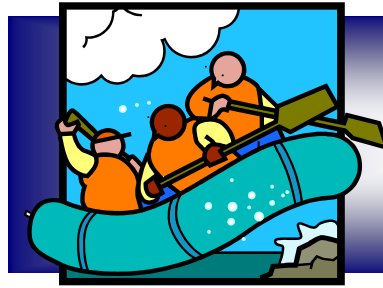


Standard treatment guidelines for GIST

Battling gastrointestinal stromal tumor



LIFE RAFT GROUP

February 2006

Allan Tobes and Russell South

Vol. 7, No. 2

By Jerry Call

This is a short review of current standard treatment guidelines. For a thorough review of these guidelines, and other subject areas such as pathology and imaging, see the material referenced. For U.S. patients, GIST treatment guidelines can be found at the National Comprehensive Cancer Network (NCCN) Web site, www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf. It is important to note that these guidelines have not yet been updated to reflect the approval of Sutent.

For patients outside the United States, the best source of general information about standard treatment guidelines may be the report of the GIST Consensus Conference of March 20-21, 2004, under the auspices of the European Society for Medical Oncology. These guidelines would not, however, replace any country specific guidelines (<http://annonc.oxfordjournals.org/cgi/content/abstract/16/4/566>).

For newly diagnosed GIST that is operable, surgery is the standard treatment. The biggest question in these cases is whether a patient should take Gleevec before or after the surgery. Clinical trials are ongoing to answer these questions but no results have been published.

Even without trial results, support for Gleevec before surgery (neoadjuvant Gleevec) seems to be pretty strong, at least in certain situations. The NCCN guidelines state that surgery "should induce minimal functional deficit." Otherwise, consider Gleevec prior to surgery. What does this mean? One example is, before consenting to surgery to remove your entire stomach, consider taking Gleevec to see if it will shrink the

GIST'ers share their Sutent experiences

Editor's note: The United States Food and Drug Administration announced Jan. 26 that it approved Sutent (sunitinib) for people with gastrointestinal stromal tumors. Here three Life Rafterers who helped bring this therapy to GIST patients by participating in the Sutent clinical trial share their stories of how the drug worked for them.

Donnie Ray Chadrick Jr. My name is Donnie Chadrick and this is a brief recall of my five-year battle with the beast we all have come to know as GIST.

It all started shortly after my 36th birthday in February 2001. I was working for a small oil company as a tanker driver here in Medford, Ore. I began to develop severe pain in my lower right quadrant and lack of energy that I ignored until I could no longer justify not seeking medical attention. I spent three weeks or so seeing my general practitioner. He finally sent me to get a CT scan. From there it was off to see the gastroenterologist, who set me down and told me those dreaded words: "You have cancer."

He told me that I had a football-size tumor growing out of my intestinal wall and that I needed surgery right away. Within two weeks, I was under the knife of a very good surgeon. When the surgery was over, he told me he was only able to debulk the tumor down to about



CHADRICK

the size of a grapefruit because there was a main artery and my urinary tract running through the center of it. They also removed some of my small and large intestines and a whole gob of grape-sized tumors they found throughout my abdominal cavity. (I wonder why they always use sports equipment and fruit to describe tumor size?)

I was given six months to a year to live. As I was recovering, my mother brought me a copy of Time magazine. On the cover was an article describing the "golden bullets" referring to the new breakthrough in cancer called STI571 aka Gleevec. I took this information to my local oncologist and she referred me to Dr. Charles Blanke at Oregon Health

See SUTENT STORIES, Page 5



MUSTARD



MARRE

See STANDARD CARE, Page 2

STANDARD CARE

From Page 1

tumor enough that you don't lose your stomach during surgery.

The question of whether to take Gleevec after surgery has completely removed all GIST (adjuvant Gleevec) is probably harder to answer than the question of taking Gleevec prior to surgery. Initial trial results may be presented at 2006 American Society of Clinical Oncology (ASCO) conference in June. The benefit for GIST at low risk for metastasis seems to be very questionable. Ongoing clinical trials may help to answer this question for high risk patients.

The NCCN GIST guidelines address the question of adjuvant Gleevec with this footnote in the "Observe" treatment phase, "Some physicians feel compelled to administer adjuvant imatinib for high risk patients, even though there are no data to support this use."

The March 2004 GIST consensus conference (ESMO) produced a stronger position statement on the use of adjuvant Gleevec, noting that "Adjuvant imatinib should only be given in clinical trials. The panelists agreed that adjuvant therapy with imatinib mesylate remains investigational. Adjuvant imatinib might be able to eradicate microscopic disease and lead to cure, but may also reduce the efficacy of the treatment of recurrent GIST and facilitate emergence of imatinib-resistant cell clones."

Despite the recommendations of the GIST consensus conference and as noted in the NCCN guidelines, some high-risk patients prefer to take Gleevec outside of a clinical trial after surgery in order to try to prevent a recurrence.

For metastatic GIST and when surgery is not possible:

Here Gleevec is the approved treatment regardless of type of mutation. The biggest question is the correct dose, or in some cases, the approved dose. Both the approved dose and the dose most likely to be recommended can vary by country or region. Doctors in the United States seem to favor the standard dose, while there seems to be more support for higher doses in Europe. The one thing that most people seem to agree on is that

800 mg. is too great a starting dose for most new patients. If high-dose Gleevec is considered, starting at a standard dose and escalating to the higher dose over time (typically a few months) seems to be much better tolerated and preferred.

Gleevec-resistant GIST with limited progression (also called "partial resistance"):

Life Raft coming attractions

March 25: Texas area Life Rafters meet 10 a.m.-noon at Gilda's Club of North Texas.

March 29: GIST Cancer Research Fund (GCRF) presentation to Memorial Sloan-Kettering Cancer Center, New York, at 3 p.m.

April 1-5: American Association for Cancer Research meets in Washington, D.C.

April 5: GCRF noon presentation to Fox Chase Cancer Center, Philadelphia.

April 8: Michigan area Life Rafters will meet 12:30-2:30 p.m. at Gilda's Club in Royal Oak.

April 28: Life Raft Board of Directors meet.

May 3-4: GCRF presentation to Oregon Health and Science University, Portland.

Sept. 14-16: Life Raft Group membership meeting in Dallas, Texas.

(more details to follow)

This is when "one or a limited number of metastasis showing a nodule within a mass and/or enlargement with increased FDG uptake on PET scan, while the other sites remain controlled by imatinib treatment," according to the GIST consensus conference.

Treatment of limited progression per NCCN guidelines includes:

- If resection is feasible, consider resection of progressing lesion(s).
- Consider radiofrequency ablation (RFA) or chemoembolization.
- Consider increasing imatinib dose as tolerated; reassess therapeutic response with PET or CT.

For generalized/widespread progression on Gleevec (called "multifocal resistance" by the GIST consensus conference) patients can try:

- Increasing the dose of Gleevec if they are tolerating the Gleevec well.
- Sutent would typically be the next step (for patients in the United States) and is effective for about 60 percent to 65 percent of patients.
- Referral to a clinical trial would typically be the next step; however, some patients might consider a clinical trial prior to Sutent, especially if they were considering a trial that had excluded previous treatment with Sutent (such as the BAY 43-9006 trial or the AMG706 trial).
- For a more complete discussion of managing GIST progression by Dr. Charles Blanke of Oregon Health and Sciences University, see www.liferaftgroup.org/treat_manag_GIST_progression.html.

The GIST consensus conference noted the following about multifocal resistance, "The role of radiofrequency ablation, tumor destruction or resection of liver and/or peritoneal metastasis or is even less well demonstrated."

Again, increasing the dose of imatinib or an alternative experimental targeted therapy are options for patients in good clinical condition. This is a situation where no standard approach can be proposed.

Explosion of GIST information raises questions

What drug, what dose?
Patients and doctors are
pondering alternatives

By Jerry Call

GIST clinicians and researchers have done a great job in dissecting the biology of GIST. This sarcoma can now be broken down in many different categories: adult GIST, familial GIST, pediatric GIST and GISTs associated with NF1 (neurofibromatosis).

Some of these categories can be broken down further or in different ways, such as by gene mutation (c-kit, PDGFRA or wild-type for both), mutation location within the gene (exon mutation or “genotyping”), and by location of primary tumor (which may cause differences in signaling).

Compared to six years ago, we have an explosion of new information about GIST.

One of the earliest fruits of this extensive GIST research is the approval of Sutent in the United States. On Jan. 26, Sutent was approved for GIST patients with Gleevec-resistant GIST, and those patients who can't tolerate Gleevec. This approval is great news for GIST patients in the U.S. and, hopefully, approval will soon follow in other countries. Sutent is the first treatment to be approved after failure of a molecularly targeted therapy (Gleevec).

When science advances as fast as it has in GIST, we are often left with as many questions as answers. Even before Sutent was approved, Richard Palmer, editor of this newsletter, raised the possibility of doctors/patients combining Gleevec with Sutent once it was approved. Palmer suggested that we acknowledge this possibility in the newsletter. I was reluctant to do this for fear that it might be interpreted as tacit approval, and was content to bury my head in the sand. This lasted about a month, then patients began raising the issue

(suggested by their doctors) and other questions triggered by the approval of Sutent.

Before we explore some of these new questions, it might be helpful for the reader to look at the short review of current GIST treatment guidelines that begin on page 1.

The effects of Gleevec as an initial targeted therapy for GIST have been extensively studied in clinical trials. The results are well documented. The most important factor in determining whether a patient is likely to respond to Gleevec appears to be what type of mutation they have.

Patients with exon 11 mutations in KIT typically have the best response rates and the longest time to disease progression. Patients with exon 9 KIT mutations tend to have an intermediate response rate and time-to-progression. Patients with wild-type GIST (no mutations in KIT or PDGFRA) tend to have poor response rates and fairly rapid

See OPTIONS, Page 4

Setting 2006 goals at LRG headquarters



Life Raft Group staff and board members are pictured meeting Jan. 28 in the LRG's New Jersey office to discuss goals for the coming year. Those present include, clockwise from left, Jerry Cudzil, Rodrigo Salas, Elizabeth Braun, Tricia McAleer, John Poss, Stan Bunn, Jim Hughes and Norman Scherzer.

OPTIONS

From Page 3

time-to-progression. Patients with exon 12 mutations in PDGFRA also tend to respond well to Gleevec; while patients with a specific type of exon 18 PDGFRA mutation, D842V, tend to be resistant to Gleevec.

The response rate of Sutent as an initial targeted therapy in GIST *has not been well studied*. The only results in this setting come from the few patients in the Sutent trials who were unable to tolerate Gleevec as initial therapy. While the response rate in this small group appears to be similar to initial therapy with Gleevec, the numbers are too small to make firm conclusions.

For patients with Gleevec-resistant GIST, the response rate to Sutent *has been studied extensively*. In this group, patients with an exon 9 KIT mutation tend to have excellent response rates, patients with wild-type GIST tend to have intermediate response rates, and patients with an exon 11 KIT mutation tend to have lower response rates.

Many of the questions about Sutent center on the response rates to exon 9 and wild-type GIST. The problem in comparing Sutent rates to Gleevec rates is that it is not an apples-to-apples comparison. The Gleevec rates are for “untreated” GISTs while the Sutent rates are for “resistant GIST.”

Still there are a number of interesting questions that cannot be answered by clinical data. For example, patients with exon 9 mutations in KIT tend to have a much better chance of having a “response” at higher doses of Gleevec. There are several theoretical possibilities for these patients (as opposed to the proven/standard recommendations) and the optimal treatment has not been defined. These same theoretical options apply to wild-type GISTs and other GISTs with a less-than-optimal history of response.

There is no data to suggest which of



THEORETICAL START WITH GLEEVEC OPTIONS

1. Start Gleevec at 400 mg. and continue until progression THEN
 - a. Crossover to high dose Gleevec (initially 800 mg.) until progression THEN
 - b. Crossover to Sutent until progression THEN
 - c. Crossover to any clinical trial that does not prohibit previous Sutent use (AMG706 and BAY 43-9006 prohibit previous Sutent)
- OR**
- b. Crossover to any clinical trial including BAY43-9006 (AMG706 isn't open at this time) until progression THEN
 - c. Crossover to Sutent.
2. Start Gleevec at a higher dose until progression THEN
 - a. Crossover to Sutent THEN (same as 1b.)
 3. Start 400 mg. Gleevec and slowly escalate to high dose (600-800 mg.) as side effects diminish, probably in a few months. Maintain until progression THEN
 - a. Crossover to Sutent THEN (same as 1b.)

THEORETICAL START WITH SUTENT OPTIONS

1. Start with Sutent as approved for prescription. Starting dose is 50 mg. daily for four weeks, then two weeks off, then four weeks on, two weeks off, etc, until progression THEN
 - a. Crossover to any clinical trial that does not prohibit previous Sutent.
2. Start with continuous use Sutent (probably 37 mg.) until progression THEN
 - a. Crossover to any clinical trial that doesn't prohibit previous Sutent.

these options would produce the greatest benefit and we are not aware of any ongoing trial that would answer this question. It is unlikely that this data will be available in the near future.

The “standard approach” would be to start with Gleevec until disease progression, THEN crossover to Sutent. The big unanswered question would be whether the mechanisms of resistance that occur with Gleevec would be likely to emerge as early if you started with Sutent. Similar types of questions apply to neoadjuvant and adjuvant Gleevec as well; for example, would Sutent be more effective neoadjuvant therapy for exon 9 GIST?

Beyond the issue of initial treatment is the theoretical issue of combining Sutent and Gleevec either for initial treatment

or for Gleevec-resistant GIST. The rationale for trying this approach is two-fold: broader-spectrum of activity against secondary mutations and additional antiangiogenesis activity due to inhibition of VEGF by Sutent. While the idea of using Sutent and Gleevec together or with another

KIT inhibitor is interesting, the best place to try this would be in the context of a clinical trial. The toxicity profile and possible drug interactions of this combination have not been studied. Other questions, such as dosing schedule, and the optimal setting (initial therapy or resistant GIST) also need answers.

Large numbers of GIST patients have participated in clinical trials. This has been an important factor in the progress

See OPTIONS II, Page 12



SUTENT STORIES

From Page 1

& Science University (OHSU). At that time, Gleevec was still in trial phase and I was prescribed 800 mg. Within a couple of CT scans, my once-growing tumor began to shrink and shrink until in about a year of starting this miracle drug my tumor was barely visible. I WAS STABLE! I had been so blessed, I wanted to shout it from the top of the highest cell tower.

Gleevec kept doing its magic until the middle of 2004. My CT scans showed three new tumors in my pelvis. In October 2004, I had surgery again but it did not do much good. Within a couple of months, as I stared into my doctor's eyes, I could hear the words from the little girl on the movie "Poltergeist" — THEY'RE BAAAAACK!

So now it was time to take my treatment into my own hands once again, and with the help of the Life Raft Group and others like Emerging Med, I found a Sutent trial close enough that I could participate in. I started Sutent on two cycles last spring in Santa Monica, Calif. and then switched trial sites to Portland. Within a couple of cycles, I had minimal shrinkage and there after stability.

A few days into a cycle I feel fatigue and weakness that increases to the point to where all I want to do is sleep, my appetite decreases, I cannot even taste food, and there's occasional vomiting, mouth sores, and dry skin to the point of cracked and bleeding feet. My facial hair has turned white, I get bloody noses, and acid reflux that prescription Nexium won't help. My liver enzymes have to be consistently monitored as they run too high at times. Also, cuts and abrasions won't heal — they seem to get better during washout but only to return once the next cycle starts.

Alternatively, my washout period when I'm off the drug is great! I almost feel like myself again, so I try to cram all my honey-do's into that two weeks of bliss.

As far as working, I went on disability in January 2003 when I was prematurely kicked off Gleevec. I was all lined up to

go to Dana-Farber for the Sutent trial and had been told I would be there for six months. I was there for only a week. When I got back, I was scared to give up my disability because I had no idea what was around the corner with my health. If something went wrong again, I would have a six-month waiting period for assistance.

I have a great boss who still pays for my insurance and in return I work about three days a month as a relief driver. It's OK with the folks at Social Security as long as I do not make more than \$580 a month. In retrospect, I'm glad I made the decisions I did because I don't think I could hold down a full time job now.

I do not know how long it will last this time but I do know how grateful I am to be here with you all. I have just finished my eighth cycle with Sutent and although the side effects can be pretty harsh, they do not outweigh the gift of life. If someone asked me advice on living with cancer I would have to say "Never give up! Be in charge of your own health care, and keep supporting the Life Raft Group — they are a port in the storm."

Nan Mustard

My GIST experience started in January 1997 when my first tumor showed up. It took the doctors a long time to locate the tumor and take it out. I eventually had four major surgeries for GIST and have tried Gleevec twice. In January 2001, I started Gleevec and stayed on it for 14 months. After surgery in 2003 I was on Gleevec for a year.

In July 2004 I had 14 tumors grow back in my pelvic area. Because one large tumor was growing to the pelvic



Donnie Chadrick with his daughter, Meghan.

wall, I was inoperable. We looked at every possible trial at that time and decided on Sutent because of its track record.

I started Sutent in August 2004. After three days I got blood clots in my lungs. Even though I am sure these were not caused by Sutent, I was told by Pfizer that I needed a Greenfield filter, that I'd have to take Lovenox daily, and my Sutent dosage was cut to 37.5 mg. This first cycle I had a 35 to 50 percent reduction in my largest tumors. From cycle 2 in September 2004 to cycle 9 in August 2005, my tumors were stable. However, during cycle 10 my largest tumor started growing and pressing into my right leg.

In September 2005 it was decided that radiation was something I needed to try. So we searched around and found a really good radiation center. But the first thing the doctor told us was, "I have never had any experience with GIST, so I do not know how it will react." Thankfully, after six long weeks of radiation, five days a week, we did have some reduction. My CT in November 2005 showed that the radiated tumor had a 35 percent reduction and all other tumors stable, except the matching tumor on the left side of the pelvic had started to grow.

At this point we made plans for Dana-Farber Cancer Institute in Boston to dis-

GIST Q&A with Dr. Peter Reichardt

Nutrition? Fatigue? Flu shot? Exercise? Vacation? Drinking? Sauna?

The House of Life, Germany's GIST organization, receives questions daily from GIST patients and caregivers concerning lifestyle do's and don'ts when having GIST and being treated with imatinib (Gleevec). Stefanie Peyk, GIST patient and co-editor of the House of Life, interviewed Dr. Peter Reichardt, the GIST expert of the House of Life.



Dr. Peter Reichardt

Is there a special diet regimen that GIST patients should follow?

No, there is no GIST diet. Dependent on the disease and on surgical interventions, there are different things which have to be taken into consideration. Patients without a stomach have to eat many small meals throughout the day and need a vitamin

B12 injection every month. Patients without a pancreas have to be careful with food that has too much fat. Patients, who lost part of the bowel need to watch the food intake. In any case, it is recommended to consult a dietician. Nutrition is always very individual and dependent on many factors.

To emphasize it again — there is no GIST diet. There is as well no need to change the diet because of GIST or because of a treatment with Gleevec. However, it is recommended to have a healthy and balanced diet — as it is recommended for healthy people too.

Very often tumor patients are advised to use multi-vitamins or dietary supplements. What do you think about this recommendation?

There is no sufficient research based evidence showing the benefit or positive influence of dietary supplements on a disease or the well-being of an individual. In reference to vitamins, a healthy and well balanced diet with fruits and vegetables cover usually the recommended daily intake of

See REICHARDT, Page 8

GIST gathering in London



Life Raft Executive Director Norman Scherzer and his German counterpart, Markus Wartenberg of Das Lebenshaus, met in London in January to help plan a GIST/CML summit meeting to take place in June. While there, they met Jan. 24 with UK GIST patients. Pictured, standing from left, are Eric Kynoch, Markus Wartenberg, Norman Scherzer and Dan Wiseman; seated from left, Sheena Kynoch, Rachel Gilbert and Julie Gilbert.

SUTENT STORIES

From Page 5

cuss other options. Since we met with Dr. Jeffrey Morgan, we found out that February 2006 was the next entry date for AMN107. There is also another trial that has just opened for IPI. Dr. Morgan's fellow, Dr. Ng, called recently to inform us that there is space in February. This is good news.

When we were at Dana-Farber, Dr. Morgan arranged to have my Sutent dosage upped to 50 mg. He also made arrangements with Dr. Warren Chow at City of Hope in Southern California to have a CT completed at the end of this cycle Feb. 1 to see if the 50 mg. has stopped growth on the one tumor. I will stay on Sutent until it no longer works for me. Thankfully there are other trials available in Boston now to choose from.

Meghan Marre
Mary Marre says her daughter Meghan was diagnosed with GIST in the fall of 2002, just a few weeks before her 21st birthday. All through high school Meghan was anemic; she was also plagued with stomach problems. Each time a doctor would say it was heavy periods, ulcers, heartburn and the like ... this to a child who outwardly seemed so healthy. She played varsity sports all through high school and was very active.

She began having more stomach problems, including some visits to the ER. It was finally recommended that she have a gastrointestinal scope in September 2002. That was when her tumor was found.

Meghan had a partial resection of her stomach in 2002. We were told to go home and see the oncologist in three months. Fortunately, we learned of Dr. Charles Blanke and immediately made an appointment to see him. The cancer had already metastasized into her liver at this point. Meghan began taking 600 mg. of Gleevec and there



Nan Mustard with her husband, Tim.

was immediate shrinkage!

At the time, Meghan was still recovering from the surgery and taking the medicine was difficult. Meghan tolerated the gel capsules fairly well but when Novartis went to the solid tablet, Meghan could not keep them down. We literally tried everything known to man — I bought gel caps and crushed the pills, made a suspension with juice, mixed it with food, etc. We worked with

a pharmacist at OHSU but to no avail. Meghan continued to try to take the meds and the cancer began to grow again.

In March of 2005, Dr. Blanke told us that Gleevec had failed and that Meghan was going to be in the Sutent trial! We were so excited and hopeful!! The drug has been an answer to prayers. Meghan began to take the drug and immediately found that it did not make her feel nau-

seous. This is such a huge improvement for her and her quality of life! There are side effects, but in Meghan's view they are nothing compared to Gleevec. One of the side effects is unpredictable and prolonged periods. Meghan is taking a birth control hormone to counteract this somewhat. She also has significant problems with muscle spasms and body aches which OHSU monitors. In December 2005 Meghan's scan showed no growth and possible shrinkage, we are so grateful. This coming only three months after Meghan had worrisome areas of growth.

At this point, life is pretty good. Meghan is enjoying relatively good health and the drug is working. She is having fun working part time, owning her first car and just enjoying being 24.



Meghan Marre is loving life with her new iPod.

REICHARDT

From Page 6

vitamins and minerals. There is no need to buy expensive supplements. We are anyway hesitant and would not actively recommend supplements.

Are there any foods that might interfere with imatinib?

Imatinib is metabolised in the liver. As such, all food and some drugs do potentially interfere with the metabolism of imatinib. This can happen in two ways. It could happen that the metabolism of imatinib is reduced so that the imatinib level in the blood would increase. This might result in an increase of side effects. Grapefruit might have this effect — therefore be very careful with grapefruit and grapefruit juice. Eating a grapefruit occasionally is OK but it should not happen regularly.

More problematic is the increased metabolism of imatinib because of food or drugs. The result could be a reduction of the blood level of imatinib. There is the danger that imatinib does not work enough! The apparently harmless St. John's wort could have this effect. St. John's wort is often taken against depression.

Does milk reduce the absorption of imatinib?

Milk has no effect on the absorption of imatinib. There are some drugs, where the calcium of the milk might bind the drugs and it is harder to absorb. There is no such information for imatinib.

At what meal is imatinib best taken?

Imatinib should not be taken on an empty stomach; it should be taken with or after a meal. Patients, who take imatinib once a day usually take it with breakfast. There are patients who tolerate the drug better when taking it with/after dinner. It does not have an impact on the efficacy. Imatinib should be taken regularly at the same time, either with/after breakfast or with/after dinner. Patients, who have to take a higher dose and who have to take the

tablets twice a day, take it automatically with breakfast and dinner.

Imatinib and alcohol — does this work?

There are no interactions between imatinib and alcohol. Alcohol has an effect on the liver. Patients who take imatinib should drink alcohol in small amounts. The information about not drinking any alcohol is not correct. Once in a while, sparkling wine, wine or beer is OK.

So patients with liver mets are allowed to have a glass of sparkling wine for their birthday?

Absolutely. As said before — once in a while is OK.

Many patients complain about fatigue. What can they do?

One of the main side effects of long-term treatment with imatinib is chronic tiredness, also known as fatigue. But fatigue is more than just being tired. It is more a feeling of lassitude, getting tired fast and feeling less efficient. To do something against it is very difficult.

Also, there are patients with a normal haemoglobin-level and they still feel tired, fatigued. That means that anaemia is not the sole reason of fatigue.

So what can one do? It is important to stay physically active and to avoid longer times of relaxation. Patients who take frequent breaks throughout the day often have sleeping problems. Patients should take walks, go swimming or try to actively do what they did prior to the disease. Physical activity often helps against fatigue.

Which drugs can you use against headache?

Paracetamol (acetaminophen) and combination drugs with paracetamol should be avoided. Drugs such as aspirin or ibuprofen can be used to treat headache.

Is it OK for GIST patients to get a flu shot?

Yes, there is no contraindication. Patients, who want to get the flu shot, should do it. If a patient does not want it or a physician is not in favor of it - GIST per se is no reason to get the shot. The decision can be made independently from the disease and from the treatment with imatinib.

Can GIST patients exercise without any limitations?

Gist patients can do any type of exercise. Some patients have limited sport efficiency due to e.g. low haemoglobin level or fatigue. Therefore patients should not overextend. They should lower their goals and should not try at all costs to be as successful as they were prior to the disease. This could be very frustrating. If somebody used to walk 25 miles, they might have a problem still doing this. So the patient could start with 10 miles and gradually add more distance. However, exercise is quite important and beneficial to treat fatigue. One should be careful with extreme sports but in theory there are no limitations. It is a very individual decision and independent of the diagnosis of GIST.

Is it OK for a GIST patient to receive a massage?

There is no reason to not get a massage. If a patient has a tumor in the abdomen, than there should be no pressure set on this area. But there is no contraindication to receive a massage at the back or neck. There is a rumor out that a massage might provoke the spread of cancer cells but that is absolutely not true for GIST. If a patient had an operation, no tumor left and no drug treatments as well, then there are no limitations at all.

Can a GIST patient go in the sauna and what rules are to follow?

Sauna is ok. The patient should of course consider his maybe limited physical efficiency (low haemoglobin, fatigue). If a patient is used to going in the sauna, then he/she knows

Allan Tobes — A celebration of life

By Kendra Tobes

Today is quiet in my home after the many family and friends paid their respects and shared the times they had with my husband. A few days after the funeral, Norm Scherzer asked me to write an article and share things you may not have known about this “mentch.”

In Yiddish, a mentch is a person who is good, kind and does things for others without need of accolades. Allan was that kind of person. He was tough when he had to be tough, but underneath he was a pussycat. Even in his last days, when staying awake was a massive effort, he answered questions and gave suggestions to those who asked.

Allan’s giving goes back to his teenage years when he belonged to the synagogue’s youth group. Detroit has a huge Thanksgiving Day parade and Allan would spend the night before the parade blowing up balloons, and sold them the next day to raise funds for the youth group.

If there was a meeting and people needed rides or accommodations, Allan was either arranging for help or doing it himself.

Allan and I met at a meeting of a B’nai B’rith group called “L’Chayim” — to life. He was on a panel; I was in the audience on the opposing side. He later asked some of his friends: “Who was the big-mouth girl in the audience?” We were married two years later.

Allan’s biggest joy was doing for others and that included me. Every night, before he came home, he’d call to see if I needed him to stop for something — even after he’d spent 13 hours at work.

When my son and daughter were younger, after tax season he would take them separately on a three-day trip. My daughter loved to shop and Allan would faithfully wait at all the places while she perused their content. Amusement parks and roller coasters were our son’s love. They became Allan’s, so that he could reconnect with his son.

After we were married, I worked at a school for emotionally disturbed chil-

dren. Allan was fascinated by my stories, and after I left the school to start a family, they asked Allan to be on their board. He stayed on the board through the school’s transition to a community mental health agency. He helped guide that agency’s merger with another. The combined group started with a budget of \$250,000; today it is a \$ 9+ million agency. He spent hours negotiating a loan to purchase and renovate three buildings for the agency’s use. He taught the bookkeeper and deputy director how



TOBES

to do the monthly statements and was the confidant for the executive director. Allan has always jumped into things with gusto and both feet, always thinking of ways to make things better. When Allan had his heart attack in 1987, he found out everything he could about what happened to him and how to improve his life. For the next 19 years — including two weeks before he died — he rose at 5:15 a.m. to attend a cardiac rehab facility that offered water aerobics at 6:30 a.m. Water was his passion and 6:30 was the only time it was offered. There he made friends with people 20 and 30 years older than himself.

One gentleman with whom Allan was especially close lost his wife and soon became too ill to visit her gravesite, which was about four hours north of where we lived. Allan picked up the gentleman and drove him there, helped him find the gravesite and then drove him home. Allan never complained about the drive, only how much he enjoyed this man’s company.

This was not unusual. When the people from cardiac rehab wanted to have a social gathering, Allan arranged it. When someone failed to show up for rehab, he called to check on them and offered to pick them up.

He always was friendly with the rehab staff and was interested in their lives,

offering help or recommendations. Soon, he became an active member of the local American Heart Association and did some work on the state level.

During this time Allan became active on other boards. One was for a halfway house on the west side of the state, a two-hour drive away. He drove most of the time and took others as well.

Another board met at 8 a.m. in downtown Detroit. He would do his cardiac rehab in the morning, drive downtown for the meeting, and then begin his work day. Sometimes he’d have another meeting after work. He was able to accomplish more in one day than some people accomplished in a month.

Allan waited all winter for summer to arrive. Some late spring days, even though the temperature wasn’t the best for boating, he would tell me to bundle up and we would go “out to the lake.” He would drive our little ski boat around, knowing that very soon we’d be enjoying the warmth of the sun and the calmness of the water.

Allan was not always known for his patience, but when it came to teaching someone how to water ski, he had all the patience in the world. He would keep trying until his “student” either skied or was worn out.

A friend of ours, Joe, likes to share this story: Allan took Joe out water skiing one day. Now Joe was an accomplished water skier, but on this particular day, Joe fell in. Instead of coming quickly to pick Joe up, Allan merely checked to make sure he was OK, then turned the boat and started heading off.

“What’s up man?” Joe yelled.

Allan replied, “How long can you tread water?” using a line from a Bill Cosby skit they had heard. They had a great laugh before Joe continued skiing.

Allan’s greatest joys were his granddaughters, Emily, 4, and Shelby, 21 months. Every day last summer, one of the best summers we had in Michigan, we were out at the lake and so were the girls. My children were raised by the water and loved it as much as their father. Emily and Shelby were there, too.

A roundup of clinical trials

By Jerry Call

AMN107 + Gleevec

We understand the phase I trial of AMN107 plus Gleevec has been rapidly accruing patients. The original intent was to evaluate doses as high as 800 mg. of AMN107 plus 800 mg. Gleevec. The trial temporarily stopped patient enrollment while the protocol is undergoing some dose-related changes. The trial is expected to reopen for accrual very soon. We expect that patients will continue to be able to access this combination as the trial expands into phase II.

The combination of AMN107 and Gleevec may have a broad spectrum of activity against primary and secondary mutations in GIST.

IPI-504

The IPI-504 phase I trial is open and accruing patients at Dana-Farber Cancer Institute, Boston. IPI-504 is an inhibitor of heat shock protein 90 (HSP90) and has been the subject of articles in the November 2005 and January 2006 editions of the Life Raft Group newsletter.

BAY 43-9006

The phase II trial for BAY 43-9006 is open and recruiting patients. Three trial sites are open in Illinois and three sites are pending in California, one in Illinois, Maryland, Michigan (this site may be delayed more than the others), New York and Wisconsin. BAY 43-9006 inhibits several kinases including KIT, VEGFR-2, VEGFR-3, PDGFR- β , RAF, FLT3, and RET.

Sutent

In the U.S., Sutent is available by prescription for patients for whom Gleevec failed or who can't tolerate Gleevec. In addition, Sutent continues to be available to patients via the "treatment use protocol." There are many sites open throughout the world. Site information changes frequently; for the most current information contact Emerging Med at 1-877-416-6248 (outside the United States) or at 1-800-620-6104 (inside the United States). If international patients have problems with the listed number,

e-mail: sutent@emeringmed.com. There is also a phase II continuous dose trial.

Genasense + Gleevec

A phase II trial testing the combination of Genasense and Gleevec in patients with Gleevec-resistant GIST recently opened. Genasense (Genta Inc.) is an antisense drug that inhibits bcl-2. Bcl-2 is a protein involved in cellular survival. It is hoped that Genasense may help Gleevec kill tumor cells by making them more sensitive to Gleevec.

This trial is currently open only at M.D. Anderson Cancer Center in Houston. Several other trial sites are planned including: Dana-Farber, University of Michigan Comprehensive Cancer Center in Ann Arbor, Mayo Clinic Cancer Center in Rochester, Minn. and Memorial Sloan-Kettering Cancer Center, New York.

Perifosine + Gleevec

Perifosine is an oral drug that inhibits the AKT protein. AKT is an anti-apoptosis protein. It is speculated that inhibition of AKT might enhance therapy. Apoptosis is a form of controlled cell death, a type of cellular suicide where the cell issues its own death warrant. The phase II trial combining Perifosine with Gleevec is open at M.D. Anderson and is accruing Gleevec-resistant GIST patients.

BMS-354825

BMS-354825 is a tyrosine kinase inhibitor of Src, abl, KIT, and PDGFR. We understand that this trial may expand to phase II soon. We will update this trial as information becomes available.

RAD001 + Gleevec

Both RAD001 and Gleevec are manufactured by Novartis. RAD001 is an mTOR inhibitor that may improve the effectiveness of Gleevec. Phase I is not completely done, however we understand that this trial will enter phase II soon. There will be continued enrollment in the next month. We will update trial sites as this information becomes available.

Global GIST Network adds new representatives



Brazil

Vanessa Passos
vanessa@endo.med.br



Canada

David Josephy
djosephy@uoguelph.ca



Columbia

Jaime Peralta
peraltas@etb.net.co



Costa Rica

Michael Josephy
mjosephy@gmail.com



Israel

Ben Shtang
ehuds@merkavim.co.il



Malaysia

Yong Choo Sian
ycspj2005@yahoo.com



Norway

Jan Einar Moe
jeinmoe@online.no



Singapore

Yong Choo Sian
ycspj2005@yahoo.com



Turkey

Haver Tanbay
tanbay@tanbay.net

Visit the Global GIST Network at www.globalgist.org

Russ South was 67

Russell South, 67, of Adamstown, Penn., died Feb. 26, 2006.

He was diagnosed with GIST May 16, 2003. After surgery, he started Gleevec in November 2003. It halted his cancer and he continued operating his campground, which he did for 13 years until his retirement in February 2005.

He is survived by a son, Mike, a daughter Leeann, and his adored granddaughter, Kayla.

Appealing Medicare's Gleevec quantity limits

By Elizabeth Braun

If the Medicare Plan D prescription program selected by a Medicare beneficiary has a quantity limitation for Gleevec, there is an exceptions process that may allow the patient to receive the amount of medication they need.

Since only 8.6 percent of the plans across the nation have a quantity limit on Gleevec, naturally, the best option is to select a prescription plan without any limitations.

If a patient needs to utilize the exceptions process, there are a few simple steps to follow. First, request a letter from your doctor enumerating the medication(s) and the dosages that require an

Steps for appeal of Medicare Plan D:

1. Obtain a letter from the patient's doctor.
2. Call the prescription plan.
3. If required, request the expedited process.
4. Copy the letter for the patient's files.
5. Send the letter to the prescription plan.

exemption along with the physician's statement of medical necessity. Call the patient's prescription plan. Notify the company that an exception is being re-

quested. Request the best address or fax number to send the letter. Keep a copy for the patient's records and send this letter to the prescription plan. The plan has 72 hours to notify the patient of their decision on the exception.

If necessary, a patient or the treating physician may request that the exceptions be processed on an expedited basis. Should this be required, let the company know when the phone call is placed that the patient is requesting an expedited exception. The company then has 24 hours from the receipt of the letter to process the request.

Should a patient need assistance navigating this process, they may contact Novartis' Gleevec Helpline at 1-800-GLEEVEC.

TOBES

From Page 9

Emily wanted her "Papa" to take her in the water and indeed he did. Emily is a fish and Allan was so proud to watch her swim and jump into his arms.

The Life Raft Group was another of his passions. When he was diagnosed with GIST, he found out as much as he could about the disease. There was no support group in the Detroit area, so Allan took it upon himself to start one. He noted the names of people from the Detroit metropolitan area who were posting to the Life Raft list and invited them to a meeting at Gilda's that he'd arranged.

He encouraged people to talk about their issues and had no qualms talking about the physicians — in spite of Gilda's policy against possible "doctor bashing." Gilda's usually supplied a support person to help run the meetings. That went by the wayside, as Allan took over. He arranged the dates, speakers if the group wanted one, and led the meetings.

When invited to be part of the Life Raft board, he worked hard to help support the organization. He was thrilled with the recent research money from

Novartis and made known his recommendations as to how it should be used.

Allan was a fighter for anything he believed worthwhile. Sometimes he was quite vocal, sometimes quiet, but always in an intelligent, articulate manner.

I could continue for many pages about the many things Allan accomplished in his life, but the most telling was how people respected him even until the end. When Allan came home from the hospital this last time, we set him up in our library. People began coming from Chicago, Florida and Ohio to tell him how much he had meant to them and how much he was loved.

Allan was extremely active and instrumental in arranging the purchase and renovation of three buildings for the community mental health agency of which we were on the board. As a further tribute to Allan, the executive director arranged with the funeral home for the cortege to pass those buildings on the way to the cemetery. As the cortege passed, standing outside were the people Allan helped to have a clean and appropriate place to do their work, standing and giving their respects.

Soon there will be a boardroom at this agency named in his honor with his portrait on the wall to remind all of how instrumental he was in the lives of others. Allan would have been proud but with humility.

Allan was a great husband, father, grandfather and friend. Everyone he met, from the grocery store clerk to the people at the cleaners, became his friends. They enjoyed talking and being with him. We have been blessed by his being.

I would like to share some words written by one of the executive directors:

"... There are no words that can convey how much he was appreciated or how much he will be missed. In helping us fulfill our mission over the years, he has indirectly improved the quality of life for over 50,000 of Detroit's most fragile and needy individuals. And if there is truth in what my grandfather used to say about the true worth of a man, the mark he leaves on this world is determined by the number of lives he has touched, and the number of thank yous he owed, then Allan was a man of tremendous worth."

OPTIONS II

From Page 4

that has been made in treating GIST. It has also been beneficial to the patients as it gives them access to the most advanced medicines prior to approval by regulatory agencies. It also gives them access to doctors and nurses who are much more experienced with GIST. We recommend that patients participate in clinical trials whenever possible.

We recognize, however, that not all patients are eligible for participation in clinical trials. Overly stringent exclusion criteria, such as only allowing ECOG status 0 and 1 patients into trials is sometimes to blame, but sometimes patients simply are too sick, can't afford it (travel adds up!), or can't participate for one reason or another.

In theory these patients could still access the latest drugs through compassionate use, but with the exception of the expanded "treatment use protocol" for Sutent (which still had exclusion criteria and required travel), the compassionate use program is difficult to navigate, slow, and seldom used successfully.

For GIST patients, there are a few options today that did not exist a few months ago. There are now two drugs approved for GIST; Gleevec for initial treatment of metastatic or unresectable disease, and Sutent for Gleevec-resistant GIST.

For patients who have exhausted all other possibilities, there is another drug, Nexavar (BAY 43-9006), which is approved for kidney cancer and is in phase II trials for GIST. Nexavar is in some ways similar to Sutent. It inhibits KIT and the VEGF receptors (like Sutent) and also adds RAF inhibition. While it is not approved for GIST, Nexavar or possibly some type of drug combination represent a potential treatment of last resort. Off-label treatments such as this have many challenges, including unproven efficacy (especially after use of Sutent, which has many similarities), unknown toxicity (for combinations), and possibly denial of coverage by insurance, but they may represent a last hope for some patients.

Despite GIST, girls just wanna have fun



Pediatric GIST patients Josalin Dunn, 8, left, of Florida and Leah Knopp, 10, of Washington state, enjoy time at Disney World and other theme parks in Orland, Fla. The two young patients connected through the Life Raft Group, and their families got together over the winter school break. If they look a little damp, it's because of the thrill ride they were just on.

Award named in memory of Nancy Ann Hughes Welsh



The Sero Symposia International conference, "From Discovery to Application – Biomarkers, Diagnostics and Molecular Therapeutics in Cancer," was held Feb. 2 in Boston. Serving on the science committee were Dr. George D. Demetri and Dr. Jonathan A. Fletcher, both of Dana-Farber Cancer Institute & Harvard Medical School. Fletcher presented the Nancy Ann Hughes Welsh award, named for the late Life Raft member and daughter of LRG board member Jim Hughes. From left are Randall Welsh, Nancy's husband, Dr. Fletcher, conference organizer Jennifer Gardella and Dr. Demetri.

REICHARDT II

From Page 8

the limits. If one never went to the sauna, be careful and start slowly.

What should GIST patients consider, when they go on vacation?

Imatinib increases the photosensitivity of the skin and makes it much harder to get a tan. The risk to get a sunburn is much higher. Proper dress, sun protection (high SPF) and not too long sunbaths are important. The sun in the mountains should not be underestimated. Where to go?

This decision depends on the stage of the disease and the current treatment. Somebody who is treated should go into countries where access to medical care is easily granted. A metastatic patient treated with imatinib should not take a Jeep tour through the Sahara. If a patient is not sure, then this question should be discussed with the treating physician.

Can a female patient treated with imatinib become pregnant and can a

male patient treated with imatinib become a father?

Women treated with imatinib should under no circumstance become pregnant. The drug has very likely a big risk to influence the development of the embryo. It is unclear if a man treated with imatinib should become a father. There is no experience or data available. However, it is recommended to not become a father. Independent of becoming a parent, patients can be sexually active.

The fear is that imatinib can influence the development of the embryo. Is there any evidence that the sperm cell or egg cell could be damaged?

No, there is no evidence. If a patient underwent successful surgery, no tumor left and received for a few years imatinib as an adjuvant treatment, then the patient can become a parent after having stopped the imatinib therapy for a while. The prognosis needs to be taken into consideration. If we talk about a high risk GIST patient with a high risk of relapse who receives imatinib adjuvant, then I would not rec-

ommend considering parenthood. If a patient makes an informed decision and still decides to become a father or mother, then there is no contraindication from a medical standpoint. This is more an ethical or moral question.

If a parent has GIST, is there a risk the kids might get GIST one day?

No. There are a very few exceptions of GIST cases running in a family but GIST in general is definitely not inheritable.

Some of the patients know that the grandparents had a tumor in the gastro-intestinal area. Could it be possible that these cases were a GIST but were not diagnosed as such?

Family based GIST is extremely rare and there are only a few cases known globally. So the chance, that this was a misdiagnosed GIST is very small. Tumors in the gastro-intestinal area are very frequently diagnosed. If it comes up in a family history, this does not mean anything.

Dr. Reichardt, thank you very much for this interview.

THE LIFE RAFT GROUP

Life Raft staff

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
Program Coordinator	Sara Rubinoff	srubinoff@liferaftgroup.org
Research Coordinator	Elizabeth Braun	ebraun@liferaftgroup.org
Research Assistant	Pamela Barckett	pbarckett@liferaftgroup.org
Science Coordinator	Jerry Call	Jerry.Call@comcast.net

Board of Directors

Executive Committee

Stan Bunn , President	SBunn@BSTGlobal.com
John Poss , Fund-raising	John@PossHaus.com

Directors

Robert Book	RMBook2@aol.com
Mia Byrne	mebmcb@wowway.com
Chris Carley	ccarley@fordhamco.com
Jerry Cudzil	Jerry.Cudzil@DACFunds.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

How to contact the Life Raft Group

40 Galesi Drive, Wayne, NJ 07470

Phone: (973) 837-9092; Fax: (973) 837-9095

Web: www.liferaftgroup.org; e-mail: liferaft@liferaftgroup.org

Life Raft volunteers

General Counsel	Thomas Overlay	guitarman335@msn.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@PossHaus.com
	& Gerald Knapp	gsknapp@winfirst.com

Arizona
Chicago
Colorado
Los Angeles
Michigan
New York
Texas

Life Raft area groups

Linda Martinez	linda.martinez1@cox.net
Richard Kinzig	rjkinz@aol.com
Jerry Call	Jerry.Call@comcast.net
Floyd Pothoven	floyd@keralum.com
Ellen Rosenthal	ebrosenthal@comcast.net
Dan Cunningham	Daniel.Cunningham2@pseg.com
Kerry Hammett	yaloo@gvtc.com
& John Poss	John@PossHaus.com

Life Raft country representatives

Brazil	Vanessa Passos	vanessa@endo.med.br	Malaysia	Yong Choo Sian	ycspj2005@yahoo.com
Canada	David Josephy	djosephy@uoguelph.ca	Mexico	Rodrigo Salas	rsalas@maprex.com.mx
China	Ruijia Mu	mu_ruijia@yahoo.com	Netherlands	Ton de Keijser	tdk@liferaftgroup.nl
Columbia	Jaime Peralta	peraltas@etb.net.co	Norway	Jan Einar Moe	jeinmoe@online.no
Costa Rica	Michael Josephy	mjosephy@gmail.com	Poland	Stan Kulisz	listy@gist.pl
France	Estelle LeCointe	gist.estelle@laposte.net	Singapore	Yong Choo Sian	ycspj2005@yahoo.com
Iran	Negar Amirfarhad	negaraf@sympatico.ca	Switzerland	Ulrich Schnorf	ulrich.schnorf@bluewin.ch
Israel	Ben Shtang	ehuds@merkavim.co.il	Turkey	Haver Tanbay	tanbay@tanbay.net
Italy	Anna Costato	anna.costato@virgilio.it	U.K.	David Cook	D.Cook@sheffield.ac.uk

Who are we, what do we do?

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

How to join

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

Privacy

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

How to help

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

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

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

Disclaimer

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