Adjuvant Treatment of Non-Small-Cell Lung Cancer: How Do We Improve the Cure Rates Further?

By Antoinette J. Wozniak, MD and Shirish M. Gadgeel, MD

Surgery remains the initial treatment for patients with early-stage non-small-cell lung cancer (NSCLC). Additional therapy is necessary because of high rates of distant and local disease recurrence after surgical resection. Early trials of adjuvant chemotherapy and postoperative radiation were often plagued by small patient sample size, inadequate surgical staging, and ineffective or antiquated treatment. A 1995 meta-analysis found a nonsignificant reduction in risk of death for postoperative cisplatin-based chemotherapy. Since then, a new generation of randomized phase III trials have been conducted, some of which have reported a benefit for chemotherapy in the adjuvant setting. The role of postoperative radiation therapy remains to be defined. It may not be beneficial in early-stage NSCLC but still may have utility in stage IIIA disease. Improvement in survival outcomes from adjuvant treatment are likely to result from the evaluation of novel agents, identification of tumor markers predictive of disease relapse, and definition of factors that determine sensitivity to therapeutic agents. Some of the molecularly targeted agents such as the angiogenesis and epidermal growth factor receptor inhibitors are being incorporated into clinical trials. Preliminary results with gene-expression profiles and lung cancer proteomics have been promising. These techniques may be used to create prediction models to identify patients at risk for disease relapse. Molecular markers such as ERCC1 may determine response to treatment. All of these innovations will hopefully increase cure rates for lung cancer patients by maximizing the efficacy of adjuvant therapy.

<table>
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<tr>
<th>Surgical Stage</th>
<th>5-yr Survival</th>
<th>Relapse Local</th>
<th>Distant</th>
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<tbody>
<tr>
<td>IA T1, N0</td>
<td>67%</td>
<td>10%</td>
<td>15%</td>
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<tr>
<td>IB T2, N0</td>
<td>57%</td>
<td>10%</td>
<td>30%</td>
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<td>T1–3, N2</td>
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NSCLC = non-small-cell lung cancer.

Adjuvant chemotherapy after surgical resection would appear to be the logical approach to reducing
disease recurrence and improving survival. Early adjuvant trials did not support the routine administration of postoperative chemotherapy. A meta-analysis published in 1995 examined the results of randomized trials of surgery compared with surgery plus chemotherapy conducted between 1965 and 1991.[2] Treatment with cisplatin-based chemotherapy resulted in a hazard ratio (HR) of 0.87 ($P = .08$) with a 13% reduction in death favoring adjuvant therapy. Although this analysis did not make postoperative therapy the standard of care, it led to a renewed interest in pursuing adjuvant trials in early-stage NSCLC. Since the appearance of this meta-analysis, the results of several randomized clinical trials now support the use of adjuvant chemotherapy after surgical resection. This article will review the results of the more recent adjuvant trials and discuss the future direction of research in this area.

### Early Adjuvant Trials

The need for postoperative adjuvant therapy was recognized early in the treatment of lung cancer. A number of trials were conducted in the 1960s and 1970s utilizing immunotherapy (bacillus Calmette-Gurin, or BCG), alkylating agents, and/or radiotherapy for the treatment of lung cancer after surgical resection. These studies were plagued by insufficient sample size, inadequate surgical staging, and inferior chemotherapy.

The Lung Cancer Study Group (LCSG) was founded in the late 1970s. Patients enrolled on the LCSG adjuvant trials underwent rigorous mediastinal lymph node sampling, which allowed for proper stratification and survival analysis. These studies[3-5] (Table 2) usually utilized CAP (cyclophosphamide, doxorubicin [Adriamycin], cisplatin [Platinol]) as the adjuvant chemotherapy. Frequently, such trials showed an improvement in disease-free survival and median survival for the patients who received adjuvant chemotherapy, but no significant improvement in overall survival was seen. Moreover, difficulty was encountered in delivering all the intended chemotherapy.

A study from Finland that also utilized CAP chemotherapy demonstrated significant improvements in disease-free survival and long-term survival (10-year survival: 61% vs 48%) favoring adjuvant treatment.[6] When the statistics were adjusted for imbalances among patient characteristics, however, the survival differences were no longer significant.

Despite the fact that no one trial among these early studies clearly supported the use of adjuvant chemotherapy, they collectively suggested that with larger patient sample sizes, uniform surgical staging, and adequate chemotherapy delivery, it would be possible to demonstrate an advantage for postoperative treatment.

### Post-Meta-Analysis Platinum-Based Adjuvant Trials

Another generation of adjuvant trials using platin-based chemotherapy were reported after the publication of the meta-analysis (Table 3). In general, these trials had more consistent surgical staging, and several employed third-generation chemotherapeutic agents in combination with a platinum.
North American Intergroup Trial
The North American Intergroup Trial (INT0115, Eastern Cooperative Oncology Group [ECOG] 3590) randomized patients with stages II and IIIA to receive radiotherapy or concurrent chemoradiotherapy after surgery.[7] This is the only trial in which all patients received radiotherapy and the adjuvant chemotherapy was delivered concurrently with the radiation. With a total of 463 patients in the study, no differences were found between groups with regard to survival and patterns of recurrence. More toxicity was seen on the concurrent arm of the study, which may have accounted for the lack of efficacy in this trial, particularly for stage II patients. A meta-analysis examining the use of postoperative radiation therapy (described in more detail below) suggested that radiation administered after surgery may be detrimental for patients with early-stage (I or II) disease.[8] This trial also evaluated the impact of p53 and K-ras abnormalities on patient outcome. Despite the lack of any demonstrative prognostic or predictive value for these molecular markers, the inclusion of scientific correlative studies was important.

Adjuvant Lung Project Italy
The Adjuvant Lung Project Italy (ALPI) enrolled 1,209 patients with stage I-IIIA disease and randomized them to receive MVP (mitomycin, vindesine, cisplatin) or observation.[9] Patients received postoperative radiotherapy as determined by the participating institution. The trial closed early because of slow accrual during the last several months of the study. The final report was based on 1,088 patients, because one center was excluded from the final analysis. No significant difference was shown in overall survival between the study arms (HR = 0.96, 95% confidence interval [CI] = 0.81-1.13, P = .589). Moreover, the researchers found no significant difference in median overall survival (55 months, MVP vs 48 months, surgery alone) and progression-free survival (P = .128). Only 69% of patients completed the planned three cycles of chemotherapy and many patients required dose reductions, possibly accounting for the poor results in the chemotherapy study arm. The molecular markers p53, Ki67, and K-ras were evaluated in available tumor tissue, but no association was seen with stage, histology, or survival.

Big Lung Trial
The Big Lung Trial (BLT) from Great Britain evaluated cisplatin-based chemotherapy in a number of treatment situations.[10] A total of 381 patients with stage I-IIIA disease were randomly assigned to cisplatin-based neoadjuvant/adjuvant chemotherapy or surgery alone. The majority of the patients (96%) received the chemotherapy adjuvantly, and 64% received three cycles of treatment. Not all of
the patients had complete surgical resections. The investigators found no difference in overall survival between the study arms, but the trial was not designed to specifically evaluate adjuvant chemotherapy. Therefore, it was underpowered to detect a significant survival difference.

**International Adjuvant Lung Cancer Trial**

The International Adjuvant Lung Cancer Trial (IALT) randomized 1,867 patients with stage I-IIIA resected NSCLC to receive three to four cycles of cisplatin-based chemotherapy or observation.[11] The "user-friendly" study design allowed the treating institution to make decisions regarding the cisplatin dose, the drug combined with cisplatin, and the administration of postoperative radiation therapy. The primary endpoint was survival, and a 5% absolute improvement in survival was anticipated. The majority of patients received the 100 mg/m² dose of cisplatin per cycle, and 74% received at least a total of 240 mg/m². Nearly half of the patients received etoposide as the second drug, and about one-quarter received postoperative radiotherapy.

The 5-year survival rate was significantly higher for patients treated with chemotherapy (44.5% vs 40.4%, HR = 0.86, P < .03). Disease-free survival was also significantly improved (P < .003). The chemotherapy-related mortality was less than 1%. Hazard ratios were less than 1 for all disease stages, with the most benefit being seen in stage IIIA. This was the first prospective randomized trial to demonstrate a survival advantage for adjuvant chemotherapy in resected NSCLC, justifying the use of this strategy in common practice.

**JBR.10 Trial**

The National Cancer Institute of Canada (NCIC) Intergroup trial JBR.10 randomly assigned 482 patients with stages IB and II resected NSCLC to receive four courses of cisplatin and vinorelbin or surgery alone.[12] Patients did not receive postoperative radiation. The most common side effect was neutropenia, and two treatment-related deaths occurred (0.08%). Overall survival was significantly prolonged in the chemotherapy group (94 vs 73 months, HR = 0.69, P = .04) as was relapse-free survival (HR = 0.60, P < .001) and 5-year survival (69% vs 54%, P = .03). The subgroup analyses according to stratification factors failed to show a significant advantage for stage IB patients. However, stage II patients who received chemotherapy had a survival of 80 months, compared to 41 months in the observation group (P = .004). The presence of ras mutations did not predict for survival.

**ANITA Trial**

The Adjuvant Navelbine International Trialist Association (ANITA) reported their randomized trial in patients with resected stage IB-IIIA NSCLC.[13] The chemotherapy employed was cisplatin and vinorelbin, and postoperative radiation was allowed. Patients treated with chemotherapy had a significant improvement in overall survival (65.8 vs 43.8 months, HR = 0.79, P = .013), disease-free survival (36.3 vs 20.7 months, HR = 0.76, P = .002), and 5-year survival (51.2% vs 42.6%). As in the JBR.10 trial, the subset analysis did not show a survival benefit for adjuvant chemotherapy in stage IB patients.

**CALGB 9633 Trial**

Cancer and Leukemia Group B (CALGB) 9633 is a unique trial because it randomized patients exclusively with stage IB NSCLC postresection to receive carboplatin/paclitaxel or surgery alone.[14] The trial was stopped early after 344 patients were accrued because the study had met its predetermined survival endpoint. The treatment was very well tolerated, with 85% of patients receiving four cycles of chemotherapy, and no treatment-related deaths occurred. When the results of the trial were initially reported with a median follow-up of 34 months, the 4-year (71% vs 59%, HR = 0.62, P = .028) and failure-free (P = .035) survival rates significantly favored chemotherapy. An update was presented at the 2006 annual meeting of the American Society of Clinical Oncology (ASCO). Unfortunately, the overall survival (HR = 0.80, 90% CI = 0.60-1.07, P = .10) no longer favored adjuvant chemotherapy.[15] These results brought up two important questions, which we will address in the following two sections.

**Stage IB Disease**

The first issue concerns the adjuvant treatment of patients with stage IB NSCLC. The Lung Adjuvant Cisplatin Evaluation (LACE) is a meta-analysis of five cisplatin-based adjuvant trials.[16] The overall survival results supported adjuvant chemotherapy (HR = 0.89, P = .004), but the benefit for patients with stage IB disease was very modest (HR = 0.92), and chemotherapy may have been detrimental for patients with stage IA disease (HR = 1.41).

The CALGB trial suggested that some patients with stage IB may benefit from postoperative treatment. The investigators found an improvement in failure-free survival for chemotherapy-treated patients (HR = 0.74, P = .030), and a subset analysis indicated a survival benefit for patients with tumors ≥ 4 cm who received adjuvant treatment (HR = 0.66, P = .04). Thus, select patients with
stage IB NSCLC may actually benefit from adjuvant treatment, and this group should continue to be included in clinical trials.

**Carboplatin vs Cisplatin**

The second question has to do with whether carboplatin can substitute for cisplatin in the adjuvant situation. The Cisplatin vs Carboplatin (CISCA) meta-analysis compared chemotherapy with these two agents in advanced NSCLC.[17] There was a slight survival benefit associated with cisplatin, which became significant when cisplatin was combined with third-generation chemotherapeutic agents ($P = .026$). This analysis was conducted in advanced NSCLC, and it may not be valid to apply these results to the adjuvant setting. Nonetheless, the data currently support cisplatin-based adjuvant chemotherapy for resected NSCLC. Carboplatin could certainly be considered in the patient who cannot tolerate cisplatin.

**UFT Adjuvant Trials**

Trials using uracil/tegafur (UFT), a well tolerated oral fluoropyrimidine, have been conducted in Japan. The largest single trial randomly assigned 979 patients with resected stage I adenocarcinoma to receive UFT for 2 years vs no treatment.[18] The overall survival rate at 5 years was 88% in the UFT group and 85% in the control group ($P = .047$). The greatest benefit was for the T2, N0 subset. A subsequent meta-analysis of postoperative UFT trials demonstrated that adjuvant therapy with UFT significantly improved overall survival, with a hazard ratio of 0.74 (95% CI = 0.61-0.88, $P = .001$).[19] To date, no confirmatory evidence has been reported outside of Japan supporting the use of UFT in the adjuvant setting.

**Neoadjuvant Chemotherapy**

The concept of delivering neoadjuvant chemotherapy prior to surgical resection in NSCLC is appealing. Potential advantages include tumor downstaging, early treatment of micrometastases, better chemotherapy delivery, and in vivo assessment of chemotherapy sensitivity. Neoadjuvant chemotherapy is a standard approach to the treatment of unresectable stage III disease and has been used preoperatively in patients with potentially resectable stage IIIA. Two small trials randomly assigned patients with potentially resectable IIIA NSCLC to receive preoperative chemotherapy or surgery alone.[20,21] In both instances, survival was significantly improved chemotherapy recipients, who showed no increase in surgical morbidity and mortality, indicating that this was a feasible approach to treatment.

The French Thoracic Cooperative Group conducted a phase III investigation in patients with stage IB-IIIA NSCLC.[22] A total of 355 patients were randomized to preoperative mitomycin, ifosfamide, and cisplatin or surgery alone. Responding patients received two additional cycles of chemotherapy after surgery and patients with stage IIIA disease received postoperative radiotherapy. The response rate to induction chemotherapy was 64%, with an 11% pathologic complete response. The chemotherapy group showed a nonsignificant 11-month improvement in median survival (37 vs 26 months, $P = .15$). Further analyses indicate that treatment benefit was confined to patients with N0 and N1 disease. The trial revealed a slight increase in postoperative mortality on the preoperative chemotherapy study arm (6.7% vs 4.5%). After 5 months, the effect of preoperative chemotherapy was significantly favorable (HR = 0.74, $P = .044$). Disease-free survival time was significantly longer in the chemotherapy group.

The Bimodality Lung Oncology Team (BLOT) trial was a phase II study that demonstrated the feasibility of neoadjuvant carboplatin/paclitaxel chemotherapy.[23,24] Ninety-four patients (stages T2, N0; T1-2, N1; T3, N0-1) received two cycles preoperatively, and three postoperative cycles were planned. The chemotherapy response rate was 56%, with 6% pathologic complete responses. The complete resection rate was 86%, with no increase in surgical mortality. Postoperative delivery of chemotherapy was poor at 45%. The 5-year survival rate was 46%. This was followed by a phase III intergroup trial—Southwest Oncology Group (SWOG) 9900—which randomly assigned similarly staged patients to receive three cycles of preoperative carboplatin/paclitaxel or surgery alone.[25] Unfortunately, the trial closed prematurely because of the emerging data showing a survival benefit for adjuvant chemotherapy, making it unethical to continue a surgery-alone arm. A preliminary report suggests that survival may favor neoadjuvant chemotherapy, but the study may be underpowered to show a significant advantage for preoperative treatment.

The use of neoadjuvant chemotherapy remains a feasible, albeit unproven, approach to the treatment of early-stage NSCLC. A number of ongoing trials in North America and Europe are attempting to compare neoadjuvant to adjuvant chemotherapy in patients with resectable NSCLC. For example, a North American trial is evaluating cisplatin/docetaxel (Taxotere) in this setting. The
Neo-adjuvant Taxol/Carboplatin Hope (NATCH) trial being conducted in Spain is near completion. This is a three-arm randomized study comparing neoadjuvant and adjuvant carboplatin/paclitaxel to surgery alone. In addition to information regarding the timing of chemotherapy, this trial could potentially give more insight into the use of carboplatin-based chemotherapy in early-stage disease.

**Postoperative Radiation Therapy**

The current role of postoperative radiation therapy (PORT) has been largely defined by the PORT meta-analysis published in 1998.[8] This analysis was based on data from 2,128 patients in nine randomized studies, dating from 1965. The results of this analysis showed that postoperative radiation had a detrimental effect on overall survival (HR = 1.21, 95% CI = 1.08-1.34). Subgroup analyses suggested that this adverse effect was restricted to patients with stage I/II disease, with no adverse effect noted in stage III patients. Radiation technology (cobalt-60 was used in seven of the nine trials), technique, dose planning, and fractionation have clearly improved since the publication of the PORT meta-analysis. Thus, it is quite likely that modern PORT may not result in a detrimental effect, but given the lack of randomized studies, it has not been possible to adequately evaluate its role utilizing current treatment standards.

The primary impact of thoracic radiotherapy is in the reduction of the risk of locoregional relapse. The risk of local relapse in patients with stage I/II disease after adequate surgery is relatively low, and the majority of recurrences are distant. In stage III disease, local recurrence rates can be greater than 30% in patients treated with surgery alone.[26] The PORT meta-analysis and several retrospective studies suggest that patients with stage III NSCLC may derive a survival advantage from the use of PORT.[27,28]

As stated earlier, the data regarding PORT in the era of adjuvant chemotherapy is limited. It has been suggested that the inclusion of PORT in the INT0115 (E3590) and ALPI trials may have contributed to the negative results and lack of benefit for adjuvant chemotherapy. A recent subset analysis of the ANITA trial found that patients with mediastinal lymph node (N2) involvement had better outcomes with PORT. The median survival of N2 patients who received chemotherapy alone after surgery was 23.8 months, compared to 47.4 months for patients who also received PORT. This survival advantage was not seen in patients with earlier-stage disease.[29] The CALGB attempted to evaluate the role of PORT in N2 patients following adjuvant chemotherapy consisting of four cycles of carboplatin and paclitaxel. Unfortunately the trial closed prematurely due to slow accrual and will be underpowered to assess the value of PORT.

Based on the available data, PORT may be considered for patients with stage III disease who have inadequate mediastinal lymph node evaluation, multistation disease, or extracapsular nodal extension in order to reduce locoregional recurrence. The radiation should be given sequentially following adjuvant chemotherapy, since there is no evidence that concurrent chemotherapy and radiation is beneficial in resected stage III patients. There remains a need for randomized trials to explore the role of PORT particularly in patients at high risk of locoregional recurrence.

**Future Directions**

The benefits of adjuvant therapy remain modest, with improvements in 5-year survival of only 5% to 15%. These data suggest that some patients relapse despite adjuvant treatment. It is also clear that based on a 5-year survival rate of 25% or greater after surgical resection alone, some NSCLC patients do not need adjuvant therapy. Thus, there is a need not only to improve the survival outcomes of surgically resected patients but also to develop better predictive markers of relapse. Further innovations in adjuvant therapy are therefore likely to result from the evaluation of novel agents, improved identification of tumor markers predictive of relapse, and a better understanding of factors that determine sensitivity to therapeutic agents.

**Novel Agents**

Improved understanding of the molecular processes involved in carcinogenesis has lead to the investigation of drugs that focus on relevant molecular pathways. Initial evaluations in the management of NSCLC have focused on drugs targeting vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR).

- **Anti-VEGF Therapy**—Tumor angiogenesis is recognized as a critical component of tumor growth and metastasis. For tumors to grow beyond 1 to 2 mm, sufficient nutrition via angiogenesis is essential.[30] The VEGF pathway plays a pivotal role in normal and tumor angiogenesis.[31,32] VEGF overexpression has been shown to be associated with relapse following surgery and poor prognosis in NSCLC.[33,34] Based on its central role in tumor angiogenesis, drugs targeting VEGF are being developed for the treatment of many cancers.
Bevacizumab (Avastin) is a humanized monoclonal antibody to VEGF that effectively prevents it from binding to its receptors. Based on the relevance of the VEGF pathway in NSCLC and promising preclinical and clinical data, bevacizumab was evaluated in combination with carboplatin/paclitaxel in advanced NSCLC patients.[35] Due to concerns raised in a prior phase II study, patients with squamous cell histology, brain metastases, history of hemoptysis or recent thrombotic episodes, and patients on anticoagulants were excluded.[36] The addition of bevacizumab improved median overall survival (12.5 vs 10.2 months) and progression-free survival (6.4 vs 4.5 months). The trial demonstrated greater toxicity in the bevacizumab arm, specifically hemorrhage (4.5% vs 0.7%), neutropenia (24% vs 16%), and thrombocytopenia (1.4% vs 0%). Bevacizumab was also associated with more treatment-related deaths (15 vs 2).

In addition, pooled analysis of various trials evaluating bevacizumab showed that patients aged 65 years and older were at greater risk of developing thrombotic episodes with the use of the drug.[37] Based on these promising data in advanced NSCLC, a phase III adjuvant trial is currently being planned that will randomize patients with resected NSCLC to receive chemotherapy with or without bevacizumab. The choice of the chemotherapy combination will be decided by the treating physician but will be restricted to cisplatin-based regimens. The proposed objective is to detect a 25% improvement in median survival, from 66 months with chemotherapy alone to 84 months in patients receiving bevacizumab.

Despite the excitement regarding this trial, there remains a sense of caution with the use of anti-VEGF therapy in the postoperative setting. Concerns include the need for postoperative healing in the presence of an antiangiogenic drug and increased toxicities such as hemorrhage, neutropenic fever, hypertension, and thrombotic episodes with the use of bevacizumab. These toxicities may be viewed by treating physicians and patients differently in the adjuvant setting, as compared to the advanced disease situation.

Inhibiting the VEGF receptor is another way of targeting the VEGF pathway. Three tyrosine kinase receptors for VEGF have been identified: VEGFR1 (Flt-1), VEGFR2 (KDR), and VEGFR3.[31,32,38] Various agents targeting these receptors are currently in development. The potential advantage of these agents over bevacizumab is their ability to inhibit receptors of other angiogenic factors such as platelet-derived growth factor (PDGF), which may result in greater antitumor effect. The role of these agents in the management of NSCLC remains to be defined.

**EGFR Inhibitors**—EGFR, a receptor tyrosine kinase, is expressed in many NSCLCs and is involved in many aspects of cancer formation and progression.[39] Based on promising preclinical data, inhibitors of EGFR tyrosine kinase (EGFR-TKIs)—erlotinib (Tarceva) and gefitinib (Iressa)—were evaluated in the management of NSCLC.[40-42] Erlotinib subsequently was approved for the treatment of relapsed NSCLC based on the results of a placebo-controlled randomized study demonstrating a survival benefit with the use of erlotinib.[43]

Data from clinical trials of EGFR-TKIs suggest that patients with certain clinical characteristics have a higher likelihood of clinical benefit.[44,45] These factors include adenocarcinoma histology, female gender, Asian ethnicity, development of a skin rash, and nonsmoking status. Retrospective analyses of tumors in patients responding to these agents revealed that the presence of activating mutations in the tyrosine kinase domain of the EGFR gene predicts for response and clinical benefit from EGFR-TKIs.[46,47] Subsequently, other investigators have suggested that increased EGFR gene copy number and EGFR expression are more predictive of benefit from EGFR-TKIs and occur more frequently in tumors of patients with clinical characteristics that are also associated with a higher likelihood of response to the EGFR-TKIs.[48] The relative importance of each factor in predicting benefit from these agents remains to be determined in prospective clinical trials.

Gefitinib has been studied in earlier-stage NSCLC. In a phase III trial conducted by SWOG, gefitinib was evaluated as maintenance therapy following completion of concurrent chemotherapy and radiation for stage III NSCLC.[49] An earlier-than-planned interim analysis was conducted after the results of the Iressa Survival Evaluation in Lung Cancer (ISEL) trial were released.[50] This placebo-controlled study showed no significant survival improvement for gefitinib recipients with advanced NSCLC after the failure of prior chemotherapy. The preliminary results of the SWOG study failed to demonstrate a survival advantage for the use of gefitinib as maintenance therapy. An NCIC adjuvant trial evaluating gefitinib was also terminated prior to proposed accrual due to the release of these negative results.

Based on the observation that EGFR expression by immunohisto-chemistry (IHC) and increased EGFR gene copy number predict for increased survival with EGFR-TKIs in relapsed NSCLC patients, a clinical trial evaluating the role of erlotinib following completion of adjuvant chemotherapy in
patients with EGFR-positive (by IHC and/or fluorescence in situ hybridization [FISH]) tumors is currently being planned.

**Tumor Factors Predictive of Relapse**

Decisions regarding the administration of adjuvant treatment in NSCLC patients are based primarily on the stage of the disease. Methods of characterizing the relapse risk more precisely are required. Systematic genomic and proteomic evaluation of lung cancers may yield better prognostic evaluations.

Recently, Potti et al reported the results of assessing gene-expression patterns to stratify risk in NSCLC patients.[51] The investigators utilized gene-expression profiles of tumors to generate a lung metagene model predictive of recurrence. When compared to clinical prognostic variables, the lung metagene model was significantly better in predicting recurrence for individual patients, including the identification of stage IA patients at risk for relapse. Based on these data, CALGB is planning a clinical trial that will stratify patients with stage IA NSCLC based on the lung metagene model to high and low risk of relapse. Patients at low risk will be observed and those at high risk will be randomized to observation or chemotherapy.

Evaluation of proteins in cancer cells can provide information not obtained by the genetic profile. The genetic alterations that lead to a malignant phenotype manifest through their expression as proteins. Therefore, assessment of the proteome or protein-expression profile of the tumor is being studied as a tool for both diagnostic and prognostic purposes. Recently, Kikuchi et al presented the results of proteomic analysis of lung cancer tumors.[52] The investigators analyzed the protein profiles of 175 lung cancers and 62 histologically normal tumors. Based on these profiles, they created a prediction model that had a high rate of predictive accuracy for tumor/normal tissue discrimination, presence of nodal metastasis, and survival. The true benefits of both genetic and proteomic assessment of tumors for risk stratification remain to be defined in prospective clinical trials. Nonetheless, the data suggest that these techniques may provide a better assessment of tumor biology than the clinical variables that are currently utilized. These new techniques may help refine the decision-making process regarding the use of adjuvant therapy in NSCLC.

**Tumor Factors Predictive of Chemotherapy Sensitivity**

Since not all NSCLC patients derive a benefit from adjuvant chemotherapy, it would be worthwhile developing markers to identify patients most likely to profit from specific chemotherapy drugs. Cisplatin binds to DNA and forms platinum-DNA adducts. Some of these adducts form covalent crosslinking between DNA strands and thereby inhibit DNA replication. Thus, DNA repair mechanisms are important in cisplatin resistance. The nucleotide-excision repair complex is a DNA repair pathway that attends to DNA damage from various factors. The excision repair cross-complementation group 1 (ERCC1) gene encodes for a protein that belongs to the nucleotide-excision repair complex and is involved in the rate-limiting step of the complex. In vitro and retrospective clinical studies have linked ERCC1 mRNA expression to platinum resistance.[53] Most of these studies have conducted their analyses through RNA or DNA assessment and could limit the wider applicability of this marker in clinical practice.

Recently, Olaussen et al reported results of the IALT Bio study, a retrospective assessment of ERCC1 expression by IHC in tumors of patients enrolled on the IALT trial.[54] The investigators evaluated ERCC1 protein expression in paraffin-embedded tumor blocks from 761 of the 1,867 patients enrolled on IALT. Tumors were assigned a semiquantitative H score based on the percentage of positive tumor nuclei and the staining intensity for ERCC1. Based on this H score, patients were classified into two groups of ERCC1-positive or negative tumors. Adjuvant cisplatin-based therapy significantly prolonged survival in patients with ERCC1-negative tumors (HR = 0.65, \( P = .002 \)) but not in ERCC1-positive tumors (HR = 1.14, \( P = .40 \)). Interestingly, among patients who did not receive adjuvant chemotherapy, the survival of patients with ERCC1-positive tumors was superior (HR = 0.66, \( P = .009 \)). These data suggest that ERCC1 expression could serve as an independent marker predicting benefit or lack thereof from adjuvant platinum-based therapy. These data need to be confirmed in a prospective trial before such a strategy can be utilized in clinical practice. Other markers such as BRCA1, RRM1, and XRCC3 polymorphisms are being assessed for sensitivity to different chemotherapy drugs.[55,56] Assessment of these markers may actually allow one to individualize chemotherapy and improve patient survival by maximizing the efficacy of adjuvant treatment.

**References:**


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