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SUPPLEMENT (SPECIAL ISSUE)

Metastatic gastrointestinal stromal tumors

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Gastrointestinal stromal tumors (GISTs) are relatively rare neoplasms though they constitute the most common mesenchymal tumors of the gastrointestinal tract. Over the last 10–15 years, considerable advances have been made in the diagnosis, classification, and treatment of this neoplasm.

While the most common location for GISTs is the stomach, followed by the small intestine, any tubular gastrointestinal organ can be the site of origin. They also occur in the omentum, mesentery, and retroperitoneum. The most common sites of metastases for GIST are the liver and peritoneum, though regional lymph node, bone, and lung metastases may rarely occur.

Molecular pathogenesis of GIST

Because GISTs and the interstitial cells of Cajal (ICC) of the myenteric plexus, the "gastrointestinal pacemaker cells", share certain differentiation markers (KIT, CD34), a relationship between the two has been proposed [1]. GISTs likely arise from the ICC, or it is possible the cells share a common ancestor; the true origin is still open to question. Approximately 95 percent of GISTs express the CD117 antigen, representing the KIT transmembrane tyrosine kinase receptor, a product of the *KIT* proto-oncogene [2]. KIT is a type III receptor tyrosine kinase that consists of an extracellular domain, a transmembrane domain, a juxtamembrane domain, and a tyrosine kinase (TK) domain that splits into two subdomains, TK I and TK II [3]. The majority of GISTs harbor *KIT* gene mutations that lead to constitutive (ligand-independent) receptor phosphorylation and activation of downstream signaling pathways that promote cell survival and proliferation [4]. Mutations in exon 11, which encodes the KIT receptor juxtamembrane domain, account for most, approximately 70 percent of the *KIT* mutations. The most common exon 11 mutations are isolated in-frame deletions. Mutations in exon 9 (extracellular region) account for 10–15 percent of the other mutations. The most commonly found mutation type is an in-frame duplication of nucleotides in exon 9 resulting in the insertion of AY residues at codon 502. Mutations in exon 13 site (TK I domain) and exon 17 (phosphotransferase domain) are less frequent and account for the remaining of the mutations [4–7].

In a subset of wild-type GISTs, mutations in a gene encoding another tyrosine kinase receptor (platelet-derived growth factor receptor alpha, *PDGFRA*) can be found. Mutations in *PDGFRA* occur mutually exclusively from *KIT* mutations [8]. Mutations in *PDGFRA* most commonly involve exon 18, the region encoding the activation loop in the TK II domain. The imatinib-resistant substitution D842 V is the single most common *PDGFRA* mutation in GIST patients (60 percent). Mutations were also found, although less frequently, in the juxtamembrane domain (exon 12) and in the first TK domain (exon 14) [9]. In approximately 15–20 percent of GISTs, no mutation can be identified in either *KIT* or *PDGFRA*. In patients with wild-type GISTs, *BRAF* exon 15 mutation (V600E) was found in a subset of patients. In two recent studies, V600E *BRAF* mutations were detected in 7 percent of adult GISTs without *KIT*/*PDGFRA* [10, 11]. No *KRAS* mutation was found in the last study [11].

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Corless and colleagues have demonstrated that *KIT* mutations are common in incidental GISTs measuring 1 cm or less in size, supporting the fact that these activating mutations occur as early events in the development of GISTs [12]. Even though *KIT* mutations play an important role in tumorigenesis of GISTs, additional genetic alterations, including chromosomal alterations, are probably required for the development from microscopic tumorlets to clinical high-risk GISTs [13]. For example, El-Rifai and colleagues have demonstrated that the number of chromosomal aberrations was more frequent in high-grade primary and metastatic GISTs compared to low-grade primary GISTs. Loss of chromosomal arms 1p, 14q, and 22q was common findings in all subgroups, irrespective of histologic grade or metastatic status. Others abnormalities, including 9p deletion, 8q and 17q amplifications, were, however, identified most frequently in metastatic GISTs [14]. A better understanding of the different pathways leading to malignant transformation of GISTs is important for a better prognostic classification of the disease and development of new drugs.

Evaluation of recurrence risk/prognostic factors

The biologic behavior and the recurrence risk of resected GISTs are variable; even very small tumors have malignant potential. Tumor size, mitotic rate, and the location of the primary tumor are the three main prognostic factors for recurrence. Gastric tumors have a more favorable prognosis than small intestinal tumors with similar parameters. Gastric GISTs measuring ≤10 cm with a mitotic rate of ≤5 mitoses per 50 high power fields (HPFs) have a less than 5 percent risk of metastases. Petite (≤5 cm) small intestinal GISTs with low mitotic indices (≤5 mitoses per 50 HPFs) also rarely recur (<5 percent risk). In contrast, all small bowel GISTs measuring >5 cm are at least at moderate risk (25 percent) for metastasis, independent of the mitotic index, and small intestinal GISTs with a mitotic rate greater than 5 mitoses per 50 HPFs have a ≥50% risk of recurrent disease [15].

Few studies have evaluated the prognostic factors in metastatic GISTs prior to the era of wide-spread tyrosine kinase inhibitor use. In a retrospective study from the Memorial Sloan-Kettering Cancer Center (MSKCC) [16], which analyzed the outcome of metastatic GIST patient diagnosed prior to July 1998 (2 years prior to the use of imatinib), the investigators found that primary tumor size >10 cm, mitotic index >5 mitoses per 50 HPFs, spindled cell morphology, longer disease-free interval, and unresected metastatic disease were associated with a worse prognosis. Mutational status did not affect the outcome after the development of metastases. For patients treated with imatinib, factors that have been shown to be associated with worse survival include male sex, older age, poor performance status, low albumin, and high baseline neutrophils count [17–19]. Particular *KIT* mutations are both prognostic and predictive. In patients with advanced or metastatic disease treated with imatinib mesylate, patients with exon 11 mutations have higher response rates, longer progression-free and overall survival versus those with tumor harboring exon 9 mutations or no mutation (see below) [5–7].

Therapeutic options

GISTs are unresponsive to conventional cytotoxic chemotherapy, including regimens effective against other soft-tissue sarcomas. Prior to 2000, no effective therapy existed for patients with disseminated advanced disease.

The finding that almost all GISTs harbor mutations leading to constitutive KIT activation [2], coupled with preclinical studies suggesting *KIT* was a druggable target [20] led to the development of effective molecularly targeted therapy. Imatinib mesylate is a small molecule that selectively inhibits the enzymatic activity of a small number of tyrosine kinases, including the BCR-ABL fusion protein important in chronic myeloid leukemia pathogenesis, PDGFRA, and KIT.

In 2001, Joensuu and colleagues described the case of a 50-year-old woman with rapidly progressive metastatic GIST resistant to multiple lines of chemotherapy, treated with 400 mg of imatinib once daily [21]. Her diagnosis was confirmed by the positive immunostaining for CD117. A *KIT* mutation, a deletion of 15 bp in exon 11, was identified. After 1 month of therapy, she had a 52 percent decrease in tumor volume on magnetic resonance imaging (MRI). Many of her liver metastases became hypodense and had a cyst-like appearance. The tumor enhancement on dynamic MRI was significantly decreased, an indicator of reduced viability. On [^{18}F]Fluorodeoxyglucose positron emission tomography (PET) scan done also after 4 weeks of imatinib therapy, no more abnormal uptake was seen in the liver, suggestive of a complete response. Histopathological evaluation of serial needle-biopsy specimens of a liver metastasis showed, with treatment, extensive fibrosis, myxoid degeneration with a few scattered nonproliferating CD117-positive cells. The patient maintained a response for more than 11 months, with minimal treatment toxicity.

The efficacy and safety of imatinib was subsequently demonstrated in three important trials:

A phase I study from the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group evaluated imatinib in 40 patients with soft-tissue sarcomas of whom 36 had metastatic GISTs at doses ranging from 400 to 1,000 mg daily [22]. Objective responses were seen in 25 of the 36 patients, 7 were stable, and 4 had progressive disease. Dose-limiting toxicities were nausea, vomiting, edema, and skin rash but were more commonly observed at a dose of 1,000 mg daily. At doses of 800 mg daily or less, these side effects were also seen but were manageable and dose reductions were rarely required.

B2222 was a randomized phase II trial conducted in the United States and Finland, in which a total of 147 patients received either 400 or 600 mg of imatinib daily [23]. Overall, 54 percent of patients had a partial response and 28 percent had stable disease. The median time to an objective response was 13 weeks; though some responses evolved slowly, after a follow-up of 71 months, two patients (1.4 percent) demonstrated complete responses and 98 patients (67 percent) achieved partial responses [18]. Early resistance to imatinib, manifested as early progression, was seen in 14 percent of patients. There were no significant differences in the rate of response between the dose levels of imatinib. Treatment with imatinib was well tolerated. The most common side effects include edema (predominantly periorbital), nausea, vomiting, diarrhea, abdominal pain, musculoskeletal pain, fatigue, rash, and headaches. Recently, concerns were raised regarding the possibility of imatinib-associated cardiotoxicity. However, imatinib-related cardiotoxicity was not confirmed in the analysis of patients in a large randomized trial [24]. A 4-year extension analysis of the B2222 trial was done [18]. Median duration of response was 29 months. The estimated median overall survival (OS) was 57 months for the total population. Most of the patients (86 percent) died of GIST, but 70 patients (48 percent) were alive at 71 months. So, nearly 50 percent of patients with advanced GIST who were treated with imatinib survived for more than 5 years, regardless of the starting dose (400 or 600 mg daily). Imatinib remained well tolerated with long-term administration.

An EORTC phase II study also assessed the activity of imatinib at a dose of 400 mg twice a day in 27 advanced and/or metastatic GIST patients [25]. Four percent of patients had a complete remission, 67 percent partial remission, 19 percent stable disease, and 11 percent progressive disease. The median time to response was 113 days. The progression-free survival (PFS) at 1 year was 73 percent. Imatinib was well tolerated at this dose.

Imatinib subsequently became the standard first-line treatment for patients with unresectable and metastatic GISTs.

The initial recommended starting dose of imatinib for most patients is 400 mg once daily. Two randomized trials have compared two potential daily initial doses, 400 and 800 mg [17, 26]. The two trials did not show benefit of higher imatinib dose (800 mg) in regards to response rate or overall survival. Higher dose was also associated with more adverse effects in both trials.

In the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group—Italian Sarcoma Group-Australasian Gastrointestinal Trials Group (EORTC-ISG-AGITG) 62005 trial, the 800 mg dose was associated with a modest but significant increase in PFS (50 vs. 44 percent at 760 days median follow-up, $P = 0.026$) [26]. Edema, anemia, rash, lethargy, nausea, bleeding, diarrhea, and dyspnea were observed more frequently in patients receiving imatinib twice a day than in patients allocated to once daily treatment. Patients assigned to twice daily imatinib were significantly more likely to have a dose reduction (60 percent vs. 16 percent) or treatment interruption (64 percent vs. 40 percent). In patient assigned to once daily imatinib, 41 percent had at least one grade 3–4 event and 50 percent on the twice daily regimen ($P < 0.0001$). Serious adverse events were similar in both arms.

In the Intergroup S0033 trial, after a median follow-up time of 4.5 years, there were no significant differences in PFS between arms (median PFS of 18 months for conventional-dose vs. 20 months for high dose ($P = 0.13$)) [17]. Forty-three percent of patients on the 400 mg daily dose experienced grade 3–5 toxicities versus 63 percent on high-dose imatinib. One percent of patients in the low-dose arm and 3 percent of patients in the high-dose arm had possible treatment-related deaths.

However, both trials' results suggested that patients with exon 9 mutations potentially benefit from higher doses of imatinib (800 mg):

The EORTC-ISG-AGITG 62005 trial described earlier showed that the use of the high-dose regimen resulted in increased in PFS with a 61 percent reduction in the relative risk ($P = 0.0013$) in tumors expressing exon 9 mutation. PFS was not affected by the initial dose in patients with exon 11 *KIT* mutations or in patients with wild-type genotype. The response rate or the OS were not affected by the dose in any of the tumor genotype subgroups [6].

In a subsequent analysis of the Intergroup S0033 trial [7], patients with *KIT* exon 9 treated with an imatinib dose of 800 mg had a longer time to progression than patients treated with an imatinib dose of 400 mg (18 months vs. 9 months), however, it was not statistically significant ($P = 0.97$). The imatinib dose did not affect the OS for any subgroups. However, the 800 mg dose was associated with a higher response rate (67 vs. 17 percent, $P = 0.02$) in patients with an exon 9 mutation.

A planned pooled analysis of the two studies, including 1640 patients, was recently published [27]. The absence of *KIT* exon 11 mutations was associated with a worse prognosis. After a follow-up of 45 months, a small but significant PFS benefit was confirmed for the high-dose imatinib, 34 percent versus 30 percent at 3 years ($P = 0.04$). Within patients with *KIT* exon 9 mutations, patients treated with the high-dose arm had significantly higher response rate (47 percent vs. 21 percent, $P = 0.0037$) and longer PFS ($P = 0.017$). However, for patients without exon 9 mutations, there was no difference between treatment arms. For the OS, no subgroup benefit from high-dose therapy.

Patients with GISTs that do not express KIT should still be offered a trial of imatinib, as their tumors are often still sensitive to this agent. For example, in the subsequent analysis of the Intergroup S0033 trial, patients with CD117-negative GIST had similar time to progression, but inferior OS, compared with patients CD117-positive disease, suggesting that this subset of patients may benefit from imatinib [7].

GIST patients should be treated until progression or development of significant toxicity. A prospective French study initially compared interruption of imatinib after 1 year of treatment versus continuous treatment, in patients with advanced GISTs responsive to that drug [28]. Discontinuation of imatinib resulted in rapid progression in many patients with advanced GISTs. The median time to progression after imatinib interruption was 6 months versus 18 months in those continuing drug. However, of the 26 patients progressing in the interruption arm, 92 percent of patients in whom imatinib was restarted (at a 400 mg daily dose) experienced response or stable disease. Even though the analysis was not powered to demonstrate equivalence in survival in both arms, with longer follow-up, there was no difference in survival between the arms. Imatinib ''holidays'' were not associated with a major improvement in quality of life. A similar randomization at 3 years again showed those stopping drug by and large experienced rapid progression. However, again, there was no impact of imatinib discontinuation on OS [29].

The evaluation of response is different for GISTs than for other solid tumors. After treatment with imatinib, GISTs may initially increase in size on conventional imaging, as a consequence of myxoid degeneration or intratumoral hemorrhage. A decrease in tumor density is an indicator of clinical response [30], as is a decrease in metabolic activity. Indeed, PET imaging can detect responses earlier and more accurately [31]. Responses can be detected as early as within 24 h of therapy initiation [23]. This diagnostic modality can also identify patients who develop secondary resistance to treatment.

Role of surgery in advanced or metastatic GIST

Surgery is the only potentially curative treatment for GISTs and is still the standard initial treatment for patients with resectable tumors. However, neoadjuvant (conversion) therapy with imatinib could be considered in the setting of a borderline resectable tumor or if initial resection would result in extensive organ disruption. A multicenter phase II trial including 63 patients with either advanced primary GIST, defined as tumor $\geq$5 cm or metastatic/recurrent $\geq$2 cm, has shown that this approach is feasible and safe [32]. Patients were treated with 8–12 weeks of neoadjuvant imatinib at a 600 mg daily dose. Imatinib was stopped on the day prior to surgery and restarted postoperatively for a 2 year time. Surgical complications were common but, consistent with surgical series involving extensive and re-operative abdominal surgery. One post-surgical death was reported, secondary to sepsis. The 2-year estimated PFS was 81 percent, overall.

Even though tyrosine kinase inhibitors are the mainstay of treatment for patients with metastatic GISTs, surgical resection of residual disease can sometimes be considered. The hypothesis is that surgery might prevent and/or delay the development of resistant clones by reducing tumor burden, and, consequently, prolong the time to disease progression. Single institution series from Dana-Farber Cancer Institute and Brigham and Women's Hospital has evaluated the outcomes of 69 patients who underwent surgery for advanced GISTs while receiving kinase inhibitors [33]. It was found that disease status prior surgery was associated with outcomes. Twelve-month OS for patients with stable disease, limited progression, and generalized progression was 95 percent, 86 percent, and 0 percent, respectively. This suggests that debulking procedures do not benefit patients with a generalized progression on imatinib. Similar findings have been found in series from the MSKCC and from an Italian center [34, 35]. However, no randomized trials are available to confirm whether surgery changes the outcomes in advanced or metastatic disease in the era of targeted therapy. One trial is currently underway to help answer this important question, and a similar study, whose results will be pooled with the European findings, is proposed in North America.

Salvage

Despite the high objective response rate and durable PFS seen with imatinib, complete responses in patients with advanced GISTs are only rarely achieved. Additionally, most patients treated with imatinib eventually acquire resistance via additional mutations in the *KIT* gene [36]. The median time to progression is approximately 2 years [18]. For patients progressing on imatinib, dose escalation up to 800 mg daily is an option in patients initially treated with an imatinib dose of 400 mg. In a subsequent analysis of the EORTC-ISG-AGITC trial 62005, of the 241 patients available for follow-up, 133 patients (55 percent) crossed over to a daily imatinib dose of 800 mg after progression on 400 mg. After dose escalation, 3 patients (2 percent) had a partial response and 36 (27 percent) stable disease. The median PFS was 81 days, and 18 percent of patients were still alive without evidence of progression 1 year after cross-over [37]. In the Intergroup S0033 trial, after progression on 400 mg daily, one-third of patients who crossed over to the high-dose imatinib regimen achieved benefits in terms of either an objective response or stable disease [17].

Sunitinib, a multi-targeted tyrosine kinase inhibitor, has demonstrated efficacy in imatinib-refractory or intolerant patients. The role of sunitinib in patients with refractory advanced GISTs has been clearly demonstrated by Demetri and colleagues in an international phase III trial. The median time to tumor progression was significantly increased compared to placebo (27 vs. 6 weeks, $P < 0.0001$) even if only 7 percent of patients in the sunitinib group showed partial response as the best response [38].

The most common toxicities of sunitinib are fatigue, anorexia, mucositis, nausea, vomiting, diarrhea, bone marrow suppression, rash, and skin discoloration. Hand-foot syndrome and hypothyroidism are two serious potential adverse effects described [38]. Hypertension and cardiac toxicity has been reported, so monitoring of blood pressure and left ventricular function is important in patients on sunitinib, specially in patients with a history of coronary artery disease or cardiovascular risk factors [39].

Conclusions

During the last decade, striking advances have been made in the understanding, characterization, and treatment of GISTs. Continuing research in this field will hopefully lead to emergence of multiple new therapeutic agents directed at this disease and the ability to individualize therapy based on tumor genetic characteristics.

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