Evolving treatment strategies for localized and advanced GIST

E. Palesandro[1], P. Boccone[1], D. Galizia[1], S. Aliberti[1], M. Aglietta[1], G. Grignani[1]

Abstract
Gastrointestinal stromal tumors (GIST) can affect anywhere along the gastrointestinal tract and are the most common mesenchymal tumors of these organs. The presence of a constitutive active form of KIT due to mutations in the KIT oncogene is the primary driver of oncogenic signaling in GIST, and several tyrosine kinase inhibitors targeting KIT have revolutionized the treatment and prognosis for GIST. Localized GIST is treated with surgery in the first instance, but good surgical technique is required because GIST tumors carry a high risk of spontaneous rupture and bleeding. Prediction of relapse risk helps to determine which patients are candidates for adjuvant therapy. Imatinib has shown value in this setting, improving progression- and relapse-free survival, but a number of important questions remains, such as the optimal duration of therapy. A number of kinase inhibitors have been used in advanced GIST, including imatinib, sunitinib and regorafenib. Improvements in progression-free survival and time to progression have been noted, but issues include development of resistance to imatinib, and disease progression after initial response. New treatment options under investigation in GIST include ponatinib, linsitinib and immunotherapies. Combination of imatinib with PI3K inhibitors is one option being investigated to overcome imatinib resistance. Recent treatment advances have widened the treatment landscape and improved patient outcomes in GIST, and current research into new options (e.g. immunotherapy) is promising. Tolerability and cost of new therapies and combinations are likely to be issues that will need addressing in the near future.

Key words: gastrointestinal stromal tumor, imatinib, immunotherapy, linstinib, ponatinib, regorafenib, sunitinib, surgery

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, occurring in approximately 15 cases per million each year [1]. GIST can occur along the entire gastrointestinal tract; the most common sites are stomach (50-70%), small bowel (25-35%) and rectum (5-10%) [2].

The pathogenic hallmark of GIST is the presence of a constitutive active form of KIT due to mutations in the KIT oncogene. Such mutations represent the primary drivers of GIST's oncogenic signaling. Mutations in KIT exon 11 are the most common (67%) and they are found in GIST distributed throughout the whole gastrointestinal tract, whereas KIT exon 9 mutations (mainly duplications) are found in 10-12% of GIST, more frequently in those localized in the small bowel. Mutations in KIT exons 13 and 17 are rare (1% each) and occur more commonly as secondary mutations. Less frequently, GIST shows PDGFRα gene mutations (approximately 5-8%); these tumors usually arise in the stomach. The remaining cases are referred to as "wild-type" GIST because they do not harbor either KIT or PDGFRα mutations. This latter heterogeneous group is currently split according to specific genetic alterations involving the succinate dehydrogenase complex (SDH-related GIST), and either RAS or B-RAF mutations [3]. Despite these advances in knowledge, there are some GIST for which we still ignore the driving mutation/s (Table 1) [4]. Management of GIST has evolved very rapidly since the role of KIT in the molecular pathogenesis of the disease has been identified. KIT has become the target of several tyrosine kinase inhibitors that have revolutionized the treatment and prognosis of GIST patients.

Localized GIST

Surgical resection with clear margins is the mainstay of treatment for localized GIST. Good surgical technique is crucial due to the fragility of these tumors and the high risk of spontaneous rupture and bleeding. This requires special caution and skill from the surgeon. A laparoscopic

[1]Medical Oncology-1, Candiolo Cancer Institute – FPO, IRCCS, Candiolo (Torino), Italy.

Correspondence to: Dr. Giovanni Grignani,
Division of Medical Oncology, Candiolo Cancer Institute – FPO, IRCCS, Strada Provinciale 142, 10060 Candiolo (TO), Italy.
Phone: +39 011 9933623
E-mail:giovanni.grignani@ircc.it

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Table 1. Mutation in GISTs. (Adapted from [4])

Gene		Frequency (%)
KIT		**~ 80**
	ex. 9	10–12
	ex. 11	67
	ex. 13	~ 1
	ex.17	~ 1
PDGFR-alfa		**5–8**
	ex. 12	~ 1
	ex. 14	~ 1
	ex. 18	6
Wild-type GISTs		**12–15**
	NF-1	2
	B-Raf	2
	SDHB/C	3
	N-Ras	?
	KRAS	?

approach should be considered in selected cases but is not recommended in patients with large GIST given the high risk of tumor rupture.

Even after optimal surgery, GIST retain the potential to relapse [5]. The most common sites of metastases are the liver and/or peritoneum, while metastases involving lymph nodes, lungs or bones are rare. The median time to recurrence is between 7 months and 2 years, but relapses even 10 years after the first surgery are well documented [6]. After the National Institutes of Health (NIH) consensus conference 2001, it was clear that GIST have a relapse risk that is better described by a continuous line rather than by clearly differentiated categories. This concept has been progressively modified by several proposals integrating GIST site of origin, tumor rupture, necrosis, and mitotic count as a continuous variable (Table 2) [7, 8]. Although mutation status as an indicator of response to different treatments is gaining increased recognition, this has yet to be included in any published GIST risk classification [9].The estimation of relapse risk after GIST resection is crucial in identifying patients who could possibly benefit from adjuvant therapy. Patients whose risk is >50% are candidates for adjuvant therapy; data show that adjuvant imatinib improves relapse-free survival (RFS) after radical resection. In particular, imatinib 400 mg/day for 1 year has been shown to prolong RFS compared with surgery alone [10]. Furthermore, 3 years of adjuvant imatinib appears to better than 1 year with respect to improvements in RFS and overall survival (OS) in high-risk GIST after complete surgery [11]. However, the optimal duration of adjuvant imatinib therapy remains to be clearly defined.

Another unknown factor is whether adjuvant treatment can eradication GIST or just postpone relapse. A subgroup of patients with KIT exon 9 mutations appear to benefit from higher doses of imatinib, meaning that treatment that should be carefully tailored to the individual patient tolerance. It is important to note, however, that at present this claim is not supported by any controlled clinical trial data but is instead based on treatment in the advanced setting in which higher dosage could overcome exon 9 intrinsic lower sensitivity. Treatment choice when facing wild-type GIST in the adjuvant setting is uncertain. One thing there is consensus on is that GIST with the exon 18 mutation D842V PDGFR gene should not be treated with adjuvant therapy because of a lack of sensitivity of this genotype to imatinib. Recently, Rutkowski and colleagues analyzed the economic impact of adjuvant therapy for high-risk GIST and showed that adjuvant imatinib, in addition to

Table 2. Rates of metastases or tumor-related death in GISTs by tumor location, grouped by tumor size and mitotic rate. (Adapted from [7])

Tumor parameters			Percent of patients with progressive disease during long-term follow-up and characterization of risk for metastasis			
Group	Tumor size (cm)	Mitotic rate (HPFs)	Gastric	Jejunal and ileal	Duodenal	Rectal
1	≤2	≤5/50	0% none	0% none	0% none	0% none
2	>2 – ≤5	≤5/50	1.9% very low	4.3% low	8.3% low	8.5% low
3a	>5 – ≤10	≤5/50	3.6% low	24% moderate	34% high	57% high ‡
3b	>10	≤5/50	12% moderate	52% high		
4	≤2	>5/50	0%; †	50% †	§	54% high
5	>2 – ≤5	>5/50	16% moderate	73% high	50% high	52% high
6a	>5 – ≤10	>5/50	55% high	85% high	86% high	71% high ‡
6b	>10	>5/50	86% high	90% high		

‡ groups 3a and 3b, 6a and 6b are combined in duodenal and rectal GISTs because of small number of cases; † denotes tumor categories with very few cases; § no tumors of such category were included in the study. HPF: high-power field.

proven clinical effectiveness and safety, is also more cost-effective than surgery alone [12].

Advanced GIST

Imatinib

Before imatinib, standard treatment for advanced GIST was conventional chemotherapy based on drugs such as doxorubicin and ifosfamide. This was associated with poor response rates (<5%) and an estimated median OS of 12-18 months. In this setting, the role of radiotherapy in disease management is limited, partially because of the relative radio-resistance of GIST and also because adjacent intra-abdominal organs have a low tolerability level for radiotherapy, limiting the ability to deliver an effective therapeutic dose. The introduction of imatinib dramatically changed the outcome of GIST and became the paradigm for molecular targeted therapy in solid tumors.

Imatinib is an oral selective tyrosine kinase inhibitor of KIT, PDGFRα, PDGFRβ, FLT3 and ABL kinases that was initially approved for chronic myelogenous leukemia (CML) with Philadelphia chromosome translocation (Ph+). The open-label, randomized, multicenter phase II trial B2222 enrolled 147 patients with advanced KIT-positive GIST and treated them with imatinib. After a follow-up of 71 months, median PFS was 24 months and median survival was nearly 57 months [13]. Two phase III trials (S0033 and 62005) were conducted to confirm these data and to identify the most effective dose of imatinib. Neither study showed any advantage with higher dose treatment (800 mg/day) in terms of OS compared with the standard 400 mg/day dosage, except in patients with tumors harboring KIT exon 9 mutations [14, 15]. This subgroup obtained benefit from the higher dose of imatinib, with higher 3-year progression-free survival (PFS) rates compared to similar patients receiving imatinib 400 mg (17% *vs* 5%; p=0.017) [16, 17].

The majority of adverse events reported in these studies were edema, fatigue, nausea and muscle cramps. Although toxicities are usually mild to moderate in severity, they should be carefully prevented and/or treated to facilitate compliance with therapy and to avoid treatment interruptions that often lead to rapid disease progression.

It is also important to note that a trial randomizing patients who responded to imatinib to continue with treatment or to stop after 1, 3 or 5 years of therapy (BFR14) showed rapid disease progressions in the majority of patients stopping imatinib [18, 19]. Therefore, imatinib therapy should be continued until disease progression [20]. However, after a median time of approximately 20-24 months, most GIST patients eventually develop resistance to imatinib treatment, due to either the acquisition of secondary KIT mutations [21] or selection of pre-existing imatinib-resistant clones [22].

Several different small series suggest that in the presence of a partial clinical response, surgical removal of residual disease can be performed followed by the resumption of imatinib treatment. The rationale behind this strategy is to remove tumor clones resistant to imatinib, delaying or preventing the requirement for second-line systemic treatment. Secondary mutations usually cluster into two KIT kinase domain regions: the activation loop that is encoded by exon 17 and exon 18, and the ATP-binding pocket that is encoded by exon 13 and exon 14. Novel strategies to overcome imatinib resistance in GIST patients have been developed over the years and this topic continues to be an interesting field of investigation; a thorough multidisciplinary approach is central to the delivery of "state of the art" treatment to patients [23].

Sunitinib

Sunitinib is an oral multikinase inhibitor with activity against KIT, PDGFRα and PDGFRβ, colony stimulating factor receptor (CSF-1R) and the three isoforms of vascular endothelial growth factor receptor (VEGFR1, VEGFR2 and VEGFR3). Sunitinib is approved for second-line therapy in advanced GIST based on the results of a phase III randomized double-blind trial demonstrating the efficacy of sunitinib in patients with advanced GIST, failing or intolerant of imatinib therapy. In this study, 312 patients were randomized (2:1) to receive either sunitinib 50 mg or a placebo orally once daily on 1-week on and 2-week off schedule until disease progression. The median time to progression was superior in the sunitinib arm (27 weeks) compared to the placebo arm (6 weeks) [24]. Later, sunitinib was showed to also be effective using a different schedule of treatment. A phase II open-label trial evaluated the activity of sunitinib at a dose of 37.5 mg continuous daily dosing in patients with advanced GIST resistant to or intolerant of imatinib showing a PFS of 34 weeks [25]. Although sunitinib had activity in this patient population, >50% of patients shows further disease progression after a median time of 6 to 9 months.

Regorafenib

Regorafenib is an oral difenilureic multikinase inhibitor which inhibits the activity of kinases involved in the regulation of tumor angiogenesis, oncogenesis and the tumor microenvironment including KIT, RET, VEGFR, B-RAF, PDGFR, and FGFR and p38 MAP-kinase. The GIST Regorafenib In Progressive Disease (GRID) trial was a randomized, double-blind, placebo-controlled, multicenter,

crossover, phase III study. From January 2011 to July 2011, this study enrolled 199 patients whose disease had progressed after prior treatment with imatinib and sunitinib. Patients were randomized 2:1 to receive regorafenib (160 mg once daily, 3 weeks on/1 week off) plus best supportive care (BSC) or placebo plus BSC. Patients in the placebo arm who experienced disease progression were offered treatment with regorafenib. The results showed that regorafenib significantly improved PFS compared with placebo (4.8 *vs* 0.9 months; hazard ratio [HR] 0.27, 95% confidence interval [CI] 0.19-0.39) [26] and regorafenib has now been approved by both the FDA and EMA.

Imatinib re-challenge

Despite dramatic improvements in clinical outcomes for metastatic GIST patients treated with targeted therapies, the risk of progression persisted over time. Relapse and progression are caused by the uprising of resistant tumor cell clones harboring different kinase mutation/s. In brief, in the late advanced stages, GIST is increasingly an oligoclonal/polyclonal disease. This biological evidence suggested that kinase inhibition should be continued even during progression to maintain some systemic control of the disease and slow down tumor growth by activity against the remaining sensitive clones [27]. For this reason, an attempt at imatinib re-challenge could be performed, if the patient's clinical condition permits. The double-blind randomized phase III RIGHT trial confirmed this strategy as a therapeutic option after failure of standard therapies. Re-treatment with imatinib was associated with an increase in PFS compared with placebo (1.8 *vs* 0.9 months) and disease control rate. The between-group difference in OS was not statistically different, probably due to post-progression crossover to imatinib in the majority of placebo-treated patients [28]. The uncontrolled progression of clones resistant to imatinib explains the brevity of the benefit of this strategy.

Future directions

Ponatinib

Ponatinib, an oral multi-TKI, has recently been approved for the treatment of CML. Ponatinib has demonstrated potent activity not only against BCR-ABL, but also against mutated forms of KIT and PDGFRα, including KIT mutations conferring resistance to other TKIs. Indeed, in a preclinical study, ponatinib potently inhibited the growth of GIST cell lines with a wide mutational spectrum, including both primary and secondary mutations [29]. Preliminary data from a phase II trial conducted in pretreated advanced GIST patients showed that ponatinib had antitumor activity, especially in tumors with mutation in KIT exon 11 [30].

Linsitinib

Insulin-like growth factor-1 receptor (IGFR1) is overexpressed in wild-type GIST, representing a potential therapeutic target [31]. Recently, a phase II trial with linsitinib, an oral IGFR1 inhibitor, was conducted in both pediatric and adult wild-type GIST patients. The clinical benefit rate and PFS at 9 months were 45% and 52%, respectively, although no RECIST responses were observed [32]. Despite these results, researchers stopped the further development of linsitinib in this setting.

Immune therapy

Recently, advances in the understanding of the balance between immune surveillance and tumor cell survival opened the way to the clinical investigation of new treatments primarily targeted at disrupting inhibitory control mechanisms of the immune system. The therapeutic effectiveness of these agents, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors and programmed-death (PD)-1/PD-L1 inhibitors, over standard care in patients with advanced melanoma, Hodgkin's lymphoma and other tumors can only be described as impressive.

Ipilimumab is a monoclonal antibody targeting CTLA-4, a protein receptor expressed in T-regulatory cells which contribute to T-lymphocytes immunosuppressive function. By releasing this kind of brake, ipilimumab enhances the immune system anti-tumor directed response. Ipilimumab was approved by the Food & Drug Administration (FDA) in March 2011 to treat patients with late-stage melanoma that had spread or could not be removed by surgery, and by the European Medicines Agency (EMA) in November 2012 for second-line treatment of metastatic melanoma. In addition to melanoma, ipilimumab is currently undergoing clinical trials for the treatment of non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), bladder cancer and castration-resistant prostate cancer. A phase Ib trial is evaluating the association of ipilimumab and dasatinib (an oral multikinase inhibitor with activity against KIT, PDGFRα and PDGFRβ, BCR-ABL) in patients with sarcoma and advanced GIST and preliminary results were presented at the American Society of Clinical Oncology (ASCO) 2014 conference [33]. Disease stability was reported in 4/5 patients who completed ipilimumab induction, suggesting an immune-mediated effect of this drug combination in accordance with preclinical in vivo data [34].

Imatinib plus PI3K inhibitors

In recent years, preclinical studies have shown that imatinib resistance may be caused not only by the presence of secondary mutations but also by the hyperactivation of downstream signaling pathways, such as PI3K/AKT [35]. On this basis, preclinical studies have been conducted to explore the efficacy of the combination of imatinib and PI3K inhibitors in GIST xenograft models. These studies show higher apoptotic activity, tumor burden reduction and durable effect with the combination compared with either agent as monotherapy [36]. Based on these encouraging data, several PI3K inhibitors or PI3K/mTOR inhibitors are being tested alone, or in combination with imatinib, in phase I trials in advanced pre-treated GIST with the aim of overcoming resistance to imatinib. These results are eagerly awaited (Table 3).

Table 3. Recent clinical trials investigating PI3K/akt inhibitors in association with imatinib

PI3K/akt inhibitor	Line of treatment	Phase
BKM120 ‡	3rd	1
BYL719 †	3rd	1
Perifosine §	2nd	2

clinicaltrials.gov. ‡: NCT01468688; †: NCT01735968; §: NCT00455559

Conclusions

The landscape of GIST treatment has radically changed in recent years with the introduction of targeted therapies revolutionizing treatment in both the adjuvant and advanced settings. Growing understanding of the mechanisms underlying treatment resistance in what was previously thought of as a "genetically simple tumor" has led to the investigation of new molecules, both alone and in combination with the standard therapy, in order to overcome such resistance. In particular, the discovery and development of immune checkpoint inhibitors and their investigation in GIST offer the potential to exploit self-immunity to enhance treatment outcomes with an acceptable toxicity profile. All these advances broaden the treatment landscape and brighten the future for GIST patients, but issues of toxicity (especially with TKI combinations) and economic sustainability are likely to be ongoing challenges. The identification of reliable predictive biomarkers for new treatments is urgently needed so that clinicians can individualize therapy for each patient and therefore maximize the risk to benefit ratio.

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