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Drug Insight: gastrointestinal stromal tumors (GIST)—the solid tumor model for cancer-specific treatment

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SUMMARY

We are living in an exciting era in the treatment of cancer, using drugs that target specific proteins rather than agents that cause more general cytotoxic effects. The identification of proteins and signal transduction pathways that play crucial roles in the pathogenesis of cancer has allowed treatments to be designed that target these tumor-driven events. Gastrointestinal stromal tumors (GIST) are rare mesenchymal tumors and were among the first solid tumor types for which such a novel treatment (in this case imatinib) became available. The tyrosine kinase inhibitor imatinib targets the human KIT receptor and the platelet-derived growth factor receptor-α. This drug exhibits impressive antitumor effects against GIST and has become the first-line therapy for advanced disease. Major insights into the mechanism of action of this drug, drug resistance, and patient management issues have been gleaned. Additionally, new drugs developed for the treatment of GIST have been identified. As a consequence, lessons learned from GIST are widely applicable to other tumor entities, thereby rendering GIST the paradigm of solid tumors treated with tyrosine kinase inhibitors. This Review discusses the pathogenesis of GIST, treatment strategies, mechanisms accounting for drug resistance, and potential future perspectives.

KEYWORDS GIST, imatinib, mechanism, resistance, prognostic factors

REVIEW CRITERIA

Data for this review were obtained by searching the PubMed database and the Proceedings of the Annual Meetings of the American Society of Clinical Oncology (ASCO) website: www.asco.org. No date limitations were applied for these searches. Both databases were searched by using the terms "gastrointestinal stromal tumors", "GIST", "imatinib", and "STI-571". Full articles were obtained and the references were checked for additional material.

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Received 8 June 2007 **Accepted** 17 September 2007
www.nature.com/clinicalpractice
doi:10.1038/ncponc1037

INTRODUCTION

The past few decades have brought us major developments in molecular and cellular biology, leading to a better understanding of numerous cellular processes and their dysregulation in cancer. As a consequence, treatments with greater specificity for targeting particular components of the cancer cell have become possible. Nonetheless, in order to understand the complexity of all events involved in cancer induction, we tend to oversimplify the full picture, which has unfortunately given rise to the term targeted therapy. In essence, every drug has a target, and even cytotoxic therapy could be classified as targeted therapy. Since the aim of cancer treatment is to avoid side effects and to be specific to the tumor, it might be better to refer to certain agents as cancer-(cell-)specific therapy rather than targeted therapy. It is important to recognize that cancer is a multifaceted disease and that we should consider targeting not only the cancer cell itself, but also its direct cellular environment.

In recent years, numerous cancer-(cell-) specific therapies have been introduced. One of the first solid tumors for which this kind of treatment became available is gastrointestinal stromal tumor (GIST). GIST is one component in a group of soft-tissue sarcomas that encompasses over 40 different subtypes. In contrast to other subtypes of soft-tissue sarcoma in the group, the malignant behavior of GIST is driven by constitutive activation of the KIT receptor or the platelet-derived growth factor receptor-α (PDGFRA).[1,2] The development of the tyrosine kinase inhibitor (TKI) imatinib, which targets both KIT and PDGFRA, considerably improved the outcome of patients with advanced GIST. Major achievements have been made in the understanding of mechanisms underlying sensitivity and resistance to imatinib. This understanding has already resulted in the development of novel treatment approaches and has enabled treatments to be individualized to the patient, thereby avoiding overtreatment and undertreatment. As lessons learned from GIST can be extended to other

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tumor types, GIST has become the paradigm of solid tumors that are treated with TKIs. This Review discusses the pathogenesis of GIST, treatment strategies, drug resistance mechanisms, and potential future perspectives.

EPIDEMIOLOGY OF GIST AND PRESENTING SYMPTOMS

GIST is a rare mesenchymal disorder of the gastrointestinal tract with an annual, worldwide incidence of approximately 1.5 per 100,000 persons. It occurs most frequently in adults aged 50–70 years and has an equal gender distribution.[1] GIST most likely develops from precursors of the cells of Cajal, a population of cells in the gastrointestinal tract with pacemaker activity.[1] The stomach is the most frequent primary site of GIST, comprising approximately 65% of cases. Other primary sites are the small intestine (25%) and, less commonly, the colon, esophagus, rectum, and peritoneum. In patients presenting with metastatic disease, metastases are mainly found in the intraperitoneal cavity and the liver. Other sites involved include the lungs, lymph nodes, subcutis, and bones, but occurrences at all these sites account for less than 5% of total cases and are seen predominantly in patients with widespread disease.[1]

PATHOGENESIS OF GIST

Since the late 1990s, insight into the pathogenesis of GIST has improved tremendously. The pivotal finding was that more than 90% of all GISTs showed overexpression of the KIT receptor, also called CD117 or stem cell factor receptor.[3] This finding prompted further research into the role of KIT, which revealed that GISTs frequently harbor gain-of-function mutations in the c-*KIT* gene.[3] In normal cells activation of the receptor only occurs after binding of the corresponding ligand—the stem cell factor in the case of c-KIT—while gain-of-function mutations result in a constitutively active receptor without the normally required ligand binding. This constitutive activation results in stimulation of numerous downstream signal transduction pathways including the RAS/RAF/ERK, JAK/STAT, PI3K/Akt/mTOR, and SRC kinase pathways,[2] and ultimately results in malignancy.

The gain-of-function mutations in the c-*KIT* gene can occur at various sites. Exon 11 of the c-*KIT* gene is mutated in about 70% of the cases; other mutations are found in exons 9, 13, and 17, with a frequency of 1–15%.[4–6] The different c-*KIT* mutations are not randomly distributed in the gastrointestinal tract but appear to be site-dependent. The vast majority of GIST lesions arising in the stomach harbor an exon-11 mutation, while exon-9 mutations are predominantly encountered in primary tumors of the small intestine.[7]

Not all GISTs express c-*KIT* mutations. In tumors without mutated c-*KIT*, activating mutations in the *PDGFRA* gene are frequently demonstrated to occur. In total, 3–5% of all GISTs harbor a mutated *PDGFRA*,[8] which induces activation of the same signal transduction pathways as gain-of-function mutations in c-*KIT*. In approximately 5–10% of tumors, neither mutations in c-*KIT* nor *PDGFRA* can be found. In such cases, phosphorylation of KIT is seen,[9] so it is likely that other kinases yet to be identified are involved in tumor development.

MANAGEMENT OF LOCALIZED DISEASE

In general, thinking suggests that all GISTs should be deemed malignant regardless of tumor size or mitotic index.[10] For localized disease, radical surgical resection is the mainstay of treatment; however, approximately 50% of the patients treated surgically relapse within 5 years.[10–12] Several prognostic factors for relapse after surgical resection have been identified, with tumor size and mitotic rate being the most important.[10–13] Using these two prognostic factors, a system for classifying patients according to their risk of relapse has been established.[10] This classification system has been externally validated and the various risk groups seem to be associated with overall survival, at least in the preimatinib era.[11,13] In addition to tumor size and mitotic index, several other prognostic factors for relapse after resection of localized GIST have been suggested. These include primary site, the presence of a c-*KIT* mutation and the exact site of mutation (Box 1).[13–22]

At present there is no established adjuvant treatment for GIST, but several ongoing studies have explored imatinib in the adjuvant setting. One study randomized patients to receive imatinib or placebo, but the trial was prematurely terminated because of a better relapse-free rate at 1 year among patients in the imatinib-treated group.[23]As adjuvant treatments aim to prevent a proportion of patients from ever relapsing, the most important end point of adjuvant studies is overall survival. Whether an improved progression-free rate at 1 year translates into an

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Box 1 Factors that have prognostic value for patients who relapse after resection of localized GIST.

Established prognostic factors

- Tumor size
- Mitotic index
- Primary site
- Microvessel density
- Alterations in DNA copy numbers
- Loss of p16 protein
- Extent of tumor necrosis
- Methylation of E-cadherin
- Presence of a c-*KIT* mutation
- Mutational site in c-*KIT*

Factors that are not prognostic

- Microscopic margins of resection
- Gender
- Age

overall survival benefit is unknown, because it is not known whether delaying imatinib treatment in patients with proven evidence of metastases can yield a similar survival to early treatment immediately after surgery. Therefore, the exact value of imatinib in the adjuvant setting can only be established in studies with overall survival as the primary end point. Once these studies have been completed, a potential benefit for a proportion of patients should be carefully weighed against the treatment-induced toxicity to which the whole group is exposed.

MANAGEMENT OF ADVANCED DISEASE

GIST is considered one of the most chemotherapy-resistant soft-tissue sarcoma subtypes.[24] Doxorubicin-based chemotherapy is the standard systemic treatment for soft-tissue sarcomas, and yields a 2-year survival rate of only 20% in patients with GIST.[25] The introduction of TKIs that target the KIT and PDGFRA receptors was, therefore, a major breakthrough. TKIs are small compounds that can specifically block the function of proteins that have tyrosine kinase activity.[26]

Imatinib was the first clinically available TKI that targets the KIT and PDGFRA kinases.[26] Given the dependency of GIST on the constitutive activity of KIT or PDGFRA, several studies were initiated that demonstrated the efficacy of imatinib in advanced disease.[25,27–29] Of all these studies, so far only one phase III study, coordinated by the European Organisation for Research and Treatment of Cancer (EORTC), has been published.[25] In a phase I study, the maximum tolerated dose of imatinib was 800 mg/day (given as two 400 mg doses)[27] and this was compared with 400 mg imatinib daily, which is the standard dose for treating chronic myeloid leukemia. A second randomized study with a similar design will soon be published. A meta-analysis of these two randomized studies, comprising data from 1,640 patients was reported.[30] Imatinib is highly active and has previously been shown to induce responses and sustained disease stability in 55% and 30% of the patients, respectively, with no differences in efficacy between 400 mg and 800 mg imatinib doses.[25] The median progression-free survival (PFS) in the meta-analysis was approximately 2 years, with a small but significant difference favoring the 800 mg dose (hazard ratio [HR] 0.89; $P = 0.041$).[30] Equivalent overall survival was observed in both arms,[25,30] with estimated median overall survival of approximately 5 years.[30,31] Treatment with imatinib should be continued until progressive disease or unacceptable toxic effects are seen. A study, in which patients' disease was controlled by imatinib, showed that treatment interruption yielded rapid disease progression in the majority of patients.[32]

Imatinib has a rather favorable toxicity profile compared with conventional chemotherapeutic agents. In a randomized trial, at doses of 400 mg, the reported grade 3–4 toxic effects were anemia (10.1%), neutropenia (4.6%), fatigue (8.3%), edema (4.2%), skin rash (2.8%), and bleeding (3.8%).[25] All these effects are more severe when imatinib is given at a dose of 800 mg. It has been suggested that the use of imatinib is also associated with the occurrence of cardiomyopathy.[33] Analysis of the EORTC database obtained from the large phase III study, however, revealed a cardiomyopathy incidence of 0.2% in imatinib-treated GIST patients, which is lower than the incidence in the general population.[34] Another analysis of data from the same database identified several predictive factors for the occurrence of the most frequent side effects.[35] Grade 3–4 anemia was independently related to imatinib dose and baseline hemoglobin, and grade 3–4 neutropenia was related to baseline levels of neutrophils and hemoglobin but not to imatinib dose. All nonhematological adverse events were related to dose and, additionally, to poor performance status (nausea and fatigue), female sex (edema, nausea,

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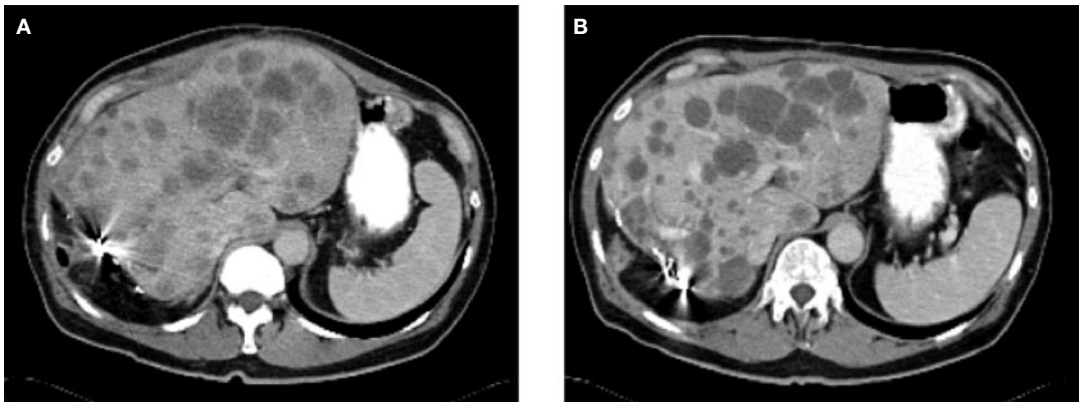

Figure 1 Imatinib-induced cystic alterations in hepatic metastases from a patient with GIST. (**A**) Before treatment. (**B**) After 10 weeks' treatment with 400 mg imatinib daily. All hepatic lesions with a solid appearance changed into cystic ones, indicating a favorable response to imatinib.

diarrhea), older age (edema, rash, fatigue), or a low tumor load (rash).[35] A risk calculator for the occurrence of several side effects, which uses these factors, has been developed.[36]

In cases of severe toxic effects, the imatinib dose can be reduced to 300 mg/day. This lower dose of imatinib seems to have equivalent efficacy to the standard 400 mg/day dose in terms of PFS, whereas patients treated with 200 mg/day imatinib dose do worse, although this observation is based on a small number of patients.[25] In view of these data, imatinib has become the first-line treatment for patients presenting with advanced GIST. Since the 800 mg dose causes more pronounced toxic effects but equivalent overall survival to the 400 mg dose, the latter is considered standard.

EVALUATION OF TUMOR RESPONSES

One of the major challenges in oncology is appropriate assessment of the antitumor activity of a given treatment at an early stage. For this purpose, standard classification systems such as the WHO and RECIST criteria, which are based on alterations in tumor size during treatment, are commonly used. Evidence is accumulating that these criteria are not the most appropriate tools with which to monitor imatinib-induced antitumor effects in patients with GIST. Patients who experience tumor shrinkage during imatinib treatment are clearly responding, but the situation is complex in cases where a patient shows stable or growing tumor lesions. Imatinib can induce solid tumor masses to become more viscous, yielding a cystic appearance on radiological assessment (Figure 1).[37] Such cystic lesions occasionally are larger than the initial solid tumor, and a size increase of this kind correlates with the definition of progressive disease according to standard criteria.[38] Histological examination has demonstrated that such cystic lesions largely consist of debris, and that cystic changes are a sign of response.[39] Lesions that increase in size but have a cystic appearance should not, therefore, be judged a sign of progression. By contrast, a solid mass developing in a cystic lesion, while the total size of the lesion remains unchanged, should be regarded as a sign of progressive disease. Given this complexity of response evaluation in imatinib-treated patients with GIST, only physicians aware of these phenomena should perform tumor evaluations. In addition, an alternative response evaluation for patients with GIST treated with imatinib has been suggested, based on changes in tumor size and density (Box 2).[40,41] Using this method, patients showing a response at 2 months have a better PFS than patients who do not show such a response. By contrast, there was no difference in PFS between responding and nonresponding patients when the RECIST criteria were applied.[40,41] Although the introduction of this alternative classification system will hinder comparisons with previous studies in which these criteria were not applied, and the application of this alternative classification system requires special CT equipment and dedicated personnel, it provides a potentially attractive tool for the early evaluation of antitumor effects.

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Box 2 Response criteria for patients with GIST treated with imatinib according to Choi *et al*.[40]

Complete response
Disappearance of all lesions and no new lesions

Partial response
≥10% decrease in tumor size (total sum of target lesions' longest diameters) and ≥15% decrease in tumor density (Hounsfield units). No new lesions. No progression of nontarget lesions

Stable disease
Not meeting criteria for any of complete or partial response or progressive disease

Progressive disease
≥10% increase in tumor size (total sum of target lesions' longest diameters) and absence of ≥15% decrease in tumor density (Hounsfield units)

New lesions
New intratumoral lesions or increase in size of existing intratumoral lesions

MECHANISMS CONFERRING RESISTANCE TO IMATINIB

A remarkable finding was observed in a randomized study exploring whether imatinib treatment could be interrupted in patients with controlled advanced disease. The study showed that a small subset of patients had durable progression-free periods beyond 1 year after cessation of imatinib.[32] This finding is consistent with our own experience, whereby a few patients who had to stop imatinib because of uncontrollable severe toxic effects remained progression-free for several years (S Sleijfer, unpublished data). Except for these very rare cases, it is generally thought that in time all patients will experience progressive disease with imatinib treatment. In recent years, progress has been made in understanding the molecular mechanisms accounting for progression, which has yielded predictive factors for treatment outcomes. Two patterns of progression with different underlying mechanisms have been identified.[42] The first is early progression occurring within 3–6 months after treatment initiation in patients who never show a response to or sustained disease stabilization while taking imatinib. This pattern is seen in 15–20% of the patients.[42] The second type of progression is late progression, which is due to resistance mechanisms that tumor cells acquire under the selective pressure of imatinib treatment. Late progression becomes apparent 6 months or more after imatinib treatment in patients who initially seem to benefit.[42]

Early tumor progression is primarily caused by resistance mechanisms present in the tumor cell prior to treatment start—so-called intrinsic or primary resistance. By far the most important resistance mechanism discovered to date is the initial mutational status of c-*KIT* and *PDGFRA*.[4,43,44] Several gain-of-function mutations are responsible for GIST and these mutations differ in their sensitivity to imatinib. This variance is reflected by the observation that the vast majority of patients with early progression after imatinib treatment have tumors with a c-*KIT* mutation in exon 9 (deletions as well as missense point mutations), a missense D842V mutation in *PDGFRA*, or a wild-type genotype with no identified mutations in both c-*KIT* and *PDFGRA*.[4,43,44] Another indication that different sensitivities exist among the various mutants is the phenomenon that patients with tumors bearing c-*KIT* exon-9 mutations had a much better PFS with the 800 mg imatinib dose than with the standard 400 mg dose. There was no difference in the efficacy between the 400 mg and 800 mg imatinib doses in patients with other mutations.[30,44] It should be noted, however, that some patients with exon-9-mutated tumors who received the standard dose achieved durable progression-free periods,[30,44] which underscores that mutational status is not the only factor that determines sensitivity to imatinib. The precise reason why patients with c-*KIT* exon-9-mutated tumors respond less well to imatinib than do patients harboring exon-11 mutations is unclear; imatinib exhibits similar *in vitro* inhibitory effects against tumors with c-*KIT* exon-9 and exon-11 mutations.[4] Another mechanism that might lead to progression shortly after imatinib initiation is the development of new secondary mutations in c-*KIT*, which have been found in approximately 10% of patients with early disease progression.[43]

Secondary mutations in c-*KIT*, which develop in addition to the initial mutations, occur not only in the context of early progression, but also in late progression. In fact, secondary mutations are the most frequently observed mechanisms of resistance to imatinib, and are found in 50–70% of the patients showing late progression.[6,43,45,46] These mutations change the conformation of the ATP-binding pocket

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Table 1 Acquired resistance mechanisms to imatinib that result in late disease progression.

Resistance mechanism	Result
Secondary mutations in c-*KIT*	Altered conformation of KIT, hampering binding of imatinib
Activation of driving factors other than imatinib-sensitive ones	Bypass of inhibitory effects of imatinib
Genomic amplification and overexpression of c-*KIT*	KIT outweighs inhibitory capacity of imatinib
Overexpression of drug-efflux pumps (P-glycoprotein and breast cancer resistance protein)	Decreased intratumoral imatinib levels
High blood level of α_1-acid glycoprotein	Binds imatinib and inactivates it
Increased clearance of imatinib over time (due to unknown mechanism)	Decreasing systemic imatinib levels

of the tyrosine kinase, thereby interfering with the binding of imatinib; however, the function of the tyrosine kinase remains unaffected because ATP is still able to bind to the receptor.[47] The most common secondary c-*KIT* mutations involve exons other than those initially affected, such as 13, 14, 17, and 18.[6,43,45,46] Secondary mutations in exon 18 of the *PDGFRA* gene can also give rise to imatinib resistance.[43] The incidence of secondary mutations is associated with the initial mutational site. In patients with late progression, secondary mutations were found in approximately 60% of the patients with an initial exon-11 mutation, but at the lower frequency of 20% in those who primarily expressed an exon-9 mutation.[6,46] Importantly, several different secondary mutations can be identified in distinct GIST lesions in patients whose tumors progressed on imatinib treatment.[43,45,46]

Another mechanism that is likely to account for acquired resistance is activation of tyrosine-kinase-dependent factors other than KIT and PDGFRA. Activation of these factors, which remain to be identified, results in activation of the same transduction pathways as those activated by KIT or PDGFRA, thereby bypassing the inhibitory effects of imatinib.[48] Several other resistance mechanisms yielding late progression have been suggested (Table 1), but their clinical relevance has not been elucidated.[43,46,49–54] Although it is unlikely that the whole spectrum of resistance mechanisms has been elucidated, knowledge about the mechanisms determining sensitivity and resistance to imatinib has increased rapidly in recent years. This knowledge is of great importance as it forms the foundation for individualization of treatment and for the development of novel treatment approaches.

APPROACHES FOR MANAGING IMATINIB-RESISTANT DISEASE

Insights into resistance mechanisms have allowed several approaches to be developed to monitor patients showing progression during imatinib treatment. Dose escalation to 800 mg imatinib in patients with progressive disease during treatment with imatinib at 400 mg is one such approach.[55] The rationale for this approach is based on observations of a greater sensitivity of some initial primary c-*KIT* mutations to higher imatinib concentrations, in particular exon-9-mutated tumors,[44] and increased imatinib clearance over time.[54] This strategy allows 18% of the patients to be progression-free 1 year after dose escalation.[55] The success of this approach depends on the primary mutational status of the tumor. Patients with a primary exon-9-mutated c-*KIT* or wild-type genotype benefit more often from this approach than GIST patients with an initial exon-11 mutation, with 55–80% versus 7% of cases achieving a favorable outcome.[44] The reason for these outcome differences is unknown, but the more frequent occurrence of imatinib-resistant secondary mutations in exon-11-mutated tumors might contribute.[6,46]

Following the development of imatinib, numerous other TKIs have become available.[56–59] Though several TKIs target KIT, they differ in their activity against the diverse *c-KIT* mutations and some exhibit inhibitory effects against imatinib-resistant mutants.[56] In addition, many of these compounds inhibit a broader range of tyrosine kinases than imatinib and are thereby more likely to exert inhibitory effects against tumors that are imatinib resistant via activation of kinases other than KIT or PDGFRA.[26] Several agents possess antitumor activity in

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Table 2 KIT targeting tyrosine kinase inhibitors assessed in GIST and their main targets.

Agent	Targets
Agents with proven benefit in GIST	
Imatinib (STI-571)	KIT, PDGFRA/B, Abl, Flt-3, LCK
Sunitinib (SU11248)	KIT, PDGFRA/B, VEGFR1-3, RET, CSF-1R
Agents currently being explored in the clinical setting	
Vatalanib (PTK787/ZK222584)	KIT, PDGFRA/B, VEGFR1–3
Nilotinib (AMN107)	KIT, PDGFRA/B, Abl
Sorafenib (BAY 43-9006)	KIT, PDGFRB, VEGFR2/3, Raf, Flt-3, RET
Masatinib (AB1010)	KIT, PDGFR, FGFR3
AMG706	KIT, PDGFRA/B, VEGFR1–3, RET
AZD2171	KIT, PDGFRA/B, VEGFR1–3, Flt-3
PKC412	KIT, PDGFRA/B, VEGFR2

imatinib-naive[57] and imatinib-resistant patients with GIST (Table 2).[59–61] Of these agents, only sunitinib has been tested in a randomized study in this disease setting.[61] Sunitinib inhibits KIT, PDGFRA, and also targets the VEGF receptor RET and other proteins,[26] which allows this agent to have effects directed towards the tumor environment. In a placebo-controlled, double-blind trial, sunitinib produced increased median time to progression (27.3 weeks versus 6.4 weeks; HR 0.33; 95% CI 0.23–0.47) and overall survival (HR 0.49; 95% CI 0.29–0.83). The response rate to sunitinib was rather low at 7%.[61] A good response to sunitinib is indicated, especially in patients who have a primary exon-9 c-*KIT* mutation. Furthermore, patients with tumors harboring a secondary mutation in exon 13 or exon 14 of c-*KIT* have a longer PFS than patients with an exon-17-mutated or exon-18-mutated tumor.[62]

Of major concern with respect to resistance in GIST is the heterogeneity of secondary c-*KIT* mutations that can occur within one patient.[43,45] As a consequence, systemic treatments should be multitargeted rather than single-targeted. Simultaneous inhibition of multiple targets can be achieved by either TKI agents that inhibit a broad spectrum of kinases or by combining different targeted therapies. Several combinations are presently in early clinical testing and including combinations of imatinib with other agents that target KIT such as PKC412 and nilotinib,[59,60] and combinations of imatinib with inhibitors of downstream factors involved in KIT-driven transduction pathways, such as RAD001 (everolimus), an mTOR inhibitor.[63] Furthermore, although GISTs are resistant to conventional chemotherapeutic drugs, there is a clear rationale for testing combinations consisting of chemotherapy with KIT inhibitors in patients with imatinib-resistant GIST. The exact reasons for the chemoresistance of GIST are unclear but it is likely that KIT-mediated mechanisms contribute. Bcl-2 and VEGF are both regulated by KIT[64–66] and are frequently overexpressed in GISTs, and such overexpression is known to confer resistance to chemotherapeutic agents. Compounds that inhibit KIT—preferably the VEGF receptor—might sensitize tumor cells to cytotoxic drugs. Another potential strategy for imatinib-resistant GIST is the application of heat-shock protein (HSP)-90 inhibitors. *In vitro* inhibition of HSP-90 induces degradation of KIT regardless of the exact mutational status.[67] In a phase I study of IPI-504, an HSP-90 inhibitor, signs of antitumor activity were seen in GIST patients who were heavily pretreated with TKIs, including imatinib and sunitinib.[68]

Thus, several potential systemic treatment options currently exist for patients whose tumors progress during imatinib treatment. Based on the insights into the mechanisms underlying sensitivity to TKIs, it is very likely that the number of treatment options for patients with GIST will expand. Before such novel treatment strategies can be widely applied, however, carefully designed studies are warranted in which patients are stratified according to the different underlying resistance mechanisms.

OPPORTUNITIES FOR INDIVIDUALIZATION OF TREATMENT

The development of novel treatment strategies coupled with the ongoing elucidation of prognostic and predictive factors provides several options for individualizing treatment for GIST patients (Box 3). Tailoring of therapy can relate to follow-up issues as well as the application of the type of systemic treatment (Table 2). For patients with localized disease who have undergone a radical resection, follow-up might be guided by factors prognostic of relapse with more-stringent follow-up evaluations possibly being suitable for patients with unfavorable tumor characteristics. When designing studies in patients with localized disease, prognostic factors might also be used to stratify patients.

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For example, randomized studies exploring the value of adjuvant imatinib in patients at high risk of developing a relapse are ongoing. In the setting of advanced disease, tumor characteristics may be used to guide follow-up. More-frequent tumor evaluations can be considered for patients with advanced disease whose tumors exhibit characteristics predictive of a poor outcome to imatinib.[4,6,43,44]

Predictive factors, in particular the primary mutational status, are likely to affect systemic treatment. Patients whose tumors bear an exon-9 mutation have a longer PFS when treated with 800 mg imatinib daily rather than 400 mg (median PFS 6 versus 18 months; $P = 0.017$);[30] however, this response does not translate into better overall survival.[30] The lack of overall survival benefit noted using the higher imatinib dose despite an improved PFS is likely to be due to antitumor activity of subsequent available treatment strategies for patients showing disease progression with 400 mg imatinib, including dose escalation to 800 mg and sunitinib. Such subsequent regimens are likely to exhibit antitumor activity in a substantial number of patients who initially progress while taking 400 mg imatinib. As a result, the overall survival of this group improves and becomes similar to that for the patients receiving 800 mg imatinib. Thus, despite notable toxic effects being associated with imatinib doses of 800 mg, the considerable improvement in PFS might mean that 800 mg doses can still be considered for those patients at low risk of developing severe imatinib-induced toxic effects (a risk calculator is available at www.eortc.be/tools/imatinibtoxicity).[36] Furthermore, dose escalation can be considered for patients treated with 400 mg imatinib who have progressive disease and who have an initial exon-9-mutated c-*KIT* or wild-type genotype. Conversely, patients with an exon-11 mutation in c-*KIT* have a much lower likelihood of benefiting from dose escalation of imatinib.[44]

The presence of certain predictive factors might help determine the exact TKI to be used. For example, sunitinib is thought to potently inhibit tumors with *c-KIT* exon-9 mutations, whereas imatinib is less active against this subtype.[62] It should be noted, however, that there is a lack of randomized data showing that sunitinib or other TKIs are better than imatinib in patients with c-*KIT* exon-9 mutations bearing tumors in terms of survival outcomes balanced against the toxic effects. Determination of the exact GIST genotype is probably the most important factor for decisions concerning individualization of treatment in terms of deciding follow-up schemes and when to start systemic treatment. No data are, however, yet available from randomized studies to show that tailoring imatinib treatment translates into better clinical outcome.

Box 3 Potential opportunities for individualizing management in patients with GIST.

Localized disease

- More stringent follow-up for patients with poor prognostic features after resection
- Exploration of adjuvant systemic treatment in patients at intermediate or high risk of relapse after resection
- Type of adjuvant systemic treatment guided by the presence of predictive factors

Advanced disease

- More stringent follow-up for patients with poor predictive features during systemic treatment
- Type of systemic treatment guided by the presence of predictive factors
- Dose of systemic treatment guided by the presence of predictive factors

CONCLUSIONS

GIST has not long been recognized as a disease driven by constant activation of factors such as KIT and PDGFRA. Nevertheless, in only a few years immense progress has been made in the understanding of the pathogenesis of GIST, the mechanisms of action of TKIs, and mechanisms conferring resistance to TKIs. On the basis of these insights, novel strategies have been designed for initial treatment as well as for patients with progressive disease. To prove that such novel approaches are indeed of additional benefit, adequately conducted clinical studies are warranted and also require close collaboration between different clinicians or centers. Although GIST itself is rare, lessons gathered from research on this disease will contribute substantially to a better understanding of the pathogenesis of other malignant diseases and their treatment with TKIs. Consequently, GIST has become a tumor type of paramount importance for oncology and the solid tumor model for cancer-(cell-)specific treatments with TKIs.

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KEY POINTS

- Improved insights into the molecular mechanisms that cause malignancy have been the foundation of the development of "cancer-(cell-)specific therapy" with tyrosine kinase inhibitors for the treatment of gastrointestinal stromal tumors (GIST)
- Understanding the mechanisms that confer resistance against tyrosine kinase inhibitors has yielded additional novel treatment strategies for GIST
- Elucidation of prognostic and predictive factors in GIST offers opportunities for individualizing patient treatment
- GIST has become the paradigm for the treatment of solid tumors with tyrosine kinase inhibitors

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Acknowledgments
This research was supported by the EC FP6 CONTICANET project (LSHC-CT-2005-018806) from the European Commission.

Competing interests
The authors declared no competing interests.

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