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EDITORIAL

The toxicities of modern targeted therapies—learning from the price of progress

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Appropriately with over a decade's experience with kinase inhibitors, this issue of *Targeted Oncology* is focused on what we have learned about the toxicities of modern anticancer therapies and what opportunities are available to do better. The cumulative experience has emphasized the need for both humility and patience. The crushing morbidity and mortality suffered by society as a result of cancer understandably generates enormous pressure for therapeutic advances. In the last few years these advances are evident. However, to merely focus on the positive with a disproportionate under emphasis on side effects is not in the best interest of our patients. This issue highlights some of the more relevant important toxicities and the challenges posed in their diagnosis and therapy.

With the completion of the human genome project, we began to get an initial idea of just how many kinases that are actually important to human function. These number in the hundreds and have quite diverse functions, structures and cell localization. Thus the difficulty in designing a truly targeted kinase inhibitor is becoming clear with time. It was a very fortunate accident that imatinib has just three significant tyrosine kinase targets. In point of fact, although imatinib has enormously improved the prognosis of patients with chronic phase chronic myeloid leukemia (CML), it was serendipity that delivered an agent that inhibits platelet-derived growth factor receptor (PDGFR), KIT and the Abelson proto-oncogene (*abl*) to the practical exclusion of other kinase targets. It was of course not serendipity, but exemplary collaboration among myriad scientific disciplines including chemistry, molecular biology, and crystallography that led to the rapid creation of the imatinib-derivative, nilotinib. Nilotinib has greater potency and much greater BCR-ABL specificity and no expansion of its targets beyond those of imatinib.

By contrast, dasatinib, an agent initially developed as a Src inhibitor, then found to have potent BCR-ABL inhibitory activity, we see the dangers posed by modern agents with significant off-target activity. Dasatinib is a very potent anti-CML weapon, but its serous inflammation, gastrointestinal bleeding, and excess myelosuppression, all presumably related to off-target activity, are severe limitations on its use. Most importantly, it may require many years of follow-up to accurately quantify the clinical consequences of prolonged Src inhibition and/or actual or potential serous inflammation.

The debate on the pros and cons of very targeted kinase inhibitors versus multi-targeted kinase inhibitors is repetitious and predictable. Narrow spectrum agents are generally less toxic and if one happens to have a multi-targeted agent, then the justification is sought that some of the non-primary targets may be relevant to the pathophysiology of the disease involved. If one compares and contrasts the clinical results with nilotinib and dasatinib in CML blastic phase disease, then unfortunately it becomes clear that whatever targets in addition to BCR-ABL we need to hit, none of them are the non BCR-ABL targets of dasatinib. We now have access to third- and fourth-generation BCR-ABL inhibitors, each with different spectrums of activity against the mutated phenotypes and each will undoubtedly be associated with either new toxicities or different toxicity

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distributions and each will in turn generate new mutated phenotypes.

Cardiac toxicities associated with vascular endothelial growth factor (VEGF) inhibitors are also highlighted in this issue of *Targeted Oncology*. Cancer is predominately a disease of the elderly, i.e., patients with the most extensive comorbidity, and it often takes many years to accurately quantify the clinical consequences of cardiovascular toxicity. This is often a difficult area in which to find objective data. If one looks at the amount of cardiovascular monitoring done before and after Viox-related publicity, there clearly has been a stark and largely illogical increase in cardiovascular monitoring in developmental therapeutics. Clearly human physiology has not altered over this period—what has altered is excess reaction to preclinical signals particularly in the area of QT prolongation. The entire area of what is necessary and prudent cardiac monitoring early in drug development and as a chronic issue, particularly with VEGF and Syk inhibitors, requires considerably more attention and these topics are very elegantly discussed in this issue.

Specific spectra of end organ damage from targeted therapies—pulmonary toxicity or pneumonitis associated with mammalian target of rapamycin (mTOR) inhibitors, skin toxicities associated with epidermal growth factor receptor (EGFR) inhibitors—are also reviewed in detail.

For many of us, minimal non-clinically significant toxicities are quite welcome on phase I studies in the sense that they at least indicate biologic activity. Of course, what is hoped for is the detection of the large margin between therapeutic and toxicity exposures. In Dr. Takimoto's discussion of moving towards more clinically meaningful end points, we address one of the more important lessons from the modern era. The traditional pursuit of dose escalation until the maximum tolerated dose is seen as increasingly irrelevant in the context of targeted agents. Allied to this issue is the need to incorporate modern study designs into early drug development.

While one must acknowledge that recently developed very targeted drugs have enormously improved the prognosis for many of our patients, the traditional principle that it is very difficult to design a therapeutic agent that is truly innocuous in all recipients remains true. When one reviews a decade of imatinib experience, we see that it possible to design highly effective, relatively safe agents. The subsequent development of nilotinib as a chemical derivative, and indeed potential successor to imatinib as front line CML therapy, is very encouraging. We can anticipate that with appropriate, focused follow-up and an honest open examination of the available facts we can look forward to the next generation of kinase pathway inhibitors with optimism.