How much molecular pathology is required to treat GI stromal tumours?

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The discovery in the late 1990s of the critical role of constitutive activation of the KIT receptor, most often due to *KIT* mutation, in gastrointestinal stromal tumours (GISTs) followed closely by the remarkable success of the selective KIT tyrosine kinase inhibitor, imatinib, has led to rapid expanding research into the underlying biology of these mutations and their implications for both prognosis and response to treatment. There would appear to be accumulating evidence of the importance of these mutations; however, the role of mutational analysis of *KIT* or *PDGFRA* in tailoring the treatment strategy for an individual patient is far from clear.

KIT (CD117) is a transmembrane tyrosine kinase receptor which under normal conditions undergo dimerisation and subsequent phosphorylation of the tyrosine kinase ATP pocket when ligand present. This leads to downstream signalling that ultimately leads to a variety of processes including proliferation. The vast majority ($\geqslant$95%) of GISTs demonstrate positive immunohistochemical staining for KIT, and this simple test has become critical in the differential diagnosis of GISTs as other mesenchymal tumours of the gastrointestinal tract will almost without exception be negative.

Activating mutations of KIT are found in at least 90% of KIT positive GISTs. These mutations lead to ligand independent phosphorylation of ATP pocket resulting in uncontrolled downstream signalling and is absolutely critical to the malignant pathogenesis of this rare tumour. Mutations within exon 11, which codes for the juxtamembrane domain, account for approximately 70% of all KIT mutations. Mutations in the extracellular domain (exon 9) occur in approximately 15%, whereas mutations within the split kinase domain (exon 13 and 17) occur only infrequently. There are a small group (~5%) of KIT positive GISTs where no mutation in KIT is seen, the so-called wild type KIT GIST. There are a small number (<5%) of GISTs that have clinical and histological features of GIST but are KIT negative, and the driving mutation for most of these is to be found within *PDGFRA* (predominantly in exon 18, close to the enzymatic pocket). These tumours appear to occur more frequently in the stomach and to a lesser extent in the omentum than in other parts of the GI tract. There is also a small number for which no mutation has been found for either of these two oncoproteins. Immunohistochemical staining for KIT does not correlate with the type of mutation. There are several types of mutations within these two oncogenes, including point mutations, deletions or duplications, and these occur at different sites within the involved exon. There is some evidence to suggest that these may have prognostic value but this needs further clarification.

Imatinib is a selective and potent inhibitor of KIT and PDGFRA tyrosine kinase receptors, and its remarkable activity in this chemoresistant tumour has been demonstrated in large multinational studies. The objective clinical response rate (partial response and stable disease) across the studies was consistently in the order of approximately 80%, with a median progression free survival that is consistently found to be about 2 years. What has been subsequently shown retrospectively through mutational analysis of archival tissue, is that the type of KIT mutation has a role in prediction of response to imatinib, and in determining progression free survival for patients being treated with imatinib. It is perhaps not surprising that exon 11 mutations, which code for the juxtamembrane domain, demonstrate significantly higher partial response rates (85%) compared with exon 13 or 17, which code for the kinase domain. In addition, there is strong evidence to suggest that exon 11 also confers a significantly longer progression free survival and overall survival for those patients treated with imatinib compared with those with the less common KIT mutations. PDGFRA mutant tumours show significantly lower and shorter responses to imatinib.

Most patients receive imatinib 400 mg as their initial treatment, based on the findings of two large

multinational studies comparing 400 mg with 800 mg daily. Both studies allowed cross over to the higher dose at time of progression for those that had initially been randomised to the 400 mg arm. In both the EORTC–ATSIG study, and the US–Canadian study, no difference in response rates was seen between the two doses. However, whilst the North American study did not show any difference in either progression free or overall survival between the two arms, the EORTC study demonstrated a progression free survival advantage for the higher dose arm. This was confirmed with the recent meta-analysis of these two studies.

There is, however, evidence that the mutational status of the patient may be important with respect to the dose of imatinib that the patient receives. There would not appear to be any survival advantage of high dose imatinib for the majority of patients with exon 11 mutations. Patients with exon 9 mutations do demonstrate improved survival if they are treated up front with high dose imatinib compared with 400 mg, although their progression free survival even at the higher dose is probably not as high as that for those patients with exon 11 mutations.

Almost inevitably, patients will progress on imatinib. One of the likely causes for this is due to development of secondary mutations, as well as selection and growth of intrinsically resistant clones within the original tumour. The question arises of what is the next most appropriate systemic option.

Increasing the dose of imatinib from 400 mg to 800 mg daily will confer disease control in approximately one third of patients who were progressing on the lower dose, and it may be (although there has been no prospective data to support this as yet) that it is those patients with exon 9 mutations who will most benefit from this strategy.

Sunitinib is a second generation tyrosine kinase receptor inhibitor with potency against both KIT and VEGF. A randomised placebo controlled study in patients with imatinib resistant disease demonstrated significant survival advantage of this agent over placebo, with the majority of best responses being stable disease. Preliminary clinical evidence has suggested that exon 9 mutation confers a higher likelihood of prolonged event free survival but the data has yet to be validated by either larger sample size or by prospective validation of these findings.

Whilst these data point toward the importance of the mutations in both predicting response and the duration of the clinical benefit, there are too many uncertainties and controversies that need to be resolved. There needs to be validation in the prospective setting of the role of the mutations in response, both in the setting of high dose imatinib, as well as for sunitinib. This caveat will have to be extended to each new tyrosine kinase inhibitor that comes along, including nilotinib.

Mutational analysis requires significant technology, expertise, and standardisation of technique and analysis, and is not without a significant cost and this will act as an impediment to the ability to perform these techniques outside of academic institutions. Most mutational analysis studies have been performed on original archival tissue and so the role of secondary mutations and other genomic changes has not been defined.

As imatinib affords significant and prolonged benefit to most patients who initially require systemic treatment for their GIST, there would not appear to be a strong case for basing initial treatment on the mutational status. At time of relapse the case is far less clear currently, but should become more so in the near future. It is, however, vital that prospective studies of the role of these mutations be undertaken if in the future we are to be able to better tailor our patient's treatments to the message in the mutation.

Conflict of interest statement

None declared.