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LUNG CANCER EPIDEMIOLOGY AND SMOKING

Globally, lung cancer remains the leading cause of cancer death. In the United States, there were 215,000 lung cancer cases and 161,000 deaths expected in 2008 (1). National trends indicate that death rates are declining in men and are reaching a plateau in women; mirroring trends in smoking prevalence over the past fifty years. Jemal and colleagues note interstate variability (1). The highest and lowest lung cancer death rates from 1975 to 2005 were in Kentucky and Utah, respectively, and the greatest decline in death rate was in California; again mirroring trends in tobacco use. Smoking prevalence is highest in Kentucky at 29.1% and has remained unchanged, whereas smoking rates are historically lowest in Utah at 10.4%. California is among the states with the largest annual decline in the rate of smoking prevalence, thus confirming the benefits of cigarette excise taxes and state-funded educational and legislative programs directed toward smoking prevention and cessation (2). Nationally, smoking prevalence rates are 21.6% (3) and have remained essentially unchanged over the past 15 years. Smoking cessation long-term abstinence rates are under 5% (4), which presents a barrier to further reductions in smoking prevalence rates. In a nested case-control study based on the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, Augustson and colleagues examined factors associated with smoking cessation success (3). They showed that compared with sustained quitters, relapsers had characteristics associated with increased nicotine dependence and more comorbid medical conditions. These results may advance efforts to adjust smoking cessation approaches for individual patients.

Fifteen percent of lifetime smokers develop lung cancer, but 10% of lung cancers occur in never-smokers (5). In nonsmokers, exposure to secondhand smoke or to other lung carcinogens, such as radon or asbestos, may be contributory. Recent studies suggest that high-dose vitamin E supplementation (6), indoor air pollution from solid fuel use (7), and cannabis smoking are similarly associated with increased risk for lung cancer. Each cannabis cigarette was equivalent to 20 tobacco cigarettes in risk of lung cancer (8).

Genetics

In both smokers and nonsmokers, polymorphisms in genes associated with carcinogen metabolism, DNA damage repair, and cell cycle control may influence lung cancer susceptibility and modify the injury response associated with exposure to carcinogens contained in tobacco smoke. Although the heritable component of lung cancer risk due to these genetic polymorphisms is most notable in early-onset cases occurring with less total smoke exposure, the overall attributable risk remains small (9). Recently, results were presented from three lung cancer genome-wide association studies that used the same platform to interrogate 315,000 tagging single nucleotide polymorphisms (SNPs). Strict *P* value criteria were specified to limit false positive findings and robust statistical approaches were employed to minimize effects of differences in population stratification and control selection. The three studies identified a lung cancer risk-common locus variant near rs1051730 and rs803419 on chromosome 15q that contains three genes encoding subunits of the nicotinic acetylcholine receptor (nAChR), CHRNA3, CHRNA5, and CHRNB4 (10–12). The nAChR holoreceptor is a pentamer surrounding a gated channel responsive to ligands such as acetylcholine, nicotine, or its highly carcinogenic derivative 4(methylnitrosamine)-1-(3-pyridyl)-1-butanone (13).

It is unclear whether the nAChR gene variants mediate susceptibility predominantly through influencing smoking behavior and nicotine dependence or through direct effects on lung tumor cell growth, angiogenesis, and apoptosis suppression (14–16). To examine this question, Spitz and colleagues expanded their genome-wide association studies (GWAS) analysis by genotyping additional cases and controls for rs1051730 (17). In contrast to the Hung International Agency for Research on Cancer (IARC) study (18), there was not an increased risk for lung cancer associated with the variant in nonsmokers but there was a strong association with the lung cancer phenotypes, the highest risk in younger, lighter smokers. Similar to the Thorgerirsson study (12), there was an association with nicotine dependence as measured by the Fagerstrom Test for Nicotine Dependence scores. These studies suggest that the effects of the 15q nAChR variants are not solely attributable to nicotine dependence but that they require exposure to nicotine for the nicotine independent effects to manifest. More recently, Wang and colleagues reported two newly associated lung cancer risk loci that mapped to chromosomes 6p21.33 (rs3117582) and 5p15.33 (rs401681) (19). Candidate genes within these loci are *BAT3* and *MSH5* at 6p21 and *CLPTMIL* at 5p15. Overall, it is estimated that these lung cancer susceptibility genotypes are unlikely to account for greater than 1% of familial risk, thus suggesting there are many important variants yet to be detected.

Epigenetics

The main epigenetic alterations associated with lung tumorigenesis (20) are DNA promoter hypermethylation, DNA global hypomethylation (21), posttranslational modification of histones

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(22, 23), chromatin remodeling, and microRNA silencing by DNA hypermethylation (24, 25). In a large, nested, case-control study of early stage non-small cell lung cancer patients, Brock and colleagues examined the prognostic significance of DNA methylation status of seven genes that are frequently hypermethylated in lung cancer (26). They observed that a four-gene panel comprised of *p16*, *CDH13*, *RASSF1A*, and *APC* was associated with increased risk for recurrence following surgical resection and with detection of methylated DNA in histologically negative lymph nodes. Once replicated, this biomarker panel may prove useful in stratifying patients for risk of recurrence and thus for selection of adjuvant therapy following resection.

Recent research has shown linkages between genetic sequence variants and epigenetic alterations such as DNA hypermethylation and miRNA expression. For example, Kerkel and colleagues reported that allele-specific DNA methylation in the Phase I xenobiotic metabolism enzyme CYP2A7 was associated with allele-specific mRNA expression and was dependent upon sequence variation in CYP2A7 SNPs (27). Similarly, Hu and colleagues examined SNPs in four pre-miRNA sequences and found that the rs11614913 SNP in has-mir-196a2 was associated with miRNA expression in lung tumor tissue and with overall survival in early stage lung cancer patients (28). These studies emphasize the importance of associations of DNA sequence variants with epigenetic alterations of biologically important genes in interpreting associations of noncoding SNPs with complex genetic diseases (27).

Genomics

The proof of concept that tumor mRNA profiling provides clinically significant information regarding patient outcome after resection has been established. For non-small cell lung cancer (NSCLC), several predictors have been developed, which for the most part are based on methodologically sound approaches that include independent validation (29–34). In the most comprehensive effort to date, Beer and colleagues in the Director's Challenge Consortium reported the results of a large, multicenter, blinded evaluation of eight novel prognosis classifiers in 442 lung adenocarcinomas (35). The addition of clinical covariates enhanced the performance of the classifiers, which performed slightly better than previously published signatures (36, 37). This landmark study is a model for the meticulous handling of challenges inherent in translational cancer genomic studies and for its vast data repository of clinical and pathologically annotated data that is now available for testing of new signatures and hypotheses. It remains unclear which genomic predictor of prognosis is best or whether specific genes or entire signatures are most important in predicting an outcome. Independent prospective evaluation of the predictive accuracy of these signatures, prospective clinical trials, and application to small biopsy specimens are appropriate and will be required to extend this important area of research.

In another landmark study, Ding and colleagues in the Tumor Sequencing Project consortium systematically cataloged somatic mutations in 188 lung adenocarcinoma specimens (38). The analysis focused on 600 genes with suspected or known links to lung adenocarcinoma. A total of 1,013 nonsynonymous somatic mutations were detected, of which 823 were not previously reported in Catalog of Somatic Mutations in Cancer (COSMIC) and Online Mendelian Inheritance in Man (OMIM) databases. Newly identified putative tumor suppressor genes were *NFI*, *RBI*, *ATM*, and *APC*, and newly identified putative proto-oncogenes were *ERBB4*, *KDR*, *FGFR4*, *EPHA3*, and *NTRK*. Previously known lung adenocarcinoma mutations in *TP53*, *DDKN2A*, *STL11*, *KRAS*, *EGFR*, and *NRAS* were

confirmed. Analysis of the distribution of mutations across molecular pathways identified significant mutations in the MAPK, Wnt, and PI3K/AKT signaling pathways, of which the Wnt pathway was not previously implicated in lung adenocarcinoma. As sequencing technology develops to allow complete resequencing of the entire lung cancer transcriptome (39), we anticipate further important insights into lung adenocarcinoma pathogenesis and identification of novel therapeutic targets.

Lung Adenocarcinoma Heterogeneity, Invasion, and Progression

Lung adenocarcinoma, the most frequent histological type of non-small cell lung carcinoma, is heterogeneous. Histologically, subclassification of adenocarcinoma is based upon World Health Organization (WHO) criteria that are determined predominantly by cell morphology and comprise a spectrum that includes noninvasive bronchioloalveolar carcinoma (BAC), pure invasive adenocarcinoma (IAC), and adenocarcinoma with mixed subtypes (AC-mixed) (40). Tumor cell invasion, which is the first step of the metastasis process, is the predominant feature that distinguishes these common histological subtypes. The clinical importance of lung adenocarcinoma invasion is supported by recent studies (41–47) indicating that the risk of death from noninvasive BAC is significantly lower than that of pure invasive tumors and of tumors with greater than 0.5 cm of linear invasion. These results suggest that the prognosis of BAC is favorable and suggest a similarly favorable prognosis for the subset of AC-mixed subtype tumors with minimal invasion (<0.6 cm) (42). We and others (48–51) have used microarray gene expression profiling of lung adenocarcinoma tumors to identify signatures associated with histologic subtype and invasion. The results of unsupervised analyses are striking in that lung adenocarcinomas in each instance segregate into three major clades comprised predominantly of BAC, AC-mixed subtype, and pure invasive tumors, providing biological plausibility for the notion that these adenocarcinoma subtypes are distinct tumors. Taken together with the clinical data indicating distinct prognoses for each subtype, these studies have motivated consideration of revising the WHO lung adenocarcinoma classification scheme to reinforce the designation of purely noninvasive tumors and to create a designation for minimally invasive tumors. Integrating these classification schemes with recently described adenocarcinoma copy number alterations (52), gene classifiers (35), and somatic mutations (38) is an important area for future investigation.

Recent research has been directed toward identifying tumor-stromal interactions (53, 54) that promote invasion, progression, and metastasis of non-small cell lung carcinoma. These interactions implicate alterations of molecules important for cell-cell adhesion, such as heparanase (55) and integrin $\alpha 1 \beta 1$ (56), secretion of chemokines, such as CXCL1 (57) and CCL5 (58), and expression of proteases, such as matrix metalloproteinases 8 (59) and 9 (60, 61) and lysyl oxidase 2 (62). The paradigm that tumor-cell invasion is required for metastasis has been challenged by an animal model of lung metastasis developed by Podsypanina and colleagues (63). They injected mice with mammary epithelial cells transduced with doxycycline-activatable myc and ras oncogenes. The cells survived in the lungs and proliferated to form metastases upon activation of the oncogenes. This result suggests that without the requirement for invasion, phenotypically normal cells can metastasize to distant organs, transform, and seed a metastatic niche. A limitation of this experimental approach is that the use of tail vein injection bypassed the requirement for invasion. The mechanisms by which normal or malignant tumor cells can disseminate to

access the circulation without invasion, survive and proliferate into metastases remain to be determined.

Lung Cancer Diagnosis: Screening and Biomarkers

While awaiting early results of the ongoing randomized trials of lung cancer screening in the United States (National Lung Screening Trial) and in the Netherlands and Belgium (The Dutch–Belgian Randomized Lung Cancer Screening [NELSON] trial) (64), the field has been dominated by controversies regarding perceived conflicts of interest and study design characteristics in recently completed trials (65–71). During this interval, Wilson and colleagues reported important findings from a cohort of individuals enrolled in the Pittsburgh lung cancer screening program (72). In 3,642 individuals that were screened initially, nodules (≥ 5 mm) were detected in 1,477 (40.5%) individuals. Among the study population, 69 primary non-small cell lung cancers were diagnosed, yielding a cancer prevalence of 1.5%, of which 50% were Stage I. The nodule and cancer prevalence rates were generally in line with those reported previously (73), but the rate of resection for benign disease was 34%, which was higher than expected. This finding emphasizes the importance of algorithmic approaches to pulmonary nodule management. Importantly, in the Pittsburgh cohort 28 patients underwent thoracotomy or video-assisted thoracoscopic surgery against or without the advice of the study investigators, thus demonstrating the importance of compliance with nodule evaluation algorithms. In a correlative study, Wilson examined the association of emphysema and airflow obstruction with lung cancer (74). Radiographic emphysema was scored using a five-level semi-quantitative scale based on the National Emphysema Treatment Trial criteria (75). Both emphysema and airflow obstruction were associated with increased risk for lung cancer in this high-risk population. These results, together with others indicating that the presence of mild emphysema in smokers (76) and of emphysema or air flow obstruction in never-smokers (77) is associated with lung cancer, provide support for common origins for chronic obstructive pulmonary disease and lung cancer that is in part independent of cigarette smoking (78, 79).

Over 75% of new lung cancer diagnoses are in patients who present with distant or regional metastatic disease. Early diagnosis remains an elusive goal with current research focused on identifying lung cancer-specific molecular alterations in accessible sites such as the airway, breath (80, 81), and blood (82). Because of tobacco smoke exposure, the bronchial airway epithelium of smokers is subject to field cancerization with alterations of airway cell DNA. Such alterations bring about oncogene activation, tumor suppressor gene silencing, and widespread loss of heterozygosity that is associated with preneoplasia and cancer. The distinction of benign smoking-associated field changes from high-risk molecular alterations is a challenge for early diagnosis strategies and has been addressed in recent studies from Jonsson and Salaun (83, 84). Jonsson performed fluorescent *in situ* hybridization on carcinoma *in situ* and severe dysplasia airway epithelium biopsy specimens acquired from smokers with airflow obstruction (83). Fluorescent *in situ* hybridization probes targeted to chromosomes 5p15.2, 7p12, and 8q24 showed aneuploidy in 64% of lung cancer cases and in 31% of controls, suggesting aneusomy is a specific lung cancer precursor lesion. Salaun examined risks for cancer in patients followed progressively for up to 12 years (84). They found that baseline airway epithelial loss of heterozygosity at chromosome 3p and carcinoma *in situ* histology were significantly associated with the subsequent development of lung cancer. These studies hold promise for molecular testing for early detection of lung cancer in high-risk individuals. We anticipate these efforts will be advanced by testing of other

promising molecular alterations that have been identified in smokers with lung cancer (29, 85) and by combining molecular testing with chest imaging.

Lung Cancer Staging: Endobronchial Ultrasound

Several researchers have directed their focus to evaluating the diagnostic performance of endobronchial ultrasound-guided needle aspiration for lung staging. The results are consistent and promising, as reflected by the widespread adoption of this technology by interventional pulmonologists. In a recent study, Wallace and colleagues compared three endoscopic techniques for lymph node assessment in patients with known or suspected lung cancer (86). They performed transbronchial needle aspiration (TBNA) and fine needle aspiration with endobronchial bronchoscopic ultrasound (EBUS-FNA) and endoscopic ultrasound (EUS-FNA) in 138 consecutive patients. The sensitivity of TBNA, EBUS-FNA, EUS-FNA, and EBUS-FNA + EUS-FNA was 36, 69, 69, and 93% respectively, while the negative predictive value (NPV) was 96, 96, 96, and 99%, respectively. This study confirms the superiority of ultrasound-guided mediastinal staging by EBUS-FNA or EUS-FNA over blind TBNA. The combination of EUS-FNA and EBUS-FNA was more sensitive than either test alone, but it is not clear that both procedures are required in all patients undergoing bronchoscopic staging of the mediastinum.

Randomized controlled trials are required to determine if these modalities are alternative methods for surgical staging of the mediastinum in lung cancer patients. Such a study was performed by Tournoy and colleagues, who randomized 40 patients to either endoscopic ultrasound (EUS-FNA) or to surgical mediastinal staging (87). In this small study, there was no difference in the diagnostic performance of the two study arms. Surgical staging occurred in 32% of patients assigned to EUS-FNA, suggesting that this approach could eliminate the requirement for mediastinoscopy as a first-step invasive staging procedure in up to 68% of similarly selected patients. The authors acknowledge that the negative predictive value of EUS-FNA requires that surgical mediastinal staging be performed to follow up a negative study. Although these results are promising, other issues need to be addressed. As discussed in the next section, current lung cancer therapy is tailored to histological subtype and to results of molecular assays such as Kras and EGFR mutation analysis. Thus, careful attention needs to be directed to ensuring that EUS or EBUS acquires specimens that are adequate for histological subtype diagnosis and for molecular testing.

TREATMENT OF LUNG CANCER

Small-Cell Lung Cancer

Small-cell lung cancer (SCLC) is well known to be exquisitely chemo-responsive, and newly diagnosed patients are treated with platinum-based chemotherapy regimens, most commonly in combination with etoposide. In newly diagnosed extensive stage SCLC, a few studies are noteworthy (Table 1). In a Japanese trial, treatment using cisplatin with irinotecan (IP) had a superior median overall survival (OS) in comparison to the combination of cisplatin with etoposide (EP) (OS 12.8 vs. 9.4 mo; $P = 0.002$) (88). The Japanese study design was replicated by two studies in the United States (89, 90). Even though the drugs used were the same in all three studies, the study by Hanna used a reduced dose of IP to accommodate the toxicities of this agent. Neither of the U.S. studies reproduced the Japanese result that IP was superior to EP. Patients in the Japanese study experienced a higher incidence of myelosuppression with both IP and EP. These three studies are outstanding examples of the

TABLE 1. EXTENSIVE STAGE SMALL-CELL LUNG CANCER PHASE III STUDIES

Study	Regimen	RR, %	TTP, mo	MS, mo
Noda (88)	Cisplatin/irinotecan	85	6.9	12.8
	Cisplatin/VP16	58	4.8	9.4, $P = 0.002$
Hanna (89)	Cisplatin/irinotecan	48	4.1	9.3
	Cisplatin/VP16	43	4.6	10.2, $P = 0.74$
Natale (90)	Cisplatin/irinotecan	60	5.7	9.9
	Cisplatin/VP16	57	5.2	9.1, $P = 0.7$
Heigener (118)	Cisplatin/VP16	45.5	6	9.4
	Cisplatin/topotecan	55.5	7	10.3, $P = 0.3$
Socinski (119)	Carboplatin/pemetrex	25	3.6	7.3
	Carboplatin/VP16	40	5.3, $P < 0.001$	9.6

Definition of abbreviations: MS = median survival; RR = response rate; TTP = time to progression.

limitations in extrapolating results of studies between different populations, most likely due to pharmacogenetic differences across different ethnic groups. Other recent studies (Table 1) have shown no distinct advantage of other chemotherapy regimens over platinum-etoposide in patients with extensive SCLC, which remains the standard front-line therapy.

In patients with relapsed and progressive SCLC, amrubicin, an anthracycline derivative of doxorubicin, was found to be more active than topotecan both in sensitive (>3 mo since primary treatment) and refractory (<3 mo since primary treatment) cases: the response rate (RR) of amrubicin and topotecan were 53 and 21% in sensitive patients and 17 and 0% in refractory patients (91–93). Single agent sorafenib, a potent inhibitor of the vascular endothelial growth factor receptor (VEGFR), produced median OS of 5 and 7 months in sensitive and refractory disease, respectively (94).

For patients with limited stage SCLC, the brain is a sanctuary for micrometastases and a common site for recurrence after primary treatment. Thus prophylactic cranial irradiation (PCI) is established as the standard of care for these patients. A recent study found no advantage in survival by increasing the dose of PCI (95). Not only was there was no difference in the incidence of brain metastases at 1 year ($P = 0.13$), the survival was worse in the high-dose PCI arm (hazard ratio [HR] 1.22; $P = 0.03$).

In conclusion, platinum with etoposide remains the standard of care in extensive stage small cell lung cancer. Despite the chemosensitive nature of this disease, relapses are common and survival is at best modest. The results of targeted and novel cytotoxic regimens are encouraging and are being pursued in ongoing clinical trials. In limited stage SCLC, PCI with standard fractionation continues to be the standard recommendation for patients who have completed definitive chemoradiation.

NON-SMALL-CELL LUNG CANCER

Early NSCLC

Adjuvant chemotherapy after definitive surgery is the standard of care for patients with early stage NSCLC (29). Three positive randomized clinical trials and a meta-analysis of cisplatin-based adjuvant chemotherapy clinical trials demonstrated the unequivocal benefit of chemotherapy in stage II and III NSCLC with questionable benefit in stage IB. The international adjuvant lung trial (IALT) had demonstrated that adjuvant cisplatin-based chemotherapy improved 5-year survival by 4% (96). Long-term follow-up after 7.5 years demonstrated loss of the early benefit of adjuvant chemotherapy (97) (HR, 0.91; 95% confidence interval [CI], 0.81–1.02; $P = 0.10$). Patients who received adjuvant chemotherapy after surgery were noted to have an excess of unexplained non-lung cancer related mortality (HR, 1.34; $P =$

0.06) that was not related to recurrent lung cancer or secondary malignancy, suggesting the possibility of late toxicity.

Before concluding that adjuvant chemotherapy should not be given, it is imperative to consider the other adjuvant chemotherapy trials. The adjuvant navelbine international trialist association (ANITA) study maintained an 8% survival benefit of adjuvant chemotherapy even at 7 years of follow-up (98). The Canadian JBR.10 adjuvant vinorelbine study demonstrated a 15% 5-year survival benefit from adjuvant vinorelbine-based chemotherapy (99). Thus the ANITA and JBR.10 studies demonstrated durable and greater benefit from adjuvant chemotherapy than the IALT study. Etoposide was the most common chemotherapy used in combination with cisplatin in the IALT study, whereas cisplatin was exclusively used with vinorelbine in the other two studies suggesting that choice of chemotherapy may affect outcomes. An early result of the IALT study that persisted over time was the Excision Repair Cross-Complementing 1 (ERCC1) biomarker analysis. As previously demonstrated, ERCC1 status was inversely correlated with survival in the adjuvant cisplatin based chemotherapy patients. Even after a 7.5-year follow-up, patients whose tumors were negative for ERCC1 expression had improved survival with cisplatin-based chemotherapy (HR, 0.76; 95% CI, 0.59–0.98). Thus, for early NSCLC, in the absence of any contra-indication, adjuvant cisplatin-based chemotherapy remains the standard of care, but long-term follow-up of patients is required. Ongoing clinical trials with targeted agents, such as bevacizumab and erlotinib, will explore the value of such agents in early disease.

Metastatic NSCLC

First-line therapy. Newly diagnosed patients with NSCLC are treated with a platinum-based chemotherapy doublet regimen or a doublet regimen plus bevacizumab in selected patients with nonsquamous histology. With regard to evaluation of other targeted agents in first-line therapy, two studies are most relevant. The First-Line Treatment of Advanced Non-Small-Cell Lung Cancer (FLEX) study compared chemotherapy (cisplatin/vinorelbine) to chemotherapy plus the monoclonal antibody endothelial growth factor receptor (EGFR) inhibitor cetuximab in a randomized phase III design in 1,125 patients whose tumors expressed EGFR protein (100). RR (29 vs. 36%; $P = 0.012$) and median OS (10.1 vs. 11.3 mo; $P = 0.044$) were in favor of the cetuximab combination. The best OS was noted in whites (median survival [MS] chemotherapy alone arm, 9.1 mo; cetuximab arm, 10.5 mo; $P = 0.003$) and those with squamous cell carcinoma (MS chemotherapy alone arm, 8.9 mo; cetuximab arm, 10.2 mo; $P = 0.05$). Whereas some might dismiss this regimen due to the marginal 1-month improvement in median survival, the following issues are noteworthy: (1) bevacizumab is currently the only targeted agent used in combination with chemotherapy, and it is not indicated for patients with squamous cell histology, (2) this study is proof of the hypothesis of targeted therapy demonstrating the most benefit in patients whose tumors express the target, and (3) in patients with modest outcomes from current treatment regimens, the FLEX regimen provides an opportunity for an incremental survival improvement.

The Iressa versus Carboplatin/Paclitaxel in Asia (IPASS) study is the first randomized trial comparing a single agent EGFR tyrosine kinase inhibitor (TKI) to chemotherapy (101). This study compared gefitinib to chemotherapy doublet carboplatin/paclitaxel. Study subjects were those with a high likelihood of EGFR mutation, adenocarcinoma histology, and no significant smoking history (94% never-smokers). Gefitinib was found to be superior to chemotherapy with 1-year progression-free survival (PFS) 25 versus 7%; HR, 0.741; 95% CI, 0.651–0.845; $P < 0.001$.

In subgroup analysis, patients with EGFR mutations fared better with gefitinib than carboplatin/paclitaxel (PFS HR, 0.48; 95% CI, 0.36–0.64; $P < 0.0001$), whereas those without mutations did better with chemotherapy (PFS HR, 2.85; 95% CI, 2.05–3.98; $P < 0.0001$). Thus, gefitinib may be a front-line choice in Asians with EGFR mutation-positive tumors. But, as seen in the SCLC studies discussed above, one cannot confidently extrapolate results of studies across different ethnic populations. In the non-Asian populations, large studies have shown that EGFR mutation is a prognostic indicator and is associated with better survival, independent of tyrosine kinase inhibitor therapy (102, 103). In addition, the overall survival results of the IPASS study are pending at this time, and it remains to be seen whether earlier administration of EGFR-TKI in patients with EGFR mutations will affect OS. If the OS is similar between the gefitinib and chemotherapy arms of this study, this would suggest that sequencing of gefitinib (front line vs. second line) is not critical, as was shown by Wu and colleagues (104).

Duration of Therapy

The standard of care for newly diagnosed patients with metastatic NSCLC is four to six cycles of platinum-based chemotherapy, with the actual number of chemotherapy cycles based on the best response to chemotherapy. Second-line single agent therapy is initiated at the time of disease progression. Recent studies have examined maintenance therapy after initial platinum-based chemotherapy with second-line agents docetaxel (105), pemetrexed (106), and gefitinib (107). Although these studies demonstrated an improvement in PFS with maintenance chemotherapy, they were unable to impact overall survival. Thus, maintenance chemotherapy has no role in the management of advanced NSCLC at the present time.

Second-line Therapy

In patients with progressive NSCLC, a phase II study of the combination of bevacizumab and the EGFR TKI erlotinib produced a PFS of 6.2 months and OS of 12.6 months, outcomes that far exceeded the expected survival for patients with relapsed disease (108). These results were followed by a randomized phase III study (109) comparing the efficacy of the bevacizumab/erlotinib combination to the current standard of care erlotinib alone. PFS and RR doubled with the combination of bevacizumab and erlotinib: median PFS 3.4 versus 1.7 months ($P = 0.0001$), and overall response rate (ORR) 12.6 versus 6.2% ($P = 0.006$). However, median OS was similar in both groups (9.3 vs. 9.2 mo). Patient selection in the phase III study may have contributed to the inability to reproduce the positive results of the phase II study.

Newer Targets

The success of targeted therapy depends on the following: (1) the target for therapeutic intervention is tumor specific; (2) the target is critical for cancer cell growth; (3) the target is measurable; (4) target is inhibited by an agent. Bevacizumab and erlotinib are the only targeted agents approved in the treatment of NSCLC, the former always in combination with chemotherapy for newly diagnosed patients, and the latter as a single agent for those with relapsed disease (110). Among other targeted agents still in investigation, cetuximab has completed evaluation in a large phase III trial as discussed above (100).

The role of the insulin-like growth factor receptor (IGFR) pathway in lung cancer has recently been established. The insulin-like growth factors IGF-1 and IGF-2 and their receptor IGF-1R are overexpressed in NSCLC (111) and IGF-1R expression is associated with worse prognosis in patients with sur-

gically resected disease (112). The IGF-1R monoclonal antibody CP-751,871 in combination with carboplatin/paclitaxel was compared with chemotherapy alone in a randomized phase II study of treatment-naïve patients with advanced NSCLC (113). The RR was higher in those who received CP-751,871 with chemotherapy than chemotherapy alone (54 vs. 41%; $P < 0.001$) with an exceptionally robust RR of 78% in patients with squamous cell histology treated on the CP-751,871 arm. There was an increase in median PFS from 4.3 to 5.6 months. As expected, inhibition of IGF-1R produced hyperglycemia, with grade three or higher hyperglycemia occurring in about 20%.

Sorafenib is a TKI that targets VEGFR and Raf. In the phase III Evaluation of Sorafenib, Carboplatin, and Paclitaxel Efficiency (ESCAPE) randomized controlled trial, carboplatin/paclitaxel chemotherapy was compared to chemotherapy with sorafenib in chemo-naïve patients with stage IIIB or IV NSCLC (114). Sorafenib did not improve survival in the chemotherapy alone group: median OS was 10.5 and 10.7 months for the chemotherapy/sorafenib arm and the chemotherapy alone arm, respectively (HR, 1.09; 95% CI, 0.93–1.28; $P = 0.849$). This is one of the many negative studies of TKI drugs in combination with chemotherapy. The standard continuous dosing of TKIs concurrent with chemotherapy is apparently antagonistic to the cytotoxic effects of chemotherapy. Appropriate sequencing of TKI with chemotherapy may abrogate this antagonism and improve antitumor effect (115). The First-Line Asian Sequential Tarceva Plus Chemotherapy Trial (FAST-ACT) trial addressed this possibility by using a pharmacodynamic separation approach (116). Patients were randomized to receive carboplatin on Day 1, gemcitabine on Days 1 and 8, and either erlotinib or placebo on Days 15–28, thereby eliminating concurrent administration of chemotherapy and TKI. Using this approach, PFS increased from 23.7 weeks with chemotherapy alone to 31.3 weeks in the combination arm (HR, 0.57; 95% CI, 0.3–0.8; $P = 0.0175$).

Personalized Medicine

Personalized medicine is an expanding area of investigation (29, 110). Recent studies indicate that NSCLC histology itself may direct therapeutic decision making. For example, pemetrexed is a cytotoxic chemotherapy agent that targets thymidylate synthase, dihydrofolate reductase, and glycylamide ribonucleotide formyl transferase. In a phase III trial where cisplatin/gemcitabine was compared with cisplatin/pemetrexed, no difference in OS was noted between the two treatment arms, with a median OS of 10.3 months with either treatment (117). However, in a histology-based subgroup analysis, adenocarcinoma patients showed improved survival with pemetrexed combination (MS pemetrexed 12.6 mo vs. gemcitabine 10.9 mo; HR, 0.84; 95% CI, 0.71–0.98; $P = 0.03$) as did large cell carcinoma patients (10.4 vs. 6.7 mo, respectively; HR, 0.67; 95% CI, 0.48–0.96; $P = 0.03$). In contrast, squamous cell histology patients fared better with the gemcitabine combination (median OS pemetrexed 9.4 mo vs. gemcitabine 10.8 mo; HR, 1.22; 95% CI, 0.99–1.50). Pemetrexed with cisplatin is currently approved for the treatment of newly diagnosed patients with *non-squamous NSCLC*. The Scagliotti study also suggested the selection of gemcitabine in combination with platinum for patients with squamous cell histology. As previously discussed, for patients with squamous cell histology, bevacizumab is contraindicated. However, cetuximab in combination with chemotherapy is effective, and among the drugs in development, inhibitors of IGF-1 are potentially more efficacious. Taken together, the selection of non-small-cell lung cancer chemotherapy is now dictated by histology; thus, a pathology diagnosis of “NSCLC

not otherwise specified” is no longer routinely acceptable, and every effort must be made to further classify the histology.

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