ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Drugs for Gastrointestinal Stromal Tumors

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H&O How has the treatment landscape evolved in recent years for patients with gastrointestinal stromal tumors (GIST)?

CG GISTs are uncommon sarcomas that arise from the gastrointestinal tract and historically are relatively resistant to cytotoxic chemotherapy[1] and radiation therapy.[2] They are believed to arise from the interstitial cells of Cajal, or the pacemaker cells of the gastrointestinal tract.[3] The discovery that the majority of GISTs harbor activating KIT mutations[4] led a Finnish group to use the BCR-ABL and KIT inhibitor imatinib (Gleevec, Novartis) in a patient with advanced GIST, with positive results.[5] Subsequent multicenter trials confirmed the initial observation that imatinib can lead to objective radiographic response rates of greater than 60%, with an associated dramatic improvement in overall survival.[6]

H&O What are the current treatment approaches for GIST?

CG Surgery remains the mainstay of treatment for patients with localized GIST.[7] Factors such as tumor size, mitotic rate, and KIT or platelet-derived growth factor receptor (PDGFR) mutation status predict for tumor relapse.[8] Adjuvant therapy may be considered for KIT-mutant tumors at high risk of relapse; although 3 years of adjuvant imatinib was shown to improve the progression-free survival, with longer follow-up, there did not appear to be a survival benefit.[9] Adjuvant imatinib is not recommended for patients whose tumors harbor a PDGFR mutation or whose tumors are KIT wild-type. For patients who have locally advanced disease deemed not surgically resectable, neoadjuvant imatinib may be able to sufficiently cytoreduce the tumor to allow for a surgical resection.[10] Patients who have large tumors (>10 cm) resected or who have metastatic disease require treatment with imatinib until evidence of intolerance or disease progression.[11]

H&O What are the challenges of current treatment?

CG While the median overall survival of patients with advanced GIST has increased to longer than 5 years with the use of imatinib, the development of resistance is a major problem. Approximately 50% of patients demonstrate resistance to imatinib at 2 years.[12] It is believed that this resistance is the result of clonal selection of populations of cells, which may lead to acquisition of a new KIT/PDGFR mutation, loss of KIT expression and activation of an alternative tyrosine kinase receptor, or activation of an alternative downstream signaling pathway and genomic amplification of KIT. At the time of progression, options include increasing the dose of imatinib to 800 mg per day[13] or switching to second-line sunitinib (Sutent, Pfizer).[14] Sunitinib is another oral agent that targets KIT, as well as the vascular endothelial growth factor (VEGF, 1-3), PDGFR α and β, and FLT3. It was proven in a randomized, placebo-controlled, phase 3 study to be superior to placebo in terms of time to progression. However,

Table 1. Tyrosine Kinase Inhibitors Currently Approved for or Undergoing Evaluation for the Treatment of Advanced GIST

Agent	Targets	Type of Study	Treatment Population	Reference
Currently Approved Agents for the Treatment of GIST				
Imatinib	KIT, BCR-ABL, PDGFR	Phase 3	Treatment-naive	6
Sunitinib Malate	VEGFR 1-3, KIT, PDGFR, RET, FLT3	Phase 3, placebo-controlled	Imatinib-refractory or intolerant	14
Regorafenib	VEGFR 1-3, PDGFR, KIT, RET, TIE2, FGFR	Phase 3, placebo-controlled	Imatinib- and sunitinib-refractory	17
Tyrosine Kinase Inhibitors Undergoing Clinical Evaluation in GIST				
Sorafenib	VEGFR 2-3, KIT, PDGFR, C-RAF	Phase 2	Imatinib- and sunitinib-refractory	21
Nilotinib	BCR-ABL, KIT, PDGFR	Phase 3	Imatinib- and sunitinib-refractory	19, 20
Motesenib	VEGFR 1-2, KIT, PDGFR	Phase 2	Imatinib- and sunitinib-refractory	22
Ganetismib	Hsp90	Phase 2	Imatinib- and sunitinib-refractory	23
Everolimus	mTOR	Phase 2	Imatinib- and sunitinib-refractory	24, 25

GIST, gastrointestinal stromal tumors.

since the trial allowed those on placebo to cross over to sunitinib, it was unable to document a survival benefit associated with its use.[14]

H&O What is the mechanism of action of regorafenib (Stivarga, Bayer) in GIST?

CG Regorafenib is an oral kinase inhibitor that inhibits multiple protein kinases, including VEGFR 1-3, KIT, RET, RAF1, BRAF, PDGFR, and fibroblast growth factor (FGF).[15] The molecular mechanisms by which regorafenib exerts its effect in GIST are unclear.

H&O What previous clinical experiences with regorafenib in patients with GIST provided the rationale for phase 3 testing?

CG A phase 2 trial of regorafenib in 34 patients with advanced GIST who had failed imatinib and sunitinib therapies was performed in the United States. This study demonstrated that, even in the refractory setting, regorafenib was associated with significant objective radiographic response rates (4 patients [12%] had a partial response), and the clinical benefit rate (a complete response, a partial response, or stable disease for ≥16 weeks) was 79%.[16] This signal of efficacy led to a large, placebo-controlled, randomized, phase 3 study in GIST patients who were refractory or resistant to imatinib and sunitinib.[17] There was a significant progression-free survival advantage in favor of the regorafenib-treated patients; crossover was allowed on the placebo arm, and 56 patients (85%) did cross over and were able to receive regorafenib. Based on these data, on February 25, 2013, the US Food and Drug Administration (FDA) approved regorafenib for patients with advanced GIST who are refractory to imatinib and sunitinib.[18]

H&O What are some promising areas of research?

CG Nilotinib, an inhibitor of BCR-ABL, KIT, and PDGFR, demonstrated efficacy in retrospective studies in treatment-refractory GIST.[19] However, a large, phase 3, randomized, placebo-controlled trial failed to demonstrate a statistically significant improvement in overall survival, although there was a trend toward improved survival that favored nilotinib.[20] A number of multitargeted tyrosine kinase inhibitors have shown early favorable results in phase 2 trials of refractory patients, including sorafenib (Nexavar, Bayer and Onyx)[21] and motesanib.[22] An early phase 2 study with the heat-shock protein 90 inhibitor ganetespib (STA-9090) demonstrated modest efficacy in 26 patients with refractory GIST, with a stable disease rate of 55%.[23] The mTOR inhibitor everolimus (Afinitor, Novartis)—which is currently approved for the treatment of kidney cancer, pancreatic neuroendocrine cancers, breast cancer, and subtypes of astrocytomas—has been studied in imatinib-refractory GIST. In a phase 2 study of 15 patients, everolimus 10 mg daily demonstrated a radiographic response rate of 27%.[24] Everolimus has been combined with imatinib in imatinib-refractory GIST; the combination was well tolerated and was associated with a stable disease rate of 36% in patients who only progressed on imatinib, and a 2% partial response rate and a 43% stable disease rate in those patients who progressed on both imatinib and sunitinib.[25]

H&O What are the biggest remaining challenges?

CG The major remaining challenges are the molecular heterogeneity of the disease and the emergence of treatment resistance. While it is possible that it reflects acquired resistance, it is more likely that treatment selects out clones of GIST which are refractory to therapy. Future mechanisms to combat resistance will likely include more combination therapies aimed at suppressing multiple oncogenic pathways. In the future, discernment of molecular mutations may identify promising novel pathways and potential molecular targets in order to identify new treatments.

H&O What does the future hold?

CG Advances in GIST are likely to continue, based on the exponential improvement in our understanding of the biology of this disease. However, the first recognition that activating KIT mutations were critical in GIST tumor biology was made by observing a family with a germline KIT mutation and hereditary GIST. Although these are rare, this somewhat serendipitous clinical observation led to a dramatic change in our understanding of GIST tumor biology. It is quite possible that other observations may lead to future quantum leaps in our understanding of GIST oncogenesis.

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