

Clinical Update on Oncology Treatments and Trends

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Abstract

This article provides a clinical update on recent trends and developments for treating non-small-cell lung, breast, and colorectal cancers and several types of non-Hodgkin's lymphoma. Included in the discussions are results from the latest clinical trials and a look ahead at further research in development. Advances in early detection and screening techniques have helped physicians to detect cancer early and increase survival rates. Monoclonal antibodies have shown promise in treating some forms of cancer and have been a successful part of treatment when coupled with chemotherapy. Such developments are helping to improve patient care and lower mortality rates.

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Treatment of Non-small-cell Lung Cancer

Lung cancer is the second most frequently occurring cancer in the United States, with more than 172 000 new cases projected to occur in 2006, and the most lethal of all cancers, with an estimated mortality of 160 000 in 2006.^{1,2} Among cancers of the lung and bronchus, non-small-cell lung cancer (NSCLC) is by far the most frequent, constituting approximately 86% of all cases of such disease.³

Although NSCLC of stages I and II is often surgically resectable, and stage IIIA disease is sometimes resectable, advanced NSCLC of stages IIIB and IV cannot be resected, and guidelines issued in 2004 by the American Society of Clinical Oncology recommend chemo- and radiotherapy for NSCLC of stage IIIB and chemotherapy alone for that of stage IV.⁴ Although chemotherapy can prolong survival in NSCLC of stages IIIB and IV,^{5,6} it has only modest activity against such advanced disease,⁷ and carries a substantial risk of adverse and potentially lethal effects, including neutropenia and thrombocytopenia, as well as nausea and vomiting.

Efforts at improving the efficacy of treatment for cancer while reducing its adverse effects have led to the development of small-molecule agents directed at inhibiting specific biologic processes within malignant cells. The most widely investigated target of these small-molecule agents has been the epidermal growth factor receptor (EGFR), also designated human estrogen receptor (HER) 1, which is 1 of 4 members of the family of transmembrane receptors collectively designated ErbB. Besides EGFR, the most well-known member of the ErbB family is *HER2/neu*, or ErbB2, a target of recent treatment for breast cancer.⁷

Two recently developed small-molecule agents, gefitinib and erlotinib, have shown promise for treating NSCLC in recent clinical studies. Both gefitinib and erlotinib are small molecule human epidermal growth factor receptor type 1/epidermal growth factor receptor tyrosine kinase inhibitors, produced by fusing rapidly growing cells derived from nonhuman tumors to plasma cells that produce an antibody directed at a specific antigen, yielding the rapidly growing cells known as hybridoma cells, which generate large quantities of the desired antibody. The finding that a positive response to gefitinib and erlotinib in some cases of NSCLC has correlated with mutations and other aberrations of the gene that encodes EGFR, in addition to correlating with increased expression of EGFR and specific clinical features of responding patients, has prompted studies designed to explain these findings.⁸⁻¹⁰

Approved by the US Food and Drug Administration (FDA) in May 2003 for compassionate use as a single agent in treating

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NSCLC that has failed to respond to chemotherapy with regimens containing platinum drugs such as cisplatin and treatment with the taxane drug docetaxel,¹¹ gefitinib (Iressa®) was the first targeted small-molecule drug to be registered for treating advanced NSCLC.⁷ It acts by binding to the protein tyrosine kinase (PTK) site of EGFR on tumor cells, thereby blocking the phosphorylation of PTK that initiates the receptor's signaling for tumor-cell replication and growth.

Clinically, gefitinib has been investigated both alone and in combination with other chemotherapeutic agents for NSCLC in a number of studies.¹²⁻¹⁷ The 2 large phase 2 studies that led to the FDA approval of gefitinib for treating NSCLC were the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and 2 studies. Both examined gefitinib alone in patients with advanced NSCLC that had progressed despite 1 or 2 prior regimens of chemotherapy, of which at least 1 had contained a platinum-based agent. In these studies, gefitinib induced responses in about 10% of patients.⁷

Although gefitinib failed to improve survival in either IDEAL 1 or 2 or the later, phase 3 Iressa Survival Evaluation in Lung Cancer study, in which it was compared with a placebo in patients whose NSCLC had progressed despite chemotherapy, analysis of data from these studies suggested that several patient- and tumor-related variables might positively influence the response to gefitinib.⁷ Other studies have examined mutations in the EGFR gene as correlates of the response of NSCLC to treatment with small-molecule inhibitors, and the concept that genetic mutational analysis may permit the selection of patients with a particular type of cancer who will respond to a particular treatment agent.¹⁸ The study suggesting that mutational analysis may be useful for selecting patients according to their likelihood to respond to a particular treatment agent was conducted at the Harvard Medical School, Harvard School of Public Health, and Massachusetts General Hospital (MGH), and was based on the observation that gefitinib produces a dramatic clinical benefit in only about 10% of the patients in whom it is used to treat NSCLC.¹⁸

The findings of the Harvard/MGH study suggest that mutations in EGFR may occur only in a subgroup of NSCLCs, and that by stabilizing and prolonging the binding of adenosine triphosphate (ATP) to the mutant amino acids in the ATP-binding cleft of the mutant EGFRs, these mutations may prolong the cell-proliferative and cell-growth effect of ATP, and therefore the growth of the NSCLC tumors in which such mutations occur. Yet these same mutations may also stabilize the interaction between gefitinib and the amino acids in the ATP-binding cleft of the mutant EGFRs, explaining the therapeutic activity of gefitinib in this subgroup of NSCLCs.¹⁸ The study suggests that by revealing mutations in EGFR that have potential therapeutic significance in NSCLC, genetic analysis may identify the subgroup of NSCLC patients who will respond significantly to gefitinib, and that such genetic analysis may also be applicable in the treatment of other cancers.¹⁸

Like gefitinib, erlotinib is directed at the PTK region of the EGFR of tumor cells. Erlotinib has been examined in several clinical studies and has been approved by the FDA for use as a single agent in treating locally advanced or metastatic NSCLC that has progressed despite one or more prior regimens of chemotherapy. A key study in the approval of erlotinib was trial BR.21, conducted by the National Cancer Institute of Canada Clinical Trials Group. A recent substudy examined the features of NSCLC that appear to be associated with responsiveness to erlotinib in 213 patients from the original BR.21 study whose tumor-tissue specimens were suitable for molecular and genetic analysis.⁸

Of these 213 patients, 106 have so far been examined for data about the EGFR genes in their tumors. Clinically, these patients showed 3 features that have been linked to a greater likelihood of responsiveness of NSCLC to erlotinib: they were more likely than the overall BR.21 study population to have had adenocarcinoma, more likely to have had more than one prior treatment regimen, and more likely to have had a longer time between the diagnosis of NSCLC and assignment to treatment in BR.21.⁸

Although substantial further work remains to be done in determining the clinical efficacy of erlotinib and gefitinib in NSCLC, and studies of both drugs are continuing, the findings with gefitinib indicate that it may have benefit as either for concurrent use with other agents in the first-line treatment of locally advanced NSCLC or for maintenance therapy in the disease. Additionally, the findings in the Harvard/MGH study of gefitinib suggest that mutational analysis of the EGFR gene may have an important role in focusing treatment for NSCLC.¹⁰

Bevacizumab in Non-small-cell Lung Cancer. Vascular endothelial growth factor (VEGF) is a peptide that binds to receptors in blood vessels to initiate the development and growth of new vessels. Besides its normal, physiologic activity in promoting such new vessel development, or angiogenesis, VEGF is now known to be produced by tumors of various kinds, in which its generation of new vessels, or neovascularization, provides these tumors with a blood supply that sustains their continued growth. Among tumors found to produce VEGF are carcinomas of the colon and rectum.

The monoclonal antibody bevacizumab is directed at blocking the binding of VEGF to its vascular receptors, and in 2004 the FDA approved bevacizumab for use in combination with 5-fluorouracil (5-FU) for the first-line treatment of metastatic carcinoma of the colon or rectum.¹⁹ The finding that tumors of various types produce VEGF has prompted investigation of bevacizumab as a VEGF-blocking agent in NSCLC as well as several other cancers in addition to carcinoma of the colon or rectum.

A randomized phase 2 trial begun at Vanderbilt University in July 2001 has reported highly favorable results with a treatment regimen consisting of bevacizumab in combination with the taxane drug paclitaxel and the platinum-containing drug carboplatin in patients with untreated advanced or metastatic NSCLC, as compared to combination chemotherapy with the latter 2 drugs alone. Both the bevacizumab-containing and the paclitaxel/carboplatin regimen are given in 3-week cycles in which both paclitaxel at 200 mg/m² and carboplatin at

an under the curve of 6 are infused during a single day, with 1 treatment group additionally receiving bevacizumab at a dose of 15 mg/kg on the same day as the paclitaxel and carboplatin. Patients in the control arm of the study, receiving paclitaxel and carboplatin without bevacizumab, have the option of receiving bevacizumab alone in a dose of 15 mg/kg once every 3 weeks if their disease progresses despite treatment with the paclitaxel/carboplatin regimen.²⁰ The study was designed to have 91% statistical reliability for detecting a 30% improvement in median survival time.²¹

As of April 2004, 444 patients had been enrolled in the paclitaxel-plus-carboplatin control arm of the study and 434 patients in the group being treated with bevacizumab plus paclitaxel and carboplatin.²¹ By June 2004, 31.5% of patients treated with the bevacizumab/paclitaxel/carboplatin-containing regimen had responded to this treatment, as opposed to 18.8% of those given paclitaxel and carboplatin only. Patients treated with the bevacizumab-containing regimen also had a longer median time before their disease once again progressed, of 7.4 months versus 4.2 months in the paclitaxel/carboplatin-treated group, and experienced a modest prolongation of survival, of 17.7 months versus 14.9 months for the patients treated with carboplatin and paclitaxel alone. Among patients whose NSCLC progressed despite treatment with paclitaxel and carboplatin, 5 of 19 who chose to receive treatment with bevacizumab alone had stabilization of their disease, and survival at 1 year in this "crossover" group was 47%.²⁰ The chief adverse event related to treatment in the study has been bleeding, consisting either of minor mucocutaneous hemorrhage or major hemoptysis, of which the latter was associated with tumors having a squamous-cell pattern on histologic study, as well as tumor necrosis and the location of NSCLC near major blood vessels.²¹

A first interim analysis of 48% of the study data was conducted in September 2004. In June of 2004, the investigators conducting the study reported that bevacizumab in combination with carboplatin and paclitaxel had improved the overall response to treatment and the time to disease progression

among patients with advanced or recurrent NSCLC.²⁰ Final conclusions to be drawn from this study await the full reporting of its data.

A key need in meeting the challenges of screening for lung cancer is a cost-effective technique that can be used for detecting the disease in populations at risk for it.

Evolving Factors in Screening for Lung Cancer. With lung cancer the second most frequently occurring malignancy in the United States and the leading cause of cancer-related death,^{1,2} its early detection remains a high priority of healthcare. Although screening for lung cancer has long been a component of public health initiatives directed at stopping smoking as a cause of this disease, such screening cannot benefit the 45 million persons in the United States who have stopped smoking and no longer do so, but who develop lung cancer as often as do currently active smokers.¹ Moreover, 75% of cases of lung cancer have already metastasized by the time they are diagnosed, yielding a 5-year survival rate of approximately 15% in this population, as compared with a 5-year survival that often exceeds 60% for the much smaller percentage of persons in whom lung cancer is still localized when detected.²²

At present, screening for lung cancer is undergoing rapid evolution, as reflected by the change in stance of the United States Preventive Services Task Force in 2004, in which this public health group changed its previous position of discouraging generalized screening for lung cancer to a position of making no recommendation for or against the use of screening for asymptomatic persons.^{23,24}

Among issues of contention in the large-scale screening of asymptomatic populations for lung cancer are overdiagnosis and overtreatment; underdiagnosis; the risk of radiation associated with screening; and the

cost of screening. In lung cancer, overdiagnosis may not be a major problem, because emerging data suggest that small cancers detected by screening have patterns of malignancy similar to those of more readily recognizable symptomatic lesions,²² and in view of a recent report of an autopsy series in which undetected lung cancer was found in only 0.8% of cases.²⁴ On the other hand, overtreatment may occur with the use of more invasive or extreme measures for disease staging or treatment than are needed to prevent early lung cancer from progressing to lethal metastatic disease, a possibility that has prompted efforts to define interventional techniques that will avoid iatrogenic complications in the management of lung cancer.²² By proving wide access to data on tumor pathology, staging, treatment, and outcome in lung cancer, national registries, such as that developed by the Society for Thoracic Surgery,^{22,25} may help improve patient-management outcomes in the disease. With regard to the risks of radiation exposure, the risk of lung cancer among older, long-term smokers has been called far greater than the risk to this population of cancer from screening-associated radiation.²²

A key need in meeting the challenges of screening for lung cancer is a cost-effective technique that can be used for detecting the disease in populations at risk for it.²⁴ Efforts at defining the risk features of a particular population to be screened for lung cancer, as well as refining the interpretation of screening results, reducing the intensity of follow-up screening, and reducing iatrogenic and other costs of screening-related care, are measures that can potentially improve the cost efficiency of screening. Although a study based on Mayo Clinic data estimated a cost of more than \$116 000 per quality-adjusted life-year under favorable circumstances for screening for lung cancer with spiral computed tomography (CT),²⁶ other analyses, based on large recent studies, have concluded that under favorable circumstances, a single, baseline, low-dose CT scan would have a far greater cost-effectiveness ratio of \$2500 for each year of life that it saved.^{24,27}

In contrast to chest radiography, which is a deficient means for detecting lung cancer

at an early and curable stage,²² spiral CT may be a promising means for providing cost-effective screening. Uncontrolled, single-group studies have reported that spiral CT yields uniformly greater rates of detection of lung cancer in stage I, which in some cases have exceeded 80%, as opposed to the current 17% overall detection rate for such disease in the United States.^{28,29} In Japan, the introduction in 1993 of spiral CT for screening large populations increased the rate of detection of stage I lung cancer to 78%, from the rate of 42% that had been achieved with chest radiography from 1975 to 1993, and this gain was accompanied by a decline from 33% to 14% in the rate of detection of cancers that had reached stages III and IV before being detected. These gains were accompanied by an increase to 84% in the 5-year survival rate for patients with lung cancer, from a prior rate of 49%.³⁰

The International Early Lung Cancer Project (I-ELCAP), which has so far screened more than 26 000 subjects, has likewise found a substantial advantage for spiral CT, identifying 82% of lung cancers while still in stage I and reporting a survival rate of better than 95%.^{27,31} In their work, the I-ELCAP investigators have developed techniques for the computer-assisted detection of clinically significant lung cancer lesions with high-resolution spiral CT, and have defined a phase of lung cancer that had not been recognized before the introduction of this modern screening technique. The I-ELCAP group has also developed algorithms and other means for improving patient management on the basis of screening results. The practices used in the I-ELCAP study have been reported to require that only 13% of screened subjects receive follow-up study, and have made serial studies of nodule growth rates an adequate means of follow-up for most of the patients who need it.³²⁻³⁴

The I-ELCAP study has been completed, and its results are expected to be reported shortly. Given the findings in I-ELCAP and other studies, the US National Cancer Institute (NCI) recently began the National Lung Cancer Screening Trial (NLST) to determine whether CT screening can significantly reduce mortality from lung cancer in

comparison with chest radiography. This study, and concurrent studies in the Netherlands and elsewhere in Europe, will use multiple CT detectors arrayed in rows.²²

Among problems remaining in achieving sensitive, safe, and cost-effective population-based screening for lung cancer are developments in screening technology. Rapid technologic advances in the sensitivity of detecting lesions may make even the newest spiral CT equipment obsolete before studies of its efficacy can complete the standard 2- to 5-year timespan needed for patient enrollment, data analysis, and evaluation. Additionally, a new CT imaging technology will be capable of 8-fold greater spatial resolution than can be achieved with available CT systems. This will yield a multifold increase in scan data, requiring the development of methods for reducing these data to a scale that a radiologist can interpret. In the face of such challenges, the NCI has initiated the Lung Image Database Consortium, which will create a database of images and clinical outcomes that can be used to expedite the development of effective image-analysis techniques for lung cancer screening.²²

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