PERGAMON

European Journal of Cancer Vol. 38 Suppl. 5 (2002) S52–S59

European Journal of Cancer

www.ejconline.com

Identification and treatment of chemoresistant inoperable or metastatic GIST: experience with the selective tyrosine kinase inhibitor imatinib mesylate (STI571)

George D. Demetri*

Center for Sarcoma and Bone Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02115, USA

Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. The concept of GIST and the definition of GIST pathology have evolved greatly over the past 5 years. GIST has been shown to share immunohistochemical, ultrastructural and histogenic similarities with the interstitial cells of Cajal. Both GIST and the interstitial cells of Cajal express KIT, the receptor tyrosine kinase that is the protein product of the c-*kit* proto-oncogene. KIT is universally phosphorylated in GISTs. Sequencing of c-*kit* complementary DNA from human GIST cells has demonstrated a high frequency of mutations that lead to constitutive activation of the KIT tyrosine kinase in the absence of stimulation by its physiologic ligand (stem cell factor). This, in turn, causes uncontrolled stimulation of downstream signaling cascades with aberrant cellular proliferation and resistance to apoptosis. Historically, malignant GIST has been highly refractory to conventional cytotoxic therapy. Signal transduction inhibition as cancer therapy was first tested successfully with imatinib mesylate (formerly known as STI571), a selective small-molecule tyrosine kinase inhibitor, with the initial target being blockade of Bcr-Abl, the oncogene with tyrosine kinase activity responsible for the pathogenesis of chronic myelogenous leukemia (CML). Imatinib was subsequently shown to block activity of the KIT tyrosine kinase as well, and in laboratory studies this led to apoptotic death of GIST cells. The first GIST patient to receive imatinib exhibited dramatic benefit despite far-advanced metastatic disease that was previously refractory to all chemotherapy. Subsequently, multicenter clinical trials have been performed to assess the safety, efficacy and biologic activity of imatinib in patients with advanced GIST. The results from these studies have established imatinib as an effective new therapeutic alternative for the majority of patients with advanced GIST, a solid tumor for which no prior chemotherapy has ever shown antitumor efficacy. This work provides proof of concept to the hypothesis that selective inhibition of aberrant signal transduction can provide important anticancer activity, if the proper signaling pathways are identified and blocked.

Keywords: Gastrointestinal stromal tumor; Signal transduction; Targeted therapy; Imatinib mesylate; Receptor protein-tyrosine kinase; Enzyme inhibitor; Oncogene; c-*kit*

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. They are derived from primitive enteric intramural cells and can develop throughout the digestive system, most commonly in the stomach (60% to 70%), followed by the small intestine (20% to 25%), colon and rectum (5%) and esophagus (<5%) [1]. Although the majority of GISTs may appear to be benign by conventional light microscopy and histologic evaluation, it is critical to recognize that approximately 20% to 30% will ultimately prove to exhibit malignant behavior in the patient. Specifically, histologically benign GIST lesions frequently recur with liver metastases or multifocal unresectable disease. It is

* *E-mail address:* gdemetri@partners.org

0959-8049/02/$ – see front matter

not fully clear whether GISTs that prove to be malignant share a common histogenesis with those that behave in a benign fashion and prove to be curable with surgery alone; at this time, it is unclear whether any specific histopathologic criteria of GIST can reliably predict future biologic behavior [2]. It is clear, however, that malignant GIST (an entity that is synonymous with gastrointestinal stromal sarcoma) is associated with significant morbidity and a rapidly fatal course if unresectable, and that current chemotherapeutic and radiotherapeutic regimens have done little to improve the prognosis [3,4]. Despite our best attempts using conventional systemic chemotherapy, median survival duration in unresectable and metastatic GIST has remained less than 2 years [3,5].

The state of knowledge regarding the origin, cellular differentiation and molecular biology of malignant GIST has advanced greatly over the last 2 years. Several pathologic features have been identified, and many of the disease's genetic and molecular pathways have been described. These exciting new developments are the first step toward a crystallized understanding of the pathophysiology and molecular basis of GIST, and toward the creation of new therapeutic targets and strategies. This paper will review recent diagnostic, molecular biologic and therapeutic advances, with particular focus on the clinical research experience with imatinib mesylate (previously known as STI571), a new targeted therapy that has already shown great promise in the treatment of GIST.

2. Understanding the nature of GIST

2.1. Clinical and pathologic features

GIST is a disease that can occur in any age group, although it has been most widely reported in patients of middle age or later. When localized, GIST lesions tend to be primarily intramural and submucosal, often evading clinical diagnosis until their size impacts GI function or unless they rupture and bleed [1,4]. Like other soft tissue sarcomas, GISTs rarely metastasize to the lymph nodes. The pattern of metastatic spread characteristically involves the liver or multifocal omental implants.

GISTs are a heterogenous group of diseases that differ in frequency, morphology and biology depending on their site of origin. They can be single or multiple (as in the multifocal GISTs that have been reported in Carney's triad), spindled or epithelioid, or mixed cell type [4]. As many as 30% are malignant, leading to intra-abdominal spread or liver metastases. However, no single histopathologic feature has yet been identified in GIST that can accurately predict the course of the disease. Certainly, one of the most important prognostic factors is size of the primary lesion, with far better prognosis for lesions <1 cm in size [6]. Given this lack of ability to know with reasonable certainty which patients will have recurrence, following resection of GIST, patients should be followed closely over the long term, because even tumors that appear benign can recur and prove fatal [6].

Table 1
Differential diagnoses to be considered in GIST with differentiating features. Adapted with permission from Miettinen M and Lasota J. *Virchows Archiv*, 2001, 438, 1–12

Tumor	Differentiating features
Esophageal leiomyoma	Well-differentiated smooth muscle cells; +for desmin and SMA
Uterine-type leiomyoma receptors	Usually pelvic; +for desmin, SMA and E+, P+
Leiomyosarcoma	Smooth muscle tumor; +for desmin and SMA; CD117-negative
Inflammatory fibroid polyp	Slender spindle cells, admixed lymphoid cells, and eosinophils
Inflammatory myofibroblastic tumor	Children or young adults; expresses ALK
Mesenteric desmoid	Characteristic pattern of myofibroblasts in collagenous background;
Dedifferentiated liposarcoma myxoid/ pleomorphic	May have lipomatous component or fibrosarcoma-like features;
Schwannoma tumors	Usually small, yellow circumscribed submucosal S100+ spindle cells in S100- fibrous background

Until recently, malignant GIST was often categorized as a tumor of smooth muscle derivation. In the mid 1980s, however, electron microscopic studies revealed a lack of typical smooth muscle differentiation [7]. GISTs have subsequently been shown to share immunohistochemical and ultrastructural similarities with the interstitial cells of Cajal [1]. This complex of "pacemaker cells" — responsible for the rate of movement in the GI tract — has been suggested as the possible cellular precursor of GIST [8–10]. Thus, GIST is a pathogenetically distinct entity and should be differentiated from leiomyosarcomas of the GI tract, true leiomyomas (which occur predominantly in the esophagus, colon and rectum) and schwannomas (spindle cell tumors, which express the S100 antigen and often are benign) (Table 1) [1]. Most tumors previously labeled as "leiomyoblastomas" or "gastrointestinal autonomic nerve tumors (GANT)" have in fact been proven to be GISTs with modern techniques. It is only through recent advances in molecular pathology and the use of increasingly sophisticated diagnostic tools, such as immunohistochemistry for the KIT transmembrane receptor protein or assessment of KIT phosphorylation, that it has become possible to distinguish GIST definitively from other rare spindle cell tumors of the GI tract. The current preferred diagnostic test for GIST is CD117 immunohistochemical staining performed by a laboratory with experience in this area. CD117 expression is found to be positive in the majority of GIST tumor cells [4,6].

2.2. Molecular biology of GIST

A proposed molecular genetic pathway for GIST was first reported in 1998 by Hirota and colleagues from Osaka, Japan. Sequencing of complementary DNA for the c-*kit* proto-oncogene, encoding the KIT receptor tyrosine kinase, revealed mutations in specimens from five human GIST tumors. The authors observed that in the presence of these mutations, the corresponding KIT protein was activated even in the absence of the KIT ligand (stem cell factor). They further found that expression of these mutant KIT proteins induced malignant transformation of Ba/F3 murine lymphoid cells and caused uncontrolled tumor growth in nude mice, thus describing the first genetic explanation for GIST pathogenesis and identifying tyrosine kinase signal transduction as a potential target to interrupt the oncogenic drive in GIST [11]. More recently, the group of Rubin and Fletcher at Harvard reported that 100% of GIST cells studied exhibited constitutive phosphorylation of the KIT protein, independent of ligand activation, even in the absence of detectable c-*kit* mutations [12].

Today, GIST is generally defined as a spindle cell or epithelioid mesenchymal tumor of the GI tract that expresses an activated KIT protein, with the surrogate marker for the majority of these being positive immunostaining for the CD117 antigen, which marks KIT [4,6]. Approximately 70% of GISTs are also positive for expression of CD34, 20% to 30% are positive for smooth muscle actin, 10% for S100 protein and <5% for desmin. The genetic mutations responsible for GIST have been identified as being quite variable. Often these mutations are small in-frame deletions that maintain an intact protein, but point mutations are also commonly noted. Generally, there is only one mutation noted in c-*kit* per individual GIST, but these vary greatly between GISTs from different patients. The most frequently noted mutations of c-*kit* have been found to involve exon 11 (therefore affecting the juxtamembrane domain of the KIT protein), but mutations in exon 9, exon 13, or even other loci have been described [12–14]. The structural biology is just now becoming understood, and there is a great deal of ongoing research to explicate how these minor structural changes in KIT protein lead to constitutive activation. Cytogenetic analyses of GISTs often show a normal karyotype, but frequently reveal losses in 14q and 22q unrelated to whether the GISTs have exhibited either benign or malignant clinical courses; aneuploidy is noted in some of the GISTs with more obviously malignant histopathologic features, often with several extra copies of chromosomes [1]. Overall, although complex molecular changes can be a feature of certain GISTs, the majority of molecular and cytogenetic evidence points to GIST as a disease in which a single critical signaling pathway goes awry early in the pathogenesis of the neoplasm. The current hypothesis is that activation of KIT is the event critical to the pathogenesis of GIST. While other molecular aberrations probably develop over time, and may differ between GISTs occurring in different patients, the crucial dependence upon the uncontrolled signals from KIT is an important characteristic of GIST. This makes this disease an ideal candidate for studying the role of a selective signal transduction inhibitor.

2.3. Signal transduction pathways and the management of GIST

Based on this substantial understanding of their molecular pathophysiology, sarcomas such as GIST represent highly informative proof-of-concept models for cancer research. The identification of critical genetic alterations in GIST and the elucidation of their relationship to signal transduction pathways generated a new focus for targeted therapeutic research. The preclinical data were further supported with the report of a Japanese family that manifested an autosomal dominant pattern of GISTs and shared a germline mutation in the locus for c-*kit*, further linking genetic mutations, KIT signal transduction and pathogenesis of GIST in humans [15].

By 1999, signal transduction inhibition as cancer therapy was in the early stages of clinical testing with a selective small molecule inhibitor of the fusion oncoprotein Bcr-Abl tyrosine kinase, which was widely held to be a crucial factor in the pathogenesis of chronic myelogenous leukemia (CML). Druker and colleagues screened a panel of small molecules of the 2-phenylaminopyrimidine class and identified a potent inhibitor of Bcr-Abl kinase activity in vitro [16]. In subsequent preclinical studies,

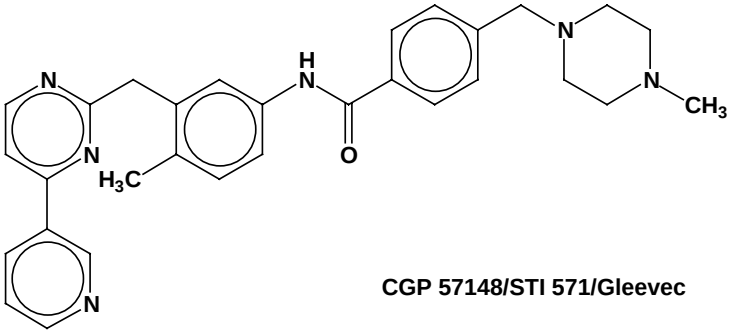

Fig. 1. Chemical structure of imatinib mesylate (4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[{4-(3-pyridinyl)-2-pyrimidinyl}amino] phenyl] benzamide methanesulfonate.

this compound, STI571 (formerly known as CGP 57148B and now known by the generic name of imatinib mesylate, or by the trade names of Gleevec™. in the US and Glivec®. in the rest of the world) (Fig. 1) was noted to selectively inhibit the Bcr-Abl tyrosine kinase, with resultant reduction in leukemic cell proliferation and inhibition of tumor formation associated with Bcr-Abl-positive cells [16–18]. The inhibitory activity of imatinib was highly selective and did not broadly affect kinases that functioned in normal cell growth and proliferation. The early clinical trials of imatinib in CML patients found that the agent was impressively safe, causing only mild to moderate nausea, myalgia, edema and diarrhea, while inducing complete hematologic response in 53 of 54 patients with CML treated at daily doses of 300 mg or greater [19].

Subsequent studies noted that the imatinib was selective, but not totally specific for Bcr-Abl or the Abl class of tyrosine kinases. Imatinib was found to block the tyrosine kinase function of receptors such as KIT, as well as the platelet-derived growth factor receptor (PDGFR). Importantly, Heinrich and colleagues at Oregon reported that the wild type (nonmutant) version of KIT was able to be inhibited by imatinib as were many mutated versions of KIT [20]. Heinrich and colleagues also reported data describing exposure of the KIT-expressing human myeloid leukemia cell line, M-07C, to imatinib in vitro [20]. Imatinib was found to decrease KIT autophosphorylation and inhibit KIT-dependent cellular proliferation, without inhibiting other signaling pathways (such as the GM-CSF receptor-dependent proliferation that characterizes this cell line). Heinrich also noted that certain human mast cell lines that had an exon 17 mutation (in the kinase domain that was predicted to be the actual binding site of imatinib) would not be inhibited by imatinib, further strengthening the link between kinase inhibition and the anticancer activity of this agent.

The efficacy of the compound in blocking cellular proliferation in hematologic malignancies, however, did not necessarily predict similar behavior in a solid tumor. Preclinical evidence specific to GIST came from Tuveson *et al.*, who reported that addition of imatinib to cell cultures of GIST with activating mutations abolished the constitutive tyrosine phosphorylation of KIT, halted cellular proliferation and induced apoptosis of GIST cells [14]. These results, in conjunction with the elegant prior GIST work from Japan and the exploration of KIT in hematologic malignancies from Oregon, provided the scientific groundwork to fully justify testing imatinib in the clinical management of patients with advanced GIST.

3. Clinical experience with imatinib in GIST

The clinical activity of imatinib in advanced GIST was quickly shown to be exceptional, beginning with the first treated patient. A 50-year-old woman with metastatic GIST that expressed an activating deletion in exon 11 of the c-*kit* gene received oral administration of imatinib at the dose of 400 mg daily, continuously for 11 months at the time of the first report [21]. The patient had previously undergone multiple surgical resections and had received several chemotherapeutic and other investigational anticancer regimens over a 2-year period with no significant improvement. Prior to the start of imatinib therapy, the summed cross-sectional measurement of eight metastatic hepatic GIST tumors totaled more than 112 cm^2. Subsequent magnetic resonance imaging (MRI) scans during treatment revealed rapid and progressive tumor regression of 28 liver metastases, including complete elimination of six (Fig. 2a and b). Serial needle biopsy specimens showed reduced density of tumor cells as well as myxoid degeneration and scarring, consistent with the anticancer effect shown on the imaging studies. Complete metabolic response in the tumors was apparent on a positron emission tomography (PET) scan, as evidenced by rapid decrease in tumor-related accumulation of ^{18}fluoro-2-deoxy-D-glucose (^{18}FDG) in metastases. The patient's performance status also improved from 1 to 0, demonstrating the clinical relevance of these imaging and pathology studies. Toxicity was minimal, comprised only of some mild dyspepsia and minimal increased frequency of bowel movements. The positive response has continued for 21 months (Joensuu, data not shown).

Based on the compelling scientific rationale and supported by this dramatic and sustained response, a multicenter, randomized clinical trial was initiated to assess the safety, efficacy and biologic activity of two different doses of imatinib given orally to adult patients with unresectable and/or metastatic malignant GIST expressing CD117 [22]. All patients had previously failed conventional therapy including surgery, chemotherapy and/or radiotherapy. One hundred and forty seven patients enrolled in the study were randomly assigned to receive either 400 or 600 mg imatinib daily. These dose levels were chosen by extrapolating from the knowledge of the pharmacologic profile of imatinib in CML patients [19] and estimating the systemic concentrations that would be needed to inhibit the KIT target in GIST. Results from this trial have confirmed the overall good tolerability and efficacy of imatinib in treating patients with advanced GIST [22]. The most serious adverse event was gastrointestinal or intra-abdominal hemorrhage, which occurred in approximately 5% of patients (primarily those with large bulky tumors). This was perhaps related to the rapid anticancer effect on the tumors, with disruption of tumor-related vasculature. However, since bleeding from advanced GIST is a well-recognized complication of the natural history of this disease, it is not possible to assess how many of the bleeding events were due to drug therapy rather than due simply to the nature of these far-advanced, bulky tumors. The impact of imatinib on tumor metabolism was also demonstrated as a rapid and dramatic decrease in ^{18}FDG uptake on PET scans [23].

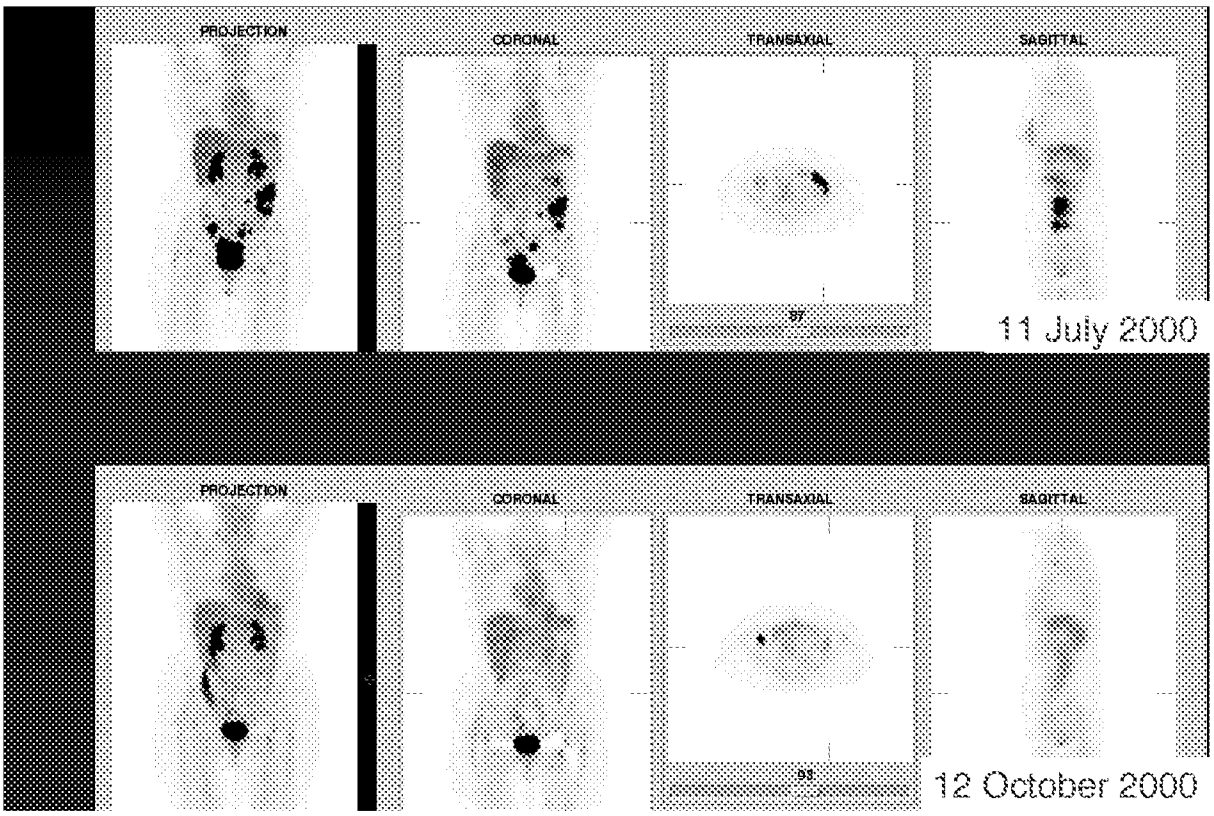

Fig. 2a. Serial PET scan images of a patient with advanced GIST, demonstrating baseline tumor uptake of ^{18}FDG. Resolution of the tumor uptake is noted in the follow-up scan, which shows only the normal renal collecting system as well as physiologic bowel uptake in the right lower abdomen.

The functional imaging with PET scans was highly predictive of subsequent anatomic response by conventional imaging with standard computed tomography (CT) or MRI scanning.

Objective response to imatinib was measured by standard oncologic criteria as tumor regression: partial response was defined strictly as patients who exhibited a 50% or greater decrease in the summed area of all measurable tumors. With median follow-up in excess of 9 months, 82% of patients remained on study without disease progression. Objective partial responses were noted in 79 of 147 patients (54% rate of PR), while an additional 41 patients (28%) had stable disease. In a subset of patients, very rapid tumor shrinkage (within 1 month) was noted. However, it was not uncommon for objective partial responses to evolve slowly in other patients (e.g., over 4 to 6 months after starting therapy with imatinib). Responses have been durable for more than 46 weeks with median duration of response not yet reached (median follow-up, 24 weeks). The estimated one-year survival for all paients was 88%. No evidence of tumor lysis syndrome was noted in this trial. There was a small subset of patients with primary resistance to imatinib, whose disease failed to exhibit response on PET or CT scanning. This group comprised less than 14% of the initial study population.

Tumor biopsies were performed before and after treatment with imatinib in a subset of consenting patients. Some of the posttreatment biopsies confirmed the diffuse myxoid tumor degeneration and fibrosis, without disturbance of intratumoral vascular architecture, which had previously been noted in the first GIST patient treated with imatinib [21].

Overall, the results of this multicenter trial indicated that imatinib induced a sustained response in over half of patients with advanced unresectable or metastatic GIST. Treatment with imatinib was acceptably well tolerated, with consistent bioavailability of the drug when administered orally despite the significantly compromised GI tract anatomy in many of the patients who had had extensive prior surgery. Although the trial was not designed to have adequate power to assess dose-related differences, no statistically significant differences were noted between these two dose levels of imatinib. Identification of the optimally effective dose of imatinib for the treatment of GIST is the subject of large, appropriately powered randomized studies now ongoing.

These data were corroborated by another trial performed by a subset of the investigators from the Sarcoma Group of the European Organization for the Research and Treatment of Cancer (EORTC), also reported at the plenary session of the American Society of Clinical Oncology in 2001 [24]. In this phase-I dose escalation study, 40 patients were entered, 36 of whom had GIST. Doses ranged from 400 to 1000 mg daily, with unacceptable toxicities

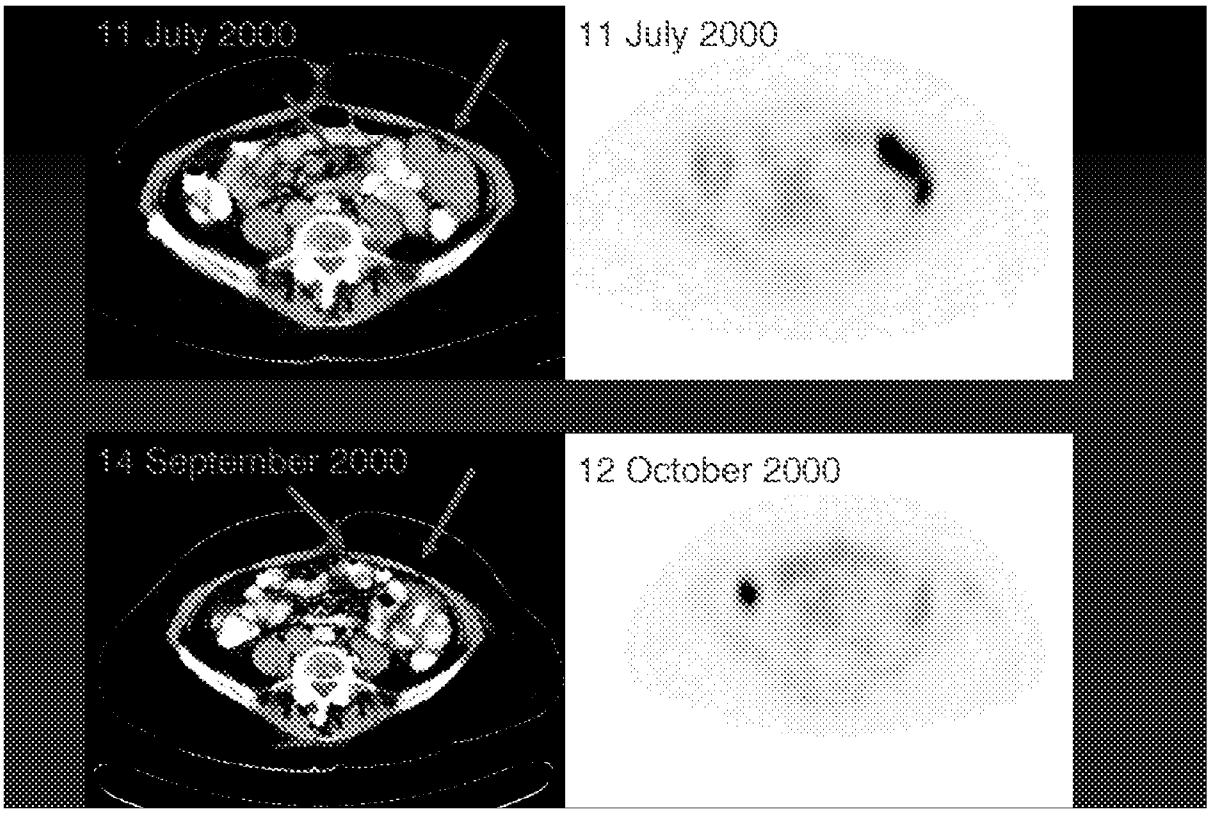

Fig. 2b. Correlative CT and PET scan responses noted in a patient with widely metastatic GIST. This patient has evidence of objective response on the serial CT scans (left side of figure), and the response is correlated with the decrease in ^{18}FDG-avidity by the tumor sites (see serial PET scans on right side of figure). The right-sided abdominal uptake on the follow-up scan is physiologic bowel uptake. This patient has continued to enjoy objective disease response more than 2 years after initiation of therapy with imatinib.

reported at the highest dose level, consisting mainly of edema (including third-spacing of fluids with dyspnea), nausea and vomiting. Of the 36 patients with GIST, 19 exhibited objective partial responses (53%) while another 13 had stable disease (36%). These results from the European multicenter study were remarkably consistent with the outcomes observed in the larger US-Finland trial noted above.

4. Summary and conclusions

The story of imatinib in GIST represents a paradigm of molecular understanding leading to improved diagnosis and, ultimately, to an effective and novel therapy targeting the Achilles heel of the cancer. The landmark work of Hirota and colleagues first identified the genetic and molecular etiology of GIST, uncovering specific and consistent gain-of-function mutations in the c-*kit* gene encoding the KIT receptor tyrosine kinase [11]. Genotyping of the c-*kit* gene with a variety of techniques has confirmed the high prevalence of mutations in this gene and has identified mutations in exon 11 (and, to a lesser extent, exon 9) as the predominant mutational sites [1,11–13]. although other loci encoding the juxtamembrane, extracellular and kinase domains have been reported as well [13,25–27]. All of these mutations have been associated with ligand-independent activation (phosphorylation) of the KIT tyrosine kinase, leading to subsequent uncontrolled cellular proliferation.

Unresectable or metastatic GISTs have traditionally exhibited a dynamic clinical course, with no evidence of benefit from any standard cytotoxic chemotherapy and an inevitably fatal outcome. No specific histologic criteria have been identified to predict accurately the clinical behavior of respectable primary GIST, although several features are considered suggestive of predilection towards a malignant course with subsequent recurrence and metastasis. These adverse prognostic features include larger tumor size (>5 cm), higher mitotic activity (>1–5 per 10 high-powered field) and locoregional infiltration or frank metastases at presentation [6]. The identification of KIT activation as an apparent early event in GIST pathogenesis led to the search for a new type of therapeutic compound to serve as a "KIT inhibitor" and to interfere with the autophosphorylation related to specific activating mutations, thereby inhibiting malignant tissue growth [28]. Clarification of the genetic etiology of GIST and the role of KIT mutations, therefore, has enabled not only improved diagnosis and differentiation of GIST from other mesenchymal

neoplasms, but has been key in identifying new targeted strategies for therapeutic intervention.

Imatinib mesylate (formerly known as STI571) is a selective inhibitor of certain tyrosine kinases that was first recognized as a potent blocker of the oncogenic Bcr-Abl kinase responsible for chronic myelogenous leukemia. Subsequently, imatinib was found to inhibit the KIT receptor tyrosine kinase that is crucial to the pathogenesis of GIST. Putting this finding to clinical use, Joensuu *et al.* described the exceptional rapid and sustained response of GIST in a patient with far-advanced, rapidly progressive, chemotherapy-resistant disease [21]. Based on the strong scientific and mechanistic rationale for KIT inhibition and the promising experience in that first GIST patient, our collaborative research team undertook a large multicenter trial to explore more fully the worth of imatinib in the treatment of metastatic or unresectable GIST. Our results show that the targeted treatment of GIST with imatinib produces major objective clinical responses in the majority of patients [22]. The rapid regression noted in many patients has been striking, in view of the traditionally chemotherapy-resistant nature of GIST. These successes were particularly exciting given that improvements have occurred even in patients with far-advanced, bulky disease as well as in patients who had previously failed multiple courses of conventional cytotoxic chemotherapies.

In summary, the potential to benefit patients with GIST, a disease that was previously untreatable with any available systemic therapy, has been greatly advanced by the knowledge of the molecular pathophysiology of this disease and the availability of imatinib, a well-tolerated agent that can inhibit the mutated signaling pathways in GIST. Molecularly targeted therapy with imatinib — a selective inhibitor of the KIT receptor tyrosine kinase — has been shown to successfully block the proliferation and growth of GIST tumor cells in patients uncontrolled with standard chemotherapies. It is the first (and currently the only) effective systemic therapy for patients with unresectable GIST. Imatinib therapy can halt and reverse the growth of GISTs in the majority of treated patients and does so with an acceptable safety profile. Furthermore, our understanding of its mechanism of action is a model for further research on signal transduction in the pathogenesis of cancer. Although resistance to single agent therapy is distressingly common in oncology, the durability of the responses to imatinib in GIST is highly encouraging, and the analysis of potential resistance mechanisms will likely lead to even more sophisticated options for therapy in the future. Combinations utilizing targeted signaling inhibitors are clearly destined for use as alternatives or additions to standard treatment regimens in cancer medicine. Other strategies are just beginning to be explored, such as the use of imatinib earlier the in course of GIST, and adjuvant therapy after definitive surgical resection of early-stage disease. Integration of signal transduction inhibitors into the armamentarium of cancer therapeutics will continue based on this important paradigm of GIST. It is a model that will be informative for the development of other targeted signal transduction inhibitors in cancer.

References

[1] Miettinen M, Lasota J. Gastrointestinal stromal tumors: definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. *Virchows Arch* 2001; **438**: 1–12.

[2] Graadt van Roggen JF, van Velthuysen ML, Hogendoorn PC. The histopathological differential diagnosis of gastrointesting stromal tumours. *J Clin Pathol* 2001; **54**: 96–102.

[3] DeMatteo RP, Lewis JJ, Leung D, *et al*. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival.*Ann Surg* 2000; **231**: 51–58.

[4] Berman J, O'Leary TJ. Gastrointestinal stromal tumor workshop. *Hum Pathol* 2001; **32**: 578–582.

[5] Goss GA, Merriam P, Manola J, Singer S, Fletcher CD, Demetri GD. Clinical and pathological characteristics of gastrointestinal stromal tumors (GIST). *Proc ASCO* 2000; **19**: 559a and manuscript submitted.

[6] Fletcher CDM, Berman JJ, Corless C, *et al*. Diagnosis of GISTs: A consensus approach. *Hum Pathol* 2002: in press.

[7] Walker P, Dvorsk AM. Gastrointestinal autonomic nerve (GAN) tumor: ultrastructural evidence for a newly recognized entity. *Arch Pathol Lab Med* 1986; **110**: 309–316.

[8] Kluppel M, Huizinga JD, Malysz J, Bernstein A. Developmental origin and Kit-dependent development of the interstitial cells of Cajal in the mammalian small intestine. *Dev Dyn* 1998; **211**: 60–71.

[9] Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol* 1998; **153**: 2008–2011.

[10] Sircar K, Hewlett BR, Huizinga JD, Chorneyko K, Berezin I, Riddell RH. Interstitial cells of Cajal as precursors of gastrointestinal stromal tumors. *Am J Surg Pathol* 1999; **23**: 377–389.

[11] Hirota S, Isozaki K, Moriyama Y, *et al*. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 1998; **279**: 577–580.

[12] Rubin BP, Singer S, Tsao C, *et al*. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. *Cancer Res* 2001; **61**: 8118–8121.

[13] Lux ML, Rubin BP, Blasé TL, *et al*. Kit extracellular and kinase domain mutations in gastrointestinal stromal tumors. *Am J Pathol* 2000; **156**: 791–795.

[14] Tuveson DA, Willis NA, Jacks T, *et al*. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene* 2001; **20**: 5054–5058.

[15] Nishida T, Hirota S, Taniguchi M, *et al*. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. *Nat Genet* 1998; **19**: 323–324.

[16] Druker BJ, Tamura S, Buchdunger E, *et al*. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. *Nat Med* 1996; **2**: 561–566.

[17] Buchdunger E, Zimmermann J, Mett H, *et al*. Alteration of the Abl protein-tyrosine kinase in vitro and in vivo by a 2-phenylaminopyrimidine derivative. *Cancer Res* 1996; **56**: 100–104.

[18] Carroll M, Ohno-Jones S, Tamura S, *et al*. 57148, a tyrosine kinase inhibitor, inhibits the growth of cells expressing BCR-ABL, TEL-ABL, and TEL-PDGFR fusion proteins. *Blood* 1997; **90**: 4947–4952.

[19] Druker BJ, Talpaz M, Resta DJ, *et al*. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic

myeloid leukemia. *N Engl J Med* 2001; **344**: 1031–1037.
[20] Heinrich MC, Griffith DJ, Druker BJ, *et al*. Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor. *Blood* 2000; **95**: 925–932.
[21] Joensuu H, Roberts PJ, Sarlomo-Rikala M, *et al*. Effect of the tyrosine kinase inhibitor STI571 in a patient with a metastatic gastrointestinal stromal tumor. *N Engl J Med* 2001; **344**: 1052–1056 [brief report].
[22] Demetri GD, Von Mehren M, Blanke CD, *et al*. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med* 2002; **347**: 472–480.
[23] Van den Abbeele A, for the GIST Collaborative PET Study Group. F18-FDG-PET Provides Early Evidence of Biological Response to STI571 in Patients with Malignant Gastrointestinal Stromal Tumors (GIST). *Proc ASCO* 2001; **20**: abstract 1444.
[24] Van Oosterom AT, Judson I, Verweij J, *et al*. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal tumors: a phase I study. *Lancet* 2001; **358**: 1421–1423.
[25] Nakahara M, Isozaki K, Hirota S, *et al*. A novel gain-of-function mutation of c-kit gene in gastrointestinal stromal tumors. *Gastroenterol* 1998; **115**: 1090–1095.
[26] Kitamura Y, Hirota S, Nishida T. Molecular pathology of c-kit proto-oncogene and development of gastrointestinal stromal tumors. *Ann Chir Gyn* 1998; **87**: 282–286.
[27] Pidhorecky I, Cheney RT, Kraybill WG, Gibbs JF. Gastrointestinal stromal tumors: current diagnosis, biologic behavior, and management. *Ann Surg Oncol* 2000; **7**: 705–712.
[28] Longley BJ, Reguera MJ, Ma Y. Classes of c-KIT activating mutations: proposed mechanisms of action and implications for disease classification and therapy. *Leuk Res* 2001; **25**: 571–576.