Credit: iStock / Getty Images Plus

MILESTONE 1

Routes to resistance

By the turn of the millennium, drugs that selectively target driver genes had been developed. For instance, tyrosine kinase inhibitors, such as imatinib, had been demonstrated to lead to sustained and durable remission in patients with advanced chronic myeloid leukaemia (CML) by targeting *BCR-ABL*, a fusion gene with constitutive tyrosine kinase activity. Furthermore, in contrast to more conventional genotoxic treatments, these drugs were believed to cause fewer adverse effects. With such precise targeted therapies, hopes were high that this new generation of drug might represent the 'magic bullet' long sought after by patients and clinicians.

Unfortunately, the reality was not so simple. Although patients (even those in advanced stages or with complex molecular alterations) initially responded to these targeted drugs, a clinical trial of imatinib reported by Druker et al. showed that in patients with acute lymphoblastic leukaemia or with CML in lymphoid blast crisis, tumours eventually returned after daily treatment for a few weeks or months. The question of how cancer can adapt to specialized strategies that directly target essential cancer machinery still remained.

Mercedes E. Gorre, Charles Sawyers and collaborators set out to answer this question. Imatinib was known to work by binding the BCR-ABL kinase domain, thus blocking its function. Because previous work by Chin et al. had shown that cancers often require the activity of their primary oncogene, Gorre et al. wondered whether imatinib-resistant tumours might still be dependent on the *BCR-ABL* fusion gene. They reasoned that if the relapsed tumours were still dependent on *BCR-ABL*, then BCR-ABL signalling activity would be evident even after treatment. Because of the fast degradation of the BCR-ABL protein, they measured the phosphorylation of one of its downstream targets, CRKL. Indeed, in tumours from 11 patients with relapse, CRKL phosphorylation was nearly as high as that in untreated patients.

The next step was to identify what allowed BCR-ABL to remain active. The authors concluded that a cell-intrinsic factor was responsible, because relapsed cells isolated from patients still showed this oncogenic activity, thus suggesting that no extrinsic factors were involved. The authors examined changes in the *BCR-ABL* gene itself and found two strikingly distinct escape mechanisms in different patients.

The first resistance-related alteration could be understood as a brute-force, all-out approach to fight against the inhibitor: the tumours of three patients who relapsed had produced multiple copies of the *BCR-ABL* gene through gene amplification. The number of copies increased with subsequent rounds of treatment; however, in one patient, these amplifications disappeared after switching to another therapy, thus suggesting that the drug was selecting for clones bearing the amplification. In contrast, the second resistance mechanism required a single modification: a point mutation changing threonine 315 of ABL1 to isoleucine was found in six patients. Because this particular amino acid is critical for imatinib binding, the mutation abrogated binding to the drug. In contrast to the wild-type *BCR-ABL*, this mutant retained activity in cell lines, even after exposure to the drug.

This study, together with similar studies published shortly afterwards—including the discovery by Kobayashi et al. of *EGFR* mutations conferring resistance to gefitinib in lung cancer—illustrates several important aspects of cancer. On the one hand, these data show that cancer is an evolutionary process: under strong selective pressure, cells with adaptations allowing them to overcome the adverse environment will dominate. Such cells may actually already be present in the initial tumour—even seemingly homogeneous cancers can harbour genetically heterogeneous populations that have an edge in the 'arms race' against therapy, as described by Dagogo-Jack and Shaw. In addition, resistance can be achieved by markedly distinct but functionally convergent approaches. On the other hand, these studies have also unmasked one critical feature of cancers: certain genes and mutations remain essential drivers of tumour growth and survival. Therefore, knowing and targeting these central drivers continues to be an important clinical strategy, which is being used to develop new generations of clinically effective tyrosine kinase inhibitors.

Targeted therapies will remain an important part of the arsenal to combat cancers, especially when tested in different combinations that can circumvent resistance to a single drug. The roles of off-target, non-genetic mechanisms in this resistance are also starting to be acknowledged and will need to be addressed with correspondingly tailored approaches. As long as the design and use of these therapeutic strategies is guided by evolutionary principles, the hope is that drug resistance in patients will one day be predicted and sidestepped.

Ilse Valtierra, *Nature Communications*

ORIGINAL ARTICLE Gorre, M. E. et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 293, 876–880 (2001).
FURTHER READING Please visit the online article for a full list of further reading.