Feature Article

GIST: the past, the present and the future

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Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasm of the gastrointestinal (GI) tract. However, they only account for <1% of primary GI neoplasms. They are commonly found in the stomach (60%) and small intestine (25%), but may also occur in the colon, rectum, oesophagus, mesentery and omentum (15% total) [1].

The incidence across genders has been reported to be similar [2,3] although some studies have found a higher predominance among men [4,5]. The median age at diagnosis is approximately 63 years [4]. In most GISTs the central oncogenic drivers are the tyrosine kinase enzymes KIT and, to a lesser degree, platelet-derived growth factor receptor alpha (PDGFR-α), both of which become constitutively activated following certain primary mutations. Such gain-of-function mutations can occur with a frequency of up to 80% in the *c-KIT* gene and 5–8% in the *PDGFR*-α gene [1].

Surgery remains the standard of care for the treatment of primary, resectable GIST. However, rates of recurrence and/or metastasis are as high as 50%; even following R0 resection, GISTs are resistant to conventional chemo- and radiotherapy [6].

In patients with *c-KIT*-positive unresectable and/or metastatic advanced GIST, imatinib provides disease control in approximately 70–85% of patients treated, with a median progression-free survival (PFS) of approximately 20–24 months and a median overall survival (OS) of approximately 5 years [1,7–10].

In cases of progression or intolerance on imatinib, second-line standard treatment is sunitinib. Sunitinib proved effectiveness in terms of a PFS of 24.1 weeks following a '4 weeks on, 2 weeks off' regimen: median time to progression (TTP) was more than four times longer with sunitinib compared to placebo at an interim analysis (27.3 *versus* 6.4 wks; HR 0.33, P<0.001), and the trial was unblinded, allowing placebo patients to cross over to sunitinib. [11]. This opens a new era of hope for patients who become progressive or intolerant on imatinib.

Recent clinical trials have evaluated the role of adjuvant therapy, since the rate of recurrence following surgery can be substantial. Neoadjuvant or preoperative therapy is another area of intense investigation for the management of marginally resectable or resectable GIST associated with a risk of increased morbidity.

Natural history

Prior to the late 1990s, GIST was a disease which was poorly understood, and whose pathogenesis, natural history and even cell of origin were unclear. In addition, GISTs were frequently diagnosed as other entities, which included leiomyosarcoma, leiomyoblastoma, bizarre leiomyoma, plexosarcoma and gastrointestinal autonomic nerve tumour (GANT), amongst others [12].

It was not until the seminal discovery by Hirota and colleagues in 1998 that the first clear insights into this disease were gained. In this landmark publication, the group reported the finding of activating *c-KIT* mutations in a significant proportion of GISTs, with constitutive ligand-independent activation of the KIT-receptor tyrosine kinase (RTK), and a near universal expression of KIT on immunohistochemistry [13]. Corroborated by Kindblom and others, it was demonstrated that GIST cells were closely related to the interstitial cells of Cajal [14].

This understanding provided the platform for accurate and uniform diagnoses of this uncommon tumour and the rational development and use of tyrosine kinase inhibitors (TKIs) in the management of GISTs.

Prognostic factors

GISTs have an uncertain clinical behaviour ranging from benign to malignant, making the outcome totally unpredictable. Over the years many factors have been examined, such as size, histopathology, immunohistochemistry and molecular genetics. It has been found that it is very difficult to predict the malignancy potential. Thus, there is no accepted staging system for GIST. Multiple parameters have been considered as predictors of malignancy. At present, size and mitotic count appear to be the most

useful predictors of malignant behaviour [15].

Tumours <5 cm are usually low risk, while those >5 cm are usually high risk. However, tumours <5 cm cannot always be predicted to be benign, as there is always a chance of metastasis [16].

Furthermore, the mitotic count is a reliable parameter. Mitoses <5 per 50 high power fields (HPF) usually characterise GISTs as benign. Duodenal stromal tumours characterised as benign have <2 mitoses per 50 HPF, while the cut-off for ileal GIST is 5 mitoses per 50 HPF. It is important to point out that 50 HPF is the minimum number necessary to generate an accurate index of proliferative activity [17]. However, GISTs in the stomach, measuring 5–10 cm, usually have a good prognosis, as long as the mitotic count or Ki67 rate is low. On the other hand, small-intestine tumours >5 cm behave in an aggressive way, regardless of the mitotic index. Finally, GISTs occurring anywhere, that measure >10 cm, tend to behave in a malignant way.

Many studies [15] have indicated that there are several features, such as sclerosing, that are related to a more favourable prognosis, while a hypercellular sarcomatous appearance predicts an aggressive behaviour. In gastric tumours, diffuse nuclear atypia, coagulative necrosis and ulceration have been found to be unfavourable prognostic features, while nuclear palisading and skeinoid fibres were favourable, in a large series by Miettinen *et al.* [4].

Immunohistochemical markers may be of importance in predicting the malignant behaviour of GISTs. Increased expression of cell cycle markers (MIB-I or Ki-67) has been linked to a less favourable prognosis in larger studies [18]. *P16* is a tumour-suppressor gene that inhibits cell cycling by arresting cells in G1 before entry into the S phase. *P16* has been found to be downregulated in malignant GISTs in some studies, and has been found to be a prognostically favourable variable in others [19].

Mutations in KIT exon 11 are found to be more common in larger tumours, and the presence of this mutation has been shown to have an adverse prognostic influence. Deletions, compared with point mutations, in exon 11 have also been found to be a significant unfavourable factor in patients with gastric GISTs [20].

The National Institute of Health (NIH) Workshop, in 2001, suggested that a classification of GISTs in terms of their relative risk of aggressive behaviour, rather than as benign or malignant, seemed to be necessary. The guidelines recommend classifying GISTs into risk categories, based on size and mitotic count, emphasising that no lesion can be de definitively labelled as benign. Until recently, only mitoses and size of tumours were considered as highly important prognostic factors when evaluating the risk for metastasis and residual disease in patients with GISTs. [21].

Management: success stories

Imatinib

A large number of clinical studies have demonstrated the effectiveness of a selective tyrosine kinase inhibitor, imatinib (Gleevec®; Novartis Oncology), in the treatment of unresectable or metastatic GIST. The preliminary results from the Phase II B2222 study, in which 147 patients with GIST received treatment with imatinib at either 400 mg/day or 600 mg/day, showed a partial response (PR) in 53.7% of patients overall (imatinib 400 mg/day 49.3%; imatinib 600 mg/day 58.1%). Treatment with imatinib was generally well tolerated and most adverse events (AEs) were mild to moderate in intensity [22]. Long-term results from the trial showed an objective response rate (ORR) of 66.7% and a complete response (CR) in 1.4% of patients. Median overall TTP was 24 months, while median overall survival (OS) was 57 months and was consistent across the two arms. This resulted in a very important observation that patients with KIT exon 11 mutations were associated with a better prognostic outcome in response to imatinib than other KIT mutations, or no mutations [7].

In two large Phase III trials performed in parallel in patients with metastatic GIST [EORTC/intergroup 62005 (n=946) and US/CDN SO033 (n=746)], comparison of imatinib 400 mg/day with 800 mg/day dosing indicated that the two dose levels resulted in similar response rates across all patients. However, treatment with imatinib 800 mg/day resulted in significantly longer median PFS in the EORTC 62005 trial, which reported disease progression at 2 years in 56% of patients receiving imatinib 400 mg/day compared with 50% of patients receiving imatinib 800 mg/day. The incidence and profile of all-grade AEs observed in the 400 mg/day and 800 mg/day treatment groups were similar, with anaemia (7% and 17%, respectively), granulocytopenia (7% each) and fatigue (6% and 11%, respectively) representing the most commonly occurring grade 3–4 AEs [23].

Furthermore, the analysis of imatinib efficacy following crossover of patients (n=133) from the 400 mg/day treatment arm to the higher dose in this study indicated a median PFS of 81 days following crossover [24]. With some focus on the mutational status, comparison of imatinib 400 mg/day with

800 mg/day dosing in advanced GIST showed greater benefit from treatment with the higher dose in patients with KIT exon 9 mutations [25].

Meanwhile, the data from the SO033 study showed no significant differences with respect to median PFS and OS between patients receiving the two imatinib dose levels, and KIT expression did not correlate with PFS in study SO033, although a significant difference in median OS was observed when KIT-positive tumours were compared with KIT-negative tumours [8].

In order to try to decide which dose is better, a meta-analysis of these two trials, based on a dataset of more than 1500 patients, confirmed the superiority of imatinib 800 mg/day in terms of PFS, but not in terms of OS [26]. Of note, the beneficial effect of the 800 mg/day dose level on PFS was confined to the subgroup of patients with GISTs showing KIT exon 9 mutations.

Multi-targeted agents have paved the way for the future: median OS in metastatic GIST patients was between 9 and 20 months before the imatinib era and is now approaching 55–57 months [27].

Sunitinib

Before the introduction of sunitinib (Sutent®; Pfizer), there was no efficient systemic treatment for patients with metastatic GIST failing imatinib 800 mg/day.

Sunitinib inhibits multiple-receptor tyrosine kinases including KIT, PDGFRs (-a and -b), 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. Sunitinib has demonstrated direct anti-tumour and anti-angiogenic activities in preclinical studies [28].

In a Phase III study of 312 patients with imatinib-resistant or -intolerant GIST, sunitinib 50 mg/day (administered in 6-week cycles of 4 weeks on treatment followed by 2 weeks off treatment; Schedule 4/2) demonstrated superior efficacy compared with placebo in an interim analysis. Median TTP, the primary endpoint of the study, was 27.3 weeks for sunitinib-treated patients and 6.4 weeks for placebo-treated patients ($P<0.0001$). Patients receiving sunitinib achieved median PFS of 24.1 weeks compared with 6.0 weeks for those receiving placebo ($P<0.0001$). In addition, sunitinib treatment resulted in improved OS compared with placebo ($P=0.007$). Treatment-related AEs were generally mild to moderate in intensity; grade 3–4 AEs observed in sunitinib-treated patients included fatigue (5%), hand–foot syndrome (4%), and diarrhoea and hypertension (3% each) [29]. Following the demonstration of significant clinical benefit in the interim analysis, the study was unblinded and patients were allowed to cross over from placebo to sunitinib treatment. Updated survival data have been published from this study; median OS was 73.9 weeks with sunitinib compared with 35.7 weeks with placebo ($P<0.001$) [30].

One of the potential limitations of sunitinib 50 mg/day administration by Schedule 4/2 is the possibility of tumour flare-up during the 2-week off-treatment period. Therefore, continuous daily dosing (CDD) of sunitinib at a dose of 37.5 mg has been investigated as an alternative dosing regimen. In a Phase II study in patients with advanced imatinib-intolerant or imatinib-resistant GIST, treatment with sunitinib 37.5 mg by CDD resulted in a median PFS of 34 weeks, with an estimated median OS of 107 weeks. Most treatment-related AEs were grade 1–2 in severity, similar to those observed with sunitinib administered by Schedule 4/2, and no grade 4 AEs were recorded. The CDD regimen was associated with relatively constant drug exposure with no signs of drug accumulation [31].

Future developments

Adjuvant therapy: who will benefit and who will not?

High-risk GIST (i.e., that with the highest incidence of recurrence following surgical resection) is the most likely to benefit from the adjuvant setting. The role of targeted therapy in the adjuvant setting for the treatment of GIST has been evaluated in several trials. Data from the Phase II Intergroup ACOSOG Z9000 study demonstrated that adjuvant imatinib treatment resulted in OS of 99% at 1 year and 97% at 2 years in patients with high-risk primary GISTs. In addition, the recurrence-free survival (RFS) in these patients was 94%, 73% and 61% at years 1, 2 and 3, respectively, following treatment with adjuvant imatinib. Patients with KIT exon 9 mutations appeared to have the highest recurrence rates [32].

These results were validated in other trials and the preliminary data from the Phase III Intergroup ACOSOG Z9001 study showed that adjuvant imatinib increased 1-year RFS compared with placebo (97% *versus* 83%, $P<0.0001$) [33].

Further data from these ongoing trials are needed to fully investigate the role of TKIs for the adjuvant treatment of GIST, with more investigation into the optimal duration of adjuvant imatinib therapy.

Novel agents

Several novel targeted therapies are being evaluated in the treatment of GIST. Many drugs under development are similar in their actions to imatinib

and sunitinib in that they inhibit the KIT and/or PDGFR proteins. Some of them also inhibit VEGF or its receptors, resulting in anti-angiogenic effects, similar to sunitinib. Most of these molecules have shown effectiveness in pre-clinical studies and Phase I studies; but they should be evaluated in larger Phase II and III clinical trials for a better estimation of their benefits.

Among these molecules there is nilotinib, which targets Bcr-Abl, PDGFR and KIT, and which has been evaluated in a Phase I study in patients with imatinib-resistant GIST. Nilotinib was evaluated as both monotherapy and in combination with imatinib. Results indicated that 78% of patients achieved stable disease (SD) lasting from 6 weeks to more than 6 months [34].

Other novel agents include motesanib, everolimus, dasatinib, sorafenib and others that are being widely investigated, especially in imatinib- and sunitinib-resistant cases, and we will await the results in the next few years [35].

Conclusion

Curative therapy for GIST remains elusive. However, PFS and overall survival have been greatly improved by treatment with TKIs alone or in combination with surgical resection. Because of the heterogeneity of the molecular, cellular, and gross pathologies of GIST, treatment regimens must be carefully planned using a multidisciplinary approach.

With greater knowledge of the prognostic factors that affect patient response, particularly tumour genotype, tailored treatment of individual patients with GIST is becoming increasingly important and should be used routinely to optimise treatment outcomes.

Nowadays, additional therapeutic options beyond first-line imatinib are required. Sunitinib has demonstrated efficacy in the second-line treatment of patients with imatinib-intolerant or imatinib-resistant GIST in a Phase III study, extending OS compared with placebo treatment in this patient group. Studies are ongoing to elucidate the effects of imatinib and sunitinib in GIST patients according to mutational status and in alternative dosing and combination therapy regimens. Several established and novel multi-targeted agents are also under investigation, which may expand the range of treatment choices available in the future for patients with advanced GIST.

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