

## TRIAL WATCH

## GIST genotyping

Imatinib (Glivec) is the standard therapy for gastrointestinal stromal tumours (GISTs), and a Phase III trial — reported recently at the 2005 Annual Meeting of the American Society of Clinical Oncology in Orlando, Florida — shows that kinase genotyping can predict the likelihood and duration of response to the drug.

Most patients with metastatic GISTs eventually develop resistance to imatinib and often acquire secondary mutations in the genes that encode kinases, such as platelet-derived growth factor  $\alpha$ -polypeptide (PDGFA) or the oncogenic tyrosine kinase KIT. The results of the trial, which were presented at the meeting by Michael Heinrich, showed that most GISTs (324 of 332 patients in the study) express constitutively activated mutant isoforms of KIT. Although the overall frequency of KIT mutations is the same for GISTs that express KIT and those that do not, the researchers found that patients who express KIT isoforms with mutations in exon 11 of the gene had a better objective response (OR) to imatinib (OR = 67%) than patients with mutations in exon 9 of the gene (OR = 40%) or patients who had no KIT mutation (OR = 39%).

In fact, when Heinrich and colleagues examined the effects of age, sex, imatinib dose and the KIT mutations, multivariate analysis showed that the presence or absence of mutations in exon 11 was the best predictor of treatment response. Furthermore, the time to treatment failure for patients with mutations in exon 11 of *KIT* was longer (576 days) than for patients with mutations in exon 9 (308 days) or those with no mutations (251 days).

There was also an indication that patients with GISTs that had exon 11 mutations had better survival than those with exon 9 mutations or no mutations, although this trend was not statistically significant. Heinrich concluded that GISTs with different KIT kinase mutations are biologically different and that the differences are reflected in clinical outcome. The authors hope that the results will drive the development of therapeutic strategies that are tailored to patients whose GISTs do not express the exon 11 mutant *KIT*.

Curiously, in another presentation at the same meeting, Robert Maki explained that the outcome of treatment with the tyrosine-kinase inhibitor SU11248 was more effective in patients with *KIT* mutations in exon 9 than in exon 11. This study showed that SU11248 — which blocks several kinases including KIT and PDGFA and has anti-angiogenic and antitumour activity — is a promising clinical therapy for imatinib-resistant tumours.

Together, the studies indicate that GISTs must respond differently to imatinib and SU11248, although it is not clear why. As one participant at the meeting, Charles Sawyers (University of California, Los Angeles), mentioned, the results of this trial emphasize the importance of testing combinations of kinase inhibitors that bind targets in different conformations.

**ORIGINAL RESEARCH PAPERS** Heinrich, M. C. *et al.* Correlation of target kinase genotype with clinical activity of imatinib mesylate (IM) in patients with metastatic GI stromal tumors (GISTs) expressing KIT (KIT<sup>+</sup>). *J. Clin. Oncol. (Suppl.)* **23**, A7 (2005) | Maki, R. G. *et al.* Results from a continuation trial of SU11248 in patients (pts) with imatinib (IM)-resistant gastrointestinal stromal tumour (GIST). *J. Clin. Oncol. (Suppl.)* **23**, A9011 (2005).



## DIAGNOSTICS

## Auspicious antigens

Tumours are often immunogenic — they produce proteins that are not normally expressed in adult tissues and are therefore not regarded as ‘self’ by the immune response. Some of these genes are also expressed by germ cells, so they can be detected in the testes (which are immunoprotected). A group led by Andrew Simpson has used massively parallel signature sequencing (MPSS) to identify several new ‘cancer–testis’ (CT) antigens, which represent promising candidates for vaccines to augment the immune response against cancer.

The authors used MPSS to create an expression profile for various human tissues. They generated millions of short sequence tags from the 3′ regions of mRNAs expressed by human tissues and most of these tags were unambiguously assigned to individual genes. Using gene-expression databases, the authors identified those genes expressed predominantly in the testes and also expressed in CT-rich cell lines.

Using this set of testis-specific genes, the authors made real-time-PCR primers to quantify the gene expression in cancer cell lines. These 21 cell lines, which were already known to express at least one CT gene, included those derived from melanoma, sarcoma, hepatocellular carcinoma, small-cell and non-small-cell lung cancer, and colon, renal and bladder cancer.

The testis-specific genes fell into three main groups. Expression of one group was highly restricted to testes and germ-cell tumours and were not expressed in somatic

tissues or non-germ-cell cancers. A second group had strong testicular expression but only marginal low-level expression in cancer lines. Both of these groups of genes probably have limited potential as vaccine targets. However, a third group represents the true CT genes; these 20 genes have strong expression in the testes and are frequently activated in cancer, probably through hypomethylation or histone deacetylation. Although there is considerable variation in the frequency with which they are expressed in cancer, it is these CT genes — which have gone undetected in other studies — that have valuable immunotherapeutic potential.

Curiously, most of the CT genes found so far — including one of those identified in the present study, called CT45 — reside on the X chromosome. Indeed, the recently completed X-chromosome sequence showed that CT gene families are a feature of this chromosome. CT45 was expressed in 13 of the 21 cell lines tested and has similar structural and expression characteristics as several important known CT vaccine candidates. The authors found that CT45 belongs to a cluster of six identical or near-identical genes, which they conclude have probably arisen through gene duplication. This distinctive X-linked CT-antigen gene family represents a set of important candidates for anticancer vaccines.

Jenny Bangham

 **References and links**

**ORIGINAL RESEARCH PAPER** Chen, Y.-T. *et al.* Identification of cancer/testis-antigen genes by massively parallel signature sequencing. *Proc. Natl Acad. Sci. USA* **102**, 7940–7945 (2005)