

Back from the brink

When Gleevec fails and options narrow, stress brings on depression

By Bernard Kaplan

For three and a half years I have been on a cancer roller coaster. For three years Gleevec managed to halt tumor growth. Periodically, though, elevated liver enzymes caused me to be taken off the medicine. I was the “On-Again Off-Again Man” of the Life Raft Group. When some of the tumors began to grow, I had to undergo massive surgery, for the second time. Finally, I was told that I had become resistant to Gleevec and my only hope was Sugem (SU11248), a trial drug from Pfizer.

I was sustained by a vision of my parents that occurred three months to the day *before* my initial diagnosis. We were on vacation, and as our plane was about to land in Israel, the steward-



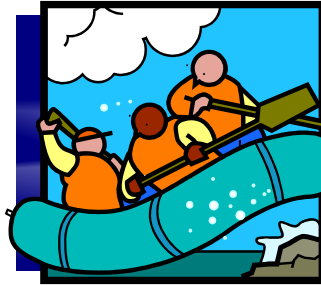
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ess asked us to sit back and relax. As I closed my eyes for a moment, I suddenly heard the voices of my parents speaking to me. Both had passed away more than 10 years earlier. I did not see them but I heard them clearly. They said one sentence to me which I can never forget — “Bernie, you will live a long life and everything will turn out fine.”

One Sunday after I was taken off Gleevec, my brother came to visit me. He is a psychiatrist and quickly diagnosed me as suffering from serious depression. I couldn't lie to myself anymore and had to face that issue as well.

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Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

May 2004

In memory of Darlene Vaughan, Sidney Locker

Vol. 5, No. 5



Barbara Kennedy of Novartis Pharmaceuticals accepts the Life Raft Group's Humanitarian Award from Norman Scherzer, executive director of the Life Raft, at the opening dinner of Life Fest 2004.

GIST patients, experts meet at Life Fest 2004

Higher doses of Gleevec linked to fewer relapses

More than 100 GIST patients and family members came from around the world to attend Life Fest 2004 held April 30-May 2 in Orlando, Florida, U.S.A. — the second general meeting of the Life Raft Group (LRG).



Sharing smiles at Life Fest 2004 are Andrea “Hugs” Fuller of Florida and Valerie Matthews of Nova Scotia.

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LIFE FEST

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Members from throughout the United States and Canada, and from Costa Rica, France, Germany and Switzerland gathered at the Embassy Suites Lake Buena Vista Resort to meet one another and to hear presentations from Life Raft Group members and many guest experts.

Following a welcoming reception Friday, the group gathered for dinner in the resort's main ballroom and were called to order by Sarah Buch, master of ceremonies and the person who arranged the meeting location and logistics. She introduced Stan Bunn, president of the LRG Board of Directors, who welcomed participants in six languages. Bunn reiterated the strategic concept for survival discussed at the directors' meeting held earlier: The time for action is now, because GIST patients with resistance to current treatment cannot wait.

Buch then introduced Executive Director Norman Scherzer who reviewed the meeting's objectives and reported on the activities and strategies of the LRG. His presentation will be posted on the Life Raft Group Web site at www.liferaftgroup.org/

Scherzer outlined five major goals for the meeting:

1. The bonding of GIST patients, family members and clinicians meeting and interacting with one another.
2. Learning about the management of GIST, which empowers patients and caregivers.
3. Building physician-patient relationships
4. Increasing the group's leverage for change
5. Survival — the mission of the LRG

He outlined the LRG strategy for the survival of GIST patients:

- To think smart enough to leverage the small number of GIST patients and to overcome the rarity of GIST
- To use LRG research and the abil-



Receiving Life Raft Group Humanitarian Awards at Life Fest 2004 are, from left, Drs. Allan Van Oosterom, Margaret von Mehren and Robert Benjamin.

ity to publish it, in this newsletter and on the LRG Web site, to secure a seat at the decision-making table

- To create a core staff, and funding, to provide a consistent and all-out survival effort

Particular emphasis was paid to the rationale and history of the unique, patient-driven research that the LRG undertakes. The rationale is to collect and share data in a timely way — faster than that provided by traditional cancer research — and to look at data in the most patient-relevant way and glean information that pertains to survival.

Scherzer noted that the LRG was the first to report on the effectiveness of Gleevec for GIST patients, the first to report that Gleevec side effects improved over time, the first to report gender differences in side effects, the first to establish a pediatric GIST database (all girls!) and the first to look at the critical differences between relapse and actual drug dosage. The LRG is currently building a database on the new SU11248 clinical trial.

LRG HUMANITARIAN AWARDS

The highlight of the evening was the presentation of the LRG Humanitarian Award to Dr. Brian Druker of Oregon

Health & Sciences University (OHSU) and to Barbara Kennedy of Novartis Pharmaceuticals. Druker's acceptance was via video tape; Kennedy accepted in person. The third honoree was Nobel laureate James Watson, Ph.D., who will accept his award at a later date.

Druker is a Howard Hughes Medical Institute investigator and Jeld-Wen Foundation chairman of leukemia research at OHSU. Druker's acceptance remarks will be posted on the LRG Web site, www.liferaftgroup.org/. Kennedy is the executive director of Novartis Oncology Scientific Operations. James Watson is the co-discoverer of the double helix in DNA. All three have made critical contributions to the survival of GIST patients.

The LRG Humanitarian Award honors those whose actions improve the survival and well-being of those afflicted by GIST. The first Humanitarian Awards were presented in May 2002 to Dr. Daniel Vasella, chief executive officer of Novartis Pharmaceuticals and to Dr. George Demetri, director of the Dana-Farber Cancer Institute's Center for Sarcoma and Bone Oncology, and associate professor of

Vasella awarded Stratton Prize

Friends of Switzerland honor Novartis CEO at Harvard Club in Boston

Daniel Vasella, chairman and chief executive officer of Novartis, and friend of the Life Raft Group, was presented the Julius Adams Stratton Prize on May 7 at the 38th annual meeting of the Friends of Switzerland.

Keynote speaker at the dinner gathering was Norman Scherzer, executive director of the Life Raft Group. The event was held at the Harvard Club in Boston.

The award is given each year to citizens of the U.S.A. or Switzerland who exemplify the fruitfulness of the exchange of ideas and technologies between the two countries.

As head of the world's seventh largest pharmaceutical company, Dr. Vasella shepherded the early development of Gleevec past those questioning the advisability of developing a drug for a rare cancer. The patient population was too small; why pour resources into a product that would never make any money?

But as initial testing revealed Gleevec's spectacular potential, Vasella pushed on "We decided that the number of patients who might benefit from such a drug should not concern us ... we had a duty to put a product on the market when there is a fair chance that it will change the practice of medicine — even if it only helps a small number of patients," Vasella wrote in his book, "Magic Cancer Bullet – How a Tiny Orange Pill is Rewriting Medical History."

The Stratton Awards are named in honor of Dr. Julius Stratton, former president of the Massachusetts Institute of Technology and a long-esteemed member of the Friends of



Norman Scherzer is flanked by the Vasellas — Anne-Laurence and Daniel — at the 38th annual meeting of the Friends of Switzerland where the Novartis CEO was awarded the Stratton Prize. Scherzer was invited to be the keynote speaker at the May 7 event. At right, Vasella thanks the Swiss group for bestowing him the honor.

Switzerland until his death in 1994. He was the recipient of the first award in 1966 "for his exemplary and lasting definition of humanistic conduct in the perplexing world of science."

Attending this year's dinner were Drs. Mark Fishman, head of the Novartis research facility in Cambridge, and David Epstein, head of Novartis Oncology worldwide; Swiss Ambassador to the U.S. Christian Blickenstorfer and a number of other distinguished guests. Norman's son, Robert, joined him for the occasion.

Friends of Switzerland was formally incorporated in 1967 to foster friend-



ship, understanding, and enjoyment between the Swiss and Americans in New England.

LIFE FEST II

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medicine at Harvard Medical School.

GENERAL SESSION HIGHLIGHTS

The Saturday general session got off the ground early in the morning with “GIST 101,” a comprehensive presentation on cancer and GIST by LRG member David Josephy, Ph.D., professor of biochemistry at the University of Guelph, Ontario, Canada. His presentation will be posted on the LRG Web site, www.liferaftgroup.org/ “Novel Clinical Trials” by Dr.

Robert Benjamin, director of the sarcoma center at M.D. Anderson Cancer Center in Houston, Texas, gave a trend-setting presentation on clinical trials. He was joined via audio-visual link to Dr. Laurence Baker, sarcoma specialist and deputy director for clinical research of the University of Michigan Comprehensive Cancer Center. Baker was attending the Southwest Oncology Group meeting in California and joined the Life Raft Group at 6 a. m. local time. The formal presentation was made by Benjamin and will be posted on the LRG Web site.

Benjamin’s presentation and discussion was wide-ranging and reviewed some of the current concepts in clinical trials, including evaluation endpoints and statistical methods. A striking recommendation was to stop using RECIST (response evaluation criteria in solid tumors) as a criteria for defining progression for solid tumor trials, especially GIST. Benjamin felt that RECIST significantly underestimates response in GIST and fails to discriminate between good and poor responders.

There was also a candid discussion on the use of placebos in clinical trials. Baker said there was no need to have a placebo for GIST patients who were resistant to current treatment and already progressing, and that the current study design for the Pfizer SU11248



David Josephy, Life Raft Group member and professor of biochemistry at the University of Guelph, Ontario, presents “GIST 101” on the second day of Life Fest 2004 in Orlando.

clinical trial was, in his view, unethical. Benjamin felt that a placebo could be justified in some situations but that its use in the SU11248 trial was flawed since the trial protocol requires that patients stop using Gleevec for two weeks prior to starting the study. This cessation in itself could cause tumors to increase their rate of growth.

NEW AMGEN TRIAL

Both Baker and Benjamin reviewed the proposed protocols for phase II studies of Amgen’s AMG706 that should be starting this summer at locations including M.D. Anderson and the University of Michigan. Two trials are planned for Gleevec-resistant GIST patients, one using response by RECIST criteria as an endpoint and one using clinical evaluation of progression in a randomized study of patients on AMG706 versus patients on a maximum dose (at least 600 mg.) of Gleevec. Importantly, placebos will not be used in either group.

AMG706 is a tyrosine kinase inhibitor that targets Kit, PDGFR and VEGF, the same targets as SU11248. There are a few other drugs in this

category from other pharmaceutical companies that the LRG is tracking. Although this new Amgen drug is thought to be similar to the Sugem drug, the Life Raft has no data yet about its effectiveness on resistant GIST. That poses a dilemma for resistant GIST patients:

Patients can enlist in the current SU11248 trial for which there is data of effectiveness for resistant GIST patients, but run the risks involved with having to stop Gleevec for at least two weeks before starting the trial, of being assigned to a placebo group, and having to wait until there is sufficient progression under RECIST criteria before learning if they were taking the placebo or the drug.

Or, patients can enlist in the new AMG706 trial for which there is no data on its effectiveness for resistant GIST — but patients won’t have to risk being given a placebo, having to stop Gleevec prematurely or waiting as long before being considered for crossover.

Adding to the dilemma: The Pfizer trial excludes patients who’ve taken

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Life Raft aids GIST dads worldwide

LRG helps patients in countries where Glivec awaits official approval

The Life Raft Group has outreach programs in many countries, including some where Novartis doesn't offer any formal assistance program through the Max Foundation. The foundation can only operate in countries where Glivec (Gleevec) has been formally approved for the treatment of CML (chronic myelogenous leukemia) or GIST (gastrointestinal stromal tumor). In these countries there is program in place for patients to apply for assistance in obtaining Glivec.

In other countries, the Life Raft Group tries to fill the gap by working behind the scenes to get Glivec to GIST patients.

Two of these countries are Poland and Iran. In both countries are GIST patients, both fathers, the Life Raft Group is helping.

Marek Szczesny was born May 5, 1939, in Poland, has been happily married for more than 35 years and is the father of two sons. One son, Bartosz, is a LRG member. Marek had no serious medical problems until his GIST was diagnosed in March 2003. Since June 2003, following surgery, he has been on Glivec with excellent response.

Gholamali Amirfarhad of Iran is also responding to Glivec. Gholamali was born in 1940 in Tehran. Married for 34

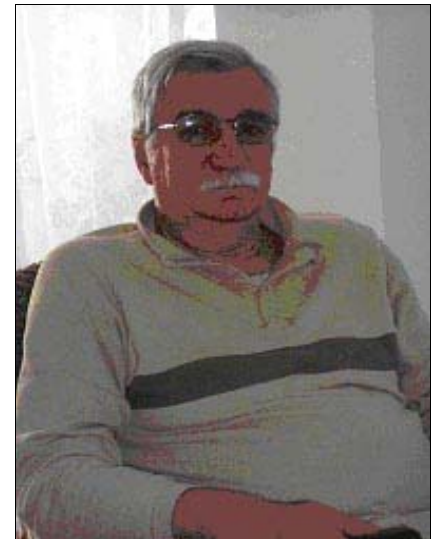


Gholamali Amirfarhad and his wife, Shahnaz, of Iran. Their daughter Negar is a member of the Life Raft Group.

years, he is the father of two daughters, Negar and Sogol, Negar is the LRG member. Gholamali was a teenager when he started building a career as a professional wrestler but had to stop in his mid-20s due to a burst appendix.

Negar writes that her dad is an individual who affects every person he meets. He has sponsored orphaned families, put employees through university and has instilled deep-rooted values of integrity, honesty, respect and responsibility in his family. A walk down a street in Tehran often includes individuals greeting him and thanking him for the influence he has had on themselves or their families.

He wrestled many champions in his day, but this is a match we pray he wins.



Marek Szczesny of Poland. His son Bartosz is a member of the Life Raft.

Texas area chapter of the Life Raft meets Saturday, June 12

The Texas area chapter of the Life Raft Group will meet at 10 a.m. Saturday, June 12 in Dallas.

You do not have to be a member of the Life Raft Group to attend. The meeting will be at Gilda's Club North Texas, 2710 Oak Lawn, Dallas, phone

(214) 219-8877.

Lodging will be at the Wyndam Dallas North, 4801 LBJ Freeway. For hotel reservations, phone the hotel at (972) 661-3600 and tell them you're with the Life Raft Group to receive the special rate of \$79 per night.

An optional dinner that evening at the Wyndam is \$25; reservations must be paid in advance by June 9.

For dinner reservations and meeting details, contact coordinator Kerry Hammett, e-mail yaloo@gvvc.com, phone (830) 935-3420.

LIFE FEST III

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the Amgen drug, and vice-versa.

NOVEL TARGETS

Dr. Margaret von Mehren, GIST specialist at Fox Chase Cancer Center in Philadelphia, talked about novel targets, focusing on two subject areas.

The first was a study to identify surrogate response markers to Gleevec therapy in GIST patients. A protein called Sprouty4A, or SPRY4A, was found to have decreased expression in responding patients and another protein, called MAFbx, was found to have increased expression in responding patients. This indicates that SPRY4A and MAFbx may be targets, and work is ongoing to develop a model in the lab to determine the importance of SPRY4A.

Von Mehren also talked on the importance of STAT3 signaling in GIST and on a new STAT3 inhibitor, JSI-124 (cucurbitacin I). STAT 3 is not generally inhibited by treatment with Gleevec. Treatment of GIST cells with JSI-124 caused cells to stop growing and caused cell death. JSI-124 does not inhibit KIT signaling and its effect on GIST is apparently related to its ability to inhibit STAT3 signaling. The next step is testing of JSI-124 in animals.

EUROPEAN PERSPECTIVE

Dr. Allan Van Oosterom, chairman of the Department of Oncology at the Catholic University of Leuven, Belgium, and recent president of the European Organization for Research and Treatment of Cancer (EORTC) traveled all night to join the group.

Both Von Mehren and Van Oosterom's presentations won't be available on the LRG Web site until they have been approved for publication.

Van Oosterom noted that almost all of his GIST patients who are on Gleevec take more than 400 mg. per



VON MEHREN



VON OOSTEROM

day. This is consistent with the ongoing European study of GIST patients on Gleevec that has found progression-free survival is related to dosage level, with longer periods correlated with higher doses. (This contrasts with the counterpart American study that has reported no difference in progression-free survival and dosage.)

Of particular significance was data that demonstrates that there was increased clearance of Gleevec in GIST patients over time. In other words, the longer you take Gleevec, the more effective your body becomes at ridding itself of Gleevec, hence decreasing the effective drug level. This is consistent with the European finding that higher doses are correlated with longer time to progression, and with the LRG relapse survey that higher doses are correlated with lower relapse rates.

Van Oosterom offered the following suggestions for GIST patients encountering progression. For localized progression, he recommends continuing on Gleevec and, if feasible, considering surgery (or when the liver is involved, radio frequency ablation). For systemic progression he recommends increasing the dosage of Gleevec to 800 mg. or 1000 mg. per day as a first step, noting this seemed to help about half of his patients in this situation (This is a higher percentage than noted in comments the LRG has received from other specialists).

Van Oosterom also noted the frequency of Gleevec-induced anemia.

He volunteered his concern about using drugs like Procrit and, while acknowledging he's unsure what the best treatment is, suggested it may be more prudent to rely upon blood transfusions.

Van Oosterom then reviewed a number of "rescue studies" for GIST patients resistant to Gleevec. Those in, or shortly to be in, clinical trial for GIST are in bold. They included:

■ **Pfizer: Sugem-SU11248:** In phase III clinical trial

■ **Novartis: RAD plus Gleevec:** The start of this second phase I study has been delayed because Gleevec slows the metabolism of RAD.

■ **Novartis: PKC412 plus Gleevec:** This phase I study has been delayed because PKC increases the metabolism of Gleevec.

■ **Amgen: AMG706:** Phase II study should begin this summer.

□ Abbot: ABT869: Similar to Sugem and Amgen; unknown clinical trial plans for GIST

□ Ariad: AP23573: An mTOR inhibitor (similar to RAD); unknown clinical trial plans for GIST (Ariad's Web site also mentions AP23464, which is in pre-clinical development, and which inhibits KIT, EGFR, HER2, Raf, Scr, and Abl.)

For those trying to compile a list of possible GIST drugs, the ones the Life Raft Group has heard of are listed below. Those in, or shortly to be in, a clinical trial for GIST are in bold. Although it is unprecedented for a rare cancer like GIST to have so many potential drugs, readers should remember that the efficacy of just two drugs, Gleevec and Sugem, is known. It is unlikely that there will be many more "home run" drugs like Gleevec in the near future.

□ Bayer's BAY439006: an oral drug which targets signaling pathways downstream from c-kit (Raf kinase).

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Unknown clinical trial plans for GIST.

□ Novartis' PTK787: an oral drug which inhibits c-kit. Unknown clinical trial plans for GIST.

■ **Bristol Myers Squibb's BMS354825:** Phase I trial to begin soon.

□ Genta's Gentasense, an antisense drug that inhibits bcl-2. On May 13, Genta announced that it had notified the U.S. Food and Drug Administration of its decision to withdraw its new drug application for Gentasense. An application had been submitted last December for using Gentasense plus dacarbazine on patients with advanced melanoma. On May 3, an FDA advisory committee voted not to recommend Gentasense for marketing approval. The future of Gentasense appears to be uncertain at this time.

□ Kirin: KRN951, a KIT inhibitor manufactured by a Japanese company. Unknown clinical trial plans for GIST

■ **AB Science:** A phase I trial has begun in France.

LRG RELAPSE SURVEY

Scherzer presented the group's relapse survey. This is a preliminary summary. Formal results are being submitted for publication and cannot be made available on the LRG Web site until then. Scherzer is a former disease management specialist for the Centers for Disease Control and a former assistant commissioner of health for the City of New York.

Relapse rates for 162 metastatic GIST patients were analyzed. All initially responded to Gleevec with shrinkage and all were on Gleevec for at least one year. Scherzer said the survey compared starting, or "intent to treat" dosage versus actual (delivered) dosage.

Using the starting dosage tended to underestimate the relationship between higher doses and lower relapse rates. When the actual dosage was studied,

Relapse rate, actual dosage		
Actual dosage	Relapse	No relapse
162 patients	71, or 43.9%	91, or 56.1%
117 on 400 mg. or less	60, or 51.3%	57, or 48.7%
45 on 600 mg. or more	11, or 24.4%	34, or 75.6%
91 men	42, or 46.2%	49, or 53.8%
63 on 400 mg. or less	32, or 50.8%	31, or 49.2%
28 on 600 mg. or more	10 or 35.7%	18, or 64.3%
71 women	29, or 40.8%	42, or 59.2%
54 on 400 mg. or less	28, or 52%	26, or 48%
17 on 600 mg. or more	1, or 5.9%	16, or 94.1%

Relapse rate, starting dosage		
Starting dosage	Relapse	No relapse
162 patients	71, or 43.9%	91, or 56.1%
99 on 400 mg. or less	48, or 48.5%	51, or 51.5%
63 on 600 mg. or more	23, or 36.5%	40, or 63.5%
91 men	42, or 46.2%	49, or 53.8%
55 on 400 mg. or less	27, or 49.1%	28, or 50.9%
36 on 600 mg. or more	15 or 41.7%	21, or 58.3%
71 women	29, or 40.8%	42, or 59.2%
44 on 400 mg. or less	21, or 47.7%	23, or 52.3%
27 on 600 mg. or more	8, or 29.6%	19, or 70.4%

Scherzer said, it was found that there was a statistically significant difference between dosage and relapse rates, with higher doses correlated with lower relapse rates, particularly among women.

Scherzer said the data is significant enough to warrant using higher doses to prevent relapse unless the patient has unacceptable side effects.

This data is consistent with the findings in the ongoing European study that showed time to progression is related to dosage, and to Van Oosterom's presentation at the meeting that that there is increased clearance of Gleevec in GIST patients over time.

LOOKING AT NEXT DRUGS

Dr. Demetri addressed the gathering from the SWOG conference in California. He reviewed the status of forthcoming drugs, including Pfizer's SU11248, currently in phase III trial, and Bristol Myer Squibb's BMS354825, which is to begin phase I trials shortly.

He suggested that BMS354825 is, in some ways, similar to a Gleevec combination trial as it inhibits KIT (the primary target) and an important downstream target, Src. He said the ongoing SU11248 clinical trial offered an important advantage: It's proven to be

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effective in a significant number of GIST patients. He urged caution about new trials such as Amgen's AMG706 as there was no data on efficacy as yet.

Demetri also commented on the LRG relapse survey. He disagreed with the methodology used (starting dosage vs. actual dosage) and said the study was biased since it looked at a subgroup of GIST patients, namely, metastatic GIST patients who had initially responded to Gleevec and had been on Gleevec for one or more years).

EUROPEAN GROUP REPORTS

Markus Wartenberg and Andrea Schumann represented Das Lebenshaus, the House of Life, the Life Raft Group's sister organization in Germany. They reviewed their rapidly expanding programs to provide information and support to GIST patients there. Ulrich Schnorf of Switzerland, representing the local Life Raft Group there, gave a similar review.

SPECIAL AWARD CEREMONY

Lunch was preceded by a special award ceremony as three surprised physicians — Benjamin, Van Oosterom and von Mehren — were presented with Life Raft Group Humanitarian Awards for their extraordinary research and clinical care efforts to help GIST patients. All three went considerably out of their way to be at the meeting and present the latest information on GIST management and research.

BREAKOUT SESSIONS

Sunday's breakout sessions offered attendees many options to gather information and support and as well as to provide input on a number of issues.

Space does not permit detailed coverage of all nine sessions. LRG Science Coordinator Jerry Call's "GIST 201," an advanced workshop on GIST scientific issues, drew a standing-room-only audience. His presentation



Two Life Raft Group members from Europe traveled to Florida for Life Fest 2004. Ulrich Schnorf of Switzerland, left, and Bertrand de La Comble of France renew their friendship and compare notes. Ulrich is the Life Raft Group representative for Switzerland; Bertrand is the LRG representative for France.

will be posted on the Web site, www.liferaftgroup.org. A review of how exon mutations affect response to Gleevec was also given. Though unable to attend, Dr. Mike Heinrich of OHSU provided this presentation.

Rita Raj's workshop on complementary medicine set the foundation for future investigations of this important topic. A LRG member, she is an acupuncturist and a student of Chinese herbal medicine. Her presentation will also be posted on the Web site.

Raj kindly volunteered to team with another workshop presenter, LRG member and registered dietician Alice Sulkowski, to develop a section on the Web site that addresses dietary and complementary medicine issues. Sulkowski co-chaired a workshop on medical procedures and side effects management with LRG member, Dr. Arnold Kwart.

John Poss, LRG fund-raising co-chairman, moderated a workshop on fund-raising, and member Kendra Tobes led a workshop for caregivers. Member Mike Matthews moderated two workshops on the SU11248 trial,

one for trial participants and one for those not in the trial but interested in it.

LRG staffers also moderated two workshops. Jim Roy, information technology director, hosted one on his specialty and Scherzer hosted one on improving the Life Raft Group. Of note was the enthusiastic endorsement for continuing LRG-directed research.

The meeting concluded with a very moving candle ceremony. As some 50 members formed a circle, LRG board member Bernie Kaplan stood in the center of the room and read off names of LRG members who have died. As the names were read, candles were distributed to the group. A single candle was then lit, followed by a moment of silence. Nothing further needed to be said. The meeting was adjourned.

This report was drafted by Norman Scherzer with input from several reporters, including Jerry Call, Jim Hughes and Tricia McAleer. Although completeness and accuracy is the goal, errors can occur. Any corrections or clarifications are welcome and will be published in the next newsletter.

Pathologists share their data on GIST

Armed Forces Institute of Pathology researchers have focused on GIST

First of two parts

By **Markku Miettinen, M.D., and Jerzy Lasota**

The opinions and assertions in this article are the views of the authors and are not to be construed as reflecting the views of the Departments of the Army or Defense. The authors work for the American Registry of Pathology, contracted to work in the Armed Forces Institute of Pathology, offering consultation to government and civilian institutions worldwide. The authors wish to acknowledge the support of Department Defense and American Registry of Pathology in writing this article, as well as the encouragement of the Life Raft Group and its executive director, Norman Scherzer.

TERMINOLOGY and BACKGROUND

Until a few years ago, the non-epithelial (mesenchymal) tumors of the gastrointestinal tract were commonly classified as smooth muscle tumors under headings of leiomyoma (an expectedly benign tumor) and leiomyosarcoma (an expectedly malignant tumor). In recent years it has been increasingly apparent that these tumors were unique, different from leiomyomas and leiomyosarcomas of the peripheral soft tissues — although a very small group of true leiomyomas and leiomyosarcomas does exist in the gastrointestinal tract. In the past six years, the understanding of these tumors has significantly advanced, including the pathologic mechanism and new treatments based on it.

Gastrointestinal stromal tumor (GIST) is now defined as a specific



MIETTINEN



LASOTA

group of immunohisto-chemically KIT-positive mesenchymal tumors of the gastrointestinal (GI) tract driven by KIT cell signaling. Alternative KIT-like receptor, PDGFRA seems to be involved in a number of cases. The specific identification of GIST and recognition of pathogenesis has gained a whole new meaning after the availability of Gleevec/Glivec, a KIT- and PDGFRA-selective tyrosine kinase inhibitor, for treating unresectable and metastatic GISTs. However, it should be stressed that a majority of these tumors are nonmalignant and benign, especially those tumors that originate from the stomach. Therefore, a majority of patients with these tumors do not require further treatment following surgery. However, clinical follow-up is generally recommended.

OCCURRENCE and ETIOLOGY (CAUSE)

GISTs are the most common mesenchymal (nonepithelial) tumors of the GI tract, and encompass most tumors previously classified as gastric and intestinal smooth muscle tumors. However, they are much less common than epithelial tumors, adenomas and carcinomas of the GI tract, comprising less than 1 percent of all GI tumors. GISTs typically show up in adults over 40 years (median age 55-60 years). Approximately 10 to 20 percent of these tumors occur in people under 40, but only 1 percent or less in children — practically never before the age of 10. These tumors often occur in old age, and are sometimes diagnosed at age 90 or beyond.

GISTs are equally common in men and women. The cause of GISTs is unknown, as is for most other mesenchymal tumors.

Rarely, GIST occurs as a part of a tumor syndrome. These syndromes are familial GISTs (extremely rare), Carney's triad (GIST, paraganglioma and pulmonary chondroma), and neurofibromatosis 1 (NF1); the latter is the most common GIST syndrome. The NF1 patients with GISTs typically have multiple small intestinal tumors, and severe bleeding can be a life-threatening complication. Patients with familial GISTs have inheritable KIT mutations, but molecular pathogenesis of GIST in the two latter syndromes is unknown. Only a very small portion of GISTs (< 5 percent) are associated with any of these syndromes.

CLINICAL PRESENTATION

GIST can present anywhere in the GI tract, from the lower esophagus to the anus. A majority of them occur in the stomach (60-70 percent) and small intestine (25-35 percent). Colon, rectum, appendix (together 5 percent) and esophagus (2-3 percent) are rare sites. Some GISTs are primary in the omentum, mesentery or retroperitoneum, unrelated to the tubular GI tract, but most GISTs in these sites are metastases from gastric or intestinal primary. Estimates of frequency of malignancy vary; our estimate for gastric GISTs is 20-30 percent, and 30-50 percent for intestinal ones. Malignant GISTs most commonly metastasize to the abdominal cavity and the liver, and rarely in bones, soft tissue and lungs.

The clinical presentation of GIST varies. Up to 30 percent of these tumors are detected as asymptomatic masses and nodules during the diagnosis and treatment of other abdominal conditions. Especially, many of these tumors in the stomach are detected as very small lesions during abdominal

PATHOLOGY

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surgery for other benign and malignant diseases. Common background situations include gall bladder surgery, endoscopic screening for cancer or other pathology, or operation for carcinomas of stomach, colon and kidney. In some cases, the patients or doctors note asymptomatic tumors; a moderate size tumor can sometimes be felt through the skin of a skinny person.

Approximately 70 percent of GISTs are symptomatic. Most commonly they cause gastrointestinal bleeding originating from an ulcerated tumor. This can be gradual and insidious internal bleeding often leading to marked anemia and weakness before the tumor is ultimately detected. In some patients, the bleeding is acute, presenting as black stools (melena), or less commonly as hematemesis (throwing up blood). Some patients have vague symptoms caused by a tumor mass or an ulcerated tumor; in the latter case the symptoms can be similar to gastric ulcer, or in case of malignant GISTs, similar to those of gastric cancer. Intestinal GISTs occasionally cause obstruction. In rare cases, the tumor ruptures inside the abdomen and causes intra-abdominal hemorrhage with acute symptoms. In some cases, large tumors originating from the stomach are clinically thought to originate from the liver or pancreas because of their proximity to these organs.

SUMMARY OF TISSUE PATHOLOGY and DIAGNOSIS

GISTs vary widely in their size and shape, and to some degree, in their microscopic appearances.

They vary from very small (almost always benign) tumors to very large (and often malignant) tumors. Small gastric and intestinal GISTs are often found as a small nodule on the external surfaces of these organs. Many tumors involve the entire wall, and some extend internally as polyps, and others externally sometimes being attached

only by a narrow pedicle. Ulceration is common in GISTs of all sites, and is not related to tumor malignancy. Calcification is relatively rare and is usually seen in small tumors. The larger tumors are often microscopically or grossly cystic, and the contents of larger cysts vary from clear fluid to dark-brown material.

The microscopic (histologic) features of GIST vary, and to some degree this variation is site-dependent, the gastric and intestinal tumors being somewhat different. Most commonly, GISTs have a spindle cell pattern composed of elongated, tapered cells (60-70 percent), whereas epithelioid cytology with polygonal cells is seen in 20-30 percent of cases exclusively or focally, and pleomorphic (atypical, anaplastic) pattern rarely (< 5 percent).

SPECIFIC DIAGNOSIS of GIST

The diagnostic specimen can be a needle biopsy, endoscopic biopsy, open biopsy or resection specimen. Needle biopsy is sometimes obtained before surgery of primary tumor, and it is the usual specimen type obtained from metastasis. Endoscopic biopsy is often successful in diagnosing an ulcerated GIST, but tumors that haven't ulcerated are usually inaccessible by endoscopic biopsy. Open biopsy during laparoscopy or laparotomy is sometimes obtained from larger tumors, and it may be submitted for rapid (frozen section) diagnosis during surgery. Resection specimen is the one originating from the definitive surgery. This can be a small or large resection of stomach or intestines, depending on the location and extent of the tumor, as required for complete tumor removal.

The histologic features of GIST include spindle cell or epithelioid morphology. Mitotic activity is the key parameter to determine biologic potential, and is typically expressed as mitoses per 50 high power fields. GISTs are typically immunohistochemically

KIT-positive, as determined from tumor tissue sections via a somewhat complex sequence of a laboratory procedure. This is a major diagnostic feature of GIST and has generally been a requirement for entering into clinical trials. This may change, if mutation status and alternative PDGFRA involvement are being considered. In summary, the diagnosis is based on the combination of histologic, immunohistochemical, and possibly analysis of KIT and PDGFRA mutations.

The second part of this article will be published in the next newsletter.

About the authors: Pathologist Markku Miettinen, 51, is the chairman and distinguished scientist of the Department of Soft Tissue Pathology of the AFIP where he's worked since 1996. His current research focus is GIST pathology. He worked eight years as a pathologist in Thomas Jefferson University Hospital in Philadelphia, Penn., and 10 years at the University of Helsinki, Finland, his native country. Jerzy Lasota, 47, has been a pathologist at the Department of Soft Tissue Pathology since 1996. He currently specializes in molecular pathology of GIST, and is responsible for the department's laboratory. He did seven years of cancer research in Kimmel Cancer Center/Department of Pathology and the Fels Research Institute in Thomas Jefferson and Temple Universities in Philadelphia, and seven years in the Medical Academy of Lodz, Poland, his native country. Together the authors have published more than 30 scientific articles on gastrointestinal stromal tumors.

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Darlene Vaughan was an early Gleevec success story

Darlene Joyce Vaughan, 61, one of the “miracle patients” whose clinical trial experience helped speed government approval of Gleevec, died April 25 in Mesa, Ariz.

Vaughan was one of the handful of clinical trial patients profiled in the book, “Magic Cancer Bullet,” written by Dr. Daniel Vasella, chairman and chief executive officer of the pharmaceutical company Novartis. She had been given just days to live when a single 100 mg. capsule of an experimental drug called STI571, now Gleevec, pulled her back from the brink and started her on the road to remission.

Vaughan was born Oct. 3, 1942, in Pasadena, Calif. She studied at California State University in Long Beach before starting her career in business and project management in the aerospace industry.

Married briefly in her 30s, she traded the big city and the corporate world for

Pueblo, Colo., where in 1994 she opened a coffee house and café in a historic building that had once housed a brothel.

She was diagnosed with leiomyosarcoma in 1998 and underwent surgery, then radiation treatment and another surgery. She also put herself on an intensive regimen of vitamins, supplements, exercise and meditation, and sold her business and the building.

In 2000, she tried an experimental antiangiogenesis, SU-6668, then a traditional chemotherapy, Dacarbazine (DTIC). That October, her friend Anne Murphy showed her an e-mail from Norman Scherzer, a member of the ACOR listserv for leiomyosarcoma. Anne had joined the list on Darlene’s behalf. Norman was urging people to check their pathology since their lei-



VAUGHAN

omyosarcoma might actually be GIST — and an experimental drug was proving amazingly effective against GIST.

By the time Darlene took her first capsule of STI571, she was near death. In the UCLA Medical Center for days, she no longer qualified for the trial but was given Gleevec on a compassionate use basis.

The afternoon of March 5, 2001, semiconscious, she took her first dose of STI571 — one 100 mg. capsule. Her weakened body couldn’t tolerate anything more.

The next morning, she was able to converse with friends. Within 24 hours, she had regained her faculties and the doctor told her she looked “fantastic.”

Darlene was soon released from the hospital. Within two months after starting the drug, her tumors had shrunk 47 percent. She had become a poster child for the drug that would be called Gleevec, and give her three more years of life.

Fourth annual Walk for a Cure set Oct. 10 in Congers, N.Y.

The GIST Cancer Research Fund has set a date for its cornerstone fund-raising event, the fourth annual Walk for a Cure. This year’s walk will be held Sunday, Oct. 10, at 10:12 :30 a.m. at Rockland Lake State Park in Congers, New York.

This year’s walk will honor the late Dean Gordanier of Cambridge, Mass.

Dean was an attorney, member of the choir of the First Church in Cambridge, and a GIST patient. He helped blaze new trails for all GIST patients with his participation in both the Gleevec and Sugen (SU11248) clinical trials. He also gave generously of his time, sharing his experience, knowledge, wit and wisdom with others, privately and through the Life Raft and GIST Support International groups.

Last year Dean made sure fellow GIST patient Dr. Mel Heller was at the third Walk for a Cure. Dean flew from his home in Massachusetts to Heller’s home on Chesapeake Bay, Maryland, then drove the octogenarian to the walk in Congers, New York. After meeting and socializing with the many other GIST patients, Dean drove his new friend back to Maryland and then flew back to Massachusetts — all in the same day.

Sadly, Dean lost his battle with GIST in February of this year.

The GIST Cancer Research Fund, started five years ago by Tania and Robert Stutman, has raised more than \$130,000 to date and provided GIST cancer research grants to Dana-Farber Cancer Institute in Boston, Mass., Fox Chase Cancer Center in Philadelphia,

Penn., Memorial Sloan-Kettering Cancer Center in New York City, and Oregon Health & Sciences University in Portland. Ninety-seven percent of all money raised has gone directly to GIST cancer research. Dr. Ephraim Casper of Memorial Sloan-Kettering is a director of the GIST Cancer Research Fund.

Last year’s walk drew GIST patients, caregivers, family and friends from all parts of the country. The same is expected this year, with people as far away as California and Georgia having already made plans to participate.

For more information, contact Tania or Robert Stutman via e-mail at Tania5kids@aol.com; phone (845) 634-6060, or by mail to: GIST Cancer Research Fund, 55 Saw Mill Road, New City, NY 10956.

Sid Locker, 76, was WWII veteran, student counselor

Sidney Locker of Willowbrook, on Staten Island in New York state, a World War II veteran and retired Port Richmond High School guidance counselor, died April 26 at Staten Island University Hospital. He was 76.

“Despite having four separate cancers (three cancers other than GIST), Sid was a fighter,” said his wife, Millie. “He was courageous and strong and never gave up hope during his 14 years of tests, surgeries and doctor visits. Sid’s perseverance and strength was a model for many of the patients he encountered.

Born in Manhattan and raised in Brooklyn, he settled in Willowbrook in 1967 with his wife and three children.

After graduating from Abraham Lincoln High School, Brooklyn, Mr. Locker entered the Navy and served during World War II.

Following the war, he received his bachelor’s degree in history and his master’s degree in education from Brooklyn College. Mr. Locker continued his education at the former Richmond College, receiving creden-



Sidney Locker is survived by his wife of 48 years, Mildred.

tials in counseling.

For more than 20 years, Mr. Locker worked as a teacher at Abraham Lincoln High School and as dean of boys at Grady High School, Brooklyn. He then worked as a counselor at Port Richmond High School for more than a decade before retiring in

the late 1980s.

For several years after retiring, he worked as a counselor for Auxiliary Services for High Schools.

Mr. Locker was a member of the Association of Teachers of Social Studies, the New York City Guidance Counselors Association, the New York State United Teachers, the American Federation of Teachers and the United Federation of Teachers (UFT). He was honored by the UFT as an outstanding teacher.

Mr. Locker enjoyed sculpting, painting and photography. He was also an avid reader and a history buff. He was a member of Congregation Temple Emanu-El, Port Richmond.

He is survived by his wife of 48 years, the former Mildred Riter; his son, Paul; his two daughters, Felice Fenwick-Smith and Emily Goldsmith; a sister, Bea Luft, and three grandchildren.

Mrs. Locker voiced her family’s appreciation for everyone in the Life Raft Group for their e-mails, advice and support, especially Norman Scherzer.

Life Raft directors focus on resistance at Orlando meeting

Eighteen Life Raft Group members attended the April 30 meeting of the Board of Directors meeting in Orlando, Florida. Five of the seven board members were there along with Life Raft staff.

The theme of the meeting was that “the time for action is now.” An increasing number of GIST patients are encountering resistance on Gleevec and the LRG must expand its efforts now to address that reality. That will mean more dollars and greater efforts to find and implement answers.

Board members voted to amend the

Life Raft Group bylaws to allow up to 11 members to serve on the board, and to redefine a meeting quorum as a majority of those present as opposed to a majority of the total number of board members.

The board also agreed to continue quarterly meetings, alternating between in-person meetings and those via teleconference. Board members also decided to purchase “key man” insurance for the executive director to ensure continuity, and to open board membership to other than GIST patients and caregivers.

Some key dates to remember:

June 11 - Chicago area Life Raft Group meeting;

June 14 - Patient Group Summit meeting, Milan, Italy;

June - Los Angeles area Life Raft Group meeting;

August - LRG Board of Directors meet;

Oct. 10 - The Fourth Annual Walk for a Cure for the GIST Cancer Research Fund, New York;

Oct. 22 - Das Lebenshaus meets, Frankfurt, Germany;

Nov. 11 - Connective Tissue Oncology Society conference in Montreal, Canada.

From planning to socializing at Life Fest



From serious talk to meeting online friends, Life Fest had something for everyone. At left, talking finances are John Poss, left, and Chris Carley. In photo at right, sharing a happy moment are Jeanne Book, left, and Nancy Welsh.



SURVIVOR

From Page 1

He told me it was quite normal considering everything I was undergoing. He recommended me to a colleague who promptly prescribed anti-depressant medicine.

After two weeks off all cancer medicine, I went back up to Boston and took the tests to see if I was acceptable for the new Sugem drug. I passed the exams and was supplied with the medicine. I was told, however, as we all know, that one of every three patients in this trial receives a placebo to test the effectiveness of the drug. This meant that the tumors in my abdomen would continue to grow if I had been given the placebo.

I was in total despair. I believed my end was near. I could barely walk and couldn't get out of a chair without the help of my wife. I had no appetite and lost more than 30 pounds in a few weeks. I was having pains from the rock-hard tumors as they grew, pressing on my kidneys. One tumor was sticking out from my stomach like the end of a pencil.

A few weeks later the doctors in Boston again examined me. When they were done, my son and I walked to the parking lot to return to New York. As we got into the car, my cell phone rang. It was

the nurse. She asked me if I was still in Boston because the doctors had decided they wanted me to have a CT scan immediately to determine the exact tumor growth. We ran downstairs, met the doctor in the lobby, and went in for the CT scan. We returned to New York late that night.

The next morning we received a phone call from Dr. George Demetri. He told us that he had decided to ask the drug company to break the code because of the growth and let him know if I was on the placebo or the real drug.

The next evening at 6 we received another phone call from Dr. Demetri. He said he would know by 10 p.m. if I was on the placebo. If I was taking the placebo, he said, then we should immediately travel to Boston to meet him in the early morning.

Can you imagine the situation? My wife and I were praying to God that I was on the placebo, not the real drug!

An hour later the phone rang again. My wife answered the phone and shouted to me to pick up the extension. My life was literally on the line. Dr. Demetri said, "Bernie, thank God, you're on the placebo, get up here as soon as possible!"

I think my wife's responding shout could have been heard across the world. Within 20 minutes we were in the car and on our way. We stopped at my sister-in-law's a few blocks away and picked up some supper for the ride to Boston. For the first time in four weeks I had some appetite and was able to eat a little.

We saw the doctor the next morning at 8 and he gave me the real drug. I was so dehydrated that he also put me on an IV.

I am happy to report that now, 12 weeks later, the real drug is doing its job. My stomach is much softer, the pencil-like tumor has receded and the pains near the kidney have significantly diminished. In addition, the small tumors are hardly visible and many of the larger tumors have shrunk 40 percent!

What the future will bring, only God knows. The good doctors in Boston helped save my life. I had faced death and collapsed. For three years I had been strong but I had reached my limit, notwithstanding the vision. I am slowly regaining my strength and have even gained some weight, but I will never be the same. One of my sons said to me that when one rebuilds, you sometimes turn out stronger. I hope he is right.

THE LIFE RAFT GROUP

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Who are we, 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. Many 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. 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.

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