

## EDITORIALS



## Targeting Targeted Therapy

Mark R. Green, M.D.

The emergence of effective cancer chemotherapy is one of the major medical advances of the second half of the 20th century. In certain neoplasms — such as gestational choriocarcinoma, childhood acute lymphoblastic leukemia, and subgroups of Hodgkin's disease and non-Hodgkin's lymphoma — chemotherapy is often curative, and the promise of long-term survival makes therapy well worth the risk of adverse effects and the financial costs. Moreover, adjuvant chemotherapy for breast, colon, or lung cancer can augment the survival benefit afforded by surgical management. Even in patients with advanced solid tumors or recurrences despite surgery, chemotherapy can offer lengthened survival of worthwhile quality. In these patients, however, the therapeutic index is narrow: responses are usually partial, often disappointingly brief, and unpredictable. These circumstances highlight the limitations of traditional cytotoxic chemotherapy.

Against this background, the advent of therapies based on mechanisms that target critical molecular pathways of tumors has evoked considerable interest. When there is a clear cut “molecular driver,” as in Philadelphia chromosome-positive chronic myelogenous leukemia, imatinib therapy induces dramatic and often durable clinical responses in most patients. The therapeutic index is high, and optimally effective treatment can be achieved at a dose below the maximal tolerated dose. In the common solid tumors, by contrast, there are many potential targets but no obvious critical molecular driver, making the development of targeted therapy much more challenging.

Signal-transduction research has shown the importance of members of the human epidermal growth factor receptor (HER) family of transmembrane tyrosine kinases in a number of solid tumors. One member of this family is HER2 (ErbB2). The gene for this receptor is amplified in up to 30 per-

cent of breast cancers, leading to aggressive behavior and an unfavorable prognosis. However, the overexpressed HER2 receptor protein also serves as a target for anti-HER2 antibody (trastuzumab) therapy. The presence or absence of amplification can be used to differentiate patients who may have a response to the antibody from those who will not have a response. The likelihood of tumor regression with trastuzumab therapy may be as high as 35 percent among patients with tumors that strongly overexpress HER2.<sup>1</sup> The addition of chemotherapy enhances responses to the antibody, and treatment of appropriately selected patients with trastuzumab prolongs overall survival.<sup>2</sup>

The epidermal growth factor receptor (EGFR, also known as ErbB1 or HER1), another transmembrane receptor tyrosine kinase of the HER family, has important roles in the proliferation and metastasis of tumor cells. It is frequently overexpressed in common solid tumors and has become a favored target for orally administered small-molecule and antibody-based therapy. In May 2003, the orally administered EGFR inhibitor gefitinib was approved by the Food and Drug Administration as third-line therapy for non-small-cell lung cancer. In phase 1 studies, gefitinib was active against non-small-cell lung cancer across a broad range of doses,<sup>3</sup> and in randomized phase 2 trials, response rates of 9 to 19 percent were reported with the use of doses of 250 or 500 mg per day. Another 30 percent or more of patients had stable disease.<sup>4,5</sup> Many patients reported symptomatic improvement. Occasional patients had dramatic, long-lasting responses. Adverse effects were dose-related, and the 250-mg dose had a favorable therapeutic index. In subsequent studies of gefitinib in a broader range of patients with non-small-cell lung cancer, the response rates were lower, but antitumor activity was evident. Disappointingly, in very recent studies, adding gefitinib

to chemotherapy did not further improve response rates or survival as compared with chemotherapy alone.<sup>6,7</sup>

Retrospective analyses of large phase 2 studies of gefitinib showed that responses were more frequent among patients who had never smoked, women, and patients with bronchoalveolar carcinoma or adenocarcinomas with bronchoalveolar features.<sup>8</sup> Yet even within these selected subgroups, only a minority of patients had a response. Furthermore, there was no correlation between the intensity of immunohistochemical staining of the tumor for EGFR and the presence or absence of a response. This situation has left oncologists with the conundrum of when to offer an approved, highly publicized, expensive, and somewhat toxic therapy and when to select another option. The work of Lynch et al., reported in this issue of the *Journal*,<sup>9</sup> has the potential to lift this burden from patients and physicians. This report also provides an explanation for the observed lack of a dose–response relation with gefitinib. More globally, it illustrates how targeted therapy of a common solid tumor can be optimized.

Lynch et al. hypothesized that a gain-of-function somatic mutation of *EGFR* accounts for the response of some patients with non–small-cell lung cancer to gefitinib. To explore this possibility, the authors sequenced the entire coding region of *EGFR* in tumors from patients with a response to gefitinib and in tumors from those without a response. They also studied tumors from 25 patients with non–small-cell lung cancer who had never received gefitinib, 95 extrapulmonary cancers, and 108 cancer-derived cell lines. Among nine patients with a response to gefitinib, eight had tumor specimens with heterozygous mutations within the tyrosine kinase domain of EGFR, the target of gefitinib. These mutations probably stabilize the interaction between the drug and the kinase, thereby enhancing the inhibitory effect of gefitinib. By contrast, no such mutations were identified in the tumor specimens from seven patients with no response to gefitinib, 23 of 25 primary lung cancers that were not treated with gefitinib, the 95 non–lung-cancer specimens, or the 108 cancer-derived cell lines.

The nine patients with a response to gefitinib had either adenocarcinoma or bronchoalveolar carcinoma. None were current smokers, and six had never smoked; six of the nine were women. The duration of the response ranged from more than 4.3 months to more than 33.5 months, with five of the patients still having a response at the time of the

last follow-up visit. Among the 25 patients with non–small-cell lung cancer who had never been treated with gefitinib, tumor specimens from 2 patients with bronchoalveolar carcinoma had similar mutations in the tyrosine kinase domain of EGFR.

The finding of heterozygous mutations suggested that the mutation caused a gain of function of EGFR. Indeed, in transient transfection experiments, exposure to epidermal growth factor doubled or tripled the activation of the mutant EGFRs, as compared with the wild-type receptor, and the mutant receptors were also more sensitive to inhibition by gefitinib. In vitro, the gefitinib concentrations needed for 50 percent inhibition and complete abrogation of phosphorylation of the mutant receptors correlated favorably with mean steady-state and trough concentrations achieved with a daily dose of 250 mg of gefitinib.

Is this pattern of somatic mutations specific for adenocarcinomas of the lung, and bronchoalveolar cancer in particular? Why does it occur most often among patients who have never smoked or those who have not smoked for many years? Will responses to erlotinib, another oral small-molecule inhibitor of EGFR, correlate with the same pattern of somatic mutations? Is this pattern relevant to the effects of anti-EGFR antibodies? How do these new data fit with the finding that more than 30 percent of patients who received gefitinib in the large phase 2 trials had stable disease? Did those trials really show an effect of gefitinib, or were we overinterpreting noncomparative phase 2 data? These and many other questions remain to be investigated.

Does the finding that one patient who had a response to gefitinib did not have a tumor with a mutation in *EGFR* signify that other facilitating mutations in non–small-cell lung cancer have yet to be identified? Does this finding suggest that the mutation is unstable and heterogeneous with respect to the tumor burden as a whole? Or, because multifocal bronchoalveolar carcinoma may be multiclonal,<sup>10</sup> is it possible that this one specimen was truly negative for mutations and that other tumor cells, which were not in the tested specimen, actually carried the mutation that was responsible for the response to gefitinib?

Can a therapy that causes tumor shrinkage in only a small subgroup of patients with lung cancer be considered meaningful? The answer is in the denominator: each year, more than 140,000 patients with non–small-cell lung cancer are identified in the United States alone, and more than a million

are identified worldwide. Most of these patients will eventually require systemic therapy. Even if less than 10 percent of them have tumors with a gain-of-function mutation, we are left with many thousands in whom gefitinib would be indicated, probably as first-line therapy for advanced disease. Phase 3 studies of adjuvant gefitinib are already under way in patients with completely resected non-small-cell lung cancer. Studies integrating gefitinib in the initial treatment of locally advanced non-small-cell lung cancer as either concurrent or maintenance therapy are also ongoing. Whether these studies will need to be redone with patients selected on the basis of *EGFR* mutation status must be considered.

The work of Lynch et al., if borne out by additional studies, will fundamentally change targeted therapy for solid tumors. For patients with lung cancer, mutational analysis of *EGFR* by experienced laboratories should provide guidance about treatment. More generally, this work suggests the relevance of a two-step evaluation of targeted therapy. Identification of the target and a therapeutic ligand will remain a critical but relatively crude initial step. Subsequent work must then facilitate the identification of the responsive subgroup. Seeking gain-of-function mutations clustered around the critical binding pocket of the tyrosine kinase domain, analogous to what has been demonstrated by Lynch et al., seems a reasonable way to begin.

From the Hollings Cancer Center and the Department of Medicine, Medical University of South Carolina, Charleston.

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## Electromechanical Associations

Joseph G. Rogers, M.D., and Michael E. Cain, M.D.

The left ventricle strives valiantly with each cardiac cycle to maximize contractility and provide protection against lethal ventricular arrhythmias. Heart failure can make this coordination difficult. Heart-rhythm and heart-failure specialists are increasingly working together to restore nature's performance and lifesaving features to the failing left ventricle. Our jobs are becoming progressively more entwined as we evaluate treatments involving pacemakers and implantable cardioverter-defibrillators (ICDs) in an effort to improve the quality of life and reduce the risk of complications and death among patients with left ventricular systolic dysfunction.

Several factors contribute to this new collaboration. First, heart-rhythm specialists acknowledge the dramatic effect heart-failure specialists have had using contemporary, evidence-based medical regi-

mens to improve left ventricular function and reduce the risks of death from arrhythmia and from any cause among patients with heart failure. However, even heart-failure specialists admit that a further benefit from drugs that antagonize neurohormonal pathways is unlikely to be achieved. Trials of new agents, such as endothelin antagonists, vaso-peptidase inhibitors, and soluble tumor necrosis factor  $\alpha$  receptors, have not shown an incremental survival benefit.<sup>1-3</sup>

Second, heart-failure specialists recognize that at least half their patients die suddenly. They also acknowledge that ICD therapy in patients with healed myocardial infarction and left ventricular dysfunction decreases overall mortality.<sup>4</sup> Third, both heart-rhythm and heart-failure specialists agree that patients with heart failure with left