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2:45 p.m.

Renal: Urologic Therapies
TBD

3:00 p.m.

Renal: Ablation and Embolization
Timothy W.I. Clark, MD
Hospital of the University Of Pennsylvania
Philadelphia, PA

3:15 p.m.

Lung: Medical Oncology
Neil E. Ready, MD

Lung cancer is a common and virulent disease with an estimated 164,000 new cases and 156,900 deaths annually in the US (1). The magnitude of the burden of lung cancer is exemplified by the fact that the number of deaths annually from lung cancer approximates the total number of deaths from the second through fifth leading causes of cancer mortality combined (colorectal, breast, prostate and pancreatic cancers). Non-small cell carcinomas (adenocarcinoma, squamous cell and large cell carcinomas) account for 80–85% of lung cancers and have been traditionally considered collectively for purposes of treatment. As our experience with molecular-targeted therapy grows, future therapy may be directed at specific molecular abnormalities associated with the different subtypes of non-small cell lung carcinoma (NSCLC). This review will cover the medical and multi-modality treatment of NSCLC.

Stage I cancers have no lymph node involvement and stage II cancers have involvement of intrapulmonary or ipsilateral hilar lymph nodes. Complete surgical resection with a minimum of a lobectomy is the treatment of choice for patients with stage I and II NSCLC. Conformal high dose radiation, wedge resection and image guided ablation are some of the modalities being studied for the treatment of early stage NSCLC that can not be treated with standard surgery due to severe comorbid medical disease. Five-year survival is approximately 60–70% for stage I and 40–50% for stage II cancers following complete surgical resection. Many patients will relapse following surgery. The results from recently reported large randomized trials have shown that adjuvant chemotherapy improves disease free and overall survival. IALT was a large randomized, multinational trial for stage IB, II and IIIA NSCLC in which 1800 patients were randomized to observation or several cycles of cisplatin based chemotherapy (2). IALT showed a statistically significant 5% improvement in disease free survival and 4% improvement in over all survival. The NCI Canada trial BR10 evaluated adjuvant cisplatin and vinorelbine combination chemotherapy versus observation in stage IB and II NSCLC (3). The arm that received adjuvant treatment had a 15% improvement in overall survival due to a de-

creased death rate from recurrent NSCLC. CALGB 9633 was a phase III trial for patients with stage IB NSCLC with a randomization between observation and four cycles of paclitaxel and carboplatin (4). The patients who received adjuvant therapy on CALGB 9633 had a 12% improvement in over all survival due to a decreased relapse rate of NSCLC. Administration of chemotherapy prior to surgical resection (neoadjuvant chemotherapy) is an attractive approach in this setting where delivery of adequate systemic therapy postoperatively is often difficult. Randomized trials of neoadjuvant chemotherapy versus adjuvant chemotherapy in this setting are underway to determine whether one strategy is more effective or less morbid than the other. During the last two years data has been presented from three large randomized phase III trials that clearly show a survival benefit from doublet, platinum based chemotherapy after resection of stage IB or II non-small cell lung cancer. The size of the survival benefit is comparable to that seen for adjuvant chemotherapy in breast cancer and colon cancer. It is now reasonable for patients to be offered chemotherapy after surgical resection of stage IB and II as part of standard medical therapy.

Stage IIIA non-small cell lung cancer is composed primarily of patients with involvement of ipsilateral mediastinal or subcarinal (N2) lymph nodes. The optimal management of these patients is controversial and the large amount of clinical data is often difficult to interpret. Patients with N2 disease are recognized to be a heterogeneous group with a wide variation in prognosis based upon the extent of mediastinal node involvement. It is clear that patients with stage IIIA NSCLC treated with surgery alone have a poor outcome. Chemotherapy before or after surgery with or without radiation improves survival but there is a great deal of uncertainty regarding the optimal strategy. The results of a large randomized phase III trial Intergroup 0139 comparing chemoradiotherapy to a dose of 60 Gy without surgery to chemoradiotherapy to 45 Gy followed by surgery were recently reported (5). There was a modest improvement in disease free survival in favor of the group getting surgery. However there was no difference in overall survival between the two groups because of increased treatment associated deaths in the arm including surgery. Some have observed that the increased deaths were at institutions that do a low volume of thoracic surgery and conclude that concurrent chemoradiotherapy followed by surgery is superior therapy. It should be kept in mind that any such analysis was unplanned and should be used primarily to generate a hypothesis for future clinical trials. In the next intergroup study for low volume stage IIIA NSCLC, patients will receive neoadjuvant chemotherapy with or without radiotherapy followed by surgery.

A combination of chemotherapy and radiation therapy is the standard treatment for most patients with unresectable locally advanced (unresectable stage IIIA and stage IIIB) NSCLC. Stage IIIB includes patients with N3 disease (contralateral mediastinal node involvement) or T4 lesions. Historically the prognosis for these patients has been dismal with 5-year survival of less than 5% with surgical resection and less than 10% with primary radiotherapy. Recent trials of combined modality therapy in this setting have shown that concurrent chemoradiotherapy (chemotherapy and radiation given at the same time) is more effective than sequential chemoradiotherapy (6). Concurrent chemoradiotherapy is considered the standard of care for good performance status patients. Ongoing trials are looking at the addition of consolidation chemotherapy to this chemoradiotherapy, or molecular therapy to standard concurrent chemradiotherapy.

Progress in the treatment of metastatic non-small cell lung cancer has been incremental and modest. Trials from the 1980's showed that cisplatin-based chemotherapy improved survival by a matter of weeks when compared to best supportive care. More recent trials using doublets of cisplatin, carboplatin, paclitaxel (Taxol), docetaxel (Taxotere), navelbine, and gemcitabine (Gemzar) have produced average survival improvements of several months. One-year survival rates of up to 50% have been reported in some aggressive phase II cooperative group trials of combination chemotherapy. These encouraging response rates have not always been confirmed in randomized trials, however. A recent Intergroup trial of over 1000 patients comparing four current generation chemotherapy regimens showed disappointing response rates of 15–20% and median survivals of about 8 months for patients with good performance status (7). No chemotherapy regimen has been shown to be clearly superior to other regimens in the initial treatment of metastatic disease. Interestingly, however, single agent docetaxel has shown improved one-year survival and enhanced quality of life as second line therapy when compared to supportive care (8). There is no demonstrated survival benefit for chemotherapy in patients with poor performance status and the decision to recommend therapy for these patients is often difficult. Novel therapeutic agents will be needed to make significant progress in the treatment of metastatic non-small cell lung cancer.

Hope for improved outcomes for patients with advanced NSCLC comes from advances in molecular biology, immunology and pharmacology. Anti-cancer therapies kill tumor cells by initiating an intracellular process of programmed self-destruction called apoptosis. Chemotherapeutic agents and radiation initiate apoptosis by damaging DNA or directly interfering with basic cellular components such as microtubules. Recent preclinical research has demonstrated that small biologic molecules or monoclonal antibodies that interfere with growth factor receptor signaling pathways can also initiate apoptosis. Typically a growth factor binds to a receptor on the cell surface which activates a signaling cascade that ultimately leads to gene expression for proteins that stimulate tumor cell growth and inhibit apoptosis. By design-