Gastrointestinal stromal tumor and its targeted therapeutics

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Abstract

Over the past 60 years, investigators of basic science, pathology, and clinical medicine have studied gastrointestinal stromal tumor (GIST) and made minor advances in patient care. Recent discoveries have led to an understanding of the biological role of KIT and platelet-derived growth factor receptor-α in GIST and the development of the tyrosine kinase inhibitor imatinib mesylate (Gleevec, formerly STI-571), one of the most exciting examples of targeted therapy to date. The success of targeted therapy in GIST has lead to new developments in our understanding of the medical and surgical management of the disease. Intense study of GIST may lead to new paradigms in the management of cancer.

Key words Gastrointestinal stromal tumor, KIT, platelet-derived growth factor receptor, imatinib mesylate

Gastrointestinal stromal tumors (GISTs) are soft tissue sarcomas affecting the gastrointestinal tract. The estimated incidence is 14.5/1000000, which equates to about 5000 new cases per year in the US[1,2]. Peak incidence occurs in the late sixth and early seventh decades of life, and there is a slight male predominance. GISTs occur most frequently in the stomach (60%) and small intestine (25%), and to a lesser extent in the colon, rectum, appendix, and mesentery (rare). Metastatic sites for GIST include the liver and omentum (most common), lungs (less common), and regional lymph nodes and bone (rare)[3].

Histopathology

GISTs share similar morphologic and immunophenotypic features with the interstitial cells of Cajal (ICC), pacemaker cells in the gut wall that regulate peristalsis[4]. Like GISTs, ICCs have both smooth muscle and neural features and tend to express Kit and CD34[5]. In addition, Kit signaling is required for proper ICC development and differentiation[6,7], whereas constitutive Kit activation by gain-of-function mutation is associated with GIST pathogenesis[8]. Thus, GISTs are proposed to originate from ICCs or stem cells that differentiate toward ICCs[9].

In 1998, Sarlomo-Rikala et al.[9] noted that GISTs stained nearly universally positive for CD117 (Kit) as compared to other mesenchymal tumors such as leiomyoma, leiomyosarcoma, and schwannoma. It is now estimated that nearly 95% of GISTs stain positive for Kit[10]. Other known immunohistochemical markers for GISTs include CD34 (70%), smooth muscle actin (35%), S-100 (10%), and desmin (5%)[2]. Additional markers, like protein kinase C-θ[10,11] and DOG-1[12], are currently being evaluated for their usefulness in identifying GIST. Furthermore, high-throughput genetic analysis revealed that obscurin and C9orf65 (Prune 2) expression distinguished GISTs from leiomyosarcomas in 99% of cases[13]. Although the function of obscurin and Prune 2 are unknown in GISTs, this two-gene classifier may be a useful tool for differential diagnosis. Nevertheless, Kit presently remains the most sensitive immunohistochemical marker for GIST diagnosis[14].

Although the aforementioned antigens are useful to distinguish GISTs from other mesenchymal tumors, they should not be relied upon solely to identify GISTs; other factors, including tumor cell morphology and clinical findings, should be considered.

GISTs exhibit three major histological subtypes: spindle cell subtype (70%), epithelioid subtype (20%), and a mixed subtype (10%)[15]. Epithelioid variants are more often seen in the stomach and, in some studies, have been linked to the expression of Bcl-2[16] and
adverse outcomes. The Bcl-2 pathway is currently under investigation as a therapeutic target in GISTs.

Many factors have been evaluated in estimating the malignant potential of primary GISTs. The three most predictive factors appear to be the site of primary tumor, the tumor size (greatest diameter), and the number of mitoses per high-powered field. Despite these criteria, the true malignant or benign activity of primary GISTs is unpredictable, as even small (< 1 cm) tumors may recur 10 years or more after diagnosis.

Pathophysiology of Kit and Platelet-Derived Growth Factor Receptor-α (PDGFRα) in GISTs

Genetic mutations in specific exons of the Kit or PDGFRα genome lead to a gain-of-function of these tyrosine kinase receptors in GISTs. Constitutive activation of Kit or PDGFRα in the absence of ligand ultimately results in oncogenesis. Notably, mutations in Kit and PDGFRα are mutually exclusive, affecting Kit in 80% of GISTs and PDGFRα in 5% to 8% of GISTs. Additionally, 10% to 15% of GISTs have no detectable mutations in either Kit or PDGFRα. The underlying mechanism of pathogenesis in these “wild-type” GISTs is unknown, although there is evidence that insulin-like growth factor receptor (IGF-1R) is overexpressed in these tumors.

Kit

Kit, the stem cell factor receptor, is encoded by the 21-exon Kit gene at the white spotting (W) locus on human chromosome 4. As a type III receptor tyrosine kinase, Kit shares structural homology with platelet-derived growth factor receptor (PDGFR), the fms-related receptor FLT3, and the colony-stimulating factor receptor-1 (CSF1R). Type III receptors are characterized by five extracellular immunoglobulin-like domains, a transmembrane domain, a juxtamembrane domain, and an intracellular kinase domain bisected by a short kinase insert. Kit ligand, deemed steel factor or stem cell factor (SCF), is encoded by its gene at the steel locus on human chromosome 12. Normal Kit activation occurs when homodimeric SCF binding induces receptor homodimerization and autophosphorylation on tyrosine residues, which serve as docking sites for substrate SH2 domain-containing proteins, including phosphatidylinositol-3-kinase (PI3K), phospholipase Cγ (PLCγ), Src-family kinases, Janus kinase 2 (JAK2), as well as the adaptor proteins growth factor receptor bound protein-2 (Grb2), SH2 domain-containing phosphatase-1 and 2 (Shp1 and 2), and SH2-containing transforming protein C (Shc). Thus, upon activation, Kit stimulates a host of cellular processes including proliferation, differentiation, maturation, survival, chemotaxis, and adhesion (Figure 1) through diverse signaling pathways. SCF-induced Kit signaling is implicated in several physiological processes, including the development and differentiation of ICCs, hematopoietic stem cells, and mast cells. Furthermore, mutations at either the W or steel locus that abrogate Kit-SCF signaling lead to piebaldism in humans and white spotting, sterility, and anemia in mice, implicating Kit and SCF in melanogenesis.
gametogenesis, and hematopoiesis.

Mutations conferring ligand-independent constitutive Kit activation have been found in a majority of GISTs [21,44-46]. These mutations can be classified as either regulatory or enzymatic, based on their location. Regulatory mutations affect regions of the receptor that control kinase activation. In Kit, these regions include the juxtamembrane domain, which is purported to prevent kinase autoactivation in the absence of ligand binding [47], and the extracellular domain, which includes the SCF-binding site. Enzymatic mutations, on the other hand, occur in the receptor’s catalytic (kinase) domain [48,49]. Kit mutations are most frequently regulatory, commonly occurring in exon 11, which encodes the juxtamembrane domain [5,21,44-46]. Mutations in exon 11 vary in type but occur most frequently between codons 550 and 580 [44,50-52]. Other gain-of-function mutations have been observed in exon 9 [21,44-46,52], which encodes the extracellular domain, as well as exons 13 [44,52,53] and 17 [44,54], which encode the intracellular kinase domain.

Several in vitro and in vivo studies demonstrate the significance of mutated Kit in GIST development. Stable transfection of juxtamembrane or kinase mutant Kit cDNA was sufficient to transform Ba/F3 murine cells and induce tumor formation when the stable transfectants were implanted in nude mice. Mutant Kit oncoproteins also showed constitutive phosphorylation and kinase activity [5,55]. More recently, studies using a knock-in approach to mimic clinically observed Kit mutations demonstrate that expression of the mutant receptor results in ICC hyperplasia and GIST formation in mice [56,57]. Furthermore, families with heritable germline Kit mutations in exons 8, 11, 13, or 17 frequently developed ICC hyperplasia and multiple GISTs [53,54,48]. These studies corroborate the link between the ICC and GIST and suggest that Kit mutation plays a significant and early role in GIST pathogenesis.

Platelet-derived growth factor receptor-α (PDGFRα)

A smaller subset of GISTs express wild-type Kit but constitutively active PDGFRα [47]. PDGFRα belongs to the diverse PDGF family of receptors (PDGFRα and β) and ligands (PDGF-A, B, C, and D). PDGFRα, which is encoded by a gene that maps to the patch locus on human chromosome 4, is a type III receptor tyrosine kinase, exhibiting topological features similar to Kit [27,28]. Normal activation is achieved by binding of homo- or heterodimeric platelet-derived growth factors (PDGF-AA, PDGF-BB, PDGF-AB, or PDGF-CC), resulting in receptor dimerization and autophosphorylation on tyrosine residues [29,30], which establishes docking sites for substrate proteins including PI3K [30], PLCγ [30], Src-family kinases [31], and the adaptor protein Crk [32]. PDGFRα signaling is implicated in numerous developmental processes, including oligodendrogenesis, lung alveogenesis, spermatogenesis, intestinal villi and hair follicle morphogenesis, somite patterning, palate formation, and embryonic development [33].

Mutations resulting in constitutive, ligand-independent PDGFRα activation have been observed in GISTs, though to a lesser extent than mutations affecting Kit. PDGFRα mutations are most commonly enzymatic, frequently occurring in exon 18, which encodes a portion of the kinase domain. Activating mutations have also been observed in exons 12 and 14, which encode the juxtamembrane domain and a portion of the kinase domain, respectively [17-19]. As with mutant Kit, mutant PDGFRα was constitutively phosphorylated in vitro in the absence of ligand [17,18]. Furthermore, stable transfection of juxtamembrane or kinase mutant PDGFRα cDNA was sufficient to transform Ba/F3 murine cells [18]. In addition, families with germline PDGFRα mutations in exons 12 or 18 were predisposed to developing multiple GISTs [54-56]. Thus, PDGFRα mutation, like Kit mutation, is considered a significant and early event in GIST development.

Oncogenic Kit and PDGFRα signaling in GISTs

Kit and PDGFRα oncoproteins activate signaling pathways, resulting in GIST cell proliferation and survival. In addition to ligand-independent constitutive Kit phosphorylation, GISTs harboring Kit mutations show activation of Kit downstream signaling pathways, including the PI3K/Akt, MAPK (Raf/Mek/Erk), and signal transducer and activator of transcription (STAT) pathways [10,77]. Of these downstream signaling targets, MAPK phosphorylation is Kit-dependent, whereas phosphorylation of PI3K, STAT1, and STAT3 is partially Kit-independent. Interestingly, Zhu et al. [78] observed PDGFRα phosphorylation in GIST samples with Kit mutations and further demonstrated that Kit oncoproteins can directly bind and phosphorylate PDGFRα and β, suggesting that PDGFR activation is a potential mechanism of oncogenic Kit signaling. Although Kit signaling has been studied more extensively in GISTs, several laboratories have shown that Kit and PDGFRα oncoproteins activate the same downstream signaling pathways [17,19].

Despite exhibiting activation of common signaling pathways, GISTs display significant heterogeneity in the strength of activation of downstream targets. One possible explanation is that GISTs expressing mutant Kit or PDGFRα exhibit unique cell signaling patterns. Indeed, Kang et al. [79] showed that Kit-mutant GISTs and PDGFRα-mutant GISTs displayed differential phosphorylation of STAT3, Akt, and Erk. Furthermore, Duensing et al. [79] showed that oncoproteins encoded by Kit with exon 11 mutations had increased Akt phosphorylation relative to exon 9 mutants, suggesting
that the site of mutation can also affect pathway activation. This differential signaling suggests that both the identity and genotype of the oncogenic kinase control GIST pathology and may explain, in part, the biological heterogeneity of GISTs. Nevertheless, mechanisms other than kinase genotype likely contribute to signaling pathway activation, as Duensing et al. further demonstrated that tumors with identical exon 9 mutations exhibited differential MAPK and STAT phosphorylation.

In summary, constitutive activation of Kit or PDGFRα drive pathogenesis in most cases of GIST. Thus, in the setting of tumor dependence on these kinases, use of small-molecule targeted agents against ATP-dependent oncogenes is compelling and has become quite successful.

Therapy of Metastatic or Unresectable GISTs

Prior to the discovery of the significance of Kit and PDGFRα in GISTs, surgery was the only viable treatment option. Chemotherapy is largely ineffective with poor response rates, and radiation therapy is often impractical because of the extent and location of the disease. Thus, the development of imatinib to block the activity of these receptors has changed the treatment and outlook of this malignancy.

Primary systemic therapy: imatinib mesylate

From the initiation of its compassionate use in a 50-year-old patient with metastatic GIST in March 2000 to its position as the standard of care in patients with metastatic or unresectable GISTs, imatinib has altered the course of this disease. Indeed, GIST patients treated with imatinib now experience prolonged disease-free and overall survival. A typical advanced GIST is shown in Figure 2. This patient had a large GIST occupying most of the left hemi-abdomen. After treatment with imatinib, the patient had marked response to therapy as demonstrated by hypoattenuation and shrinkage of the tumor.

The standard dose of imatinib was established by van Oosterom et al. in a European Organization for Research and Treatment of Cancer (EORTC) trial, which included 36 patients with GISTs. These patients were randomized to a dose of 400 mg per day, 300 mg twice per day, 400 mg twice per day, or 500 mg per day. Toxicity and efficacy were monitored and the findings showed that the best tolerated dose was 400 mg per day. The adverse events were manageable and most commonly included edema, nausea, diarrhea, malaise, and fatigue. Rare adverse events, which included myelosuppression, hemorrhage, and elevated transaminases, required interruption or discontinuation in treatment. Several phase II and III clinical trials have been designed to assess the efficacy of imatinib in the metastatic setting. Based on the data from these studies, the observed response to imatinib ranged from 48% to 71% of patients and disease stabilization ranged from 70% to 85% of patients, whereas the median progression-free survival (PFS) ranged from 20 to 24 months.

Two large international studies randomized patients with metastatic GISTs to standard dose (400 mg per day) or high dose imatinib (800 mg per day). In study S0033 conducted by the North American Sarcoma Intergroup, which consists of the US cooperative oncology groups (Southwest Oncology Group, Cancer and Leukemia Group B, and the Eastern Cooperative Group) and the National Cancer Institute of Canada Sarcoma Group, 746 patients were randomized to receive the 400 mg daily dose but were allowed to cross over to the 800 mg daily dose if they experienced disease progression. Median overall survival (OS) approached 5 years in both arms with all patients

Figure 2. Computed topography (CT) scan showing the result of imatinib treatment of advanced GIST. A, the large GIST arising from the stomach wall has ulcerated area and contains air and oral contrast. B, the GIST arising from the small bowel (yellow arrow) is large and heterogeneous with central necrosis (pink arrow). C, after imatinib therapy, the viable portion of the tumor (yellow arrow) markedly decreased in size, whereas the necrotic portion of the tumor increased to compose the majority of the mass (pink arrow).
surviving a median of 57 months\textsuperscript{[81]}. Although the $P$ value was greater than 0.05, there was a superior PFS rate for patients with metastatic GISTs treated at an initial dose of 800 mg per day. The 2-year estimated PFS rates were 50% for the 400 mg arm and 53% for the 800 mg arm. The 2-year estimated survival rates were equivalent between the two arms (78% for the 400 mg arm and 73% for the 800 mg arm). Interestingly, of the 106 patients who crossed over to the higher dose after having progression of disease on the 400 mg daily dose, 3% had partial response and 29% had stable disease, indicating that patients benefit from dose escalation at the time of progression. The EORTC Soft Tissue and Bone Sarcoma Group, Italian Sarcoma Group, and Australasian Gastro-Intestinal Trials Group conducted a similarly designed phase III trial of imatinib mesylate in 952 patients with unresectable or metastatic GISTs. Patients were randomized to receive imatinib mesylate at a dose of either 400 mg daily or 800 mg daily. The objective response rates were 50% and 54% for the 400 mg and 800 mg arms, respectively. The 2-year estimated OS rates were 69% for patients treated at an initial daily dose of 400 mg and 74% for those started at 800 mg daily. PFS rates were significantly higher for patients allocated to 800 mg daily of imatinib than for those who received the lower dose (52% vs. 44%, $P = 0.026$). It is possible that different results in the two studies are due to the greater number of patients enrolled in the EORTC study, thus allowing more power to detect statistical differences. Interestingly, those patients with Kit exon 9 mutation were found to benefit from the 800 mg dose of imatinib\textsuperscript{[86]}. The combined observations of superior PFS with high dose imatinib and benefit from dose escalation at the time of progression suggest that there is a dose-response relationship for imatinib in GISTs. Determining which patients will benefit from higher doses of imatinib is important in view of the greater toxicity at higher doses.

### Imatinib-resistant GISTs

Resistance to imatinib appears to occur as the result of acquired mutations which develop during the course of therapy. In patients with imatinib-naïve GISTs, most mutations occur in the juxtamembrane (exon 11) or extracellular domain (exon 9) of Kit. In patients with acquired resistance, mutations are predominantly located in the intracellular kinase domain of Kit. Six rapidly progressive imatinib-resistant implants from 5 patients were found to encode an identical novel Kit missense mutation, 1982T to C, which resulted in Val654Ala in the Kit tyrosine kinase domain. This novel mutation was not present in pre-imatinib or post-imatinib residual quiescent GISTs and strongly correlated with clinical imatinib resistance. Allele-specific sequencing data showed that this new mutation occurred in the allele that harbored the original activating mutation of Kit\textsuperscript{[87]}. The end result of acquired mutations is primarily thought to be the formation of a stable activated form of the Kit homodimer due to mutations in exon 17 or, less commonly, a change in the 3-D conformation of the homodimer preventing imatinib binding and activity due to a mutation in exon 14\textsuperscript{[88]}.

In patients for which no secondary mutations in Kit or PDGFR$\alpha$ are found, other events, such as mutations in other tyrosine kinase genes or activation of survival pathways, may play a role in resistance\textsuperscript{[89]}.

### Systemic therapy of imatinib-resistant metastatic GIST

Widespread progression of disease generally requires systemic therapy. The initial approach should be to maximize the dose of imatinib to 800 mg daily. As discussed previously, patients who undergo dose increase to 800 mg daily from 400 mg daily were found to experience a 3% partial response rate and a 29% stable disease rate\textsuperscript{[81]}. After progression on the maximum tolerated dose of imatinib, patients should be evaluated for a clinical trial or may be treated with a recently FDA-approved tyrosine kinase inhibitor named sunitinib. Sunitinib (SU11248) potentially possesses both anti-angiogenic and anti-oncogenic properties since it inhibits the vascular endothelial growth factor receptor and the Kit receptor, respectively. Sunitinib was investigated in 97 patients with imatinib-resistant GISTs. All patients received a daily dose of 50 mg of the drug and 22 patients obtained either partial response or stable disease after a year\textsuperscript{[89]}. In a phase III study on metastatic, imatinib-resistant GISTS, sunitinib was found to have a 7% partial response rate and a 58% stable disease rate after imatinib discontinuation. This phase III study randomized patients to receive either sunitinib or placebo. Thus, the benefit of sunitinib over continued imatinib remains unknown\textsuperscript{[89]}.

### Imatinib combined with surgery for primary GISTs

#### Neo-adjuvant imatinib

Although its use in patients with metastatic or unresectable GISTs is compelling, imatinib use in patients with resectable primary GISTs is investigational. Neo-adjuvant imatinib allows assessment of imatinib-sensitivity and an opportunity to avoid a potentially morbid surgical procedure in patients with aggressive, imatinib-resistant GISTs. Additionally, preoperative administration of imatinib allows reliable administration of therapy prior to the difficulty a patient may have with oral intake postoperatively. Moreover, the pharmacokinetics of imatinib in patients with dumping syndrome or who have had portions of their stomach and small intestine removed is not known. Other possible
benefits of preoperative imatinib include decreases in tumor rupture and hemorrhage during the surgical procedure. The largest retrospective study published to date, performed at M. D. Anderson Cancer Center (MDACC), evaluated 126 patients with pathologically confirmed and unresectable GISTs.[94] All patients received neo-adjuvant imatinib and 17 patients subsequently underwent surgical resection of their GISTs. These patients received imatinib for a median of 10 months and response to the drug was assessed preoperatively by CT imaging. Prior to surgery, the radiographic overall response was 76% (1 complete response, 12 partial response). Two patients were found to have no viable tumor cells at the time of surgical resection. This study demonstrated that preoperative imatinib may be useful in a subset of patients with initially surgically unresectable GISTs. Moreover, patients with partial response to imatinib may experience complete histopathologic response. However, no long-term follow-up data has yet been accrued to determine if there is a survival benefit in patients who underwent surgical consolidation.

**Adjuvant imatinib** Imatinib therapy may be potentially beneficial in eliminating micrometastatic disease after surgical resection. Experience in the administration of adjuvant imatinib is limited and published data is scarce (Table 1). The American College of Surgical Oncology Group (ACOSOG) multicenter phase III study Z9001, conducted by DeMatteo et al.[95], randomized 713 patients with Kit-positive, primary, localized GISTs larger than 3 cm to receive imatinib (400 mg daily) or placebo for 1 year following complete resection. With a primary endpoint of recurrence-free survival (RFS), and median follow-up of 19.7 months, recurrence or death occurred in 8% and 20% of patients in the imatinib and placebo groups, respectively. RFS at 1 year was significantly improved by imatinib (98%, 95% CI = 96%–100%), compared with placebo (83%, 95% CI = 78%–88%), translating to a hazard ratio (HR) of 0.35 (95% CI = 0.22–0.53) (P < 0.0001). Although the study was not designed to assess subgroup differences, RFS benefit was the greatest in patients with GISTs larger than 10 cm (HR = 0.29, 95% CI = 0.16–0.55, P < 0.0001), compared with 3 to 6 cm (HR = 0.23, 95% CI = 0.07–0.79, P = 0.011), or 6 to 10 cm tumors (HR = 0.5, 95% CI = 0.25–0.98, P = 0.041). Differences in OS between imatinib and placebo groups were not observed (HR = 0.66, 95% CI = 0.22–2.03, P = 0.47), although this may be explained by the short median follow-up, and the study design which allowed patients progressing on placebo to cross-over to imatinib treatment at unblinding or recurrence. Importantly, preliminary data from Z9001 surpassed the interim analysis efficacy boundary, leading to early trial closure and FDA approval of imatinib for adjuvant therapy. Interestingly, the FDA did not stipulate a dose or duration for adjuvant imatinib but left that decision to the physician.

The prospective phase II study ID03-0023 by McAuliffe et al.[96] examined the safety and efficacy of adjuvant imatinib (600 mg) for 2 years in 19 patients with GISTs who underwent surgical resection, preceded by brief neoadjuvant (3, 5, or 7 days) imatinib. With a high-risk cohort (mean tumor size of 9.5 cm, 30% with small bowel tumors, 30% with recurrence or metastasis), and median follow-up of 32 months, the 1- and 2-year disease-free survival (DFS) rates were 94% and 87%, respectively, translating to a median DFS of 46 months, a significant improvement compared with historical controls.

Two additional prospective, randomized phase III studies of adjuvant imatinib have completed accrual and are undergoing analysis. With primary endpoint of PFS, the Scandinavian Sarcoma Group (SSG) study SSGXVIII is evaluating the optimal duration of adjuvant imatinib, comparing 12 versus 36 months in patients at high risk of recurrence. The primary endpoint is OS in the European Organization for Research and Treatment of Cancer (EORTC) study 62024, which examines 24 months of adjuvant imatinib versus observation in high-risk patients.

**Combined neo-adjuvant and adjuvant imatinib** The combined use of neoadjuvant and adjuvant imatinib and its role in the therapy of GISTs is appealing and is under evaluation in two clinical trials. Studies currently in progress at MDACC[97] and the Radiation Therapy and Oncology Group (RTOG)[98] treat patients with preoperative imatinib, surgical resection, and postoperative imatinib for 2 years (Table 1). These trials provide innovative approaches with important biologic correlates that may provide insight into the mechanism of action of imatinib in GISTs. In MDACC ID03-0023, patients with resectable GISTs undergo preoperative imatinib for 3, 5, or 7 days, surgical resection, and subsequent adjuvant imatinib mesylate for 2 years. To understand the early molecular and pathologic changes in GISTs treated with imatinib mesylate with respect to PET response, patients undergo baseline studies including a tumor biopsy followed by therapy with imatinib mesylate and surgical resection. PET is a useful imaging modality since response of GIST patients to imatinib may be observed as early as 24 h after the first dose (Figure 3). This allows correlation of early response with genomic changes, Kit signaling, tumor vascularity, and apoptosis before and after imatinib therapy. RTOG S0132 has a similar design, though patients are treated to maximum
### Table 1. Preoperative and postoperative trials of imatinib in gastrointestinal stromal tumors (GISTs)

| Trial characteristics | Endpoints | Adjuvant/neoadjuvant therapy | Patient / GIST characteristics | Results |
|-----------------------|-----------|-------------------------------|--------------------------------|---------|
| ACOSOG-Z9001          | RFS       | Adjuvant imatinib 400 mg daily, or placebo, for 1 year | 713 patients KIT<sup>+</sup> primary GIST > 3 cm imatinib (n = 359) or placebo (n = 354) | 1-year RFS Imatinib: 98% Placebo: 83% |
| RFS                   |           |                               | OS, RFS                        |         |
| ACOSOG-Z9000          | OS, RFS   | Adjuvant imatinib 400 mg daily for 1 year | 107 patients, KIT<sup>+</sup> primary, localized GIST high risk of recurrence median tumor size of 13 cm (3–42) 42% small intestine 50% stomach | 1-year OS: 99% 2-year OS: 97% 3-year OS: 97% RFS 1-year RFS: 94% 2-year RFS: 73% 3-year RFS: 61% |
| AMC-ONCGI-0501        | RFS       | Adjuvant imatinib 400 mg daily until progression, toxicity, or 2 years | 47 patients KIT<sup>+</sup> primary, localized GIST High risk of recurrence Median tumor size of 7.5 cm Median mitotic index of 13/50 HPF | 1-year RFS: 98% 2-year RFS: 93% |
| CSTI571BK/R08         |           |                               |                               |         |
| MDACC ID03-0023       | DFS       | Neoadjuvant imatinib 600 mg daily for 3, 5, or 7 days | 19 patients resectable or partially resectable GIST mean tumor size of 9.5 cm 30% small intestine 30% with recurrence or metastasis | 1-year DFS: 94% 2-year DFS: 87% |
| DFS                   |           | Adjuvant imatinib 600 mg daily for 2 years |                               |         |
| RTDG S0132/ ACRIN 6665 | PFS, OS, ORR | Neoadjuvant imatinib 600 mg daily for 8–12 weeks | 52 patients KIT<sup>+</sup>-GIST 30 patients with primary GIST (Group A) 22 with operable metastatic GIST (Group B) | 2-year PFS Group A: 83% Group B: 77% |
|                       |           | Adjuvant imatinib 600 mg daily for 2 years | 2-year OS Group A: 93% Group B: 91% Response rate Group A (7% partial, 83% stable, 10% unknown response) Group B (4.5% partial, 91% stable, 4.5% progression) |         |

RFS, recurrence-free survival; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; ORR, objective response rate.

### Figure 3. Positron emission tomography (PET) scan shows early response of a GIST to imatinib treatment. A, the patient was found to have an FDG-avid GIST on PET imaging before imatinib therapy. B, after 24 h of imatinib therapy, the patient underwent complete metabolic response.
Surgical therapy of metastatic disease

GISTs frequently metastasize to both the liver and peritoneum. The most sensitive means of detecting metastatic disease is CT imaging, which frequently underestimates the extent of peritoneal disease. Although patients with metastatic disease are not generally considered for surgical resection, there are special circumstances in which these patients should be evaluated to determine the estimated risks and benefits of local therapy for metastatic disease. The patient described in Figure 4 depicts an individual with liver metastases who experienced initial response and then limited progression after 27 months of therapy[95].

The role of surgical intervention in metastatic disease is limited to solitary metastatic lesions. In a study performed by DeMatteo et al.[96] where 60 patients with metastatic GIST underwent surgery of these isolated metastases, the median survival was only 20 months and was not influenced by tumor-free margins. These statistics reflect metastectomy in the preimatinib era and may change with the institution of imatinib therapy and the conversion of unresectable metastatic or locally advanced disease to resectable disease.

Hepatic artery chemoembolization of metastatic disease

With the emergence of imatinib and its efficacy on metastatic disease, the role of hepatic artery embolization has decreased. Hepatic artery embolization should be considered in either patients who are refractory to treatment with imatinib or patients with liver lesions not amenable to surgical intervention. Optimal candidates for such intervention include patients without portal vein thrombosis, ascites, or hyperbilirubinemia.

Hepatic artery embolization capitalizes on several characteristics of tumor pathophysiology. First, tumors are angiogenic entities that require an ample blood supply to survive and grow. Gastrointestinal stromal tumors are known to be highly vascular tumors. Embolizing the segment of the hepatic artery supplying the tumor causes ischemia and leads to cell death. Second, using a medium such as poppy seed oil or polyvinyl alcohol sponge particles to introduce chemotherapeutic agents can increase the intratumoral concentration of these agents while minimizing systemic exposure and toxicity. In the setting of intratumoral ischemia, much of the resistance to systemic chemotherapy is thought to be overcome[97].

Patients who underwent hepatic artery embolization had a median survival ranging from 18 to 20 months and a mean duration of response of 10 months[98]. The risks associated with this procedure include post-embolization syndrome (fever, abdominal pain, nausea, and ileus), sepsis, hepatic necrosis, abscess, cholecystitis, pancreatitis, or death. In summary, hepatic artery embolization offers moderate benefit to patients with end-stage GISTs.

Radiofrequency ablation of metastatic disease

Radiofrequency ablation (RFA) is another surgical alternative in patients with unresectable hepatic metastases. This technique has been successful in treating hepatic metastases from other solid malignancies, including, most notably, colorectal cancer.

Figure 4. GIST progression during imatinib therapy. A, the patient has multiple, bilobar hepatic metastases that appear cystic due to imatinib therapy. B, while on imatinib therapy, the liver lesion drastically increased in size (green arrow), whereas the remaining liver lesions are controlled by continuation of imatinib therapy. C, the GIST patient has a large, necrotic hepatic metastasis except for one peripheral radiodense nodule (pink arrow). D, after increasing the patient’s imatinib dose to 800 mg, the enhancing nodule continues to increase in size with no measurable decrease in radiodensity (green arrow).
RFA uses hyperthermia administered via a catheter to cause local tissue destruction and cell death. The procedure may be performed percutaneously, laparoscopically, or via laparotomy. The percutaneous approach is the preferred approach in patients with easily accessible peripheral hepatic metastases. Laparoscopy affords the surgeon a better perspective on the size of the lesion and the location near any major blood vessel to better direct the catheter. It also provides information on metastatic disease within the peritoneal cavity which may preclude intervention. An open surgical approach is taken in patients with large lesions (> 5 cm), adhesions from prior surgery, or lesions abutting major blood vessels\[99\]. The benefit of RFA in GISTs has not been specifically studied, but several large studies have evaluated the efficacy of this technique in an array of metastatic lesions. One study conducted by Curley et al.\[100\] at MDACC evaluated 123 patients that underwent radiofrequency ablation. Seventy-five of these patients had hepatic lesions secondary to metastases from a variety of tumors. At a median follow-up of 15 months, the local recurrence rate was 1.8% , and metastatic disease developed in 27.6% of patients. Other studies have noted that the risk of local tumor recurrence occurs in larger lesions (> 4 cm) and that local recurrence occurs at the edge of previously treated lesions\[99\]. Complications from this procedure include fever, hepatitis, and hepatic abscess. While the experience of treating unresectable GISTs is predominantly limited to major academic centers and few cases, the procedure appears to offer disease control with minimal morbidity.

**Conclusions**

The understanding of the molecular pathogenesis and the therapeutic interventions for GISTs has changed dramatically over the past decade. GIST has evolved from a poorly understood, under-diagnosed, and treatment refractory tumor to a well understood, accurately-diagnosed, and treatment responsive tumor. Discovery of the role of Kit and PDGFRα in GIST pathogenesis and the ability of imatinib to target the oncogenic activity of these kinases has resulted in improved survival and quality of life of patients with metastatic or unresectable GISTs. Imatinib has shown its greatest effects in the metastatic setting, but it may also prove to be beneficial in patients with locally unresectable disease. Optimal candidates to undergo neoadjuvant or adjuvant therapy are still being defined. The development of alternative tyrosine kinase inhibitors and other drugs may benefit patients who have imatinib-refractory disease or who may benefit from combination therapies to improve response rates. The flurry of clinical advances in GISTs makes the outlook for these patients very bright now and in the future.

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