Optimizing Imatinib Mesylate Treatment in Gastrointestinal Stromal Tumors

Yixing Jiang, Lee Ming, Alberto J. Montero, Eric Kimchi, Mehrdad Nikfarjam, Kevin F. Staveley-O’Carroll

ABSTRACT

Improvements in the understanding of molecular oncogenesis and mechanisms of drug resistance have presented new opportunities for the treatment of gastrointestinal stromal tumors (GIST). In particular, the discovery of c-kit genomic mutations in GIST and the development of targeted therapy with imatinib mesylate and sunitinib have heralded a new era in the treatment of this disease. Due to its high activity in GIST, imatinib has become the standard of care in treating both advanced disease and localized disease with high-risk features. On the other hand, these developments have provided new challenges in optimizing the use of our drug armamentarium in conjunction with surgery. This review focuses on the molecular oncogenesis of GIST and provides a summary of recent approaches in the management of this disease.

Gastrointestinal stromal tumors (GIST) are relatively rare malignancies of the GI tract. In the past, traditional chemotherapy and radiotherapy had little effect on the natural history of this disease. Significant advances in diagnosis and treatment resulted once it was recognized that the expression and mutation of a cell-surface receptor tyrosine kinase, c-KIT, is the primary oncogenic force driving the development of GIST.1 The availability of imatinib mesylate, a tyrosine kinase inhibitor of c-KIT, platelet-derived growth factor receptor alpha (PDGFR-α), and breakpoint cluster region/Abelson (BCR-ABL), has dramatically changed management of GIST. Studies have shown that over 80% of patients with metastatic GIST treated with imatinib derive clinical benefit.3–7 The development of imatinib resistance, however, has emerged as a major problem.

Sunitinib, an inhibitor of multiple tyrosine kinase receptors, including c-KIT and PDGFR-α, was developed to overcome imatinib resistance in tumors. Although both imatinib and sunitinib have altered traditional management strategies for GIST, the cure rate for patients with advanced GIST remains low. This article reviews the epidemiology, molecular oncogenesis, mechanisms of drug resistance, and multidisciplinary management of GIST.

EPIDEMIOLOGY OF GIST

GIST encompasses the most common nonepithelial malignancies of the GI tract and represents a subset of soft tissue sarcomas classified only relatively recently. The incidence of GIST was previously considered to be very low. Data from the Surveillance Epidemiology and End Results survey in the 1990s indicated an estimated 500 to 600 new cases of GIST annually in the United States.8 Experience gained from clinical trials over the past several years, however, indicates that the incidence of GIST is much higher, with estimates of at least 4,000 to 6,000 new cases annually.9–10 The discrepancy in estimates is largely attributable to the lack of rigorous diagnostic criteria. In 1998, Hirotta et al showed that 94% of GIST express c-KIT (CD117) detectable by immunohistochemistry,1 and this diagnostic methodology was subsequently confirmed in other studies.11–14 The use of immunohistochemical staining has significantly improved the ability to diagnose GIST correctly. In 2005, Nilsson et al reported an estimated yearly incidence of 14.6 cases per million in a population-based Sweden pathology study.15 Similarly, Goettsc et al reported an incidence of 12.7 per million in the Netherlands in 2003.16 Both studies also indicated that the incidence of GIST has been stable since 2000.

The peak incidence of GIST occurs in the late sixth and early seventh decade of life, with a slight predominance among men.17 GIST can occur anywhere in the GI tract, including the gall bladder and mesentery. However, about 60% of GIST originates in the stomach, 25% in the small intestine, and 10% in the large bowel.18,19 Gastric GIST is associated with a better prognosis than extragastric GIST.19

Although some cases of hereditary GIST have been described, the majority of cases are sporadic. Familial GIST syndrome represents a very small subset of GIST, with few cases reported worldwide. Familial GIST has a number of clinical features that are distinct from sporadic GIST; eg, it usually presents at a similar age and typically consists of multiple synchronous tumors, which frequently occur in the small bowel. Mutations in the c-kit gene are relatively rare malignancies of the GI tract. In the past, traditional chemotherapy and radiotherapy had little effect on the natural history of this disease. Significant advances in diagnosis and treatment resulted once it was recognized that the expression and mutation of a cell-surface receptor tyrosine kinase, c-KIT, is the primary oncogenic force driving the development of GIST.1 The availability of imatinib mesylate, a tyrosine kinase inhibitor of c-KIT, platelet-derived growth factor receptor alpha (PDGFR-α), and breakpoint cluster region/Abelson (BCR-ABL), has dramatically changed management of GIST. Studies have shown that over 80% of patients with metastatic GIST treated with imatinib derive clinical benefit.3–7 The development of imatinib resistance, however, has emerged as a major problem.

Sunitinib, an inhibitor of multiple tyrosine kinase receptors, including c-KIT and PDGFR-α, was developed to overcome imatinib resistance in tumors. Although both imatinib and sunitinib have altered traditional management strategies for GIST, the cure rate for patients with advanced GIST remains low. This article reviews the epidemiology, molecular oncogenesis, mechanisms of drug resistance, and multidisciplinary management of GIST.

EPIDEMIOLOGY OF GIST

GIST encompasses the most common nonepithelial malignancies of the GI tract and represents a subset of soft tissue sarcomas classified only relatively recently. The incidence of GIST was previously considered to be very low. Data from the Surveillance Epidemiology and End Results survey in the 1990s indicated an estimated 500 to 600 new cases of GIST annually in the United States.8 Experience gained from clinical trials over the past several years, however, indicates that the incidence of GIST is much higher, with estimates of at least 4,000 to 6,000 new cases annually.9–10 The discrepancy in estimates is largely attributable to the lack of rigorous diagnostic criteria. In 1998, Hirotta et al showed that 94% of GIST express c-KIT (CD117) detectable by immunohistochemistry,1 and this diagnostic methodology was subsequently confirmed in other studies.11–14 The use of immunohistochemical staining has significantly improved the ability to diagnose GIST correctly. In 2005, Nilsson et al reported an estimated yearly incidence of 14.6 cases per million in a population-based Sweden pathology study.15 Similarly, Goettsc et al reported an incidence of 12.7 per million in the Netherlands in 2003.16 Both studies also indicated that the incidence of GIST has been stable since 2000.

The peak incidence of GIST occurs in the late sixth and early seventh decade of life, with a slight predominance among men.17 GIST can occur anywhere in the GI tract, including the gall bladder and mesentery. However, about 60% of GIST originates in the stomach, 25% in the small intestine, and 10% in the large bowel.18,19 Gastric GIST is associated with a better prognosis than extragastric GIST.19

Although some cases of hereditary GIST have been described, the majority of cases are sporadic. Familial GIST syndrome represents a very small subset of GIST, with few cases reported worldwide. Familial GIST has a number of clinical features that are distinct from sporadic GIST; eg, it usually presents at a similar age and typically consists of multiple synchronous tumors, which frequently occur in the small bowel. Mutations in the c-kit gene

Address correspondence to: Yixing Jiang, MD, PhD, Penn State Hershey Medical Center, 500 University Drive, H046, Hershey, PA 17036. Phone: 717-531-7568; Fax: 717-531-0647; E-mail: yjiang@hmc.psu.edu

September/October 2008

www.myGCRonline.org
appear to have an autosomal dominant inheritance pattern. Clinical presentations can also vary depending on the locus of the mutation on c-kit. Germline mutations in the juxtamembrane domain of c-kit have been reported to be associated with a syndrome of mastocytosis, hyperpigmentation, and GIST.21-25 Germline mutations occur more frequently in c-kit, but are also seen in PDGFR-α.26 Two hereditary syndromes associated with GIST are type I neurofibromatosis (Von Recklinghausen’s disease) and the Carney’s triad, which consists of pulmonary chondromas, paragangliomas, and GIST.27 However, Carney’s triad lacks c-kit or PDGFR-α mutations and, thus, may represent a different disease mechanism.23

Molecular Oncogenesis

A breakthrough in identifying the molecular oncogenic basis of GIST came in 1998, when Hirota and colleagues described the expression of and mutations in c-kit in the disease. Using immunohistochemical staining, these investigators found that the c-kit protein is expressed in 94% of GIST samples.2 A subsequent study suggested that more than 95% of GIST samples are positive for c-kit.28 In the past decade, c-kit positivity has become a key diagnostic feature in differentiating GIST from other mesenchymal tumors of the GI tract. Further analysis of c-kit DNA by Hirota et al showed that gain-of-function mutations occurred in the cytoplasmic domain. Subsequent research established several additional mutations in the extracellular, juxtamembrane, and kinase domains. The mutations are mainly localized in exons 9, 11, 13, and 17. Approximately 80% of GIST samples contain active mutations in c-kit.23 Exon 11 (juxtamembrane domain) is the most frequent mutation, accounting for somewhere in the order of 66% to 70% of all mutations.29-35 Approximately 15% to 18% of GIST samples harbor mutations in exon 9, which is located in the extracellular domain; exon 13 and 17 mutations are uncommon, accounting for less than 5% of all mutations.36-41 Interestingly, exon 9 mutations are usually 2-codon 502-503 duplications, and occur predominantly in small intestinal GIST.22,37 The location of the c-kit mutation is clinically relevant, because studies have shown that mutational status largely determines the clinical response to imatinib.51-43

The highest overall response rates to imatinib (approximately 85%) have been reported in patients with GIST harboring c-kit exon 11 mutations. The clinical response rate decreases to 45% in patients with c-kit exon 9 mutations. Both progression-free survival (PFS) and overall survival are longer in patients with exon 11 mutations than in those with exon 9 mutations. However, patients with exon 9 mutations treated with imatinib 800 mg had PFS similar to those with exon 11 mutations treated with imatinib 400 mg.44

The oncogenic characteristics of gain-of-function mutations of c-kit have been well described in the literature. Several groups have demonstrated that transgenic mice expressing gain-of-function mutations of c-kit developed GIST.45,46 In agreement with this observation, the presence of germline mutations of c-kit in the familial GIST syndrome suggests that activation of c-kit probably is an early step in the development of GIST. Hence, it is thought that most cases of GIST are dependent on constitutive c-kit activation.47-49 However, c-kit mutations have also been found in some GIST patients with relatively benign clinical courses.22,43,50

A small proportion of GIST patients (5%) have c-kit-negative tumors; these usually have PDGFR-α mutations and are almost exclusively gastric in origin, with a small number of cases arising in the omentum and mesentery. These tumors usually exhibit an epitheloid or mixed histology.48,51-55 The most frequent mutations in these cases occur at exon 18 in PDGFR-α, accounting for about 4% of all GIST cases.50

Similar to c-kit mutations, the position of the mutation within exon 18 determines sensitivity to imatinib. Corless and colleagues demonstrated that exon 18 point mutations involving amino acids 841-843 (D842V, R842K, D842V-843IM) are clinically resistant to imatinib.56 However, the single exon 18 mutation D842Y is associated with sensitivity to imatinib, as are other exon 18 mutations, including D846Y, N848K, Y849K, and HDSN845-848P. Less common mutation sites include exons 12 and 14, with these mutations being associated with some sensitivity to imatinib.57-61

Finally, it has been noted that a subset of c-kit-positive GIST contains no mutations in c-kit or PDGFR-α (“wild-type” GIST).56,57 Immunohistochemical analysis of the wild-type GIST usually demonstrates positive staining for c-kit and phosphorylated c-kit, supporting the hypothesis that activation of the c-kit signaling pathway is essential in GIST.58 Clinical response to imatinib can be achieved in these tumors, as well.

Although tumors with wild-type c-kit respond to imatinib, the efficacy of imatinib is largely dependent on the presence of c-kit mutations and not the level of expression of c-kit. For example, in a retrospective study, Chirieac and colleagues from M. D. Anderson Cancer Center found that the expression level of c-kit determined by immunohistochemical staining did not predict tumor response or PFS.58

It has been shown that c-kit is expressed in both GIST and hematopoietic cells, and the signaling cascade resulting from c-kit activation is cell type dependent. For instance, in T lymphocytes, c-kit interacts with the IL-7 receptor, ultimately activating the JAK/STATs pathway, resulting in progenitor cell proliferation and differentiation. In GIST, constitutive c-kit expression leads to activation of three major pathways—RAS/ MAP kinase, AKT, and PI3 kinase.54,53,50 Among these, the AKT and PI3 kinase pathways are thought to be essential in maintaining the c-kit-mediated oncogenic phenotype. It has been elucidated that the antitumor effect of imatinib is largely mediated by the PI3 kinase pathway, whereas the AKT pathway is more important for glucose transport in GIST.42,63

Tarn et al demonstrated that constitutive activation of AKT does not rescue imatinib-mediated cell apoptosis in GIST, suggesting that imatinib-induced growth inhibition and cell death are AKT independent.64 Findings reported by Rossi and colleagues supported the notion that AKT is probably not a critical player in imatinib tumor response.64 In that study, using a GIST transgenic mouse model constitutively expressing a juxtamembrane mutation (exon 11, V558Δκαι), mice treated with imatinib showed significant histologic response (hematoxylin and eosin staining).
and decreased phosphorylation of PI3 kinase and mammalian target of rapamycin (mTOR). Mice treated with the mTOR inhibitor RAD001 also exhibited tumor response. The combination of RAD001 and imatinib, however, did not produce a synergistic antitumor effect. These data suggest that the therapeutic effect of imatinib is probably not dependent on the AKT pathway. The combination of imatinib and mTOR inhibitor in treating GIST merits further investigation.

Interestingly, the study by Tarn and colleagues also demonstrated that glucose uptake in GIST is regulated via the activation of AKT. Rapid inhibition of AKT activity by imatinib leads to negative fluoro-deoxyglucose-positron emission tomography (FDG-PET) findings in GIST. Nonetheless, the investigators hypothesized that reduction of PET-FDG activity may not absolutely relate to decreased cell growth. This theory has been supported by the clinical observation that some patients exhibit PET-FDG response but not tumor shrinkage or tumor density changes on computed tomography scans.

The signaling pathways of c-kit in GIST and the molecular response to imatinib (or sunitinib), thus, are not yet fully understood. In addition, it is not clear whether individual mutations of c-kit produce distinct signaling pathways that result in different sensitivities to imatinib.

MULTIDISCIPLINARY MANAGEMENT OF GIST

GIST is resistant to traditional cytotoxic agents and radiation. Numerous studies have shown the activity of imatinib in GIST. Demetri and colleagues reported a proof-of-concept study in 147 patients with advanced GIST who were randomized to receive either 400 mg or 600 mg of imatinib daily. A partial response rate of 53.7% was achieved (49.3% in the 400 mg group and 58.1% in the 600 mg group). To assess the differential response between high and low doses of imatinib, two large international studies randomized patients to receive either 400 mg or 800 mg daily. Verweij et al reported the findings of the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group, the Italian Sarcoma Group, and Australasian Gastro-Intestinal Trials Group in 2004. In that study, a total of 946 patients with advanced GIST were assigned to receive imatinib 400 mg or 800 mg. Comparable response rates and overall survival were observed in the two groups. However, PFS was more favorable in patients receiving the higher dose. Similarly, in a North America Sarcoma Intergroup Study (SOO33) examining these two dose levels in 746 patients, the projected 2-year overall survival was similar in the two groups.

Previous studies have demonstrated that tumors with high-risk features often relapse after surgical resection. A population-based study by Nilsson et al showed that survival was directly related to the size of the GIST tumor and Ki67 index. It was also found that the risk of dying of GIST increases 5% with each centimeter increase in tumor size. DeMatteo et al stratified GIST tumors into three size categories (< 5, 5–10, and > 10 cm) and showed that tumor size correlated with recurrence and survival.

Gold and colleagues reported a retrospective study of 119 patients with metastatic GIST treated at Memorial Sloan-Kettering Cancer Center between 1981 and 1998. Patients with tumor size less than 5 cm had a median survival of 40 months, whereas those with tumor size greater than 10 cm had median survival of 14 months. A high mitotic index (> 5 mitoses per 50 high power fields) was also clearly associated with shorter survival time.

The morbidity, mortality, and high recurrence rate in GIST led to the evaluation of adjuvant therapy with imatinib in patients undergoing surgical resection. A North American Intergroup phase III trial (ACOSOG Z9001) was designed to address whether 1 year of adjuvant imatinib would significantly improve disease-free and overall survival rates. A total of 708 patients with resected tumors measuring at least 3 cm and expressing c-kit were randomized to receive either imatinib 400 mg daily or placebo. The interim analysis presented by DeMatteo and colleagues showed a significant improvement in 1-year disease-free survival in patients receiving imatinib (97% vs. 83% P = .0000014). The findings in this trial have already altered clinical practice in the treatment of patients with surgically resected GIST with high-risk features. However, longer follow-up is needed to determine the effect of 1 year of adjuvant imatinib therapy on overall survival.

The use of imatinib has revolutionized management of advanced GIST and altered its natural history. Treating inoperable or metastatic disease requires a multidisciplinary approach. The idea of initiating primary therapy with imatinib prior to surgical resection to prolong survival or improve cure rates is very appealing. Neoadjuvant therapy presents the potential advantages of down-staging inoperable tumors to resectable tumors. Andtbadka et al from M. D. Anderson Cancer Center reported a series of 46 patients with recurrent metastatic or locally advanced GIST treated with imatinib for a median duration of 12.9 months in the neoadjuvant setting. Twenty-two patients underwent complete resections. Patients with radiographic response had a significantly higher resection rate than those who did not respond (91% vs. 4%).

Another study conducted by DeMatteo and colleagues from Memorial Sloan-Kettering Cancer Center demonstrated that neoadjuvant imatinib is an effective approach in patients with metastatic GIST; patients with imatinib-sensitive tumors had markedly better survival than those with resistant tumors after surgical resection of residual disease (2-year overall survival 100% vs. 36%). Gronchi et al also showed that incorporation of surgery for patients who responded to imatinib might be beneficial, with the benefit of surgery in those progressing on imatinib being uncertain. In addition, a number of small case series have indicated that neoadjuvant imatinib is a feasible approach, providing encouraging survival data and suggesting that neoadjuvant treatment could improve resectability rates.

Although the approach of neoadjuvant imatinib in advanced or metastatic GIST is appealing, numerous issues remain to be addressed. These include the duration of imatinib therapy prior to surgery, the optimal timing of surgery after a response to imatinib, and the initial dose of imatinib. In addition, for patients who do not have tumor size reduction by Response Evaluation Criteria in Solid Tumors (RECIST) criteria but have cystic changes on imaging studies, would surgical resection still
be of benefit? When should sunitinib be added to the treatment schema? Without clearly delineated guidelines, neoadjuvant therapy needs to be carefully carried out in select patients using a multidisciplinary team approach. A well-designed randomized, prospective study is needed to further address the role of neoadjuvant therapy in combination with surgery in advanced disease.

MECHANISMS OF IMATINIB RESISTANCE

Although imatinib has shown remarkable activity in GIST, development of drug resistance is a clinical problem. Sunitinib, a multi-tyrosine kinase inhibitor (targeting c-kit, PDGFR, all three forms of vascular endothelial growth factor receptor, and fms-related tyrosine kinase 3 receptor), was designed to overcome imatinib resistance. Demetri and colleagues showed that patients with imatinib-resistant GIST treated with sunitinib had a median time to tumor progression of 27.3 weeks compared with 6.4 weeks in placebo-treated controls, although there was no comparison to continuation of imatinib.

Several different mechanisms of imatinib resistance in GIST have been described: primary resistance; secondary mutations; c-kit overexpression and genomic amplification; alternative activation of receptor tyrosine kinases; and ATP-dependent imatinib efflux. Heinrich et al showed both primary and secondary resistance mutations in tumor specimens harvested from patients enrolled in a phase II imatinib trial. Primary mutations consisted mainly of exon 9 and PDGFR DB42V mutations, with secondary mutations being found in exons 9, 11, and 13. Tumor cells derived from these patients have constitutive phosphorylation of c-kit that cannot be inhibited by imatinib, even at high concentrations. In addition, the authors found constitutive activation of AKT and MAP kinase pathways in the primary resistant tumor specimens, indicating a distinct molecular pathogenesis of GIST in this subgroup of patients. Recently, Bauer et al demonstrated that the PI3 kinase/AKT pathway plays an important role in imatinib-resistant GIST, suggesting that targeting this pathway may be an alternative therapeutic approach.

Although the role of AKT in the development of GIST is debatable, the PI3K pathway is consistently considered to be critical in c-kit-mediated tumorigenesis.

**DISCUSSION**

The availability of imatinib provided the first effective specific treatment for advanced GIST. Even with current knowledge, individualized treatment should be offered to patients with GIST to optimize the benefits of imatinib therapy, and efforts should continue to determine how best to use this agent in a multidisciplinary approach. Development of drug resistance is a significant challenge, particularly since sunitinib overcomes only a small portion of imatinib resistance. Strategies targeting individual resistant mechanisms and alternative signaling pathways are being developed.

**REFERENCES**


73. Haller F, Detken S, Schulten HJ, et al: Surgical management after neoadjuvant imatinib therapy in gastrointestinal stromal tumors (GIST)

Disclosures of Potential Conflicts of Interest
The authors report no potential conflicts of interest.