Adjuvant therapy for resected non-small cell lung cancer

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Abstract: Surgery remains the initial treatment for patients with early-stage non-small cell lung cancer (NSCLC). The frequent occurrence of distant metastases and local regional failure after surgical resection would indicate that additional treatment is necessary. 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. This was followed by a new generation of randomized phase III trials some of which have reported a benefit for chemotherapy in the adjuvant setting. Based on the results of these trials, platin-based chemotherapy has become the standard of care for resected stages II and IIIA NSCLC. The role of postoperative radiation therapy remains to be defined. In the future, improvement in survival outcomes from adjuvant treatment is 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. Gene expression profiles and proteomics are techniques being used to create prediction models to identify patients at risk for disease relapse. Molecular markers such as ERCC1 may determine response to treatment. Increasing the understanding of the molecular makeup of lung cancer will hopefully increase cure rates for patients by maximizing the efficacy of the adjuvant therapy.

Keywords: adjuvant therapy, lung cancer

Introduction

Lung cancer remains one of the leading causes of cancer deaths worldwide. Surgery is the standard of care for the treatment of early stage non-small cell lung cancer (NSCLC) but less than one-third of patients present with disease that is potentially resectable. Clinical staging has improved with the use of positron emission tomography and this alone may result in stage migration and an apparent improvement in survival for early stage resected NSCLC. However, outcome is closely linked to the pathologic stage therefore, it is of utmost importance that intra-operative staging be performed especially adequate lymph node sampling. Surgery, however, is an imperfect therapy and 5-year survival rates have been disappointing because of distant and local recurrences (Table 1) [Mountain, 1997].

Distant metastases after surgery largely account for treatment failure and patient mortality from NSCLC. Adjuvant chemotherapy after surgical resection would appear to be the logical approach in order to reduce disease recurrence and improve survival. The need for adjuvant chemotherapy was recognized in the 1960s and 1970s. These early adjuvant trials utilized immunotherapy (bacillus Calmette-Guerin), alkylating agents, and/or radiotherapy but they were plagued by inaccurate staging, inadequate surgery, insufficient sample size, and inferior adjuvant treatment. In the late 1970s, the Lung Cancer Study Group (LCSG) conducted a number of trials that required that patients undergo rigorous mediastinal lymph node sampling, which allowed for proper stratification and survival analysis [Feld *et al.* 1993; Lad *et al.* 1988; Holmes *et al.* 1986]. These studies

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Table 1. Outcome by stage following surgical resection in non-small cell lung cancer.

Surgical stage		5-year survival (%)	Relapse (%)	
			Local	Distant
IA	T1N0	67	10	15
IB	T2N0	57	10	30
IIA	T1N1	55		
IIB	T2N1	39	12	40
	T3N0	38		
IIIA	T3N1	25	15	60
	T1-3N2	23		

were able to demonstrate an improvement in disease-free and median survival rates favoring adjuvant therapy but were not able to show an overall survival benefit for the treated patients. A meta-analysis published in 1995 examined the results of randomized trials of surgery compared with surgery plus chemotherapy conducted between 1965 and 1991 [Non-Small Cell Lung Cancer Collaborative Group, 1995]. Treatment with cisplatin-based chemotherapy resulted in a hazard ratio (HR) of 0.87 ($p=0.08$) with a 13% reduction in death supporting adjuvant therapy. This analysis did not justify the routine use of postoperative therapy, but renewed an interest in pursuing adjuvant trials in early stage NSCLC. Currently, the results from several randomized clinical trials now support the use of adjuvant chemotherapy after surgical resection. This article will review the data from these modern trials and discuss the future direction of research in this area.

Modern adjuvant trials

In the last 10 years, the results from a new generation of adjuvant trials have been reported. In general these trials had more consistent surgical staging and have usually employed platinum-based chemotherapy (Table 2).

The first reported study was the North American Intergroup Trial (INT0115, ECOG 3590) [Keller *et al.* 2000]. Patients with stages II and IIIA NSCLC were randomized to receive radiotherapy or concurrent chemoradiotherapy after surgery. This trial was unique in that all patients received postoperative radiotherapy and the adjuvant chemotherapy was delivered concurrent with the radiation. There were no differences between the patient groups with regard to survival and patterns of recurrence. There was more toxicity on the concurrent arm of the study, which may have accounted for the lack of efficacy on this trial particularly for the stage II

patients. It is important to note that scientific correlative studies were included as part of the study design to explore the impact of molecular markers, p53 and K-ras, on patient outcome [Schiller *et al.* 2001]. Tumors from 197 patients were analyzed. Neither p53 mutations, p53 protein expression, or K-ras mutations correlated with survival or progression-free survival.

The Adjuvant Lung Project Italy (ALPI) was probably the first adequately powered trial enrolling over 1200 participants [Scagliotti *et al.* 2003]. Patients with stages I–IIIA were randomized to receive MVP (mitomycin, vindesine, cisplatin) or observation. Postoperative radiotherapy was allowed. The trial was terminated early because of slow accrual during the last several months. There was no significant difference in overall survival between the study arms (HR 0.96, 95% CI: 0.81–1.13, $p=0.589$). Problems with chemotherapy delivery and toxicity may have accounted for the lack of benefit for the adjuvant chemotherapy. An exploratory analysis of molecular markers p53, Ki67, and K-ras was conducted in available tumor tissue but no association was established with stage, histology, or survival.

The Big Lung Trial (BLT) evaluated cisplatin-based chemotherapy in a number of treatment situations [Waller *et al.* 2004]. Patients with stages I–IIIA NSCLC were randomly assigned to cisplatin-based neoadjuvant/adjuvant chemotherapy or surgery alone. Not all of the patients had complete surgical resections or were able to complete chemotherapy. There was no difference in overall survival between the study arms but this trial was not designed to specifically evaluate adjuvant chemotherapy, therefore it was underpowered to detect a significant survival difference.

The International Adjuvant Lung Cancer Trial (IALT) was a landmark study that initially justified the use of adjuvant chemotherapy in resected NSCLC [The International Adjuvant Lung Cancer Trial Collaborative Group, 2004]. This trial employed a ‘user friendly’ study design allowing the treating institution to make the decisions regarding the cisplatin dose, the drug combined with cisplatin, and the administration of postoperative radiation therapy. Over 1800 patients with stages I–IIIA resected NSCLC received three to four cycles of cisplatin-based chemotherapy or observation. The primary endpoint was survival and a 5% absolute improvement in survival was anticipated. The 5-year survival (44.5% *versus*

Table 2. Recent platin-based adjuvant trials.

Trial	Patients	Stage	Chemotherapy	RT	5-year (%)*
INT0115	488	II–IIIA	Cis, VP-16	Yes	33 vs 39
BLT	381	I–III	Cis-based	Yes	58 vs 60 (2-yr)
ALPI	1209	I–IIIA	MVP	Yes	HR 0.96
IALT [†]	1,867	I–IIIA	Cis-based	Yes	44.5 vs 40.4
NCIC [‡]	482	IB–II	Cis, Vnr	No	69 vs 54
ANITA [‡]	840	IB–IIIA	Cis Vnr	Yes	8.6 Improved
CALGB [†]	344	IB	Pac, Carbo	No	64 vs 61

*Chemotherapy arm *versus* control arm

Carbo, carboplatin; Cis, cisplatin; HR, hazard ratio; MVP, mitomycin, vindesine, cisplatin; RT, radiotherapy; Vnr, vinorelbine. Trial abbreviations: INT0115, North American Intergroup Trial; BLT, Big Lung Trial; ALPI, Adjuvant Lung Project Italy; IALT, International Adjuvant Lung Cancer Trial; NCIC, National Cancer Institute of Canada; ANITA, Adjuvant Navelbine International Trialist Association; CALGB, Cancer and Leukemia Group B.

[†]Initially significant improvement in survival for adjuvant chemotherapy. Overall survival benefit no longer significant with longer follow-up

[‡]Significant improvement in survival for adjuvant chemotherapy

40.4%, HR 0.86, $p < 0.03$) and disease-free survival ($p < 0.003$) was significantly higher for the patients treated with chemotherapy. The toxicity was acceptable and benefit was seen for all disease stages with the most survival advantage being in stage IIIA. After an additional follow up of 3 years, the results of the IALT were re-evaluated [Le Chevalier *et al.* 2008]. Interestingly, the survival and disease-free survival benefit was no longer apparent for the adjuvant population. This was thought to be secondary to an increased number of non-lung cancer deaths in the patients who had received postoperative chemotherapy, indicating the importance of long-term follow up.

The National Cancer Institute of Canada (NCIC) Intergroup trial JBR.10 was conducted in patients with stages IB and II resected NSCLC randomized to receive four courses of cisplatin and vinorelbine or observation [Winton *et al.* 2005]. Overall survival was significantly prolonged in the chemotherapy group (94 *versus* 73 months, HR 0.69, $p = 0.04$) as was relapse-free survival (HR 0.60, $p < 0.001$), and 5-year survival (69 *versus* 54%, $p = 0.03$). A subgroup analysis indicated that the significant survival benefit was only seen in patients with stage II disease ($p = 0.004$). The results of long-term follow up of this trial are anticipated in the near future.

The Adjuvant Navelbine International Trialist Association (ANITA) reported a randomized trial in patients with resected stages IB–IIIA NSCLC [Douillard *et al.* 2006]. As in JBR.10, the chemotherapy employed was cisplatin and vinorelbine. Postoperative radiation was allowed. For the patients treated with chemotherapy

there was a significant improvement in overall survival (65.7 *versus* 43.7 months, HR 0.80, $p = 0.017$). Survival at 5 years improved by 8.6% with chemotherapy and was maintained at 7 years. A subset analysis did not show a survival benefit for adjuvant chemotherapy in stage IB patients.

The Lung Adjuvant Cisplatin Evaluation (LACE) was a meta-analysis of the last five described trials [Pignon *et al.* 2008]. The overall HR of death was 0.89 ($p = 0.005$) corresponding to a 5-year absolute benefit of 5.4% from chemotherapy. Benefit varied with stage (HR for IA = 1.40, IB = 0.93, II = 0.83, III = 0.83) but not with type or dose of chemotherapy. The only other parameter that predicted for a higher chemotherapy effect was better performance status.

Cancer and Leukemia Group B (CALGB) 9633 was a unique trial because it included only patients with resected stage IB NSCLC and carboplatin-based chemotherapy was utilized as adjuvant treatment [Strauss *et al.* 2008]. The trial was stopped early after 344 patients were accrued when a predetermined survival endpoint was met. Chemotherapy compliance was very good and toxicity was low. When the results of the trial were initially reported with a median follow-up of 34 months, the 4-year (71 *versus* 59%, HR 0.62, $p = 0.028$) and failure-free ($p = 0.035$) survivals significantly favored chemotherapy [Strauss *et al.* 2004] however, with longer follow up the overall survival (HR 0.83, 90% CI: 0.64–1.08, $p = 0.12$) no longer favored adjuvant chemotherapy [Strauss *et al.* 2008].

The results of the CALGB trial bring up two contentious issues. The first is with regard to the adjuvant treatment of patients with stage IB NSCLC. The LACE meta-analysis indicated that the benefit for stage IB was very modest (HR 0.93). A subset analysis of the CALGB trial indicated a survival benefit for patients with tumors ≥ 4 cm who received adjuvant treatment (HR 0.69, $p = 0.043$). These data suggest that select patients with stage IB NSCLC may actually benefit from adjuvant treatment and this group should continue to be included in clinical trials.

The second issue has to do with the choice of the platinum (cisplatin or carboplatin) for treatment in the adjuvant situation. The CISCA meta-analysis evaluated cisplatin *versus* carboplatin-based chemotherapy in advanced NSCLC [Ardizzoni *et al.* 2007]. There was a slight survival benefit for cisplatin-based chemotherapy which became significant in patients treated with nonsquamous histology and those treated with third-generation chemotherapeutic agents. Although this analysis was in advanced NSCLC the demonstration of a slight survival advantage for cisplatin may be of more importance in a curative situation, that is, adjuvant chemotherapy.

Although most of the trials discussed thus far utilize platin-based chemotherapy, it is worthwhile mentioning the adjuvant studies conducted in Japan employing UFT, an oral fluoropyrimidine. A meta-analysis of postoperative UFT trials demonstrated that adjuvant therapy with UFT significantly improved overall survival with an HR 0.74 (95% CI: 0.61–0.88, $p = 0.001$) [Hamada *et al.* 2005]. To date, there has been no confirmatory evidence 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 has some potential advantages including: tumor downstaging, early treatment of micrometastases, better chemotherapy delivery, and an *in vivo* assessment of chemotherapy sensitivity. There are two small trials that randomly assigned patients with potentially resectable IIIA NSCLC to receive preoperative chemotherapy or surgery alone [Rosell *et al.* 1999; Roth *et al.* 1998]. In both instances, survival was significantly improved in the chemotherapy group without an increase in surgical morbidity and

mortality indicating that pre-operative chemotherapy is a feasible approach.

The French Thoracic Cooperative Group conducted a phase III trial in patients with stages IB–IIIA NSCLC [Depierre *et al.* 2002]. Patients were randomized to pre-operative mitomycin, ifosfamide, and cisplatin or surgery alone. Stage III patients received postoperative radiotherapy. There was a nonsignificant 11-month improvement in median survival for the chemotherapy group (37 *versus* 26 months, $p = 0.15$) with a slight increase in postoperative mortality (6.7 *versus* 4.5%). Treatment benefit was confined to N0 and N1 disease.

The Bimodality Lung Oncology Team (BLOT) trial was a phase II study that demonstrated the feasibility of neoadjuvant carboplatin/paclitaxel chemotherapy [Pisters *et al.* 2000]. The following phase III trial, Southwest Oncology Group (SWOG) 9900 randomly assigned patients with stages IB–IIIA (T3N1) to receive three cycles of pre-operative carboplatin/paclitaxel or surgery alone [Pisters *et al.* 2005]. 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. Although survival appears to favor neoadjuvant chemotherapy, the study may be underpowered to show a significant advantage for pre-operative treatment. A similar situation occurred with another randomized Phase III study, Ch.E.S.T. (Chemotherapy for Early Stages Trial) [Scagliotti *et al.* 2008b]. Benefit for pre-operative chemotherapy was seen in stages IIB–IIIA but outcome was likely affected by early termination of the trial. A meta-analysis of 12 randomized pre-operative chemotherapy trials demonstrated a survival benefit for chemotherapy with a hazard ratio of 0.82 [Burdett *et al.* 2006]. This survival advantage is similar to what is seen with chemotherapy delivered after surgery.

The use of neoadjuvant chemotherapy remains a feasible, albeit unproven, approach to the treatment of early-stage NSCLC. The NATCH trial could answer the question regarding optimal timing of chemotherapy in early-stage NSCLC. It is a three-arm randomized study comparing neoadjuvant and adjuvant carboplatin/paclitaxel to surgery alone. The results will be presented at the 2009 American Society of Clinical Oncology annual meeting.

Postoperative radiation therapy (PORT)

The current role of PORT has been largely defined by the PORT meta-analysis [PORT Meta-analysis Trialists' Group, 1998]. This analysis included the data of 2128 patients from nine randomized studies dating from 1965. The results indicated that there was 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 and lung cancer staging have clearly improved since the publication of the PORT meta-analysis. It is possible that modern PORT may not result in a detrimental effect. Unfortunately, there is a lack of randomized studies to adequately evaluate its role utilizing current treatment standards.

The primary importance of thoracic radiotherapy is in the reduction of local-regional relapse. In patients with stages I and II disease after adequate surgery the risk is low. 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. In stage III disease, local recurrence can be greater than 30% in patients treated with surgery alone [The Lung Cancer Study Group, 1986]. The PORT meta-analysis and several retrospective studies suggest that patients with stage III NSCLC may potentially derive a survival advantage from the use of PORT [Machtay *et al.* 2001; Sawyer *et al.* 1997]. A 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 as compared to 47.4 months for the patients who also received PORT. This survival advantage was not seen in patients with lower stage disease [Douillard *et al.* 2006].

Currently, 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 local-regional recurrence. The radiation should be given sequentially following adjuvant chemotherapy since there is no evidence that concurrent treatment is beneficial in resected stage III patients. The Lung Adjuvant Radiotherapy Trial (LungART) which is being

conducted by the EORTC is designed to evaluate PORT in patients with N2 disease.

Future directions: novel agents, new trials and customizing treatment

The benefits of adjuvant therapy remain modest, with improvements in 5-year survival of only 5–15% indicating the inadequacy of current available treatment. It is also clear that some NSCLC patients do not need adjuvant therapy after surgical resection. 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 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

Pemetrexed is a multitargeted antifolate that has been approved for the first-line treatment of NSCLC. In a recent randomized Phase III trial it was combined with cisplatin and compared to cisplatin/gemcitabine in the treatment of advanced NSCLC [Scagliotti *et al.* 2008a]. The overall outcome for both doublets was similar however, the pemetrexed combination was significantly better in patients with nonsquamous histology. The pemetrexed/cisplatin doublet is currently being included in adjuvant trials for patients with resected nonsquamous NSCLC.

Greater insight into the molecular processes involved in carcinogenesis and cancer progression has led to the development of drugs that target 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).

Tumor angiogenesis is recognized as a critical component of tumor growth and metastasis and the VEGF pathway plays a pivotal role in normal and tumor angiogenesis [Hicklin and Ellis, 2005; Ferrara, 2002]. VEGF overexpression has been shown to be associated with relapse following surgery and poor prognosis in NSCLC [Yuan *et al.* 2001; Fontanini *et al.* 1997]. Based on its central role in tumor angiogenesis, drugs targeting VEGF are being developed for the treatment of many cancers.

Bevacizumab is a humanized monoclonal antibody to VEGF that effectively prevents it from binding to its receptors. Bevacizumab was evaluated in combination with carboplatin/paclitaxel in advanced NSCLC patients in a phase II trial [Johnson *et al.* 2004]. Concerns were raised regarding the incidence of pulmonary hemorrhage in patients with squamous histology, so these patients were excluded from the Phase III trial that followed. Exclusions also included patients with brain metastases, history of hemoptysis or recent thrombotic episodes, and those on anti-coagulation. Eastern Cooperative Oncology Group trial, E4599 randomized advanced NSCLC patients to receive carboplatin/paclitaxel $\pm$ bevacizumab [Sandler *et al.* 2006]. The addition of bevacizumab improved median overall survival (12.3 *versus* 10.3 months) and progression-free survival (6.2 *versus* 4.5 months). There was greater toxicity in the bevacizumab arm, specifically hemorrhage (4.4 *versus* 0.7%), neutropenia (25.5 *versus* 16.8%), and thrombocytopenia (1.6 *versus* 0.2%). In another phase III study, the AVAiL trial, the addition of bevacizumab to cisplatin/gemcitabine improved the primary endpoint of progression free survival but did not improve overall survival [Reck *et al.* 2009]. Based on the data in advanced NSCLC, a phase III adjuvant trial, E1505, is currently underway randomizing patients with resected NSCLC to receive chemotherapy $\pm$ bevacizumab. The chemotherapy is restricted to cisplatin-based regimens including cisplatin/pemetrexed for nonsquamous histologies. Patients with squamous cell histology are allowed in this trial since the primary tumor is resected prior to chemotherapy thus eliminating a potential source for tumor-related hemorrhage. The proposed objective is to detect a 25% improvement in median survival 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. There may be concerns regarding postoperative healing and toxicities such as hemorrhage, neutropenic fever, hypertension, and thrombotic episodes. In addition, the long-term toxicities of a year of bevacizumab are unknown and will be defined by this trial. These toxicities may be viewed differently by both treating physicians and patients in the adjuvant setting as compared to the advanced disease situation. New agents targeting the various VEGF receptors are in development and hopefully they will be less toxic alternatives if proven to be efficacious in lung cancer treatment.

Epidermal growth factor receptor (EGFR), a receptor tyrosine kinase, is expressed in many NSCLCs and is involved in many aspects of cancer formation and progression [Arteaga, 2003]. Inhibitors of EGFR tyrosine kinase (EGFR-TKIs), erlotinib and gefitinib, have been evaluated in the management of NSCLC [Perez-Soler *et al.* 2004; Fukuoka *et al.* 2003; Kris *et al.* 2003]. 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 [Shepherd *et al.* 2005]. Data from clinical trials of EGFR-TKIs suggest that patients with certain clinical characteristics such as adenocarcinoma histology, female gender, Asian ethnicity, and nonsmoking status had a higher likelihood of clinical benefit [Kris *et al.* 2004; Miller *et al.* 2004]. Retrospective analyses of tumors of 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 [Lynch *et al.* 2004; Paez *et al.* 2004]. Subsequently, other investigators have suggested that increased EGFR gene copy number and EGFR expression may be more predictive of benefit from EGFR-TKIs [Cappuzzo *et al.* 2005]. The relative importance of each factor in predicting benefit from these agents remains to be determined in prospective clinical trials.

Based on the observation that EGFR expression by immunohistochemistry and increased EGFR gene copy number may predict for increased survival with EGFR-TKIs in relapsed NSCLC patients, a clinical trial, called the RADIANT trial, evaluating the role of erlotinib in patients with EGFR-positive (IHC and/or FISH) tumors is currently ongoing. Patients are allowed to receive adjuvant chemotherapy and then randomized to erlotinib or placebo. Gefitinib has been studied in earlier stage NSCLC. In a NCIC trial, JBR.19, patients with resected NSCLC were allowed to receive adjuvant chemotherapy and then went on to receive gefitinib or placebo. The trial was terminated after the release of negative results from the ISEL trial, which showed no survival advantage for gefitinib in advanced-stage NSCLC [Thatcher *et al.* 2005]. The results of the NCIC study have not yet been released. The RADIANT trial and other such prospective studies will potentially define the role of EGFR-TKIs in the adjuvant therapy

of NSCLC and until these results are available these agents should not be used in the adjuvant setting in unselected patients.

MAGE-A3 (melanoma antigen family A, 3) is expressed in many human cancers including lung cancer [Sienel *et al.* 2004]. The MAGRIT trial is an ongoing Phase III study evaluating GSK1572932A, an antigen-specific (MAGE-A3) cancer immune therapeutic, as adjuvant therapy in patients with resected NSCLC. The tumors must express MAGE-A3 as an eligibility criteria for trial entry.

Tumor factors predictive of relapse

Decisions regarding the administration of adjuvant treatment in NSCLC patients are based primarily on the stage of the disease. The biologic factors that regulate metastases and relapse have not been further characterized. Systematic genomic and proteomic evaluation of lung cancers may yield information regarding risk of relapse and thus lead to better prognostic assessments. Recently Potti and colleagues reported the results of assessing gene expression patterns in stratifying risk in NSCLC patients [Potti *et al.* 2006]. 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 identifying 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 protein expression. Assessment of the proteome profile of the tumor could be a tool for both diagnostic and prognostic purposes. Recently Kikuchi and colleagues presented the results of the proteomic analysis of lung cancer tumors [Kikuchi *et al.* 2006]. The protein profiles of 175 lung cancers and 62 histologically normal lung tissues were analyzed. Based on these profiles, a prediction model was created 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 and potentially could 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 the patients most likely to profit from specific chemotherapy drugs.

Cisplatin binds to DNA and forms platinum-DNA adducts thus inhibiting DNA replication. The nucleotide excision repair complex is a DNA repair pathway that attends to DNA damage from various factors and plays an important role in chemotherapy resistance. The ERCC 1 (excision repair cross complementation group 1) 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 [Reed, 2005]. 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 and colleagues reported results of the IALT Bio study, a retrospective assessment of ERCC1 expression by immunohistochemistry in tumors of patients enrolled on the IALT trial [Olaussen *et al.* 2006]. ERCC1 protein expression was evaluated in paraffin-embedded tumor blocks of 761 patients. Tumors were assigned a semi-quantitative H score based on the percentage of positive tumor nuclei and the staining intensity for ERCC1 and then classified as positive or negative. Adjuvant cisplatin-based therapy significantly prolonged survival in patients with ERCC1 negative tumors (HR 0.65, $p=0.002$) but not in ERCC1 positive tumors (HR 1.14, $p=0.40$). These data suggest that ERCC1 expression could serve as an independent marker predicting benefit or lack thereof from platin-based therapy. These data need to be confirmed in a prospective trial before this marker can be utilized in clinical practice.

Other markers such as BRCA1, RRM1, XRCC3 polymorphisms, are being assessed for sensitivity to different chemotherapy drugs [Rosell *et al.* 2006; Bepler *et al.* 2005]. RRM1 (ribonucleotide reductase M1) has been associated with resistance to gemcitabine. SWOG 0720 is a feasibility trial in stage I (T > 2 cm) resected NSCLC. Patients with tumors that have low expression of ERCC1 and RRM1 will receive adjuvant chemotherapy with cisplatin/gemcitabine while those with high expression will not receive chemotherapy.

Assessment of all these markers may actually allow one to customize chemotherapy and improve patient survival by maximizing the efficacy of the adjuvant treatment.

Conclusion

The recent clinical trials assessing chemotherapy after surgical resection of lung cancer have changed clinical practice. There is no doubt that NSCLC patients are living longer as a result of receiving adjuvant treatment. However, it is also clear that patients still die of their disease despite chemotherapy and that some patients may not even require additional treatment after surgery. The lung cancer population is very heterogeneous, thus understanding the molecular makeup of individual tumors is vital in order to determine which patients are at risk for disease relapse and to better select effective adjuvant treatments. It is important to support innovative clinical trials in order to advance our understanding of lung cancer and hopefully achieve a cure for the patients afflicted with this disease.

Conflict of interest statement

Antoinette J. Wozniak, MD: Speakers' Bureau – Genentech, Lilly; Advisory Board – Genentech, Lilly, AstraZeneca, Bristol Myers Squibb; Research Funding – Lilly.

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References

Ardizzoni, A., Boni, L., Tiseo, M., Fossella, F.V., Schiller, J.H., Paesmans, M. *et al.* (2007) Cisplatin-versus carboplatin-based chemotherapy in first-line treatment of advanced non-small-cell lung cancer: An individual patient data meta-analysis. *J Natl Cancer Inst* 99: 847–857.

Arteaga, C.L. (2003) ErbB-targeted therapeutic approaches in human cancer. *Exp Cell Res* 284: 122–130.

Bepler, G., Zheng, Z., Gautam, A., Sharma, S., Cantor, A., Sharma, A. *et al.* (2005) Ribonucleotide reductase M1 gene promoter activity, polymorphisms, population frequencies, and clinical relevance. *Lung Cancer* 47: 183–192.

Burdett, S., Stewart, L.A. and Rydzewska, L. (2006) A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. *J Thorac Oncol* 1(7): 611–621.

Cappuzzo, F., Hirsch, F., Rossi, E., Bartolini, S., Ceresoli, G.L., Bemis, L. *et al.* (2005) Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. *J Natl Cancer Inst* 97: 643–655.

Depierre, A., Milleron, B., Moro-Sibilot, D., Chevret, S., Quiox, E., LeBeau, B. *et al.* (2002) Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIA NSCLC. *J Clin Oncol* 20: 247–253.

Douillard, J.-Y., Rosell, R., De Lena, M., Carpagnano, F., Ramlaui, R., Gonzales-Larriba, J.L. *et al.* (2006) Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB–IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. *Lancet Oncol* 7: 719–727.

Feld, R., Rubinstein, L., Thomas, P.A. and the Lung Cancer Study Group. (1993) Adjuvant chemotherapy with cyclophosphamide, doxorubicin, and cisplatin in patients with completely resected stage I NSCLC. *J Natl Cancer Inst* 85: 299–306.

Ferrara, N. (2002) Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. *Semin Oncol* 29(suppl 16): 10–14.

Fontanini, G., Lucchi, M., Vignati, S., Mussi, A., Ciardello, R., De Laurentis, M. *et al.* (1997) Angiogenesis as a prognostic indicator of survival in non-small-cell lung carcinoma: a prospective study. *J Natl Cancer Inst* 89: 881–886.

Fukuoka, M., Yano, S., Giaccone, G., Tamura, T., Nakagawa, K., Douillard, J.-Y. *et al.* (2003) Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). *J Clin Oncol* 21: 2237–2246.

Hamada, C., Tanaka, F., Ohta, M., Fijimura, S., Kodama, K., Maizumi, I. *et al.* (2005) Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. *J Clin Oncol* 23: 4999–5006.

Hicklin, D.J. and Ellis, L.M. (2005) Role of the vascular endothelial growth factor pathway in

- tumor growth and angiogenesis. *J Clin Oncol* 23: 1011–1027.
- Holmes, E.C. and Gail, M. for the Lung Cancer Study Group. (1986) Surgical adjuvant therapy for stage II and stage III adenocarcinoma and large-cell undifferentiated carcinoma. *J Clin Oncol* 4: 710–715.
- Johnson, D.H., Fehrenbacher, L., Novotny, W.F., Herbst, R.S., Nemunaitis, J.J., Jablons, D.M. *et al.* (2004) Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 22: 2184–2191.
- Keller, S.M., Adak, S., Wagner, H., Herskovic, A., Komaki, R., Brooks, B.J. *et al.* (2000) A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or III non-small cell lung cancer. *N Engl J Med* 343: 1217–1222.
- Kikuchi, T., Massion, P.P., Shyr, Y., Altorki, A.J., Dannenberg, M., Li, A. *et al.* (2006) Proteomic analysis of lung cancer tumors. *J Clin Oncol* 24(18S): 7028a.
- Kris, M.G., Natale, R.B., Herbst, R.S., Lynch, jr T.J., Prager, D., Belani, C.P. *et al.* (2003) Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. *JAMA* 290: 2149–2158.
- Kris, M.G., Sandler, A., Miller, V., Cespon, M., Zakowski, M., Pizzo, B. *et al.* (2004) Cigarette smoking history predicts sensitivity to erlotinib: Results of a phase II trial in patients with bronchioloalveolar carcinoma. *J Clin Oncol* 22(14S): 7062a.
- Lad, T., Rubinstein, L., Sadeghi, A. for the Lung Cancer Study Group. (1988) The benefit of adjuvant treatment for resected locally advanced non-small cell lung cancer. *J Clin Oncol* 6: 9–17.
- Le Chevalier, T., Dunant, A., Arrigada, R., Bergman, B., Chabowski, M., LePechoux, C. *et al.* (2008) Long-term results of the International Adjuvant Lung Cancer Trial (IALT) evaluating adjuvant cisplatin-based chemotherapy in resected non-small cell cancer (NSCLC). *J Clin Oncol* 26(15S): 7507a.
- Lynch, T.J., Bell, D.W., Sordella, R., Gurubhagavatulu, S., Okimoto, R.A., Brannigan, B.W. *et al.* (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 350: 2129–2139.
- Machtay, M., Lee, J.H., Sjrager, J.B., Kaiser, L.R. and Glatstein, E. (2001) Risk of death from intercurrent disease is not excessively increased by modern post-operative radiotherapy for high risk resected non-small cell lung carcinoma. *J Clin Oncol* 19: 3912–3917.
- Miller, V.A., Kris, M.G., Shah, N., Patel, J., Azzoli, G., Gomez, J. *et al.* (2004) Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced non-small-cell lung cancer. *J Clin Oncol* 22: 1103–1109.
- Mountain, C.F. (1997) Revisions in the international system for staging lung cancer. *Chest* 111: 1710–1717.
- Non-small Cell Lung Cancer Collaborative Group. (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *Br Med J* 311: 899–909.
- Olaussen, K.A., Dunant, A., Fouret, P., Brambilla, E., Andre, F., Haddad, V. *et al.* (2006) DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. *N Engl J Med* 355: 983–991.
- Paez, J.G., Janne, P.A., Lee, J.C., Tracy, S., Greulich, H., Gabriel, S. *et al.* (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 304: 1497–1500.
- Perez-Soler, R., Chachoua, A., Hammond, L.A., Rowinsky, E.K., Huberman, M., Karp, D. *et al.* (2004) Determinants of tumor response and survival with erlotinib in patients with non-small-cell lung cancer. *J Clin Oncol* 22: 3234–3247.
- Pignon, J.-P., Tribodet, H., Scagliotti, G.V., Douillard, J.-Y., Shepherd, F.A., Stephens, R.J. *et al.* (2008) Lung Adjuvant Cisplatin Evaluation: a pooled analysis by the LACE Collaborative group. *J Clin Oncol* 26: 3552–3559.
- Pisters, K., Vallieres, E., Bunn, P., Crowley, J., Ginsberg, J., Ellis, P. *et al.* (2005) S9900: A phase III trial of surgery alone or surgery plus preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): preliminary results. *J Clin Oncol* 23(16S): 7012a.
- Pisters, K.M., Ginsberg, R.J., Giroux, D.J., Putnam, J.B., Kris, M.G., Johnson, D.H. *et al.* (2000) Induction chemotherapy before surgery for early-stage lung cancer: a novel approach. Bimodality Lung Oncology Team. *J Thorac Cardiovasc Surg* 119: 429–439.
- PORT Meta-analysis Trialists' Group. (1998) Postoperative radiotherapy in non-small-cell lung cancer: Systemic review and meta-analysis of individual patient data from nine randomized controlled trials. *Lancet* 352: 257–263.
- Potti, A., Mukherjee, S., Petersen, R., Dressman, H.K., Bild, A., Koontz, J. *et al.* (2006) A genomic strategy to refine prognosis in early stage Non-Small Cell Lung Cancer. *N Engl J Med* 355: 570–580.
- Reck, M., von Pawel, J., Zatloukal, P., Ramlau, R., Gorbounova, V., Hirsh, V. *et al.* (2009) Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for non-small-cell lung cancer. *J Clin Oncol* 27: 1227–1234.

- Reed, E. (2005) ERCC1 and clinical resistance to platinum-based therapy. *Clin Cancer Res* 11: 6100–6102.
- Rosell, R., Cecere, F., Santarpia, M., Reguart, N. and Taron, M. (2006) Predicting the outcome of chemotherapy for lung cancer. *Curr Opin Pharmacol* 6: 323–331.
- Rosell, R., Gomez-Codina, J., Camps, C., Sanchez, J., Maestre, J., Padilla, J. *et al.* (1999) Pre-resectional chemotherapy in stage IIIA non-small cell lung cancer: A 7-year assessment of a randomized controlled trial. *Lung Cancer* 26: 7–14.
- Roth, J.A., Atkinson, E.N., Fossella, F., Komaki, R., Bernadette Ryan, M., Putnam, J.B. *et al.* (1998) Long term follow-up of patients enrolled in a randomized trial comparing preoperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell lung cancer. *Lung Cancer* 21: 1–6.
- Sandler, A., Gray, R., Perry, M.C., Brahmer, J., Schiller, J.H., Dowlati, A. *et al.* (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med* 355: 2542–2550.
- Sawyer, T.E., Bonner, J.A., Gould, P.M., Foote, R.L., Deschamps, C., Trastek, V.F. *et al.* (1997) Effectiveness of postoperative irradiation in stage IIIA non-small cell lung cancer according to regression tree analyses of recurrence risks. *Ann Thorac Surg* 64: 1402–1408.
- Scagliotti, G.V., Fossati, R., Torri, V., Crino, L., Giaccone, G., Silvano, G. *et al.* (2003) Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIA non-small cell lung cancer. *J Natl Cancer Inst* 95: 1453–1461.
- Scagliotti, G.V., Parikh, P., von Pawel, J., Biesma, B., Vansteenkiste, J., Manegold, C. *et al.* (2008a) Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced stage non-small cell lung cancer. *J Clin Oncol* 26: 3573–3581.
- Scagliotti, G.V., Pastorino, U., Vansteenkiste, J.F., Spaggiari, L., Facciolo, F., Orlowski, T. *et al.* (2008b) A phase III randomized study of surgery alone or surgery plus preoperative gemcitabine-cisplatin in early-stage non-small cell lung cancer (NSCLC): Follow-up data of Ch.E.S.T. *J Clin Oncol* 26(15S): 7508a.
- Schiller, J.H., Adak, S., Feins, R.H., Keller, S.M., Fry, W.A., Livingston, R.B. *et al.* (2001) Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small-cell lung cancer on E4592: A laboratory ancillary study on an Eastern Cooperative Oncology Group prospective randomized trial of postoperative adjuvant therapy. *J Clin Oncol* 19: 448–457.
- Shepherd, F.A., Rodrigues Pereira, J., Ciuleanu, T., Tan, E.H., Hirsh, V., Thongprasert, S. *et al.* (2005) Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 353: 123–132.
- Sienel, W., Varwerk, C., Linder, A., Kaiser, D., Teschner, M., Delire, M. *et al.* (2004) Melanoma associated antigen (MAGE)-A3 expression in stages I and II non-small cell lung cancer: results of a multi-center study. *Eur J Cardiothorac Surg* 25: 131–134.
- Strauss, G.M., Herndon, J., Maddaus, M.A., Johnstone, D.W., Johnson, E.A., Watson, D.M. *et al.* (2004) Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): report of Cancer and Leukemia Group B (CALGB) Protocol 9633. *J Clin Oncol* 22(14S): 7019a.
- Strauss, G.M., Herndon, J.E., Maddaus, M.A., Johnstone, D.W., Johnson, E.A., Harpole, D.H. *et al.* (2008) Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group study groups. *J Clin Oncol* 26: 5043–5051.
- Thatche, R.N., Chang, A., Parikh, P., Rodrigues Pereira, J., Ciuleanu, T., von Pawel, J. *et al.* (2005) Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 366: 1527–1537.
- The International Adjuvant Lung Cancer Trial Collaborative Group. (2004) Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 350: 351–360.
- The Lung Cancer Study Group. (1986) Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. *N Engl J Med* 315: 1377–1381.
- Waller, D., Peake, M.D., Stephens, R.J., Gower, N.H., Milroy, R., Parmar, M.K. *et al.* (2004) Chemotherapy for patients with non-small cell lung cancer. The surgical setting of the Big Lung Trial. *Eur J Cardio Thorac Surg* 26: 173–182.
- Winton, T., Livingston, R., Johnson, D., Rigas, J., Johnston, M., Butts, C. *et al.* (2005) Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 352: 2589–2597.
- Yuan, A., Yu, C.J., Kuo, S.H., Chen, W.J., Lin, F.Y., Luh, K.T. *et al.* (2001) Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non-small-cell lung cancer. *J Clin Oncol* 19: 432–441.