PERSPECTIVE

Combined forces

Beginning treatment with a combination of drugs should help to stop drug resistance developing, says **Charles L. Sawyers**.

The approval of imatinib in 2001 was a turning point in the treatment of chronic myeloid leukaemia (CML). Since then, imatinib — marketed by Novartis as Gleevec in the United States and Glivec elsewhere — and other, similar drugs have increased the lifespan of people diagnosed with CML from 5–6 years to 10–20 years.

This success is based on using imatinib as an opening salvo early in the course of the disease, and then deploying one of four next-generation drugs for those who develop resistance to it.

The current protocol is sequential: after failing to respond optimally to one drug, the patient is switched to another. But experimental evidence (and simple logic) shows that this approach increases the risk of multidrug resistance. There is, however, a better therapeutic approach that should delay or even prevent resistance: administering combinations of these drugs at the same time.

One can even envisage the possibility that combinations of these or other targeted therapies might do more than merely extend remissions of some with CML, and actually cure the disease. Considering that patients today are committed to decades of therapy with unknown long-term side effects and significant economic cost, it is time to re-examine the sequential-therapy model.

Imatinib, a tyrosine-kinase inhibitor (TKI), works by blocking the activity of an enzyme called ABL. There is no question that, used alone, imatinib gives durable responses for most newly diagnosed cases of CML. About 80% of those who take it will have complete cytogenetic remission (no evidence of cells in the bone marrow bearing the abnormal chromosome that defines CML) within five years.

The durability of response is impressive but not indefinite. Although 84% of patients in one large study were alive after 8 years, half were no longer receiving imatinib owing to treatment failure[1]. The fact that most of these resistant patients respond to next-generation ABL inhibitors is one reason why survival remains high.

Resistance to imatinib most often results from a mutation of the driving oncogene in CML, known as *BCR–ABL*[2]. More than 50 distinct *BCR–ABL* mutations have been reported. Amazingly, the current repertoire of TKIs covers all known resistance mutations; however, no single drug can prevent all forms of resistance. This means that sequential therapy can select for subpopulations of cells within the tumour that have multiple *BCR–ABL* mutations, conferring resistance to all TKIs[3].

The next-generation drugs are more potent TKIs and produce more rapid declines in CML disease burden than imatinib. This translates into improved response rates and more durable remissions.

Dasatinib, marketed as Sprycel by Bristol-Myers Squibb, and nilotinib, marketed as Tasigna by Novartis, are already approved for frontline therapy of CML based on superior clinical outcomes in head-to-head comparisons against imatinib. Bosutinib, marketed by Pfizer as Bosulif, may follow suit based on similar clinical results. Ponatinib is newer, so limited clinical data are available. This drug is particularly promising because it has the unique property of inhibiting a mutation called T315I that confers resistance to all the other CML drugs[4].

The compelling clinical data argue that next-generation ABL inhibitors should replace imatinib. Caution is still in order, however, as these new agents have been studied for only 3–4 years compared with the 8–10 years of data that have amassed for imatinib.

Instead of focusing on which individual drug is best as a monotherapy, it is time for the CML community to consider whether combination therapy makes sense. Extrapolating from the experience with single- versus multi-agent therapy for tuberculosis and HIV/AIDS, a combination of two or three ABL inhibitors with non-overlapping *BCR–ABL* mutation resistance profiles would almost certainly prevent the emergence of drug resistance. This is particularly true in the light of ponatinib's success against T315I.

EXPERIMENTAL EVIDENCE SHOWS THAT A SEQUENTIAL APPROACH INCREASES THE RISK OF MULTIDRUG RESISTANCE

An additional lesson from antiretroviral therapy is that combinations can greatly enhance the rapidity and depth of response. Indeed, investigators in France have already demonstrated that patients with the deepest responses (no *BCR–ABL* detectable for more than two years) may no longer need imatinib at all. They found that 40% of patients had not relapsed after 18 months, a result that raises the possibility that a cure may be in sight[5].

The facts that next-generation ABL inhibitors have greater potency in clinical trials, and that two-drug combinations are superior to monotherapies in preclinical studies, suggest that more intensive upfront therapy, with the goal of eliminating all CML cells, deserves serious consideration.

Much has been said about the enormous cost of targeted cancer therapies, including a recent call by more than 100 CML experts to lower the price of all the tyrosine kinase inhibitors[6]. Multidrug therapy would lead to a further increase in the cost of CML therapy, but this additional expense would lead to substantial long-term savings if patients could be cured after just one or two years of treatment. ■

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