



Tania and Robert Stutman model the GIST T-shirts they had made for the GIST Walk for a Cure held Sept. 16 in New York state, U.S.

## GIST walk raises \$23,000-plus; fund nears \$40k

**B**y any yardstick, the first GIST Walk for a Cure held Sept. 16 in Congers, New York, was a huge success: More than 150 people showed up at Rockland Lake State Park to raise more than \$23,000.

Life Rafter and organizer Tania Stutman and her husband, Robert, personally raised \$7,000. Life Raft Group Coordinator Norman Scherzer was there, bringing \$1,000 collected by his daughter and grandchildren. And the walkers — including Life Rafter Bernie and Dr. Ephrian Casper, chief of medical oncology at Memorial Sloan Kettering Cancer Center in New York City — brought in more than \$16,000. And more was pledged.

Thanks to the walk, the GIST Cancer Research Fund now has close to \$40,000. “Not bad for amateurs,” said Robert Stutman. “After a week filled with sorrow, some good news out of the Big Apple.”



## LIFE RAFT GROUP

October 2001

Special Side Effects Survey issue

Vol. 2, No. 9

# Life Raft patients report fatigue is top side effect

Edema and diarrhea tie for second; skin rashes are third most reported

**By Norman J. Scherzer**

Life Raft Group Coordinator

with **Janet Hendrickson**

Life Raft Group Medical Librarian

**I**n our April 2001 newsletter, the Life Raft Group presented its first survey of the side effects that member patients have experienced with Gleevec. This very early study with a small number of participants gave us our first data on the side effects experienced by GIST patients in the Gleevec clinical trials. Member patients were asked to list up to three significant side effects and to rank them as low, medium or high.

The dramatic responses of most Life Raft members to Gleevec, along with a growing realization that GIST is becoming a chronic disease — which may necessitate remaining on Gleevec for long periods of time — prompted us to again explore side effects.

Since this first study, the Life Raft Group has grown significantly, and a higher daily dosage of 800 mg has been introduced with the phase III trials. This side effects survey of 61 member patients attempts to be more

comprehensive in scope and detail.

We have tried to respond to the suggestions and critiques of our earlier study. Were the side effects present before taking Gleevec? Have they changed over time? Is the ranking of severity consistent among members? Do side effects affect our ability to function and, if so, how? Does weight make a difference? How are side effects being managed? How reliable is the reporting of side effects?

Members were asked to list all significant side effects and to rank them over four time periods: before starting Gleevec, the first three months on the trial, the second three months, and the subsequent period on the trial (ranging from month seven to month 12).

Building on work done by the medical community to evaluate pain, we introduced a new scale for rating the severity of side effects. (See Exhibit A/Side effects on Page 8).

For the first time we attempt to evaluate the quality of medical management of side effects, the sources of information patients rely upon, and whether patients would minimize their side effects to remain in the trials.

## Objectives

The survey's major objectives:

- To provide patients/caregivers and

See Survey, Page 2

Table 1: Summary of Reported Side Effects

Side Effect	No. rept'd	Percent rept'g	No. severe	% severe of no. rept'd	Patient rating by time period			
					Pre trial	1st Qtr	2nd Qtr	Subseq period
<b>Total</b>	<b>273</b>	<b>98%</b>	<b>119</b>	<b>44%</b>	-	-	-	-
Fatigue	38	62%	19	50%	2.7	5.4	4.8	4.0
Edema	33	54%	21	64%	0.6	5.4	4.3	3.1
Diarrhea	33	54%	13	39%	1.5	5.1	4.9	4.6
Skin *	29	48%	13	39%	0.3	4.1	4.3	3.7
Nausea	23	38%	9	39%	0.3	4.3	2.8	2.2
Eye puffiness	22	36%	4	18%	0	4.0	3.7	4.1
Cramping	19	31%	6	32%	0.7	3.6	4.0	3.7
Reflux	12	20%	2	17%	2.2	4.7	3.4	4.0
Pain	10	16%	5	50%	2.3	3.6	3.5	1.8
H.G.B. (Anemia)	8	13%	2	25%	1.6	3.4	5.0	2.8
Wt. change +/-10%	7	11%	-	-	-	-	-	-
Eye blurriness	7	11%	3	43%	0	5.0	4.3	3.0
Liver enzymes	6	10%	5	83%	2.7	2.3	3.0	-
Fever	4	7%	3	75%	2.0	5.2	5.2	4.0
Mood	4	7%	1	25%	0	1.3	3.0	2.3
Hair thinning	4	7%	0	0%	0	2.7	4.0	4.0
GI bleed	3	5%	1	33%	0	1.0	0.5	2.5
White blood cells	2	3%	2	100%	3.5	7.5	3.5	3.54
Neutrophils	2	3%	2	100%	3.5	7.5	3.5	3.5
Dizziness	2	3%	2	100%	0	7.0	5.0	4.0
Miscellaneous**	12	20%	6	50%	2.2	5.6	2.2	3.0

Table 1 data based on reports from 61 of 67 Life Raft Group patients active as of Aug. 1, 2001. \* Skin side effects include patient-reported neuropathy. \*\* Miscellaneous side effects include shortness of breath (2 reported), metallic taste, low blood pressure, constipation, and difficulty concentrating.

### Caveats:

We repeat our standard caveats. Although many of us come from professional backgrounds, we are not professional researchers and our data may be subject to the twin demons of inaccuracy and distortion. Although we continue to strengthen our survey techniques and our quality control procedures, patient-based reporting may not always be accurate and, although we have a larger study group than ever before, we do not know how representative we are of the clinical trials as a whole. Finally, we remain aware of the pitfalls of small numbers. A small change can have a disproportionate statistical effect.

## Survey

From Page 1

physicians with better information about the type and severity of side effects that GIST patients are experiencing with Gleevec;

- To evaluate the medical management of these side effects;
- To empower patients/caregivers in their relationships with physicians.

### The side effects

The survey data is based upon the

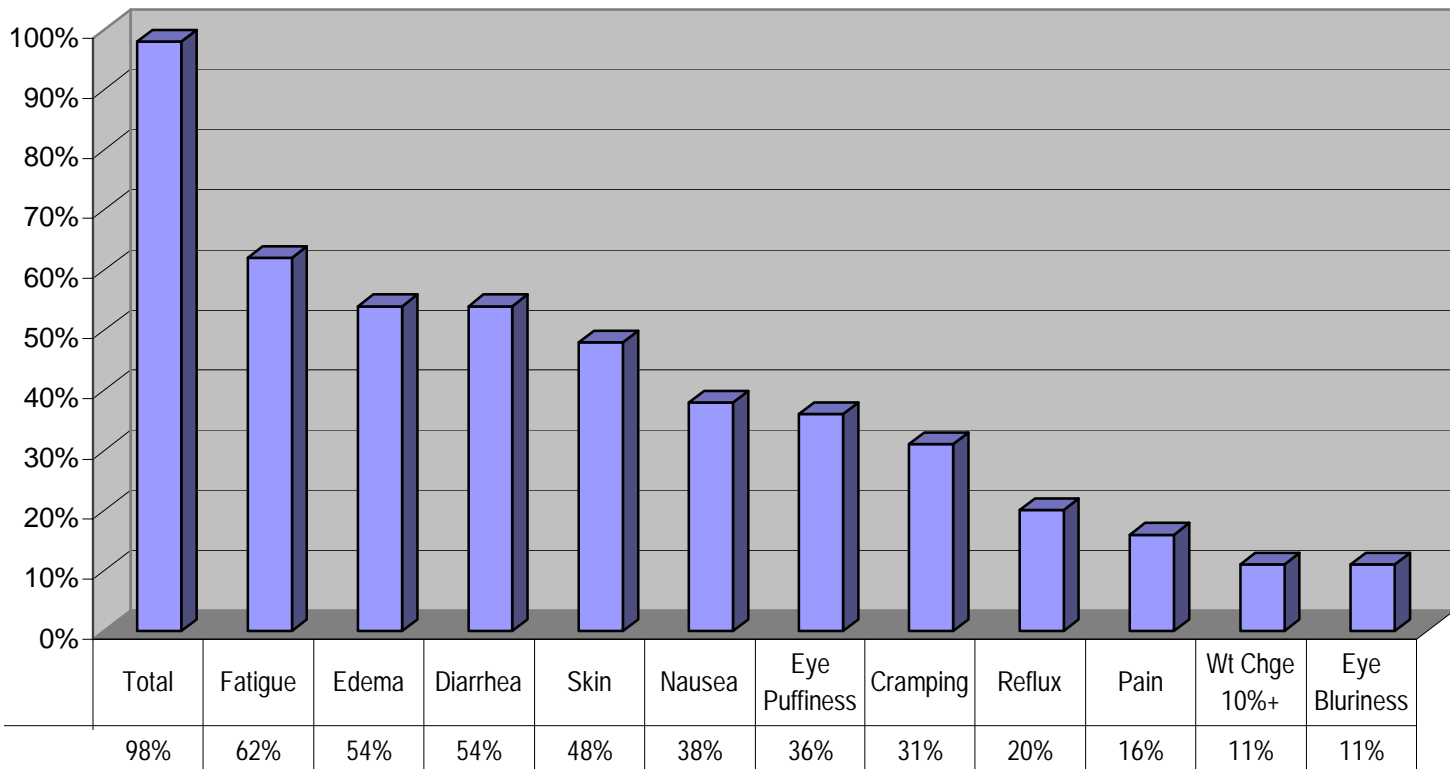
reports of 61 of the 67 active member patients on board as of Aug. 1, 2001, a response rate of 91 percent. Not included were six of seven members who died in the past year, those removed from the trials for lack of response, and the significant number of patients who joined the Life Raft Group since Aug. 1. Included are two GIST patients taking Gleevec who are not on the clinical trial.

Sixty (60) of the 61 respondents, or 98 percent, reported a total of 273 side effects for an average of 4.6 per patient. Forty-five (45) of the 61 respondents, or 74 percent, reported 119 severe side effects for an average of 2.6 for the 45. (See Table 1, above).

The most common side effects reported are fatigue, edema, diarrhea, skin problems, nausea, eye puffiness,

See Severe side effects, Page 3

**Chart 1: Major side effects reported (by more than 10% of respondents)**



## Severe side effects

From Page 2

cramping, reflux, pain, weight change and eye blurriness. (See Chart 1, above).

### Severe Side Effects

Side effects were rated as severe if they received an average patient rating of 7 or more in any given time period, or if they were cited as a reason for stopping the drug or for lowering the dosage. The greatest number of severe side effects reported were fatigue, edema, diarrhea and skin. (See Tables 1 and 3, previous page and right).

Of those reporting severe side effects, 24% reported only one, 24% reported two and 52% reported three or more. (See Table 2, above right).

### Stopping/decreasing the dosage of Gleevec

Of the 61 total respondents, six had

See Stop/decrease, Page 4

Table 2: Number of severe side effects reported

Number of severe side effects reported	Number of respondents	Percent reporting
One	11	24%
Two	11	24%
Three	11	24%
Four	8	18%
Five	3	7%
Six	1	2%
<b>Totals</b>	<b>45</b>	<b>99%</b>

Table 3: Reasons for stopping and/or

	Number	Percent
Edema	8	33%
Skin (includes patient reported neuropathy)	7	29%
Liver enzymes	3	13%
Multiple reasons	3	13%
Eye blurriness	1	4%
White blood cells	1	4%
Fever	1	4%
<b>Totals</b>	<b>24</b>	<b>100%</b>

## Stop/decrease

From Page 3

their drug dosages increased, five because of tumor growth and one because their side effects improved to permit increasing above an initial 100 mg/day level (this was one of the non-trial participants). Of the remaining 55 respondents, 24, or 44%, reported having their drug stopped for a period of time, or their drug dosage reduced because of side effects, with edema and skin problems being the most common cause. (See Table 3, previous page).

### Functional side effects

We asked each respondent to separately list the functional impact that their side effects were having on their lives. Almost half report having to cope with fatigue. About one third report functional decreases in physical activities, sleep, mood and appetites. About a fifth report an impact upon their ability to work, to conduct daily activities and to concentrate. Finally, about one out of 10 report an impact upon their relationships, general and sexual. (See Table 4, above right).

### Life style changes

We asked each respondent to note any lifestyle changes that they have made since starting Gleevec. Significant numbers report changes toward a healthier lifestyle, most being prompted by clinical protocol admonitions. The result, whatever the reason, is that there has been a significant decrease in the intake of caffeine and the use of alcohol. (See Table 5, above right).

### Side effects over time

Respondents were asked to describe and rank each of their side effects in severity (see Exhibit A/Side effects, Page 8, for scale). Each side effect was ranked for each of four time periods. We then averaged each side effect for each time period and analyzed their

See Side effects/ time, Page 5

Table 4: Functional side effects (61 reporting)

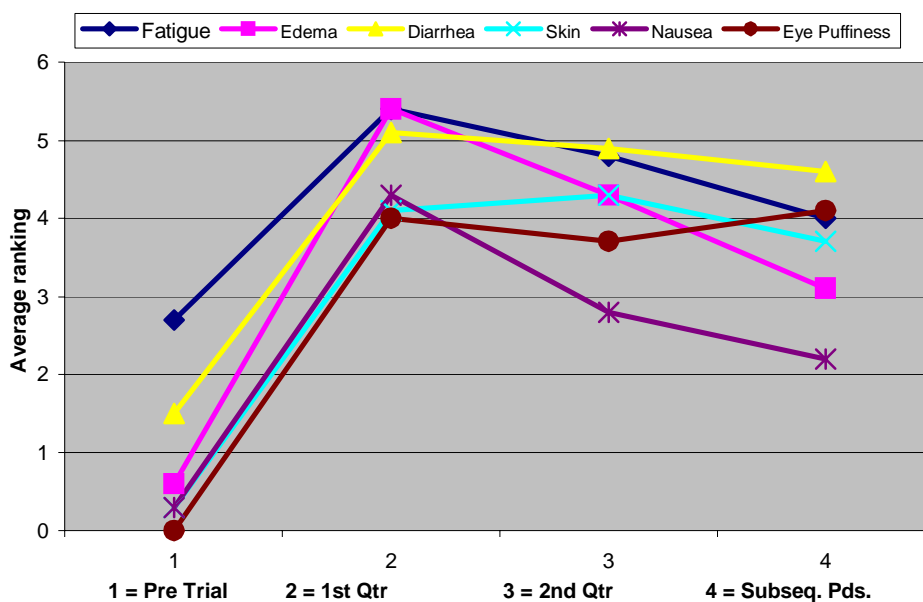
Functional Side Effect	Number reporting	Percent reporting
Fatigue	30	49%
Physical activities	20	33%
Sleep	19	31%
Mood	18	30%
Appetite	17	28%
Work	14	23%
Daily activities	14	23%
Concentration	11	18%
Sexual relationships	8	13%
General relationships	4	7%

Table 5: Life style changes after starting Gleevec (61 reporting)

	Number	Percentage
Decreased caffeine	28	46%
Decreased alcohol	26	43%
Diet changes	21	34%
Decreased smoking *	2	3%

\* Very few members smoked prior to the trial

Chart 2: Six major side effects ranked over time



## Side effects/time

From Page 4

patterns over time.

Chart 2 (see facing page) displays the changes in time of the six major side effects. Most had some incidence prior to the start of Gleevec and increased sharply in the first three months of Gleevec use. Following the end of the second quarter, all but eye puffiness seem to level off or decrease.

Chart 3 (at right) is a case study of those patients who reported very severe skin side effects in the first quarter (rating of 8 to 10). All of these showed substantial improvement over time, with two resolving completely. This seems to indicate a fairly common pattern with other severe side effects, with side effects peaking, leveling off and decreasing. Some reach this peak in the first quarter, but some seem to reach it later on.

This does not mean, however, that all is well given enough time. Many patients have to live with significant side effects for the foreseeable future.

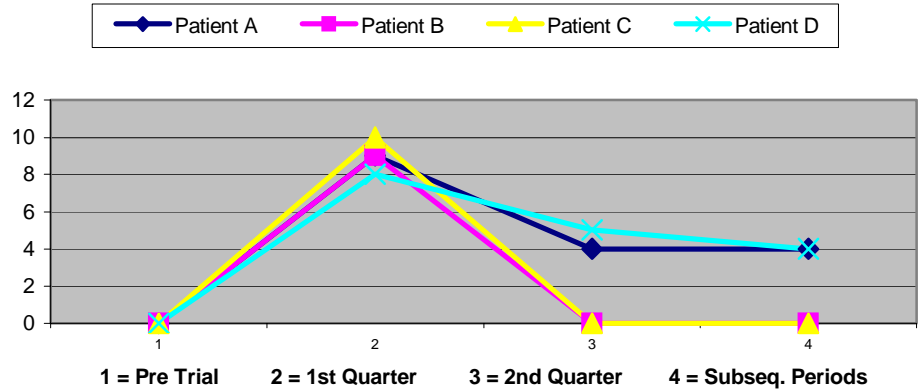
### Side effects: Dosage, gender and Weight

Because of small numbers, we were unable to compare 600 mg versus 800 mg daily doses, and had to combine these into 400 versus 600-plus.

As was the case with our first side effects survey, it is clear that the severity of side effects is closely correlated with dosage and with gender. As we looked at dosage at the start of the trial, and as many of the higher doses were subsequently decreased, our data most likely significantly underestimates the impact of higher doses.

For the first time we looked at the weight of the patient at the start of the trial to see if this was related to the severity of side effects. It was not, with both weight categories we created having identical results. (See Table 6 and Chart 4, at right).

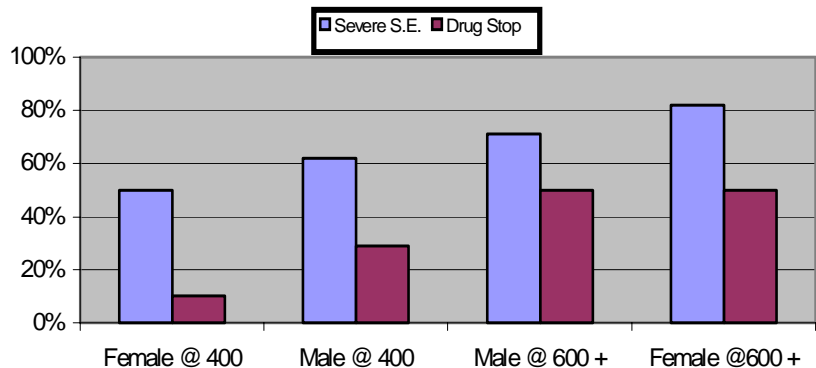
**Chart 3: Skin side effects with severity ranking of 8 or more in the 1st quarter**



**Table 6: Gender, dose and weight (61 patients reporting)**

Gender and starting dosage	% With severe side effects	% Requiring drug stoppage and/or dose decrease
<b>Totals</b>	<b>74%</b>	<b>44%</b>
<b>Gender and dosage</b>		
Female @ 400 mg/day	50%	10%
Male @ 400 mg/day	62%	29%
Male @ 600 plus mg/day	71%	50%
Female @ 600 plus mg/day	82%	50%
<b>Weight at start of drug</b>		
Under 150 Pounds	74%	46%
Over 150 Pounds	74%	48%

**Chart 4: Gender & drug dose correlated with severe side effects and drug stoppage/decrease**



## Side effect info

From Page 5

### Side effect information

We asked each patient to rate the importance of different sources of information about side effects. As expected, the primary source was the Life Raft Group, but this is a biased result given that these patients are Life Raft Group members. Trial doctors and nurses were the most significant medical sources of information, with local oncologists playing a much less important role and local primary care physicians almost out of the picture. (See Table 7 at right).

### Role of the trial doctor

We asked each patient to assess the role of the trial doctor both as a source of information about, and as a manager of, their side effects. It is striking that less than half considered their trial doctor to be their primary source of information about side effects and that 25% did not consider their trial doctor to be their primary source for the medical management of their side effects. (See Table 8 at right).

### Medical management of side effects: How good?

We asked each patient to rate the quality of the medical management of their side effects. On a scale of 0 to 10, with 10 being the highest, the average for all doctors was 6.3. For facilities with 3 or more patients represented, three received a rating of 7 or above. Facility F received a rating of only 3.2.

The Life Raft Group held an open debate as to whether to publish the names and ratings of all the doctors or facilities, including those who rated poorly. There was not clear consensus and some were concerned about repercussions to themselves should we do so. As a result, the decision was made not to identify any facilities. (See Table 9, right).

See Concerns ..., Page 7

Table 7: Patient rating of sources of information about side effects

On a scale of 0 to 10, with 0 being totally irrelevant and 10 being absolutely indispensable (60 patients reporting)

Trial Doctor	6.1
Trial Nurse	5.9
Local Oncologist	4.0
Local Primary Care Physician	2.4
Life Raft Group	8.5

Table 8: Patient perception of role of trial doctor (60 patients reporting)

	As primary source of side effect information*	As primary provider of side effect medical management
Yes	44%	75%
No	54%	20%
N.A.	2%	5%
	100%	100%

\* Where the trial doctor received the same rating as another category, the trial doctor was considered to be the primary source.

Table 9: Rating of quality of the medical management of side effects

(Facilities with 3 or more patients represented, 56 patients reporting)

**On a scale of 0 to 10, with 0 being nonexistent and 10 being extraordinary, how would you rate the care you have received from your clinical trial doctor and staff in managing your side effects?**

7 Or Above	Facilities A, B and C
6.0	Facility D
5.6	Facility E
3.2	Facility F
<b>6.3</b>	<b>Overall average, all trial doctors/facilities regardless of the number of patients</b>

Table 10: Accuracy of reporting — Correlation with patient concerns and with patient rating of the quality of medical management of side effects

	Would You Consider Minimizing The Reporting Of Your Side Effects To Avoid Being Taken Off Of Gleevec?				
	Yes	Maybe	Subtotal	No	N.A.
<b>Total, all respondents</b>	18%	32%	<b>50%</b>	46%	4%
<b>Among the 48%* concerned about being taken off trial :</b>	38%	34%	<b>72%</b>	28%	0
<b>Correlated with side effect medical management rating:</b>					
<b>16% rate as 3 or below</b>	22%	56%	<b>78%</b>	22%	-
<b>36% rate between 4 and 6</b>	30%	20%	<b>50%</b>	45%	5%
<b>48% rate as 7 or above</b>	7%	33%	<b>40%</b>	56%	3%

\*In response to our question, “Have you ever been concerned about being taken off of Gleevec because of side effects,” 36% responded yes and 12% responded *maybe* (60 patients reporting).

## Concerns about being taken off trial

From Page 6

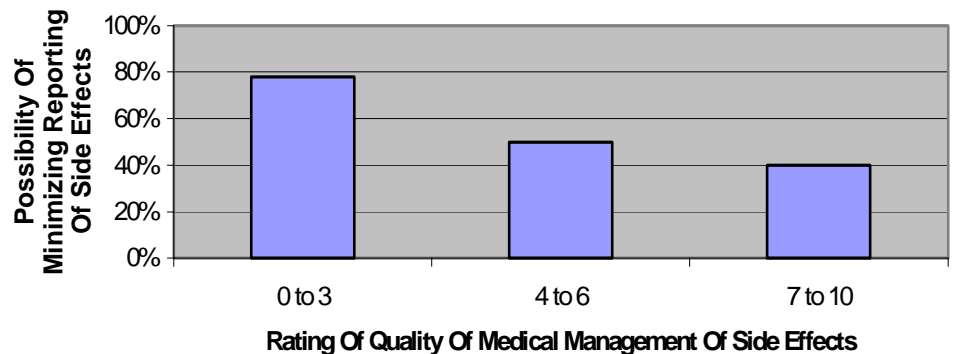
### Patient concerns correlated with quality of medical management of side effects

We asked each patient whether they were concerned about being taken off the trial because of side effects and 48% reported that they were. We then correlated this level of concern with whether the patient would consider minimizing the reporting of their side effects to avoid being taken off of Gleevec. As might be expected, there was a clear correlation, with 72% of those who were concerned about being taken off the trial reporting that they might (*yes* or *maybe* in response to our question) consider minimizing their side effects to remain on Gleevec.

We then correlated the relationship between their medical management rating and whether the patient would consider minimizing the reporting of their side effects.

The results were quite striking. The

Chart 5: Minimizing reporting of side effects correlated with medical management rating



lower the medical management rating, the higher the likelihood that the patient would consider minimizing the reporting of their side effects. Only 40% of those respondents rating their

medical management of side effects as 7 or above would consider minimizing their side effects as contrasted to 78% of those rating their medical manage-

### Exhibit A

Side Effects						
Describe and rank each side effect. In addition to issues that make you feel bad (previously reported issues have included skin rash & burning, fatigue, insomnia, edema-including eye puffiness, diarrhea, reflux, nausea and cramping), also list any significant blood test abnormalities such as white blood cell, hemoglobin, neutrophils, bilirubin and platelets, and any emergency issues such as GI bleeding.						
<b>List each side effect below</b> If more than five, use Remarks Section on page 8		Using the severity scale in the right column as a reference, rate each side effect on a severity scale of 0 through 10 in the time periods indicated below			<b>Severity scale for rating side effects</b>	
<b>Side Effect</b>		<b>Prior to starting Gleevec</b>	<b>First 3 months on trial</b>	<b>Second 3 months on trial</b>	<b>Subseq. periods on trial</b>	0 None
1.						1
2.						2 Mild
3.						3
4.						4
5.						5 Moderate
						6
						7
						8 Severe
						9
						10 Unbearable

### Exhibit B

Gleevec Dosage				
Start Date	Change Date	Change Date	Change Date	Change Date
Start Dosage	New Dosage	New Dosage	New Dosage	New Dosage
In the appropriate date column, indicate reason for dosage change or for being taken off the drug.	Reason	Reason	Reason	Reason
Reported reasons have included GI bleeding, hepatoxicity (liver), neutropenia (neutrophils), infection, edema (fluid retention) and hematological (blood) toxicities such as WBC (white blood cells), HGB (hemoglobin) and PLT (platelets).  If you need more room, use the Remarks Section on page 5.				

### Exhibit C

**Functional impact of side effects:**

Describe if side effects have had any impact upon what you do (Sleep, Appetite, Mood, Exercise and Other Physical Activities, Relationships (Social and Sexual), Concentration, AbilityToWork, etc.)?

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# Methodology

From Page 7

ment as 3 or below. (See Table 10 and Chart 5, page 7).

The importance of quality medical care in helping to ensure reporting accuracy is quite significant and has long range implications for those conducting clinical trials.

## How we did the survey

The survey form used was developed over time, critiqued by the Life Raft Group Science Team and a number of clinical researchers in the United States and Europe, and pre- tested by 10 Life Raft Group patient volunteers.

## Side effect rating and description:

Respondents were asked to describe and rank each of their side effects us-

ing the severity scale in Exhibit A (see facing page). Each side effect was ranked for each of four time periods. We then averaged each side effect for each time period and analyzed their patterns over time. Side effects were rated severe if they received an average rating of 7 or more in any given time period, or if they were cited as a reason for stopping the drug or for lowering the dosage (see Exhibit B, facing page).

Finally, each respondent was asked to describe the functional effect of their side effects (see Exhibit C, facing page).

## Side effects assessment: Life Raft vs. Novartis

Using the latest side effect data published by Novartis in a Memorandum to pharmacists dated August, 2001, we compared the frequency of side effects reported by the Life Raft Group to

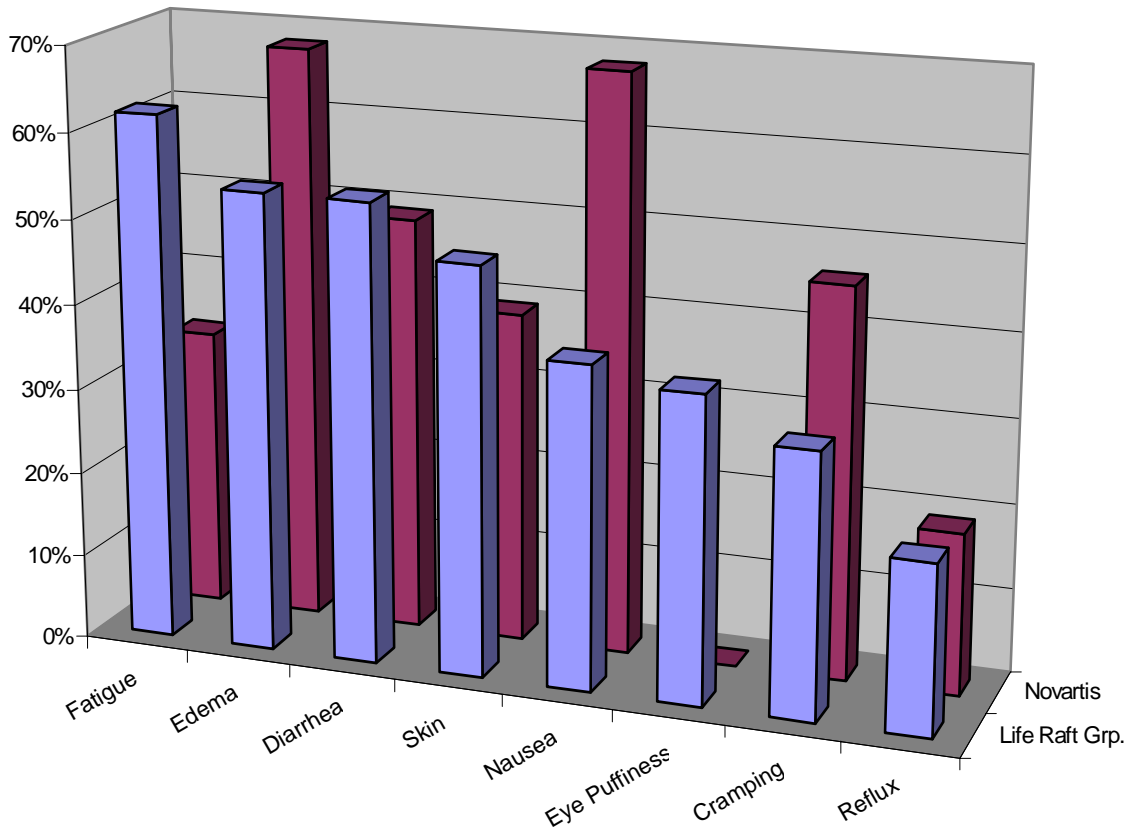
those reported by Novartis. The Novartis data refers only to patients using Gleevec for chronic myelogenous leukemia. The Life Raft Group data refers only to patients using Gleevec for GIST.

For most side effects, the data is fairly similar, with the Life Raft Group reporting a higher amount of fatigue, diarrhea and skin problems, and the Novartis Group reporting a higher amount of edema, nausea and cramping. Reported reflux was about the same. Only one side effect, namely eye puffiness, was reported by the Life Raft Group and not by Novartis, although that might be explained by a different method of categorization. (See Chart 6, below). *As we go to press we have, in fact, learned from Novartis that they classified eye puffiness as edema.*

Where there are significant differ-

See Comparison, Page 10

Chart 6: Comparison of major side effects reported by the Life Raft Group (for GIST) and by Novartis (for chronic myelogenous leukemia)



## THE LIFE RAFT GROUP

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**Who are we and what do we do?** We started as GIST patients and caregivers (spouses and others) in the Gleevec (STI571) clinical trials, and have since extended membership to all GIST patients on Gleevec. We come together to share our experiences and support each other. We focus on symptoms, side effects and other drug-related issues. Members correspond privately to each other and to the group as appropriate.

**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. To assist in that goal, the secure e-mail listserv does not include professional members of the various study sites. However, this newsletter does serve as an out-

reach and is widely distributed. Hence, all items in the newsletter are edited to maintain the anonymity of members, unless members have granted publication of more detailed information.

**Method:** Our primary means of communication is through a confidential, secure listserv operated by the Association of Cancer Online Resources, ACOR ([www.acor.org](http://www.acor.org)).

**Disclaimer:** We are patients and caregivers, not doctors. Any information shared among the group should be used with caution, and is not a substitute for careful discussion with your doctor.

**Newsletter note:** Read at your own risk! Every effort to achieve accuracy is made, but we are human and errors occur. Please advise the newsletter editor of any errors you may find.

## Comparison

From Page 9

ences is in the reporting of the severity of side effects, with the Life Raft Group tending to define a greater number of side effects as severe.

There are two major reasons for these differences.

The first is that Novartis, like all clinical researchers, uses the toxicity standards established by the NCI (National Cancer Institute), whereas the Life Raft Group uses its own patient severity rating scale.

The second is that Novartis derives its data from the reports of clinicians, whereas the Life Raft Group derives its data directly from the patient. This raises the issues of whether the clinician correctly hears, interprets and records what the patient says, and whether the patient chooses to accurately report their side effects. It also raises the issue of whether the Life Raft Group correctly interprets what the patient has written and whether the patient has accurately reported their side effects.

Although we have no Novartis data on GIST-Gleevec severity, we do have the reports of the clinical researchers at the May, 2001, conference of the American Society of Clinical Oncologists. The GIST-Gleevec trial researchers used the NCI toxicity standards, with grade 3 and 4 events being reported by the U.S. trials and grade 2, 3, and 4 being reported by the European trials. Let's compare the U.S. report, using grades 3 and 4 to define toxicity, to the Life Raft Group methodology. We will use as an example the fact that a clinical trial patient has diarrhea.

The U.S. ASCO report notes that, of 145 study participants, there were 0 cases of diarrhea as a grade 3 or 4 toxicity. The Life Raft Group notes that, of 61 study participants, there were 13 cases of diarrhea reported to be severe.

How could this difference occur? Assume that a patient had three incidents of diarrhea per week before beginning Gleevec, and three incidents *per day* since beginning Gleevec.

Using the current NCI toxicity scale that situation would rate a one, on a scale of 0 to 5, with 0 being none and

5 being death.

Using the Life Raft Group Severity Scale, the patient might conclude that three episodes a day of diarrhea for the indefinite future, might rate a 7 on our scale of 0 to 10, thus qualifying for a ranking of severe. One might ask the NCI analyst who did the scale: How would you rate the severity of having to cope with three episodes of diarrhea per day for the rest of your life?

Given that about half of those amongst the Life Raft Group who report severe side effects, report three or more, this poses an interesting dilemma. How do you combine the several different side effects into one quality of life whole? To some extent we have begun trying to do this by looking at functional effects, in addition to rating side effects separately. (See Table 4, page 4).

We may return to this in the future. Our purpose is to point out the different perspectives of a patient group and a clinical trial group in looking at the severity of side effects, and to suggest that both may help understand what a patient is actually going through as he/she tries to live their life.