Annual Review of Advances in Non-small Cell Lung Cancer Research

A Report for the Year 2010

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Lung cancer is the leading cause of cancer mortality in the United States and worldwide,[1,2] and the prognosis remains poor with an estimated 5-year overall survival (OS) rate of 15%.[2] Approximately 85% of the cases of lung cancer are non-small cell lung cancer (NSCLC), and the majority of patients have advanced stage disease at the time of diagnosis.[3] Significant investigations into the etiology, molecular characteristics, and the development of novel therapies for NSCLC have been performed and are ongoing. Consequently, NSCLC research and care have evolved into a multidisciplinary approach. As a variety of disciplines perform important research and the results are published in multiple journals, it has become increasingly difficult to remain current on the recent publications. We sought to provide a concise review of the major publications related to lung cancer in the fields of molecularly biology, surgery, radiation oncology, and medical oncology. We restricted the review to clinical trials that were published in peer-reviewed journals to the calendar year of 2010; given the rapid developments within the field of molecular biology, abstracts and presentations from 2010 and early 2011 were included in this review. Unfortunately, no appreciable progress was made in small cell lung cancer in the year 2010; therefore, the focus on the review will be NSCLC.

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MOLECULAR BIOLOGY

The ongoing identification of novel recurring molecular abnormalities in lung cancer continues to present exciting opportunities in targeted therapy for this deadly cancer. This theme remains the defining story for lung cancer science in the 21st century. In this brief review, there will be an effort to discuss some of the developments in lung cancer biology and its application to therapy.

Without doubt, the major development in 2010 that will soon impact lung cancer therapy is the identification of translocations of the echinoderm microtubule associated protein-like 4 (*EML4*) and anaplastic lymphoma kinase (*ALK*) gene in NSCLC. As has been well described, the most common abnormality activating the ALK protein is the result of in-frame translocations between the *EML4* and *ALK* genes. In this acquired molecular abnormality, the *ALK* gene is constitutively activated after fusion with the *EML4*. In 2010, a number of presentations at the American Society of Clinical Oncology (ASCO) Annual Meeting held in Chicago in June demonstrated the presence of these translocations in approximately 2 to 5% of NSCLC tumors. The importance of this molecular alteration was underscored by the results of the phase I/II study of the results of the clinical study using crizotinib, a novel inhibitor of both ALK and c-MET. In patients with tumors that possess a translocation, the disease control rate for this agent has been up to 90%.[4]

Even now, there remains debate about the best method for detection of *ALK* translocations in NSCLC. This also was highlighted at the 2010 ASCO meeting when a number of abstracts were presented detailing methods of fluorescent in situ hybridization (FISH),[5] polymerase chain reaction (PCR),[6–8] and immunohistochemical (IHC)[9,10] systems of detection. Although the current clinical studies have largely relied on FISH-based methods to confirm the presence of activating *ALK* translocations, all three of these technologies seem equivalent in their sensitivity based on the data presented at the 2010 ASCO meeting. PCR has a theoretical advantage of detecting all possible isoforms, but the advan-

tage of this in clinical practice is unclear. The technique of IHC would seem appealing as well, as the novel chimeric fusion protein between *EML4* and *ALK* should be unique, and thus, an antibody with high specificity for this protein could be quite useful. Other strategies in development include using both IHC and FISH testing in an algorithm in which tumor samples undergo initial testing with IHC; tumors that are positive by IHC undergo confirmatory testing by FISH or tumors that have intermediate IHC score undergo testing by FISH to investigate for ALK rearrangement.[11,12] Unfortunately, although such antibodies have been reported, their limited widespread availability remains a limiting factor in their development and application. Of the three technologies, both PCR and FISH have shown utility in predicting for crizotinib sensitivity, while the application of IHC remains in development.

Additional data presented at ASCO in 2010 confirmed the relatively exclusive expression patterns of *K-ras* mutations, epidermal growth factor receptor (EGFR) mutations, and the previously mentioned EML4-ALK translocations. Indeed, as of 2010, there is only a single case reported of a NSCLC tumor possessing both an activating EGFR mutation and an *EML4-ALK* translocation.[5] In addition, the presence of K-*ras* mutations, found almost exclusively in adenocarcinoma of the lung and associated with a smoking history, has been shown to be exclusive of these other mutations. Of interest, Salama et al.[13] demonstrated that acquired c-MET mutations (the receptor for hepatocyte growth factor) in this critical receptor occur in 10% or more of NSCLC tumors and is also exclusive of the previously described mutations in EGFR, *K-ras*, and translocations of *ALK*. A paradigm is clearly developing that will impact clinical practice in which up to 25 to 50% of NSCLC adenocarcinomas will soon be characterized by the presence of mutations in one of these genes. Targeted drugs are available or in clinical testing for all these pathways.

There remains continued interest in a number of other predictive markers for response to therapy in NSCLC. The previously mentioned *K-ras* mutations were once described as a significant negative predictor for benefit to adjuvant chemotherapy in NSCLC in the JBR10 trial.[14] In addition, ERCC1 (DNA repair gene) expression has received much interest as a potential negative marker for platinum sensitivity.[15,16] Both of these markers remain under intense investigation, and their utility remains unclear. The ongoing Lung Cancer Adjuvant Cisplatin Evaluation (LACE) Bio-Consortium effort grouping the major adjuvant trials in Europe and North America continues to address these biomarkers and their utility in guiding therapy for NSCLC.[17]

Serum-based markers remain an active area of interest in lung cancer biology. In 2009, the Veristrat serum proteomic test became widely available in North America. In 2010, there were data reported on the application of the Veristrat test to blood specimens from a phase II study of erlotinib plus bevacizumab for metastatic NSCLC.[18] There was a significant benefit retrospectively predicted for erlotinib-based therapy indicated by the Veristrat test. This was an important follow-up to previously published studies on samples from the Eastern Cooperative Oncology Group 3503 study using first-line therapy with erlotinib in NSCLC.[19]

Finally, there remains continued interest in genomic models for both prognostic and predictive use in NSCLC. Although numerous models have been published, including both standard messenger RNA expression profiling and miRNA profiling,[20,21] no model has been proven acceptable for clinical use. The clinical lung cancer community remains unsatisfied with the current classification of tumors based on the arbitrary retrospective analysis of tumor size leading to the recommendation of adjuvant therapy for tumors greater than 4 cm. A robust and reproducible molecular assay to identify those at high risk or relapse is sorely needed.

In summary, NSCLC will continue to be increasingly classified by the acquired mutation profile present in the primary tumor. Standard of care will increasingly dictate that all NSCLC tumors be subjected to genetic testing, probably mandating repeat biopsies in many cases. Predictive markers, such as ERCC1, remain in development and the subject of large scale testing by international groups. Serum markers will continue to be the standard to which investigators should strive, so that NSCLC may in the near future have blood tests as valuable as the prostate-specific antigen.

STAGING

In 2007, the International Association for the Study of Lung Cancer revised the lung cancer staging system based on a large international database.[22] Although this improved our ability to predict outcomes of a given cohort of patients, several authors have identified additional modifiers to predict prognosis. Igai et al.[23] demonstrated that even patients with T1N0 lung cancer have significant differences in 5-year disease-free survival rate if they had elevation in preoperative carcinoembryonic antigen (50.8% versus 95.1%) and blood or lymphatic vessel invasion (40.0% and 95.8%). This work was corroborated by Shoji et al.[24] who demonstrated that blood vessel invasion in patients with pathologic T-1 tumors predicted worse disease-free survival. In fact, the survival of a pathologic T-1b lesion without blood vessel invasion was similar to a pathologic T-1a tumor with blood vessel invasion suggesting vascular invasion may be used to further refine prognosis.

Accurate assessment of lymph nodes status is critical for accurate staging. Saynak et al.[25] demonstrated that meticulous analysis of N1nodes (in addition to N2 nodes) and attention to defining the N1 station improve local regional control. Many patients had undefined (i.e., "peri-bronchial" descriptor without defined station location) N1 nodes reported as negative. These patients had higher risk of recurrence versus those with a negative defined N1 station (i.e., level 10 and level 11). Furthermore, although multiple lung tumors in the ipsilateral lung have been downstaged from M1a to T4 in the new staging system, the presence of nodal disease was the largest predictor of 5-year survival rate (57% versus 0%).[26]

Another key factor in staging is pleural cytology. An international study pooling data from 22 centers demonstrated the finding of positive cytology from saline instilled

into a chest during surgery conferred a risk of poor outcome similar to a single increase in the T stage.[27] Aokage et al.[28] refined this further by analyzing results of lavage before and after resection in more than 2000 patients. Almost all patients with positive postsurgical pleural lavage relapsed within 5 years. They suggest that all these patients be treated as having advanced stage disease. The results of American College of Surgical Oncology Group (ACOSOG) Z0040 trial, which address this question, are expected in the coming year.

STAGING OF THE MEDIASTINUM

Newer lesser invasive strategies have become the standard for mediastinal nodal staging. Annema et al.[29] demonstrated that in patients at high risk for N2 disease (enlarged mediastinal nodes on computed tomography, positron emission tomography-positive mediastinal or hilar nodes, and patients with central tumors) endobronchial ultrasound (EBUS) followed by mediastinoscopy if the EBUS was negative was superior to mediastinoscopy alone, in avoiding unnecessary thoracotomy. The addition of mediastinoscopy to negative EBUS in these patients at risk for N2 disease significantly improves the sensitivity for detection of malignant N2 lymph nodes from 85 to 94% ($p = 0.02$). Other single-center studies confirm that in patients suspected to have N2 disease, there is value to mediastinoscopy after a negative EBUS. Defranchi et al.[30] performed a retrospective review of 494 patients with suspected or confirmed lung cancer undergoing mediastinoscopy after a negative EBUS; the nodal station-specific negative predictive value of an EBUS was 86% (95% confidence interval [CI], 75–97%) and the patient-specific negative predictive value of 72% (95% CI, 56–89%). Cerfolio et al.[31] found a negative predictive value of 80% for endoscopic ultrasound (EUS) and EBUS in patients suspected of N2 disease. Szlubowski et al.[32] demonstrated that in patients with low preoperative probability of N2 disease, the negative predictive value of EBUS and EUS was 91%. All patients in the study had EUS and EBUS and surgical staging by transcervical extended mediastinal lymphadenectomy. The pretest probability of N2 disease should guide the physician in determining adequacy of staging.

MINIMALLY INVASIVE SURGERY

The surgical literature continues to validate the beneficial outcomes of minimally invasive video assisted thoracic surgery (VATS) compared with thoracotomy. Traditionally, pulmonary function tests (PFTs) have been used to predict postoperative morbidity and mortality in patients undergoing lung resection. In a study of 340 patients with diffusion capacity of lung carbon monoxide or forced expiratory volume in 1 second <60% undergoing lobectomy by either thoracotomy or VATS, there was 17% incidence of pulmonary complication.[33] Nevertheless, in multivariate analysis, preoperative PFTs were significant predictors of pulmonary morbidity only in the thoracotomy group. In patients with poor PFTs (predicted postoperative forced expiratory volume in 1 second < 40%) who underwent anatomic lung resection, the VATS approach conferred survival advantage illustrating the impact of operative technique minimizing chest wall dysfunction.[34]

In a large prospective study designed to assess the efficacy of lymph node dissection versus sampling in early-stage lung cancer, propensity analysis comparing VATS versus open procedure revealed a significantly shorter operative time and median length of stay and a lower rate of chest tubes draining more than 7 days with the VATS approach.[35] The number of lymph nodes retrieved was equivalent, and the operative mortality was similar. Review of the Society of Thoracic Surgery database (a detailed nationwide data set of US patients) identified 5042 open procedure, and 1281 patients undergoing VATS resection propensity analysis showed not only fewer respiratory complications but also fewer cardiovascular complications.[36] Handy et al.[37] reported that VATS patients performed better or the same as open resection in all categories of quality of life (QOL). Patients undergoing VATS had a better preservation of preoperative performance status; at 6 months postoperatively, use of pain medications and hospital readmission was lower in the VATS group.

Early criticism of VATS technique was concern about oncologic equivalence of open thoracotomy versus VATS resection. Flores et al. report the Memorial Sloan Kettering experience of patients undergoing lobectomy for clinical stage IA disease by either VATS or open resection with more than 500 patients in each group. They report equivalent outcomes in terms of clinical upstaging and recurrence rates.[38] Kim et al.[39] further reported that in patients with clinical stage I NSCLC resected by VATS resection but were found to have N1 or N2 disease, they had no worse rate of survival or recurrence when compared with open technique. Finally, despite initial concerns that VATS is more expensive, a US analysis of open versus VATS approaches documented significant cost savings to VATS approach in the first 30 days of an operation.[40]

EARLY-STAGE DISEASE

The introduction of stereotactic body radiotherapy (SBRT) has radically changed management of high-risk patients with early-stage NSCLC with local tumor control rates exceeding 90% reported across multiple studies. Nevertheless, the results from Radiation Therapy Oncology Group (RTOG) 0236 are particularly meaningful as it is one of few prospective multiinstitutional cooperative group trials that required pathologic confirmation of NSCLC and also restricted entry to high-risk patients.[41] Fifty-five high-risk patients with peripheral T1 or T2 N0 NSCLC (<5 cm) were treated with SBRT to a dose of 6000 cGy in three fractions of 2000 cGy. The treated population consisted predominantly of women (62%) and T1 lesions (80%). With follow-up of 34.4 months, only one relapse in the primary site was observed. Local tumor control in the involved lobe was 90.6%, and estimated 3-year survival exceeded 50%. Treatment seemed tolerable with protocol-specified grade 3 and grade 4 toxic events in 14% and 4% of patients, respectively. At the same time, six additional patients had adverse events that were not classified prospectively as protocol specified, including three

patients with grade 3 soft tissue (skin or rib) treatment-related complications.

Given the results of RTOG 0236, trials comparing SBRT with surgical resection for high-risk patients seem justified, and a phase III study comparing the RTOG SBRT regimen with sublobar resection (±brachytherapy) is planned. In the meantime, a retrospective comparison from William Beaumont Hospital compared SBRT and wedge resection in 128 patients with stage I NSCLC ineligible for anatomic lobectomy.[42] After excluding patients with synchronous primary lesions, SBRT was associated with reduced local relapse (5% versus 24%), although there was no difference in cause-specific survival, freedom from any failure, or distant metastasis between the two groups.

Although trials have not been completed directly comparing SBRT with traditionally fractionated radiotherapy, an analysis of 875 elderly (>75 years of age) patients diagnosed with stage I NSCLC from the Amsterdam Cancer Registry suggests that the introduction of SBRT had a substantial impact on both patient care and outcomes.[43] Overall radiotherapy use increased with SBRT availability corresponding to a decrease in untreated patients. During the most recent time period analyzed, more than half of patients treated with radiotherapy received SBRT. Median survival for all patients increased from 16 months in the time period before SBRT (1999–2001) to 21 months when SBRT was readily available (2005–2007), and the improvement was confined to radiotherapy patients.

An alternative strategy for treating early-stage NSCLC, accelerated hypofractionated radiotherapy was studied by the Cancer and Leukemia Group B (CALGB) in one of the first prospective multiinstitutional cooperative group studies designed for high-risk patients with T1N0 or T2N0 (<4 cm) NSCLC.[44] Thirty-nine eligible patients meeting defined criteria for pulmonary dysfunction were treated with involved field three-dimensional conformal radiation therapy. The total dose was kept constant at 70 Gy, whereas treatment was reduced from 29 fractions of 2.69 Gy to 17 fractions of 4.1 Gy. Patients with either peripheral or centrally located lesions were eligible. Overall treatment was well tolerated; there were two grade 3 nonhematologic toxicities and no grade 4 or greater toxicity. With median follow-up of 53 months, three local failures have been identified (7.7%), and median survival is 38.5 months. This experience compares well with reports of SBRT. In both RTOG 0236 and CALGB 39904, the most common site of failure was distant, and a joint trial is planned to assess the role of adjuvant systemic chemotherapy after SBRT or hypofractionated radiotherapy for high-risk patients with T1b or T2a N0 NSCLC.

ADJUVANT CHEMOTHERAPY

The NSCLC Meta-Analyses Collaborative Group performed a meta-analysis using individual patient data comparing surgery with chemotherapy with surgery alone based on 34 trials including 8447 patients.[45] The combination of surgery and chemotherapy resulted in an improvement in OS (hazard ratio [HR] = 0.86; 95% CI, 0.81–0.92; $p < 0.0001$) representing an absolute increase of 4% at 5 years (from 60 to 64%). A second meta-analysis compared surgery, chemotherapy, and radiation therapy with surgery and radiotherapy based on 13 trials including 2660 patients.[45] A benefit of surgery, chemotherapy, and radiation compared with surgery and radiation therapy was observed (HR = 0.88, 95% CI, 0.81–0.97; $p = 0.009$) representing an absolute improvement of 4% at 5 years. The effect of chemotherapy did not differ significantly by age, sex, histology, performance status, or stage.

TABLE 1. Long-Term Follow-Up of Adjuvant Cisplatin-Based Chemotherapy Trials

First Author (Analysis)	HR for Overall Survival	*p* Value for Interaction in Subset Analyses
Arriagada et al.[46]		
Intent to treat	0.91 (95% CI, 0.81–1.02; $p = 0.10$)	0.006
≤5 yr[a]	0.86 (95% CI, 0.76–0.97; $p = 0.01$)	
>5 yr[a]	1.45 (95% CI, 1.02–2.07; $p = 0.04$)	
Butts et al.[47]		
Intent to treat	0.78 (95% CI, 0.61–0.99; $p = 0.04$)	0.09
Stage IB	1.03 (95% CI, 0.7–1.52; $p = 0.82$)	
Stage II	0.68 (95% CI, 0.5–0.92; $p = 0.01$)	

[a] The data in related to ≤5 yr and >5 yr are data from the update publication by Arriagada et al.[46]
CI, confidence interval.

Long-term results of two phase III trials of adjuvant cisplatin-based chemotherapy, the International Adjuvant Lung Cancer Trial and JBR-10, were reported as well (Table 1).[46,47] International Adjuvant Lung Cancer Trial revealed an improvement in the 5-year OS rate with adjuvant chemotherapy compared with observation, but with further follow-up (a median follow-up of 7.5 years), this difference was not statistically significant. The analysis for nonlung cancer deaths for the whole study period was HR = 1.34 (95% CI, 0.99–1.81; $p = 0.06$). In JBR-10 with a median follow-up of 9.3 years, observation was associated with a higher risk of death from lung cancer ($p = 0.02$) with no difference in death from other causes or second primary observed between the treatment arms. There was a trend for interaction with disease stage ($p = 0.09$).

LOCALLY ADVANCED DISEASE

For patients with unresectable stage IIIA or IIIB disease who have good performance status and adequate organ function, the combination of chemotherapy and radiation therapy compared with radiation alone results in improved overall survival. Multiple trials have investigated sequential chemotherapy and radiation compared with concurrent chemoradiotherapy, and the NSCLC Collaborative Group performed a meta-analysis comparing the two treatment approaches.[48] Data from six trials consisting of 1205 patients were included, and the median follow-up was 6 years. There was a significant improvement in OS with the concurrent chemoradiotherapy compared with sequential chemotherapy and radiation (HR = 0.84, 95% CI, 0.74–0.95; $p = 0.004$) with an absolute benefit of 5.7% at 3 years (from 18.1 to 23.8%) and

TABLE 2. Phase III Trials Comparing Chemotherapy Combinations with Concurrent Thoracic Radiation

Authors	Chemotherapy (Number)	TRT	Median OS	5-yr OS
Yamamoto et al.[51]	Mitomycin, vindesine, cisplatin ($N = 146$)	60 Gy	20.5 mo	17.5%
	Carboplatin, irinotecan[a] ($N = 147$)	60 Gy	19.8 mo	17.8%
	Carboplatin, paclitaxel[b] ($N = 147$)	60 Gy	22.0 mo	19.8%
Segawa et al.[52]	Mitomycin, vindesine, cisplatin ($N = 99$)	60 Gy	23.7 mo	NR
	Cisplatin, docetaxel[c] ($N = 99$)	60 Gy	26.8 mo	NR

[a] Treatment was carboplatin AUC = 2 and irinotecan 20 mg/m^2 weekly for 6 wk concurrent with TRT, followed by carboplatin AUC = 5 and irinotecan 50 mg/m^2 day 1 and day 8 every 21 d for two cycles.
[b] Treatment was carboplatin AUC = 2 and paclitaxel 40 mg/m^2 weekly for 6 wk concurrent with TRT followed by carboplatin AUC = 5 and paclitaxel 200 mg/m^2 every 21 d for two cycles.
[c] Treatment was cisplatin 40 mg/m^2 and docetaxel 40 mg/m^2 on days 1, 8, 29, and 36.
OS, overall survival; NR, not reported; TRT, thoracic radiation therapy.

4.5% (from 10.6 to 15.1%) at 5 years. Concurrent therapy reduced the rate of loco-regional progression (HR = 0.77, 95% CI, 0.62–0.95; $p = 0.01$) but had no impact on distant disease progression (HR = 1.04, 95% CI, 0.86–1.25; $p = 0.69$). The rate of grade 3 or 4 esophageal toxicity was increased with concurrent therapy from 4 to 18% (relative risk of 4.9, 95% CI, 3.1–7.8; $p < 0.001$). This analysis provides an accurate estimate of the long-term benefit and increased esophageal toxicity associated with concurrent chemoradiotherapy.

Most of the trials that have investigated concurrent chemoradiotherapy compared with sequential chemotherapy and radiation have been employed older or second-generation chemotherapy combinations.[49,50] In 2010, two phase III trials which compared second-generation with third-generation combinations concurrent with thoracic radiation were published. The West of Japan Thoracic Oncology Group compared four cycles of mitomycin, vindesine, and cisplatin (MVP) with thoracic radiation therapy (TRT) (arm A) with the concurrent carboplatin (area under the curve [AUC] of 2) and irinotecan 20 mg/m^2 weekly for 6 weeks with TRT to 60 Gy followed by two cycles of carboplatin (AUC of 5) and irinotecan 50 mg/m^2 days 1, 8 every 21 days (arm B) or carboplatin (AUC of 2) and paclitaxel (40 mg/m^2) weekly for 6 weeks concurrent with TRT followed by two cycles of carboplatin (AUC of 5) and paclitaxel (200 mg/m^2) every 21 days (arm C).[51] The median OS and 5-year OS observed in all three arms were similar (Table 2). The rate of grade 3 or 4 neutropenia, febrile neutropenia, and gastrointestinal toxicity was significantly higher in arm A than arm B or C. The Okayama Lung Cancer Study Group performed a phase III trial, which compared MVP with cisplatin (40 mg/m^2) and docetaxel (30 mg/m^2) on days 1, 8, 29, and 36 with TRT.[52] The OS at 2 years and the primary endpoint favored the cisplatin and docetaxel arm compared with the MVP arm ($p = 0.056$), and the median OS was similar (Table 2). The rate of grade 3 febrile neutropenia was higher in the MVP compared with the cisplatin and docetaxel (39% versus 22%, $p = 0.012$), and the rate of grade 3 or 4 esophagitis was lower (6% versus 14%, $p = 0.056$). These two trials suggest that carboplatin/paclitaxel and cisplatin/docetaxel are acceptable chemotherapy combinations with TRT of 60 Gy.

The potential promise and perils of combining molecular targeted agents with (chemo) radiotherapy were illustrated in recent reports of prospective trials for locally advanced disease. CALGB 30106 evaluated the addition of the EGFR gefitinib to sequential or concurrent chemoradiotherapy in unresectable stage III NSCLC.[53] After two cycles of induction paclitaxel and carboplatin chemotherapy, a poor-risk stratum (≥5% weight loss and/or PS 2) received radiotherapy to 66 Gy and gefitinib 250 mg daily, whereas a normal-risk stratum received the same radiotherapy/gefitinib regimen plus weekly paclitaxel and carboplatin. Treatment was well tolerated without unexpected toxicity. Surprisingly, the median survival of the poor-risk cohort reached 19 months, whereas the median survival of the normal-risk cohort was only 13 months, suggesting potential synergy between the EGFR inhibitor and radiotherapy that may be abrogated by concurrent chemotherapy. The trial was prematurely terminated based on data from external trials using gefitinib, but a follow-up study assessing erlotinib and radiotherapy in poor-risk patients (CALGB 30605) is near completion.

On the other hand, integration of the antiangiogenic agent bevacizumab with combined modality therapy has been more challenging. A report from the Sarah Cannon Oncology Research Consortium included data on prospective phase II trials in limited stage small cell lung cancer and NSCLC combining bevacizumab with radiation and chemotherapy.[54] Both trials were closed early due to severe toxicity. Of 29 patients in the limited stage small cell lung cancer study, two patients developed tracheoesophgeal fistulae and one additional patient died of aerodigestive hemorrhage. Moreover, two of only five patients accrued to the NSCLC trial developed tracheoesophgeal fistulae.

TRIMODALITY THERAPY

The landmark 2009 trial of trimodality compared with chemoradiotherapy for patients with stage IIIA lung cancer revealed no difference in OS in the intent-to-treat patient population.[55] The postoperative mortality among patients undergoing pneumonectomy after chemoradiotherapy was prohibitive. A subset analysis of patients who received chemoradiotherapy followed by lobectomy compared with

TABLE 3. First-Line Trials Comparing EGFR-TKI with Platinum-Based Chemotherapy

Authors	Treatment Arm	ORR	Median PFS	Median OS
Maemondo et al.[64]	Gefitinib ($N = 115$)	73.7%	10.8 mo	30.5 mo
	Carboplatin + paclitaxel ($N = 115$)	30.7%	5.4 mo	23.6 mo
		$p = 0.001$	HR = 0.30, $p < 0.001$	$p = 0.31$
Mitsudomi et al.[63]	Gefitinib ($N = 86$)	62.1%	9.2 mo	Not available[a]
	Cisplatin + docetaxel ($N = 86$)	32.2%	6.3 mo	Not available
		$p < 0.0001$	HR = 0.489, $p < 0.0001$	

[a] Survival data immature due to the low number of events in both arms.

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

matched patients who received chemoradiotherapy alone suggested that neoadjuvant chemoradiotherapy followed by resection conferred a survival advantage. Survival was highest for those who were downstaged to pathologic N0 or N1 disease compared with persistent N2 disease (45% versus 20%). European centers report a lack of surgical morbidity for patients undergoing a pneumonectomy after neoadjuvant therapy.[56] In 827 patients in whom 80% of who received chemotherapy and radiation and 176 pneumonectomies were performed, the 90-day mortality was 3%, and 5-year survival was 38%. Using neoadjuvant chemotherapy alone, Stefani et al.[57] report a mortality of 4.5% after surgical resection; 79 of the 175 patients underwent pneumonectomy. Similar to other reports, clinical downstaging was predictive of survival. Five-year OS was higher with among patients who responded to chemotherapy (5-year OS rate of 42% was observed among patients who experienced a response and 10% among nonresponders) and mediastinal downstaging (5-year OS rate of 45% was observed among patients with mediastinal nodal clearance and 22% for patients with persistent N2 nodal involvement). These studies indicate the importance of reassessing patients after neoadjuvant therapy to ensure that they are still candidates for surgical resection.

In support of the safety of neoadjuvant therapy, a review of the American Society Thoracic Surgery database and propensity analysis revealed no difference in mortality between patients undergoing neoadjuvant chemotherapy followed by surgery and surgery alone.[58] The University of Maryland group extended the regimen of trimodality therapy to given mean radiation dose of 61.1 Gy. In the 29 patients treated by pneumonectomy, the 90-day mortality was 3.4%; 15 of these patients underwent right pneumonectomy.[59]

ADVANCED STAGE DISEASE

Although there is lot of excitement and enthusiasm in the oncology community regarding molecularly targeted therapies, majority of clinical trials in patients with advanced cancer are designed somewhat empirically and are seldom driven by biomarker-based patient selection. In a review of the ongoing clinical trials in NSCLC listed on the clinicalTrials.gov data base, Subramanian et al.[60] reported that only 7.9% of clinical trials in NSCLC were biomarker driven.

The results of subset analysis from the Iressa Pan-Asia study published in 2009 revealed that patients with an *EGFR* mutation experience a statistically significant superior response rate and progression-free survival (PFS) with gefitinib compared with carboplatin and paclitaxel in the first-line setting.[61] A separate trial screened lung cancers from 2105 patients for EGFR mutations, and EGFR mutations were detected in 350 tumors; 217 patients with an EGFR mutation-positive tumors received erlotinib.[62] The median PFS and OS were 14 months and 27 months, respectively. Two phase III trials published in 2010 were selected for the presence of an EGFR mutation for enrollment and compared platinum-based double-agent chemotherapy with gefitinib. In both trials, patients in the gefitinib treatment arm experienced a statistically significant superior response rate and PFS (Table 3).[63,64] These results confirm that for patients with an EGFR mutation, first-line therapy with EGFR tyrosine kinase inhibitor is a standard of care.

The identification of oncogenic fusion gene consisting of the *EML4-ALK* in subgroup of patients with NSCLC has allowed for the development of crizotinib, a small molecule inhibitor of the ALK tyrosine kinase.[4] This agent was investigated in phase I/II trial with an expanded cohort in patients with advanced NSCLC demonstrating the presence of the *ALK* rearrangement; of the 1500 patients with NSCLC, *ALK* rearrangements were identified in 82 patients. The mean treatment duration was 6.4 months, and the overall response rate observed was 57%, and the rate of stable disease was 33%. The 6-month PFS observed was 72%, and the median PFS has not been reached. The most common adverse events were grade 1 or 2 gastrointestinal events, and 41% of patients reported mild visual disturbances. Grade 3 elevations of the alanine aminotransferase and aspartate aminotransferase were observed in 5% and 6% of patients.

An intriguing trial investigated the early integration of palliative care with standard therapy to standard therapy for patients with advanced NSCLC; the primary endpoint was QOL at 12 weeks.[65] Patients assigned to early palliative care compared with the patients assigned to standard therapy had a statistically significant better QOL, a lower rate of depressive symptoms, and a longer median survival (11.6 versus 8.9 months, $p = 0.02$). Patients in the early palliative care arm received aggressive end-of-life care (defined as any of the following three criteria: chemotherapy within 14 days of death, no hospice care, or admission to hospice $\leq$ 3 days before death) at a lower rate (33% versus 54%, $p = 0.05$).

CONCLUSIONS

In summary, it is very clear that therapeutic impact is greater when critical oncogenic drivers are targeted for therapy. The challenge in the coming years is to identify and validate significant and recurring molecular changes in large numbers of carefully selected specimens from patients with lung cancer. Ongoing studies using massively parallel-sequencing technologies will hopefully reveal a significant number of new targets. Not only this effort will spur interest in developing novel agents but also should force us to consider reevaluating some agents deemed ineffective when used previously in a group of unselected patients.

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