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Imatinib

A Viewpoint by John M. Goldman

Imperial College School of Medicine, London, England

The chronic phase of Philadelphia chromosome positive chronic myeloid leukaemia (CML) has been known since the 1980s to be closely linked to the presence of a *BCR-ABL* fusion gene that expresses a BCR-ABL oncoprotein with greatly enhanced tyrosine kinase activity compared with the normal ABL protein. Thus the aberrant phosphorylation of 1 or more downstream substrates is thought to play a key role in 'causing' CML. This knowledge led logically in the 1990s to attempts to construct small molecules that would inhibit ABL kinase activity and hopefully prove clinically useful in treating CML. The molecule, originally called CGP 57148B, later STI571 and now imatinib, is the culmination of these efforts and is arguably the first convincing example of a 'rationally designed' drug that has turned out to be impressively effective in treating leukaemia. It has already displaced interferon-α (IFNα) as the drug of choice for treating newly diagnosed patients. It opens the door to a era of molecularly targeted therapy for all malignancies and thus hopefully signals the death-knell for the 'pan-toxicity' of many of the chemotherapy agents used so widely in the last century.

What then is so special about imatinib? First, it induces haematological remission in almost all chronic phase patients with great rapidity. Hydroxyurea will do the same at a much lower cost but its mechanism of action is essentially unknown. Second, and quite remarkably, imatinib induces major cytogenetic responses in about 50% of previously treated patients and this figure may be nearer 80% in previously untreated patients (cytogenetic responses are surrogate markers for survival but their value in imatinib-treated patients still needs to be proved). Third, the toxicity profile is generally acceptable for a drug used in the treatment of leukaemia.

What then are the problems? Mainly the fact that we do not yet have clear evidence that the drug will actually prolong survival; this seems probable but we need 1 or 2 more years follow-up. We do not know how many patients will achieve molecular remission which is undoubtedly a prelude to cure. We suspect that patients may acquire resistance to imatinib, although this may prove to be preventable. Finally, we know nothing of its possible late toxicity, but so far there are few indications that this will prove a limiting factor.

Patients treated with IFNα have a median survival of 6 to 7 years. Many are resigned to its considerable subjective toxicity and the inconvenience of daily injections. Imatinib has already proved itself substantially more acceptable than IFNα in the short term. Alone or in combination with other agents, it could cure some patients which is a goal hitherto achieved only in the minority of patients who successfully undergo allogeneic stem cell transplant. ▲