nature medicine

Look before you leap

Individualized healthcare, once a seemingly utopian fantasy, is steadily gaining ground as a rational approach to cancer treatment. But recent developments emphasize the need for basic scientific insight as therapies move from the lab to the clinic.

In May 2003, the US Food and Drug Administration (FDA) accelerated the approval of the tyrosine kinase inhibitor gefitinib (Iressa) for the treatment of advanced non-small-cell lung cancer in patients who failed to respond to prior chemotherapy. Amid skepticism about its efficacy, provoked by the low response rate and lack of evidence of survival advantage when added to standard chemotherapy, the FDA stipulated in its approval the requirement for three additional trials to verify clinical benefit. Despite a wealth of negative data, ~10% of patients do show a dramatic response to gefitinib. Now, two studies in *Science* and the *New England Journal of Medicine* report that mutations in the epidermal growth factor receptor (EGFR) correlate with this response to therapy (see also related News and Views on page 577).

At the time of its approval, gefitinib's mechanism of action was unclear and tumor EGFR expression did not correlate with patient response. The new studies suggest that activating mutations in the kinase domain of EGFR render cells expressing the mutant receptor more susceptible to the growth-inhibitory effects of gefitinib. Although the findings require confirmation in larger cohorts, they support the addition of gefitinib to the small but growing armamentarium of targeted therapies that provide the potential for customized cancer treatment. Trastuzumab, used for the treatment of HER2-overexpressing breast cancers, and imatinib, used for Bcr-Abl-positive chronic myelogenous leukemia (CML) as well as gastrointestinal stromal tumors with activating mutations in c-Kit, are two other drugs in this category that allow tailored treatment of specific patient populations with the hope of improved efficacy.

What are the prospects for tailored therapy? Though the cost and logistics of implementing individualized therapy may appear prohibitive, the reality is that cancer is not a single disease. The huge diversity in phenotypes and genotypes between and within tumor types underscores the need for personalized therapy. Taken to an extreme, the notion of tailoring tumor therapy might mean a custom cocktail of cancer drugs for every patient.

The appeal of customized therapy is evident. Treatment with a single agent invariably leads to resistance. In the case of CML, some patients treated with imatinib acquire mutations in Bcr-Abl and ultimately progress to an acute phase of the disease. A combination of targeted agents and chemotherapy may help prolong the efficacy of a drug's action and delay selection of mutations and drug resistance.

The future success of cancer therapy rests on the accurate identification of patient populations before clinical trials are launched. Trials of gefitinib as well as matrix metalloproteinase inhibitors have suffered from such lack of knowledge. The enormous success of imatinib in treating CML might have been missed had the trial not selected for patients with the chromosome bearing the Bcr-Abl fusion. Countless other drugs in the past may have been shelved by companies or rejected by the FDA due to the masking of responders in large trials of unselected patients.

What are the means for tailoring treatment? Advances in proteomics and array technologies, improved diagnostics, classification of tumor types and prediction of response should permit better patient and risk stratification. Clinical trials must be designed to include surrogate markers of efficacy and molecular correlates that identify responding patients. Whether an agent succeeds or fails, the underlying mechanisms must be elucidated from the outset rather than after the failure of multiple large-scale trials. Although it may not be possible to mandate follow-up in industry-sponsored trials, collaborative efforts with the academic community must be fostered and facilitated to ensure that these studies are pursued.

But customized combination therapy comes at a price. *A priori* selection of patients may be expensive and the smaller pool may reduce the potential revenue of an agent. The pharmaceutical industry must establish collaborations to test, both preclinically and clinically, combinations of drugs that are marketed by separate companies. The added cost of development would eventually be borne by the patient or healthcare system.

And yet all parties stand to win, to some degree. Restriction of trial make-up and size to those patients who would likely benefit from the treatment might increase the patient response rate, thereby lowering the risk of rejection of a new drug application. Industry collaboration may reduce the cost of a trial for an individual company. In cases, such as CML, where drugs are administered over the long term, chronic treatment of cancer offers a growth market to pharmaceutical companies. The burden on the healthcare system to provide available therapy to large numbers of patients, in spite of poor response rates and insufficient validation, might be lessened. Most importantly, patients gain by the improved chance of effective therapy.

The moral of the Iressa tale is that effective translation to a therapeutic advance is impossible without the solid foundation of basic science. The value of targeted therapy is lost when treatment validation is the secondary outcome rather than the primary goal of a clinical trial. But the eventual benefits to patients of laying the groundwork should surely justify the effort and expense.