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Why do Kinase Inhibitors Cause Cardiotoxicity and What can be Done About It?

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Abstract Cancer growth and metastasis are often driven by activating mutations in, or gene amplications of, specific tyrosine or serine/threonine kinases. Kinase inhibitors (KIs) promised to provide targeted therapy—specifically inhibiting the causal or contributory kinases driving tumor progression while leaving function of other kinases intact. These inhibitors are of 2 general classes: (1) monoclonal antibodies that are typically directed against receptor tyrosine kinases or their ligands and (2) small molecules targeting specific kinases. The latter will be the focus of this review. This class of therapeutics has had some remarkable successes, including revolutionizing the treatment of some malignancies (eg, imatinib [Gleevec] in the management of chronic myeloid leukemia) and adding significantly to the management of other difficult to treat cancers (eg, sunitinib [Sutent] and sorafenib [Nexavar] in the management of renal cell carcinoma). But in some instances, cardiotoxicity, often manifest as left ventricular dysfunction and/or heart failure, has ensued after the use of KIs in patients. Herein we will explore the mechanisms underlying the cardiotoxicity of small-molecule KIs, hoping to explain how and why this happens, and will further examine strategies to deal with the problem. (Prog Cardiovasc Dis 2010;53:114-120)

Keywords: Kinase inhibitors; Cardiotoxicity; Heart failure

Protein kinases and cancer

Protein kinases are enzymes that catalyze transfer of a phosphate residue from ATP to tyrosine, serine, or threonine residues in their substrate proteins. This phosphorylation of substrates results in changes in substrate activity, subcellular location, stability, etc. Although the gain-of-function mutations, gene amplifications, and/or overexpression that drive tumorigenesis can occur in a variety of different gene classes, these genes, in many cases, encode protein kinases, typically tyrosine kinases (TKs).[1] Approximately 90 of the 518 kinases in the human kinome are TKs.[2] Tyrosine kinases play central roles in transducing extracellular signals (ie, growth factors and cytokines) into activation of signaling pathways that regulate cell growth, differentiation, metabolism, migration, apoptosis, etc. Kinases that are mutated or overexpressed in cancers typically activate cellular pathways that lead to promotion of cell cycle entry (proliferation), inhibition of proapoptotic factors, activation of antiapoptotic factors, and/or promotion of angiogenesis.

Data from tumor sequencing projects have found remarkable mutation rates in protein kinases. One study found that mutations in as many as 120 kinases (approximately 25% of the kinome) were present in some cancers.[3] Furthermore, many of these mutations were not just "bystanders" but were so-called driver mutations (ie, playing a role in tumor progression). Given this complexity, it seems inconceivable that inhibiting individual kinases in cancer would be effective, except for the relatively rare malignancies that are truly "oncogene-addicted" to a specific mutated kinase (eg, chronic myeloid leukemia

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Abbreviations and Acronyms

TK = tyrosine kinase

KI = kinase inhibitors

TKI = tyrosine kinase inhibitors

CML = chronic myeloid leukemia

GIST = gastrointestinal stromal tumors

LV = left ventricle

AMPK = AMP-activated protein kinase

VEGFR = vascular endothelial growth factor receptor

PDGFR = platelet-derived growth factor receptor

PI3K = phosphatidylinositol 3-kinase

[CML] and Bcr-Abl).[4] Surprisingly, "targeted therapeutics" have radically transformed the treatment of some hematologic malignancies and solid tumors.

Kinase inhibitors

The identification of mutated or amplified kinases has allowed the development of therapeutics specifically targeting the oncogenic kinases. Although oncogenic mutations commonly occur in other classes of proteins in addition to kinases, such as cell cycle regulators and proapoptotic or antiapoptotic factors, kinases have become favorite targets of the pharmaceutical industry due not only to their importance in tumor initiation and progression but also to the relative ease with which inhibitors can be made (see below). This has led to an explosion in drug development targeting TKs (TK inhibitors) and, to a lesser but increasing extent, serine/threonine kinases. At present, 12 small-molecule kinase inhibitors (KIs) are Food and Drug Administration (FDA)–approved for cancer therapy (Table 1), with several more seeking approval over the next 2 years[7] and many more (>100) in various phases of development. The first KI to reach market was imatinib in 2001.[8] It is still the most commercially successful KI, with sales close to $4 billion in 2009. Imatinib revolutionized the treatment of CML. Before the introduction of imatinib, CML was uniformly fatal within 5 years, whereas now, ≈90% of patients are alive 5 years after diagnosis. Indeed, this and other drugs have changed our thinking about some cancers that can now be viewed as a group of diseases that, even if not curable, can be managed effectively for years, similar to many other chronic diseases.

Mechanisms of action of KIs

Small-molecule KIs typically compete with ATP for binding to the ATP pocket of the kinase. If ATP cannot bind, phosphotransferase activity is blocked and downstream substrates cannot be phosphorylated, even if the kinase is fully activated. In the cell, ATP is present in millimolar concentrations, but KIs will be present in nanomolar to very low micromolar concentrations. Thus, the KIs must bind with very high affinity. Because the structure of the ATP pocket is known for many kinases and is highly conserved across the human genome, it is relatively easy to make an inhibitor that blocks the ATP pocket of a kinase of interest. These inhibitors are termed type I inhibitors. Given the degree of conservation, it is not surprising that lack of selectivity is an issue with most type I inhibitors.[5] Type II inhibitors (eg, imatinib and the related nilotinib) not only bind the ATP pocket but also interact with a site adjacent to the pocket, generally making them more selective.[9] Furthermore, unlike type I inhibitors, which only bind to an active kinase (because the ATP pocket is only accessible when the kinase is activated), type II inhibitors can also bind to the kinase

Table 1
FDA-approved KIs for cancer therapy

Agent (Trade Name)	Targets		Representative Malignancies
	Primary	Other	
Imatinib (Gleevec)	Bcr-Abl	Abl, c-Kit, PDGFRs, DDR1, etc[5,6]	CML, Ph^+ ALL, CMML, HES, GIST
Nilotinib (Tasigna)	Bcr-Abl and most IRMs	Abl, c-Kit, PDGFRs	Imatinib-resistant CML, ALL, GIST
Dasatinib (Sprycel)	Bcr-Abl and most IRMs	Abl, c-Kit, PDGFRs, DDR1, etc[5,6]	Imatinib-resistant CML, ALL, GIST
Sunitinib (Sutent)	VEGFRs, PDGFRs, c-Kit	CSF-1R, FLT3, RET, etc	RCC, GIST
Sorafenib (Nexavar)	Raf-1/B-Raf, VEGFR2, PDGFRβ	c-Kit, FLT3, etc	RCC, hepatocellular carcinoma
Lapatinib (Tykerb)	EGFR (ERBB1), HER2 (ERBB2)	NI	$HER2^+$ breast cancer, ovarian cancer, gliomas, NSCLC
Gefitinib (Iressa)	EGFR	NI	NSCLC, gliomas
Erlotinib (Tarceva)	EGFR	NI	NSCLC, pancreatic cancer, gliomas
Pazopanib (Votrient)	VEGFR, PDGFR, c-Kit	NI	RCC
Temsirolimus (Torisel)	mTOR	NI	RCC
Everolimus (Afinitor)	mTOR	NI	RCC
Sirolimus (Rapamune)	mTOR	NI	RCC

Abbreviations: IRMs indicates imatinib-resistant Abl mutants; NI, none identified; Ph^+ ALL, Philadelphia chromosome–positive acute lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; HES, hypereosinophilic syndrome; NSCLC, non–small-cell lung cancer; CLL, chronic lymphocytic leukemia; RCC, renal cell carcinoma; CSF-1R, colony-stimulating factor 1 receptor; FLT3, FMS-like tyrosine kinase 3; RET, rearranged during transfection; mTOR, mammalian target of rapamycin. Please see text for additional abbreviations.