Targeting cancers with tyrosine kinase inhibitors: lessons learned from chronic myeloid leukaemia

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We have entered an era of increased understanding of the molecular basis of many human cancers, and we can anticipate a major shift in the treatment paradigms. Conventional cancer treatments were largely introduced at a time when little was known about the underlying molecular oncology and the treatments employed in the last century have, for the most part, had limited success. Recent advances in our understanding of the genetic and biochemical mechanisms underlying specific cancers have resulted in better ways to diagnose and monitor response to cancer treatment. The new treatments are often referred to as 'targeted' treatments as they interfere with specific molecular abnormalities in individual cancers. Following further insights into functional genomics and proteomics, the introduction of cancer-specific, perhaps even patient-specific, treatments has begun. Much of this progress has resulted from the lessons learned from patients with chronic myeloid leukaemia (CML), particularly the understanding of resistance to targeted treatment and, remarkably, strategies for circumventing resistance.[1,2]

Chronic myeloid leukaemia is a clonal myeloproliferative disorder that probably, in general, starts as a single well-defined molecular abnormality in a haematopoietic stem cell. The initiating event has been reasonably well defined in the last 20 years. All the progeny of the affected leukaemia stem cell have a consistent cytogenetic abnormality, referred to as 22q– or the Philadelphia (Ph) chromosome, that is associated with a BCR–ABL fusion gene expressed as an oncoprotein, $p210^{BCR\text{-}ABL}$. The Bcr–Abl oncoprotein has a greatly increased tyrosine kinase activity and is probably the direct 'cause' of the clinical features of CML. Efforts began in the 1990s to produce a small molecule that would block this increased kinase activity, and the result was a 2-phenylaminopyrimidine derivative, imatinib mesylate (IM), which is exquisitely active in the treatment of CML.[3]

Oral administration of IM reduces the leukaemia cell mass by at least two logs in almost all patients with early-phase CML and probably substantially prolongs life in comparison with previous treatments. Sustained complete molecular remissions, however, are less common, and more than 50% of patients who respond well to IM still have low levels of leukaemia detectable by very sensitive molecular methodologies.[4,5] The drug is also active in more advanced phases of CML characterised by multiple genetic abnormalities in addition to the cytogenetic abnormality in the BCR–ABL fusion gene, but here the responses tend to be short-lived.[6,7]

Imatinib mesylate works mainly by occupying the adenosine triphosphate (ATP)-binding pocket (phosphate-loop) of the Bcr–Abl protein, where it blocks binding of ATP and so prevents phosphorylation of any substrate; it also makes contact with parts of the kinase domain outside the P-loop (Fig 1).[8] Preclinical studies confirmed that IM also inhibited the enzymatic activity of three related tyrosine kinases – platelet-derived growth factor receptor (PDGFR) kinase, stem-cell factor receptor (KIT) kinase and Abl-related gene (ARG) kinase – but had little effect on most of the other tyrosine kinases known to be involved in malignant diseases, such as members of the Src and Jak kinase families, Fms kinase, Flt3 kinase, vascular endothelial epithelial growth factor receptors, epidermal growth factor receptors and Her-2/Neu kinase. The restricted activity of IM led to efforts to characterise the structural mechanism of this selective inhibition, which targets Abl kinase but leaves unaffected, for example, Src tyrosine kinase with which Abl kinase shares many physicochemical features.[9] It seems that IM achieves its high degree of specificity by targeting and stabilising the activation loop of Bcr–Abl protein, thereby maintaining the enzyme in its inactive state. The conformation of this loop is distinct among the various tyrosine kinases and may explain the high affinity and high specificity of IM for Abl kinase. Relapse is often caused by mutations in the kinase domain of Bcr–Abl that interferes with IM binding. Dasatinib (BMS-354825, Sprycel), an Abl kinase recently approved (in the USA) for patients with CML who are resistant or intolerant to IM, differs from the original drug in that it binds to both the active and inactive conformations of the Abl kinase domain.[10]

These observations lead to a number of important conclusions that may have more general application:

- Where the initiating lesion in a given

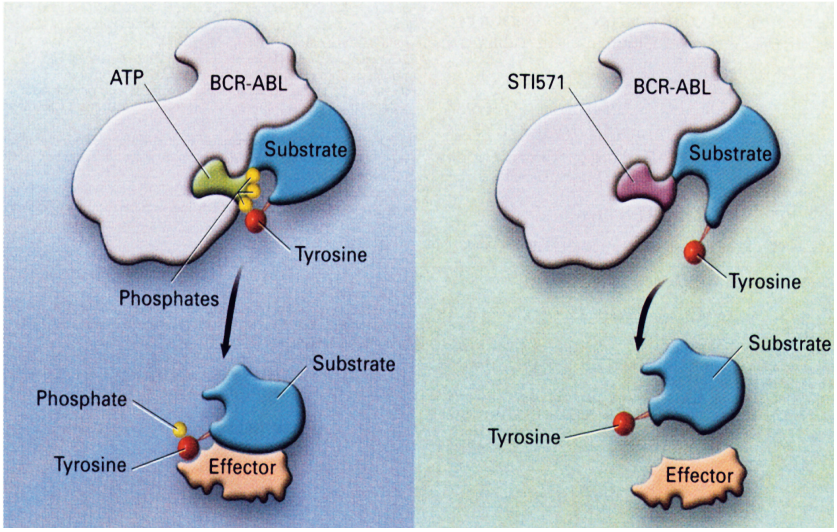

Fig 1. Likely mode of action of imatinib. Reproduced with kind permission of Blackwell Publishing.[8]

malignancy is well characterised, molecular targeting may be a remarkably effective therapy.

- Complete eradication of residual disease may depend on the capacity of the drug or drugs to target leukaemia stem cells as well as their more mature progeny.
- When the initiating molecular event is unknown, molecular targeting of a downstream kinase or adaptor molecule involved in signal transduction may still be clinically useful.

This last point would explain the benefit attributable to the use of most, if not all, of the increasing number of different small molecule kinase inhibitors in cancers with mutations in a kinase gene not known to be the initiating lesion; examples include Flt 3 kinase, epidermal growth factor receptor (EGFR) and B-Raf kinase, each of which, when inhibited, can lead to increased progression-free survival but with little effect on the overall survival.

Following the remarkable initial success of imatinib, patients with advanced non-small cell lung cancers were treated with gefitinib (Iressa) following the preclinical observations of the drug's activity in EGFR-expressing tumours.[11] The two pivotal phase II studies (IDEAL 1 and 2) conducted thereafter did not require the precise details of the EGFR status, but tumour samples were retained for subsequent analysis by immunohistochemistry. On the basis of the modest benefit observed, the drug was granted a conditional approval by the US Food and Drug Administration (FDA) for treatment of advanced, chemorefractory non-small cell lung cancer but was relabelled for restricted use only after following the negative results of the phase III ISEL trial. Subsequent molecular studies suggested that patients with constitutive activation of EGFR or another kinase were the ones most likely to benefit.[12,13] A similar agent, erlotinib (Tarceva), has yielded slightly better results in a broader sense, but again these studies did not assess the molecular aspects.

Currently a large number of such targeting agents are in clinical trials, some of which are shown in Table 1. Others are either in the early stages of being submitted or have received regulatory approval in the USA. Other forms of targeted therapies, particular antibodies against cell surface proteins, such as trastuzumab (Herceptin), which targets HER-2, are effective for early and late stage breast cancer.[14,15] Lapatinib, which targets HER-1 and HER-2, is remarkably effective in advanced breast cancer refractory to trastuzumab and is also effective in patients with brain metastases.[16] Rituximab, active against the CD20 antigen expressed on many B cells, is highly active in some patients with diffuse large cell and all small cell lymphocytic lymphomas.[17] In March 2006, rituximab was also approved in the USA for use in patients with rheumatoid arthritis.

Although further research is needed before we can develop reliable algorithms that encompass targeting agents for most cancers, we are living in enormously exciting times. We need to ensure that the challenge is met

Table 1. A selected representation of tyrosine kinase targeting drugs.

Molecular inhibitor	Target	Disease (current/potential)
Imatinib mesylate	Abl	CML – all phases, Ph-positive ALL
Imatinib mesylate	KIT	Gastrointestinal stromal tumours
Imatinib mesylate	FIP1L1-PDGFR	Eosinophilic leukaemias
Dasatinib	Abl, Src	CML – all phases, Ph-positive ALL
Nilotinib	Abl	CML – all phases, Ph-positive ALL
Gefitinib, erlotinib	EGFR	Metastatic non-small cell lung cancer
Gefitinib, erlotinib	EGFR	Metastatic colon carcinoma
Sunitinib	Ras, VEGF	Renal cell carcinoma, malignant melanoma
Sorafinib	B-Raf, Hsp90	Renal cell carcinoma, others
Trastuzumab	Her-2	Breast
Lapatinib	Her-1, Her-2	Breast, lung, others
Rituximab	CD20	Lymphomas

ALL = acute lymphoblastic leukaemia, CML = chronic myeloid leukaemia.

by a well-orchestrated effort that involves molecular and cellular biologists together with specialists in other disciplines, including structural biology and computational chemistry, who can help identify the precise signatures of the target cancers and the appropriate agents that target them and the various surrogate molecular endpoints. It may be a long time, however, before change in overall survival is noted; a fact that will be of considerable interest to the National Institute for Health and Clinical Excellence. Major issues that relate to the acquisition of mutations in tumour-associated genes, the origin of primary and secondary resistance and other developments still need to be addressed.

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