Battling gastrointestinal stromal tumor

LIFE RAFT GROUP

December 2007 | In memory of Gerald Snodgrass | Vol. 8, No. 12

LRG webcasts keep drawing high interest

By Sara Rothschild
LRG Program Coordinator

In June 2007, the Life Raft Group held its first webcast in a series of educational "virtual seminars". Dr. Jonathan Trent from M.D. Anderson Cancer Center in Houston, TX kicked off the series by discussing "New Developments in GIST for Patients and their Families." Since then we have successfully shown a webcast every month. Dr. Jonathan Fletcher from Dana-Farber Cancer Institute spoke next on the "Pathway for a Cure" in July, followed by Jerry Call, LRG science coordinator, and David Josephy, PhD, LRG science team member in August. They gave a comprehensive presentation on "GIST: The Basics". Drs. Chris Corless and Mike Heinrich from Oregon Health & Science University spoke in September on

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Apoptosis: How to kill a GIST cell

By Dr. Anette Duensing
University of Pittsburgh Cancer Institute

Most GISTs are caused by activating mutations of the *KIT* or platelet derived growth factor receptor A (*PDGFRA*) tyrosine kinases, which makes them amenable to successful treatment with the small molecule kinase inhibitor imatinib mesylate (Gleevec). It is well known, that imatinib inhibits the activation of normal and mutated KIT, PDGFRA as well as a number of other protein kinases. However, despite high initial response rates, durable, complete responses are unfortunately rare and the majority of GIST patients acquire resistance to imatinib over time. Although the inhibitory action of imatinib on the KIT and PDGFRA kinases is well established, the mechanistic events by which kinase-inhibition leads to clinical responses on a cellular basis are not known in detail. However, it is important to identify the biochemical mediators of imatinib-induced GIST cell death in order to develop innovative strategies. Such strategies atttempt to induce more complete responses, overcome imatinib resistance, and to thus enable more effective disease control with an aim towards cure.

DUENSING

Working with a GIST cell line model that was originally developed in Dr. Jonathan Fletcher's lab (GIST882)(1), we were interested in the biochemical players in GIST cell death

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'Tis the season to be jolly?

By Erin Kristoff
LRG Newsletter Editor

You walk out of your house and wrap your coat tightly around you. Sitting in your car, you let it run a few extra minutes while the engine warms up. On every street you pass, people are stringing up lights and inflating massive snowmen and snowglobes. Fathers and sons are balancing precariously on rooftops. Shop fronts are plastered with snowflake decals and forty percent off signs. Parking lots resemble demilitarized zones and you engage in a hazardous game of musical parking spots.

Its official: The holidays have arrived.

Family togetherness, caroling and candle-lighting aside, there's no question about it, the holidays can be hard on everyone. But GIST and other cancer patients can have a harder time than others. So I asked some of our members how they deal with the chaos of the holidays and got some tips on how to alleviate the stress.

The "Rush"

Between treatments, shopping and preparing for get-togethers a GIST patient has to know and accept their own limitations and learn how to work with them. Nora Fraser, who has been on Gleevec since June 2006, is all too familiar with this. "I try to not focus on it. I focus on what I

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Dana Farber study focuses on wild-type Kit and pediatric GIST

By Jerry Call
LRG Science Coordinator

The Connective Tissue Oncology Society (CTOS) recently held its 2007 meeting in Seattle, Washington. At the meeting, Dr. Katherine Janeway, Department of Pediatrics, Dana-Farber, gave a presentation about Pediatric GIST: "Pediatric KIT and PDGFRA-wildtype GISTs share KIT activation but not genetic progression mechanisms with adult GISTs".


JANEWAY

Dr. Janeway and her colleagues reported that, like adult GISTs, the KIT protein is activated in pediatric GIST despite the fact that KIT rarely is mutated in pediatric patients. In adults, the KIT protein is mutated over 80 percent of the time and these mutations cause the activation of KIT which is the primary driving force of adult GIST.

In this study, the patients ranged in age from six to 22 years old at the time of diagnosis, 85 percent were female, two patients had Carney's Triad and three of 27 (11%) pediatric GIST patients had KIT mutations. The three mutations included one KIT exon 11, one KIT exon 9 and one PDGFRA exon 18 mutation. Combining these 27 patients with 31 previously published cases, the authors noted that KIT or PDGFRA mutations are only present in about 15 percent of pediatric GIST cases.

Wild-type is the genetic term used for the typical form of a gene, organism, strain or characteristic as it was first observed in nature. When someone refers to "wild-type KIT", it means that the KIT gene is "normal"; it has no detectable mutation. GIST patients can have mutated KIT (>80% in adults), mutated PDGFRA (about 6-7% in adults) or they have both wild-type KIT and wild-type PDGFRA (>10% in adults and about 85% in pediatric GIST). Since it is somewhat clumsy to say that a GIST patient has wild-type KIT and wild-type PDGFRA, we often shorten this to say a person has "wild-type GIST". It means that they don't have a mutation in either of the two genes (KIT and PDGFRA) that typically play the dominant role in GIST.

In this study, 12 of 13 pediatric GIST tumors had activated KIT even though the KIT protein was not mutated (wild-type). Janeway and her colleagues noted that, in general, these patients had about the same amount of KIT protein in their tumors and it was activated as strongly as it is in adults with mutated KIT.

Blocking the growth/survival signal of KIT (or PDGFRA) with Gleevec is the main treatment for adults with metastatic GIST and it is very effective, at least initially. A number of different groups have reported that Gleevec is more effective at inhibiting the most common type of KIT mutations, exon 11 mutations, than to wild-type KIT. In fact, in test tube experiments, inhibiting wild-type KIT typically requires ten times the concentration required to inhibit exon 11 KIT (a typical concentration required to effectively inhibit V560G exon 11 is 0.01–0.025 µM; for wild-type KIT it is 0.1–0.2 µM).

In addition to providing the major driving force in GIST tumors, KIT signaling is important in a number of normal cell types in the body (for example, the normal development of blood cells). In patients with exon 11 mutations (most adults and very few children), the difference in Gleevec sensitivity between the mutant KIT in tumors and the normal (wild-type) KIT in the rest of the body provides a "therapeutic window". The goal would be to have a dosage high enough to inhibit the mutant KIT in tumors, but not so high as to inhibit the (wild-type) KIT signal used by some

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The Life Raft Group

Who are we, what do we do?

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

How to join

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

Privacy

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

How to help

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

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

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

Disclaimer

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

December 2007 international clinical trial update

By Jim Hughes
Science Team Member

Due to many recent changes in United States trials, these updates have been added this month. The table below will still only include international trials, in keeping with our system which alternates United States and international trials each month.

US Trials

AUY922 Phase I: A phase I dose escalation study of AUY922 administered intravenously on a once weekly schedule in adult patients with advanced solid malignancies. AUY-922 is an HSP-90 inhibitor manufactured by Novartis. Patients may not have had prior HSP-90 or HDAC inhibitor therapy. Locations include UCLA, contact: Carolyn Britten, M.D. 310-825-5268; Dana Farber contact: Stephen Hodi, M.D. 617-632-5053; Washington University (St. Louis, MO) contact: Paula Fracasso, M.D. 314-362-5654; Nevada Cancer Institute (Las Vegas, NV) contact: Sunil Sharma, M.D. 702-822-5360. Novartis also lists a central contact number 1-800-340-6843. Novartis study ID is CAUY922A2101 and the NCT is NCT00526045.

Perifosine plus Sorafenib Phase I: Oncology Specialists in Park Ridge, IL has called to inform us they have Phase I Perifosine + Sorafenib. Perifosine is an HDAC inhibitor. Sorafenib inhibits multiple tyrosine kinase targets associated with GIST. Patient contact Kathy Tolzein, RN, 847-268-8200. NCT is NCT00398814.

STA-9090 Phase I: STA-9090 is an HSP-90 inhibitor. According to the Synta press release, in preclinical studies, "STA-9090 has shown the ability to inhibit multiple kinases with comparable potency to, and a broader activity profile than specific kinase inhibitors such as imatinib, erlotinib, and sunitinib. In addition, STA-9090 has shown potency ten to 100 times greater than the geldanamycin family of Hsp90 inhibitors, as well as activity against a wider range of kinases. In in vivo models, STA-9090 has shown strong efficacy in a wide range of cancer types, including cancers resistant to Gleevec, Tarceva, and Sutent." This open-label Phase 1 study in patients with solid tumors is designed to identify the maximum tolerated dose of STA-9090 based on a twice-a-week intravenous dosing schedule. In addition to an evaluation of safety and tolerability, patients will be assessed for response rate based on the RECIST criteria. A second Phase 1 study with an alternative, once-a-week dosing schedule is planned. Contact Jeffrey Shapiro, MD, PhD at Dana-Farber: (617) 632-4942.

SNX-5422 Phase I: "Safety and pharmacology of SNX-5422 mesylate in subjects with refractory solid tumor malignancies" has opened in Nashville, TN and Scottsdale, AZ. SNX-5422 is an HSP-90 inhibitor made by Serenex. Contact: Trisha L. Hoyle, B.A. 919-792-3740. NCT is NCT00506805.

XL765 Phase I: Manufacturer Exelixis is sponsoring a Phase I trial of its PI3K and mTOR inhibitor XL765 at two sites in the United States: Wayne State Univ., Detroit, MI, contact Theresa Laeder 313-576-9386 and START, San Antonio, TX, contact: Gina Mangold, 210-413-3594. NCT is NCT00485719.

International Trials

AB1010 Phase II: The AB1010 Phase II trial in France is closed. Results were presented at the American Society of Clinical Oncology in June. Preliminary reports are that 90 percent of untreated GIST patients had benefit. Plans are underway for two first and second line randomized trials.

Imatinib + RAD001 Phase II: There are 11 clinics in Germany where the trial is listed as open. Contact information is available at the Novartis web site in Germany www.novartis.de. Locations and contact information are listed after selection of a postal code area. Novartis also supplied a telephone number in Basel: 41 61 324 111.

Glivec + IL2 Phase I: Please see page 9 for full article.

PTK787: This trial is now listed as closed.

XL765 Phase I: Manufacturer Exelixis is sponsoring a Phase I trial in cancer of its oral PI3K and mTOR inhibitor XL765 at Hospital Universitario Vall d'Hebron Barcelona, Spain. A thirty day drug holiday may be required prior to trial start.

AMN107 (nilotinib, Tasigna®)

Efficacy and safety of AMN107 compared to current treatment options in GIST patients who failed imatinib and sunitinib

Phase: III
Conditions: GIST
Strategy: Inhibit KIT
NCT#: NCT00471328
Contact: Novartis gives a central contact #
Telephone: 862 778 8300
Sites: We have reports of as many as 32 international sites being open and 10 pending. We were unable to confirm this at the time of this publication. Use the central contact number for the latest information. Study ID CAMN107A2201

Imatinib + RAD001 (everolimus)

Treatment with everolimus + imatinib in progressive GIST and imatinib-resistance

Phase: II
Conditions: GIST
Strategy: Inhibit target KIT downstream signaling
NCT#: NCT00510354
Telephone: 41 6 1324 1111
Sites: Clinicaltrials.gov lists 10 sites as open in Germany. We could not independently verify this at the time this newsletter was published. Please use the Novartis number above for specific site information or visit the German Novartis site (www.novartis.de).

AZD2171

The biological activity of AZD2171 in GIST

Phase: II
Conditions: GIST, Sarcoma
Strategy: Multiple targets
NCT#: NCT00385203
Telephone: l-866-992-9276
Sites: Christie Hospital NHS Trust
Manchester, United Kingdom
Dept. of Cancer Therapeutics
Institute of Cancer Research
Sutton, Surrey, United Kingdom

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HOLIDAYS

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need to do and get it done." As a mother, she is accustomed to rushing around and making things work. However, as a GIST patient she understands that things are a little different now. "Gleevec causes my white blood count to go down, so I am extremely tired on top of everything else." Trekking into the busy city to see her doctors during this time can also be difficult. "Do a lot of online shopping and stay away from stores as much as possible."

Katharine Kimball is a five-year GIST survivor so she is no stranger to dealing with GIST and crowds during the holidays. "Start early and only do a little at a time." She also suggests combining shopping with having lunch with a friend.

Traveling and Holiday preparation

If traveling is difficult for you at this time, don't feel pressured. Host a dinner at your house if you feel better there. Ask others to pitch in. "I let others do most of the cooking or at least help with it," says Katharine, "Just do the best you can, allow others to help and mainly relax and enjoy!"

Gift-giving to GIST patients

Sometimes what a GIST patient needs more than anything is a little peace of mind or a little time off. Katharine suggests restaurant gift certificates, for a nice break; jewelry, if you need to feel good, and get-a-ways. "One of my daughters took me on a week long cruise for my last birthday. We got to spend time together as well as having fun."

Nora agrees, "I honestly think a manicure/pedicure or a massage is a great gift for a GIST patient. That just makes me feel great."

No matter what you do for the holidays or how you feel, it is natural and common to feel anxiety. You may feel depressed and withdrawn. Remember that more than the discounts and the gimmicks, the TV specials and the Rockettes, the winter holidays are about being with friends and family. Appreciating who you are with and the time you have with them. Nora says it best, "Spend as much time with family as possible."

French patients hold general assembly in Paris

By Estelle Lecointe
President, Association Française des Patients du GIST: Ensemble conte le GIST

French GISTers held their general assembly this year on November 17 in Paris. Despite the huge transport strike occurring everywhere in France, more than twenty people came from all over France to attend this meeting.

LECOINTE

I was a little bit anxious about this day because it was the very first time I would meet the people from the group as we've been used to communicating through the discussion forum since the launching of our organization. Anyway, this feeling disappeared quite quickly as I realized that we all felt a kind of relief meeting each other and exchanging our experiences. Indeed, the atmosphere was very friendly and we spent quite a good time together.

We first had a quick breakfast together so as to "break the ice" and learn a little bit about each other before we started the meeting.

The first part of the day was dedicated to the presentation of our group: what we've done in 2007, our collaboration with networks of scientists (such as the "French Sarcoma Group" and the "CONTICANET" network), our relationship with the French Health and Cancer institutions, Global GIST-network, and of course, the projects we would like to achieve in 2008.

In the afternoon, Dr Axel Le Cesne joined us to make a presentation on "GIST management" and another one on "Second- and Third-line treatments". His participation was highly appreciated from all the people since for many of them, it was the very first time they could get so much information from a GIST specialist and ask him questions.

At the end of the afternoon, people exchanged their phone numbers and e-mail addresses, feeling they had found new friends who could understand what they live and how they feel.

French patients discuss GIST management and treatment at a Paris assembly.

Since Saturday, people have not stopped posting messages on the [French] discussion forum, explaining how important this meeting has been for them and that having met their peers have given them hope and bravery. Now, they're asking me for another meeting. Some of them want to get involved in the group so as to improve and extend its efficacy.

I think this is the best reward I could receive as it makes me realize how helpful my personal implementation can be to others. Now, I only have one thought in my mind: planning another patient meeting and building up a strong French GIST patient community.

WEBCASTS

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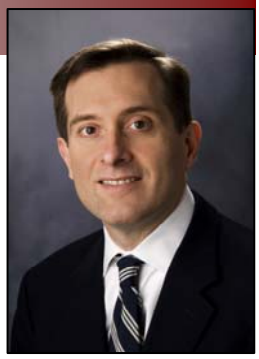
the hot topic of "Mutational Testing: Broken Down"; Monica Davey, clinical research nurse coordinator from Fox Chase Cancer Center, gave a much-needed presentation on "Living Well with Side Effects: A Guide to Side Effects Management. Our latest webcast in November was presented by Alice Sulkowski, GIST patient and nutritionist, who discussed "You Are What You Eat: Healthy Living with GIST."

Each webcast has provided valuable information for our patients and caregivers, as well as the medical professional community. The presentations are archived on the website and people view them from all over the world. The feedback is overwhelming—everyone loves them and they want more!



DEMATTEO

We look forward to our December 19 webcast at 5:00 pm by Dr. Ron DeMatteo from Memorial Sloan-Kettering Cancer Center, on the topic of "Surgery and Molecular Therapy for GIST."

To register, learn more or view archived webcasts, please visit http://www.liferaftgroup.org/news_webcasts.html or e-mail us at liferaft@liferaftgroup.org.

Member Suggestions

LRG member Sally Jackson offers her suggestions on how to cope with GIST and help others.

I walk 3 miles everyday and it does make me feel better, mentally and physically. During my walk I get my mind off of myself and think how I could make a difference in someone else's life. There are so many people who need our prayers, love and understanding and giving up some of our worries could be a positive relief for someone else.

WILD TYPE

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normal cells in the body, thereby avoiding unwanted toxicity to normal cells. However, the difference in sensitivity does raise the question of how well Gleevec is able to inhibit KIT activation in tumors with wild-type KIT including most pediatric GIST tumors.

Sutent (sunitinib) is known to be a potent inhibitor of wild-type KIT and has shown activity in adult patients with wild-type GIST. Combining this knowledge, along with the knowledge that KIT was activated in pediatric GIST, Dr. Janeway and her clinical colleagues have treated six pediatric GIST patients with advanced tumors that are resistant to imatinib with Sutent. Five of the six patients have had disease stabilization or a partial response. In four of the five patients the duration of response was longer than was seen with the previous imatinib treatment. This finding appears to suggest a possible role for Sutent in pediatric GIST. It also raises the question of whether other drugs that are potent inhibitors of wild-type KIT might also have a role in pediatric GIST. Nilotinib and several other KIT inhibitors are also known to be potent inhibitors of wild-type KIT.

In addition to the central finding that KIT is activated in wild-type pediatric GIST, the study found that the larger scale genetic changes that typically occur in adult GIST were rare in the wild-type pediatric GISTs. In adult GIST, KIT mutations are a very early event in the life of a tumor. These GISTs do not usually become malignant until other genetic changes occur; specifically the loss or gain of chromosomes is typical with metastatic GIST. According to Janeway, ". . . our present findings show that pediatric malignant GISTs are the first clinically aggressive solid tumor, in which cytogenetic aberrations, even when queried by high-resolution SNP assays, are undetectable in most cases."

She summarized, "Our findings suggest that pediatric GISTs are biologically distinct from adult GISTs and that targeted therapies for pediatric GIST should focus on inhibitors of KIT activation or signaling molecules downstream of KIT with an emphasis on those agents that strongly inhibit wild-type KIT."

Previous states that have hosted the LRG's biennial (every two year) membership meeting have been Massachusetts, Florida and Texas. Be a part of the process and vote today at www.liferaftgroup.org!

Tips from the Nutritionist

Post-Gastrectomy?

Alice says…

Do not drink any liquids until 45-60 minutes after meals. Fluids should be taken between meals, rather than with meals.

Columbia researchers say CT scan overuse may lead to significant public health problem

20 Million Adults – and 1 Million Children – May be Irradiated Unnecessarily Each Year in the U.S.; Fewer Scans Should be Considered when Appropriate, Particularly for Children

The following is a press release from Columbia University Medical Center.

New York, NY, Nov. 28, 2007— Computed Tomography (CT) scans are an increasingly used X-ray-based tool for providing a three-dimensional view of a particular organ or tissue. The value of CT scanning to diagnose injury, cancer and other health problems is undisputed. But are these scans being used too frequently, in some cases unnecessarily? What are the health consequences of having too many CT scans over the course of a person's life?

In the Nov. 29, 2007 issue of *The New England Journal of Medicine*, David J. Brenner, Ph.D., and Eric J. Hall, Ph.D., from the Center for Radiological Research at Columbia University Medical Center, argue that the potential carcinogenic effects from using CT scans may be underestimated or overlooked. This is of particular concern, because perhaps one-third of all CT scans performed in the United States may not be medically necessary, the radiation researchers say.

It is estimated that more than 62 million CT scans per year are currently given in the United States, compared to three million in 1980. Because CT scans result in a far larger radiation exposure compared with conventional plain-film X-ray, this has resulted in a marked increase in the average personal radiation exposure in the United States, which has about doubled since 1980, largely because of the increased CT usage.

It used to be widely believed that all radiological examinations were essentially harmless, because of the small amounts of radiation involved, but Drs. Brenner and Hall show that this is unlikely to be true for CT scans. In particular, Japanese atomic bomb survivors who were about two miles away from the explosions, actually received radiation doses quite similar to those from a CT scan. Sixty years of study of these survivors have provided direct evidence that there will be an increased individual cancer risk, though small, for those who have this same dose of radiation from CT scans. Although the individual risk is small, the large number of CT scans currently being given may result in a future public health problem. In particular, Drs. Brenner and Hall suggest that, in a few decades, about 1½ to 2 percent of all cancers in the United States may be due to the radiation from CT scans being done now.

Defensive Medicine May Lead to Overuse

Drs. Brenner and Hall suggest that the rapid increase in CT usage represents a potential public health problem in the United States that should be proactively addressed. This is particularly important for children, who are more sensitive than adults to radiation exposure. The issue arises, for example, when CT scans are requested in the context of so-called "defensive" medicine, or when scans are repeated as a patient passes through different parts of the medical system. Compounding the issue, surveys suggest that the majority of radiologists and emergency-room physicians may not appreciate that CT scans are likely to increase the lifetime risk of cancer. Ultimately, the health care system, the doctor, and the patient (who can perhaps best track of the number of CT scans performed when dealing with multiple doctors) may have to share the burden of monitoring the appropriate dosage and number of scans.

A CT scanner is a doughnut-shaped machine that takes pictures of cross-sections of your body, called "slices".

Drs. Brenner and Hall suggest three strategies for proactively addressing the potential increased radiation risks associated with CT scans:

Reduce the CT-related radiation dose in individual patients.

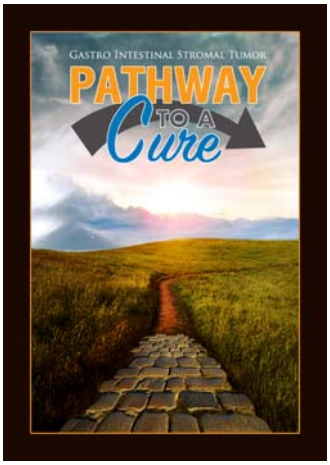
Replace CT use, when appropriate, with other options that have no radiation risk, such as ultrasound or magnetic resonance imaging (MRI).

Decrease the total number of CT scans prescribed.

Drs. Brenner and Hall suggest in their paper's conclusion that these strategies could potentially keep 20 million adults and, crucially, more than one million children annually in the United States from being irradiated unnecessarily. They stress, however, that in the majority of individual cases, the benefits associated with a correct diagnosis through CT will far outweigh the individual risk.

‘Pathway’ campaign off to a great start

This year’s holiday campaign, “Pathway to a Cure”, officially kicked off and has already been very successful. We would like to thank everyone who has participated by sending out their cards or donating themselves. We would also like to encourage anyone who has not yet had a chance.



Place a donation envelope in this card to participate.

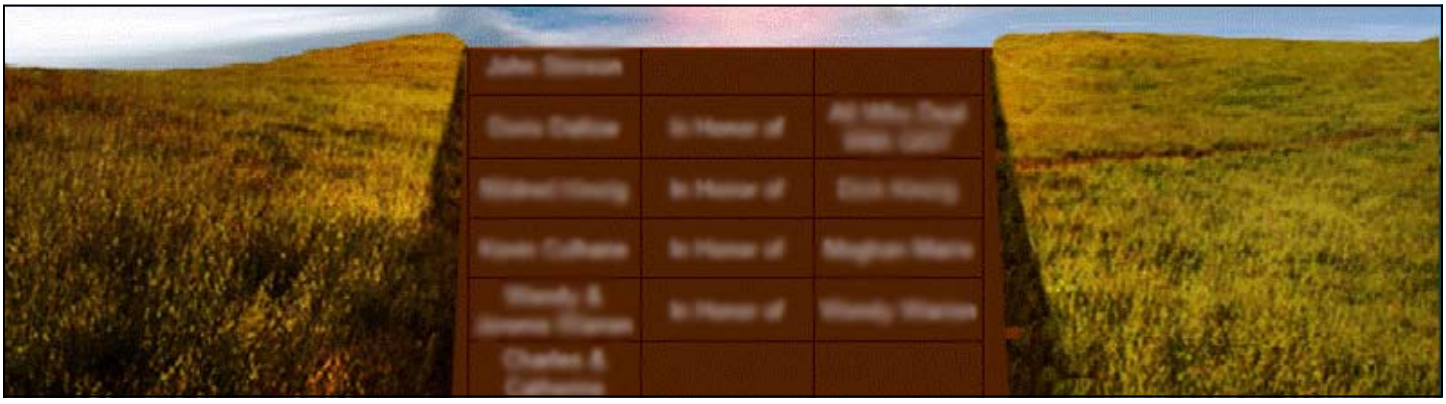
Each package contains ten cards with donations envelopes and ten mailing envelopes to send them. At this time of the year it is often uplifting to give to a cause that so greatly affects a loved one.

Remember: One hundred percent of campaign donations will go to the Life Raft Group’s Resistance Research Team. Dr. Jonathan Fletcher and his colleagues are working tirelessly in the search for the cure but additional funding is sorely needed.

If you have not yet received your package, would like to request additional materials or another package, please call the LRG office at (973) 837-9092 or email Nicole Burke at nburke@liferaftgroup.org.

Also, spread the word. This year you can actually see your donations helping build the pathway to a cure! The LRG website has a moving pathway listing every “brick on the path”. Go to www.liferaftgroup.org to see for yourself. You can also view a video explaining the urgent need for research and how the LRG Research team works.

New member? Learn more about the resistance Research Team at www.liferaftgroup.org/research.html.



Michele Scheiperpeter, wife, mother, grandmother, sister and friend

Reprinted from the *Palisadian-Post*

Michele Scheiperpeter, who lived in Ventura for the last eight years, passed away peacefully October 21 at age 52, surrounded by her family in her home in Ventura.

Michele grew up in Pacific Palisades, where she attended Corpus Christi School, St. Monica's High School and Palisades High. She met Carl Scheiperpeter of Pacific Palisades in high school. They were married for 34 years and lived in Mar Vista before moving to Ventura.

After raising two children, Michele went back to school at Cal State Northridge, where she earned a degree in physical therapy. She was working in Ventura and Ojai prior to her death. She fought GIST for three years before finally succumbing to it.


SCHEIPERPETER

In 2006, Michele organized the first West Coast GIST Cancer Research Fund walk to raise money for GIST research. She was a caring, loving person and was always there for her family and friends.

Michele was a runner and a hiker and loved camping with her family and friends. Her favorite place to camp was along the Kern River in Kern County. The last few years they camped along the coast in Ventura in their five-wheel camper.

Michele was the daughter of Bonnie and Wally Miller of Pacific Palisades. She is also survived by her husband, who works for the City of Ventura; her daughter Naomi, 33, a teacher in Boise, Idaho; her son Jason, 31, who works in Las Vegas; her grandson Jacob; her sister Lisa Miller, who lives in Cambria with daughter Rose and son Brian; and her brother Jeff Miller, who lives in Seattle with his wife Colleen and their sons Brendan and Devon.

In lieu of flowers, donations are welcomed at the Life Raft Group for GIST cancer research, 40 Galesi Dr., Suite 19, Wayne, New Jersey 07470.

APOSTOSIS

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(apoptosis). We made an important observation when treating these cells with imatinib: The inhibition of the KIT or PDGFRA kinases was a very early effect. Two hours after starting the treatment, a complete inhibition of the kinase activity could be demonstrated. The same was true for the inhibition of the immediate "downstream" kinases of KIT and PDGFRA, such as AKT and MAPK (2). However, following the cells closely over several days, we noticed that a significant increase of GIST cell apoptosis did not occur until two to three days after the start of imatinib treatment (3). This indicates that there is a substantial lag period between imatinib action (complete kinase inhibition) and the onset of apoptosis.

This pattern of a delayed onset of cell death after start of a cytotoxic treatment reminded us of what had been reported for "conventional" chemotherapeutic agents, which often work by inducing DNA damage. We therefore decided to examine the expression levels of molecules that are involved in the response to DNA damage after treating GIST cells with imatinib. One of the proteins that we were interested in was histone H2AX.

Let me give you a quick overview about histones and the DNA damage response. Histones are proteins that are mainly involved in the compaction of DNA. As you know, the DNA molecules in each and every cell in our body would be very long if they were stretched out (approximately 2 meters) and have to be compacted to make them fit into the nuclei of our cells. This is achieved by wrapping the string of DNA around so-called nucleosomes ("beads-on-a-string" configuration). Nucleosomes are comprised of histones containing two molecules each of histone H2A, H2B, H3 and H4. Histone H2A (amongst others) can occur in several related forms (variants), one of which is histone H2AX. Histone H2AX is randomly distributed throughout the nucleosomes instead of H2A. Although histones have mainly been known as structural proteins, it has recently emerged that they also have other functions. Just a few years ago, histone H2AX has been identified to be a key player in the response to DNA damage. H2AX is rapidly phosphorylated (activated) after DNA damage and it then functions to recruit other repair proteins to the site of damage (4,5).

When treating GIST882 cells with imatinib, we found a massive increase of H2AX with levels beginning to rise already after eight hours, meaning that this occurred during the lag period between kinase inhibition and onset of apoptosis (3). Interestingly, we found that not only the phosphorylated form of H2AX increased, but also the non-activated form. In addition to that, we noticed that the majority of H2AX was not strictly localized to the chromatin (DNA plus nucleosomes) anymore, but was free inside the nucleus and rest of the cell (cytoplasm). These findings pointed to a potentially unknown function of H2AX that is not necessarily coupled to DNA damage-response and a possible causative role in the onset of apoptosis after imatinib treatment in GIST cells.

We therefore performed various follow-up experiments to prove this hypothesis. We first engineered GIST882 cells to overexpress (make more) histone H2AX and found that this led to increased cell death. When we reduced histone H2AX levels in GIST882 cells (using a technique called small interfering RNA, or siRNA), the cells were protected from apoptosis when treated with imatinib. No changes could be detected when looking at histone H2A (and not the variant H2AX) meaning that histone H2AX has specific functions that it does not share with H2A. Taken together, the outcome of our experiments suggests that the increase in histone H2AX after imatinib treatment has a causative role in killing GIST cells and hence the therapeutic response to imatinib.

Histones- Proteins mainly involved in the compaction of DNA

To corroborate our data, we performed a series of further studies. We first were interested in the pathway that leads to increased H2AX levels in GIST cells after imatinib. When we treated GIST882 with various compounds that inhibit signaling cascades downstream of KIT, we were only able to induce increased H2AX levels with inhibitors of the PI3K/AKT pathway, whereas an inhibitor of the MAPK pathway did not have an effect. These findings are in line with the notion that the PI3K/AKT pathway is more important for GIST cell survival (6). We also found that GIST cells are able to downregulate levels of H2AX using the protein degradation machinery of the cell (ubiquitin-proteasome system). This means that GIST cells are able to routinely get rid of what can potentially kill them. Only when they are treated with imatinib, this pathway is inactivated and H2AX levels rise again. Further experiments (in collaboration with Dr. Jonathan Fletcher) showed that Gleevec-resistant GIST cell lines were not able to increase their soluble H2AX levels after imatinib treatment, showing that it is indeed the action of imatinib that causes H2AX levels to rise. Lastly, we asked whether our findings can also be recapitulated in vivo. In collaboration with Dr. Cristina Antonescu and Dr. Peter Besmer, we stained paraffin-embedded tissue sections of GISTs that developed in mice harboring a germline-activating KIT mutation (7). An increased number of cells expressing histone H2AX were found in mice that were treated with imatinib further corroborating our results.

Finally, we addressed the question of how increased levels of soluble histone H2AX in a cell could induce apoptosis. When we examined cells overexpressing H2AX in more detail, we found that their nuclei showed a clumped appearance of their chromatin, also called chromatin aggregation. It is known that histones can bind unspecifically to DNA

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Opening of 'Gleevec+IL2' phase I trial at Gustave Roussy

By Estelle Lecointe
President, Association Française des Patients du GIST: Ensemble conte le GIST

After several years of research and months of expectation, Professor Laurence Zitvogel's research team at the Gustave Roussy Institute in France finally got the agreement from the AFSSAPS (The French Health Products Safety Agency) and the support from Novartis to launch a phase I clinical trial called "IMAIL-2" combining "Gleevec + Interleukine 2" .


ZITVOGEL

This clinical trial has two major objectives:

- Assessing the efficacy of the chemical "Gleevec+IL2" combination in the treatment of various cancers, including GIST.
- Identifying the existence of IKDC cells in the human body.

Brief reminder about IKDCs:

IKDCs (Interferon Killer Dendritic Cells) are cells of the immune system which are naturally produced by mice bodies and located in the bone marrow, liver, spleen and ganglions. Their peculiarity lies in their capacity to kill cancer cells.

Several tests conducted on mice, allowed Professor Zitvogel's team to highlight that, when IKDCs are numerous and stimulated, they spontaneously move to the tumor cells and reduce them to nothingness in a few hours. This is thanks to the large amount of interferon gamma (IFN-y) and complex lyse systems (perforine/granzyme, TRAIL) they naturally secrete or secrete after a stimulation. Unfortunately, IKDCs are very rare and therefore have an extremely limited natural effect on tumors.

Considering this, the "IMAIL-2" clinical trial is aiming at assessing if the "Gleevec+IL2" combination can:

- Contribute to increase the secretion of interferon gamma in the human body so as to boost the immune system and make it more potent to fight against tumor cells.
- Stimulate the production of IKDCs and increase their activity within the human body.

Eligibility:

- Primary or secondary Gleevec resistance; progressive disease on Sutent
- No brain metastasis
- Good liver and kidneys functions

Number of GIST patients expected to be included: 4 or 5 minimum.

Progress of the clinical trial:

One week of Gleevec (400mg/day) plus one week of Gleevec and IL2, then one week off. The duration, as well as the number of cycles will depend on the clinical response.

Pre-treatment:

Three weeks prior to the beginning of

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TRIALS

From Page 3

Radiation Therapy as Palliative Treatment of GIST (GIST RT)

Phase: I/1l
Conditions: GIST
Strategy: Kill GIST cells (Radiation)
NCT#: NCT00515931
Telephone: 947173208 Ext. 358
Sites: Helsinki Univ. Central Hospital Helsinki, Finland

OSI-930

Dose escalation study of daily oral OSI-930 in patients with advanced solid tumors

Phase: I
Conditions: Solid Tumors/Sarcoma
Strategy: Multiple Targets
NCT#: NCT00513851
Contact: ContactUs@emergingmed.com
Telephone: (877) 601-8601
Sites: Dept. of Cancer Therapeutics Institute of Cancer Research Sutton, Surrey, United Kingdom

Glivec + Interleukin 2 (IL2)

Phase I trial in solid tumor and GIST resistant to imatinib and/or sunitinib (IMAIL-2)

Phase: I
Conditions: Solid tumors and GIST
Strategy: Kill GIST cells (Immunotherapy)
Contact: Dr. Nathalie Chaput
nathalie.chaput@igr.fr
Telephone: +33(0)1 42 11 50 05
Sites: Institute Gustave Roussy Villejuif, France

XL765

Study of safety and pharmacokinetics of XL765 in adults with solid tumors

Phase: I
Conditions: Cancer
Strategy: Target KIT downstream signaling
NCT#: NCT00485719
Contact: Gemma Sala
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APOPTOSIS

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because of their negative electric charge. It has also been reported that an excess of histones can lead to impaired gene transcription, and we were able to show that excessive amounts of H2AX can abrogate transcription in an in vitro assay. We can then hypothesize that excess soluble histone H2AX can cause chromatin aggregation and impaired gene transcription, thereby sensitizing the cells to undergo apoptosis. Moreover, GIST cells appear to be particularly sensitive to reduced gene transcription when compared to cells that are not malignant. This was also shown in a recent study that used the CDK2/ transcriptional inhibitor flavopiridol (8).

Taken together, our study highlights the role of histone-mediated cytotoxicity in GIST cell death induced by imatinib and establishes an unexpected role of H2AX in this process. However, given that KIT activates several downstream signaling pathways, it is possible that this is not the only mechanism contributing to GIST cell apoptosis.

We believe that our results have various implications for GISTs and cancer therapy in general. First, the observation that H2AX upregulation is critical for GIST cell sensitivity to imatinib suggests novel therapeutic approaches in which H2AX induction might be accomplished by alternative mechanisms thereby countering imatinib resistance. Second, the observation that PI3K inhibition leads to induction of H2AX expression provides a novel mechanistic basis for anti-apoptotic roles of PI3K, and suggests that PI3K as a promising therapeutic target in GIST, either combined with KIT inhibition or alone. Third, our findings suggest that H2AX upregulation by tyrosine kinase oncoprotein inhibitors may restore tumor sensitivity to conventional chemo- or radiotherapy. Further understanding of how oncogenic protein kinases overcome anti-cancer barriers during tumor evolution is likely to improve the therapeutic and preventive use of targeted small molecule inhibitors.

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IL2

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the "Gleevec+IL2" treatment, patients will be prescribed "cyclophosphamide" pills (Endoxan) they will have to take every day during this period. The aim of this pre-treatment is to regulate the activation of the Treg cells and thus to stimulate the production of NK and IKDC cells. This pre-treatment does not imply any side-effect.

Expecting dosages:

- Three levels of dosage escalation are expected (gradually up to nine million of IU/M2/day, three times a week).
- There will be no dosage escalation concerning Gleevec which will be maintained at 400mg/day during the entire study.

In case of progression during trial:

Only the dosage of interleukine 2 will be increased. Gleevec will always be maintained at 400mg/day.

In case of complete remission:

The discontinuation or the continuation of the treatment is still a debate. The only thing known is that there won't be any randomization as it doesn't exist in phase I clinical trials. A phase II clinical trial is planned to be opened as soon as the dosage/efficacy ratio is determined in 2009.

For more information, please contact: Dr. Nathalie Chaput, Nathalie.chaput@igr.fr, +33(0)1 42 11 50 05.

Tips from the Nutritionist

Got nausea?

Alice says…

Eat slightly salty and/or sour/tart foods. These are often better tolerated

Dehydrated?

Alice says…

Drink small amounts of fluid, especially Gatorade or juices, every hour.

Washington GISTers meet

Since Norman Scherzer, executive director of the LRG, Jerry Call, science coordinator, and Erin Kristoff, assistant program coordinator, were in Seattle, Washington on November 4 for the Connective Tissue Oncology Society, the group met with Washington GIST patients to discuss challenges facing them. Present at the breakfast meeting was Rebecca Haines, who added, "With such a rare diagnosis as GIST, it's encouraging to meet others traveling the same pathway. We were treated to such an occasion when some Life Raft Group folks came to Seattle for a seminar recently. We had an informative, yet pleasurable time at breakfast at a Seattle hotel, hearing stories from some patients and some family members, as well as the latest research leanings from Norman. How nice to finally meet some of the LRG faces behind the names."

Caraway, 72, fought heroic battle

Bob Caraway, 72, passed away October 5 at his home in Denton, TX.

He attended the former North Texas State University for two years after graduating from Tyler Junior College in 1955. He also attended Baylor Law School and graduated from there in 1960.

Caraway was a Golden Eagle, celebrating his 50th alumni year, in 2007 and he and his wife, Georgia, were selected by President Alfred F. Hurley in 1987 to receive the President's Citation for extraordinary service to the university. An endowed scholarship at UNT has been established in Caraway's name to help students who need financial aid.

After earning his law degree at Baylor University, Caraway became a law clerk for Judge Joe W. Sheehy in Tyler, and practiced law in Dallas for 25 years. He was also a real estate broker and investor. One of the most successful times in his career was when he was the attorney for the Wilmer Hutchens ISD. Representing the school district, he appeared before the U.S. District Judge William Wayne Justice and fought for equal rights for minority students.

CARAWAY

Bob fought a heroic battle with GIST for 15 years. "He was very grateful to have the Life Raft to hang on to for many of those 15 years," said Georgia.

Caraway was born on February 14 in Tyler to Everett Jewell and Maggie (McBride) Caraway. He is survived by his wife, Georgia, his daughter, Gretchen Gudger, and her husband, Greg.

Kwart represents LRG at this year's NORD conference

Life Raft Group board member, Dr. Arnold Kwart represented the Life Raft Group at this year's National Office of Rare Diseases (NORD) Conference. Kwart attended a few lectures including, "Creating and Maintaining a Patient Registry" and "Special Challenges for Rare Disease Research". Kwart felt that the Registry lecture emphasized the "importance, influence and effectiveness [the LRG has] on patients with GIST.

KWART

The lecture relating to special challenges and research highlighted the lengthy process developing a successful research program for studying disease. "Getting permission of investigational new drugs and getting institutional review board approval is increasingly difficult." This is a topic very important to GIST patients and one that has been covered many times in this newsletter (See November 2007 issue for example).

Kwart learned a good deal of information from the lectures that has expanded his knowledge of GIST as a doctor and as a patient.

Mark your calendars!

Don't miss the next LRG webcast on December 19 at 5 PM. Dr. Ronald DeMatteo will be presenting "Surgery and Molecular Therapy for GIST". Go to www.liferaftgroup.org to register.

Shhh. Pass the secret. The LRG will be debuting a new website with new features and design. Watch for it in January.

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