

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

Current and Future Management of GIST

Charles Blanke, MD
Associate Professor of Medicine, Division of Hematology and Medical Oncology
Oregon Health and Science University

H&O What is the current standard of care for advanced-stage gastrointestinal stromal tumors?

CB For advanced gastrointestinal stromal tumors (GIST) not amenable to surgery, the current standard of care is imatinib mesylate (Gleevec, Novartis) at a dose of 400 mg/day. There are some emerging data indicating that select patient groups, based on genetic analysis, may require a higher starting dose; however, this approach is not yet part of standard care, as only retrospective analyses have been conducted thus far.

For individuals who have failed treatment with imatinib, the subsequent approach becomes more complicated, as it can depend on the sites of failure, complications associated with this failure, and other related issues. A common intervention is to continue with imatinib but at an increased dose of 800 mg/day; this approach benefits approximately one third of patients. Depending on the site, number of metastases, and other considerations, some patients may be eligible for surgery. For patients who are clearly imatinib-refractory or -intolerant, sunitinib (Sutent, Pfizer) has been approved by the US Food and Drug Administration for salvage use, and represents the standard of care in the salvage setting.

H&O How does sunitinib differ from imatinib?

CB Both sunitinib and imatinib are targeted agents. Sunitinib is somewhat more promiscuous in that it has more targets. Also, sunitinib may have antiangiogenic activity, which is not seen with imatinib.

H&O What are the current questions regarding the treatment of advanced disease?

CB Several important issues remain regarding the treatment of advanced disease and these are being addressed in ongoing clinical trials. As mentioned above, preliminary data indicate that certain patients may benefit from a higher dose of imatinib. In the studies with sunitinib in the second-line setting, the degree of benefit differed among patients with different mutations. This is also true for imatinib in the first-line setting. Also, it may be that sunitinib would be beneficial in the upfront setting; there are no data addressing this question as of yet.

Another question is: when should surgery be integrated into the treatment approach? Salvage surgery alone has not been found to be of benefit, but surgery in conjunction with these targeted agents may have a long-term benefit. For patients with limited spread of the disease, it is often difficult to determine whether a different drug, a higher dose, or removal of the resistant malignant clone would be best.

H&O How are clinical trials in GIST changing as therapeutic advances are made?

CB In the past, all of the patients who enrolled in a trial were treated in the same way. This approach is changing. One of the main questions being asked now with regard to trial design and conduct is: should all patients be enrolled with retrospective analyses conducted to garner data on particular subsets, or should investigators try to enrich the population of a trial for the specific subset of interest? For example, patients may be selected for a trial based on genetic mutations or other factors. This type of approach is clearly one of the waves of the future, and is an area of debate right now with regard to clinical trials for GIST. Selecting patients may make conducting a trial more difficult, but the results may be more useful for specific individuals.

H&O How are patients with GIST treated in the adjuvant setting?

CB GIST has a postsurgery recurrence rate of 50–90%, and perhaps the most important question being asked

now regarding the treatment of GIST is whether imatinib should be used in the adjuvant setting following resection of intermediate- or high-risk disease. In the metastatic setting, imatinib has been found to benefit approximately 90% of patients, and so it is logical to consider this agent for treatment in the adjuvant or even the neoadjuvant setting in order to down-stage tumors. We do not yet know whether imatinib would be effective in this setting or, if it is effective, at what dose and for what duration.

Several ongoing trials are evaluating this issue. The American College of Surgical Oncologists has completed study Z9000, evaluating adjuvant imatinib in high-risk patients. Only safety data have been presented thus far and the efficacy results are eagerly awaited. In the ongoing randomized study Z9001, intermediate- and high-risk patients are receiving placebo versus 1 year of imatinib. In Europe, studies are evaluating 0 versus 2 years of imatinib therapy and 1 versus 3 years of imatinib therapy.

H&O Could you describe other agents currently under investigation for the treatment of GIST?

CB There are numerous agents being investigated, all in the salvage setting after imatinib failure. Among these, some of the most promising are sorafenib (Nexavar, Bayer), nilotinib (formerly AMN107, Novartis), and the heat shock protein inhibitor IPI504 (Infinity). Some of these agents are again less specific inhibitors than imatinib, in that they hit multiple targets, and some are more potent KIT inhibitors. IPI504 is particularly interesting. This drug potentially inhibits Hsp90, which controls cell-signaling proteins.

H&O Are studies to identify prognostic factors in GIST ongoing?

CB Yes. Much of this work is being conducted by Drs. Chris Corless, Michael Heinrich, and Jonathan Fletcher. Currently, all patients receive imatinib, and so prognostic and predictive factors would not have an immediate significant influence on treatment decisions. However, this work will likely lead to the ability to select specific drugs for specific individuals, and thus these are very important studies for the future.

H&O Have any specific markers for treatment been identified?

CB Studies have found that specific genetic abnormalities are associated with specific sites of the body. For

example, exon 9 mutations are common in small bowel primary GISTs. In addition, it has been demonstrated that patients with exon 11 mutations, which are the most common type of mutation, do best when treated with imatinib compared to other patients. Patients with no detectable exon 11 mutation fare the worst. These data are very important, although these so-called wild-type patients are still treated with imatinib.

H&O Is imatinib-based combination therapy being explored?

CB Yes, combination therapy is certainly of interest. An ongoing intergroup trial conducted by the Southwest Oncology Group and the International Coalition Against Cancer, which is about to begin accruing patients, will be the largest first-line trial in GIST and will evaluate bevacizumab (Avastin, Genentech), a potent angiogenic inhibitor that has shown efficacy in the treatment of colon, breast, and kidney cancers. In the GIST study, patients will receive imatinib with or without bevacizumab.

Another important question is whether imatinib can be combined with sunitinib. A trial is currently being designed to address this issue.

Suggested Reading

Blanke CD, Corless CL. State-of-the-art therapy for gastrointestinal stromal tumors. *Cancer Invest.* 2005;23:274-280.

Bui BN, Le Cesne A, Ray-Coquard I, et al. Do patients with initially resected metastatic GIST benefit from "adjuvant" imatinib (IM) treatment? Results of the prospective BFR14 French Sarcoma Group Randomized phase III trial. *J Clin Oncol.* 2006;24(18S pt 1). Abstract 9501.

Casali PG, Garrett CR, Blackstein ME, et al. Updated results from a phase III trial of sunitinib in GIST patients (pts) for whom imatinib (IM) therapy has failed due to resistance or intolerance. *J Clin Oncol.* 2006;24(18S pt 1). Abstract 9513.

Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002;347:472-480.

Heinrich MC, Maki RG, Corless CL, et al. Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correlates with *KIT* and *PDGFR4* mutation status. *J Clin Oncol.* 2006;24(18S pt 1). Abstract 9519.

Janeway KA, Matthews DC, Butrynski JE, et al. Sunitinib treatment of pediatric metastatic GIST after failure of imatinib. *J Clin Oncol.* 2006;24(18S pt 1). Abstract 9519.

Morgan JA, Garrett CR, Schutte J, et al. Sunitinib patients (pts) with advanced imatinib (IM)-refractory GIST: early results from a "treatment-use" trial. *J Clin Oncol.* 2006;24(18S pt 1).

Verweij J, Casali PG, Zalberg J, et al. Progression-free survival in gastrointestinal stromal tumors with high-dose imatinib: randomised trial. *Lancet.* 2004;364:1127-1134.