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Optimising therapy for GIST patients

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Abstract

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the digestive tract, although their incidence is low. Management of GIST patients has evolved rapidly following discovery of the role of constitutively activated KIT tyrosine kinase in GIST oncogenesis. Elucidation of the oncogenic mechanism for GIST formed the basis for immunohistochemical diagnosis of GIST as well as for treatment by molecular targeting with the tyrosine kinase inhibitor imatinib. Imatinib has been shown in clinical trials to be efficacious and well tolerated for treatment of unresectable or metastatic GIST. Trial data show that median survival has not yet been reached at more than 3 years of imatinib therapy for patients with advanced GIST, an improvement of at least 2 years over previous therapy. Advancements in the diagnosis and treatment of GIST provide the basis for key strategies to optimise management. These strategies include the use of imaging in assessment and optimisation of therapeutic response, management of imatinib toxicity, optimisation of dose, and duration of therapy. Imatinib should be administered initially at 400 mg or 600 mg/day until signs of progression. Recent studies have revealed a relationship between *KIT* mutation genotype and response to imatinib therapy. Dose escalation should be instituted after an evaluation for potential underlying causes of low drug exposure. This review summarises developments in the treatment of GIST and the consensus on management with the goal of optimising patient care.

Keywords: Gastrointestinal stromal tumour; KIT; PDGFR; imatinib mesylate; tyrosine kinase inhibitors

1. Introduction

Gastrointestinal stromal tumours (GISTs) are life-threatening soft tissue sarcomas of the gastrointestinal tract. Identification of the role of KIT or PDGFRα tyrosine kinase activity in GIST tumorigenesis has led to advances in molecularly targeted therapy for this disease. Effective systemic treatment of recurrent or metastatic GIST was shown for the first time with the introduction of imatinib, an inhibitor of activated mutant isoforms of KIT and PDGFRα tyrosine kinases [1]. This review summarises the clinical evidence supporting the therapeutic advances for GIST and provides a practical guide to making treatment decisions in the clinical management of patients with GIST.

2. Optimising GIST diagnosis

2.1. GIST clinical presentation

Clinically significant symptoms of GIST may be nonspecific and include early satiety, bloating, and abdominal discomfort. Gastrointestinal bleeding is the most common sign of GIST, and while fatigue from anaemia is a frequent symptom indicative of chronic bleeding, acute haemorrhage can also occur [2]. The average duration of presenting symptoms for GIST patients is about 4–6 months [3]. A palpable tumour mass and abdominal pain may be present with larger tumours, many of which are likely to be metastatic. GIST metastasises most frequently to the liver and the peritoneum.

2.2. Diagnostic imaging and staging in GIST diagnosis

Numerous radiologic methods are useful in GIST imaging. Computerised tomography (CT) scan is the common initial imaging approach for abdominal neoplasms [3]. CT is useful for delineation of large masses, identification of metastases, and guiding GIST biopsy [4]. CT should be performed with the use of oral and intravenous contrast.

Small to moderately large GISTs are usually localised intramural masses that appear hyperdense with sharply delineated margins and homogeneous contrast enhancement [5]. Larger GISTs may be exophytic and hypervascular, and often appear more complex as a result of central necrosis and haemorrhage [4]. CT is a sensitive method of detecting GIST metastasis to the liver, omentum, peritoneal cavity, or abdominal wall. In general, magnetic resonance imaging (MRI) offers little additional information on tissue characterisation of GISTs. The multiplanar imaging capabilities of MRI may facilitate localisation and delineation of large exophytic tumours and GISTs at the anorectum [4].

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In cases of suspected GIST, preoperative biopsy of a resectable mass is unnecessary as it risks intraperitoneal seeding. Biopsy should be reserved for unresectable disease in which other diagnoses can be ruled out based on pathologic findings [6,7].

3. Optimising surgical treatment of resectable GIST

Surgery is the first-line treatment for primary resectable GIST in the absence of metastasis or a high risk of organ dysfunction from lesion resection [7–10]. The goal of surgery is complete resection of the mass without disruption of the commonly present pseudocapsule. Larger GISTs are often fragile and care is needed to avoid rupture, which is associated with a poor prognosis. GISTs generally protrude from the tissue of origin and displace surrounding structures rather than infiltrate [11]. Achieving negative microscopic surgical margins is usually possible. Vital structures should not be sacrificed if GIST excision is achieved with negative gross margins, as there is no evidence that procedures beyond removal of the neoplasm – including dissection of macroscopically uninvolved lymph node – prolong survival or delay recurrence [9,12]. The pathologic status of the margin of resection is not associated with recurrence or survival, and the success of resection probably depends more on whether the tumour sheds surface cells into the peritoneal cavity than on surgical margins [6,12].

Evaluating outcomes of surgical treatment of GISTs is difficult, because reports include few patients or heterogeneous patient groups in which risk factors may not be separated, cover long periods, and use conflicting methodologies. In addition, many reports combine results for patients with primary and with recurrent disease [8].

Most patients, except for very-low-risk patients, develop recurrence with complete surgical resection of GIST, probably as a result of microscopic metastatic or systemic disease. Although unpredictable, most recurrences (80%) occur within the first 2 years after surgical resection, with a median disease-free interval of 18 months [6,12]. Together, these studies demonstrate that surgery alone may be inadequate for treatment of GIST.

4. Optimising GIST pathologic and differential diagnosis

Postoperative pathologic assessment is essential to diagnose GIST. While surgical and gross findings provide a strong basis for identification of GIST, the accurate diagnosis of GIST must be made on the basis of histologic, immunohistologic, and, in some cases, molecular confirmation. As GISTs are rare, general pathologists may see only a small number of cases. It is therefore important that a highly experienced pathologist confirms the diagnosis of GIST. Modern criteria involved in the consideration of a GIST diagnosis are discussed in detail in the papers by Drs Joensuu and Heinrich in this supplement.

5. Optimising treatment of metastatic and unresectable GIST with imatinib

5.1. Molecular targeting of GIST with imatinib

Identification of the molecular oncogenic mechanism of GIST has provided a target for rational therapeutic intervention. Imatinib is a small, orally bioavailable molecule that competitively binds to the adenosine triphosphate-binding pocket of certain tyrosine kinases, thereby inhibiting kinase activity and blocking downstream signalling. In addition to activity against KIT, imatinib also inhibits the tyrosine kinase activity of PDGFRα, PDGFRβ, and macrophage colony stimulating factor receptor, as well as ABL and the ABL-related gene, ARG [1,13,14]. Initial development of imatinib for inhibition of the BCR-ABL kinase in the treatment of leukaemia resulted in an indication for imatinib in all phases of chronic myelogenous leukaemia (CML).

5.2. Clinical evidence of imatinib efficacy in GIST therapy

Clinical activity of imatinib was first demonstrated in a 50-year-old woman with multiple recurrent, unresectable, and metastasised GISTs [15]. A subsequent phase I dose-ranging study demonstrated efficacy of imatinib in patients with GIST. Thirty-six patients with immunohistologically confirmed advanced GIST received imatinib at doses ranging from 400 mg to 1000 mg daily [16]. Patients at all doses within this range showed responses, and 25 of 36 patients had objective tumour regression. Of these, 19 had confirmed partial responses after 8 weeks. After a minimum follow-up of 9 months, 18 patients (51%) continued to have partial responses and 11 (31%) continued to have stable disease [17]. Dose-limiting toxicities included nausea, vomiting, oedema, and rash. Imatinib was well tolerated and the maximum tolerated dose was 400 mg twice daily.

The compelling scientific rationale for imatinib efficacy in treating GIST was supported by clinical evidence demonstrating responses to imatinib in patients with advanced GIST. Based on these findings, the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group initiated a multinational phase II study examining efficacy and safety of imatinib 400 mg twice daily in 27 patients with metastatic and/or unresectable GIST [18]. At 1 year, 73% were free from progression and response rates were comparable to those of previously examined doses. Imatinib was well tolerated and no patient discontinued therapy because of toxicity.

In an open-label, randomised, multicenter phase II study conducted in the USA and Finland, 147 patients

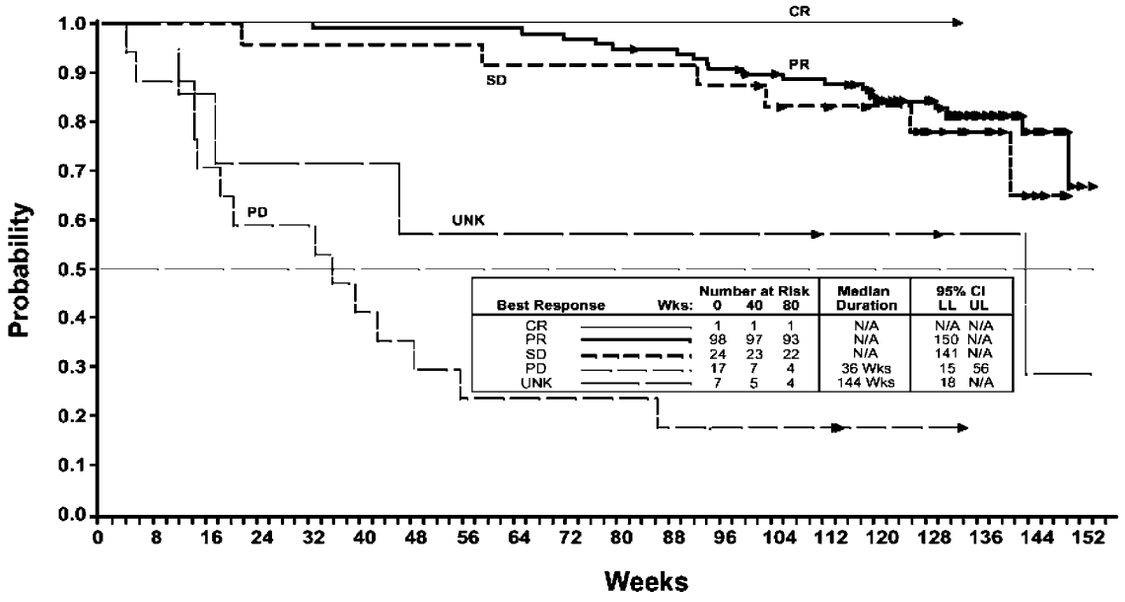

Fig. 1. Estimate of survival for patients with unresectable or metastatic GIST receiving imatinib in the US–Finland phase II trial. CR: complete response; PD: progressive disease; PR: partial response; SD: stable disease. Adapted from von Mehren and Watson, 2005 [21].

with metastatic or unresectable CD117-positive GIST were randomised to receive either 400 mg or 600 mg imatinib daily [19]. Tumour size and volume were monitored by CT scans and metabolic activity was examined by FDG-PET. Response was monitored clinically by MRI and CT scans. Partial response was observed in 54% of patients, while 28% of patients had stable disease. For either 400 mg or 600 mg daily, over 80% of patients achieved a clinical benefit from imatinib. In a 34-month follow-up, 67% of patients achieved a partial response and 16% of patients had stable disease [20]. There was no significant difference in response between doses. The median time to an objective response was 13 weeks, while the median duration of response was 27 months. The median time to treatment failure (progressive disease or discontinuation) was 84 weeks. The estimated survival rate at 83 weeks was 95% in patients with partial response, 92% in patients with stable disease, and 24% in patients with progressive disease. Most patients benefited from imatinib, and the survival rate in patients with stable disease as their best response was comparable to the survival rate in patients with partial response [21] (Fig. 1). Median survival had not been reached at 152 weeks, suggesting that disease control is durable. A further follow-up analysis at 42 months showed that the estimated median survival rate for patients with stable disease, partial response, or complete response was >3 years [22]. No differences were observed in efficacy or tolerability between 400 mg or 600 mg daily doses of imatinib, although the study was not powered statistically to determine dose superiority.

To determine optimal dosage of imatinib for patients with advanced GIST, over 1700 patients were enrolled in 2 large phase III trials conducted in Europe, North America, and Australia. Imatinib doses of 400 mg/day and 800 mg/day were compared in patients with metastatic or unresectable KIT-positive GIST. The North American Intergroup trial (S0033) enrolled 746 patients [23]. Survival estimates at 2 years were 78% and 73% for the 400-mg and 800-mg daily arms, respectively. The second study was initiated by EORTC and enrolled 946 patients [24]. Overall survival estimates at 1 year were 85% and 86% for the 400-mg and 800-mg daily arms, respectively. Overall survival estimates at 2 years were 69% and 74% for the 400-mg and 800-mg daily arms, respectively. Although both trials reported superior 2-year progression-free survival with a higher daily dose, the difference between the 400-mg and 800-mg daily doses was statistically significant in the EORTC study (50% vs 56%; $P = 0.026$), but non-significant in S0033 (50% vs 53%; $P > 0.05$) [23,24]. The reason for this difference is unknown, but longer follow-up may be needed to resolve this discrepancy. Current evidence-based recommendations for imatinib therapy in the treatment of unresectable and/or metastatic GIST are illustrated in Fig. 2 [7,10,11].

6. Optimising treatment with imatinib

6.1. Predicting outcomes: KIT mutations and expression

The specific *KIT* or *PDGFRA* mutations present in a GIST influence the response to imatinib treatment. Although most GIST patients benefit from imatinib therapy, it has been shown that there is a correlation between the mutational status of *KIT* and clinical outcome. Advanced GIST patients with exon 11 mutations were more likely to achieve partial response with imatinib therapy, compared with patients expressing *KIT* exon 9 mutations or wild-type *KIT* [25]. A detailed discussion of the correlation between

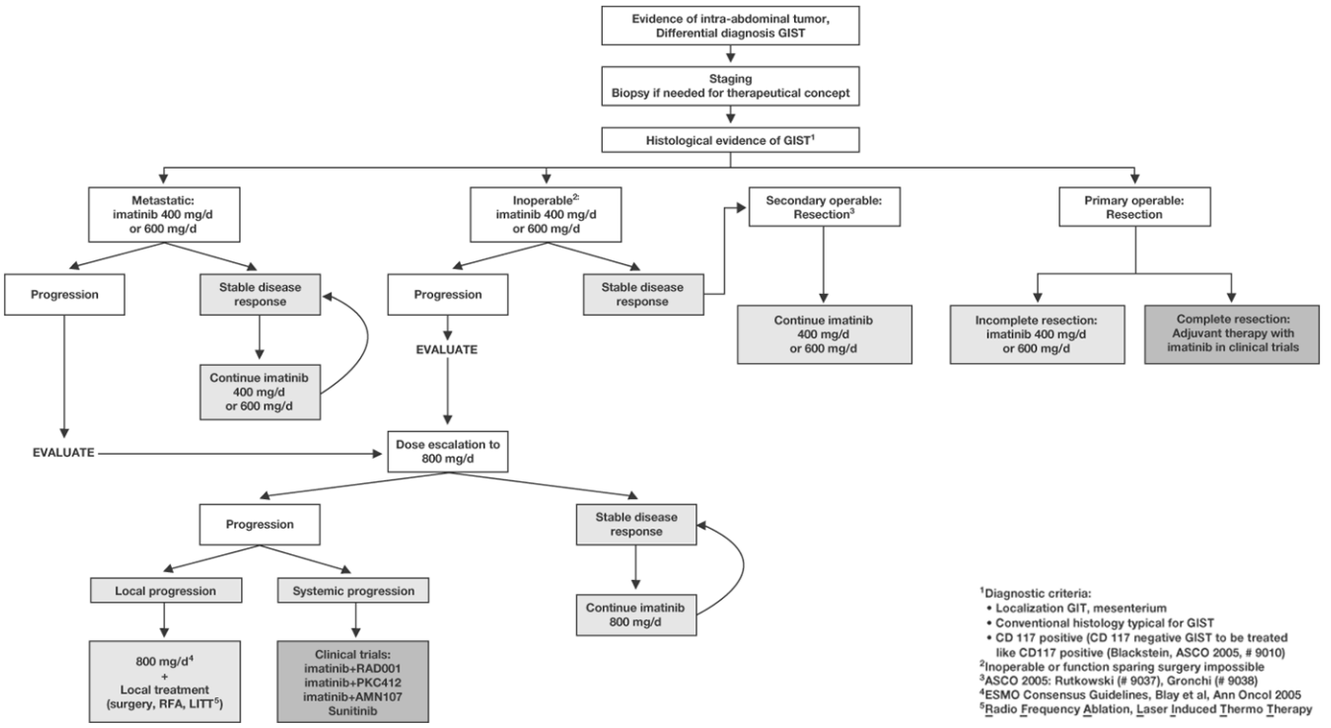

Fig. 2. Treatment algorithm for patients diagnosed with confirmed GIST.

GIST genotype or KIT immunostaining and response to imatinib is presented in the article by Dr Heinrich entitled *Molecular basis for treatment of gastrointestinal stromal tumours* in this supplement.

6.2. Tolerability and management of adverse events

Phase II and III clinical trials demonstrated that imatinib was generally well tolerated at doses up to 800 mg daily. While most patients had some mild or moderate adverse events at higher doses, little serious toxicity was noted. Similar to the findings in CML-trial patients, most adverse events in patients receiving imatinib for GIST were minor and manageable without the need for dose adjustment. The most commonly reported side effects included oedema (usually periorbital), diarrhoea, nausea/vomiting, abdominal pain, muscle aches, fatigue, and rash [19]. The side-effect profile of imatinib may improve with prolonged therapy [18]. The most serious adverse event was intra-abdominal haemorrhage in patients with bulky GISTs, a well-recognised complication of GISTs probably based on the rupture of cystically transformed lesions as a result of response to treatment. Anaemia was common and mild, while grade 3 or 4 haematologic toxicities were infrequent in GIST patients receiving imatinib. Serious neutropaenia and thrombocytopaenia were rare and patients may safely continue therapy with absolute neutrophil counts >1000 [7]. In the most recent phase III trial, patients taking a higher dose of imatinib (400 mg twice daily) were more likely to have some adverse events, compared with those receiving a lower dose (400 mg once daily) [18]. Anaemia and granulocytopaenia occurred in 93% and 42% of patients, respectively. Hepatotoxicity reported in some CML patients receiving imatinib was rare, of short duration (median = 1 week), and managed by dose reduction.

6.3. Pharmacokinetics and drug–drug interactions

The pharmacokinetic profile of imatinib in patients with GIST is comparable to that seen in patients with CML [2]. Imatinib has an oral bioavailability of about 97% and is highly bound to serum proteins. Peak plasma levels of imatinib occur in about 4 hours, and levels reach steady state within a week. Most of the drug is metabolised by the cytochrome P450 isoenzyme 3A4 (CYP3A4), so co-administered drugs that induce or inhibit this enzyme may increase or decrease clearance of imatinib, respectively. Imatinib is a moderate inhibitor of CYP3A4 and may increase exposure to drugs metabolised by this isoenzyme, such as some statins [7].

6.4. Assessing response and resistance

Surveillance after surgery or during imatinib therapy is an important part of the overall strategy to optimise management of GIST. Following response or stabilisation with therapy, patients should be evaluated for response every 3 to 4 months [7,11]. Response to imatinib is established by imaging, which reveals marked decreases in tumour vessels and enhancing nodules after treatment. In response to therapy, GIST metastases on a CT scan appear better defined, more homogeneous, and significantly

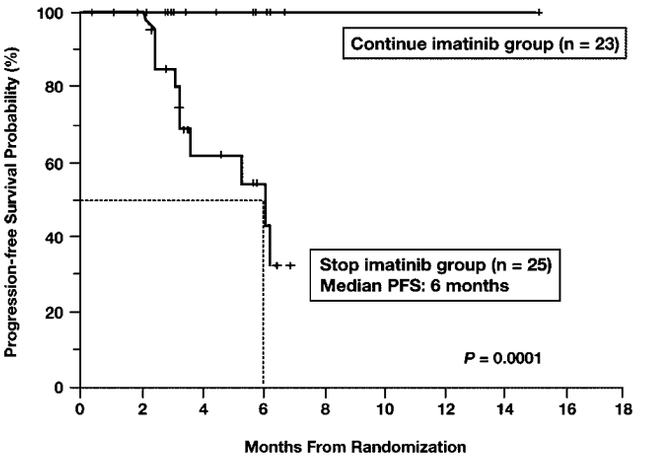

Fig. 3. Patients with advanced GIST who stop imatinib therapy experience rapid and frequent re-progression. Adapted from Blay *et al.*, 2004 [26].

less attenuating. While the success of imatinib treatment of GIST highlights the role of CT imaging in following response, imaging analysis also underscores the shortcomings of current criteria for gauging responses to molecularly targeted therapy [27]. Response Evaluation Criteria in Solid Tumors (RECIST) are based on size-based findings alone, and may underestimate early responses to imatinib in GIST. GISTs undergoing targeted therapy with imatinib may decrease minimally in size, or even increase slightly in size. As a result, many patients with clinical responses as determined by CT can be misdiagnosed using the RECIST criteria [27,28]. For targeted therapies, assessment of clinical response requires response criteria suited to the underlying mechanism of action [29]. Imaging enhancement characteristics, although more subjective, seem to be a more sensitive measure of GIST response to imatinib therapy. FDG-PET has been shown to be sensitive and can resolve ambiguous CT results, but its applicability is limited, as up to 20% of small-to-moderate tumours have no appreciable FDG uptake at baseline [28].

Tumour progression developing either early or later during imatinib therapy is a clinical challenge in the management of patients with GIST. Progression can be seen by the presence of tumour growth on CT or MRI scans. In a small subset of patients, primary resistance to imatinib is manifested by initial disease progression with therapy. In the US–Finland trial, early resistance was seen in 14% of patients after 24 weeks [19]. In contrast, secondary resistance to imatinib may occur after initial stabilisation and regression of disease, and is often noted focally. In a 39-month follow-up, 42 of 89 (47%) patients with a partial or minor response to imatinib had documented disease progression, of which half had evidence of clonal resistance to imatinib [30]. On imaging, this secondary GIST resistance is heralded by the appearance of new enhancing nodular focus within a previously responsive hypodense mass [7,11]. This change reflects the emergence of a resistant clonal nodule in a surrounding tumour that remains responsive to imatinib. Current evidence suggests that the mechanism of imatinib resistance in GIST, characterised by intratumoural nodules, is the emergence of secondary mutations in tumour genotype [30,31]. These results underscore the need to avoid therapy interruptions. In the French Sarcoma Group trial, 58 patients with at least stable disease during imatinib therapy for GIST were randomised to continue therapy or interrupt treatment. Interruption of imatinib was associated with a significantly reduced progression-free survival rate, compared with continuous therapy ($P = 0.0001$) (Fig. 3) [26,32]. Although the effect of treatment interruptions on the emergence of resistant clones is unclear, these data support continued therapy for patients with stable disease or response to imatinib.

6.5. Clinical management of GIST disease progression

The currently recommended dose for initial imatinib therapy in patients with advanced or unresectable GIST is 400 mg or 600 mg daily until signs of progression appear (Fig. 2). At this point, an evaluation to rule out insufficient compliance, a drug–drug interaction or other explanations for inadequate drug exposure should be conducted. Imatinib dose escalation to 800 mg is then recommended as some patients may benefit from an increased dose. Based on the evidence from cross-over in phase III trials, an increase in daily dose from 400 mg to 800 mg can be expected to prolong tumour control in about 30% of patients [23,33]. In a sub-study of the EORTC phase III trial, 143 patients with disease progression on 400 mg imatinib daily were crossed over to a dose of 800 mg daily. Dose escalation improved the therapeutic benefit of imatinib, with 26% of patients remaining free from progression at 1 year [33]. Increased fatigue and anaemia were noted after dose increase, but dose reduction was infrequent. Clinical trials showed that patients in whom imatinib was stopped before initiation of an alternate therapy experienced tumour flare and increased clinical symptoms [34,35]. Imatinib therapy should therefore be continued for as long as it is well tolerated in patients who have evidence of some continued benefit [11].

Although imatinib is a highly efficacious treatment for GIST, some patients with lesions refractory to treatment may require local treatment or alternative therapeutic approaches. For patients with isolated progression unresponsive to imatinib, surgical removal of a viable tumour might be feasible [7]. In patients with localised progression, radiofrequency ablation combined with imatinib dose escalation can be used to manage the disease with no complications [36].

Combination therapy with imatinib and a second agent may provide additional therapeutic benefits in GISTs that are resistant to imatinib. Everolimus (RAD001) is an inhibitor of the KIT downstream molecular target of rapamycin, a member of the phosphatidylinositol 3-related kinase family that regulates cell-cycle progression, proliferation, and survival. In a phase I/II clinical trial

Table 1
Ongoing randomized adjuvant trials with imatinib in GIST

Trial	#	Statistics	Tx	Primary endpoint	Eligibility
Z9001 (ACOSOG)	450/732	HR 1.4	400 mg/1 year vs placebo	RFS	T ⩾ 3 cm
SSG/AIO	140/240	RFS at 5 years (30–40%) 62%, 80%	400 mg/1 year vs 400 mg/3 years	RFS	High risk and very high risk (rupture, R1, R0 mets.)
EORTC 62024	120/400	HR ⩽ 0.62	400 mg/2 years vs control	OS	Intermediate risk and high risk (incl. R1 and rupture)

using a combination of imatinib and everolimus, 6 of 18 patients whose disease had progressed during treatment with ⩾600 mg/day imatinib were progression-free for more than 4 months including 2 partial responses [37]. Co-administration of imatinib resulted in a moderate increase in everolimus levels.

The oral staurosporine derivative PKC412 has inhibitory activity against KIT, PDGFRα, PDGFRβ, and vascular endothelial growth factor (VEGF) [38]. An open-label phase I study examined combination therapy with imatinib and PKC412 in 19 patients with GIST whose disease progressed with imatinib alone; results showed stable disease in 2 patients. Adverse pharmacokinetic interactions between these agents required dose escalations of imatinib and dose reductions of PKC412 [38].

Alternative options for those who have exhausted the benefit of therapy with imatinib include other investigational kinase inhibitors. Sunitinib (SU11248) is an orally administered, multi-targeted agent with activity against KIT, PDGFR, and fms-like tyrosine kinase 3, as well as anti-angiogenic activity mediated by inhibition of VEGFR. In phase I and II studies, sunitinib induced objective responses and controlled progressive disease in patients with *KIT* mutations. In 98 patients with imatinib-resistant GIST who received 50 mg sunitinib daily, 54% achieved objective response or stable disease for ⩾6 months [39,40]. In an extension study, 26 of 32 patients remained on study >1 year, while 6 had progressive disease. For 22 patients with evaluable disease, neither median time to progression nor overall survival had been reached. A randomised phase III trial of sunitinib in imatinib-resistant GIST patients was recently halted because efficacy endpoints had been reached with a significantly superior progression-free survival rate of 6.3 months with sunitinib compared to 1.5 months with placebo [41]. The dosing schedule for sunitinib in this trial was 4 weeks on therapy and 2 weeks off.

6.6. Adjuvant and neoadjuvant imatinib

The favourable response rates with imatinib in the treatment of advanced GIST have generated great interest in the use of imatinib also in the adjuvant and neoadjuvant settings. Currently three randomised phase III trials are being conducted to assess the efficacy of imatinib as adjuvant therapy after complete resection of GIST (Table 1). Strategies include the comparison of imatinib to placebo or control for 1 year in the American and 2 years in the EORTC trial, respectively. Furthermore, a Scandinavian–German trial is comparing 1 to 3 years of treatment with imatinib. Several trials are evaluating the role of preoperative imatinib, also including translational research [42].

7. Conclusion

GIST is a rare mesenchymal tumour of the digestive tract. GIST is refractory to chemotherapy and was previously controlled only by surgery, which remains the first-line treatment for resectable masses. Understanding the molecular basis of GIST oncogenesis has improved the diagnosis, treatment, and management of these tumours. Elucidation of the role for KIT in GIST oncogenesis led to the development of imatinib, the first rationally designed, small-molecule therapy targeting tyrosine kinase activation. As a result, this tyrosine kinase inhibitor has become the paradigm of oncogene targeting of solid tumours [11]. In most patients with unresectable or metastatic GIST, imatinib has resulted in either a partial response or stable disease. Trial evidence indicates that, compared with a median survival time of ⩽1 year with previous therapy for advanced GIST, median survival for advanced GIST patients treated with imatinib is longer than 3 years [20,22]. In addition to its high efficacy as a treatment for GIST, imatinib has also been shown to be a well-tolerated agent in patients with advanced GIST. Most of the imatinib-associated adverse events are mild or moderate, and are manageable without the need for treatment interruptions.

The use of targeted agents has underscored the need for imaging modalities for response assessment in GIST; the result has been a greater appreciation for the pivotal role of CT and FDG-PET imaging in determining therapeutic effects of targeted treatments like imatinib [28,29].

Treatment response to imatinib can be influenced by the specific *KIT* or *PDGFRA* mutations expressed by GIST. Clinical data have shown that patients with *KIT* exon 11 mutations achieve a better clinical response to imatinib than patients with GIST harbouring *KIT* exon 9

mutations or wild-type *KIT* [43,44]. This understanding of the correlation between the mutational status of *KIT* or *PDGFRA* and the response of GIST to imatinib may aid in guiding therapy and predicting the clinical outcomes of imatinib therapy in some patient subsets.

Resistance to imatinib has now become a clinical challenge in the management of patients with GIST. Several strategies are currently being investigated to overcome resistance to imatinib in GIST. These strategies include dose escalation and combination therapy with imatinib and other molecularly targeted agents. Interruption of imatinib treatment does not delay the emergence of resistance to imatinib in patients with advanced GIST, and imatinib therapy should be maintained for as long as it is well tolerated [11,20,26].

Advances in our understanding of the underlying mechanism of GIST oncogenesis have led to considerable improvements in the diagnosis, treatment, and management of GIST. Due to its efficacy, safety, and tolerability in patients with advanced GIST, imatinib has been a key contributor in the arena of targeted therapeutic approaches for oncology.

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