Gastrointestinal stromal tumours (GIST): biology and treatment

I. Judson

Cancer Research UK Centre for Cancer Therapeutics, The Institute of Cancer Research, Sutton, UK

Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GISTs) are rare, but are nevertheless the commonest mesenchymal tumours to arise in the gastrointestinal tract. Estimates vary but it seems likely that the incidence is in the region of 10 per million per annum. While previously diagnosed as leiomyosarcomas, it was recognised some years ago that there was a group of sarcomas, arising from the gastrointestinal tract, that did not have the typical features of leiomyosarcoma, e.g. immunohistochemical staining for desmin and smooth muscle antigen (SMA). It was noted that these GISTs could be identified by staining for CD34 [1, 2]. More recently, it was discovered that they also expressed the receptor tyrosine kinase KIT (CD117) [3, 4] and that this expression was often associated with gain of function mutations [5]. Hirota and others proposed that in view of the fact that these immunohistochemical features are shared with the interstitial cells of Cajal, perhaps these, or a common progenitor, are the cell of origin for GIST [3, 5, 6]. Cajal cells form a network within the myenteric plexus of the gut and coordinate slow wave contractions or peristalsis. They are also known as pacemaker cells. Cajal postulated in 1893 that the cells he described might play an important role in gut movement. This function has recently been confirmed by electrophysiological measurements demonstrating rhythmic depolarisation.

Immunotyping for KIT has since formed the basis for more accurate diagnosis and has led to a better understanding of the molecular basis of the disease. Gastrointestinal stromal tumours display a wide variety of grades of malignancy, but there is doubt that any are truly benign. It is true that low grade, small tumours that have been completely excised rarely give rise to subsequent problems. However, even apparently benign, larger tumours can subsequently recur locally, spread trans-peritoneally and metastasise to the liver. It is best to regard all of them as of uncertain malignant potential and important to note that the majority of them have activating mutations in the \( c-kit \) proto-oncogene [7].

Molecular biology of GIST

It is now known that in the majority of cases, KIT is constitutively activated by \( c-kit \) mutations (Table 1). The commonest mutations, in exon 11, affect the juxtamembrane region of the receptor [7, 8]. Receptor dimerisation normally occurs on binding of stem cell factor to the extracellular domain and leads to cross-phosphorylation of tyrosine residues, activation and subsequent phosphorylation of downstream targets. This results in activation of both the PI3-kinase and MAP kinase signalling pathways. Gain of function, or activating mutations lead to a persistent growth or survival signal, in the absence of an external stimulus in the form of growth factor binding. One effect is to remove inhibition of dimerisation in the absence of stem cell factor.

Gastrointestinal stromal tumours (GIST) occur mainly in the stomach (60%), with the remainder in the small intestine (15%) and other sites, including large bowel, oesophagus, rectum, mesentery and omentum. They may present with a variety of symptoms such as vague abdominal pain, gastrointestinal bleeding, fever, night sweats and weight loss. Surgery remains the most important treatment modality, but, as will be discussed below, this may in the future be combined with drug therapy.

Development of imatinib

It was the discovery of specific molecular abnormalities driving individual malignancies and the unravelling of the growth factor signalling pathways that led to the belief that this would be fertile ground for anticancer drug discovery. This development was facilitated by the techniques of high throughput screening and generation of large chemical libraries that became available in the 1990s. Bcr–Abl, a fusion protein produced by chromosomal translocation, and responsible for the fundamental malignant process in chronic myeloid leu-
kaemia, was only one of a series of tyrosine kinase molecules initially chosen as targets. The majority of which were membrane receptors, such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR). This work led to the discovery of imatinib (STI571, Gleevec), a molecule with the ability to inhibit Bcr–Abl positive cells and with in vivo activity in animal models [9].

**Clinical trials in chronic myeloid leukaemia (CML)**

Early studies by Druker et al. [10] reported dramatic results using STI571, as it was then known, in patients with CML who had failed standard treatments. Astonishingly, in the initial phase I trial, the majority of patients with chronic phase CML who had failed interferon-α, achieved a complete response at doses of ≥300 mg a day. This meant that the blood counts returned to normal and in 13% of patients there was complete disappearance of Philadelphia-positive cells from the bone marrow. When first reported most patients were still responding at just under a year. In addition to the anticancer effect, this drug displayed high selectivity for the chosen target, was apparently lacking in major toxicities and, because of a median elimination half-life of 14–16 h, could be given orally once a day. Subsequent trials showed that even those patients with more advanced aggressive disease could benefit from treatment, albeit the responses were less durable.

**Imatinib in gastrointestinal stromal tumours**

As mentioned above, imatinib not only inhibits Bcr–Abl, but also PDGFR and KIT.

Until the advent of imatinib, there was no effective treatment for unresectable or metastatic GIST. Conventional sarcoma chemotherapy agents such as doxorubicin and ifosfamide do not work [11, 12]. Knowing that imatinib also inhibited other tyrosine kinases, a systematic search for other disease targets was made. The recent identification of KIT expression as a defining characteristic in GIST made this disease an obvious place to start. One patient was successfully treated in Helsinki in the Spring of 2000 [13] and trials in patients with GIST began in the US and Europe in the Summer of that year. The European trial included some patients with other sarcoma types, in the knowledge that PDGFR is often over-expressed. In Europe, a dose escalating phase I trial was performed, over the dose range 400–1000 mg daily, since no such study had been done in solid tumour patients.

A similar range of side effects were observed to those seen in CML patients, namely indigestion, nausea, oedema, rash and mild myelosuppression. Side effects were dose-limiting at 1000 mg daily and 800 mg was deemed to be a feasible dose to be explored in subsequent studies [14].

The speed and extent of tumour regression seen in some patients was truly astonishing. Significant numbers of patients reported almost immediate relief from symptoms such as fever, sweats and anorexia, after starting imatinib, in parallel with rapid softening of massive intra-abdominal tumours and regression of liver enlargement. Even patients with advanced cachexia and a limited life expectancy were found to respond, with an improvement in weight and performance status. This has enabled a number of patients to return to work and regain their zest for life in general. An example of the dramatic reduction in tumour volume over a 3 month period is shown in Figure 1A and B.

Doctors in Leuven and Boston reported seeing rapid normalisation of positron emission tomography (PET) scans, indicating a rapid impact on glucose transport or metabolism. This could happen within a week, even within hours, and predicted for a subsequent measurable response on computed tomography (CT) scan. Conventional imaging also proved to be unusual. Well before formal criteria of response were met, tumours appear to liquefy, appearing much less dense on CT scan. Subsequent tumour shrinkage may take many months.

The first study in the USA compared 400 mg and 600 mg daily [15] and both this and the results of the phase I trial in Europe [14] indicated that 50–60% of patients may expect to have major tumour shrinkage, up to 80% will have clinical benefit, as measured by a substantial improvement in symptoms and at least stabilisation of their disease, with only a
minority failing to respond at all. These results have so far been supported by the results from subsequent phase II and phase III trials. As yet there is no clear evidence for a dose-response relationship but the phase III trials have compared starting doses of 400 mg and 800 mg daily. It will be some time before a comparison can be made in the median progression-free and overall survival times for the two groups but once the trial has closed a comparison of response rates will be possible.

Mutations and resistance to imatinib

The likelihood of response to imatinib in GIST is linked to the nature of the c-kit mutation, as shown in Table 2. It is said that the duration of remission in those patients that do respond follows the same ranking, with exon 11 patients having responses of 12 months or more, exon 9 patients tending to relapse after 6 months and wild type being associated with transient or no response. However, the published data are sparse and predictions are unreliable.

In addition to the fact that certain mutations are unfavourable for a response to imatinib, in CML it has been shown that amplification of bcr–abl may occur, overwhelming the inhibitory capacity of the drug. In some patients an increase in the dose is effective in regaining control of the disease. Mutations might also arise that are unfavourable for binding of imatinib. In addition, other chromosomal changes occur in GISTs, essentially deletions that might represent loss of tumour suppressor genes. Anecdotally, there are GIST patients who have progressive disease at an initial dose of 400 mg who have stabilised on a higher dose. Similarly, patients progressing after an initial response might possibly respond again to a higher dose, although this strategy has yet to be confirmed in practice.

Future studies

There remain many questions to be asked, some of which may be answered as the current trials mature and data become available. For example, we still do not know the optimum dose of imatinib to be used in the treatment of GIST. We need to know how best to use the drug in the pre-operative setting, will it be helpful, could it lead to easier, less hazardous surgery.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>PR (%)</th>
<th>SD (%)</th>
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<tbody>
<tr>
<td>Exon 11</td>
<td>70</td>
<td>15</td>
</tr>
<tr>
<td>Exon 9</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>None (wild type)</td>
<td>12</td>
<td>20</td>
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PR, partial response; SD, standard deviation.

Would neo-adjuvant or adjuvant treatment result in prolonged survival?

References
