SELECTED SUMMARY-II

Newer Tyrosine Kinase Inhibitors for CML

Talpaz M, Shah NP, Kantarjian H, Donato N, Nicoll J, Paquette R, *et al.* **Dasatinib in Imatinib-Resistant Philadelphia Chromosome-Positive Leukemias. N Engl J Med 2006;354:2531-41**
Kantarjian H, Giles F, Wunderle L, Bhalla K, O'Brien S, Wassman B, *et al.* **Nilotinib in Imatinib-Resistant CML and Philadelphia Chromosome-Positive ALL.**
N Engl J Med 2006;354:2542-51

COMMENTARY:

CML is a disease that continues to command attention disproportionate to its incidence. With very good reasons, one might add. Philadelphia chromosome was the first specific chromosomal abnormality associate with human cancer and imatinib was the first specific, targeted tyrosine kinase inhibitor demonstrated to be effective (in CML). In fact it would not be an exaggeration to state that the discovery of imatinib divides therapeutic cancer research into 'pre-TKI' and 'post-TKI' eras. The June 15 issue of the New England Journal of Medicine continues this tradition with the publication of two ground breaking articles. It is a testament to the pioneering nature of these papers that despite being conventional phase 1 studies, both of them have been published in a journal that is usually a forum for more mature studies.

In the first study, Talpaz and colleagues describe the use of the Bristol Myers Squibb drug Dasatinib in 84 patients with various phases of CML or Ph-positive ALL who were resistant or intolerant to imatinib. Dasatinib is an orally available drug that was initially developed as an inhibitor of SRC kinase and was subsequently found to have inhibitory action on a distinct spectrum of other kinases including the ABL kinase. It differs from imatinib in several respects. It is more potent than imatinib. Unlike imatinib that binds exclusively to the inactive conformation of ABL kinase, dasatinib binds to both its conformations. Because of its less stringent binding requirements it was demonstrated to be active against many kinase domain mutants that were resistant to imatinib. The only exception is the mutant T 315I (threonine to isoleucine in the ATP binding pocket) that confers high grade resistance to imatinib, dasatinib and nilotinib. Dasatinib, unlike imatinib, is not a substrate for the drug efflux pump P-glycoprotein. In chronic phase CML patients (n=40), 80% of whom resistant to imatinib, the rates of hematologic CR and major cytogenetic response were 92% and 45% respectively. In patients with accelerated phase, blast crisis or Ph-positive ALL (n=44) the rates of major hematologic and cytogenetic response were 70% and 25% respectively. The responses were sustained in 95% of chronic phase and 82% of accelerated phase patients but there was a high rate of relapse in patients with blast crisis or ALL. An important component of the study was the BCR-ABL kinase domain mutational analysis by cDNA based sequencing. This was done for at least 10 independent clones from each patient. Sixty (71%) patients in the study had baseline BCR-ABL mutations of which 4 had not been previously described. Hematologic and cytogenetic responses were observed in all BCR-ABL genotypes with the exception of T315I. The range of doses used in the study was 15 to 240 mg per day. Dasatinib was generally well tolerated. The most common toxicity was myelosuppression with grade III-IV neutropenia in 44% and grade III-IV thrombocytopenia in 35% patients. One unique effect observed in this group of patients was pleural effusion in 13% patients. The common side effects of imatinib like periorbital edema and muscle cramps were rarely seen.

In the second study, Kantarjian and colleagues describe the use of the Novartis drug Nilotinib in 119 patients with various phases of CML or Ph-positive ALL who were all resistant to imatinib. Nilotinib is a derivative of imatinib that has higher binding affinity (ranging from 3 to 50 times in different CML cell lines) and selectivity for ABL kinase. Patients were successively assigned to one of the nine dose cohorts ranging from 50 to 1200 mg once daily

and 400 to 600 mg twice daily. An interesting finding from the pharmacokinetic data was the plateau in peak concentration and AUC at the once daily dose of 400 mg (i.e. no further increase in serum concentration beyond this dosage when administered on a once daily basis). Modification of the administration schedule to twice daily dosing again increased the plasma drug concentration and AUC. On the basis of pharmacokinetic data, toxicity profile and efficacy the recommended dosage for phase 2 studies is 400 mg twice daily. The rates of hematologic and cytogenetic responses in patients with chronic phase, accelerated phase and blast crisis were respectively, 92% & 53%, 74% & 55% and 39% & 27%. It is worth repeating that all these patients were resistant to imatinib. Of the 91 patients who underwent baseline mutational analysis, 37 had evidence of ABL mutations. There was no difference in the activity of nilotinib in patients with and without mutations. However two patients who had T315I mutation did not respond. The assessment of biomarker inhibition revealed significantly decreased phosphorylation of the 4 chosen signaling molecules that are known substrates of BCR-ABL kinase. The most common adverse effect was myelosuppression but there was a unique pattern of non-hematologic toxicity. There was an elevation of bilirubin (predominantly unconjugated) in 14% of patients that was found to be associated with the genotype of Gilbert's syndrome. The other toxicities of note were elevations of amylase and lipase (some associated with clinical pancreatitis) and prolongation of the QT interval.

What lessons should be learnt from these studies?

The most important lesson is probably the paradigm shift in the discovery and development of new therapies for malignant diseases. While the earlier approach was largely empirical (but also effective) the current and future strategies are likely to be based on a detailed understanding of the molecular targets. This 'targeted approach' has already paid rich dividends in many disorders, of which CML is but the prime example. A related matter is the methodology by which new drugs would be researched and brought into clinical use. The technology of randomized trial has served us well in the empirical era when the actual drug targets were elusive and the chemotherapeutic agents were administered to groups of patients with a particular pathologic diagnosis without heed to the molecular heterogeneity of tumours. Consequently these trials were typically powered to detect survival (or other end point) advantages ranging from less than 5% to 20% and more, requiring hundreds to thousands of patients. In the future this is unlikely to remain the central theme of new drug development, for a number of reasons. The most important among these is the limited number of patients and the large number of candidate drugs to be tested. However to make things easier we would probably not require large numbers of patients in future trials because the target population would be enriched for tumours that are most likely to respond based on sound biochemical, structural and physiological understanding of the drug and its target(s). The two studies discussed above and the earlier example of imatinib are very good examples of this paradigm where high quality basic science would drive rapid and rational drug discovery and development. Aside from being examples of targeted drug development these two drugs would be of immediate practical use to the growing number of patients who develop resistance to imatinib. Moreover with increasing understanding of the genetic basis of drug resistance, exemplified by kinase domain mutations in CML, it is possible that combinations of targeted drugs would be tested in the near future that might lead to further improvement in outcome of newly diagnosed CML and even cure. However, the increasingly evident non classic adverse effects (like pleural effusion and hyperbilirubinemia) of these new agents suggest that a close watch over the long-term outcome is mandatory even after they are approved for routine use.

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