Leukemia patients find 800 mg. effective, safe

WASHINGTON, D.C. – The cancer drug imatinib mesylate, also known as Gleevec, has proven to be increasingly effective at higher doses, according to a new study published in the April 15 issue of Blood, the official journal of the American Society of Hematology.

Researchers from The University of Texas M. D. Anderson Cancer Center in Houston examined 114 patients recently diagnosed with chronic myelogenous leukemia (CML), a cancer that is diagnosed in about 4,600 people in the U.S. every year. CML is classified into three stages: chronic, accelerated, and blastic. Study participants were all in chronic phase, the least severe of the three. The current dosage

Higher doses of Gleevec work best for CML

The largest-ever gathering of GIST patients and GIST specialists will take place for three days beginning Friday, April 30.

“Life Fest 2004” will be held in Orlando, Fla. Dozens of GIST patients and doctors from across the United States and Europe will meet at Embassy Suites Lake Buena Vista Resort to discuss the latest strategies for combating GIST.

The event will include a report titled “Preventing Resistance” from the Life Raft Group on the relationship of Gleevec dosage levels and relapse. “Reversing Resistance” will be the topic for a panel of doctors who will discuss novel targets and novel clinical trials in the United States and the European Union.

Life Fest 2004 has received support from Novartis Pharmaceuticals, the Salas family and the Bunn family.

For the draft agenda of Life Fest 2004, see Page 5. For late registration or more information, call the Life Raft Group office at (973) 837-9092, or see the Life Raft Group Web site at www.liferaftgroup.org

By Jerry Call
Science Coordinator, Life Raft Group

Some emerging drugs ready for clinical trials

Editor’s note: Jerry Call attended the 95th annual meeting of the American Association for Cancer Research held March 27-31 in Orlando, Florida. This is his report on the handful of sessions (out of 250-plus) that he was able to attend. Jerry adds that he is a layperson with no formal medical or scientific training.

By Jerry Call
Science Coordinator, Life Raft Group

The good news emerging from the AACR meeting is that researchers are pursuing many treatment avenues that could work on GIST, and

The AACR held its 95th annual meeting in Orlando, Florida.

some of these new drugs are or will soon be in early clinical trials.

The treatment strategies represented at the meeting can be divided into

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three main categories. The first were highly specific treatments aimed at very specific targets. These include small molecule inhibitors (such as Gleevec), antisense drugs, and monoclonal antibodies. The second category consists of newer types of chemotherapy aimed at rather broad targets. This class appeared dominated by three main types of drugs: heat shock protein 90 (hsp90) inhibitors, proteasome inhibitors, and histone deacetylase inhibitors. A third category of less concern to GIST patients was the more traditional treatments such as traditional cytotoxic chemotherapy and radiation. GIST is relative immune to such treatments.

Small molecule inhibitors (such as Gleevec) are probably the best representatives of the highly specific treatments. Gleevec is a small molecule “tyrosine kinase” inhibitor. It inhibits KIT, PDGFR, as well as various forms of ABL (such as Bcr-Abl). Many of the tyrosine kinase inhibitors inhibit several different kinases.

As targets are identified, researchers seem to be able to make drugs that more potently inhibit the target. Two examples of this were in drugs that inhibit KIT/Bcr-Abl, and STAT-3 (KIT is implicated in GIST, as is STAT3, to a lesser degree). Aberrant Bcr-Abl signaling is the primary cause of chronic myelogenous leukemia (CML).

Gleevec is the treatment of choice for CML and metastatic GIST. A new drug being developed by Bristol-Myers Squibb was reported to be 100 to 1,000 times as potent as Gleevec at inhibiting Bcr-Abl (this does not mean that it would be 100 to 1,000 times as effective). Researchers at Moffitt Cancer Center working on drugs that inhibit STAT3 signaling have achieved a 10-fold increase in STAT3 inhibition in one year and expect another 10-fold increase in another year.

The point: new drugs that inhibit old targets (perhaps more potently) appear to be one option for better treatments.

The new Bristol-Myers Squibb drug, BMS-354825, inhibits Bcr-Abl as well as KIT and PDGFRA signaling, according to Frank Y.F. Lee, Ph.D., senior principal scientist with Bristol-Myers Squibb. After his presentation, I spoke to Lee with Penny Duke, a member of both the Life Raft Group and GIST Support International. Lee told us that plans are under way for a phase I trial of BMS-354825 for patients with solid tumors. This trial will be at Dana-Farber Cancer Institute in Boston. It remains to be seen whether this drug, or another new KIT/ PDGFR inhibitor such as AMG-706, will be effective in GIST.

Other KIT or PDGFR inhibitors we were already aware of include the Novartis drug PKC412. According to Dr. Jonathan Fletcher, PKC412 may target KIT and PDGFRA differently from Gleevec, especially the kinase domain mutants typically resistant to Gleevec. My impression: the new PKC412 plus Gleevec trial at Oregon Health & Sciences University in Portland may be a good choice for GIST patients with PDGFR mutations that are resistant to Gleevec.

While KIT remains the primary target in GIST (with PDGFR the primary target in GISTs with PDGFR mutations), several new abstracts were presented on other GIST targets.

Wei Shen of Fox Chase Cancer Center presented a poster of the effects of a novel STAT3 inhibitor, JSI-124 (Cucurbitacin I) in GIST cells. In the past six months or so, several articles have described the importance of STAT3 signaling in GIST, while noting that Gleevec does not always inhibit STAT3 signaling. The authors of this poster tested JSI-124 on GIST882 cells and found that it inhibited cell proliferation and induced apoptosis (cell death) in this cell line at clinically achievable drug concentrations.

The authors concluded, “These studies suggest that JSI-124 may be an alternative or complementary drug for the treatment of primary and refractory GIST.”

Dr. Annette Duensing of the University of Pittsburgh, while working in the Fletcher’s lab at Dana-Farber, found that protein kinase C theta (PKC theta), was highly activated in GISTs. They found that PKC theta was activated not only in GISTs with c-kit mutations, but also in GISTs with PDGFR mutations (although at about 50 percent lower levels). Duensing and her colleagues found that “PKC theta was strongly phosphorylated in all GISTs at Thr538 and Ser676, and the phosphorylation at both these residues...
Life Rafters meet in San Jose, Costa Rica

Life Rafters Elsie Hernandez, left, and husband Michael Josephy of Costa Rica got to meet fellow Life Rafter Andrea Fuller of Florida on April 6 in San Jose, Costa Rica, while she was on a horticultural tour with the Florida Master Gardeners. Andrea got to visit with the couple before heading off to remote parts of the country, starting with Sarapiqui. They were looking forward to meeting again at the Life Fest 2004.

CML

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recommended by the federal Food and Drug Administration for chronic phase CML patients is 400 mg. of Gleevec daily, with higher doses of 600 to 800 mg. recommended only for patients in the later stages of CML.

Researchers, hypothesizing that higher dosages given in the earlier chronic stage could be more effective than the standard treatment, provided patients with 800 mg. of imatinib daily (administered in two 400 mg. oral doses).

All of the patients in this study also had a genetic abnormality called Philadelphia translocation (common to 95 percent of CML patients) in which some of the DNA on chromosomes 9 and 22 are switched. A result of the switch is the development of a hybrid gene called BCR-ABL, which codes for an enzyme that causes the overproduction of white blood cells in the bone marrow, crowding out normal blood cells and platelets. Therefore, the primary goal of CML treatment is complete cytogenetic response (CCR), the elimination of cells with this genetic defect.

Ninety percent of the patients in this study experienced CCR, a significantly greater result than seen in patients in a prior study who were taking the standard dosage of imatinib. Those patients had a CCR rate of 60 to 75 percent.

The high percentage of CCR among these patients is of significant importance as previous studies of another cancer drug (interferon alpha) have shown that CCR is associated with a 70 to 80 percent chance of 10-year survival, a positive prospect as the survival time for newly diagnosed CML patients is typically about five years.

Another measure of successful treatment is the number of patients with complete molecular response, occurring when the levels of BCR-ABL are so low that they are undetectable using a highly sensitive method called polymerase chain reaction. In past studies, patients who had undetectable levels of BCR-ABL after treatment have not relapsed after long-term follow up. In high-dose therapy patients, the incidence of complete molecular response was 28 percent compared to only 7 percent of patients taking the standard dosage of imatinib.

“The high rates of complete cytogenetic and molecular response that we’ve seen in this study are unprecedented. If such responses have similar
PKC
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was two- to five-fold greater in the GISTs than in Jurkat cells and normal thymus (cells considered to have high PKC theta activation). Treatment of the GIST430 cell line with the PKC theta inhibitor Rottlerin (3 μM) led to inhibition of PKC theta and AKT phosphorylation, and induction of cell death.”

I believe that Rottlerin is more of a lab chemical than a drug that will be developed for patients. The authors conclude, “PKC theta expression is characteristic of GISTs, and of potential diagnostic utility, particularly in KIT-negative GISTs. PKC theta is constitutively phosphorylated (activated) in GISTs and — given its role as a positive regulator of cell survival in other cell lineages — might represent a novel therapeutic target in GISTs.”

While not specific to GIST, a session titled “Sarcoma Diagnosis and Treatment” presented a few new pieces of information about GIST. Speakers included Dana-Farber’s Fletcher, Dr. Lee J. Holman from the National Cancer Institute, Dr. Brian O’Sullivan from Princess Margaret Hospital, Toronto, and Dr. Matt Van de Rijn of Stanford University Medical Center.

Van de Rijn has identified a novel marker for GIST that may be more specific than c-kit. This marker which Van de Rijn has named “dog1” reacts with KIT-negative GISTs as well as KIT-positive GISTs (about 97 percent of GISTs are “KIT positive”). Further work is needed to validate dog1 as a marker in GIST.

Fletcher noted that one major challenge (and opportunity) is that there seems to be a greater-than-expected heterogeneity (variation/subclones in tumors/tumor cells) in GIST. He said that by using several drugs together, researchers hope to make progress.

Other downstream KIT and PDGFRA targets include the PI3K/AKT pathway (including mTOR) and the MAPK pathway. Approved drugs (Rapamycin) and those in clinical trials (RAD001 and others) target mTOR. Several new drugs that inhibit PI3K and AKT appear to be in preclinical development. One new tyrosine kinase inhibitor, BAY 43-9006, inhibits RAF, which is in the MAPK pathway. It is conceivable that this drug may one day be useful in GIST.

NEWER CHEMOTHERAPIES AIM AT BROAD TARGETS

This group seems to be dominated by three main targets. The general strategy of this group seems to target the processes (or “machinery”) that cells depend on, the theory being that cancer cells may be more dependent on these processes than normal cells.

The first of these targets is heat shock protein 90 (hsp90). Hsp90 is one of the most abundant proteins in most cells, accounting for 2 to 4 percent of total cell protein. It is required for refolding of proteins and participates in maturation of some proteins (AKT and others).

Treatment with hsp90 inhibitors results in the degradation of some proteins including: HER2, MET, RAF kinase, Steroid receptors, and AKT. In addition, KIT protein (as reported last year at ASCO) may also be degraded by hsp90 inhibitors. This includes types normally resistant to Gleevec, such as kinase domain mutations.

Hsp90 degraded proteins are “marked” with “ubiquitin”. Proteins marked with ubiquitin are then degraded by a “machine” called a proteasome. Proteasomes serve a housekeeping function in the cell. As proteins are no longer needed, they are degraded by the proteasome. Proteasome inhibitors are second in this class of drugs aimed at broad targets.

The third target in this general class is histone deacetylase. A histone is a basic protein found in the nucleus of a cell. This protein, found as a complex with DNA, is specifically found in chromatin and chromosomes, and may function as a repressor of gene transcription.

Because histones are involved in transcription, one of the first steps in cell division, and cancer is caused, generally, by uncontrollable cell replication, they are targets for cancer research.

All three of these new, general acting chemotherapies have shown some in-vitro (test tube) activity in CML cells, either alone or in combination with Gleevec, or in some type of combination of the three inhibitors. Of these three types, I am only aware of an hsp90 inhibitor (17-AAG) being tested for inhibition of KIT. This was an in-vitro test with mast cells that expressed a KIT mutation that would normally be resistant to Gleevec.

The authors concluded “17-AAG may have a role in the treatment of other diseases where c-kit plays a crucial role in pathogenesis, including GIST, mast cell leukemia, some types of acute myelogenous leukemia and testicular cancer.”

It seems possible that one or more of these general chemotherapies, or a combination of them, might be useful in GIST (perhaps in combination with Gleevec or another KIT inhibitor).

One concern with this group is that proper drug sequencing will probably be very important or critical, and would have to be determined for each combination.

Velcade is the only approved proteasome inhibitor that I am aware of. It is approved for Multiple myeloma.

The hsp90 inhibitor that is furthest along in trials is probably 17-AAG. This drug has some drawbacks including poor solubility.

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Tentative agenda for Life Fest 2004

FRIDAY, APRIL 30
3-5:30 p.m. Registration
5:30-7:30 p.m. Cocktail reception
7:30-9:30 p.m. Dinner
Master of Ceremonies: Sarah Buch
Welcoming remarks by Stan Bunn, Life Raft Group board president; executive director remarks by Norman Scherzer.
This evening’s honorees will be Dr. Brian Druker, Oregon Health & Sciences University, and Barbara Kennedy, Novartis Oncology

SUNDAY, MAY 2
9 a.m. Break-out Sessions
“Improving the LRG” with Norman Scherzer, executive director
“Complementary Medicine” with Rita Raj, acupuncturist
“Sugen Discussion Group—Focus: Non-trial Participants” with Michael Matthews, Sugen group coordinator
Noon: Reconvene
Closing remarks by Norman Scherzer
Candle-lighting Ceremony, location to be announced.

CHEMOTHERAPY
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At least two newer hsp90 inhibitors were reported at AACR. One was 17DMAG, which is water soluble, orally bioavailable, and does not appear to undergo metabolism to toxic species. In other words, this drug is an improvement over 17-AAG. Phase I trials are just starting (at the University of Pittsburgh, I believe).

The other is PU24FCI (reported by Memorial Sloan-Kettering Cancer Center in New York). A representative of the hsp90 inhibitors that exhibit in vivo antitumor activity, PU24FCI, has anti-tumor effects on all tested cancer cell lines.

Histone deacetylase inhibitors represent one other class. Novartis (LAQ824) and others are developing histone deacetylase inhibitors.

AACR is the world’s largest professional organization devoted to cancer research. This year more than 15,000 participants gathered to discuss some 6,000 abstracts and to hear more than 250 presentations on new discoveries in cancer research.
long-term significance as seen in previous studies, this translates into a major improvement in the prognosis of patients with CML,” states Dr. Hagop Kantarjian, chairman of the Department of Leukemia at M. D. Anderson Cancer Center and the lead author of the study.

Researchers found that the high dosage of imatinib was generally well tolerated, with a similar rate of side effects as standard dose imatinib. To reduce more severe side effects, the dosage of imatinib was lowered to 600 mg. or 400 mg. daily for some patients, though a majority remained at the target dosage.

The disease did not transform beyond the chronic phrase in any of the study patients, and 98 percent had a complete hematologic response, meaning the number of white blood cells was no longer out of control and the signs and symptoms of leukemia were gone.

The results of the study indicate that patients in the early stage of this cancer may benefit from higher doses of the drug imatinib in their initial treatment to safely and effectively improve their condition and improve their chance at long-term survival. According to hematologist Dr. George Daley of Children’s Hospital and Harvard Medical School, “This is a remarkable study. It shows that because highly targeted therapy incurs fewer side effects, dosages can be increased to achieve truly astounding rates of remission.”

This work was supported by Novartis Pharmaceuticals Corporation, the Betty Foster Leukemia Research Fund, and the CML PO1 CA49639.

To receive a copy of the study, please contact Aislinn Raedy at 202-776-0544 or araedy@hematology.org.
Curtis Berry, 42, fought GIST three years

Mr. Curtis R. Berry, age 42, of Plano, Texas, died Tuesday, April 6, 2004 at his home.


He is survived by his wife, Anne; daughters, Peyton Vaughn Berry of Plano and Joni Ann Staton of Neb.; soon-to-be-expected son, Cameron Ross; mother, Edith Berry of Phoenix, Ariz.; father, C. Curtis Berry of Glendale, Ariz.; and three grandchildren. A memorial service was held April 9.

Memorials may be made to the Curtis and Anne Berry’s Children’s Scholarship Fund at Bank One.

Arthur ‘AD’ Rhea involved with his community

Arthur Dakota “AD” Rhea III, 47, died April 20, 2004, at his Canton, Conn., home surrounded by his family.

AD was born April 26, 1956, in Richmond, Va., and spent his early years in Colonial Williamsburg. He attended schools in Baltimore, Md., and graduated from the Baltimore Polytechnic Institute. He received his undergraduate degree in mechanical engineering from the University of Vermont in 1978. He worked for Janos Technologies as the director of business development.

AD devoted himself to community service. In East Hartland, he was a member of the Democratic Town Committee, the Board of Finance and the School Building Committee. Many of his happiest moments were spent coaching children in soccer and basketball. He was a member of the vestry of Trinity Episcopal Church and served as a lay reader and Eucharistic minister.

AD met the challenge of his cancer by participating in two clinical trials dedicated to researching the cause and cure of a rare sarcoma.

AD is survived by his wife, Carlene (Coates) Rhea, and their three children, Tyler, Katherine and Anne; two brothers and their families, R. Douglas and Lisa Rhea, and Clifton and Sarah Rhea. The son of Arthur D. Rhea Jr. and Dorothea (Coutu) Rhea, and son-in-law of Carlisle J. and Pauline (Giroux) Coates, he was the brother-in-law of Robert Coates and Russell Fellows, Timothy and Lori Coates, John and Suzette Coates, and Patricia Coates and Michael Carrese, and many nieces and nephews.

A memorial service was held Saturday, April 24, at Trinity Episcopal Church in Canton. Donations may be made to Dana-Farber Cancer Institute, c/o Dr. George Demetri, sarcoma director, 44 Binney St., Boston, MA 02115.
The best part of surgery ...

Some might say there’s nothing fun about surgery, but newsletter editor Richard Palmer would disagree. During his week at M.D. Anderson Cancer Center in Houston, Texas, Richard got to meet up with Life Raft friends old and new. Here’s a look at some GIST survivors so you can connect names and faces the next time they post an e-mail to the Life Raft.

Richard Palmer, left, of Hawaii with Roberta Gibson of Oklahoma and Ed Martinka of Texas.

Just after he was discharged, Richard got to meet Betty Arnett of Texas, above, and her husband Ronnie.

Marty Scharf of Illinois and Richard visited at the Rotary House hotel attached to M.D. Anderson.

Above, Richard is flanked by Roberta Gibson, left, and teacher Bari Funda of Texas. At left, Richard talks with Dr. Lei Chen, a researcher at M.D. Anderson who wanted a sample of Richard’s tumor to see what it looked like after three years on Gleevec.
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 listserves 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:

The Life Raft Group
40 Galesi Drive
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.