

Targeted Therapy in Non-Small Cell Lung Cancer

Dr. Scott Gettinger and Dr. Hari Deshpande

In May of 2003, the first targeted agent for non-small cell lung cancer, gefitinib (Iressa), an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), received accelerated approval for the management of patients with incurable non-small cell lung cancer (NSCLC) after failure of both platinum-based and docetaxel chemotherapies. This designation was reached after review of two randomized phase II trials comparing different doses of gefitinib, IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) 1 and 2, which found encouraging response rates. However, after the confirmatory ISEL (Iressa Survival Evaluation in Lung Cancer) trial, a phase III trial comparing gefitinib to placebo in the second or third line setting, did not find a significant survival advantage with gefitinib, the FDA revised the labeling in June of 2005, with continued use only approved for those who had previously responded to gefitinib.

In November of 2004, the FDA approved another oral EGFR TKI, erlotinib (Tarceva), for the treatment of incurable NSCLC refractory to at least one prior chemotherapy regimen. Unlike the ISEL trial, the similarly designed National Cancer Institute of Canada Clinical Trials Group BR.21 trial did find a survival advantage with the use of erlotinib compared to placebo in the second or third line setting in patients with incurable NSCLC. This benefit translated into a two month

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TARGETED AGENTS AVAILABLE TO LUNG CANCER PATIENTS AT YALE CANCER CENTER		
Agent	Class (route)	Target
On Clinical Trial (Phase I)		
Sunitinib (Sutent)	TKI (PO)	VEGFR; PDGFR; KIT; FLT-3; RET
Sirolimus (Rapamycin)	STKI (PO)	mTOR
AEE788	TKI (PO)	VEGFR; EGFR; HER2
PXD101	HDACi (PO)	HDAC
Sorafenib (Nexavar)*	TKI (PO) STKI	VEGFR; PDGFR; KIT; FLT-3; RET ; RAF
Off Trial		
Bevacizumab (Avastin)	Mab (IV)	VEGF
Erlotinib (Tarceva)	TKI (PO)	EGFR

TKI – tyrosine kinase inhibitor; STKI – serine-threonine kinase inhibitor
 FLT – Fms-like tyrosine kinase; HDAC(i) – histone deacetylase (inhibitor)
 Mab – monoclonal antibody; EGFR – epidermal growth factor receptor;
 mTOR – mammalian target of rapamycin
 VEGF(R) – vascular endothelial growth factor (receptor)
 HER2 – human epidermal growth factor receptor 2
 PDGFR – platelet-derived growth factor receptor
 *Trials with sorafenib in combination with chemotherapy soon to be open at YCC.

Thoracic Radiotherapy

Dr. Lynn Wilson

Radiotherapy has been an integral part of the management of locally advanced lung cancer for many years, but technological advances have enabled the incorporation of higher doses of radiotherapy in conjunction with chemotherapy and with improved safety and toxicity profiles. Enhanced accuracy of target delineation has contributed to more conformal and smaller radiotherapy fields that allow for the exclusion of normal structures such as non-involved lung, esophagus, cardiac,

and other soft tissues. Yale thoracic radiotherapy physicians evaluate patients in conjunction with medical oncologists, surgeons, pulmonologists, and other specialists in a weekly multidisciplinary clinical setting as part of the Yale Cancer Center Thoracic Oncology Program (TOP). All patients who will be receiving radiotherapy undergo positron-emission tomography (PET)-Computed tomography (CT), which is incorporated into the 3-dimensional radiotherapy treatment planning and simulation process. This is an important step in customizing radiotherapy portals, as we know that localization and targeting are enhanced through the incorporation of PET-CT.

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Editor's Letter

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A multidisciplinary approach to cancer treatment is not a new concept. However, the Yale Cancer Center Thoracic Oncology Program (TOP) offers a genuine multidisciplinary approach with a focused collaboration and a wide range of exciting and promising clinical research studies. TOP places great emphasis on developing interdisciplinary translational research initiatives.

Chemotherapy options for patients with thoracic malignancies have evolved. New approaches on the horizon include targeted therapy or techniques that characterize the tumor biology of patients and may lead to the ability to tailor chemotherapeutic treatment for individual patients. In this issue, Drs. Scott Gettinger and Hari Deshpande discuss these exciting new approaches to chemotherapy treatment.

Surgical and radiotherapy techniques have also continued to advance with the goal of maximizing the cure rate while minimizing toxicity and morbidity. In this issue, Dr. Frank Detterbeck and Dr. Lynn Wilson discuss inspiring new approaches to surgery and radiotherapy, respectively.

Effective early detection methods for thoracic tumors have been difficult to achieve. Dr. Lynn Tanoue discusses the obstacles in lung cancer screening and some of the risks and benefits of the new approaches that are currently being examined.

The Yale Cancer Center Thoracic Oncology Program will continue to discuss the difficult issues and newer therapeutic approaches through subsequent issues of this newsletter and I hope you find the information useful in your practice.

Sincerely,

Joseph M. Colasanto, MD

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improvement in the overall median survival (6.7 vs. 4.7 months with a hazard ratio (HR) of 0.70; $p < 0.001$). Like gefitinib, erlotinib was generally well tolerated with the main adverse reactions consisting of rash and diarrhea.

The use of gefitinib and erlotinib was further investigated with standard first-line NSCLC platinum-based chemotherapy regimens in four Phase III clinical trials. All four trials reported no clinical benefit with the addition of these targeted agents to chemotherapy. However, one encouraging subset analysis of the TRIBUTE trial reported a one year survival advantage in 'never smokers' treated with chemotherapy and erlotinib (72 patients) compared to chemotherapy alone (44 patients).

Retrospective analyses of the above mentioned trials generated a clinical picture of who might respond to therapy with an oral EGFR TKI. In particular, a history of never smoking, East Asian descent, female sex, and adenocarcinoma histology appeared to be significant predictors of response. Of these characteristics, a history of never smoking emerged as the most powerful predictor of benefit. Another observation included the suggestion that the development of a rash was a possible sign of efficacy. However, the majority of patients in the BR.21 trial developed a rash without clinical benefit. On the other hand, if one did not develop a rash on therapy, it was unlikely that he or she was responding.

Molecular predictors of response to gefitinib and erlotinib were also evaluated in these trials. Although it is hard to interpret this retrospective data, as it is not statistically robust, it appears that the identification of certain EGFR mutations as well as overexpression of EGFR via FISH (fluorescent in situ hybridization) may be important predictors of clinical benefit with this class of agents. More controversial is the predictive power of EGFR overexpression by traditional IHC (immunohistochemistry). Another exploratory analysis of k-RAS mutations in tumor tissue suggested that the identification of this mutation may be a negative predictor of response to EGFR TKIs. At this time, molecular analysis of tumor tissue is not routinely done to guide therapy. However, in certain situations, clinical characteristics, in particular a history of never smoking may assist in treatment planning, i.e. a Korean woman with Stage IV adenocarcinoma who has never smoked. It would not be unreasonable to start with erlotinib in this scenario. Clinical trials are underway to prospectively evaluate both clinical and molecular predictors.

Another targeted therapy that is expected to be approved for NSCLC this year by the FDA is bevacizumab (Avastin), a monoclonal antibody to the vascular endothelial growth factor (VEGF). The FDA is presently reviewing recently presented data from the Phase III ECOG (eastern cooperative oncology group) 4599 clinical trial randomizing 878 patients with Stage IIIB (with pleural or pericardial effusion) or IV NSCLC to first-line chemotherapy with paclitaxel and carboplatin, or the same chemotherapy with the addition of bevacizumab. This trial notably excluded patients with squamous cell histology as earlier NSCLC clinical trials with bevacizumab reported a higher incidence of significant hemoptysis with this histology. Also, patients with a history of brain metastases, hemoptysis or a condition requiring anticoagulation were ineligible secondary to concerns of bleeding with bevacizumab. The results of this trial were presented at the annual ASCO (American Society of Clinical Oncology) meeting in 2005. Median survival with bevacizumab was 12.5 months compared to 10.2 months ($p = 0.0075$) with chemotherapy alone. At one and two years, 52% and 22% of patients receiving bevacizumab were alive, respectively, compared to 44% and 17% in those receiving only chemotherapy. Treatment with bevacizumab was generally well tolerated, with slightly more grade IV neutropenia (24 vs. 16.4%; $p = 0.006$) and grade III or IV hemorrhage (4.5 vs. 0.7%, $p < 0.001$).

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CLINICAL TRIALS Thoracic Oncology Program



LUNG CANCER:

HIC 26573	Phase I Feasibility Study: Combined Modality Treatment with Transimmunization for Non-Small Cell Lung Cancer	Lynn Wilson, MD (203) 737-1202
HIC 27219	A Phase II Trial of CLORETAZINE (VNP40101M) for Patients with Relapsed or Refractory Small Cell Lung Cancer	Scott Gettinger, MD (203) 785-7564
HIC 0511000795	A Phase III Comparison of Prophylactic Cranial Irradiation Versus Observation in Patients with Locally Advanced Non-Small Lung Cancer	Lynn Wilson, MD (203) 737-1202
HIC 0604001307	A Phase II Trial of Neoadjuvant Therapy with Concurrent Chemotherapy and High Dose Radiotherapy followed by Surgical Resection and Consolidative Therapy for Locally Advanced Non-Small Cell Lung Carcinoma	Joseph Colasanto, MD (203) 737-2758

PHASE I:

HIC 0511000860	A Phase I Study of the mTOR Inhibitor Rapamycin (Rapamune, Sirolimus) in Combination with Abraxane (Paclitaxel protein-bound particles) in Advanced Solid Cancers
HIC 0510000723	A Phase I Trial of the Combination of Sirolimus and SU11248 (Sutent) in Patients with Advanced Solid Tumors that are Non-Curable with Standard Therapy
HIC 0508000436	A Phase IA, Multicenter, Dose-Escalation Study of Oral AEE788 on a Continuous Daily Dosing Schedule in Adult Patients with Advanced Cancer
HIC 0604001305	An Open Label, Dose Escalation Trial of Oral PXD101 in patients with Advanced Solid Tumors

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There was a 1.9 % treatment related death rate with bevacizumab compared to 0.4% with chemotherapy alone.

The role of targeted therapy is just beginning to be defined in NSCLC. Although some progress has been made, clearly there is much room for further improvement in symptom control and survival. To this end, clinical investigators are focusing on determining who might respond to these costly therapies. Strategies include prospectively testing predictive biomarkers and ultimately stratifying patients in trials according to molecular or clinical characteristics. The era of targeted therapy has just begun; with the intelligent design of clinical trials and the collaboration of researchers around the globe, the promise of targeted therapy is sure to be realized.

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Low Dose Computed Tomography: Is it a Good Option for the Early Detection of Lung Cancer?

Dr. Lynn Tanoue

The lack of defined screening tools for the early detection of lung cancer is a major obstacle to improving outcomes. Most patients with lung cancer have advanced disease when diagnosed. Screening programs for breast, colorectal, and prostate cancer are well defined and widely practiced, and have contributed to earlier detection and better cure rates than lung cancer. Lung cancer claims more lives annually than these cancers combined. At present, less than one third of lung cancer patients are diagnosed at early stage when surgical resection is possible and cure is most likely. For decades, this has fueled efforts directed at developing effective screening, yet there are still no screening methods that have been demonstrated to decrease lung cancer mortality. As a result, neither the National Cancer Institute nor any major medical society currently recommends screening for lung cancer.

From the 1960s to 1980s, large randomized controlled trials in the United States and abroad failed to demonstrate screening efficacy with chest radiography or sputum cytology. Intense interest is currently focused on whether low dose computed tomography (LDCT) scanning will be an effective lung cancer screening tool. LDCT scanning is very sensitive, and can routinely identify lung nodules as small as 2 mm. In observational studies evaluating screening with LDCT, the following points have become clear: 1) LDCT detects far more lung cancers than chest radiography; 2) The majority, though not all, of lung cancers detected by LDCT are early stage and potentially curable; 3) The false positive rate of LDCT is high. In patients with a history of smoking, LDCT identifies lung nodules in a large percentage of patients (as many as 60%), the vast majority of which are benign; 4) Evaluation of false positive LDCT findings can incur physical, emotional, and economic cost; 5) Identification of indolent cancers unlikely to cause mortality (overdiagnosis) is a concern; 6) The risk of radiation exposure related to repeated LDCT examinations is as yet undefined; 7) A mortality benefit related to LDCT screening has not been demonstrated.

Patients with identifiable risk factors for lung cancer – tobacco use, environmental smoke exposure, exposure to carcinogens in the workplace or in the home, a family history of lung cancer, personal history of malignancy, etc. – will likely be target populations for future screening studies. LDCT as a screening modality is currently being rigorously scrutinized in the National Lung Screening Trial, sponsored by the National Cancer Institute. The results of this study will be available in several years and will hopefully contribute to the development of effective lung cancer screening.

Video Assisted Thoracic Surgery

Dr. Frank Detterbeck

Minimally invasive approaches in thoracic surgery are ushering in a new era for patients at Yale Cancer Center. Although Video Assisted Thoracic Surgery (VATS, also known as thoracoscopy) is not conceptually new, this approach has reached a stage of development that is dramatically changing the experience for patients. Even complex procedures, such as a lobectomy or esophagogastrectomy, can now be routinely accomplished. In fact, minimally invasive resection is the standard practice within the Yale Section of Thoracic Surgery for the vast majority of patients that have tumors confined to the lung or esophagus. Open approaches are reserved for those patients with tumor extension to adjacent structures such as the carina, chest wall, or vertebral column that require more extensive resection and reconstruction.

The techniques and instrumentation for VATS have evolved so that a lobectomy can now be accomplished entirely with video camera visualization, and the lobe is removed through a small 5 cm access incision. In the past, what was claimed to be a VATS lobectomy included procedures done through a larger incision with rib spreading. This is no longer an acceptable standard, because the avoidance of trauma to the ribs is the key to minimizing pain and speeding the recovery for our patients. Currently, the median length of hospital stay after a VATS lobectomy is 2-3 days and patients are able to resume fairly normal activities within a few weeks. A reduced need for narcotics also minimizes side effects and allows for a more rapid return to normal.

Minimally invasive lobectomy or esophagogastrectomy have been shown to be oncologically sound approaches. Adherence to standard oncologic principles is important, such as careful hilar dissection and the systematic dissection of mediastinal lymph nodes. Long term survival after a VATS resection is at least as good as survival following an open resection, stage for stage. In fact, the more rapid recovery is likely to increase the ability to administer postoperative chemotherapy, which has also become the standard of care for most patients with lung cancer. Combined, all of these advances have created a dramatic improvement in care for patients with a thoracic malignancy at Yale Cancer Center.

>> THORACIC RADIOTHERAPY continued from page 1

Following target delineation and initial field design, additional steps are taken to ensure that the volume of normal lung receiving radiation is appropriate to minimize the risk of radiation pneumonitis. This is achieved through the calculation of V20 in addition to other volumetric parameters. The V20 represents the volume of lung that receives a dose of 20 Gy after subtraction of the planned target volume. This parameter correlates very closely with risk of pneumonitis and is strictly adhered to within the Yale program in an effort to minimize risk for the patient.

Yale Therapeutic Radiology is currently in the process of installing new equipment that will allow even greater precise target localization on a daily basis through the use of image guided radiotherapy (IGRT). This technique will allow a cone beam CT scan to be performed on the linear accelerator on a daily basis, followed by immediate field adjustment if necessary, in addition to traditional laser alignment. The new equipment will also allow for stereotactic radiotherapy to be delivered to small, medically inoperable lesions, and this will afford the potential for enhanced local control through radiation dose escalation with fewer treatments and enhanced convenience for our patients. Respiratory gating, which is a method that takes movement of the tumor within the chest into account over time (4-dimensional radiotherapy with time representing the 4th dimension), will also provide for enhanced targeting with additional accuracy.

Yale Therapeutic Radiology continues to be a leader in clinical care and in moving the field forward through clinical research. The concept of post operative radiotherapy for patients found to have positive lymph nodes at the time of surgery has been a controversial issue. Based on the findings of the PORT meta-analysis published in 1998, radiotherapy was thought to potentially enhance local control for those found to have mediastinal adenopathy at surgery, but a survival benefit was not evident. Yale Investigators evaluated the national SEER registry in an effort to learn more regarding outcomes for patients who receive post operative radiotherapy in the modern era. The study evaluated a cohort of over 7000 individuals, all of whom had stage II or III non-small cell lung cancer. The results of the study¹, published in the *Journal of Clinical Oncology* in July 2006, revealed a significant survival benefit for those with positive mediastinal nodes, receiving post operative radiotherapy (27% versus 20% survival at 5 years for those receiving versus not receiving radiotherapy postoperatively). It is likely that more modern techniques such as 3-dimensional therapy and the use of the modern linear accelerator, contributed to this finding. Other studies regarding minimization of treatment toxicity, radiotherapy outcomes, and enhanced targeting techniques are currently underway as Yale Therapeutic Radiology and Yale Thoracic Oncology physicians continue to make important discoveries that will move the field forward.

1. Lally BE, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. Postoperative radiotherapy for stage II or III non-small cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998-3006.

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