Non-Small Cell Lung Cancer: New Hope for a Chronic Illness

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Since the 1980s, important advances have been made in the treatment of non-small cell lung cancer (NSCLC). The advances have doubled the cure rate, allowing more patients with NSCLC to live longer with improved quality of life. Since the 1980s, studies using "conventional chemotherapy" have shown that adjuvant chemotherapy for early-stage NSCLC can prolong survival and improve cure (Arriagada et al., 2004; Pignon et al., 2006; Pisters, 2005; Shepherd et al., 2005), that chemotherapy is superior to best supportive care (defined as aggressive symptom management, including palliative radiotherapy when indicated) in patients with advanced NSCLC (Grilli, Oxman, & Julian, 1993; Marino, Pampallona, Preatoni, Cantoni, & Invernizzi, 1994; NSCLC Collaborative Group, 1995; Souquet et al., 1993), and that active, evidence-based first-, second-, and third-line treatments are available for advanced disease (Fossella et al., 2000; Hanna et al., 2004; Shepherd et al., 2005; Socinski, Morris, Masters, & Lilenbaum, 2003). Treatment with targeted therapies (epidermal growth factor receptor [EGFR] and vascular endothelial growth factor [VEGF] inhibitors) and new molecular biology discoveries have come of age and can help predict response and select patients for lung cancer treatment (Eberhard et al., 2005; Herbst, Onn, & Sandler, 2005; Olaussen et al., 2006; Potti et al., 2006; Rosell, Cecere, Santarpia, Reguart, & Taron, 2006). Lung cancer in women continues to be an area of concern and scientific investigation. Recent advances in the understanding of the epidemic in women also will be reviewed.

Tobacco use continues to rise in developing countries; as a result, lung cancer mortality rates will continue to worsen in men and women (Alberg, Brock, & Samet, 2005). This article will propose everyday interventions that nurses can use to help control tobacco use. Control of tobacco use, new information on the molecular biology of lung cancer, and modern developments in treatment can lead to curtailment of the disease and continued improved outcomes.

Lung Cancer Overview

In 2007, lung cancer will be diagnosed in more than 213,000 people and more than 160,000 will die from the disease (Jemal et al., 2007). That is more deaths than those from colorectal, prostate, and breast cancers combined for the same year. The incidence of new cases and deaths from lung cancer are declining in men but continue to rise in women. This reflects differences in smoking patterns: Women's cigarette smoking peaked 20 years after men's (Jemal et al.). Cigarette smoking is associated with the greatest risk of lung cancer; however, lung cancer also is seen in people who have never smoked cigarettes.

NSCLC is the most common type of lung cancer, comprising approximately 80% of all cases. Small cell lung cancer, almost always seen in past or current cigarette smokers, accounts for the other 20% of those diagnosed with the disease. In NSCLC, adenocarcinoma is the most common cell type and accounts for nearly 46%. Adenocarcinoma is seen in those who have a history of cigarette smoking and is the most common cell type seen in people who have never smoked cigarettes. Other cell types include squamous cell and large cell carcinomas. Squamous cell lung cancer is almost always associated with cigarette smoking. Bronchioloalveolar carcinoma is a subtype of adenocarcinoma that is more common in women and those who have never smoked. It is associated with mutations of EGFR (Miller, Hirsch, & Johnson, 2005).

At time of diagnosis, more than two-thirds of patients present with advanced disease (stage IIIB–IV) and nearly half have metastatic disease (stage IV) (Schrump et al., 2005). Fewer than 20% are diagnosed with early-stage disease. Lung cancer usually is present for many years before symptoms develop; the presence of symptoms generally is indicative of later-stage disease and poorer prognosis. Those with early-stage disease are less likely to be symptomatic.

Table 1 outlines five-year survival rates by stage of disease. Accurate clinical staging of NSCLC is of utmost importance because clinical stage directs treatment and predicts prognosis. The best chance for five-year survival is in patients with stage I disease; survival rates can be as high as 60%–70% (Mountain, 2000). As stage of disease increases, survival decreases. The five-year survival rate for stage II disease ranges from 38%–55%, and fewer than 1% of patients with stage IV disease survive five years.

Complete surgical resection is the standard of care for those with stage I or II disease. Multimodality therapy, consisting of chemotherapy plus surgery, is recommended for patients

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Digital Object Identifier: 10.1188/07.ONF.963-970

Table 1. Five-Year Survival Rates for Non-Small Cell Lung Cancer

Stage	Tumor, Node, Metastasis Status	Five-Year Survival (%)
IA	T1N0M0	67
IB	T2N0M0	57
IIA	T1N1M0	55
IIB	T2N1M0	39
	T3N0M0	38
IIIA	T3N1M0	25
	T1–3N2M0	23
IIIBa	T4N0–2M0	7
	T–any N3M0	3
IV	T–any N–any M1	< 1

Note. Based on information from Mountain, 2000.

with stage IIIA disease, whereas those with stage IIIB disease usually receive chemotherapy and radiotherapy. Chemotherapy is recommended in those with stage IV disease. Chemotherapy palliates symptoms and extends life. Radiotherapy also may be used for palliation of symptoms.

Characteristics of Non-Small Cell Lung Cancer

Since the 1980s, significant advances have been made in the treatment of all stages of NSCLC. Clinical, pathologic, and molecular characteristics direct treatment and predict response to treatment. Adjuvant treatment improves survival in those with early-stage and locally advanced disease. For patients with advanced disease, platinum-based chemotherapy can improve survival and quality of life. Second- and third-line treatments have shown benefit in those with advanced disease, and targeted therapies can improve survival in such patients.

Figure 1 outlines selected patient characteristics that should be considered during treatment decisions; some of the characteristics have been demonstrated to affect survival.

Clinical factors include gender, ethnicity, and history of tobacco use. Studies since 1986 have shown that women live longer than men, whether they have early-stage or advanced disease (Alexiou et al., 2002; O'Connell et al., 1986; Patel, Bach, & Kris, 2004). Eastern Asian ethnicity is associated with improved outcomes in those taking erlotinib or gefitinib (Thomas et al., 2006). Clinical trials also have demonstrated that patients who have a limited cigarette smoking history and those who never have smoked are more likely to respond to chemotherapy and the EGFR tyrosine kinase inhibitors (TKIs) (Miller et al., 2004; Pao et al., 2004; Tsao, Liu, Lee, Spitz, & Hong, 2006).

Selected molecular characteristics can direct treatment and affect survival. Studies have shown that EGFR-tyrosine kinase (TK), when mutated, becomes a potent oncogene that is central to tumor development (Baselga & Arteaga, 2005; Pao & Miller, 2005). In 2004, investigators demonstrated that mutations in the TK domain of EGFR were strongly associated with tumor response in patients with NSCLC given gefitinib and erlotinib (Lynch et al., 2004; Paez et al., 2004). Pham et al. (2006) recently demonstrated that EGFR mutations are more likely to occur in patients who have never smoked cigarettes. The researchers examined 265 tumor specimens from patients with adenocarcinoma of the lung for EFGR mutations and examined the smoking history of each patient to determine whether a correlation existed between smoking history and EGFR mutation (see Table 2). The results demonstrated that 51% of the 67 patients who never smoked cigarettes harbored an EGFR mutation. Additionally, as the number of pack years increases, the percentage of EGFR mutations decreases. The authors proposed that smoking history is valuable in helping to direct treatment in patients with lung adenocarcinomas when insufficient pathologic material exists for molecular studies.

K-ras is an oncogene that is believed to play a role in signal transduction. Mutations in the *K-ras* oncogene lead to malignant transformation, resulting in NSCLC. In several studies, *K-ras* mutations have been correlated with smoking; one study found that *K-ras* mutations and EGFR mutations were mutually exclusive (Ahrendt et al., 2001; Eberhard et al. 2005). *K-ras* mutations are associated with poor prognosis and resistance to erlotinib and gefitinib (Pao et al., 2005). Winton et al. (2005) demonstrated that adjuvant cisplatin-based chemotherapy did not confer a survival advantage in patients with *K-ras*–positive tumors, suggesting cisplatin resistance in that group.

The *excision repair cross-complementation group 1* (*ERCC1*) gene contains an enzyme needed for repair of DNA damage from platinum chemotherapies and other alkylating agents (Reed, 2006). Olaussen et al. (2006) examined tumor specimens from patients enrolled in the International Adjuvant Lung Cancer Trial for *ERCC1* expression. Results demonstrated that patients whose tumors tested negative for *ERCC1* had significantly longer survival when given adjuvant cisplatin-based chemotherapy compared to patients with *ERCC1*-positive tumors given the same chemotherapy.

Researchers from Duke University evaluated gene expression profiles from tumors of patients with resected early-stage lung cancer (Potti et al., 2006). Risk of disease recurrence was predicted significantly better with the lung metagene model compared with use of clinical prognostic factors in early-stage lung cancers. The authors predicted that use of the lung metagene model could eliminate chemotherapy for patients with lower risk of disease recurrence, whereas patients with high risk of disease recurrence could be given aggressive treatment. A phase III clinical trial testing the lung metagene model in the United States and Canada is under way.

Molecular profiling of NSCLC is an exciting area of research that continues worldwide. In the near future, treatment for NSCLC will be directed more by the gene profile of a patient's tumor and less by clinical characteristics. In

Clinical Characteristics That Indicate Better Prognosis and Response
- Female gender
- Eastern Asian ethnicity
- Limited tobacco history

Molecular and Pathologic Factors
- Epidermal growth factor receptor mutation
- *K-ras* mutation
- *Excision repair cross-complementation group 1* status
- High-risk metagene profile

Figure 1. Selected Characteristics Affecting Survival and Directing Treatment

Table 2. Epidermal Growth Factor Receptor (EGFR) Mutations and Smoking History

Number of Patients	Number of Pack Years	EGFR Mutations (%)
67	Never smokers	51
19	1–5	37
22	6–10	46
10	11–15	30
22	16–25	9
67	26–50	9
30	51–75	10
28	> 75	0

Note. From "Use of Cigarette-Smoking History to Estimate the Likelihood of Mutations in Epidermal Growth Factor Receptor Gene Exons 19 and 21 in Lung Adenocarcinomas," by D. Pham et al., 2006, *Journal of Clinical Oncology, 24,* 1701. Adapted with permission.

cases where tumor tissue cannot be obtained for molecular profiling, clinical staging and patient characteristics should guide treatment.

Women and Lung Cancer

Lung cancer surpassed breast cancer as the leading cause of cancer death in women in 1987. In 2007, lung cancer will account for 26% of all deaths from cancer in women in the United States (Jemal et al., 2007)—more than breast, ovarian, and uterine cancers combined. Tobacco use is the biggest contributor to lung cancer in women. Many women and teenage girls continue to smoke. In 2004, 18.5% of women in the United States smoked and 22% of high school girls were current smokers (Centers for Disease Control and Prevention, 2005a, 2005b). Women have been targeted by tobacco advertising that features thin, attractive, and athletic models; teenage girls also are influenced by advertisements promoting cigarette smoking for thinness and weight control (U.S. Department of Health and Human Services, 2001).

Hormonal and molecular differences also are believed to contribute to the epidemic of lung cancer among women (Patel, 2005). Evidence is conflicting whether women are more susceptible to the carcinogenic effects of cigarette smoke (Patel). The debate will continue. Carcinogens in tobacco smoke exert their effects by forming DNA adducts in tissues, causing gene mutations. High concentrations of DNA adducts are thought to contribute to the pathogenesis of lung cancer (Swenberg, Richardson, Boucheron, & Dyroff, 1985). Studies have shown that women with lung cancer have more DNA adducts than men with lung cancer (Cheng et al., 2001).

Female smokers are more likely to get adenocarcinoma. People who never have smoked are more likely to have adenocarcinoma and are 2.5 times more likely to be women (Ferguson, Skosey, Hoffman, & Golomb, 1990; Radzikowska, Glaz, & Roszowski, 2002; Thun et al., 1997). Bronchioloalveolar carcinoma, a subtype of adenocarcinoma, is two to four times more prevalent in women, especially those who never have smoked (Barsky, Cameron, Osann, Tomita, & Holmes, 1994; Radzikowska et al.). Studies from 1986 to the present have demonstrated that women live longer than men whether they have early- or late-stage disease (O'Connell et al., 1986; Radzikowska et al.).

Estrogen receptor alpha has been found in more lung cancers in women than in men, and estrogen receptor beta is more common in adenocarcinomas compared with squamous cell lung cancers. Both of the factors may contribute to the pathogenesis of the disease (Fasco, Hurteau, & Spivack, 2002; Fu, Ying Kau, Severson, & Kalem Kerian, 2005; Kaiser et al., 1996). One study found a reduced risk of lung cancer in women with early menopause, a higher risk of developing adenocarcinoma in women who used hormone-replacement therapy (HRT), and a synergistic effect of smoking and HRT in developing adenocarcinoma (Taioli & Wynder, 1994). More research is needed to further define the role of estrogen in the development of lung cancer.

Chemotherapy

Adjuvant Chemotherapy

Until recently, surgery was the best chance for cure in patients with stage I–IIIA disease. However, the rate of relapse for patients with early-stage disease was high, even in those with stage I disease. Relapse usually occurred at distant sites and was fatal (Feld, Rubinstein, & Weisenberger, 1984; Immerman, Vanecko, Fry, Head, & Shields, 1981). Early trials (in the 1970s and 1980s) using adjuvant chemotherapy in resected NSCLC did not show a survival advantage over observation alone. However, the older trials were designed poorly and used inactive chemotherapy regimens (alkylating agents without cisplatin) (Pisters & LeChevalier, 2005). Later trials used cisplatin-based combinations, but the studies were too small to detect a benefit (Pisters, 2005).

A 1995 meta-analysis showed that cisplatin-based adjuvant chemotherapy improved survival by 5% and reduced death risk by 13% (NSCLC Collaborative Group, 1995), but the numbers were small and not significant. However, the results of the analysis renewed interest in cisplatin-based chemotherapy in the adjuvant setting, which spurred new clinical trials.

Multiple trials have reported the benefit of adjuvant chemotherapy, but some results were more impressive than others. Three trials supporting the use of adjuvant chemotherapy are listed in Table 3. All patients had early-stage disease (IA–IIIA), but stage of disease differed in all trials. In all three trials, patients were randomized to a cisplatin-based chemotherapy regimen or surgery alone. For each trial, the median survival and five-year survival were extended in patients who received adjuvant chemotherapy. In the ANITA (Adjuvant Navelbine International Trialists Association) trial (Douillard et al., 2006), adjusted death risk was significantly reduced in patients who received chemotherapy compared with observation (hazard ratio 0.80 [95% confidence interval 0.66–0.96], $p = 0.017$). In the JBR1.0 trial (Winton et al., 2005), overall survival was significantly better in those given chemotherapy (94 versus 73 months; hazard ratio for death 0.69, $p = 0.04$). Finally, at five years, the IALT (International Adjuvant Lung Cancer Trial Collaborative Group) trial (Arriagada et al., 2004) also demonstrated significantly improved survival compared with observation (44.5% versus 40.4%; hazard ratio for death 0.86 [95% confidence interval 0.76–0.98], $p < 0.03$). In the ANITA and JBR1.0 trials, no survival advantage of chemotherapy was found in patients with stage IB disease.

Results of the Lung Adjuvant Cisplatin Evaluation were reported at the annual American Society of Clinical Oncology

Table 3. Adjuvant Chemotherapy Trials for Non-Small Cell Lung Cancer

Study	Stage	N	Regimen	Median Survival (Months)	Five-Year Survival (%)
IALT	IA–IIIA	932	Two-drug, cisplatin-based	51	45
(Arriagada et al., 2004)		935	Surgery alone	44	40
JBR1.0	IB–II	243	Cisplatin plus vinorelbine	94	69
(Winton et al., 2005)		238	Surgery alone	73	54
ANITA	IB–IIIA	407	Cisplatin plus vinorelbine	66	51
(Douillard et al., 2006)		433	Surgery alone	44	43

ANITA—Adjuvant Navelbine International Trialists Association; IALT—International Adjuvant Lung Cancer Trial Collaborative Group

(ASCO) meeting by Pignon et al. (2006). The trial examined pooled data from five of the largest adjuvant trials, which enrolled 4,484 patients given cisplatin-based chemotherapy. Median follow-up was 5.1 years. Results demonstrated an absolute benefit of 4.2% in patients who received chemotherapy (hazard ratio for death 0.89 [95% confidence interval 0.82–0.96], $p < 0.005$). The authors concluded that adjuvant cisplatin-based chemotherapy improved survival. Patients with stage II–III NSCLC benefited most, and results showed that patients with stage IA disease likely do not benefit from adjuvant treatment.

Cancer and Leukemia Group B (CALGB) 9633 was another adjuvant clinical trial conducted in 344 patients with resected stage IB disease (Strauss et al., 2004, 2006). Initial results were reported at the 2004 ASCO meeting, and updated results were reported at the 2006 meeting. In the trial, patients were randomized to four cycles of carboplatin plus paclitaxel or observation. It is the only large adjuvant trial that used carboplatin rather than cisplatin. Initial results (Strauss et al., 2004) reported significant improvements in overall and disease-free survival. Median follow-up at 34 months in patients randomized to adjuvant treatment demonstrated a 38% reduction in risk of death (hazard ratio for death 0.62 [95% confidence interval 0.41–0.95]). Overall survival at four years was 71% versus 59%, a 12% improvement for those who received adjuvant treatment. Because of the impressive results, the trial was stopped early.

In 2006, Strauss et al. presented updated results of CALGB 9633. The median follow-up was 54 months. Overall survival was no longer statistically significant. However, median survival was longer (95 months versus 78 months) for those who received adjuvant chemotherapy compared with those in the observation group (Strauss et al., 2006). The authors concluded that the early closure of the initial trial and its small sample size may have contributed to the results.

The results of the three adjuvant trials of NSCLC reviewed demonstrate a survival benefit in patients with resected stage II–IIIA disease. Therefore, patients with stage II–IIIA disease should be offered platinum-based chemotherapy (cisplatin or carboplatin) postoperatively. More research should be conducted to determine whether patients with stage IB disease benefit from adjuvant treatment; adjuvant treatment is not recommended for those with stage IA disease at this time.

Chemotherapy for Advanced Non-Small Cell Lung Cancer

Survival for patients with advanced NSCLC (stage IIIB–IV) is dismal. The median survival is four or five months, and one-year survival without treatment is only 10% (Schiller et al., 2002). Five-year survival is less than 1%. Multiple factors affect survival. Stage of disease at diagnosis is prognostic; patients with stage IIIB disease have better outcomes than those with stage IV disease (Mountain, 1997). Multiple sites of metastases and specific sites (e.g., liver, bone) carry worse prognosis. Individual patient characteristics also influence survival. The most important is performance status at diagnosis (Harpole, Herndon, Young, Wolfe, & Sabiston, 1995). Patients with a Karnofsky Performance Scale score less than 70% and Eastern Cooperative Oncology Group scores greater than 1 have even worse prognosis (Socinski et al., 2003). Weight loss greater than 10 pounds is a negative sign. Absence of symptoms such as cough, hoarseness, pain, anorexia, and signs of metastases carry independent favorable prognosis (Ingle, 2000).

The single most important prognostic factor and the one proven most clearly in clinical trials is whether patients are given chemotherapy. However, treatment for patients with stage IIIB or IV disease is not curative but palliative.

Multiple randomized trials and several meta-analyses have documented improvement in one-year survival in patients given platinum-based chemotherapy compared with best supportive care (NSCLC Collaborative Group, 1995; Socinski et al., 2003; Spiro et al., 2004). Additionally, chemotherapy reduced tumor size and alleviated symptoms, which resulted in improved quality of life in addition to improved survival.

The trials that have been reported to date (from the 1980s to the present) have used cisplatin- or carboplatin-based regimens. The earlier trials used cisplatin with first-generation agents such as mitomycin and ifosfamide, second-generation trials typically used etoposide, and third-generation trials added agents such as gemcitabine (Schiller et al., 2002). The trials using platinum-based regimens with the newer or third-generation agents documented high response rates and improved survival (Schiller et al.). Figure 2 lists older platinum chemotherapy regimens (first and second generation) and newer agents (third generation) that are used in combination with platinums. No one regimen is clearly better than another; overall response rates are 25%–35%; median and one-year survival rates are 8–10 months and 30%–40%, respectively (Schiller et al.; Socinski et al., 2003).

Multiple studies have been conducted to determine the number of cycles of chemotherapy that should be used and who should be offered treatment. Current recommendations, based on clinical trials, advise four cycles of chemotherapy because longer duration of treatment does not improve survival and can lead to increased toxicity (National Comprehensive Cancer Network [NCCN], 2007; Socinski et al., 2003). Additionally, the NCCN recommended treatment for patients

with good performance status, including older adult patients. For those who do not tolerate treatment, chemotherapy doses can be reduced. Single agents may be useful in those who are very old and those with poor performance status.

Another new development in the treatment of advanced NSCLC is the approval of second- and third-line treatment regimens. Docetaxel, pemetrexed, and erlotinib have shown benefit in patients with good performance status who have progression of disease during or after first-line treatment (Fossella et al., 2000; Hanna et al., 2004; Shepherd et al., 2000, 2005). Response rates are in the range of 5%–7%, with one-year survival rates of 19%–21%. Erlotinib also demonstrated activity over placebo in patients given third-line therapy; response rates ranged from 9%–19%, and one-year survival rates ranged from 24%–40% (Shepherd, 2005). This is a significant improvement compared with patients given third-line chemotherapy with "standard" agents, where response rates of 2% and median survival of months were observed.

To summarize, chemotherapy for advanced NSCLC improves survival, reduces disease-related symptoms, and improves quality of life. Patients with good performance status should be offered platinum-based chemotherapy in combination with one of the newer agents. The regimens have documented the biggest increase in survival. Prolonged treatment is not needed because the most benefit occurs in the first three or four cycles of chemotherapy. Second-line therapy is indicated in those with good performance status, and third-line therapy with erlotinib has demonstrated improved survival and control of symptoms.

Targeted Therapies

Another new development in the treatment of NSCLC is the use of targeted therapies. Clinical trials using such therapies were initiated in the late 1990s and included agents that blocked the EGFR and angiogenesis (VEGF) pathways. The EGFR pathway is one of many signal transduction pathways. Signal transduction is the movement of signals from outside the cell to inside the cell. The eventual outcomes of signal transduction are alteration in cellular activity and changes in gene expression (King, 2006). EGFR is a transmembrane receptor composed of an extracellular ligand binding domain, a transmembrane segment, and an intracellular tyrosine kinase domain (EGFR-TK).

"Older" Platinum-Based Regimens
- CAP: cyclophosphamide, adriamycin, and cisplatin
- VdP: vindesine and cisplatin
- EP: etoposide and cisplatin
- EC: etoposide and carboplatin
- MVP: mitomycin, vinblastine, and cisplatin
- MIP: mitomycin, ifosfamide, and cisplatin

Newer Platinum-Based Agents
- Paclitaxel
- Docetaxel
- Gemcitabine
- Vinorelbine
- Irinotecan
- Pemetrexed

Figure 2. Chemotherapy for Advanced Non-Small Cell Lung Cancer

EGFR is expressed by a wide variety of human solid tumors, particularly epithelial malignancies such as NSCLC. In tumor cells, the EGFR-TK signal is aberrantly activated and leads to the hallmarks of malignancy: increased cell proliferation, invasion, angiogenesis, and metastases. Additionally, EGFR-TK activity blocks apoptosis, which is thought to contribute to tumor resistance to chemotherapy or radiotherapy.

Two EGFR-TKIs, gefitinib and erlotinib, have been approved for the treatment of NSCLC. The mechanism of action is the same for both drugs—they are small molecules that enter the cell and bind to the tyrosine kinase domain of EGFR, resulting in the blockage of signal transduction. Gefitinib was the first to be approved. Its use is restricted to clinical trials, patients currently benefiting from the drug, and those who responded previously to the drug. Erlotinib was the second of the small-molecule TKIs approved. Erlotinib's use is approved in the second- and third-line settings for patients with advanced NSCLC. The dose of erlotinib is 150 mg daily; 50 mg and 100 mg pills are available in the event that dose reduction is needed for side-effect management. Side effects are mostly mild and easily managed. The two most common side effects are diarrhea and rash.

Phase I and II trials with both drugs demonstrated improved survival and symptoms. Phase III clinical trials have been conducted with both drugs (Herbst et al., 2004; Herbst, Prager, et al., 2005). In the trials, patients were given a platinum-based chemotherapy regimen and were randomized to receive either gefitinib versus placebo or erlotinib versus placebo. Neither trial demonstrated a survival benefit, but investigators have examined subsets of patients from the trials and found that patients who never smoked and those with bronchioloalveolar carcinoma had improved outcomes (Herbst, Prager, et al.; Miller et al., 2004).

Angiogenesis is another pathway by which tumors grow. In healthy adults, angiogenesis is well controlled and is limited to normal physiologic processes such as wound healing and menstruation. Cancer cells rely on the angiogenesis pathway for growth. Tumors must recruit a new blood supply to grow larger than 1–2 mm in size and must have access to circulation to metastasize. Angiogenesis is involved from the first stage of cancer development through tumor growth and the final stage of metastases. VEGF plays a key role in angiogenesis and is critical for blood vessel growth (Herbst, Onn, et al., 2005; Sun & Schiller, 2007). One study documented that patients with highly vascularized tumors had significantly reduced survival (Fontanini et al., 1997).

The transition of a tumor from the inactive or latent stage to the invasive phase of malignancy is called the angiogenic switch (Herbst, Onn, et al., 2005). Initiation of angiogenesis is dependent on the switch. In tumor development, the angiogenic switch leads to a complex series of events. Initiation of angiogenesis begins with a mutation in tumor cells, followed by expression and secretion of angiogenic factors by the tumor cells. Next comes the secretion of growth factors by the tumor tissue, which results in the stimulation of angiogenesis, leading to rapid tumor growth and metastases. The blood vessels that are recruited for tumor growth are dense and twisted in appearance; normal blood vessels appear in a grid-like pattern (Marx, 2003). Angiogenic inhibitors are believed to reverse the process.

Bevacizumab is a humanized monoclonal antibody that is directed at VEGF. It works outside the cell by binding to VEGF, thereby blocking the angiogenesis pathway. It was

approved for the treatment of colorectal cancer in 2004 and is the first angiogenesis inhibitor approved for use in the United States. Most recently, bevacizumab was approved for the treatment of NSCLC in combination with chemotherapy.

In 2006, Sandler et al. reported the results of a randomized phase III trial comparing paclitaxel and carboplatin (PC) versus paclitaxel, carboplatin, and bevacizumab (PCB). Patients randomized to the two-drug combination were given six cycles of chemotherapy every three weeks, followed by observation. Those randomized to the three-drug combination also received six cycles of chemotherapy followed by single-agent bevacizumab every three weeks until disease progression.

A statistically significant improved overall response rate was found in patients given PCB compared to PC (35% versus 15%, respectively; $p < 0.0001$). Additionally, one-year and two-year survival rates were improved in those who received PCB versus PC (51% versus 44% and 23% versus 15%, respectively). As a result, NCCN (2007) guidelines have been updated to include the addition of bevacizumab to carboplatin and paclitaxel as first-line treatment in advanced NSCLC.

Adverse events were more common in patients given the PCB combination. Grade 4 neutropenia occurred more often in those given PCB compared with patients given PC (25.5% versus 16.8%, $p = 0.002$). Additionally, grade 4 thrombocytopenia was seen with more frequency in the PCB group (1.6% versus 0.2%, $p = 0.04$). Nonhematologic side effects included hemorrhage and hypertension. Grade 3 hemorrhage of any type was significantly higher in those given PCB (19% versus 3% , $p < 0.001$). Grade 3 hypertension also was more common in those given PCB compared to the two-drug regimen (30% versus 3%, $p < 0.001$).

Currently, patients who are candidates for a bevacizumab-containing regimen should be selected with the side effects in mind. Guidelines should include the use of prophylactic pegfilgrastim for all patients given a platinum, taxane, and bevacizumab combination (Sandler et al., 2006). Additionally, bevacizumab is not recommended for patients with squamous cell lung cancers or centrally located tumors because they are at higher risk for bleeding. Bevacizumab is contraindicated in patients with metastatic cancer to the brain. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, and blood thinners also is contraindicated.

Extensive research continues with new agents, combinations of older targeted therapies, and agents that target other pathways involved in tumor growth and development. Multiple studies are under way and include the use of antiangiogenic agents and other types of chemotherapy, combinations of targeted therapies, and targeted therapies in combination with radiotherapy.

Nursing Considerations

Lung cancer is the leading cause of death worldwide but could be virtually prevented with the cessation of tobacco use. However, even if smoking was eliminated today, lung cancer would continue to affect individuals because more former smokers are diagnosed with the disease than current smokers (Alberts, 2003).

Nurses can have an impact on the disease in two ways, without adding excessive work to their everyday personal and professional activities. First, get the word out that lung cancer is a serious but treatable illness. Educating ourselves, our colleagues, and patients about the disease and its treatment may influence patient outcomes. Education regarding new advances in treatment and other discoveries may encourage clinicians to treat patients or refer them to centers where they will be offered appropriate treatments for different stages of disease.

Encouraging patient participation in clinical trials is another way to advance treatment and prolong survival in NSCLC. Many clinical trials available throughout the United States are actively recruiting patients. Treatment is the focus of some of the trials, whereas others seek to procure tumor tissue and blood so that scientists can learn more about the pathologic, molecular, and genetic bases of the disease. Participation in clinical trials may be as simple as providing a tube of blood or as rigorous as being part of a phase I clinical trial. Education regarding clinical trials can advance the treatment of lung cancer.

Tobacco education and cessation are other ways nurses can have an impact on lung cancer. First the good news: Tobacco control has been cited as the major contributor to the decline in all cancer deaths in 2003 and 2004 (Jemal et al., 2007). Now the bad news: In January 2007, *The New York Times* reported, "Stigma Aside, Wall Street Finds a Lot to Like About Tobacco" (Martin, 2007). Included in the article were a graph showing the stock price of Altria (formerly Philip Morris) soaring and this sentence, "The future of cigarettes appears to be brighter than ever." Despite the good news, our job is far from over; we need to continue to educate others about the harmful effects of tobacco and at every opportunity encourage people to stop smoking.

Annually, 5 million people die worldwide from tobacco-related illness; in the United States, it is estimated that 4.5 million teenagers try smoking or are smoking; and in 2006, the U.S. Surgeon General reported that no safe level of second-hand smoke exists (Centers for Disease Control and Prevention, 2005a, 2005b). Tobacco companies have targeted children and teenagers, as evidenced by their advertisements and characters such as Joe Camel and the Marlboro Man. The ads are dominated by themes that cigarettes are desirable and associated with independence. This is especially prevalent in movies, with many showing actors smoking cigarettes. Young women also are targeted by cigarette companies, as evidenced by brands of cigarettes for women only. Most adults who smoke began when they were teenagers. Nurses have many ways to be involved. One is to target children and teenagers by providing education in our communities, schools, and families.

Tobacco Free Nurses is the first national organization that provides support for nurses who smoke and outlines a framework to engage nurses in tobacco cessation (www.tobaccofreenurses.org). Available on the Web site is a guide titled *Helping Smokers Quit.* It is a valuable resource for nurses and includes interventions they can use daily in counseling tobacco cessation. Linda Sarna, DNS, RN, is involved with the organization and received an award for her leadership in the promotional campaign.

Conclusion

NSCLC can be considered a chronic disease for some patients. Overall, improvements in survival and delayed progression of disease can occur for many individuals with NSCLC. Adjuvant chemotherapy for NSCLC has come of age. Studies

have shown improved survival in those with resected stage II–IIIA disease; more research should be conducted to determine the absolute value of adjuvant chemotherapy for those with resected stage I disease. For patients with advanced NSCLC (stage IIIB–IV), clinical trials with chemotherapy have shown improved survival, reduced symptoms, and improved quality of life compared to basic supportive care. First-line platinum-based chemotherapy regimens are recommended for those with good performance status. Docetaxel, pemetrexed, and erlotinib have been approved for second-line treatment, and erlotinib has shown improved responses compared with chemotherapy alone in the third-line setting. Molecular evaluations of tumor tissue can direct treatment and predict survival. Multiple studies are under way for all stages of NSCLC.

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