Cancer experts on GIST

Gleevec dosage level is still unresolved at the 40th annual ASCO meet

By Jim Hughes and Norman Scherzer

Conflicting interim study results on GIST progression and dosage levels cropped up again at the 40th annual meeting of the American Society of Clinical Oncology held June 5-8. The meeting drew more than 27,000 cancer professionals to New Orleans, La.

Updated results for the U.S. phase III Gleevec (Glivec/imatinib) dosage study S0033 were presented by Dr. Cathryn Rankin (abstract 9005). The European phase III Gleevec dosage study 62005 update was given by Dr. John R. Zalcberg (abstract 9004). Abstracts relating to GIST oral presentations and posters can be found online at the ASCO Web site, www.asco.org, and will soon be on the Life Raft Web site, www.liferaftgroup.org.

Both oral presentations were summarized by Dr. Allan Van Oosterom. The U.S. and European trials continue to report differences with regard to dosage level and time to disease progression. The Americans report no difference in time to progression between 400 mg. and 800 mg., while the Europeans report that higher doses were correlated with longer time to progression. Van Oosterom offered that the differences might be due to the size of the study cohorts — that the smaller American study group (746 patients) would have the same results as the European group (946 patients) if the two studies were the same size.

PHASING IN HIGHER DOSES POSSIBLE

Van Oosterom reviewed Zalcberg’s data that showed patients who started at 800 mg. were more likely (55 percent) to reduce their dosage than patients who increased their dose to 800 mg. (25 percent) due to disease progression. He also said that 90 percent of those who started at 800 mg. and reduced their dosage did so within the first six months. The presumption is that side effects decrease over time and patients can tolerate the higher doses after being on Gleevec for some time (see Gleevec Clearance). He indicated that Novartis has now agreed to study this issue. This is important because a precise sub-group of patients that may need the higher dose has not yet been identified. He expected that by next year we might know how the dose could be modified based on mutations.
GLEEVEC CLEARANCE
DATA COMING

Van Oosterom gave an oral presentation on Gleevec clearance rates. He had previously shared this data with the Life Raft Group at the Life Fest 2004 in May – namely, that Gleevec clearance rates have been observed to increase over time. Van Oosterom indicated that Dr. Ian Judson will publish this finding shortly in the journal Cancer Chemotherapy and Pharmacology. Van Oosterom said pharmacokinetic data “showing Gleevec levels in patients in which we increased dosage (upon progression) was substantially lower (than at the beginning of treatment).”

INCREASE TO 800 mg.
SHOWS BENEFIT

Overall benefit from crossover to 800 mg. on progression ranged from 33 percent to 39 percent in two phase III study updates involving more than 200 patients who had disease progression on 400 mg.

Zalcberg reported European study results for patients crossing over to a higher dosage after progression. A total of 133 went from 400 mg. to 800 mg. in accordance with the study protocol. Of these, 2.5 percent achieved some tumor shrinkage and 30.3 percent had stable disease. The higher dose did cause more fatigue and anemia. Curiously, neutropenia was more likely to get better. In a growth modulation index analysis, the time to progression improved by more than 30 percent in a quarter of the patients who crossed over in the European study. In his conclusions, Zalcberg said the study suggests that 800 mg. of Gleevec has specific activity in a proportion (25 percent) of patients who have disease progression on 400 mg.

In the U.S. study, Rankin reported that of the 77 patients who crossed over, five (7 percent) achieved some tumor shrinkage and 25 (32 percent) achieved stability.

INTERMITTENT GLEEVEC
NOT ADVISED

Dr. Jean-Yves Blay (abstract 9006) reported on a French study that compared continuous to intermittent Gleevec treatment. Not unexpectedly they found that there was a high risk of progression after stopping Gleevec. Referring to this study in his summary list of “GIST Treatment Certainties,” Van Oosterom included the advice “Do not stop (Gleevec) even if CR (complete response)” and that Gleevec dose interruption should occur “only in carefully designed clinical trials.”

STOPPING GLEEVEC
RISKS FLARE-UP

A major finding at ASCO was that patients who stop Gleevec experience tumor “flare-up” on PET scans in just seven to 10 days. Flare-up indicates increased tumor activity. The precaution that patients should not stop Gleevec treatment even if progressing was common. Van Oosterom reported that CT scans did not show this same progression for two to three months. In Van Oosterom’s words, “in normal cells [and] cancer cells, renewal and growth is a continuing process; administering a tyrosine kinase inhibitor intermittently might therefore not be optimal.”

Dr. Charles Blanke of Oregon Health & Sciences University reported that the National Comprehensive Cancer Network’s GIST Task Force has recommended patients with limited progression on Gleevec do continue the drug. (You can see the current NCCN GIST Practice guidelines at: http://www.nccn.org/professionals/physician_gls/PDF/sarcoma.pdf; go to pages 14-18)

PROMISING NEW THERAPIES
ON THE HORIZON

SU11248: On Sunday, June 6, Dr. George D. Demetri gave an oral presentation on very promising data from the phase II trial of SU11248 (abstract 3001). Some 65 percent of 98 patients had overall objective benefit, including 8 percent who had a “partial response” based on RECIST criteria.
GIST patients meet around the world

GIST patients and members of gistsupportUK met Thursday, May 20 in Leeds, U.K. Participating was Dr. Mike Leahy, clinical director of medical oncology at Leeds National Health Service and senior lecturer for Cancer Research UK, who spoke and answered questions. The U.K. group has a Web site at www.gistsupportUK.com

At the June 14 European Patient Summit in Milan, Italy, were, from left, Ton De Keijser, Carolien Verhoogt, Norman Scherzer and Marlies BruinsmaBol — all but Norman from the Netherlands. Some 40 patient group representatives from 20 countries met. The GIST community had representatives from the U.K., France, Switzerland, Netherlands, Italy, Hungary and Germany.

The first North Carolina GIST/Life Raft Group gathering was held Saturday, April 17 at the Raleigh home of Chuck and Peggy Korte. Pictured, from top left, are co-hosts Larry and Julie Royster, and Ingrid Salter with, seated, David and Peggy Wicker and Chuck Korte. “We had a very good time together,” relates Chuck, “with significant sharing — our cancer journey, Gleevec/Sugen experiences, side effects and nutritional issues. We hope to meet again with hopefully more people in attendance.”

Photo by Peggy Korte
(tumor shrinkage of 30 percent or more as measured by CT scans). The overall benefit rate (complete response + partial response + stable disease) compares well with the early phase III Gleevec results of 75 percent presented last year at ASCO. However, the RECIST-based response of 8 percent lagged behind the 43 percent for Gleevec phase III trial. This confirms earlier reports that SU11248 does not shrink tumors as much as Gleevec. However, when looking at the durability of the response in those patients with 10 to 20 percent shrinkage, Demetri reported that there is a good indication of longer-term benefit with SU11248. In other words, RECIST is not a good indicator of the benefits of SU11248.

Less shrinkage may have another benefit. For the small number of patients who can’t tolerate the bleeding caused by tumors shrinking on Gleevec, SU11248 may be a less risky option.

Particularly striking in Demetri’s report was the fact that for the 41 trial patients for whom GIST genotype data was available, this drug seemed to work best against genetic mutations for which Gleevec was only moderately effective.

Gleevec seems to do best against exon 11 mutations. SU11248, in contrast, seems to work best against exon 9 mutations. For 15 patients who had exon 9 mutations, the response rate was virtually the same as that for all patients in the Gleevec phase III study. Six (40 percent) had objective response and 12 (80 percent) showed overall benefit.

Caution is advised as the numbers are still small. There were nine wild-type GISTs (no detectable KIT or PDGFRA mutations) in the genotype data group; one obtained RECIST response and five obtained benefit. This is a teasingly small sample but it is of particular interest to pediatric GIST patients, almost all of who demonstrate the wild-type KIT/PDGFRA GISTs.

Another facet of Demetri’s presentation was the availability of molecule structure data for the KIT tyrosine kinase. The crystal structure of KIT, done by C. Mol at Cyrix and published in the Journal of Biological Chemistry 2004, will permit 3-D structural analysis of KIT interaction with Gleevec and other tyrosine kinase inhibitors. This will show “how they (TKI’s) interact mechanistically with the three-dimensional conformation of the KIT kinase and eventually mutate,” said Demetri. This is a very promising development for the design of future KIT inhibitors.

If this genetic mutation response data holds up, one could speculate that a combination of Gleevec and SU11248 offers some promise, given the complementary targets of the two drugs. Demetri was asked about future trials combining Gleevec and SU11248, and replied, “certainly that’s a study that is planned for the future and not too distant future at that.”

No data was available yet from the relatively new phase III trial of SU11248 trial that started in December at sites around the world. Accrual of approximately 350 patients is in progress. During Q&A after his presentation, Demetri was asked about the controversial inclusion of a placebo in the phase III trial, the crossover design and the washout period.

“We do have a crossover in that study,” Demetri replied. “It is a two-to-one asymmetric randomization. Two patients get, in a blinded way, the SU11248, one patient, in a blinded way, receives placebo. And there is a very close follow-up of those patients. And if they worsen, then they are able to cross over to the active study drug in an unblinded way. But we felt for a drug (SU11248) that does not have a major objective remission rate, that this was the safest and most effective way to prove the worth of this agent and not run the risk of inappropriately calling an active agent inactive…”

“The other important thing that I would say that you brought up is patients, once taken off Gleevec, can progress quickly; we really have to minimize the washout period before patients enter this study. And I think that is an important consideration as kinase inhibitors seem to need to be dosed continuously.”

RAD001 + Gleevec: Van Oosterom presented the first data from the phase I trial for RAD001 (Everolimus) plus Gleevec. So far, no objective response has been observed. However, there will be a new phase I trial soon with a very different dose regimen. The reason for this is the knowledge gained about the drug interaction between RAD001 and Gleevec.
What dose Gleevec is best?

It isn’t as simple as measuring the level of Gleevec in your system. A host of factors — from size to age to stress — may come into play.

By Jerry Call

The debate over what dose of Gleevec will best prevent disease progression continues, as the initial results of the two large phase III trials continue to show crucial differences.

The Europe/Asia/Australia study is finding a longer time to progression at 800 mg. vs. 400 mg. The U.S./Canada study has not found any such correlation between dosage level and time to progression. A recent Life Raft Group analysis of patient-reported data showed fewer relapses at higher doses -- especially when the analysis was based upon actual dose delivered instead of the starting or “intent to treat” dose.

In a recent presentation given by Dr. Allan Van Oosterom at the Life Raft Group meeting in Orlando, Fla., the Life Raft Group learned that the Europeans have been monitoring blood levels of Gleevec in phase III patients and that these levels tend to decrease over time. It has been speculated that this may be why patient side effects often lessen over time. The study differences, as well as the declining Gleevec levels in the blood, has led some patients to ask whether all patients’ blood levels should be monitored. This article intends to provide a foundation to more fully understand this question.

Two important areas in the study of drugs are pharmacodynamics and pharmacokinetics. Pharmacodynamics (PD) is basically “what the drug does to the body.” Pharmacokinetics (PK) is “what the body does to the drug.”

The introduction of a few important PK concepts may be helpful to the reader.

CLEARANCE

Clearance (CL) is one of the primary PK parameters. Clearance describes the efficiency of elimination of a drug from the body. It is defined as “the volume of blood cleared of drug per unit time”. As an example; if liver blood flow is 90 liters (L) per hour and clearance were 60 L/hour, then about two-thirds (60/90) of the drug entering the liver is removed or cleared by the liver in one pass. A higher clearance rate means the drug is being removed from the body faster. Variations in clearance from one person to another or in the same person over time might require an adjustment in dose.

Drug interactions can also affect clearance. This is the basis of the well-known “drugs to avoid” list that was distributed in the early days of the phase II trials. Gleevec is metabolized in the liver by at least two enzymes, CYP3A4 (primary) and CYP2D6 (secondary). Other drugs and even “natural” supplements can affect these enzymes, causing either an increase in activity (an inducer) or a decrease in activity (an inhibitor).

Drugs that induce either CYP3A4 or CYP2D6 can cause a decrease in Gleevec drug concentrations by increasing clearance of Gleevec from the body. This could result in not enough Gleevec to prevent tumor progression. This type reaction might be more worrisome for a patient on a lower dose of Gleevec. It might also concern a patient who was experiencing a decrease in side effects.

Drugs that inhibit either CYP3A4 or CYP2D6 can cause an increase in Gleevec drug concentrations by reducing the clearance of Gleevec from the body. This could result in higher levels of Gleevec in the body, possibly resulting in increased toxicity. This might be more of a concern for a patient already on a higher dose of Gleevec or one who was having significant side effects.

Variations in CYP3A4 and CYP2D6 result in patients metabolizing Gleevec at different rates. This means different levels of Gleevec in different patients. Data supplied to the U.S. Food and Drug Administration showed drug concentrations varied up to 40 percent between patients taking the same dose. Some other sources cite higher variation, with one source citing variability up to four-fold. (ASCO 2003, Imatinib Elimination: Characterization by in vivo testing of pheno-
type and genotype, http://www.asco.org/ac/1,1003,_12-002511-00_18-0023-00_19-002003,00.asp). Polymorphisms in the ABCB1 gene (MDR1) appeared to be the primary cause of the variation in this study.

Data submitted to the FDA suggests that clearance of Gleevec is related to both age and weight. (However, another study of CML patients found that weight did not seem to be a factor in clearance.) The information from the FDA suggested that older age and lighter weight seemed to reduce clearance (increasing Gleevec blood levels) and that younger patients and heavier patients tended to clear Gleevec faster (decreasing blood levels).

Variations in protein binding to Gleevec in the blood may also affect clearance. More will be said about this later.

**DRUG CONCENTRATION**

“C” designates the concentration of a drug in the body. $C_{\text{max}}$ is the maximum concentration (occurring once a day when taking pills a per day). This occurs about two to four hours after taking Gleevec. $C_{\text{min}}$ is the minimum concentration of drug. The minimum concentration occurs at about the time (or just before) Gleevec is taken.

**HALF-LIFE**

The half-life ($t_{\frac{1}{2}}$) of a drug is the time taken for the amount of drug in the body (or the blood) to fall by half. It is a composite PK parameter determined by both clearance (CL) and volume of distribution (V). Although volume of distribution is an important PK parameter, it is a little beyond the scope of this article.

Half-life is important because:

- It determines the duration of a drug’s action after a single dose. The longer the half-life, the longer the drug concentration stays in the effective range.
- It determines the dosing frequency. The fluctuation in drug concentrations is determined by the half-life and the frequency of doses. A drug with a shorter half-life requires more frequent doses.
- It determines the time required to reach steady state drug concentrations with chronic dosing. It typically requires about three to five half-lives to reach steady state concentrations.

**PARENT DRUG and METABOLITE**

There are at least two important versions of Gleevec in the body. The first is unchanged Gleevec (called the “parent drug”). It normally accounts for about 75 to 85 percent of the total active Gleevec in the body.

The second form of active Gleevec is a metabolite called CGP 74588 (a form of Gleevec altered by the body’s metabolism). CGP 74588 accounts for the remaining Gleevec in the body (about 15 to 25 percent). Both of these Gleevec components have approximately equal anti-tumor effects.

Another difference between these two forms of Gleevec is that they have different half-lives. The parent drug (Gleevec) has a half-life of about 18 hours while the metabolite (CGP 74588) has a half-life of about 40 hours. Both of these have considerable variation in half-lives between different patients. The effect of half-life is more important if you are trying to measure Gleevec levels in the first few weeks of exposure to Gleevec, and become less important to measuring levels as time goes by.

**PROTEIN BINDING**

Another important, and often overlooked, point is that all drugs bind to other proteins in the blood and only a fraction of the drug is actually available to enter tissues and tumors. The amount of protein binding varies greatly among drugs. It is not the amount of protein binding that causes problems in determining standard dosage levels; it is the variation in protein binding between patients that could cause problems.

Gleevec is approximately 95 percent protein-bound. That means that 95 percent of the Gleevec that a patient
takes is stuck (bound) to a protein in the blood, and that a mere 5 percent of the Gleevec is unbound or “free” Gleevec. Only free Gleevec is available to enter tissues/tumors. If everyone had 95 percent of their Gleevec bound to protein, then protein binding would not matter and measuring Gleevec levels in the blood might be adequate by itself to determine if a person was getting adequate Gleevec. The amount of protein binding depends on a number of things including the drug concentration.

In personal communications with Dr. Bin Peng of Novartis, he states that protein binding of the CGP 74588 metabolite of Gleevec is approximately the same as the parent drug.

Dr. Carlo Gambacorti-Passerini has done a number of experiments that show that high levels of alpha-1-acid glycoprotein (AGP) can cause increased Gleevec binding to AGP and thus reduce the amount of “free Gleevec.”

AGP is an acute-phase protein that is increased when the body is under great stress. This especially includes infections, but also includes cancer, inflammation and post surgery. It has been suggested that larger tumor burdens generally result in higher levels of AGP.

The table above is from Gambacorti-Passerini’s paper “Alpha-1-acid Glycoprotein Binds to Imatinib (STI571) and Substantially Alters Its Pharmacokinetics in (CML) Patients.” It shows the effects of inter-patient variability of protein binding. All of these patients were on 400 mg. of Gleevec. These patients were treated with clindamycin for established infections or for prophylaxis. Since they had infections, their levels of AGP might have been higher than normal.

If we look at the second column (Cmax), we can see that maximum drug levels varied by 3.25 fold. The sixth column shows that most of these patients had higher protein binding than reported as average/typical (95 percent is typical). The last column shows that free Gleevec levels varied by 5.2 fold.

AGP levels and they have increased over time as follows:

As this patient’s AGP levels have increased, so has the amount of drug that the patient has been able to tolerate. This patient started at 600 mg., was reduced to 400, then 300 mg. for side effects, and today is able to tolerate 700 mg.

Gambacorti-Passerini also found that Gleevec drug concentrations tended to be higher in CML patients that had higher AGP levels. This finding seems to find support in a 2004 ASCO abstract “Inflammatory response affects the pharmacokinetics (PK) and pharmacodynamics (PD) of imatinib and CGP 74588 in patients with advanced gastrointestinal-sarcoma (GIST),” by C. Delbaldo and others. Although the conclusions of this abstract are difficult to interpret, they seem to have found that high AGP levels decrease clearance of Gleevec and CGP 74588 (and therefore would increase the total levels of Gleevec). The higher drug levels in this group may however, be misleading. Along with the higher AGP levels, protein binding may increase offsetting the higher drug levels. For that matter, protein binding may more than offset the higher drug levels, possibly resulting in ineffective amounts of “free Gleevec” even though total blood levels would seem to be adequate.

Patient | Cmax (µg/ml) | AUC (µg/ml h) | Clss (liter/h) | Vss (liter) | % protein bound | Free Gleevec (µg/ml)
---|---|---|---|---|---|---
001 | 8.09 | 70.47 | 5.68 | 84.7 | 99.5 | .04
002 | 2.90 | 42.70 | 9.37 | 185.2 | 97.4 | .0654
0503 | 3.06 | 43.20 | 9.26 | 152.3 | 99.2 | .0245
0502 | 7.08 | 97.70 | 4.09 | 86.3 | 99.5 | .0354
0501 | 2.49 | 33.38 | 11.98 | 266.8 | 99.5 | .0125

The role of AGP in the pharmacokinetics of Gleevec remains controversial and computer analysis suggests that AGP levels do not affect the amount of free Gleevec available (personal communications with Novartis).

A commercial test to measure AGP levels is available. One Life Raft Group patient has been monitoring AGP levels and they have increased from 150 mg/dL in June 2001 to 278 mg/dL in October 2003.

| AGP levels (reference range 39-115) | Date | Remarks |
---|---|---|
150 mg/dL | 6/12/01 | 7 months after start of Gleevec |
172 mg/dL | 1/4/02 | Three weeks after infection requiring hospitalization |
254 mg/dL | 9/8/03 | |
278 mg/dL | 10/27/03 | |

See BLOOD LEVELS III, Page 8
What is uncertain from these two studies is to what degree the higher drug levels offset the higher protein binding.

Three main proteins, Erythrocytes (red blood cells), albumin, and AGP, appear to be largely responsible for variations in protein binding between patients. Dr. Ian Judson and the European groups have reported that hemoglobin (a protein related to red blood cells) and albumin both affect response/side effects. They report that this appears to be due to their known influence on Gleevec pharmacokinetics. They do not report on AGP and perhaps, they did not include AGP in their analysis.

There may be a potentially important difference in protein binding between AGP and either erythrocytes/hemoglobin or albumin. The difference is in the direction of variation from normal. Patients that have variations from normal in erythrocytes/hemoglobin and albumin tend to have lower than normal values.

Theoretically, a patient that is varying from normal might actually have less protein binding than normal, potentially having more drug/more side effects than normal. On the other hand, AGP tends to vary from normal to levels that are up to four to five times higher than normal in some cases. So a variation in AGP from normal would tend to increase protein binding, potentially causing a reduction in free drug AND a reduction in the efficacy of the drug.

One thing to be aware of is that very important is that in the early CML trials, a better correlation was found between dose and response than either C_max or C_min and response. So this leaves us with the question: Should we be monitoring blood levels? Given care to interpret the results, monitoring levels might be useful in the following places:

- To follow a trend in blood levels. For example, if clearance decreases over time as reported by the Europeans.
- To help detect drug interactions. We have seen from the early phase I combination trials that Gleevec may interact with other drugs, as it does with PKC412 where Gleevec levels are dramatically reduced. Many, if not most, GIST patients also take other drugs.
- They might be useful as a general tool to tell if a patient were getting adequate amounts of drug IF a method to estimate or measure the effects of protein binding is developed.

Disclaimer: This report was drafted by Jerry Call, science coordinator of the Life Raft Group, and edited by Norman Scherzer, executive director of the group. Neither are physicians, scientists or professional researchers. The article is intended to provide basic information about a very complex but important subject area, and to provoke thought and comment. As survival time for GIST patients is of the essence, our intent is to push the envelope of scientific thought so as to hasten the day when GIST will be considered a chronic disease. We welcome corrections and comments.
A wish list for keeping GIST patients alive

There is something particularly cruel when GIST patients who have responded so well to Gleevec begin to encounter resistance. The trauma of having the miracle of this magic bullet taken abruptly away assaults even the most optimistic souls. The added burden of having to navigate a placebo-driven clinical trial in order to access the only drug with a track record for helping Gleevec resistant patients, Pfizer’s SU11248, is almost too much to bear.

Although we expect to see Amgen’s AMG707 in a phase II trial sometime this summer, this drug as yet has no track record for helping GIST patients resistant to Gleevec. What is promising, however, is that the Amgen trials do not contain a placebo. Should this new drug begin to help Gleevec-resistant patients, one can only wonder whether GIST patients will continue to enroll in a placebo-based trial.

Other drugs that seem promising are in early phase I trials and the number of slots available for GIST patients is far too small. Until these new drugs come further along, many GIST patients with resistance to Gleevec will have to fall back on long-shot measures, including higher doses of Gleevec, surgery, radio frequency ablation and a variety of combination therapies such as Gleevec with PKC412, Gleevec with RAD, Gleevec with interferon beta, Gleevec with Gemzar and so on. Any steps that can be taken to prevent or delay resistance, therefore, take on great urgency.

We are but a small patient advocacy group and we certainly do not have the resources to save GIST patients without the help and cooperation of others.

We offer this series of recommendations to the medical, research, pharmaceutical and governmental communities. We are not scientists and we are certainly not your adversaries. But the death of 50 Life Raft Group members in two years gives our voice extraordinary credibility.

- Move to higher doses of Gleevec/Glivec: We now have substantial evidence from both the European trials and our own Life Raft Group data that higher doses are correlated to less resistance over time. We have seen new data that Gleevec clearance levels increase over time. We have seen reports that show that it is very difficult to reverse tumor growth by crossing over to higher Gleevec doses. We have seen reports that show that side effects get better over time and that phasing in higher doses of Gleevec helps minimize them. Although the U.S. study continues to suggest that higher doses are not related to relapse, we believe that this study is critically flawed since it only looks at starting dose and not at the actual dose patients end up taking.

- Even if there is some reasonable doubt about the issue of dosage levels and relapse, we believe that the inconsistencies should be resolved, for now, by erring on the side of protecting GIST patients by moving all those who can tolerate it to higher doses of Gleevec.

- Initiate an expanded access program for Pfizer’s SU11248 for GIST patients who are ineligible for the clinical trial or cannot access it because of where they live or for financial reasons.

- End the use of a placebo in the SU11248 clinical trial. There is enough data on hand now to show that this drug is working. Continued use of a placebo is just unnecessary. Be aware that we now have reports of several GIST patients dying who had the misfortune of being given the placebo. We cannot prove that the placebo caused the deaths, but no one can prove it didn’t.

- Unblind the placebo versus drug when a patient dies. It is bad enough that the only option for the deceased and family members was this kind of trial. At least give them the peace of mind and the closure of knowing what they were on.

- To the general pharmaceutical, research and governmental community: Hurry. You are moving too slow and we are dying too fast.

- Novartis, Pfizer, Amgen, Bristol Myers Squibb, we need you now.

- Move faster. Collaborate with one another. Why do the only combination trials for GIST drugs happen to be for those made by the same company?

- And to our friends in the legislative and executive branches of government, do not abandon us. Consider what you expended in response to the anthrax outbreak. Five Americans unfortunately died. Contrast that to the hundreds of cancer patients who die each day.

- And while we have your attention, in a few days you will begin to implement a lottery to determine which Medicare cancer patients will have access to prescription drug coverage for oral cancer drugs. A lottery! What happens to the losers?

- Finally, to the institutional review boards: Exercise due diligence, to be sure — but isn’t it possible to meet more than once a month? Please, add a sense of urgency to your deliberations.

— Norman Scherzer

executive director, Life Raft Group
Pathologists predict behavior of GIST

Armed Forces Institute of Pathology researchers have focused on GIST

Second of two parts. The first part can be found in the May newsletter.

By Markku Miettinen, M.D., and Jerzy Lasota

The opinions and assertions in this article are the views of the authors and are not to be construed as reflecting the views of the Departments of the Army or Defense. The authors work for the American Registry of Pathology, contracted to work in the Armed Forces Institute of Pathology, offering consultation to government and civilian institutions worldwide. The authors wish to acknowledge the support of Department Defense and American Registry of Pathology in writing this article, as well as the encouragement of the Life Raft Group and its executive director, Norman Scherzer.

PREDICTION of TUMOR BEHAVIOR

The largest clinicopathologic series indicate that GISTs have a spectrum from small benign, typically incidentally diagnosed nodules to malignant tumors (sarcomas) at all sites of occurrence. Perhaps 20 to 30 percent of all GISTs are malignant; the percentage in published series have varied as, for example, series from cancer hospitals have understandably included more malignant tumors.

Mitotic activity and tumor size are the most important gross and microscopic features in the assessment of malignancy. Typically, tumors smaller than 5 cm. with less than 5 mitoses per 50 high magnification fields often behave in a malignant manner with potential for metastasis. Tumors greater than 5 cm. with low mitotic activity are somewhat unpredictable. However, they seem to be much more favorable in the stomach than in the intestines. The mutation type may be a prognostic factor, but information is still limited.

MOLECULAR PATHOLOGY OF GISTS

The structure of KIT and PDGFRA genes and their encoded proteins are reviewed here briefly as a background for understanding of KIT and PDGFRA mutations, which are believed to play important role in GIST pathogenesis.

Normal KIT gene and protein: KIT and PDGFRA genes are located on chromosome 4q12. KIT and PDGFRA display extensive structural homology and are members of the type III tyrosine kinase receptor family. Both proteins consist of extracellular, transmembrane, juxtamembrane, and a two-part intracellular tyrosine kinase domain. Activation of TK type III receptors by their ligands leads to downstream phosphorylation of substrate proteins and subsequently activates networks of signal transduction pathways, which regulate important cell functions. In the GI tract, KIT is expressed in interstitial cells of Cajal.

Pathologic activation of TK receptors correlates with enhanced proliferation and development of cancer; its inhibition is considered an important therapeutic approach in oncology.

KIT mutations: Somatic (non-inheritable) activating (gain-of-function) mutations in the KIT gene are believed to be a major driving force in the pathogenesis of sporadic non-familial GISTs, and structurally similar, constitutional (inheritable) mutations have been found in patients with familial GISTs. In general, these mutations are believed to confer KIT an independence of the ligand binding signal. Most of the KIT mutations have been heterozygous in nature, consistent with the concept of a dominant oncogene activated by monoallelic mutation. Of some of the specific mutation types, the transforming or auto-phosphorylating nature has been demonstrated experimentally in vitro. Germ-line KIT mutations similar to those identified in sporadic GISTs have been reported in human familial GIST syndrome characterized by hyperpigmentation and/or urticaria pigmentosa, ICC hyperplasia, and GISTs. Introduction of KIT exon 11 activating mutation into mouse genome reproduced features of human familial GIST syndrome in a mouse model and confirmed the critical role of KIT alteration in GIST development.

Four different regions of KIT have been found to be involved. They are, in decreasing order of frequency: exon 11 (juxtacelular domain), exon 9 (extracellular domain), exon 13 and exon 17 (tyrosine kinase domain).

Exon 11: The most common region involved by KIT mutations in GIST is exon 11, the juxtamembrane domain. This portion, just inside the cell membrane, is a helical domain of KIT, which seems to functionally represent an inhibitory region that regulates the KIT autophosphorylation in response to growth factor signal by KITs ligand, stem cell factor.

Exon 11 mutations were the first KIT mutations described in GISTs and are
$50,000 awarded to GIST researchers

Robert and Tania Stutman, Life Raft members and founders of the GIST Cancer Research Fund, this spring awarded a total of $50,000 to GIST researchers at Fox Chase Cancer Center in Philadelphia and Oregon Health & Sciences University in Portland.

The money comes primarily from the annual Walk for a Cure held at Rockland Lake State Park in Congers, New York. Last year’s walk raised $59,900, more than the two previous walks combined. This year’s walk will be held Sunday, Oct. 10.

The first presentation took place April 7 at Fox Chase, which hosted a luncheon in honor of the Stutmans. Among those present were Drs. Margaret Von Mehren and Andrew Godwin, and members of the sarcoma study group; Kathleen Price, special gifts director, Sandra Weckesser, Fox Chase attorney, and several member of GIST Support International.

GSI/Life Raft member Mel Heller, M.D., was among those present and offered the following observation:

“Let me tell you why this unrestricted gift of $20,000 might seem so very special to Dr. Von Mehren’s GIST research group. Gifts of that size and even more, I dare say, are not that unusual, especially at places like Fox Chase … This check was very special because Robert and Tanya did not make this generous contribution the easy way, out of a deep, comfortable and tax-advantaged pocket. No — the Stutmans went out and earned that gift the hard way, with their own labor, working the phones, doing all the things those two people know how to do when working for a worthy cause. … they gave freely of their limited and very precious personal time and energy.

The Stutmans, noted Heller, “frightened as they may have been and are by Tanya's sarcoma, emerge for us as resolved, resilient and exemplary fighters against GIST, rather than as passively defeated and weepy victims of it.

The OHSU grant was awarded during a two-day visit to Portland May 5-6. The Stutmans were accompanied by GIST patients Mark Landesman, Marina Symcox and Richard Palmer (with his wife, Linda), and caregivers Linda Hughes, Mary Marre and Rebecca Murray.

The Stutman entourage met May 5 with Dr. Brian Druker, one of the researchers who developed Gleevec for treatment of chronic myelogenous leukemia. The meeting was more of a reunion, as the Stutmans first met Druker a year earlier when GIST Cancer Research Fund presented $15,000 to OHSU.

The next morning, the GIST patients and caregivers were treated to a roundtable breakfast discussion with researchers Drs. Charles Blanke, Chris Corless and Mike Heinrich.
by far the most common KIT mutations in GIST. The three mutation types involving exon 11 are, in decreasing order of frequency: 1) in frame deletions, usually in the proximal part of the exon; 2) missense mutations, and 3) insertions in the distal part of the exon.

A majority of exon 11 mutations have been in frame deletions of one to several base pairs, in some cases apparently leading also to point mutations occurring in either end of the deletion. Typically these mutations involve the sequences between codons GCC TAT, encoding Ala502, Tyr503. The frequency of this mutation varies from 3 to 18 percent, but this mutation has a strong predilection to intestinal tumors, and therefore its frequency in GIST series will depend on the number of intestinal vs. gastric tumors included. Also, most tumors with the exon 9 mutation have been clinically malignant, suggesting that this type of KIT mutation identifies a clinically aggressive subset of GIST.

**Exon 9:** This exon encodes the distal part of the extracellular domain, and seems to be the second most commonly involved region after exon 11. All mutations have been structurally identical duplications of six nucleotides GCC TAT, encoding Ala502, Tyr503. The frequency of this mutation varies from 3 to 18 percent, but this mutation has a strong predilection to intestinal tumors, and therefore its frequency in GIST series will depend on the number of intestinal vs. gastric tumors included. Also, most tumors with the exon 9 mutation have been clinically malignant, suggesting that this type of KIT mutation identifies a clinically aggressive subset of GIST.

**Exon 13:** Identical missense mutations, resulting in substitution of Glu for Lys642 in exon 13 encoding the tyrosine kinase I, ATP-binding domain of KIT, have been reported with a very low (1-2 percent) frequency. Homozygous exon 13 mutations have been found to lead into constitutive KIT tyrosine phosphorylation. Based on the published series, this mutation seems to be associated with malignant tumor behavior. This mutation was shown to be sensitive to imatinib mesylate (Gleevec/Glivec, formerly STI571), which was able to abolish the phosphorylated status of KIT in a cell line.

**Exon 17:** This exon encodes part of the catalytic, phosphotransferase domain of KIT, tyrosine kinase II domain. KIT activating replacement mutations causing substitution of Asp816 have been previously reported in mastocytoma, seminoma, and sinonasal natural killer/T-cell lymphoma but a large initial series of GISTs was negative for exon 17 mutations. Subsequently, isolated cases of GISTs with mutations involving this exon have been reported. The number of cases is too small for clinicopathologic correlation.

**PDGFRA mutation:** Recently, platelet-derived growth factor receptor α (PDGFRA) was shown to be pathologically activated in GISTs. Gain-of-function PDGFRA mutations affecting the activation loop (exon 18 [tyrosine kinase domain]) and juxtamembrane domain (exon 12) were found in 14 of 40 (35 percent) KIT-mutation-negative GISTs. It was suggested that mutational activation of KIT or PDGFRA are mutually exclusive and represent two different alternative oncogenic events leading to similar biological consequences.

**Exon 18:**Gain-of-function mutations in exon 18 appear to be the most common PDGFRA mutations in GISTs. A great majority of these mutations represent simple T to A missense mutation at the codon 842 leading to substitution of the Val for Asp842. However, in-frame deletions and deletions with point mutations clustering between codons 841-847 were also reported. Germ-line PDGFRA mutations leading to substitution of Tyr for Asp846 has been reported in familial GIST syndromes. Tumors with point mutations affecting codon 842 are smaller and show lower mitotic activity compared to one with deletions. Also PDGFRA exon 18 mutations have a clear predilection to epithelioid morphology and gastric over intestinal location of tumor.

**Exon 12:** PDGFRA exon 12 mutations are rare, some five to six times less frequent than exon 18 mutations. A majority represent either point mutation leading to substitutions of Asp for
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Val561 or in-frame deletions with or without coexisting point mutations clustering between codons 566 and 571. Because of their rarity, their clinical significance is somewhat unclear.

Recently, Gleevec was successfully introduced in the treatment of clinically advanced, metastatic GISTs. However, based on “in vitro” studies, it has been suggested that KIT and PDGFRA activated by mutation in the tyrosine kinase domain might not respond well to Gleevec-based TK-inhibition. Recent clinical studies on the response of metastatic GISTs to the Gleevec-based treatment revealed limited therapeutic effect in PDGFRA exon18 mutant tumors, however, GISTs with PDGFRA exon 12 mutations maintained a response similar to GISTs with PDGFRA activated by mutation in the tyrosine kinase domain might not respond well to Gleevec-based TK-inhibition. Recent clinical studies on the response of metastatic GISTs to the Gleevec-based treatment revealed limited therapeutic effect in PDGFRA exon18 mutant tumors, however, GISTs with PDGFRA exon 12 mutations maintained a response similar to GISTs with KIT exon 11 mutations.

CONCLUSION
Several aspects of GISTs are under intense investigation. These include the correlation between natural history and mutations, treatment prospects, proper patient selection and mechanisms for possible primary and secondary resistance.

REFERENCES

About the authors: Pathologist Markku Miettinen, 51, is the chairman and distinguished scientist of the Department of Soft Tissue Pathology of the AFIP where he’s worked since 1996. His current research focus is GIST pathology. He worked eight years as a pathologist in Thomas Jefferson University Hospital in Philadelphia, Penn., and 10 years at the University of Helsinki, Finland, his native country. Jerzy Lasota, 47, has been a pathologist at the Department of Soft Tissue Pathology since 1996. He currently specializes in molecular pathology of GIST, and is responsible for the department’s laboratory. He did seven years of cancer research in Kimmel Cancer Center/Department of Pathology and the Fels Research Institute in Thomas Jefferson and Temple Universities in Philadelphia, and seven years in the Medical Academy of Lodz, Poland, his native country. Together the authors have published more than 30 scientific articles on gastrointestinal stromal tumors.

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ASCO III
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GIST – WHAT’S NEW
Blanke, in his summary analysis of the Sugen and RAD001 presentations, commented on the controversial design of the phase III SU11248 trial.

“Historically new compounds are used in refractory populations. Usually the first line therapy to which the tumor is resistant, in this case being Gleevec, is stopped. There may even be a significant washout period required when the patient receives no therapy.

“Besides setting the bar rather high by selecting such resistant clones, I believe a major problem with this strategy is the discontinuation of Gleevec … If a new drug must be tested second line, I believe it should be added to Gleevec. The Pfizer phase III concept testing SU11248 against placebo is somewhat bothersome to potential patients and possibly rightly so. As we just talked about in differing from the front line situation, patients discontinuing Gleevec after showing progression tend to get sick very quickly. They may never have the opportunity for benefiting from the new drug.

“If agents must be tested alone in refractory patients, the study participants should be watched extremely closely. And the period off Gleevec and/or the potentially active new agent must be as short as possible.”

Regarding SU11248, Blanke added the drug “shows activity across a wide range of patients.” In a press release issued shortly after ASCO, Blanke announced that OHSU would go ahead with the phase III trial of SU11248.

“A lot is new under the sun,” Blanke concluded. “Today’s presentations were good. But it is certainly too early to say we have a second magic bullet against GIST.”

NO DISCUSSION OF PKC412
This long-delayed trial of PKC412 plus Gleevec did not come up either in formal or behind-the-scenes discussions. This phase I trial should be under way at OHSU.

See ASCO IV, Page 14
INTERFERON
There was an interesting poster (abstract 9027) by Dr. Ernest Borden of Cleveland Clinic on an in-vitro study of interferon (IFN-B) and GIST cell lines. Borden is interested in working with the Life Raft Group to explore starting a clinical trial. This poster showed that Interferon alpha 2, and especially Interferon beta, were able to inhibit KIT and AKT, and cause cell death in the GIST cell line tested. In these laboratory studies on GIST cell lines, interferon beta appeared to be as effective as Gleevec.

**BMS354825**
This phase I trial for solid tumors, including GIST, should begin shortly at Dana-Farber in Boston and in Glasgow, Scotland. This promising drug targets SRC in addition to C-Kit and PDGFR. SRC is a downstream target of KIT. This trial builds upon the phase I experience with 30 chronic myelogenous leukemia patients. It will be a dose escalation trial starting at 70 mg. per day, which is higher than the beginning dose in the phase I CML trial. Although there is no clinical data yet, this drug occupies a high profile spot on both Bristol Meyer Squibb and Life Raft Group radar screens.

**AMG706**
This Amgen drug was not on the ASCO agenda but it is due to undergo clinical trials starting this summer in a number of locations. The Life Raft Group now has anecdotal reports of two GIST patients responding to this drug, one with tumor shrinkage and one with stability.

**ARIOAD (AP23573)**
This interesting drug was presented in a poster session (abstract 3076) presented by Dr. Monica M. Mita. This is a new rapamycin analog that is heading toward a phase II trial. Mita showed data regarding one GIST patient who is projected to have partial response on AP23573. Dr. A. A. Desai of the University of Chicago also presented a poster (abstract 3150) showing phase I PK/PD data for this drug.

**GLEEVEC + BEVACIZUMAB**
According to Dr. Blanke “A trial design combining Bevacizumab (Avastin) with Gleevec is going before the NCI shortly.”

Disclaimer: This report was prepared by Life Raft Group member Jim Hughes and Executive Director Norman Scherzer and edited by Life Raft Group Science Coordinator Jerry Call and Newsletter Editor Richard Palmer. Corrections and comments are welcome.

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L.A. area GIST patients meet July 11
Southern California area GIST patients will gather Sunday, July 11, at the Lakewood home of Life Raft area coordinator Floyd Pothoven. The meeting will begin at 1 p.m. GIST patients, caregivers and family are invited. “Everyone is welcome, no matter where you live,” says Floyd. E-mail Floyd at floyd@lasersealer.com, or call him at (562) 920-6411.

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DONATIONS
Joining the group was Carol Koller, director of development for OHSU, Rachel Hunsinger, associate director of development, and Lisa Nolen, administrative coordinator. The breakfast offered patients and caregivers to voice their appreciation to the scientists whose efforts have, and continue to, let them enjoy full lives.

Fortified with an excellent buffet breakfast, the Stutmans got down to the serious business of the day: presentation of $30,000 to the three GIST researchers.

Then it was off to the research labs of Drs. Heinrich and Corless, where two surprises awaited. The first was mounted on the wall next to the lab entrance: an engraved plaque proclaiming: “The OHSU Cancer Institute gratefully acknowledges the GIST Cancer Research Fund for its generous support of GIST cancer research.”

Then came a PowerPoint presentation about the recent work of the two researchers, including the difference between GIST that’s initially resistant to Gleevec (called primary resistance) and GIST that becomes resistant over time (secondary resistance).
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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