Nature Reviews Clinical Oncology **8**, 509 (2011); published online 19 July 2011; doi:10.1038/nrclinonc.2011.105

TARGETED THERAPIES

Retargeting imatinib

Imatinib is an anticancer therapy that acts as a tyrosine kinase inhibitor of the BCR–ABL oncoprotein, as well as c-Kit and the platelet-derived growth factor receptor. This targeted therapy is the standard of care for adults newly diagnosed with chronic myeloid leukemia (CML) in the chronic phase and has demonstrated efficacy in patients with gastrointestinal stromal tumors who have a mutation in the kinase domain of c-Kit. These successes, and our growing knowledge of the molecular biology of a range of cancers, have led to the recent report of two successful clinical trials assessing the use of imatinib in novel patient groups. These trials were conducted in two very different patient populations, the first was in children with newly diagnosed CML in the chronic phase and the second in patients with acral or muscosal metastatic melanoma.

The trial in the children with CML was initiated owing to the success of imatinib in adult patients with the same disease and after two other studies had indicated that the treatment might also be successful in children. The French group, led by Frédéric Millot, achieved an impressive enrollment of 81% of the potentially eligible children, resulting in 44 patients aged from 10 months to 17 years with newly diagnosed CML taking part in the phase IV, open-label study. The patients typically received a dose of 260 mg/m^2 of imatinib and were followed up for a median of 31 months. At 36 months, the progression-free survival rate was 98%. Millot and his coauthors comment, "these results are comparable to those obtained in adults" and "despite a short median observation time (31 months), this trial shows clinical benefit." Based on these impressive data, it is hard to imagine that, after sufficient follow up, imatinib will not soon be the recommended first-line therapy in this patient population.

In the second trial, the patient population had a much lower survival rate (5-year overall survival of 6%) compared with the first study and, at present, the standard of care for these patients is to enroll them onto a clinical trial. Jun Guo, a lead investigator on the trial, says "I think that individual treatment for melanoma patients is the future direction. Before this study was completed, there were three investigator-initiated trials that used imatinib in unselected stage IV melanoma patients, they all failed." The difference in the current study was that out of 501 hospitalized patients, only the 43 patients with mutations or amplifications in *c-Kit* were enrolled to receive 400 mg imatinib daily. In these selected patients, the 6-month progression-free survival rate was 36.6%, and the median progression-free survival was 3.5 months. Guo comments, "the study demonstrated that patient selection is very important. The three previous trials all failed, but now we reported an approximately 60% disease control rate."

Taken together, these two trials demonstrate that by using careful patient selection, targeted therapies that have efficacy in one cancer population can be usefully translated to other patient groups. Our growing knowledge of the molecular biology of the disease and of the mechanisms of resistance should enable more of this 'retargeting of targeted therapies' to take place.

Rebecca Kirk

Original articles Millot, F. *et al*. Imatinib is effective in children with previously untreated chronic myelogenous leukemia in early chronic phase: results of the French National phase IV trial. *J. Clin. Oncol*. doi:10.1200/JCO.2010.32.7114 | Guo, J. *et al*. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. *J. Clin. Oncol*. doi:10.1200/JCO.2010.33.9275