Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

August 2004 In memory of Carol Berres, Mitsuru Hayami Vol. 5, No. 8

Bulletin! AMGEN launches phase II clinical trial for GIST patients- see page 9 for story

When the patient is a doctor

Dr. Arnold Kwart learns what life is like on the other side of the desk

By Arnold Kwart, M.D.

I am a 62-year-old urologic surgeon who has lived in Washington, D.C. since 1977. I have been happily married to my wife, Cathy, for 20 years. As chairman of a department of urology at a local hospital, I have administrative, teaching, research and patient responsibilities. My medical practice is primarily limited to patients with genitourinary cancers.

KWART

I frequently consult with patients, they on one side of the desk and me on the other, wearing a long white coat. We have lengthy discussions regarding the nature of their illness, treatment options and how those options apply to their specific problem. I attempt to remain responsive to their individual concerns, be compassionate and informative, always keeping in mind the patient's quality of life.

I have always believed that I will have a lengthy life, as my parents were in their late 80s when they passed away from natural causes. I was quite shocked when I learned I had a rare illness. I could become the topic of medical journals and perhaps grand rounds, the educational forums in hospitals.

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Nobel winner accepts Life Raft Group award

Watson's co-discovery of the structure of DNA provided the foundation for targeted cancer treatment.

By Norman Scherzer

The drive from our Life Raft Group office in New Jersey to Cold Spring Harbor Laboratory in New York took about 90 minutes but it seemed to be a journey back in time and place. It was 1951 and James Watson and Francis Crick began making 3-D models of DNA at the Cavendish Physics Laboratory of Cambridge University, Cambridge England. Eighteen months later they had found that the DNA molecule took the shape of a double helix. They had found, as the far from shy Crick exclaimed, "the secret of life." James Watson was 24

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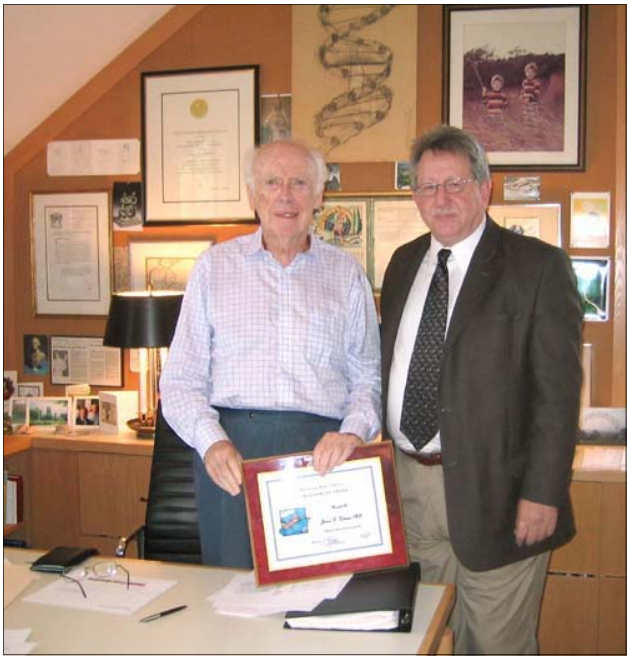

Nobel Prize winner Dr. James Watson and Life Raft Group Executive Director Norman Scherzer stand in front of the historic double helix.

UK prepares to OK Glivec for GIST

To qualify, patients must have GIST that is not operable or has spread

Good news for GIST patients in the United Kingdom: The National Institute for Clinical Excellence (NICE) announced Aug. 12 that it intends to approve the use of Glivec (imatinib) for treatment of gastrointestinal stromal tumors.

All citizens of the United Kingdom receive free health care through the National Health Service (NHS). But new therapies like Glivec must undergo exhaustive scientific review and cost-benefit analysis before patients are entitled to them.

NICE has been weighing Glivec for GIST for many months, even though the Scottish Medicines Consortium (SMC) advised the NHS that Glivec can and should be used for treating GISTs without restrictions two years ago. NICE's final decision on Glivec for GIST isn't quite as encompassing: Glivec will only be considered first-line treatment for patients with unresectable (inoperable) or metastatic (spreading) disease. And, if a patient has GIST that initially responds to Glivec but later has some tumor growth, the approved dose of Glivec (400 mg.) won't be increased.

The expense of Glivec may have given NICE pause. NICE's appraisal committee estimates that some 240 GIST patients will be diagnosed with inoperable or metastatic disease each year. It will cost just under £19,000 ($34,500 U.S.) a year to provide a patient with 400 mg. of Glivec. That will cost the NHS about £4.5 million ($8.2 million U.S.) a year.

Indeed, an initial decision by NICE's appraisal committee last spring alarmed both doctors and patients due to the restrictions it placed on the use of Glivec for GIST. The initial recommendation said that Glivec would be stopped if CT scans didn't show measurable tumor shrinkage within 12 weeks. Also, the initial decision proposed halting Glivec if only some — but not all — tumors responded.

Among those leading the charge for more comprehensive use of Glivec for GIST was Dave Cook, Life Raft Group member and founder of GIST Support UK.

"As a patient group we have been able to supply positive evidence about Glivec's effectiveness and remarkably mild side effects compared to conventional cytotoxic chemotherapy," Cook told PR Newswire Europe. "Prior to this decision it has only been possible for GIST patients to get the drug by taking part in clinical trials and at a

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years old. Nine years later (1962) Dr. James Watson and Dr. Francis Crick traveled to Sweden to receive the Nobel Prize.

Fast forward to January, 2004. The Life Raft Group was planning its May membership meeting and wrote to Dr. Watson:

"Dear Dr. Watson,

I realize that you have received many awards and accolades in your career and I would like to offer you now the sweetest one of them all ...

We would like you to stand before several hundred GIST patients to receive the Life Raft Group Humanitarian Award and, more important, to be able to look into the eyes of so many cancer patients who would not be standing there but for the pioneer work you have done. I believe that this would be the fitting connection to the 50th anniversary of your milestone research.

We are the testament to your efforts."

Dr. Watson could not make our membership meeting and the occasion had finally arrived when we could present his award in person. We pull into Cold Springs Harbor. I am accompanied by Barbara Kennedy, Executive Director of Novartis Oncology, a fellow 2004 LRG Humanitarian Award Winner, and Tricia McAleer, LRG Administrative Assistant. We seek out Dr. Watson's office on the sprawling 100 acre campus on the Long Island Sound, where Dr. Watson lives and works, and I am in awe and somewhat intimidated at the thought of meeting a Nobel prize winner. Suddenly a young women balancing several feet of culture plates piled one on top of the other dashes by our car, followed by another runner and then another. It is, we discover, part of an annual ritual and I am made calmer by the absurdity and sheer fun of it all.

We are met at the waiting room by Dr. Watson who had come out to greet us. We sit before his desk for over an hour listening and then discussing genetics and Gleevec and GIST. I have to process slowly in my mind that we are discussing genetics with the scientist who helped write the book. Finally I interrupt to present his award. I forget most of what I had planned to say and instead declare that what he had

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Her dad's story: Thriving on life's lemons

Daughter learns from her father's response to his cancer diagnosis

By Bianca Szyszkowski

Life is the type of gift that once given, it is up to the recipient to form and use it as they choose.

Although everyone's life path is different, in every life there are pleasures, joys and sadness. However, I believe, as the saying goes, when life gives you lemons, make lemonade. As cancer is becoming the world's major home-wrecker, many people need to learn how to cope; how to make lemonade. This is my story of how my dad chose to take something that could easily destroy his life and turn it into something that has benefited him greatly.

For my father, Marcel Szyszkowski, travel has always been one of the greatest treats. He enjoys meeting people, seeing places and learning about other cultures. He would not have had an opportunity to go to East Coast if he was not sick. In 2000, when his cancer recurred, he got to travel for surgery to Philadelphia. He used this location as a springboard to visit New York City and Washington, D.C. At the time I was a freshman/sophomore in high school and when I went with him to the East Coast, I was able to see many of the famous places I was learning about in history class.

Another recurrence in 2003 forced my dad to look for a new drug. He found one in Boston, Massachusetts. He enrolled in a clinical trial for a drug available then only in Dana-Farber Cancer Institute. He made several trips to Boston, and again used this city as a starting point to visit more famous places. On one occasion he took my stepmother and they drove to Niagara Falls. From there they made a huge tour that involved Toronto, Ottawa and Montreal. Although my father is a Canadian citizen he never had a chance to see Eastern Canada. He was amazed how different that part of Canada was from the western part he knew so well.

Marcel Szyszkowski and his daughter, Bianca, are seen during a float trip on the Yakima River in Washington state earlier this month. Marcel has combined his battle against GIST with his love of travel, seeking treatment at cutting-edge cancer centers from Philadelphia to Boston to Santa Monica, Calif., far from his home in Washington state.

After switching his treatment to the John Wayne Cancer Institute in Santa Monica, Calif.,in late April of this year,:now, instead of riding commercial airplanes on long, tiring flights, dad flies with Angel Flight, a volunteer organization that caters to medical patients with flights to many parts of the U.S. These trips are made in smaller, private airplanes and these planes fly considerably closer to the ground. As a result he is able to see much more of what is on the ground. I flew with him and have seen many breathtaking views, such as Mount Shasta in California and many beautiful rivers and plains. Recently, I flew with Dad on a Piper Malibu Mirage, a small aircraft with a jet engine that is worth over $1.8 million. The owner of this stunning piece of equipment was the former president of Angel Flight!

Dad took me, my little brother Paul and his wife Maggie on trips to Santa Monica and we visited all of the tourist sights there and in L.A .. Our favorite activity is riding the municipal bus. Riding these buses also gave me a window to the inside, as we all know that many interesting people ride public transportation.

So in conclusion, not all tragedies in life are completely bad. Cancer could have easily put a stop on my Dad's traveling. Instead, he took initiative and used his cancer to see beautiful, fun and exciting places. I was lucky enough to take part in the process: taking life's lemons and find out how to make lemonade. It's very easy to sit back and let life pass you by, but ironically, we experienced more than we would have if my father had not contracted cancer.

Bianca Szyszkowski is a recent graduate of River Ridge High School, Olympia, Wash.

M.D. PATIENT

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I will attempt to do the best I can to relate my experience, as I became the patient on the other side of the desk.

In July 2001, my wife and I planned to join a lifelong friend and his wife on a Baltic Sea cruise to celebrate his 60th birthday. We joined them in Copenhagen. The cruise was extraordinary and rather gourmet.

I was determined to work out with a personal fitness trainer every day. Five days into the trip, I was exercising while lying on my abdomen when I felt an unusual discomfort in my left upper quadrant. I rolled over and to my surprise felt a mass. I was stunned.

I immediately visited the ship's doctor. He did not confirm the presence of the mass — or maybe he was just reluctant to tell me. We decided that we would watch things for the time being. I considered being evaluated in Stockholm, our next port of call; however, it was a national holiday. I felt well but was extremely alarmed.

The doctor suggested that I was coming down with gastroenteritis, an inflammation that occurs on cruises. For the next three nights my abdomen had all kinds of bizarre symptoms that I couldn't put together. I became bloated. One night in particular, I told my wife that the pain was so severe that, if I were home, I would go to an emergency room. I endured.

My symptoms went away after a few days. As the others were dining on caviar and champagne, I had put myself on a bland diet of chicken soup. I could not partake in various activities aboard the ship. For most of the cruise I was confined in my "deluxe stateroom." I did participate in a number of onshore excursions and was able to visit St. Petersburg, an incredible place.

I examined myself after the symptoms dissipated. The mass had increased appreciably in size. It was obvious to me that what was happening was, in fact, dynamic. I thought that perhaps I might have bled into whatever I had noticed in the days prior.

"I saw my own films as they were developing — and was horrified. A very large mass was originating in the back of my stomach, pushing every adjacent organ aside."

I returned to the ship's doctor and we made arrangements for my medical evaluation at the next port of call, in former East Germany.

Early that morning a cab drove Cathy and me to Rostok University Hospital. A physician who spoke in broken English evaluated me. He examined me, confirmed the presence of the mass, and obtained blood work. I had bled into the mass. Subsequently, I had an abdominal and pelvic CAT scan. I saw my own films as they were developing — and was horrified.

A very large mass was originating in the back of my stomach, pushing every adjacent organ aside. I could not believe what was happening within me. I'd had a physical exam once a year. I thought I was aware of my own body.

It became apparent that we would have to fly home immediately. The concierge made arrangements for our flight from Berlin. We managed to pack in seconds. Tearfully, we said goodbye to our close friends, fearing I might never see them again. I thought I was facing my own demise.

"Although I had Cathy's loving support, I felt incredibly frustrated. … I began mourning for myself … I envisioned my funeral service … Some thoughts I would relate to my wife and others were too morbid to say aloud."

The next 36 hours were incredibly difficult. We took a cab from the last port of call to Berlin. As I pondered my fate, supported ever so much by my wife, we zoomed down the autobahn at more than 100 mph. Although I had Cathy's loving support, I felt incredibly frustrated. I called several people at home to alert them of my early arrival. We stayed overnight in Berlin and flew the next day directly to Washington, D.C.

During that time, I began mourning for myself. I did not think I would be using the plot at the Garden of Remembrance so soon. I envisioned my funeral service. I would cry spontaneously. Some thoughts I would relate to my wife and others were too morbid to say aloud. I realized I had a responsibility to remain rational throughout this ordeal. However, words do not convey the anxiety, frustration and fear that engulfed me.

We arrived in Washington without any problems. We immediately went to consult with several gastrointestinal physicians, as well as a well-respected radiologist. The mass could not be diagnosed. This heightened my fear. I was advise to rest over the weekend and return Monday for a series of evaluations, examinations and a consultation with the surgeon specializing in gastrointestinal malignancies.

Over that weekend I decided to call a physician at another hospital. I thought he might be able to give me guidance. My call was warmly received. He invited my wife and I for an informal

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Pam Barckett knows orphan disease

Meet Pam Barckett, medical research assistant for the Life Raft Group. In her position, Pam collects member patients' updates and other information that enables the group to produce the data that helps doctors and other patients with GIST.

Pam grew up in Totowa, New Jersey. She graduated from William Paterson University of Wayne, New Jersey with a bachelor's degree in accounting and business. Pam's dream was to be a professional dancer and ice skater. She is an experienced ballet dancer and also coaches her daughter's cheering squad.

Pam lives in Little Falls, New Jersey with her husband, Dave, and her 9-year-old daughter, Danielle.

Danielle has a rare metabolic disorder called tyrosinemia. Three months after Danielle was born, her stomach filled with fluid. She was rushed to the hospital. Several tests and doctors later, they discovered she has this rare disease. To date, Danielle is a normal little girl who is on a low-protein diet, special formula and an orphan drug called Orfadin. Danielle loves cheerleading, gymnastics, ice skating and dancing.

Pam is a member of NORD (National Organization for Rare Disorders) and participates in fund-raising for her daughter's cause. Pam's father is also very active in the fund-raising effort — and to date they have raised approximately $250,000. The funds go to the Danielle A. Barckett Clinical Research Fund/NORD for education and research. Pam co-manages a tyrosinemia Web site and is also on the board of directors of the National Coalition for PKU & Allied Disorders, a nonprofit organization concerned with metabolic disorders.

Pam found the Life Raft through a mutual friend of Anita Scherzer's. Pam and Anita go to the same hair stylist and she spread the word that the LRG was looking for someone to take on the LRG data. Pam jumped right in.

Pam Barckett, medical research assistant for the Life Raft Group, knows about rare diseases like GIST. Her daughter has a rare metabolic disorder called tyrosinemia and takes the orphan drug Orfadin.

Worldwide GIST Calendar

Sept 13-14: Rockefeller University, New York City-Cancer on the Internet-Presentation by LRG Executive Director

Sept. 18: Dallas, Texas-Texas LRG meets at Gilda's Club

Sept. 22: New York City area-educational focus group meets -site to be determined

Sept. 25: Scherpenzeel, Netherlands-LRG Nederlands meets at De Witte Holevoet Restaurant

October 10: Congers, New York-4thAnnual Walk for a GIST Cancer Cure at Rockland Lake State Park

October 22-23: Frankfurt Germany-Das Lesbenhaus GIST forum meets at Novotel

October 26: Worldwide-LRG Board of Directors meet by teleconference.

October 29: Worldwide-Kickoff of LRG Annual Thanksgiving Fundraising Campaign

November 7: New York City-Team Life Raft runs NYC Marathon as fundraiser.

November 11-13: Montreal, Canada-LRG relapse study paper presented to Connective Tissue Oncology Society

KWART

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consultation at his office Sunday. This physician is well known in the medical community and is perhaps one of the brightest surgeons in the United States.

He reviewed the films and, for the first time, we were given a glimmer of hope. He related that although the mass was large and complex, it was merely pushing against everything rather than invading it. He felt that there was an excellent chance of a cure. I held on to this hope and was extremely grateful for the consultation.

Monday morning I went through a number of diagnostic tests. The findings on the CAT scan where confirmed and there was no evidence of spread elsewhere.

The next stop was a consultation with a surgical oncologist, known to be a superb technician. Even though he had gone out of his way meet with us, I found this consultation unsatisfying. It was brief and impersonal. He also said that there might be out-of-pocket expenses for potential treatment that was somewhat controversial. Although I initially agreed, I remained unsettled. This surgeon had a plan from which he was not going to deviate, and more importantly, my quality of my life seemed to be a non-issue, which I found disconcerting. Although capable, it was clear to me that he would probably not be the surgeon for me.

That day, I called the physician we'd met on Sunday. He again was responsive, gracious and accepting. He suggested a meeting with him and the principal cancer surgeon of his department. We met for an hour and a half that evening. During the discussion, two things were salient in my mind. The first was a statement made by both, that the most important consideration in what was to be a lengthy surgery was that intraoperative judgment and decisions were critical. A surgeon had to go into this procedure with no time constraints whatsoever. The second was the fact that quality-of-life issues were addressed.

"I called Norman Scherzer and related my story. He quietly replied, 'You have lost your innocence'."

Though I might be inconvenienced initially, I would eventually have a pretty normal quality of life. I would lose a significant part of my stomach, my plumbing would be rearranged and I would have to eat multiple small meals. Over the ensuing months my stomach would enlarge so I could eat steak with the boys. We felt more satisfied that I was not just another person on the conveyer belt.

However, I didn't know the surgeon very well. I wasted little time checking him out. The opinions resounded that he was a superb surgeon and a caring person.

With that, I cancelled surgery with the first surgeon, then called the other facility to see if they would take me as a patient. I was reassured that I should have no problem.

I underwent a 7 1/2-hour procedure July 12, 2001. Two thirds of my stomach was removed along with a mass of about seven pounds, the size of a healthy baby. Throughout my hospitalization, I remained in disbelief. My recovery was smooth. I gained weight and over time was able to eat normally. My quality of life was quite tolerable. I resumed my busy schedule.

I was monitored closely receiving PET and CAT scans every three to four months. I did very well until April of 2002. That was when the floor fell from beneath me again; my surgeon reported that the scans had shown an isolated recurrence. I was crushed. I accepted the fact that I was to start on 800 mg. of Gleevec daily.

Other than fatigue and an occasional upset stomach, I tolerated the medication quite well. Very quickly the PET scan became negative and the CAT scan demonstrated considerable shrinkage. I elected a "second-look" operation in October 2002 and had my abdomen explored. The shrunken tumor was removed and demonstrated a minute focus of GIST surrounded by scar tissue. The remainder of my abdomen was clean. After recovering, I resumed Gleevec at 400 mg.

I again gained weight, ate normally, and resumed normal activities with close monitoring. I was not mentally prepared for the ensuing roller coaster ride I was to experience.

All studies were negative until May of 2004. Again, scans showed an isolated recurrent mass. Again, I sunk to new lows, called my wife and related that I would undergo surgery the following week.

It was incredibly difficult to call my patients and tell them that I would be transferring their care to other physicians. My support system at home and at work was incredible as schedules were shuffled and people were informed of my upcoming surgery. I called Norman Scherzer and related my story. He quietly replied, "You have lost your innocence."

On May 26 I was re-explored through the same incision. Fortunately, the recurrence was isolated, removed and had the same histological appearance as the original and second-look tumors. But the first weeks were very difficult as I again went through a personal mourning process.

As of late, a good pathology report, the ongoing support of many, and knowledgeable physicians have made me increasingly hopeful that the future is bright and filled with better times.

Perhaps it is the human spirit in all of us but it is needed to continue on our journey through this lifetime. It is just a few months from my surgery and I have been able to resume my life. I, like so many others, continue to have hope that there are no more surprises in the future and, if there are, they can be treated "simply" with a pill.

few centers where such trials have

UK OK

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taken place."

NICE's final appraisal determination (FAD) adopts the criteria of the United States' Southwest Oncology Group (SWOG), which counts stable disease as a good result. The FAD also says Glivec use should be decided by GIST specialists, and treatment decisions should be judged on the basis of individual symptoms and "other factors."

"We know that Glivec is highly effective in controlling tumor growth and improving quality of life," Dr. Ian Judson, consulting medical oncologist at the Royal Marsden NHS Foundation Trust, told PR Newswire Europe. "This decision should mean that all patients who need the drug will receive it and that it will be used appropriately."

Cook echoed Judson's views. "This decision is good news for patients who will have full access to the only effective treatment option available to them," he said. "This is particularly important for patients who are not suitable for surgery, as for them Glivec is potentially life-saving."

NICE's decision will ease the anxiety of patients trying to cope with cancer. "Glivec has already made a huge difference to my life, and now I know it will be available on the NHS," said Life Raft member Dan Wiseman of London. "I can look ahead without worrying about how I receive my treatment in the future."

NICE's final determination is subject to appeal through Aug. 26. After that, the determination will be forwarded the NHS for implementation by October.

Hayami-san faced GIST with 'ganbatte'

After a five-year battle with GIST, Life Raft Group member Mitsuru Hayami died July 12 in Tokyo, Japan. Despite the global distances involved, two Life Rafters met Hayami— Carol Donnell of New Zealand and Rita Raj of New York City. Carol learned of Hayami's death while in Melbourne, where she and Hayami had traveled to participate in the clinical trial of SU11248. Carol shared the sad news with the Life Raft, and Rita, who had met Hayami in

Japan, responded with the following tribute:"When I read Carol's note about Hayami-san's death, I immediately called his home. I had been meaning to get in touch with him and have been thinking a lot about him lately. I spoke to his wife, Mayumi, who informed me that Hayami-san died 12 July in Japan. He was on the phase III trial at Peter MacCallum Cancer Centre in Melbourne. …He had written me in May this year hoping that he was on the real thing as his complexion was getting yellow….

"I started a long and close e-mail relationship with him in 2002. I met him, his wife and daughter, Eri, in Tokyo on Christmas Eve 2002. We had made an appointment to meet at a station near my sister's home. A slim and smiling man rushed to me with a single rose. He said he recognized me from my Gleevec eyes! We had lunch together, sharing our Gleevec success and similar reactions and side effects. He brought many documents with him to our meeting.

Hayami-san with daughter Eri and wife Mayumi

He was working in a pharmaceutical company, and with a science background, had done a lot of desk research on GIST. As my scientific and medical vocabulary and knowledge, especially in Japanese, is quite basic, he patiently explained many things to me.

"It was an exhilarating time for both of us and also for his lovely wife and daughter. We promised to continue our friendship and keep in touch. He planned to visit New York with his family.

"After this meeting, we wrote to each other often, called up each other at odd times due to our 13-hour difference. When I was diagnosed with a regrowth, he supported me and encouraged me to get on the Sugen trial.

"Our constant greeting and farewell word was 'ganbatte,' which means 'persevere, fight, do your best.' He would call me, 'Rita-san, ganbatte.' He was always happy to hear about my good results.

"Then he had a regrowth and liver problems and ascites as well. He was in a lot of pain. He wrote for information and advice on where he could go in the United States for the Sugen phase III trial. This was last December. Norman, Trish, Bernie and I all tried to get the information for him to come here. The cost of his coming to the United States for treatment was estimated to be at least $100,000.

Hayami-san wrote to the Peter MacCallum Cancer Centre in Australia, a country he knew as he had spent about a year there before. He was accepted into the Sugen trial on May 7. …

"I have lost a very good friend. He gave me so much hope and support." Even when he was frantically looking for what to do for himself, he cared for his friends. He wrote to Tim in Hong Kong who was looking for alternatives for his mother.

"For himself, he was so determined to live, but he was aware of the constraints. He discussed with me his three options, i.e., a) ..., b).., and c) wait for death to come.

"On Monday, Aug. 30, 49 days after his death, in the Japanese Buddhist practice, his ashes will be placed in his grave. Let's light a candle for him. And to all of us, Hayami-san will say, 'ganbatte.'"

EDITORIAL

More study needed to determine optimal Gleevec dose

The dose that works at first may not be enough to keep relapse at bay

By Jerry Call
Life Raft Group Science Coordinator

Several large clinical trials have compared different doses of Gleevec in an attempt to identify the optimal dose. Differences in the initial results of the large phase III trials conducted by the U.S./Canadian group and the European/Asian/Australian group have been reported. The European study found a longer time to progression at 800 mg. vs. 400 mg. The U.S. study did not find any such correlation between dosage level and time to progression. A recent Life Raft Group study of patient-reported data showed fewer relapses at higher doses, especially when the analysis was based upon actual dose delivered instead of the "intent to treat" (starting) dose.

A phase II study of Japanese patients was also reported at the 2004 meeting of the American Society of Clinical Oncology. This study compared 400 mg. vs. 600 mg. This study found a higher partial response rate at 600 mg. vs. 400 mg. (60.9 percent vs. 46.4 percent), but found that this difference was not statistically significant. It is interesting that the original phase II trials found a similar partial response rate when comparing 600 mg. to 400 mg. (58 percent vs. 49.3 percent as of 8/15/02).

Clinical trials use the dose that the patient was randomized to receive as the reported dose. That means the dose reported in a trial may not reflect the dose the patient actually receives. For example, a patient with unacceptable side effects at 800 mg. may have his or her dose reduced to 400 mg. (or in a few cases, less than 400 mg.). This patient could receive 400 mg. for most of the time they were in the trial -- but they would still be counted in the 800 mg. arm. Using the starting dosage as the basis for statistical analysis is called "intent to treat."

Drug treatment produces both desired effects and undesired effects. The acceptable level of side effects with oncology drugs is much higher than for most other diseases. One of the primary reasons to use "intent to treat" analysis is to try to measure the "real world results" of benefit plus toxicity. A patient on 400 mg. will probably have some level of benefit and some level of toxicity. A patient receiving 800 mg. may have some level of benefit greater than at 400, but the patient will probably have a greater level of toxicity. Intent-to-treat analysis attempts to answer which dose has the most clinical benefit. In theory, it should take into account beneficial effects, toxicity, a patient's ability to tolerate the drug, and even dose reductions.

The intent-to-treat method of analysis can be a useful tool and has had a valuable place in clinical trials. However, it falls short in the Gleevec-for-GIST trials when used as the sole reporting method. The problem: It fails to adequately account for the fact that side effects, for most patients, improve over time. For many patients, side effects get MUCH better. Dr. Allan Van Oosterom, Dr. Ian Judson, and their European colleagues have provided a possible explanation for this effect. They have found that the body's ability to get rid of Gleevec increases over time, resulting in patients having lower drug concentrations.

When I look at the results of all of the GIST/Gleevec trials, it is apparent that a starting dose of 800 mg. causes significant side effects for most patients, and is probably too high a starting dose. My impression is that 600 mg. may still be too high of a starting dose for many patients. In a Japanese study, 70 percent of the patients started at 600 mg. required dose reductions. Clearly there is a concern about the greater side effects that occur at higher doses.

Where do we go from here? After the remarkable early results in the original phase II Gleevec-GIST trials, the phase III studies were organized and started in a mere five weeks! This was an amazing accomplishment -- and desperately needed by GIST patients with no other effective therapy. At that time however, no one really knew that levels of Gleevec in the body would tend to fall over time. As a result, the trials were not really optimized to consider this phenomenon.

At the Life Raft Group membership meeting in April and at the ASCO meeting in June, Dr. Van Oosterom suggested that phasing-in higher doses of Gleevec might be possible. Interestingly, this is the method that was used by Dana-Farber Cancer Institute prior to the early phase III results. This is also the method that I favor.

While I believe that investigators will still learn more from the current phase III trials, I have my doubts that these trials can establish an optimal dose. Deficiencies also exist in the Life Raft Group study on dose. These include: patients not randomized (may introduce bias) and lack of central review (non-standardized response criteria).

What I would like to see is a dose-optimization trial of Gleevec where the high-dose arm has the higher dose phased in. This trial would have one arm at 400mg. vs. another arm where the dose was "optimized" for each

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September Newsletter Coming Attractions

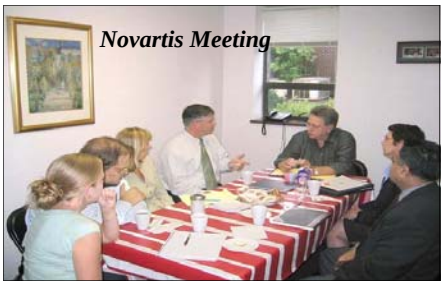
Ariad Meeting

Meet Ariad Pharmaceuticals: Planning for early 2005 phase l clinical trial for AP23573 for GIST patients. Report on meeting with ARIAD President Paul Sekhri, Chief Scientific Officer Timothy Clackson and Chief Medical Officer Camille Bedrosian.

Latest LRG surveillance of new drugs for GIST patients, including early feedback on the new BMS354825 phase l clinical trial for Gist patients.

AMGEN: Planning for phase ll AMG706 clinical trials continues; U.S. and worldwide trial site list expected. Report on meeting with David Parkinson, VP Oncology, Daniel Stepan, Director Clinical Research and marketing & communications staff.

Planning new educational materials and outreach. Report on meeting with Novartis Global Marketing team.



Novartis Meeting

And … Reports from Texas and the Netherlands Life Raft Group meetings, a special report from Das Lebenshaus, our sister organization in Germany plus meet our newest GIST dad from China and meet NYC Marathon Team Life Raft.

AMGEN launches phase II clinical-No placebo

After meeting by teleconference to discuss the new phase ll clinical trial for AMG706 we asked AMGEN pharmaceuticals to summarize their presentation. The following was submitted by AMGEN:

"AMG 706 is a potent, oral, multi-kinase inhibitor with anti-angiogenic and anti-tumor activity achieved by selectively targeting all known VEGF, PDGF, Kit and Ret receptors.

The safety profile observed in the ongoing Phase I study supports continuous uninterrupted once daily dosing. Continuous suppression of the mutant KIT kinase appears to be important in control of GIST tumors, as the Gleevec® experience has demonstrated.

There are currently two open enrolling clinical studies of AMG 706 in advanced cancers; the ongoing Phase I study and the new Phase II Gleevec-resistant GIST study. The Phase I experience with AMG 706 has shown sufficient evidence of clinical benefit to warrant a Phase II GIST study.

The Phase II GIST study is a single arm, open-label trial. All patients will receive AMG 706 at a single initial dose level that has been demonstrated in the Phase I study to be safe and well tolerated.

The phase II study is accepting adult patients with advanced GIST who have had progressive disease despite at least 2 months of Gleevec at doses of at least 600 mg daily. Patients must have adequate organ function and radiographic evidence of disease progression by the RECIST definition. No previous exposure to AMG 706 or other tyrosine kinase inhibitors of c-kit (except Gleevec) or VEGF (vascular endothelial growth factor) type (e.g., SU11248, PTK787) or anti-VEGF antibody (Avastin®) is allowed.

The ongoing Phase I study has recently been amended to include patients with GIST who have also progressed on SU11248. If this amendment is approved at the 2 sites, these patients who otherwise meet eligibility criteria will be permitted.

A brief synopsis of the study appears on the www.amgentrials.com site and on www.clinicaltrials.gov site

The best way for patients to find out if there is a site open near their location is to call the Amgen Call Center (866-57AMGEN or 866-572-6436)…"

Comments: As the LRG has previously reported AMGEN is extending its phase l trial to permit SU11248 trial patients who will be excluded from the phase ll trial to receive AMG706. They are also planning a second arm of the phase ll study in the near future to compare patients on Gleevec to patients on AMG706, with Gleevec patients switching to AMG706 at the first sign of progression. Our understanding is that this cross-over will be based upon clinical observation rather than RECIST criteria. Most importantly there will be ***no placebo*** *in either study arm*

Finally, AMGEN will make a list of clinical trial sites available to the LRG very shortly. Watch our website at www.liferaftgroup.org.

Norman Scherzer and Jerry Call

Dutch Life Rafters plan national gathering

The Dutch Life Raft Group is planning the first Netherlands gathering of GIST patients and caregivers Saturday, Sept. 25 at the De Witte Holevoet hotel/restaurant in Scherpenzeel.

More than 50 Dutch GIST patients and caregivers have said they'll participate in "Lotgenotendag 2004 Life Raft Group Nederland." The day will begin at 10:30 a.m. with a reception where GIST patients who know each other via e-mail meet face-to-face.

The program begins at 11 a.m. with a welcome by Ton de Keijser, voorzitter (president) of the Dutch LRG. At 11:15 a.m., Dr. Winette van der Graaf, one of the leading GIST experts in the Netherlands, will give a presentation. Van der Graaf works at AZG (Academic Hospital Groningen) and is the leader of trials for Glivec and the experimental GIST drug SU11248.

At noon, Van der Graff will be joined by representatives of Novartis, maker of Gleevec, and Pfizer, maker of SU11248, for a panel discussion. Following the 1 p.m. luncheon will be time for fellowship and discussion.

Thanks to sponsors (families, friends, Novartis and Pfizer) the event will be free of charge to all participants. Life Rafters from around the world are invited. Dutch-speaking patients and caregivers can read more information at the Dutch Web site, www.liferaftgroup.nl.

Dutch LRG volunteers have been busy for the past several months, getting the group's first newsletter published and expanding the group's Web site, which now has "lots of medical information about GIST in the Dutch language, but have also made links to English articles that might be interesting," said Marlies Bruinsma.

The first newsletter published in July reported how the Dutch LRG started and what the group has accomplished in the first few months of its existence.

For more information, e-mail info@liferaftgroup.nl. For participation in the Sept. 25 gathering, e-mail lotgenotendag2004@liferaftgroup.nl.

OVER-LEVEN MET GIST
Life Raft Group Nederland

Nieuwsbrief Juli 2004 — Jaargang 1, No. 1

OPRICHTING

Goedereede, 16 oktober 2003

Oprichting van Life Raft Group Nederland. De eerste onofficiële lotgenotendag op 28 juni 2003 bij Ton en Ineke de Keijser in Ridderkerk. Door een zestal vrijwilligers werd een bestuur van een stichting opgericht. Na veelvuldig en vruchtbaar overleg tussen dit bestuur, was het 16 oktober 2003 zover, de statuten van Life Raft Group Nederland waren gereed voor ondertekening bij de notaris.

Ton de Keijser (voorzitter), Lonie Flaten (penningmeester) en Marlies Bruinsma (secretaris) hadden een afspraak gemaakt bij Notaris De Kooning te Goedereede. Na een korte voorlezing van de opgemaakte statuten, die overigens waren goedgekeurd door het bestuur, werden deze ondertekend door bovengenoemde aanwezigen.

Na deze officiële oprichting van onze stichting hebben we een glaasje gedronken en zijn hierna allen weer vertrokken.

FOLDER

In de maanden oktober en november is het bestuur bezig geweest een folder te maken die beknopte informatie bevat over GIST en de Nederlandse LRG. Wat de behandelmethoden zijn, hoe men ons kan bereiken, en wat wij als Stichting willen bieden. Vooral de lay-out is danig onder handen genomen, Ander moderner logo, kleuren die meer sprekend zijn en opvallen. Natuurlijk zijn er vele tekst wijzigingen gedaan, maar uiteindelijk hebben we een folder gemaakt waar we wel mee voor de dag kunnen komen.

Omdat de LRG uitgenodigd was voor een workshop van de stuurgroep weesgeneesmiddelen, was het nodig om folder-materiaal te hebben. In vergelijking met andere folders van andere patiëntenverenigingen lijkt het dat we een vrij complete folder hebben samengesteld.

De eerst 200 folders zijn gekopieerd. Nadat op 7 december de folder, tekst en lay-out, is goedgekeurd door het bestuur, zijn er 6000 folders gedrukt.

Binnenkort worden deze verspreid over ziekenhuizen, oncologen en patiënten.

WEBSITE

Na de bestuursvergadering in Ridderkerk van 7 september jl. is Hilbrand Bruinsma begonnen met het opzetten van de website. Na wat voorbeelden te hebben bekeken van andere patiëntenorganisaties hebben we gezamenlijk gekozen voor de huidige versie. Nadat het nieuwe logo bekend was in dit ook geïmplementeerd en zo ook wat algemene informatie over GIST, Glivec, het aanmelden bij onze stichting, etc.

Het is de bedoeling dat alle(laatste)nieuwtjes en veranderingen ook op de website komen en dat dit eigenlijk de hoofdbron van informatie wordt. Een aantal mensen zullen dan ook een toegangscode krijgen om zelf op gedeeltes van de website nieuws te melden. Ook dit staat allemaal nog in de kinderschoenen en zal nog verder geoptimaliseerd worden. Zo wordt op dit moment de eerste Nederlandstalige medische GIST informatie op de website geplaatst.

Website: www.liferaftgroup.nl Informatie: info@liferaftgroup.nl KVK nr. 20112471, Breda
Uw donatie is van harte welkom. Girorekening 96 77 464, Rijswijk t.n.v. Life Raft Group Nederland

The first Dutch Life Raft Group newsletter, edited by Marlies Bruinsma.

EDITORIAL

From Page 8

patient. This would require the key pharmacokinetics researchers and clinicians reaching a consensus on what parameters need to be included to determine an optimum dose.

In my vision of this trial, it would start the "optimized" patients at 400 mg., measure drug concentrations and variables at one month, then, as tolerated, raise dose to "optimal" levels after another month, again at the third month, then every three months (scheduled to match CT scans). The timing of the phase in would have to be determined by the experts.

This type of trial is in line with current medical practice of proving what we think we know. It also makes better use of the intent-to-treat principal. If we think that phasing-in a dose is the way to go, then the intent-to-treat principal will test whether this method truly is better. I do believe, however, that the actual dose should generally be reported in addition to the intent-to-treat dose in most clinical trials. I think this will help identify potential concerns in some cases. I believe that analyzing actual dose was one factor in focusing attention on the question of optimal dose in GIST. The other key factor was the finding by the Europeans that Gleevec concentrations tend to decrease over time.

Until we can either have the current phase III studies analyzed by both intent-to-treat AND actual dose, or we can do a trial similar to the one proposed above, patient and their doctors will have to educate themselves about the pluses and minuses of each study and make the best decision about what dose to administer. The questions that I urge patients to ask themselves are: Do I fit the profile described in the LRG study? That is, patients with metastatic GIST who had initial shrinkage? If the answer to that question is yes, *then* ask: Have my side effects gotten better over time? If the answer to both these questions is yes, *then* consider that a dose increase may be needed to maintain the drug concentration you started with.

Of course, no matter what *you* decide, you will still have to convince your doctor to change your dose.

Carol Berres persisted in life's journey

By Amy Rabideau-Silvers
Milwaukee Journal Sentinel
(reprinted with permission)

Carol Berres was making a new life for herself when life itself became the goal.

She woke in sudden pain - a searing pain that temporarily immobilized her - and went to an urgent care clinic that morning.

That was on July 3, 2000.

Doctors found a tumor the size of a bowling ball growing behind her stomach. Surgery was planned. Nothing about the prognosis was good. Berres, the mother of two young daughters, asked stunned friends to witness her signature on a will and power of attorney.

"It doesn't matter where you are when you first hear it - in a doctor's office, over the telephone at home, or in my case, a sterile waiting area," she later wrote for the Journal Sentinel. "There is a single instant that a person with cancer will never forget: It's the moment they're told they have the disease.

"It's our moment and ours alone, and it's the beginning of the most solitary of journeys."

Berres' journey ended Wednesday. She died in hospice care at her home in Milwaukee, in the presence of family. She was 47. Doctors first believed that her cancer was an extremely rare form called leiomyosarcoma. Later they determined it was something called gastrointestinal stromal tumor, or GIST, equally rare and even more persistent.

"They initially gave her maybe 13 months," said Judith Gifford, her sister. "She survived four years."

Following her first surgery, Berres

decided that she had to try chemotherapy. She knew in her heart of hearts this was not going to add to her life and certainly not to her quality of life," said her sister. "She later said, if she hadn't had children, she might have made a different decision."

Thanks in part to her own persistence, Berres was accepted into one - then a second - drug trial. She was the first Wisconsin resident to take part in a nationwide clinical trial of the drug Gleevec, which has shown promise in shrinking some tumors.

"I'm thrilled," Berres later said of the study. "I'm not one of the lucky ones who have had a lot of shrinkage."

She later traveled to Boston to participate in the second drug trial.

She did it all for her children. She also did it for the science and what doctors could learn about treating cancer.

Berres was beginning to feel a little better again - even talking about taking a daughter to New York City - when she suffered a stroke in January. It became increasingly hard for her to regain her strength and fight the cancer.

The former Carol Gifford grew up in West Allis, graduating from West Allis Central High School. She began working office jobs, including at Moebius Printing. She married and began a family.

In her 30s, she also decided to go to college, picking Mount Mary College for a communications degree.

"She would bring Caitlin, who was 6 or 7," Judith Gifford said. "Caitlin would work on 'homework' in the back of the classroom. She brought Cassie as an infant to the college nursery program, so she went to college, too."

Berres moved into marketing at Moebius, and most recently worked in marketing for the Journal Sentinel.

She was divorced just before the diagnosis of cancer. She had already bought another house but had to delay moving into it until after surgery.

Berres found support through the Life Raft Group, first started as a way for patients in the Gleevec trial to communicate with each other. She also became active with Gilda's Club, which helps provide meeting places and emotional support for those dealing with cancer.

John Ptacek, a former co-worker at Moebius, recalled how they became good friends as both were awaiting their first children.

She was always a good listener, someone interested in other people, he said.

"You'd have a conversation," Ptacek said. "And she'd say, 'But how are you doing? How's your life?'

"It's not that she wasn't mortally aware of everything going on with her body. But she wasn't dwelling on it."

"She was delightful," Judith Gifford said. "Her humor was delightful. She was fun. She was a risk-taker, even before she got sick, but especially after. She was an adventurer."

Her daughters, Caitlin and Cassandra, are now ages 16 and 8. Survivors include mother Beulah Gifford; Judith and three other sisters, Gloria Harter, Patricia Carlin and Ruth Gifford; brothers Michael, Gerald and William R. Gifford; nieces and nephews.

Memorials are suggested to Gilda's Club. For information, go to www.gildasclub.org.

Watson

From Page 2

done had saved my wife's life and I wanted to thank him. I do, and then add a few remarks on behalf of all the members of the Life Raft Group.

After graciously posing for photos Dr. Watson asks what we are doing for lunch. We respond in unison that we have no plans and after a breath taking walk to keep up with him as we cross the campus, we join him in the cafeteria where he proposes a collaborative GIST research project that would draw upon the technology and expertise of the Cold Springs Harbor Laboratory.

Lunch ending, I remark to our new friend Jim Watson how much he had put us at ease. He replies that this was a skill he learned from his mother.

Three hours after we arrive we head back to New Jersey after a day to be remembered.

The Life Raft Group

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Who are we, what do we do?

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

How to join

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

Privacy

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

How to help

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

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

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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.

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