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Imatinib Mesylate

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Imatinib mesylate (imatinib) represents an extremely important therapeutic advance in the treatment of both chronic myeloid leukaemia (CML) and gastrointestinal stromal tumour (GIST). In both diseases a specific molecular abnormality occurs at an early point in malignant development. In the case of CML this is the activation of the Abelson (ABL) protein by the t(9;22) translocation that creates the BCR-ABL fusion protein. In the case of GIST, gain of function mutations in *KIT* result in an activated KIT protein that is capable of dimerisation and cross-phosphorylation in the absence of growth factor binding.

Imatinib is an effective inhibitor of KIT, acting by preventing adenosine triphosphate binding to the active site of the tyrosine kinase domain, and has proven extremely useful in the treatment of GIST. It is only within the last 5 years that expression of KIT, as assessed by immunohistochemistry (CD117), has become accepted as the key diagnostic marker for GIST, emphasising the astonishing pace of this development. Prior to the introduction of imatinib there was no effective therapy for patients with locally advanced inoperable or metastatic GIST. This drug has revolutionised the treatment of this disease and as a result is now licensed for this indication in the US and Europe. The majority of patients receiving imatinib experience clinical benefit for periods of up to 2 years or more. In most cases this is associated with only mild, manageable adverse effects.

The commonest exon 11 *KIT* mutation, affecting the juxtamembrane region, is associated with the highest response rate; other mutations are less favourable and the presence of wild type *KIT* is especially unfavourable, presumably because such tumours are driven by a different molecular process. There remains much to learn about how best imatinib might be used in the neoadjuvant and adjuvant settings and what factors determine the development of resistance. These issues are the subject of ongoing or imminent clinical trials. ▲