman of the National Cancer Institute, the thought occurred to us that we could create an international panel of physicians with both an interest in pediatric GIST and a complementary set of skills.

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Norman Scherzer discussed idea of a pediatric review board with Dr. Lee Helman of the National Cancer Institute.

Gleevec still beneficial, despite evidence of heart disease

By Jerry Call

On July 23, 2006, the medical journal *Nature Medicine* published an article about heart damage caused by Gleevec. Many news agencies have picked up this story. This story is very new and further information may become available over time.

Norman Scherzer, Executive Director of The Life Raft Group and Jerry Call, LRG Science Coordinator, attended a Novartis briefing.

Novartis shared some of the following information:

Ten Gleevec patients from M.D. Anderson experienced some degree of heart failure or heart dysfunction. Three of these patients had previous heart disease and some of the others had risk factors such as high blood pressure and diabetes. Several details were not reported. These include the number of total patients examined for heart problems as well as the number of patients that could be expected to have these type problems in a normal population. Without such a comparison, we cannot determine whether the Gleevec patients are at higher risk than a normal population. Novartis reports that they have not seen



any significant trend of heart problems in their large database of Gleevec patients.

In addition to the report of 10 patients with heart dysfunction, the *Nature Medicine* article reported on mice studies that showed some heart damage from Gleevec. Some caution should probably be used in applying these findings to humans. For instance, liver toxicity occurred in dogs in preclinical testing of Gleevec, but it turned out that the liver toxicity in humans was lower than would have been predicted from the dog studies.

The authors of the article performed experiments that suggest the probable cause of the heart damage in mice to be inhibition of the c-abl protein. Gleevec inhibits c-abl (and other forms of abl such as bcr/abl), KIT and PDGFR. They speculate that other drugs that inhibit c-

abl (such as dasatinib and AMN107) might also cause heart damage.

Apparently, the authors of the mouse study have recommended routine heart screening for patients taking Gleevec. According to Novartis, they have backed off of this recommendation in communications to Novartis. Novartis recommends screening only for patients who are having symptoms of heart dysfunction.

We should note that a decrease in left ventricular ejection fraction (LVEF) has also been reported for Sutent as well, but only 1 percent of patients had reductions below 40 percent (grade 3 reductions). Because of this, the Sutent.com website says "... baseline and periodic evaluations of LVEF should be considered."

Gleevec is intended to treat very serious diseases. We know that without Gleevec (or a similar drug), metastatic GIST will progress, ending in death. All medicines balance risk versus benefit. We know that for most patients with metastatic GIST, Gleevec provides great benefit. At this time these benefits seem to far outweigh the risks for the great majority of patients. We will continue to monitor this situation and report on new developments. We also welcome comments from experts in the field.

REVIEW BOARD

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We would create a virtual center of excellence by presenting individual cases, including well documented medical histories and test results, to the panel on an ongoing basis. We could begin with those pediatric GIST patients needing urgent consultation and use the over 25 cases in the Life Raft Group medical database (the largest such active patient database in the world). Where appropriate, the patient's physician would be invited to present the case and participate in the discussion. The Life Raft Group would provide the coordination to assemble the necessary patient information, manage the discussion logistics

(likely by teleconference) and, if necessary, act as an honest broker to shield the identity of the patient to comply with privacy and confidentiality issues.

Dr. Lee Helman, to his great credit, agreed on the spot to participate. Following ASCO we then reached out to Dr. Cristina Antonescu, the Memorial Sloan-Kettering pathologist who is developing our pediatric GIST tissue bank; to Dr. Michael LaQuaglia, the Memorial Sloan-Kettering pediatric oncology surgeon with experience operating on pediatric GIST patients; and to Dr. Alberto Pappo, pediatric oncologist at the Hospital for Sick Children in Toronto, with

experience in the clinical care of pediatric GIST patients. All instantly agreed subject to appropriate legal and professional safeguards. A few weeks later at a meeting in Budapest we presented this idea to Dr. Frederica Grosso of Milan, Italy, the physician caring for one of our pediatric GIST patients in Italy. She immediately agreed to cooperate.

So there we are with a new idea, not much in the way of precedent, and no dedicated funding. We intend to expand this core group on our panel and to figure the rest out as we go along. Our pediatric GIST kids are too important not to try again.

Pastor Paul Isaak lived his life for everyone

By Erin Kristoff

Paul and his wife, Beryl moved around a lot over the 53 years of their marriage. GIST never hindered his quest or slowed him down. “He was a man who visited. I don’t think there was a coffeshop in any town we lived in that we didn’t visit,” said Beryl. In fact, others called these visits, Pastor Paul’s “coffeshop ministry.” He liked to talk with people, people who he might not necessarily meet elsewhere, “He did a healing thing for them and for himself.”

His wife is not the only one who felt that way, “The gal at the clinic in the oncology department that helped us on the Sutent trial said he had a calming presence about him; she felt it every time he was around.”

He touched people’s lives in other ways too. He loved to dig into the past and wrote various histories, including

one for their former town of Deer Creek on their 100th anniversary and one for his family. He also loved to write, acting as the Inman, Kansas correspondent for the local paper.

But his love was in the church, “that was his calling and he never wavered.” He was ordained in 1956 and this year on June 11, the Bethel Mennonite Church in Inman celebrated his 50th anniversary in the church’s service. When Paul and Beryl left Deer Creek and returned to Inman where they had previously lived from 1968-81, the leaders in the church knew that he was not done working and asked him to be a pastor. The older folks in town remembered him and were glad to have him back.

On July 2, four days before he peacefully died, Pastor Paul was giving a sermon in church, where he belonged. He left behind a wife, three children and grandchildren.



PASTOR PAUL ISAAK
Photo courtesy of Bethel Mennonite Church in Inman, Kansas

Washington Life Raft Group



The first Washington Life Raft meeting was held on Saturday July 8th at the home of GIST patient Gerald Snodgrass. Attending were five other GIST patients and their spouses/caregivers for a total attendance of 12 people (plus Ginger the dog).

Attendees had the opportunity to share experiences and concerns. Standing from left: Gerald Snodgrass, Deanne Snodgrass, Peggy Barton, Bill Barton, Rebecca Haines, Joy Knopp, Doug Knopp, and Wendy Reed. Kneeling from left: Malgosia Szyszkowski, Leah Knopp, and Marcel Szyszkowski. Photo taken by Greg Mullen (Rebecca Haines’ son).



The fourth international conference for organizations representing people with CML or GIST was hosted in Budapest.

GIST patient groups convene in Budapest

By **Tricia McAleer and Norman J. Scherzer**

GIST patient group representatives from Europe, the United States and Mexico came together with their CML (Chronic Myelogenous Leukemia) colleagues from around the world to meet in Budapest, Hungary for a patient summit meeting.

Plenary session presentations covered such topics as the role of patient organizations in the research process (presented by the Life Raft Group), empowerment through global understanding and collaboration and improving compliance. Workshops ranged from patent-led research, a GIST patient group roundtable and pediatric GIST (all led by the Life Raft Group), access to treatment, patient compliance and the

health care professional's prospective on communication.

Some of the most important work took place behind the scenes. Of particular note, extensive discussions took place with Antonio Lopez Picazos, our newest colleague from Mexico, about supporting our recently announced clinical trial initiative in Mexico. Discussions also took place with Dr. Frederica Grosso of Milan, Italy about the formation of an international pediatric GIST review board (see page 10).

Amongst the most important presentations was that of Dr. Peter Reichardt of Germany who reported on the latest data about Gleevec dosage that clearly showed a benefit from higher doses for GIST patients with an exon 9 mutation. Reichardt also suggested that patients with an exon 11 mutation continue to derive at least 5 additional months of

progression-free survival on 800mg of Gleevec.

Our pediatric GIST workshop was very well received. The teleconference was chaired from Colorado by Jerry Call, LRG Science Coordinator, and managed from the LRG office in New Jersey by Elizabeth Braun, our Research and Administrative Coordinator. The conference included presentations by Dr. Michael LaQuaglia, pediatric cancer surgeon, and Dr. Cristina Antonescu, pathologist (and head of our pediatric GIST tissue bank), both from Memorial Sloan-Kettering in New York City. Norman Scherzer and Dr. Reichardt served as respondents at the Budapest end. We would like to express a word of thanks to our telecommuting guests who got up around 4:00 a.m. their time to catch up with our Budapest time zone.

BUDAPEST

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From left to right: Jan-Einar Moe, LRG Norway representative, Ulrich Schnorf, LRG Switzerland representative, and Kai Pilgermann of Das Lebenshaus, listen to presentations about the role of patient groups internationally.



From left to right: Norman Scherzer, LRG Executive Director, Anna Costato, LRG Italy representative, and Estelle LeCointe, LRG France representative, discuss pediatric GIST.



From left to right: Norman Scherzer, Life Raft Executive Director, and Dr. Peter Reichardt, German GIST expert, listen to Dr. Cristina Antonescu, Memorial Sloan-Kettering pathologist, via telephone. Pediatric GIST was one of the workshops presented at the Budapest Summit meeting which served as a stepping stone to future discussions about finding a cure for pediatric GIST.

ASCO 2006

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JUDSON

tion of the gene that codes for the drug/ATP binding pocket of the protein. All of the mutations in exon 13 were V654A mutations. This was by far the most common secondary mutation (n=12). Heinrich reported that, in the lab, the exon 13 and exon 14 mutations were resistant to Gleevec but sensitive to Sutent.

Almost half of the secondary mutations occurred in exon 17, the kinase activation loop. Five different exon 17 mutations were reported and one exon 18 mutation was reported. Dr. Heinrich reported that, in the lab, these mutations were resistant to Sutent and Gleevec.

Heinrich and colleagues then demonstrated that the lab tests correlated with benefit in patients. They found that the median PFS in patients with sunitinib-sensitive secondary mutations (KIT exons 13 and 14) was 8.1 months compared to only 2.3 months for patients with sunitinib-resistant secondary mutations (KIT exon 17 and 18).

Dr. Heinrich concluded that “sunitinib exhibits significant clinical and biological activity in patients with imatinib-resistant GIST.” The “clinical benefit of sunitinib was strongly influenced by

both primary and secondary mutations in . . . KIT.” Sunitinib was particularly effective for treatment of wild-type GISTs or KIT exon 9 mutations and sunitinib is more potent than imatinib against secondary mutations involving the KIT/ATP drug binding pocket.

4. “Mutation-directed management of GIST—Should genotyping be part of routine practice?” Judson et al.

Dr. Ian Judson of the Royal Marsden Hospital, London, UK, was the discussant for Dr. Heinrich’s presentation in a talk titled “Mutation-directed management of GIST—should genotyping be part of routine practice?” Dr. Judson noted the “. . . big challenge for people that don’t have access to this technology.”

Dr. Judson began his talk by noting that the initial (primary) genotype can predict not only how patients are likely to respond to Gleevec, but also how likely they are to respond to Sutent as second-line therapy. Judson then reviewed the mechanisms of resistance to Gleevec with a focus on the fact that secondary kinase mutations (the most common reason for resistance) were much more common in GIST with primary KIT exon 11 mutations (62%) than in GISTs with primary KIT exon 9 mutations (16%).

Dr. Judson reviewed the EORTC (European Organization for Research and Treatment of Cancer) Gleevec dose response data by genotype (Debiec-Rychter et al.) noting the superior PFS for KIT exon 9 mutations at higher doses of Gleevec. Also noted was the poor response of wild-type KIT, which was worse at higher doses, prompting Judson to speculate that Gleevec may “. . . be doing nothing at all for these patients” (Note: However, there have been some wild-type responses in the phase III trials). Judson noted that in this analysis (which is a subset of the entire EORTC dataset) there was no significant difference in response by dose when all genotypes were combined or for KIT exon 11 patients.

A graph of the Heinrich presentation on Sutent was reviewed and showed the PFS by primary (pre-imatinib) KIT genotype. Gleevec-resistant patients with wild-type GIST and KIT exon 9 mutations both did quite well on Sutent, with a median PFS of 20.9 months and 19.4 months respectively. Gleevec-resistant patients with KIT exon 11 primary mutations had a median PFS of only 5.1 months on Sutent.

Although patients with imatinib-resistant GIST and KIT exon 11 mutations progress faster on sunitinib than other types, this does not necessarily mean that the drug is intrinsically less active against exon 11 tumors. Dr. Judson speculated that the exon 11 patients were likely to have had a longer imatinib treatment period (median 2 years), having more time to acquire secondary mutations, some of which are resistant to sunitinib (as well as imatinib).

Dr. Judson’s concluded that genotyping at, or soon after, a diagnosis of advanced GIST would clearly benefit patients with KIT exon 9 mutant GIST. In addition, a trial is indicated to compare sunitinib vs. imatinib 800 mg in exon 9 mutant GIST. There is also a case for a study of sunitinib vs. imatinib for first line therapy since relative inactivity vs. exon 11 mutant tumors may reflect longer duration of imatinib therapy and selection pressure to develop secondary resistance mutations.

**New website
launched for Global
GIST
Network!**



**Go visit
www.globalgist.org**

THE LIFE RAFT GROUP

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