Role of Molecular Targeted Therapy in Adult Gastrointestinal Stromal Tumors

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Abstract
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of gastrointestinal tract. GISTs can occur anywhere along the GI tract but are most common in the stomach (50%) and small bowel (25%). Colon (10%), omentum / mesentery (7%), and esophagus (5%) are less common primary sites. Liver metastases and/or dissemination within the abdominal cavity are the usual clinical manifestations of malignancy. Lymph node metastases are extremely uncommon; its spread to the lungs or other extra-abdominal locations is also extremely rare. Survival has greatly improved since 2002, when imatinib mesylate was approved by the Food and Drug Administration (FDA) for unresectable, recurrent or metastatic gastrointestinal stromal tumors (GISTs). In January 2006, the FDA approved second-line use of sunitinib in patients with advanced GIST resistant or intolerant to imatinib. This review article discusses the optimal approach for care of patients with GIST and role of molecular targeted therapy in management of GIST.

INTRODUCTION
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of gastrointestinal tract, the neoplastic GIST cells appear to arise from a common precursor cell, which gives rise to the interstitial cells of Cajal in the normal myenteric plexus. The median age of adults at diagnosis of GIST ranges from 66 to 69 years. GISTs can occur anywhere along the GI tract but are most common in the stomach (50%) and small bowel (25%). Colon (10%), omentum / mesentery (7%), and esophagus (5%) are less common primary sites. Liver metastases and/or dissemination within the abdominal cavity are the usual clinical manifestations of malignancy. Lymph node metastases are extremely uncommon; its spread to the lungs or other extra-abdominal locations is also extremely rare. Clinically GIST patients present with either emergency presentation because of intra-abdominal hemorrhage, GI bleeding, perforation, or rarely bowel obstruction (i.e., acute abdomen); or large mass suspicious for GIST (abdominal swelling, upper GI bleeding) with or without symptoms (e.g., early satiety or fatigue due to anemia). Typically, a GIST appears as a solid hyperdense-enhancing mass on Contrastenhanced Computed tomography (CECT) scan. However, large GISTs (> 10 cm) are often more complex because of necrotic, hemorrhagic, or degenerating components. GISTs have a characteristic immunohistochemical profile that is useful for confirming diagnosis. About 95% are positive for KIT (CD117), 60% to 70% for CD34, 30% to 40% for smooth muscle actin, 5% for S-100 protein, 1% to 2% for desmin, and 1% to 2% for keratin. Approximately 80% of GISTs have an oncogenic mutation in the KIT tyrosine kinase. Most of these mutations affect the juxtamembrane domain encoded by KIT exon 11, allowing spontaneous (ligand-independent) receptor dimerization and kinase activation. However, mutations also occur in exons 9, 13, and 17, and these may support constitutive KIT signaling through other mechanisms. A subset (5%–7%) of GISTs has an activating mutation in the KIT-homologous tyrosine kinase PDGFRA. About 10% to 15% of GISTs are negative for KIT and PDGFRA gene mutations; these tumors are often referred to as wild-type GISTs. New immunomarkers that have been explored in the diagnosis of KIT-negative GISTs include protein kinase C theta (PKCtheta), PDGFRA, and DOG-1.

MANAGEMENT
RESPECTABLE DISEASE
All GISTs 2 cm in size or greater should be resected. Although a 2-cm cutoff is somewhat arbitrary, recent data suggest that it is reasonable. The management of incidentally encountered GISTs less than 2 cm in size
remains controversial.

UNRESECTABLE OR METASTATIC DISEASE

ROLE OF CHEMOTHERAPY

In a large study of patients with metastatic GIST, the response rate to any cytotoxic chemotherapy regimen was 0%. (15) Other trials, which also included patients with the specific diagnosis of GIST, have reported very low objective response rates (0%–5%). (16,17) There is universal agreement that standard chemotherapy should not be used in patients with GIST as primary therapy. The median survival for patients with GIST who are treated with standard cytotoxic chemotherapy is generally less than 2 years (range, 14–18 months).

ROLE OF MOLECULAR TARGETED THERAPY

IMATINIB MESYLATE

In 2002 imatinib mesylate was approved by the Food and Drug Administration (FDA) for Gastrointestinal stromal tumors (GISTs). (18) Imatinib mesylate is a selective, potent, small molecule inhibitor of a family of structurally related tyrosine kinase signaling enzymes, including (a) KIT; (b) the ABL family of tyrosine kinases, including the leukemia-specific BCR-ABL chimera; and (c) PDGFR. In laboratory studies, imatinib inhibited proliferation of leukemic cells expressing BCR-ABL as well as both leukemia and GIST cells that harbored activated KIT. (19-21,22) Based on in vitro studies, the mutant isoforms of KIT that are commonly identified in primary GISTs are fully sensitive to the kinase inhibitor imatinib. (19-21) In contrast, GIST-associated mutation in PDGFRA confers complete resistance to this drug. (23, 24) Kinase genotype has predictive significance with regard to response to imatinib therapy. The presence of a KIT exon 11 mutation was the single best predictor of a favorable response to imatinib in the U.S.- Finnish B2222 phase II trial, the EORTC (European Organization for Research and Treatment of Cancer)- Australasian GI Trials Group phase III trial EORTCISG- AGITG trial), and the North American SWOG (Southwest Oncology Group) S0033 phase III trial. Correspondingly, patients with exon 11-mutant GIST have superior progression-free survival (PFS) and overall survival as compared with those with exon 9-mutant or wild-type tumor. (25,26) In Patients with unresectable disease, Imatinib can be considered as the first-line anticancer therapy until the optimal time for surgery (when the GIST becomes resectable and the chance of morbidity is acceptable), which can take as long as 6 to 12 months. (27) Maximal response is defined as no further improvement between 2 successive CT scans. However, it is not always necessary to wait for a maximal response to perform surgery if the tumors are still responding to therapy. Data from the EORTC trial indicated that the median time to development of secondary resistance was about 2 years. (28) Thus, surgery (if planned) should be done before 2 years, and most experts would recommend discussing surgery after 6 to 12 months of disease stability or response. The therapeutic effect should be monitored using positron emission tomography (PET) or CT. The CT response criteria proposed by Choi et al. (29-31) use both tumor density and size to assess the response of GIST to TKI therapy. Choi et al.’s CT response evaluation criteria are described in Table 1. These criteria correlate much better with PET in predicting response to imatinib than do Response Evaluation Criteria in Solid Tumors (RECIST) criteria. (30,31) The two most important prognostic features of a primary tumor are its size and mitotic index. (6)

DOSE INTENSITY

What optimal dose of imatinib should be used to begin dosing for patients with advanced metastatic or unresectable GIST? Two separate phase III trials have been conducted using imatinib: a) by the North American Sarcoma Intergroup, consisting of U.S. cooperative oncology groups.
IMATINIB MESYLATE RESISTANCE

Imatinib resistance can be managed by increasing the dose of imatinib to 800 mg/day; however, the median time to progression is about 11 weeks. An alternative method of managing imatinib resistance is to switch patients directly to sunitinib from low-dose imatinib (400 mg/day). In January 2006, the FDA approved second-line use of sunitinib in patients with advanced GIST resistant or intolerant to imatinib. Sunitinib malate (SU011248, Sutent) is an oral TKI that is less specific than imatinib mesylate. In addition to inhibiting KIT and PDGFR, sunitinib acts on vascular endothelial growth factor receptors (VEGFR1-3), Fms-like tyrosine kinase-3, colony-stimulating factor 1, and RET. Thus, sunitinib possesses potential antiangiogenic activity in addition to antitumor action related to receptor tyrosine kinase inhibition. Patients should remain on imatinib or sunitinib as long as possible; however, if the patient is no longer receiving clinical benefit from imatinib or sunitinib, then the drugs should be continued and best supportive care used. To date, no other drugs have been approved for treatment of GIST. Various promising agents are in early or late phase testing, some aiming at similar pathways (e.g., sorafenib, AMG706, or nilotinib [AMN107]; which are more potent KIT and PDGFR inhibitors) and some inhibiting novel targets (e.g., bevacizumab, which binds to VEGF, and IPI-504, which antagonizes heat shock protein 90).

References

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