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Lecture

Advancing treatment of Gastrointestinal Stromal Tumors (GIST)

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Once a poorly defined pathologic oddity, in recent years, gastrointestinal stromal tumor (GIST) has emerged as a distinct oncogenetic entity that is now center stage in clinical trials of kinase-targeted therapies. Gastrointestinal stromal tumors (GISTs) are an uncommon malignancy of the gastrointestinal (GI) tract, accounting for only 0.2% of all GI malignancies. However, they are the most common sarcoma of the abdomen. Primary GISTs arise throughout the GI tract, most commonly in the stomach (40% to 70%), followed by small bowel (20% to 40%), colon and rectum (5% to 15%), and esophagus (< 5%).GISTs exhibit a broad spectrum of clinical behavior, with some low-risk lesions remaining stable for years, while others progress rapidly to widely metastatic disease. Many GISTs are asymptomatic, discovered incidentally during imaging or at laparotomy for unrelated reasons. Between 15% and 50% of GISTs are metastatic at the time of diagnosis.

Approximately 85% of GISTs express the CD117 antigen, part of the KIT receptor tyrosine kinase. In 1998, Hirota et al identified gain-of-function mutations of the *KIT* proto-oncogene in the majority of GISTs. Similar activating mutations have been identified in a related receptor tyrosine kinase, platelet-derived growth factor receptor-alpha (PDGFRA).

Before 2001, surgery was the only effective treatment for GISTs. Five-year survival rates for patients with GISTs ranged from 28% to 80%. In approximately 50% of patients, complete resection was not possible, and median survival ranged from 10 months to 23 months. Patients treated before 2001 achieved little benefit from chemotherapy or radiation therapy. Dramatic improvement in GIST management occurred with the recognition that mutational activation of KIT or PDGFRA stimulated growth of these cancer cells. This led to effective systemic therapies in the form of small molecule inhibitors, such as imatinib mesylate (Gleevec; Novartis Pharma, Basel, Switzerland) or sunitinib malate (SU11248; Sutent, Pfizer Inc, New York, NY). These agents block signaling via KIT or PDGFRA by binding to the adenosine triphosphate-binding pocket required for phosphorylation and activation. In 2002, a large, multicenter trial of imatinib for patients with metastatic GIST demonstrated partial responses in 54%, stable disease in 28%, and disease progression in 14%. Imatinib was approved for treatment of metastatic or unresectable GISTs in February 2002. Phase I/II and III studies have shown that sunitinib demonstrates antitumor efficacy in patients resistant to imatinib.Sunitinib was approved for treatment of metastatic or unresectable GISTs in January, 2006.

The 52-month efficacy data from the pivotal phase II trial of imatinib (US-Finland Study B2222) found that 400 mg or 600 mg daily achieved an 84% clinical benefit rate and overall survival of 4.8 years in patients with metastatic or unresectable gastrointestinal stromal tumor (GIST). Differences in *KIT* mutation status stratified patients with respect to survival: those with a mutation in exon 11 had the best survival results. In the phase 3 studies comparing 400-mg versus 800-mg initial dosing, significantly better progression-free survival was obtained with the 800-mg starting dose. About a third of patients whose imatinib dose was increased to 800 mg/d upon progression had an objective response or stable disease. Data are now available regarding GIST mutation status and imatinib response, and there is emerging guidance on when, how, and in whom to use high-dose imatinib therapy. Criteria for evaluating GIST response to treatment with kinase inhibitors, which have both cytostatic and cytoreductive properties,

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are rapidly evolving in light of evidence that the traditional size-based tumor-response benchmarks are inadequate in the era of molecularly targeted therapy. Fluorodeoxyglucose positron-emission tomography (FDG-PET) has been shown to demonstrate very early tumor responses to imatinib. Investigators have recently correlated computed tomography findings with FDG-PET results and imatinib treatment outcomes.

Researchers have found that to avoid subtherapeutic drug levels and to help circumvent potential resistance, a brief "drug holiday," if necessary, is generally preferable to reduced dosing to allow a side effect to resolve. The goal then is to reinstitute therapy as soon as possible at the optimal therapeutic dose. Side effects in patients receiving imatinib tend to diminish over time, even at doses above 600 mg/d. Most side effects tend to be mild to moderate in severity and manageable. Failure to achieve 100% adherence to antineoplastic therapy can have adverse consequences for outcomes. In this era of oral, outpatient therapy for cancer, adherence is a key issue. Patient understanding of the need for continuous dosing for continuous tumor suppression, even when they are feeling well, is critical to the success of treatment. Patient registries, which are being established globally, are expected to provide considerable insight into "real world" practices in the management of GIST.

Surgery remains the initial intervention of choice for patients with localized primary resectable GIST. Yet such tumors may recur in about half of patients by 5 years after the initial resection. Ongoing clinical trials are investigating the effect of adjuvant imatinib therapy on postoperative recurrence in high-risk cases of primary resectable GIST: large or mitotically active tumors, ruptured or bleeding tumors, or incompletely resected tumors. Neoadjuvant imatinib therapy is also under investigation. Neoadjuvant administration is intended to down-stage primary resectable or marginally resectable GISTs to achieve a better operation, spare organs, or reduce complications and postoperative morbidity. Before the availability of imatinib, surgery had little or no role in treating advanced disease. However, a novel pattern of focal recurrence observed in imatinib-treated patients has proved amenable to surgical control. Use of surgery as an "adjuvant" to imatinib therapy in advanced disease is central to a "multi-modality" approach in treating patients with GIST throughout the disease course. A purpose of surgery in the advanced setting is to extend the time patients can benefit from first-line kinase-inhibitor treatment and potentially improve the quality of response. Imatinib is indicated as first-line therapy for metastatic or unresectable GIST, even if surgery is contemplated later.

Although imatinib-treated patients with advanced GIST have achieved unprecedented median overall survival of nearly 5 years (based on 52-month follow-up in the US-Finland Study B2222), late progression—usually resulting from resistance—is observed in a minority of patients. Primary resistance manifests itself in the small percentage of patients (~12% in Study B2222) who lack or lose clinical benefit (response or stable disease) within 6 months after the start of therapy. The first steps when resistance is suspected are to confirm GIST progression and reevaluate treatment. Measures that can be considered include investigation of adherence to prescribed therapy (eg, serum drug-level testing) and evaluation for possible pharmacokinetic factors unique to the individual patient. Imatinib dose escalation to 800 mg/d may restore response or stabilize the disease, especially when the GIST harbors a *KIT* exon 9 mutation. Mutational analysis can be considered if the mutation status is not known and signs suggesting resistance are detected. A surgical consultation may be appropriate when foci of reactivated GIST appear during imatinib treatment. Once first-line kinase inhibitor treatment has been optimized, consideration can be given to alternative approaches. Sunitinib is approved for the treatment of advanced GIST after disease progression on or intolerance to imatinib. Another option is enrollment in a trial of a new drug, such as nilotinib, which is an investigational second-generation kinase inhibitor being tested in GIST and in BCR-ABL–positive hematologic malignancies. RAD001, an investigational inhibitor of the mammalian target of rapamycin (mTOR), blocks signaling pathways downstream of KIT. It is hoped the addition of RAD001 to a KIT inhibitor might control resistant disease in GIST patients.

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