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Advances in the treatment of gastrointestinal stromal tumours

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Imatinib, a selective tyrosine kinase inhibitor, is currently the standard of care first-line treatment for unresectable or metastatic gastrointestinal stromal tumour (GIST), improving survival time and delaying disease progression in many patients. Nevertheless, primary and secondary (acquired) resistance to imatinib is a substantial problem in routine clinical practice. Sunitinib is an oral, multitargeted tyrosine kinase inhibitor that was approved for the treatment of imatinib-resistant or -intolerant GIST. In the pivotal phase III study, sunitinib provided substantial clinical benefits including disease control and superior survival versus placebo as second-line treatment. Treatment with sunitinib was reasonably well tolerated. The availability of sunitinib represents an important clinical advance in GIST management, providing physicians and patients with an effective therapy when resistance to imatinib develops.

Key words: GIST, imatinib, KIT, PDGFR, sunitinib

introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumour of the gastrointestinal (GI) tract, although they account for <1% of all GI tumours. Approximately 20%–30% of GISTs are high-risk/overtly malignant [1, 2]. The estimated incidence of GIST is 15 cases per million, and the median age at presentation is ~60 years [3]. Tumours are most commonly found in the stomach and small intestine [4], but can also occur in the colon and other parts of the GI tract. Patients usually present with non-specific abdominal pain and GI bleeding [4]. The primary indicators of prognosis for patients diagnosed with GIST are the size of the primary tumour and the mitotic rate [measured per 50 high-power fields (HPF)] [1]. Tumours that are >10 cm in size or have a mitotic rate of >5 per 50 HPF have a high risk of recurrence and metastatic spread and are associated with a poor prognosis.

Surgery forms the mainstay of treatment as the only curative modality. However, recurrence is common in high-risk tumours. The 5-year survival rate for GIST patients with primary disease who undergo surgical resection of their tumours was found to be 54% [5]. At the time of diagnosis, many patients with GIST already have metastatic disease; in a study of 200 patients with malignant GIST, approximately half were found to have metastasis at presentation [5]. Metastases are most frequently found in the liver and peritoneal cavity. Complete resection of liver metastasis has been shown to prolong survival in selected patients. However,

the median survival of patients with metastatic GIST remained ~19 months in this study [5].

The majority of GISTs carry *KIT* mutations that result in a constitutively activated form of KIT protein tyrosine kinase [3, 6, 7]. KIT plays a variety of roles in normal physiological and developmental functions. Relevant downstream pathways affected by KIT stimulation include proliferation and control of apoptosis [8]. A small proportion of GISTs are associated with mutations in *PDGFRA*, the gene encoding platelet-derived growth factor- α (PDGFR- α) [9]. Downstream activation targets of KIT associated with tumour progression are also activated by mutant forms of PDGFR- α in GIST [10].

The discovery of the molecular basis of GIST led to the investigation of agents that block KIT- and PDGFR-mediated signalling mechanisms for clinical treatment, the first of these being imatinib, originally developed for the treatment of chronic myeloid leukaemia, in which disease it inhibits the BCR-ABL fusion protein. This review will provide an overview of existing targeted treatment options for GIST, focusing on imatinib (Glivec®, Novartis Pharma AG) and sunitinib (SUTENT®, SU11248, Pfizer Inc.).

existing treatment options

In patients for whom curative surgery is not feasible, or who develop recurrent metastatic disease, the conventional chemotherapeutic agents used for the treatment of other sarcomas, such as doxorubicin and ifosfamide, are ineffective [8]. Radiotherapy is of limited value in the treatment of GIST owing to the sites of disease and the limit this places on the doses that can be employed. Techniques such as hepatic arterial embolisation and debulking surgery followed by i.p.

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chemotherapy have been investigated but are also of limited value [8].

imatinib

Imatinib was the first targeted therapy to be approved for the treatment of GIST. Imatinib inhibits several receptor tyrosine kinases including KIT and PDGFR- α and - β , and has become the treatment of choice for advanced GIST, substantially improving survival time and delaying disease progression in many patients.

In a pivotal, open-label, randomized, multicentre trial, 147 patients with advanced GIST were randomly assigned to receive either 400 or 600 mg imatinib daily [11]. Patients whose tumours progressed while receiving the 400-mg/day dose were permitted to increase their dose to 600 mg/day. A partial response (PR) to treatment was observed in 54% of patients, and tumour bulk was reduced by between 50% and 96%. A further 28% of patients achieved stable disease (SD) [11]. After a median follow-up of 24 weeks, the median duration of response had not been reached while median time to achieve an objective response was 13 weeks. Treatment with imatinib was generally well tolerated. Although all patients experienced adverse events, the majority were mild or moderate in severity. The most frequently observed adverse events were oedema (74%), nausea (52%), diarrhoea (45%), myalgia/musculoskeletal pain (40%), fatigue (34.7%), dermatitis/rash (31%), headache (26%) and abdominal pain (26%) [11].

The effect of increasing the dose of imatinib to 800 mg/day (400 mg twice daily) has been assessed in two phase III studies [12, 13]. In the European–Australasian study reported by Verweij *et al.* [13], 946 patients with advanced or metastatic GIST were randomly assigned to receive imatinib 400 mg either once or twice daily. Patients in the 400-mg group who showed disease progression were given the option of crossing over to the 800-mg group. At a median follow-up of 760 days, progression-free survival (PFS) was significantly longer in patients who received imatinib 400 mg twice daily compared with those who received only one daily dose (50% versus 56% had disease progression, respectively, $P = 0.026$; Figure 1A). Although both treatments were relatively well tolerated, more patients in the 800-mg group required dose reductions and treatment interruptions. Up to 7% of treatment interruptions were due to haematological toxicity (Table 1) [13]. In the second comparative study, no significant difference in PFS was reported after 2 years of treatment with imatinib 400 or 800 mg/day (50% versus 53%; $P > 0.05$) [12]. Patients with an initial dose of 400 mg/day who had disease progression were considered for crossover to 800 mg/day. Approximately 20% of patients who crossed over to the higher dose in the European Organization for Research and Treatment of Cancer study remained on treatment 12 months later but their remission status is unclear [14].

Despite its beneficial effects, resistance to imatinib is a substantial problem. In the study by Demetri *et al.* [11], 14% of patients suffered disease progression within the first 3 months, with 5% of patients showing evidence of imatinib resistance in the first 2 months of treatment. In the European–Australasian study, between 9% and 13% of patients showed

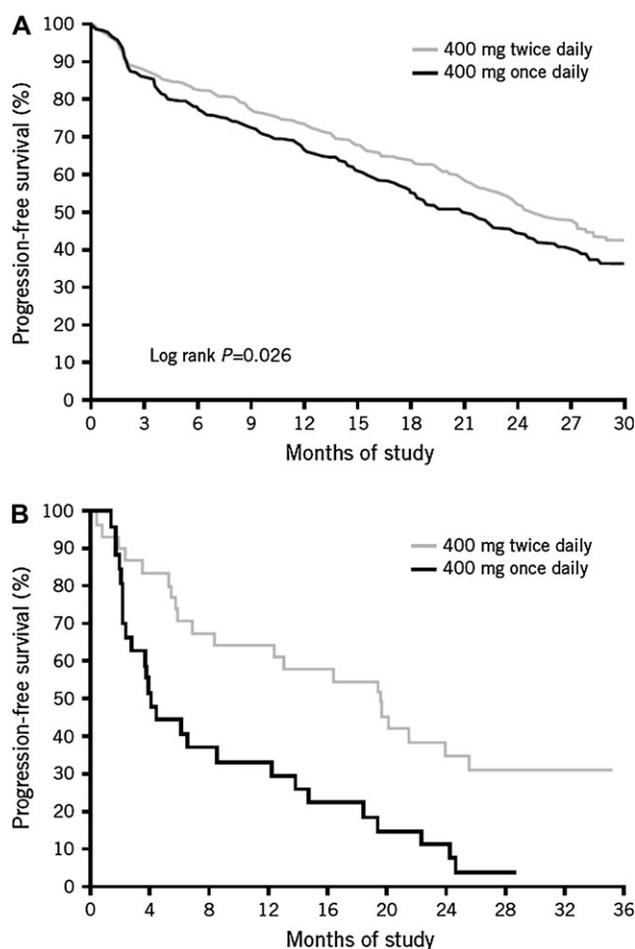


Figure 1. (A) Progression-free survival with imatinib 400 and 800 mg/day [13]. (B) Impact of the randomly allocated initial dose of imatinib on time to progression for patients with tumours bearing KIT exon 9 mutations [16].

primary resistance to imatinib [13]. Furthermore, >40% of patients who were initially responsive to imatinib (defined as patients who were progression free and alive at 3 months) developed late resistance after a median follow-up of 25 months [15].

Clinical studies of imatinib have demonstrated that the location of mutations within the pathogenic kinase is an important factor in both treatment response and the development of imatinib resistance. For example, the PR rate was higher in patients with mutations in KIT exon 11 than in those with a mutation in KIT exon 9 (84% versus 48%; $P = 0.0006$). Patients with no detectable mutation of KIT or PDGFRA had even poorer outcomes (objective response rate, 0%; $P < 0.0001$) [10]. It has been shown that for some patients with imatinib-resistant tumours, increasing the imatinib dose from 400 to 800 mg/day may overcome or balance the effects of drug resistance and improve PFS time [16]. However, the success of this approach appeared to be limited, except in tumours with primary mutations in KIT exon 9 [16] (Figure 1B). For other tumours, the dose of imatinib required to successfully overcome drug resistance and prevent or delay tumour progression is prohibitively high [10]. Primary

Table 1. Treatment interruptions and dose reductions with imatinib [13]

	Treatment interruptions (%)*		Dose reductions (%)*	
	400 mg (n = 470)	800 mg (n = 472)	400 mg (n = 470)	800 mg (n = 472)
Overall	40	64	16	60
Toxic effects				
Haematological	6	7	2	4
Non-haematological	23	43	10	42

*P < 0.0001.

imatinib resistance commonly occurs in tumours with mutations in *KIT* exon 9 [17]. Acquired resistance to imatinib has been reported most frequently in GISTs in which the primary mutation has occurred in *KIT* exon 11, which account for up to 67% of GISTs. Secondary mutations are rare in tumours that exhibit primary resistance to imatinib and those with wild-type *KIT* (10%), but are significantly more frequent in GISTs that show secondary resistance (67%, *P* = 0.002), presumably because patients with initially imatinib-sensitive tumours have been treated for longer periods, providing both the selection pressure and time for the emergence of imatinib-resistant clones [17].

sunitinib

Sunitinib has been approved multinationally for treatment of patients with imatinib-resistant GIST or those who are intolerant of the drug. Sunitinib inhibits multiple receptor tyrosine kinases including *KIT*, *PDGFRs* (- α and - β), vascular endothelial growth factor receptors -1, -2 and -3, *FMS*-like tyrosine kinase-3 receptor, the receptor for macrophage colony-stimulating factor and glial cell line-derived neurotrophic factor receptor (REarranged during Transfection) [18–22]. Sunitinib has demonstrated direct antitumour and antioangiogenic activities in preclinical studies [18, 20–24].

The efficacy and safety of sunitinib in imatinib-resistant GIST have been evaluated in an open-label phase I/II study [25, 26] and in a placebo-controlled, phase III trial [27]. The optimal dosing strategy for sunitinib was investigated in the initial portion of the phase I/II study. Patients (*n* = 97) received 25, 50 or 75 mg/day on one of three treatment schedules: 2 weeks on treatment followed by 1 week off treatment, 2 weeks on treatment followed by 2 weeks off treatment or 4 weeks on treatment followed by 2 weeks off treatment (4/2 schedule). The sunitinib dose chosen for further development was 50 mg using the 4/2 schedule [25, 26]. During the study, 7% of patients achieved a PR and 73% of patients experienced SD, which lasted \geq 6 months in 29% of patients. The median time to tumour progression (TtP) and PFS were both 7.8 months, and the median overall survival (OS) time was 19.0 months [25, 28]. At the end of the phase II portion of the study, patients with a PR or SD for >6 months were eligible to take part in a continuation study designed to monitor tumour progression and drug safety. Of the 32 patients who took part, 15 continued to be free from progressive disease for a median treatment time

of >1.5 years [26]. Analyses of tumour biopsies from 59 patients enrolled in the study suggested that primary and secondary mutations in *KIT* and *PDGFR*A may influence treatment outcomes in patients with imatinib-resistant GIST [25]. Sunitinib was effective for treatment of GISTs of all pre-imatinib genotypes, but especially those with a wild-type genotype, a primary *KIT* exon 9 mutation or secondary *KIT* mutations in exon 13 or 14 [25]. As previously stated, the incidence of secondary mutations was greater in those patients with initially imatinib-sensitive disease, especially those with exon 11 *KIT* mutations and certain of the secondary mutations confer resistance both to imatinib and sunitinib.

In the pivotal phase III trial, 312 patients with imatinib-resistant/-intolerant, locally advanced or metastatic GIST received sunitinib 50 mg/day (*n* = 207) or placebo (*n* = 105) on the 4/2 schedule [27]. The primary end point of the study was TtP, and the trial was unblinded early when a planned interim efficacy analysis showed that sunitinib was associated with a significant improvement in median TtP of more than four-fold compared with placebo (Figure 2). The effects of sunitinib treatment on disease control (measured using TtP) were unaffected by baseline characteristics such as age, time since initial diagnosis, duration of imatinib treatment, dose of imatinib, weight, race, pain score, performance status or study location. Median PFS for patients receiving sunitinib was significantly greater than for those receiving placebo (sunitinib, 24.1 weeks versus placebo, 6.0 weeks; *P* < 0.0001). After 6 months, only 1% of patients in the placebo-treated group were free from disease progression compared with 16% of sunitinib-treated patients. Sunitinib also significantly improved OS (hazard ratio, 0.49; 95% confidence interval, 0.29 to 0.83; *P* = 0.007; Figure 3), and at the time of the interim analysis, the median OS had not been reached in the group receiving sunitinib. More patients treated with sunitinib had an objective response compared with placebo (6.8% versus 0%; *P* = 0.006).

Adverse events reported during the double-blind phase of the study were generally mild or moderate and, in most cases, could be managed by reducing the dose of sunitinib, interrupting treatment or administering a supportive therapy. Only 19 patients (9%) discontinued sunitinib due to adverse events [eight placebo-treated patients (8%) also discontinued due to adverse events]. Fatigue was considered likely to be at least partly attributable to the burden of advanced GIST, as the frequency of grade 1/2 fatigue was similar in sunitinib- and placebo-treated groups (34% versus 32%) [28]. Haematological and other adverse events of interest were consistent with previous clinical studies using sunitinib and included neutropenia, anaemia, thrombocytopenia, cardiac disorders and hypothyroidism. Most of these were grade 1 or 2 in severity and were judged to be manageable. Although more reports of adverse events were recorded by patients taking sunitinib than those taking placebo, this may be balanced (at least in part) by the correspondingly longer exposure time in the sunitinib-treated group (two cycles, range 0–9 versus one cycle, range 0–6) [27].

As a consequence of the positive results obtained in the interim analysis, the blinded phase of treatment was terminated on the recommendation of the Independent Data and Safety Monitoring Board. Following unblinding, all patients could

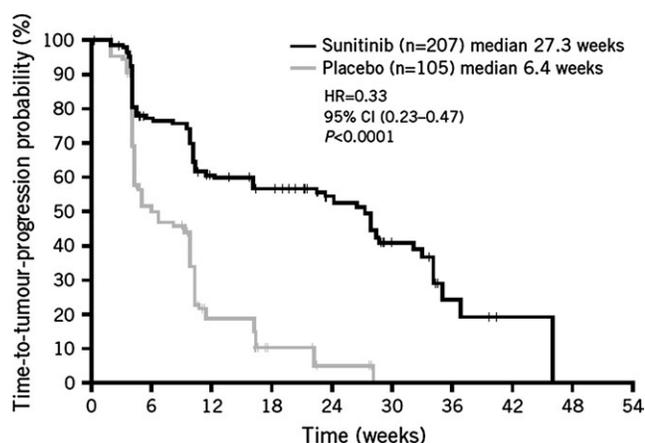


Figure 2. Effect of sunitinib on time to tumour progression in patients with refractory gastrointestinal stromal tumour in the blinded portion of the phase III trial [27].

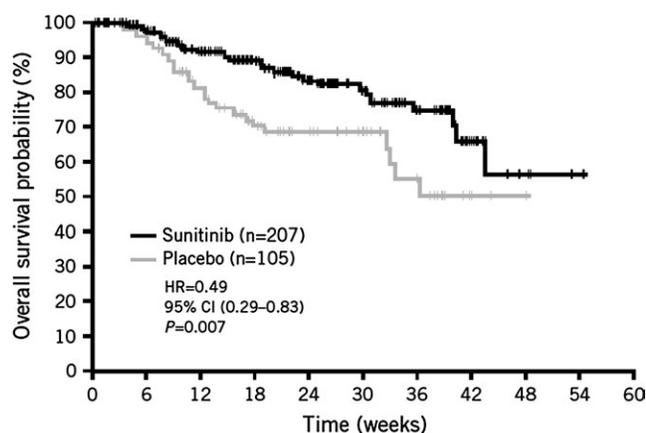


Figure 3. Effect of sunitinib on overall survival in patients with refractory gastrointestinal stromal tumour in the blinded portion of the phase III trial [27].

receive open-label sunitinib treatment. Significant and clinically meaningful improvements in TtP with sunitinib treatment compared with placebo continued to be maintained across the entire study encompassing both the blinded and open-label phases (28.4 weeks versus 8.7 weeks, $P < 0.0001$), despite the fact that during the open-label phase, increasing numbers of patients randomized to the placebo arm received sunitinib [28, 29]. Approximately 13 weeks after beginning treatment, the survival rate for patients who had been randomly assigned to receive placebo during the blinded phase of the study began to improve (at this timepoint, 70% of patients randomized to placebo had crossed over to sunitinib treatment). Across the blinded and open-label phases of the study, OS became similar between the two treatment groups [28, 29], as 88% of patients ultimately crossed over from placebo to sunitinib. The crossover design of this study also allowed comparison of two different modes of sunitinib administration: immediate (i.e. administration of sunitinib from the beginning of the study) and delayed (i.e. administration of sunitinib following crossover from placebo). The efficacy of receiving delayed

sunitinib treatment in improving TtP was comparable to that of receiving sunitinib immediately upon entering the study (delayed, 24.3 weeks versus immediate, 28.9 weeks). In the long term, patients initially treated with placebo benefited from improvements in OS after crossing over to sunitinib treatment. One year after entering the study, the OS probability for patients initially randomized to receive placebo was comparable to that of patients who had received sunitinib throughout the study [28, 29].

As in the blinded phase, sunitinib was reasonably well tolerated across the entire study. The most common adverse events experienced by patients who were randomly assigned to receive sunitinib were fatigue, diarrhoea, abdominal pain, nausea and anorexia. Rates from the open-label phase indicated that incidence of most adverse events increased slightly with longer term use. The majority of adverse events were grade 1 or 2 in severity and were manageable by reducing the dose of sunitinib, interrupting treatment or giving supportive therapies.

Assessment of sunitinib in GIST is ongoing in a multicentre, open-label 'treatment use' trial [30]. This study is intended to allow those patients who are ineligible for sunitinib clinical trials access to sunitinib. As of August 2006, 698 patients (all of whom were resistant to or intolerant of imatinib) had received at least one dose of 50 mg daily sunitinib on the 4/2 schedule and been treated for a median of three treatment cycles (range, 1–15). Safety analyses demonstrated a similar safety profile to that observed in previous GIST studies and in other patient populations. Likewise, sunitinib was found to be effective in this patient population.

An additional ongoing study is evaluating the effects of sunitinib administered on a continuous daily dosing schedule. Preliminary data indicate that the efficacy and safety profile of continuous dosing are similar to those of the standard dosing schedule [31].

conclusions

Although imatinib improves outcomes for many patients with GIST, its effectiveness is limited by primary and secondary (acquired) resistance. There is a need for alternative therapies for patients with metastatic GIST who are resistant to or intolerant of imatinib.

The results of the pivotal phase III study establish sunitinib as an effective option in the second-line setting. Sunitinib provided substantial clinical benefits in patients with imatinib-resistant GIST, including disease control and superior survival [28]. Treatment with sunitinib was reasonably well tolerated. Based on these results, sunitinib may have potential as first-line therapy. A head-to-head study directly comparing the effects of sunitinib and imatinib in treatment-naïve patients with GIST is planned.

Since the GIST genotype appears to be an important indicator of treatment response to both imatinib and sunitinib, obtaining genotype information from individual patients may, therefore, allow therapy to be targeted based on the specific mutations present in their tumours. For example, genotyping before treatment with imatinib may help to identify those patients at greatest risk of disease progression due to primary

resistance to imatinib. If the genotype of a tumour is known before treatment initiation, this may allow appropriate imatinib dose selection or an alternative drug at an early stage of treatment. Further studies investigating patients' mutational status and treatment response are warranted.

In conclusion, the availability of sunitinib represents an important clinical advance in GIST management, providing physicians and patients with an effective treatment to use when resistance to imatinib develops.

disclosures

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