

A surgeon reports on his experience as a patient in an ACOSOG trial



by Ralph Keill, MD, FACS, Monterey, CA

I had been retired from my last position as a hospital medical director for about two years when I first noticed some soreness in my abdomen after doing curls at the gym. I thought the pain was just the result of a strained rectus muscle, so I avoided abdominal exercises for several weeks, but when I tried again, the soreness returned. I decided to avoid abdominal exercises altogether and experienced no more pain. However, over the next month or so, my abdomen seemed to feel increasingly full and firm. I figured I may have developed a rectus muscle hematoma because I had been taking 1,000 mg of aspirin daily since having a stroke in 1998. The symptoms persisted, but no others developed.

Diagnosis

The timing was very bad because my physician had just closed his practice, and I had yet to establish care with a new physician. My elderly mother-in-law's health was declining, and my son was about to get married, so I planned to postpone seeing anyone about my concerns until these other situations settled down.

As fate would have it, I received a mailing about a screening ultrasound in the area and, thinking I certainly didn't want to be sitting on an aortic aneurysm, I decided to go. The results revealed no aneurysm but did show a large abdominal mass with mixed echoes. I had never seen anything like it. Having been in the private practice of general and vascular surgery for 22 years, those results convinced me that I needed to see someone.

I called to make an appointment the next day with an internist in my community. He scheduled a computed topography (CT) scan, which revealed a large, well-circumscribed mass arising from the anterior wall of my stomach. The next day I had an ultrasound-guided biopsy, the results of which showed I had a stromal tumor. The biopsy itself was completely painless and interesting to watch. At the time, they also aspirated 1,000 cc of serous but blood-tinged fluid from the mass. Afterward, I felt much less bloated.

I knew nothing about the surgeons in the area because my last position had been at a hospital in a nearby community. I called an infectious disease specialist who was on staff at all the hospitals in the county for a recommendation. I had become acquainted with him in my medical director posi-

tion, knew him to be an excellent physician, and believed he would make a good recommendation. He suggested a surgeon, and I made an appointment.

Hope

I felt very good about the surgeon, Lane Verlenden, MD, FACS, when I met him. After a visit, some preoperative lab work, and some time spent giving a unit of blood for autotransfusion, on November 7, 2002, I had the mass, along with a portion of my stomach, resected. My postoperative recovery was uneventful, almost easy. Before I left the hospital, however, I again was told that I had a stromal tumor with a low mitotic rate. It was at this time that I first heard about a new oral drug called Gleevec that had been used to treat this tumor and another condition.

After my discharge from the hospital, I began researching Gleevec on the Internet and first came across the term gastrointestinal stromal tumor (GIST). I also received some recent literature from a friend's son who had recently completed his surgical residency. I learned that GIST is rare, that it is sometimes benign and sometimes malignant, and that it is difficult to tell which tumors will behave which way.

The surgeon provided me with a copy of my pathology report, and further research showed that my tumor had mostly benign but some malignant characteristics. I also had learned that Gleevec was very effective against this tumor, but it had only been used and approved for treatment of patients with recurrent or unresectable tumors. I began thinking about possibly taking the drug as a form of adjuvant therapy. The surgeon referred me to an oncologist to discuss this possibility.

I immediately liked the oncologist. We had much in common. We had both been in the military during the Vietnam era, had begun practice within a few years of each other, and had both been instrumental in getting a hospice established in our communities. He learned that the American College of Surgeons Oncology Group (ACOSOG) was initiating a clinical trial to study the effects of Gleevec on GIST. The only difficulties with regard to participating in the ACOSOG trial were that the study had a tight timeline for entry, it required taking the drug for a year, and it would involve a detailed and long-term follow-up process.

Entering the study

I decided to try and gain entrance to the ACOSOG trial and quickly set about arranging the necessary exams, blood tests, and CT scans. The side effects described seemed to be mostly of the aggravating but not dangerous variety. No one had much experience with the drug, and the oncologist had only used it on a handful of patients for its other indication. I was accepted into the study and began taking the medicine January 27, 2003, at the protocol's prescribed dose of 400 mg/day.

The dose consisted of four 100 mg tablets each day after a large meal, preferably the evening meal. The informed consent included a disclosure of the common (greater than 10%) and uncommon (less than 10%) side effects. I also was informed that the study would consist of about 89 subjects nationally. I began taking Gleevec and quickly discovered that if I took it as recommended, I experienced absolutely no side effects. If I forgot to take the medicine right after dinner and instead took it before I went to bed, I would have mild diarrhea. I quickly fell into a routine and never missed a dose. My weight remained stable, and I felt well and completely normal.

The first two months I was on the medication, I saw the investigating physician and had blood tests every two weeks. This regimen was to be followed by visits and tests once a month for another four months, then every three months for the first two years, and then every six months for the next three years. In addition, I was supposed to have a thoracic, abdominal, and pelvic CT scan every three months for the first two years and then every six months for the next three years.

The investigating physician had a nurse whose only responsibility was to coordinate clinical research studies, and she kept my treatment scheduled and on track. I was in regular communication with her and found that her efforts kept me organized with respect to what was expected and planned. Participating in the study did not affect my lifestyle at all, and I could continue all my normal activities. My red blood cell count did decrease somewhat but not to anemic levels.

Side effects arise

In mid April 2003 my wife and I went on a trip to Paris and Ireland. Several days after arriving in Paris, I became aware that I was having edema of

my feet, lower legs, and hands, and a pruritic rash covered my body. I also developed large blisters on the soles of my feet. I was aware that edema was one of the known side effects of the medicine. I also thought the edema might be related to the long airplane flight and remembered that I developed a skin rash after being on Ticlid for over a month due to the previously mentioned stroke. Additionally, I wondered if the rash could be due to something the bed sheets had been washed in, because it was worse on my back. A few days after the onset of these conditions, I stopped the Gleevec for several days, but noticing no improvement, I resumed taking the medicine. The rash and edema persisted throughout the trip, but I continued the medication until I returned home.

Once home, I checked the Gleevec Web site and learned that 38 percent of the people taking the medicine developed a rash and other skin conditions and 76 percent developed edema. I saw the oncologist, who stopped the medicine and started me on a diuretic. The edema quickly resolved and the rash began to disappear. Most of my symptoms abated within a week of being off the medication, so I went back on it at a lower dose, per study protocol. Within a week, the rash and edema came back with a vengeance. This time I developed very hypertrophic skin with flaking and extreme dryness on some parts of my body, along with fissuring on my fingertips and on my feet. My wife remarked that it looked like my skin had aged 10 years in a week. I was again taken off the medication, and, although the edema disappeared within a week, it took several weeks for my skin to return to normal. My physician contacted the study leader, and they decided that I should not resume the drug therapy. Thus, I stopped Gleevec after being on it for between three and four months.

Normal life resumes

In late July 2003, I had follow-up blood tests and a CT scan as required by the study. At that point I was about nine months postoperative. My hemogram, which had decreased a bit while on the medication, was back to normal levels, and the liver function tests and the CT scan were normal. Another set was planned when I approached the one-year anniversary of the operation. I have not found the frequency of the follow-up visits and studies to be problematic at all, and I have been able to con-

continue all my activities and travels without interruption.

Two important lessons

I would certainly participate in the clinical research study again if confronted with the same decision, and believe I have reached two major conclusions as a result of this experience. First, "a physician who treats himself has a fool for a patient." Second, clinical trials are useful tools in determining how to effectively treat many diseases.

The relationship between a physician and a patient is a partnership in which both people need to have a voice in decisions. When physicians become patients they probably have a greater understanding of the issues than a random patient, so they can be more active participants in the decision-making process. Ultimately, though, it is the treating physician who must decide on the best course of care. Physician/patients do a disservice to themselves if they try to manage or dictate their own care.

I had a previous significant experience as a patient when I had the major stroke mentioned previously. In that instance, I was hospitalized for three weeks, underwent therapy for eight months, and received follow-up care from several physicians for a number of years. During that time I had to accept that I was dependent on others and felt I had a real partnership with my physicians. I had the same experience this time as a physician/patient. In both these cases, I had no previous contact with the physicians involved but still felt a closeness and confidence with those caring for me.

The second lesson learned involves my feeling about the importance of clinical research studies in general. The first time I entered a clinical trial, I participated in a physician's health study conducted at Harvard to determine if low-dose aspirin lowered the incidence of heart disease in normal males and if betacarotene lowered the incidence of certain types of malignancies in normal males. It was a double-blind study, so we didn't know whether we were taking the items being studied or a placebo. The aspirin part of the study stopped after five years because it was clear that aspirin did reduce the incidence of heart disease, but the betacarotene part was carried out for 10 years before it was discontinued. I still receive a questionnaire 20 years later for follow up.

I firmly believe that these clinical research studies are a worthwhile tool for determining the best therapy for patients. The Harvard study was invaluable in revealing that low-dose aspirin had a protective effect on lowering the incidence of heart disease in normal males and that betacarotene was not beneficial in protecting against certain types of malignancies.

Hopefully, this study about Gleevec in treating GIST will reveal if it has a place as an adjuvant therapy for this rare gastrointestinal tumor. Even though I was unable to tolerate the medication for the duration of the study, my participation may be helpful in determining the optimal length of therapy. We are all aware that the initial length of adjuvant therapy for breast cancer was much longer than it is today. That determination was most likely gleaned from the results of study participants.

To conclude, I am happy to report that I just completed my one-year follow-up exam, blood tests, and CT scans with no evidence of recurrence. I intend to continue to participate in the follow-up studies as long as it is requested. I would certainly participate in the study again if the same choices were presented to me. I also would encourage any physician confronted with being a patient to be exactly that. Don't try to manage your own illness, but work in partnership with your physician to achieve the optimal care for your illness or problem.

Finally, I would like to thank ACOSOG for undertaking this study of the adjuvant use of Gleevec in GIST at just the perfect time for my participation. □

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