Long-term Disease Control with Imatinib Treatment in Metastatic Gastrointestinal Stromal Tumours

a report by
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Gastrointestinal Stromal Tumours – 20th Century Management

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumour of the intestinal tract. Historically, these tumours were labelled leiomyosarcomas, leiomyomas or leiomyoblastomas. In 1983, Mazur and Clark reclassified these tumours as GIST because they contained both smooth muscle and neural features.[1] Later studies found these tumours also expressed CD34 and KIT, further aiding in their classification.[2,3] The most common site of primary tumours is the stomach (39–70%), followed by the small intestine (31–45%), colon, rectum and anus (10–16%), mesentery and peritoneum (8%), with rare cases arising in the oesophagus.[4-8] Metastatic disease is most commonly found in the liver, as well as the peritoneum and omentum, with less common sites of spread involving the lung and bone.

In 2000, patients with metastatic GIST had only one viable treatment option – surgical resection. This was an appropriate option for a subset of patients; however, despite surgery, some patients were destined to relapse.[6] Systemic therapy for GIST with standard chemotherapy was largely ineffective. Patients with metastatic disease had rapid progression of disease, with an average survival of 12–18 months.[9] There was clearly a need for effective therapeutic options.

The discovery of KIT as the biologic driver of GIST provided the rationale for the testing of imatinib, a tyrosine kinase inhibitor with specificity against ABL, KIT, platelet-derived growth factor receptor (PDGFR) and TEL.[10,11] Imatinib had been shown to have efficacy against chronic myelogenous leukaemia with the Philadelphia chromosone, the BCR-ABL translocation.[12,13] The identification of PDGFR as an alternative oncologic driver provided further rationale for the use of imatinib in GIST.

The US-Finland Trial

The US-Finland trial was the first multi-institutional study of imatinib in metastatic GIST. It was designed to evaluate two doses of imatinib – 400mg and 600mg daily – based on safety data from an on-going phase I trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC).[14] The number of patients included in the trial was initially planned to be 36. However, this was increased once the initial benefits had been observed. The sample size of the study, however, was not sufficient to determine whether one dose level was superior to the other. The initial trial planned to monitor patients for three years. Patients at the lower dose level were allowed to cross over to the higher dose level at the time of tumour progression. With the completion of the phase I trial demonstrating the safety of imatinib at 400mg twice daily, the trial was amended to allow patients to have their dose increased to a maximum dose of 800mg daily.

Imatinib – Response and Tolerability

The early period of the trial was positive as patients experienced rapid symptomatic relief. With longer follow-up, the symptomatic benefit translated into radiographic responses using bi-dimensional tumour (see *Table 1*). The majority of patients achieved a partial response (66.7%) with only two patients (1.4%) achieving a complete response. An additional 15.6% of the patients attained stable disease, for an overall clinical benefit of 83.4%.

The rate of progression was 11.6% with an additional 4.8% of patients who were removed from study prior to disease response evaluation. Responses evolved over time, with a median time to response of 12 weeks. However, the maximum time to response was 171 weeks. In addition, not only were patients responding to therapy, but they were tolerating imatinib with very acceptable safety profiles. Grade III and IV adverse events included fluid retention (6.8%, 12.2%), abdominal pain (12.3, 5.4%), haemorrhage (5.5, 10.8%) liver toxicity (5.5, 8.1%), diarrhoea (2.7, 6.8%), and nausea (5.5, 4.1%), respectively, in the 400 and 600mg cohorts. No

cases of congestive heart failure were observed in this group.

The Extension Trial

At the end of three years, 67 (48%) patients remained on study with disease control. These patients were offered enrollment onto a four-year extension trial. Fifty-six patients (38% of the original study cohort) entered this extension trial. Imatinib was now commercially available and some patients, many of whom travelled a great distance to be treated at participating centres, opted to stay closer to home. The remaining patients have been continuously monitored and, at the time of the last data analysis, 48 patients (33%) remained on study. The reasons for leaving the extension trial are primarily due to progressive disease.

Table 1: US-Finland Response Rate

	400 mg N=73 n (%)	600 mg N=74 n (%)	All Patients N=147 n (%)
Complete Response	0	2 (2.7)	2 (1.4)
Partial Response	50 (68.5)	48 (64.9)	98 (66.7)
Stable Disease	10 (13.7)	13 (17.6)	23 (15.6)
Progression	11 (15.1)	6 (8.1)	17 (11.6)
Not evaluable/ Unknown	2 (2.7)	5 (6.8)	7 (4.8)

trend as overall survival: patients with exon 11 mutations have a longer progression-free survival compared with exon 9 and wild-type tumours.

Response rates also varied by site of mutation, with exon 11 tumours having a objective response rate greater than 80%, followed by approximately 48% response rate for exon 9 patients, and no objective responses noted in the wild-type tumours. The efficacy of imatinib in patients with metastatic and unresectable GIST from this trial has been confirmed in two large phase III trials.[17,18]

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Overall, analysing data from both the primary and extension studies, the disease-free progression survival and overall survival has not varied by dose level. The median time to progressive disease was 84 weeks and in responders the median duration of response was 118 weeks. Overall survival for all patients is 248 weeks, which contrasts markedly with 12–18 months survival in the era prior to KIT-directed therapy. Importantly, patients with stable disease as best response had an equivalent overall survival to patients with partial or complete responses.

Like other tyrosine kinase inhibitors, the efficacy of imatinib has been correlated with the site of mutation in the target gene. Imatinib response was greatest in tumours with an exon 11 KIT mutation. In this small cohort, exon 9 patients had a better survival compared with patients with wild-type KIT tumours. The median overall survival for patients with exon 11 tumours has not been reached, whereas for exon 9 it is 192 weeks versus 36 weeks for patients with wild-type tumours. The subsequent phase III studies have confirmed the improved outcome for tumours with exon 11 mutations.[15,16] However, in the EORTC-led phase III study, the benefit for tumours with wild-type and exon 9 mutations are similar, although inferior to GIST with exon 11 mutations.[16] Progression-free survival in the US-Finland study followed the same

Conclusion

The results of the US-Finland trial of imatinib in GIST demonstrate that the use of a biologically relevant targeted therapy can lead to long-term control of metastatic tumours. GIST is an ideal tumour model because of the simplicity of its biology. KIT and PDGFR serve as the biologic drivers for growth and cell division. When imatinib turns off these receptors, the growth stimulus is removed and tumours stop increasing with some even decreasing in size. However, the biology of GIST is more complicated than first impressions would suggest. The differences in response, time to tumour progression, and overall survival based on genotype of the oncogenic driver inform us about the manner in which imatinib interacts with the KIT receptor, but also leaves open questions about the differences in tumour biology with alternate kinase mutations.[19]

The 21st century management of GIST remains a

clinical challenge. The long-term survival of patients on imatinib has been gratifying, yet those whose disease progresses require alternative approaches. Second-line therapy with sunitinib malate is now available, although with shorter disease control than was seen with imatinib.[20] Surgery, which for a time appeared to be supplanted by imatinib, still has a part in the control of metastatic disease, but its role is still being defined.[21,22] Testing of novel compounds is needed and is on-going, as is the need to continue investigating the biology of GISTs. ■

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