Double-Edged Sword of the New Cancer Therapeutics

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Protein kinases regulate a vast array of cellular processes including, but not limited to, cell proliferation, differentiation, motility, death, and survival. They regulate these and other processes by attaching phosphate groups onto various proteins (substrates), changing the substrate’s activity, subcellular localization, and resistance to (or promotion of) cell death. There are >500 kinases in the human genome (referred to as the kinome).

Dysregulation of kinases is responsible for a multitude of pathologies, and nowhere is that more evident than in cancer.1 Numerous malignancies are driven by mutations in protein kinases. The first definitive identification of a mutation within a kinase leading to a malignancy was chronic myeloid leukemia, driven by the balanced translocation that creates the Philadelphia chromosome.2 The resulting fusion protein of BCR (for breakpoint cluster region, a protein kinase of poorly understood function) and Abl, a tyrosine kinase implicated in a number of cellular processes, leads to constitutive activation of the fusion protein and transformation of myeloid progenitors in the bone marrow, driving the malignancy. Since that initial discovery, numerous mutations in kinases have been identified that drive a wide variety of malignancies, either directly promoting cancer growth or promoting neovascularization of the tumor.3 In the case of chronic myeloid leukemia, 3 kinase inhibitors have been approved for use (imatinib, dasatinib, and nilotinib, with others in development), and they have literally revolutionized the treatment of the disease, leading to prolonged remissions in the majority of patients.4 The identification of these drugs that target BCR-Abl and other drugs that target a very wide range of other mutated or overexpressed kinases driving other cancers has become the primary focus of drug development for many pharmaceutical companies. Further fostering development is the relative ease of getting these drugs to market compared, for example, to novel drugs for treating heart failure.5

Although many of these agents have significantly improved outcomes in patients, in some instances it has come at a cost of a variety of toxicities, including cardiovascular toxicity.6,7 This was something of a surprise because it was hoped that these targeted therapeutics, which were believed to specifically inhibit the culprit kinase, would have minimal toxicity, especially when compared to standard chemotherapeutics such as the anthracyclines. In many instances, that has proven to be the case, with notable exceptions (see below).

In this issue of Circulation, Montani et al8 identify a new kinase inhibitor-induced toxicity: precapillary pulmonary hypertension seen with dasatinib therapy. Precapillary pulmonary hypertension is characterized by a normal pulmonary capillary wedge pressure, is often idiopathic, can be heritable, drug-induced, or associated with various disease states. There had been several case reports published, dating to 2005, that suggested a link between dasatinib and pulmonary hypertension,9 but this article by Montani et al is, by far, the most definitive report to appear. The authors used the French pulmonary hypertension registry, which allows investigators to follow epidemiological trends, to identify 9 clear-cut cases of patients who presented with what appeared to be new-onset symptomatic precapillary pulmonary hypertension who were also taking dasatinib. Importantly, no cases were seen in patients taking imatinib or nilotinib. Furthermore, all but 1 patient had measurable improvements after withdrawal of the drug. The authors then used the French Pharmacovigilance Agency (which identified an additional 4 cases), and, with data on total number of prescriptions from the makers of the 3 drugs, calculated the lowest estimate of PH in patients treated with dasatinib to be 0.45%. This figure likely underestimates the true percentage because asymptomatic and mildly symptomatic patients would not likely have been identified. This potential underestimation of cases could be worsened by physicians ascribing patients’ symptoms to the relatively common development of peripheral edema and pleural effusions seen with dasatinib therapy.10

On the surface, this consequence of dasatinib therapy would appear to contradict a growing basic and clinical literature, including a Phase II clinical trial, suggesting that imatinib actually reduces pulmonary hypertension.11–13 Similarly, nilotinib does not appear to be associated with pulmonary hypertension. One possible explanation for this is that dasatinib is simply more potent than imatinib and nilotinib; although that may be the case with imatinib, it is likely not the case with nilotinib. Rather, the most plausible explanation is that dasatinib-induced pulmonary hypertension is due to so-called off-target effects of dasatinib. Off-target effects arise when a drug inhibits a kinase that was not intended to be a target of the drug.6 If inhibiting that off-target kinase leads to toxicity, it is termed off-target toxicity. Off-target toxicity arises from the inherent lack of selectivity of the vast majority of small-molecule kinase inhibitors.14,15 That is, one may set out to make a compound targeted at a specific kinase (eg, BCR-Abl) but it is the very rare compound that is truly selective. This is highlighted in Table 5 of Montani et al, which shows the rather promiscuous selectivity profile of dasatinib (with >40 kinases as possible targets) compared with imatinib and nilotinib, 2 of the most selective agents on the market.
It is these off-target effects that appear to account for much of the toxicity of kinase inhibitors in general. This lack of selectivity is due in large part to the fact that many kinase inhibitors bind to a region of the kinase that is relatively highly conserved among the >500 protein kinases of the human kinome. Thus it is the rule, rather than the exception, that kinase inhibitors target multiple kinases. This can make it very difficult to identify the specific kinase(s), inhibition of which leads to toxicity. However, we believe that it is important to attempt to do this because in some cases the drug can be redesigned to no longer inhibit the problematic kinase. If the redesigned inhibitor maintains activity against the target kinase, anticancer efficacy will be retained. Although such a task would be feasible, one can imagine that it can be daunting in the case of drugs like dasatinib with its multiple targets. Even a cursory look at the selectivity profile of dasatinib identifies several candidate kinases that could account for the toxicity when inhibited. These include kinases regulating autophagy (serine threonine kinase-36/uncoordinated 51-like kinase), response to pressure overload and cell survival (Raf1 and BRAF), the vascular response to pressure overload (platelet-derived growth factor receptor β), and, as noted by the authors, maintenance of the vasculature (Src family and members of the EPH receptor A family). Identification of the specific culprit can probably best be addressed in rodent models.

What do we need going forward to limit kinase inhibitor-induced toxicity? Most importantly, we need a better understanding of the roles played by kinases in the heart and vasculature so that we can begin to predict potentially problematic drugs on the basis of their selectivity profile. To accomplish that, we obviously need full disclosure of all selectivity profiles of new kinase-inhibitor therapeutics. Second, I believe it is obvious that we need to take a systems biology approach to this problem rather than serially focusing on individual kinases. Third, as highlighted by Montani et al, I would make a case that, where possible, more selective agents be used, hopefully limiting off-target toxicities. Fourth, we need more careful scrutiny, both before and after approval, of these agents. Understandably, it may be difficult to detect a signal of toxicity with a rate as low as was seen with dasatinib without a careful approach like that employed by Montani et al. That said, Montani et al highlight the feasibility of detecting toxicity even at relatively low incidences. In contrast to the situation with dasatinib, one would think that problems should have been much more apparent (and readily detectable) for a kinase inhibitor like sunitinib with its significant adverse effects on blood pressure and left ventricular function. Fifth, in screening for problematic agents, Montani et al suggest that one would not necessarily need sophisticated (and expensive) monitoring. One need only be aware of the potential problem of kinase-inhibitor toxicity, to exercise good clinical judgment, and to sound the alert if concerns arise. Finally, on the basis of current trends in drug development, we are going to be facing a deluge of kinase inhibitors on the market. And although that is very good news for cancer patients (and patients with other disease states driven by aberrant activity of kinases), we need to be ready for it.

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**References**


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