Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

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Fifty-one weeks from diagnosis to remission

Gleevec, surgery, family, friends, and prayer key to a new lease on life

By Rebecca A. Haines

Mid-year 2003, I thought I had an ulcer. Anti-ulcer medications seemed to help until year's end. A visit to the primary physician and a referral to a gastroenterologist set me up for an endoscopy. Although this wise diagnostician admitted that he'd never seen a GIST, or gastrointestinal stromal tumor, he said it was a real possibility. His biopsy, however, was "inconclusive."

HAINES

Eventually, I went for an ultrasound endoscopy and biopsy. This time the diagnosis was confirmed with a positive c-kit test Feb. 13, 2004. The softball-sized tumor was in the top part of my stomach, near the esophagus.

I saw a gastric surgeon, who basically said the tumor was large to try to remove, and suggested that we shrink it with an oral chemotherapy pill. I met with an oncologist March 1, who talked to me about Gleevec. I agreed to try it with the hope of surgical removal in the future.

Over time, my personal treatment plan evolved to include the best the Seattle, Wash., area can offer. It included walking and swimming for exercise and fun, lots of good nourishment, high calorie foods to keep my

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SU11248 works, trial ends 7 months early

Patients on placebo can switch to real SU11248

GIST patients and their doctors may have another weapon in their arsenal in the not-too-distant future. The phase III trial of SU11248 was stopped early after proving it works, through the Pfizer drug must still win government approval before it can be prescribed.

In the meantime, patients who might benefit from SU11248 can receive the drug through a "treatment use" protocol set up by Pfizer.

SU11248 is similar to Gleevec in the way it works. It is a small molecule inhibitor of the receptor tyrosine kinases PDGFRA, VEGFR, KIT and FLT3.

For patients with KIT or PDGFRA mutations, the main targets of this drug are still KIT and PDGRFA. SU11248 also inhibits VEGFR. This provides an anti-angiogenic effect in addition to the primary anti-tumor effect. All tumors need new blood vessels (angiogenesis) in order for tumor growth to occur; treatments that block the growth of these new blood vessels are called "anti-angiogenesis" treatments.

DEMETRI

SU11248 is proving to be effective for about 65 percent of GIST patients for whom Gleevec fails, according to interim data presented by Dr. George Demetri at the 2004 American Society of Clinical Oncologists (ASCO) meeting. Demetri is the director of the Center for Sarcoma and Bone Oncology at Dana-Farber Cancer Institute in Boston.

On Jan. 29, Demetri posted the following message to the global GIST community: "... The data monitoring board (a team of experts separate from the investigators involved in a research study) met this week to evaluate the data obtained to date from the global phase III randomized study of SU11248 for patients with GIST for whom Gleevec was not able to control the disease.

"This data monitoring board ... has now recommended that this trial can stop immediately due to having successfully met its efficacy endpoint. We have sent out a letter worldwide to

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weight up, family and social support, meaningful work, guided imagery, humor and prayer. I wanted to cover as many bases as possible.

In March, I was at my weakest. I only read paperback books because hard-backed ones were too heavy to hold! Gradually, I began to feel better and stronger as I continued with Gleevec.

I had monthly check-ups and CT scans every three months. Some shrinkage occurred but not much. Finally, after eight months, the oncologist decided that the results from Gleevec had stabilized, with little additional shrinkage expected. Time to re-visit the surgeon.

He said it would be a "de-bulking" procedure. He told me that a total gastectomy and probable splenectomy would be necessary to remove the tumor. I'd probably need a feeding tube until I could maintain my own weight with a pouch-like stomach shaped from part of my intestines.

Quite invasive, but I agreed to it. There didn't seem to be any alternative. My surgery was set for Nov. 30, 2004. I had family, church, and social support on board since the diagnosis. Now I really needed their support and prayers.

I arranged time off from work. I readied myself for the surgery. I listened to a guided imagery CD for cancer patients. It helped me feel calm, accepting and positive about the surgery. I managed to gain a few extra pounds before surgery. In June, I'd started swimming a half-mile every week and thought that would speed my recovery.

I spent the night before surgery at my son's house. He and his wife live near the hospital. That lessened the worry about traffic or arriving late. When the time approached, I felt an urgency to get to the hospital. I wanted to get on with it.

Photo courtesy Beth Bennett

Rebecca Haines, right, is seen with daughter, Beth Bennett, and granddaughters Maddy, left, and Lexi. This photo was taken 10 days after Rebecca's surgery.

We arrived in plenty of time. My daughter also arrived before they swooshed me away to a pre-operative area. I traded my clothes for the bare-back hospital gown we all know. Then my children joined me. We had a Reader's Digest and were reading the jokes and guessing the word meanings. Soon, it was time to say goodbye to my family and tell them I love them. I also said that I knew the surgery would ago well.

Before they rolled me into the operating room, the surgeon came to see me. I told him that many people were praying for his wisdom during the procedure, and for a positive outcome. I added that I knew the surgery would turn out all right. Then it was time.

I remember the operating staff busy with their preparations. I heard them counting sponges and such things. They told me I'd be going to sleep.

That's all I remember until I awoke about five hours later. I still had my stomach and spleen. The tumor was gone. I didn't need a blood transfusion. I didn't need a feeding tube.

Later, the surgeon explained that the orange-sized tumor peeled away from the walls of the spleen and the stomach, except for small area of the stomach, which he removed. However, he said he thought he saw spots of tumor cells remaining in my stomach.

He'd explained his reasoning before surgery: Chemotherapy has a better chance against 100 cells after surgery than 1,000 cells before surgery. Therefore, he decided to leave my stomach intact, to enhance my quality of life. I think he showed both wisdom and grace.

As soon as I could tolerate food, I resumed Gleevec. The hospitalization is partly a blur, partly vivid observations. I treasure the moments when someone met a need, eased a pain, gave me a warm blanket. I especially appreciated the nurses who silenced the obnoxious beeping of the IV machine! One nurse told me where there were nice places to walk around the hospital, which my son and I enjoyed. Another nurse gave me the greatest cap with shampoo in it to wash my hair while in bed!

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Photo by Tricia McAleer

At the pediatric GIST meeting held Feb. 9 at Memorial Sloan-Kettering in New York were, from left, Dr. Leonard Wexler, Dr. Mary Louise Keohan, Dr. Cristina Antonescu, Michael LaQuaglia and Pamela Merola; LRG Executive Director Norman Scherzer, Dr. Larry Engel, and Life Raft Group members Raymond Montague and Dorothy and Brian McBride

Pediatric GIST families to meet in New York

Leading specialists will discuss treatment plans

The Life Raft Group will host the first meeting of pediatric GIST families the weekend of May 20 in the New York City area.

All pediatric GIST families are invited to attend. The event will allow both adults and children to get acquainted, attend some social events planned in New York City, and meet leading medical specialists to talk about treatment plans.

"In addition to leading medical specialists such as Dr. Cristina Antonescu, Memorial Sloan-Kettering pathologist, we have invited Tania Stutman and her husband, Robert," said Norman Scherzer, Life Raft executive director. "We hope the Stutman's GIST Cancer Research Fund will play a key role in the development of pediatric GIST research."

Ray and Sheila Montague, whose son died of GIST, and Brian and Dorothy McBride, whose daughter helped spearhead a fund-raising campaign for pediatric GIST this past year, are helping to plan the event.

This family gathering advances the ongoing campaign of the Life Raft Group to address the special needs of pediatric GIST patients. In November 2003, an initial meeting was held with key staff at Memorial Sloan-Kettering to discuss the development of a center for excellence for pediatric GIST (see November-December 2003 newsletter). One year ago, the Life Raft Group began developing a pediatric GIST database, now the largest in the world. Last November, we put our database online and then hosted the first-ever international meeting of GIST experts from the United States, Canada, the United Kingdom and the Netherlands to address the issue of pediatric GIST (see November-December 2004 newsletter). Last December the Life Raft's newly formed pediatric GIST families committee met (see the January 2005 newsletter).

Life Raft members met again Feb. 9 with Memorial Sloan-Kettering staff, including Drs. Cristina Antonescu (pathology), Larry Engel

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SU11248

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the global team of SU11248 investigators so that they can get in touch with all of the patients on this trial and allow patients to obtain unblinded SU11248 immediately [a third of the participants were randomly assigned to a placebo]."

The trial's early conclusion, Demetri said, "should be a very positive step towards establishing beyond any doubt another therapeutic option for patients with GIST using a novel molecularly-targeted agent if Gleevec proves inadequate to control the disease."

Demetri thanked the "selfless" patients and caregivers who supported the trial, "so that we could prove to any regulatory agency the value of this new therapy and thereby quickly make this agent available to patients and their physicians who wish to offer them the best care and the most effective options.

"I am also tremendously indebted to the global network of collaborators and the team that has made this positive study a reality. We must never stop in our quest to understand and defeat this disease, and to learn from GIST lessons that will be useful to improve the therapy of other cancers as well."

In a Feb. 1 follow-up e-mail, Demetri answered some of the questions asked by GIST patients. Most were about how patients can get SU11248 while Pfizer is awaiting government approval.

"First, please rest assured that our global study team will be working with all due diligence and speed along with the study sponsor, Pfizer, to collect and fully analyze the study data and discuss these data with regulatory agencies worldwide," Demetri said.

"Second, while the data are being analyzed and evaluated fully, patients with GIST for whom Gleevec is no longer effective will be able to access SU11248 through the treatment use programs that are open at sites internationally.

With several sites now open and more opening each week, "the best thing to do would be to contact either Dana-Farber's Sarcoma Center, (617) 632-5122, or the SU11248 Information Service at (877) 416-6248 toll free," Demetri said, to find the nearest site.

"I hope this helps to address several of the concerns I have seen in e-mails and phone calls from many concerned individuals," said Demetri. "Please let me know if there is anything else we can do at this early stage to help allay concerns and address questions."

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Why SU11248 works when Gleevec fails

In his presentation last June at the 40th annual meeting of the American Society of Clinical Oncology, Dr. George Demetri speculated on why Pfizer's SU11248 works where Gleevec fails:

— SU11248 could interact differently with structural variants of new kinase mutants in GIST clones resistant to Gleevec.

— The simultaneous inhibition of multiple signaling pathways (such as VEGF, in addition to PDGFRA and KIT) by SU11248 may be important for controlling GIST.

Mutations in the c-kit gene (85-90 percent), or a closely related gene, PDGFRA (5 percent), appear to be the primary genetic defects that cause GIST. Mutations typically occur in exon 11 (67 percent) or exon 9 (18 percent) of the c-kit gene.

One of the most common forms of resistance to Gleevec appears to be the acquisition of a second mutation in the c-kit gene. In these cases, in addition to the initial primary mutation (typically in exon 11 or exon 9), a second mutation occurs in some tumors. These secondary mutations typically result in resistance to Gleevec.

Secondary mutations have been reported in exons 13, 14, 15, and 17 of the c-kit gene. While surgery or other intervention, such as radiofrequency ablation (RFA), may be a way to deal with some of these rogue tumors, these approaches may not be feasible due to location, size or other problem.

SU11248 appears to have activity against at least some of these secondary mutations. At the ASCO meeting, Demetri reported that tumors with secondary KIT mutations in exons 13 and 14 were "highly sensitive" to SU11248, with a 56 percent of patients benefiting. Of 16 patients, two had a "RECIST response" (significant shrinkage), and nine had stable disease for at least six months.

Demetri found that patients with secondary KIT mutations in exon 17 were less sensitive to SU11248. In this small group, three of eight patients (38 percent) had stable disease lasting at least six months, but there were no RECIST responses.

Treatment with Gleevec is typically more effective in patients with an exon 11 mutation and somewhat less effective in patients with an exon 9 mutation.

Interestingly, SU11248 appears to have the opposite activity profile, at least in Gleevec-resistant patients. In these patients, it appears to be more effective in those with exon 9 mutations, with a 40 percent RECIST response and another 40 percent achieving stable disease. It appears to be less effective in Gleevec-resistant patients with exon 11 mutations.

Patients without KIT or PDGFRA mutations (called "wild-type" KIT/PDGFRA), are another group of GIST patients that typically do not respond to Gleevec but seem to benefit from SU11248. In the small group reported at ASCO, four of nine patients had stable disease for at least six months, and one had a RECIST response.

Leukemia researchers strive for a cure

CML research may have implications for GIST

By Jerry Call
Life Raft Group science coordinator

Why is cancer so hard to treat and why does it return even after all visible signs are gone? Some researchers trying to answer these questions believe that cancer stem cells may be "the roots" that feed at least some cancers.

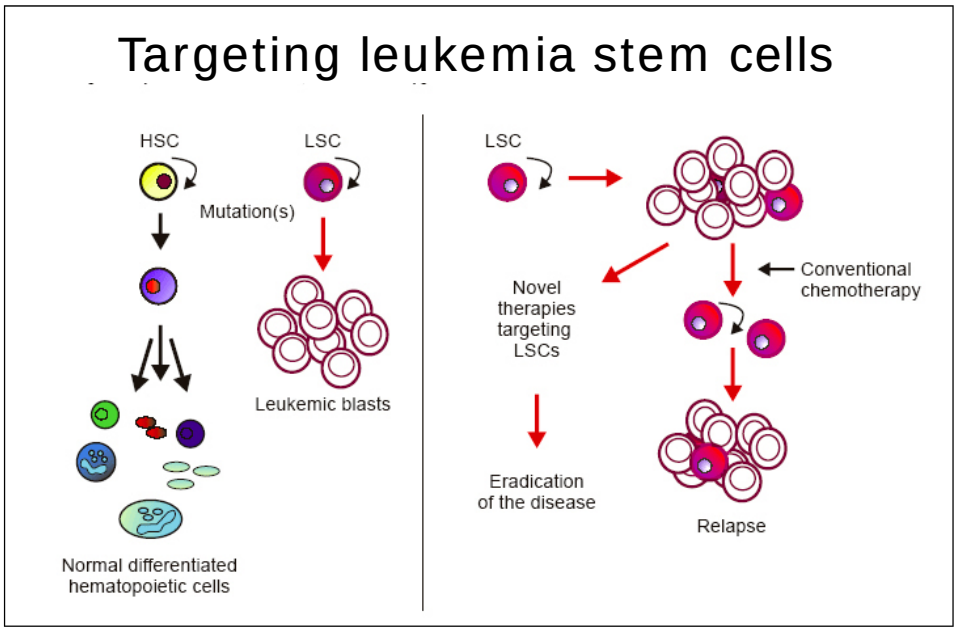
Cancer researchers have several competing visions of tumors. In one vision, all tumor cells are pretty much the same, or closely related, and have an equal capacity to divide and form new tumors. In a second vision, only a few cells have the capacity to initiate new, full-fledged tumors. These "bad seeds" are "cancer stem cells." Some researchers would probably add a third vision, a "clonal vision," where groups of cells descend from a common clone, and the cells that make up a clonal group all behave similarly, but different clonal groups may behave differently.

What are stem cells, and why are they so important? There are several different types of stem cells in adults, including hematopoietic stem cells, mesenchymal stem cells, neural stem cells, epithelial stem cells and skin stem cells. All stem cells — regardless of their source — have three general properties: they are capable of dividing and renewing themselves for long periods; they are unspecialized; and they can give rise to specialized cell types — for instance, hematopoietic stem cells are capable of producing all of the different types of blood cells. When needed in adults, stem cells are able to re-supply the body with many different types of tissues.

Finally, stem cells often exist in a quiescent state, meaning that the cells are not dividing. Quiescent, non-proliferating cells are insensitive to traditional chemotherapy that kills fast-growing cells. Some believe that these quiescent cells may be resistant to Gleevec as well.

Some leukemias, including chronic myelogenous leukemia (CML), acute myelogenous leukemia (AML) and some solid tumors, including brain cancers and breast cancers, have been shown to originate from cancer stem cells. The March 2004 issue of Science News magazine reported on the work of John E. Dick from the University of Toronto. A decade ago, Dick led a research team that showed that only some cancer cells from leukemia patients could reproduce leukemia in rodents. Science News also cited the work of Michael F. Clarke of the University of Michigan Medical School, who reported similar results for breast cancer cells. Clarke found that perhaps one in 100 breast cancer cells forms tumors when implanted into mice.

In 2003, two research teams presented evidence that cancer stem cells underline brain tumors as well. "I think the cancer stem-cell hypothesis will apply to every kind of cancer," Dick told Science News.



Monica L. Guzman, Ph.D., and Craig T. Jordan, Ph.D. Reproduced with permission.

The leukemic stem cell (LSC) model at left proposes that leukemic blasts originate from a common primitive progenitor that has the capacity to self-renew. Conventional therapy regimens for leukemia, right, have been designed to eliminate leukemic blasts. These regimens may not effectively ablate the LSC population, which eventually regenerates the disease. The ability to design therapies that can target LSCs should yield more effective eradication of the disease.

Researchers studying CML and AML are finding ways to target their respective stem cells. Craig T. Jordan, Ph.D., of the University of Rochester, and Monica L. Guzman, Ph.D., have suggested that in AML conventional chemotherapy kills the leukemic blast cells (the progeny of the leukemic stem cells), but does not kill the leukemic stem cells (the parent cells). While this provides initial control of the disease, patients relapse as the leukemic

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STEM CELLS

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stem cells repopulate the leukemic blast cells.

Since these leukemia blast cells greatly outnumber the stem cells, response to treatment is almost always measured by a drug's effect on the blast cells. Thus, while treatments often reduce the bulk of disease, they often fail to target the rare stem cells that many researchers feel must be killed to prevent recurrence of the disease. It is very difficult to assess the effect of treatment on these stem cells because they are so rare.

Guzman, Jordan and others have suggested that in addition to targeting the bulk of the disease, stem cells must be targeted to prevent relapse. They have found that leukemic stem cells in AML are dependent on a survival protein, NFkappaB, while normal hematopoietic stem cells are not. They devised a strategy where they stress these cells with idarubicin, a traditional chemotherapy, while at the same time inhibiting the survival protein, NFkappaB, by adding a "proteasome" inhibitor, MG-132. This strategy of stressing the cell and at the same time inhibiting an important survival protein worked well in the lab.

CML and GIST have so far proven remarkably similar in their biology, treatment with drugs, and resistance mechanisms. If you want to know what's going to happen in the GIST world, sometimes you can look at what's happening in the CML world. The existence of a primitive quiescent stem cell population that is resistant to Gleevec has been detected in CML. It is speculated that failure to eliminate this stem cell population may be why Gleevec eventually fails some patients.

A recent paper, "Punish the Parent, Not the Progeny" by Lucy J. Elrick, Heather G. Jorgensen, Joanne C. Mountford, and Tessa L. Holyoake, from the University of Glasgow, extends the cancer stem cell theory to CML. These researchers noted that a small population of quiescent leukemic cells exists in CML patients and this population cannot be eliminated with Gleevec. These cells remain after Gleevec therapy, even when apparently complete responses are achieved, and probably explain molecular disease persistence.

"The emergence of drug resistance with imatinib (Gleevec) monotherapy also argues in favor of complete disease eradication that we believe should remain the ultimate therapeutic goal in CML," noted the authors. New approaches to the elimination of these primitive CML cells may thus be crucial to the development of curative strategies."

Several theories have been proposed to explain why Gleevec doesn't kill these cells:

— A greater role for multi-drug resistance proteins.

— The quiescent state of the cells

— Pre-existing kinase mutations.

— Unknown mechanisms?

The Glasgow researchers, led by Dr. Tessa Holyoake, seem to get a little more speculative on their Web site (as opposed to their paper) about why the quiescent CML stem cell population might be insensitive to Gleevec.

"Indeed, we have demonstrated that, in vitro, quiescent CML stem cells are completely insensitive to imatinib at concentrations up to 10-fold higher (10mM) than those achievable in vivo, whilst proliferating cells are exquisitely sensitive to less than 1mM. One possible explanation for these findings is the conformation of the Bcr-Abl kinase in the quiescent versus proliferating stem cells. Recent studies suggest that Bcr-Abl conformation is absolutely critical for imatinib binding and function. Active Bcr-Abl is in an open (non-accessible) conformation, thus sensitivity to imatinib in CML is presumed to result from a dynamic switch between open and closed conformations possibly linked to cell cycle progression. This switch may not be triggered in quiescent cells; hence, imatinib may not be the optimal choice of agent to eradicate this population. A new generation of combined Src/Bcr-Abl kinase inhibitors that do not appear to be conformation sensitive and are 10-20-fold more potent than IM is now available and should therefore be more effective than imatinib."

This new generation of Src/Bcr-Abl inhibitors mentioned on the Glasgow University Web site includes the new Bristol-Myers Squibb drug, BMS-354825. If the Glasgow research group's theory is correct, then BMS-354825, or a similar drug, might be able to kill the resistant CML stem cells. It is interesting to note that in mouse models of CML, BMS-354825 is curative over a 40-fold dose range, while Gleevec is not curative, even at the maximum tolerated dose. If correct, this theory has implications for GIST — *if* both the active and inactive forms of KIT or PDGFRA are inhibited by BMS-354825, *and* residual quiescent tumor tissues that are still viable after treatment with Gleevec have activated KIT due to an active kinase formation. (this would be true whether or not the residual tissue had a stem cell origin or a clonal origin).

If the theory that quiescent cells have an active kinase conformation and are therefore resistant to being killed by Gleevec is correct, it would present a number of interesting questions:

— Could a drug that inhibits both the active and inactive kinase conformation have better efficacy than Gleevec? Could it be curative in some cases if used as front line treatment?

— In some patients with stable disease, are there tumors that are in a quiescent state, and therefore resistant to

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Gastric GIST behaves better than expected

Pathologists find more people survive longer with gastric disease

By Dr. Markku Miettinen
Armed Forces Institute of Pathology

For GIST patients and their doctors, the projected behavior of gastrointestinal stromal tumors is a critically important issue. One particular question that comes up often is what might be the benefit of using drugs such as Gleevec as preventive treatment following surgery for primary tumors. Some older studies had suggested that most GISTs tumors are uniformly aggressive with high tumor-related mortality (death due to tumor). However, the possibility of better behavior of gastric GISTs, as opposed to GISTs originating elsewhere in the body, has been occasionally suggested.

In our recently published study

MIETTINEN

(Miettinen M, Sobin LH, Lasota J, Am J Surg Pathol 2005;29:52-61), we analyzed more than 1,000 patients with gastric GISTs with long-term follow-up. Essentially all were prior to the Gleevec era. GIST was defined in this study as a KIT-positive tumor, with a provision for KIT-negative cases (including PDGFRA-mutants). Gastric GISTs comprise approximately 60 percent all GISTs.

The overall tumor-related mortality for gastric GISTs was 18 percent. The tumors could be stratified into prognostically significant groups by tumor size and mitotic activity. The sample size given below refers to the number of patients with full follow-up. Tumor-related mortality shown below refers to death due to tumor (GIST). The number of these patients has been combined with the number of the patients living with metastatic disease, both groups together representing patients with progressive disease. Because gastric GISTs often occur at an older age, (median age 60 to 63 years) many patients die of unrelated causes during long-term follow-up.

Summary of tumor-specific mortality by size and mitotic activity:

— Small tumors 2 cm. or less with low mitotic activity (no more than 5/50 high power fields, or HPF) had no tumor-related mortality (sample size: 76).

— Relatively small tumors, 2 to 5 cm., with low mitotic activity (see above definition) had a very low tumor-related mortality/metastatic rate, less than 2 percent (sample size: 320).

— Moderate size tumors of 5 to 10 cm. with low mitotic activity (see above definition) had a low tumor-related mortality/metastatic rate of 4

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apoptosis?

— What is the right drug or drug combination for adjuvant therapy?

— Are researchers getting not only Gleevec-resistant tissue, but also residual viable tissues from patients responding to Gleevec?

One of the biggest challenges facing cancer stem cell research is the ability to separate the suspect cancer stem cells from the overwhelming majority of non-stem cell cancer cells. As hard as this is in leukemia, it is even more difficult in solid tumors like GIST.

A Jan. 20 article on the NewScientist.com Web site describes new tests to identify cancer "ringleaders." New techniques to do this have been developed at the University of Cambridge, U.K., and Kumamoto University, Japan, and have been licensed for commercialization to Stemline, a biotechnology company in New York.

"Once we have eradicated the cancer stem cells, in essence we have destroyed the engine responsible for treatment failure and disease recurrence, the major problems for fighting cancer," says Ivan Bergstein, chief executive of Stemline.

It seems evident that there are at least two target populations in GIST and most cancers: those tumors/cells that respond to treatment (which often form the bulk of the tumors), and those that don't respond to treatment. Proponents of a clonal vision of cancer might argue that there are many different target populations, each representing a different clone, and therefore each might require a separate drug or drug combination. The heterogeneity noted in GIST tumors to date might argue for the clonal vision. Whether these non-responding tumors/cells have a stem cell origin or a clonal vision, they still form a separate, often much smaller, population, and the effect of a drug is typically measured by its effects on the larger population. A drug or drug combination that might work perfectly on a second or third, smaller, population could appear to have no effect because response would be measured on the larger population.

Norman Scherzer, Life Raft Group executive director, contributed to this report

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(epidemiology), Mary Louise Keohan (adult sarcoma/GIST specialist), Michael LaQuaglia (pediatric surgery), Pamela Merola and Leonard Wexler (pediatric oncology). All renewed their commitment to support pediatric GIST research and to expand the scope of the Life Raft Group database to include a genetic patient profile. Dr. Antonescu offered to test pediatric GIST tissue free of charge.

Memorial Sloan-Kettering also agreed to create a pediatric GIST review board to ensure the coordination of every relevant discipline in ongoing clinical management and to help expand the knowledge of pediatric GIST. Finally, those at the meeting agreed to work together to pursue future clinical trials of new drugs for pediatric GIST patients not responding to Gleevec.

Life Raft Group's Norman Scherzer speaking to Dr. Larry Engel, Memorial Sloan-Kettering epidemiologist, about proposed GIST epidemiological study.

GASTRIC GIST

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percent (sample size: 229).

— Large tumors greater than 10 cm. with low mitotic activity (see above definition) have a relatively low tumor-related mortality/metastatic rate of 11 percent (sample size: 140). The malignant potential of this group had been previously overestimated.

In all, patients with gastric GISTs with low mitotic activity (no more than 5 mitoses/50 high power fields) have a low, 4 percent tumor-related mortality/metastatic rate (sample size: 765).

However, patients with gastric GISTs with mitotic activity greater than 5/50 high power fields had a 51 percent tumor-related mortality/metastatic rate in average (sample size: 320). The outcome was size-dependent in the following manner:

— Small tumors less than 2 cm. with elevated mitotic rate turned out to be extremely rare, but no patient developed progressive disease (sample size: 6).

— Relatively small tumors 2 to 5 cm. with mitotic activity greater than 5/50 high power fields had a 16 percent tumor-related mortality/metastatic rate (sample size: 99).

— Moderate-size tumors 5 to 10 cm. with mitotic activity greater than 5/50 high power fields had a 49 percent tumor-related mortality/metastatic rate (sample size: 96).

— Large tumors of more than 10 cm. with mitotic activity greater than 5/50 high power fields had an 86 percent tumor-related mortality/metastatic rate (sample size: 108).

The above data shows a significant correlation between tumor size, mitotic rate and tumor behavior of gastric GISTs. We believe that these parameters should be recorded for all GISTs as basic clinicopathologic parameters useful in the estimation of outlook and the possible need for adjuvant treatment such as Gleevec.

Gastric GISTs with mitotic activity no greater than 5/50 high power fields and less than 10 cm. have so low a metastatic rate, that preventive treatment with Gleevec might not be necessary at all.

However, patients with gastric GISTs larger than 5 cm. with mitotic rate greater than 5/50 HPFs have a high metastatic rate and tumor-related mortality, and for this group of patients, preventive treatment with Gleevec or by other means could be beneficial.

Gastric GISTs larger that 10 cm. but with mitotic rate no higher than 5/50 HPF, or those no larger than 5 cm. with mitoses greater than 5/50 HPF, have a low to moderate risk for metastasis. Hopefully, this risk could be lowered with an aggressive surveil-

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Arizona group meets despite record rainfall

At the Feb. 12 meeting of Arizona GIST'rs were, from left, Dick Kinzig, Linda Martinez, Blanche Ferris (husband Delle also in attendance), Billie Baldwin and Eleanor Lewis (husband Steve was also in attendance)

The Arizona Chapter of LRG held its third annual meeting Saturday, Feb. 12, in Scottsdale during the worst rain storm to come through drought-stricken desert in ages.

The Virginia G. Piper Cancer Center was the meeting place where seven GIST'ers and their spouses got together to renew stories and update each other about our progress since last we met. Candles were lit in memory of Lupe Zertuche (June 20, 2004) and Darlene Vaughn (April 25, 2004) who died this past year.

Attendees included Arizona coordinator Billie Baldwin, Blanche and Delle Ferris, Eleanor and Steve Lewis, Linda Martinez, and Dick Kinzig visiting from Illinois.

Billie Baldwin expressed the desire to retire from the chapter's coordinator position after the death of her beloved husband, Joe, who died a month earlier. We certainly want to thank Billie for her hard work and dedication in getting the LRG group established in Arizona, and welcome her participation at future meetings.

Linda Martinez volunteered to take on the responsibility of coordinator for the Arizona group and will be making contact with old and new members in the state. Linda gave us a brief update on the progress of the Sugen trial of which she is participating because Gleevec started to fail her after three years. Thank you Linda for taking on the responsibility and for passing out heart valentines of chocolates.

The meeting adjourned to nearby restaurant where the lively discussions continued before saying farewell until the next meeting. All suggested we meet more frequently in the future.

— From Dick Kinzig

MORE SU11248

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The Life Raft Group contacted Emerging Med, the company selected by Pfizer to match clinical trials of SU11248 to GIST patients. Emerging Med declined to provide The Life Raft Group with the sites where SU11248 will be available. Patients must contact Emerging Med at (877) 601-8601 for the most up-to-date listing of trial sites.

The Life Raft Group has learned, however, that SU11248 will be available in Boston, Mass.; Detroit, Mich.; Minneapolis, Minn.; Park Ridge, Ill.; St. Louis, Mo.; Santa Monica, Calif.; Washington, D.C. and Montreal, Canada. The U.S. government's Web site, www.clinicaltrials.gov, also lists Framingon Hills, Mich., East Melbourne, Australia, and Singapore.

SU11248 appears poised to move into clinical practice, possibly within the year. As more drugs become available to treat GIST both in clinical practice and in trials, it seems logical that further molecular analysis of tumors could help direct patients to the best drug for their particular molecular "fingerprint."

The first step in developing this molecular fingerprint has been in place since the early Gleevec clinical trials. That step is "staining" tumors to see if they express the c-kit protein, also known as CD117. This helped establish that the tumors really were GIST and likely to respond to Gleevec.

The second step in developing a molecular fingerprint is already clinically available. This is the mutation testing service offered by Oregon Health Sciences University and at other locations. Patients can have their tumor samples tested to identify what type of KIT or PDGFRA mutation they have. This service is covered by insurance in many instances. This type of testing will become more important as patients and their doctors have more treatment options. It is likely to evolve even further over the coming years.

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lance program to catch early recurrences and metastases. It is also possible that preventive treatment with drugs such as Gleevec could improve the outlook for patients with such tumors.

It is hoped that clinical trials will show improvement of GIST prognosis with the new treatments.

Gastric GISTs can be morphologically divided into spindle cell tumors including sclerosing, palisaded-vacuolated, hypercellular and sarcomatous types. The epithelioid gastric GISTs can be divided into sclerosing, dyscohesive, hypercellular and sarcomatous types. These types correlate with tumor behavior, most importantly that the sarcomatous tumors with significant atypia and mitotic activity have a high rate of metastases.

Another aspect of GIST management aided by this study is devising a specific follow-up strategy. Clearly, close surveillance is necessary for any subcategory of tumors that has substantial risk for subsequent development of metastases. This may include clinical and radiologic (CT, ultrasound) surveillance methods. The interval of surveillance will depend on many factors, but the above results could help in setting specific guidelines for this. However, long-term follow-up would be necessary for most patients (perhaps excluding the patients with very small tumors incidentally detected during other medical procedures). Long-term follow-up is necessary because gastric GISTs can develop intra-abdominal and liver metastases a long time after the primary surgery. However, the study found that very rarely does a metastasis occur more than 15 years after the primary tumor, but it can occur well after 10 years.

For some reason, gastric GISTs located in the upper part of stomach (cardia, fundus) seem to be malignant

See GASTRIC GIST III, Page 11

MORE 51 WEEKS

From Page 2

I used the hospital's newsletter and asked my "surgical team" to find space on it to sign their names for me. I have close to 40 signatures on it and know that I missed some of them. I thank all of them for being on my healing team.

My pastor visited me in the hospital. When I told him I still had my stomach, he quietly said that there were 100 people on the prayer chain. I still feel humble to experience the power of prayer at work in my life.

After discharge, I went to my daughter's house. My son took time off work to be with me. My sister flew across the country to help me make the transition back to my apartment. She's a good cook, and put three meals a day in front of me that were much nicer than I'd have prepared for myself.

Friends and co-workers sent flowers, food and cards. I'd set up a telephone and e-mail tree to let folks know how the surgery went. Somehow, and unfortunately, I forgot to have someone call my boss!

My precious granddaughters saw me with "bed hair" and asked how my hair stood up on end. They brought me "get well" pictures made with their own loving hands. They gave me hugs and kisses. They saw me progress from having lots of tubes to helping them decorate the Christmas tree. I hope to be around to watch them grow from the 9- and 6-year-old darlings they are now to being "all grown-up" and self-sufficient adults.

Fast-forward to last month. My latest scan showed no evidence of the disease! NO ONE led me to believe they could remove all of the cancer. A nodule assumed to be metastasis was, in fact, benign. Now I'm told they DID get all of the tumor. I'm to continue on Gleevec for about another year. As the oncologist said, our Life Raft is in "uncharted territory."

In the meantime, with the first anniversary of my diagnosis, I've asked all of my family and supporters to go to a nearby pool for a celebration swim. This is not just for me but for all the folks who have the dubious distinction of dealing with a malignancy yet continue to trudge on!

My incision spans the front of my midriff. I'd told the surgeon that I swim, and when they were removing the staples, I asked him when I should get the two-piece swimsuit to show off his handiwork. He didn't miss a beat, and said that I should be ready by summer. Keeping a sense of humor has helped me through some rough spots.

I'm back at my one-day-a-week nursing job at an assisted living facility. I'm also swimming a half-mile per week again. I still welcome suggestions for high calorie food/snacks to help me maintain my weight. The latest suggestion was Hawaiian poi, and a trip to Hawaii to get it!

The next chapter of my life is not written yet. Whatever the outcome, I have been blessed. As I resume the activities that had before surgery, I feel differently about each of them. This gift of life is ever-present with me. If this were my last day, would I do things differently? My goal is to be able to answer, mostly, "No." I also continue to shorten my list of "I-wish-I-had" items. Every time I eat a normal-sized meal, I'm thankful for the quality of life I enjoy.

I ran into an acquaintance the other day who said, after hearing my story, "You must have a new lease on life."

Well said. I must.

Rudi Holzapfel, Irish poet, battled 3½ years

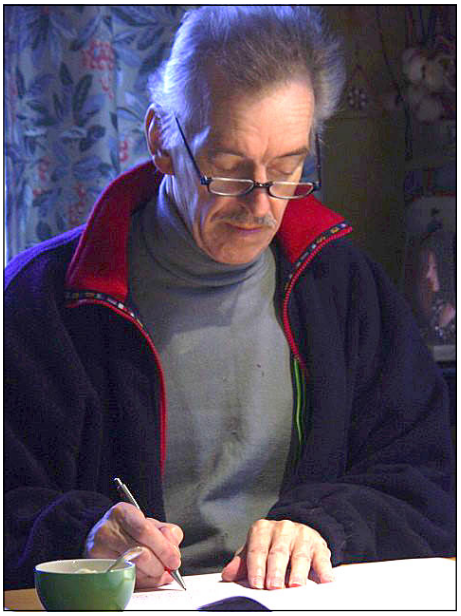
Rudi Holzapfel, poet, writer, scholar and owner of The Poor Sinner Bookshop in Tipperary, Ireland, died Feb. 6, 2005, after a 3 ½-year battle with GIST.

Rudi loved all things beautiful. Aside from being an extraordinary poet, he loved old books and fine art. He was a teacher in Germany for more than 20 years before opening bookshops in Ireland.

The written word was Rudi's life. He advised on the establishment of the Fethard Historical Society Book Fair in Ireland in 1996 and participated in the fair for nine years. The 10th annual book fair, held one week after Rudi's death, was the only one he missed. A moment of silence held in his honor ensured that he was present in spirit.

Luke Golobitsh, Life Raft Group member and Rudi's caregiver, said, "A doctor once told me people who are mean just get meaner when they are dying. Rudi just got more polite and gentlemanly as he got closer to death; he has always been an inspiration to me to be polite."

He is survived by his wife, Ulla, daughter, Marja, son, Francis and dog, Inde, whom Luke swears prolonged



Rudi Holzapfel was owner of The Poor Sinner Bookshop in Tipperary, Ireland.

Rudi's life.

The following is a poem written by Rudi's friends: Nora, Danny, Thomas, Martin and Mairead:

A scholar, a poet, a neighbor, a friend
A man of letters and words
A dreamer, a realist, all rolled into one
Emotional, pragmatic, sublime
A man who cared, who laughed, who dared
Who shared his thoughts with the world

A man who lived not one, but ten lives
In the short time he spent on this earth

A man who listened, who heeded and advised
Expressed his views but never criticised
A man who despised those damned politicians
Their corruptness, their greed their shame
A man who loved this country and village
The red hills of Cappawhite
A man who loved his house in Monevaun
Enjoying his privacy therein

Imaginative, inventive, creative, expressive
True, loyal, gentle and kind
Interesting and interested in all he met
In their views, their thoughts, their minds
A man who dined at our table so often
Who regaled us with his adventures and tales
A man who exchanged gifts with us
Who shared our lives and woes

A man who has left a void in our lives
A community who grieves for the poet
A light extinguished but his spirit lives on
In our memories, our hearts and our thoughts.

— By Erin Kristoff

GASTRIC GIST III

From Page 10

more often than those in the antrum.

Mutation type seems to be a significant factor since patients whose GISTs had KIT exon 11 point mutations fared better than those whose GIST had exon 11 deletions.

Immunophenotype is also a potential prognostic factor, considering that gastric GISTs that were positive for smooth muscle actin or desmin fared better than those that were negative. These tumors did not include true leiomyomas, which form a separate category of uncommon tumors, about 1 to 2 percent of all mesenchymal tumors of stomach.

It needs to be noted that the above applies only to gastric GISTs. Small intestinal tumors are more aggressive, and a similar follow-up study of them is underway in our institute. Also, studies to correlate tumor behavior and other biomarkers are also continuing based on our follow-up material.

Our study was performed in the Armed Forces Institute of Pathology, devoted to tumor diagnosis, education and research. We hope that there will be a united front of supporters to ensure that this type of research can be continued as fully funded in the future.

Editor's note: Markku Miettinen, M.D., is chairman of the Department of Soft Tissue Pathology at the Armed Forces Institute of Pathology in Washington, D.C.

The Life Raft Group

Executive Director	**Norman Scherzer,** nscherzer@liferaftgroup.org	
Executive Assistant	**Tricia McAleer,** tmcaleer@liferaftgroup.org	
Administrative Assistant	**Erin Kristoff,** ekristoff@liferaftgroup.org	
IT Director/Web Master	**James Roy,** jroy@liferaftgroup.org	
Research Assistant	**Pamela Barckett,** pbarckett@liferaftgroup.org	
Science Coordinator	**Jerry Call,** Jerry.Call@comcast.net	
Special Assistant	**Matthew Mattioli,** mmattioli@liferaftgroup.org	

Contact the Life Raft Group
40 Galesi Drive
Wayne, NJ 07470
Phone: 973-837-9092
Fax: 973-837-9095
Internet: www.liferaftgroup.org
E-mail: liferaft@liferaftgroup.org

Life Raft volunteers

Chief Financial Officer	**Allan Tobes**	atobes@comcast.net
General Counsel	**Thomas Overley**	guitarman335@msn.com
Accountant	**Roberta Gibson**	dnrgibson@yahoo.com
List Manager	**Mia Byrne**	mebmcb@wowway.com
Newsletter Editor	**Richard Palmer**	richardpalmer@hawaii.rr.com
Web Designer	**Tami Margolis**	tami@comcast.net
Fund-raising co-chairs	**John Poss**	john@celeritylogistics.com
	and **Gerald Knapp**	gsknapp@winfirst.com

Life Raft country representatives

Australia	**Greg Ladbrooke**	lad57b@bigpond.com
China	**Ruijia Mu**	mu_ruijia@yahoo.com
France	**Bertrand de La Comble**	bdelacomble@oreka.com
Iran	**Negar Amirfarhad**	negaraf@sympatico.ca
Italy	**David Massaria**	davidmax@libero.it
Mexico	**Rodrigo Salas**	rsalas@maprex.com.mx
Netherlands	**Ton de Keijser**	akeijser1@chello.nl
Poland	**Bartosz Szczesny**	bsz1974@yahoo.com
Switzerland	**Ulrich Schnorf**	ulrich.schnorf@bluewin.ch
United Kingdom	**David Cook**	D.Cook@sheffield.ac.uk

Life Raft area groups

Arizona	**Linda Martinez**	linda.martinez1@cox.net
Chicago	**Richard Kinzig**	rjkinz@aol.com
Detroit	**Allan Tobes**	atobes@comcast.nett
Los Angeles	**Floyd Pothoven**	floyd@keralum.com
New York	**Dan Cunningham**	CunninghamDA@coned.com
Texas	**Kerry Hammett**	yaloo@gvtc.com
	and **John Poss**	john@celeritylogistics.com

Board of Directors

Executive Committee

Stan Bunn, President	SBunn@BSTGlobal.com
Allan Tobes, Secretary-Treasurer	atobes@comcast.net
John Poss, Fund-raising	john@celeritylogistics.com

Directors

Robert Book	RMBook2@aol.com
Mia Byrne	mebmcb@wowway.com
Chris Carley	ccarley@fordhamco.com
Jerry Cudzil	jerry.cudzil@csam.com
Jim Hughes	tjhughes43@comcast.net
Gerry Knapp	gsknapp@winfirst.com
Dr. Arnold Kwart	amkbmp@aol.com
Rodrigo Salas	rsalas@webtelmex.net.mx
Silvia Steinhilber	nswplas@mb.sympatico.ca

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.
Wayne, NJ 07470

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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.