Adjuvant cisplatin-based chemotherapy for resected NSCLC: one size fits all?

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The standard of care for resected stage II – IIIA non-small-cell lung cancer includes adjuvant chemotherapy based on the results of randomized trials using cisplatin regimens. A recent meta-analysis (Lung Adjuvant Cisplatin Evaluation) showed no survival benefit for this modality in stage IB disease. Therefore, the role for stage IB disease remains controversial. The Lung Adjuvant Cisplatin Evaluation meta-analysis, which is based on pooled data of five randomized trials, has shown a 5.3% absolute survival benefit at 5 years. However, long-term results of the International Adjuvant Lung Cancer Trial evaluating adjuvant cisplatin-based chemotherapy in resected non-small-cell lung cancer indicated a possible late adjuvant chemotherapy-related over-mortality. Tumor stage currently is the benchmark standard use for identifying patients who would benefit from adjuvant treatment. In the knowledge of late adjuvant chemotherapy-related over-mortality it is therefore critical to identify subsets of patients who would or would never benefit from adjuvant cisplatin. This review will discuss the extent to which individualized adjuvant treatment can be provided. *Anti-Cancer Drugs* **21:799–804**
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Introduction

Lung cancer – predominantly non-small-cell lung cancer (NSCLC) – is the most common cause of death from cancer worldwide [1]. Even in resectable early-stage NSCLC the relapse rate within 5 years after potentially curative resection ranges from only 30 to 60% [2]. Recurrences leading to death occur mainly in extrathoracic sites, which explain the urgent need for effective adjuvant systemic treatment.

Large randomized trials (Adjuvant Lung Project Italy; International Adjuvant Lung Cancer Trial, IALT; National Cancer Institute of Canada JBR.10 trial, JBR.10; Adjuvant Navelbine International Trialist Association; Big Lung Trial) and a meta-analysis including the data of those five, cisplatin-based studies (Lung Adjuvant Cisplatin Evaluation) found a 5.3% absolute survival advantage at 5 years [hazards ratio (HR), 0.89; 95% confidence interval (CI), 0.82–0.96, P 0.004] for adjuvant cisplatin therapy overall [3]. The subset of patients with stage IB disease trended towards benefit, but failed to reach statistical significance [4]. Moreover, a detriment for chemotherapy was suggested in stage IA patients [3]. An unplanned subset analysis within patients on CALGB 9633 with tumors of at least 4 cm did have an overall survival advantage, with an HR of 0.66 ($P = 0.04$) [4]. At this time, the role of adjuvant cisplatin-based chemotherapy is clear for resected stage II and IIIA, but remains controversial for patients with stage IB and is contraindicated for those with resected stage IA disease [5]. However, these data are hampered by long-term results of the IALT evaluating adjuvant cisplatin-based chemotherapy in resected NSCLC indicated a possible late adjuvant chemotherapy-related over-mortality [6]. Nevertheless, the indications of adjuvant chemotherapy in NSCLC might extend from stages I to III, which means that most patients should be recommended to receive adjuvant cisplatin-based chemotherapy after surgery.

It is a sad scenario when many patients are attributed to receive a relatively toxic regimen with marginal or sometimes detrimental results. Therefore, it is critical to identify those subsets of patients who would have a real benefit from an adjuvant treatment.

This paper will review the molecular markers that have immediate impact on treatment decisions in routine practice, and which merit further study in the next generation of adjuvant chemotherapy trials. Moreover, it will discuss the extent to which individualized adjuvant treatment can be provided.

Methods

The MEDLINE database was searched from 1990 through to 2010 using variations on the search terms: 'NSCLC, resected NSCLC, early-stage NSCLC, adjuvant treatment, adjuvant chemotherapy, cisplatin, biomarkers'. Moreover, the American Society of Clinical Oncology Annual Meeting proceedings were searched from 2000 to 2010 for reports of new or ongoing trials.

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A search was also conducted for published practice guidelines, meta-analyses, and systematic reviews.

Relevant articles and abstracts were selected, and the reference lists from these sources were searched for additional trials.

Articles were selected for inclusion in this review of the evidence if they were fully published reports or published abstracts of clinical trials or meta-analyses of clinical trials. Trials published in a language other than English or German were excluded because of limited translation resources.

Benchmark standard use for adjuvant chemotherapy in non-small-cell lung cancer

Tumor stage

Tumor stage currently is the benchmark standard use for identifying patients who would benefit from adjuvant treatment. The role of adjuvant cisplatin-based chemotherapy is clear for resected stage II and IIIA. Moreover, adjuvant cisplatin is clearly contraindicated for patients with resected stage IA disease but it still remains controversial for patients with stage IB disease. Data from the CALGB 9633 trial indicated that the subset of patients with tumors larger than at least 4 cm in size may be more likely to benefit, but this hypothesis needs further validation [3–9].

In summary, stage is the most important factor to consider when prescribing adjuvant chemotherapy. The higher the stage the worse the prognosis and the more likely adjuvant chemotherapy may be beneficial [3–11].

Age, Eastern Cooperative Oncology Group performance status, renal function

The overall survival for patients greater than 75 years compared with those aged 66–74 years was worse with adjuvant cisplatin-based chemotherapy [12]. Patients over the age of 65 years with a good performance status (PS) benefit, but those over 75 years of age require further study [5].

Moreover, patients who were attributed to receive adjuvant chemotherapy should have an Eastern Cooperative Oncology Group PS of greater than 2 [3,10,12].

The trend towards superiority of cisplatin over carboplatin matters in the adjuvant setting with the goal of cure [13]. Cisplatin-based adjuvant chemotherapy should remain the standard, with carboplatin as a substitute, only in patients with clear contraindications to cisplatin (e.g. impaired renal function) [5,13].

Histology

Recent studies of pemetrexed have identified a predictive role for NSCLC histology [14–16]. The consistency of these results across studies confirms the predictive effect of histology for pemetrexed and the survival advantage for pemetrexed in patients with nonsquamous histology. Restrictively, these data have been collected in studies for advanced and metastatic NSCLC. Further analysis of the relationship between the chemotherapy regimen and thymidilate synthase (TS) will be done in a prospective manner (ITACA trial) [14].

Currently, there are no data from a randomized trial, which indicated that histology alone serves as a valid criterion for identifying patients who would benefit from adjuvant cisplatin for resected NSCLC.

Biomarkers and molecular markers in non-small-cell lung cancer

Excision repair cross-complementation group 1

Cisplatin–DNA adducts are repaired by nucleotide excision repair. Excision repair cross-complementation group 1 (ERCC1) is 1 of 16 genes that encode the proteins of the nucleotide excision repair complex [17]. In excising DNA damage, ERCC1 forms a heterodimer that performs a 5′ excision in the DNA strand, relative to DNA damage; after all, other excision substeps have been completed.

Several groups have investigated the influence of ERCC1 on resistance to chemotherapy. These data suggest that ERCC1 is a good marker for resistance to cis-, carbo- and oxaliplatin [18,19].

The IALT Bio Study was the first large clinical study in which ERCC1 expression was assessed retrospectively [20]. The patients had been enrolled in the IALT, thereby allowing a comparison of the effect of adjuvant cisplatin-based chemotherapy on survival, according to ERCC1 expression. ERCC1 expression was determined by immunohistochemical (IHC) analysis in operative specimens of NSCLC.

ERCC1 expression was evaluated by IHC in 761 tumor samples. Among these analyzed tumors, ERCC1 was expressed in 335 (44%) tumors. A benefit from cisplatin-based adjuvant chemotherapy was associated with the absence of ERCC1 (test for interaction, $P = 0.009$). Cisplatin-based adjuvant chemotherapy, as compared with observation, significantly prolonged survival among patients with ERCC1-negative tumors (HR, 0.65; 95% CI, 0.50–0.86; $P = 0.002$) but not in ERCC1-positive cases (HR, 1.14; 95% CI, 0.84–1.55; $P = 0.40$). Among patients who did not receive adjuvant chemotherapy, those with ERCC1-positive tumors survived longer than ERCC1-negative cases (HR, 0.66; 95% CI, 0.49–0.90; $P = 0.009$). The investigators concluded that solely patients with resected ERCC1-negative NSCLC appear to benefit from adjuvant cisplatin-based chemotherapy.

Thymidylate synthase

TS is the main target of pemetrexed, which acts as an antifolate that inhibits multiple enzymes involved in purine and pyrimidine synthesis. Preclinical data indicate that overexpression of TS correlates with lower sensitivity

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to pemetrexed. Expression of TS was significantly higher in patients with squamous cell carcinoma compared with those with adenocarcinomas. This might be part of the explanation for the higher response of adenocarcinoma to pemetrexed. There is a clinically relevant relationship between the histological subtype of NSCLC and the sensitivity to pemetrexed, restrictively these data have been reported solely in the metastatic setting [14–16].

The noninferiority, phase III, randomized study of Scagliotti *et al.* compared the overall survival between treatment arms in 1.725 chemotherapy-naive patients with stage IIIB or IV NSCLC and an Eastern Cooperative Oncology Group PS of 0 to 1. Patients were randomly assigned to received cisplatin (75 mg/m^2) on day 1 and gemcitabine (1.250 mg/m^2) on days 1 and 8 ($n = 863$) or cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) on day 1 ($n = 862$) every 3 weeks for up to six cycles. Overall survival for cisplatin and pemetrexed was noninferior to cisplatin or gemcitabine (median survival, 10.3 vs. 10.3 months, respectively; HR = 0.94; 95% CI, 0.84–1.05). Analyzing histological subgroups, overall survival was statistically superior for cisplatin and pemetrexed versus cisplatin and gemcitabine in patients with adenocarcinoma ($n = 847$; 12.6 vs. 10.9 months, respectively) and large-cell carcinoma histology ($n = 153$; 10.4 vs. 6.7 months, respectively). Patients with squamous cell histology experienced a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed ($n = 473$; 10.8 vs. 9.4 months, respectively) [15].

The reported, prospective phase III study has shown survival differences based on histological type. But it is critical to discuss that these data have been collected in studies for advanced/metastatic NSCLC. Currently, there are no data from a randomized trial in early-stage NSCLC allowing an individually tailored adjuvant regimen by histology alone. Such data will be available in the near future from a trial that prospectively analyzes the relationship between the chemotherapy regimen and TS (ITACA trial) [14].

Ribonucleotide reductase M1

The ribonucleotide reductase M1 (RRM1) gene encodes the regulatory subunit of ribonucleotide reductase, the molecular target of gemcitabine. The overexpression of RRM1 mRNA in tumor tissues is reported to be associated with gemcitabine resistance.

Reynolds *et al.* [21] reported on a randomized phase III study that investigated the relationship between tumoral RRM1 protein expression level and the response to gemcitabine. They evaluated the efficacy of single-agent gemcitabine vs gemcitabine/carboplatin in 170 patients with advanced NSCLC and a PS of 2 and assessed whether tumoral RRM1 and ERCC1 protein levels are predictive of response to therapy. RRM1 and ERCC1 protein expression were determined by an automated quantitative immunofluorescence-based technology. Overall median survival was 5.1 months for gemcitabine and 6.7 months for gemcitabine/carboplatin ($P = 0.24$). RRM1 and ERCC1 values were significantly and inversely correlated with disease response ($r = -0.41$; $P = 0.001$ for RRM1; $r = -0.39$; $P = 0.003$ for ERCC1; i.e. response was better for patients with low levels of expression). A model for response prediction that included RRM1, ERCC1, and treatment arm, was highly predictive of the treatment response observed ($P = 0.0005$). There was no statistically significant association between survival and RRM1 or ERCC1 expression level [21].

Dong *et al.* investigated whether RRM1 expression in peripheral blood mononuclear cells (PBMCs) or SNPs were associated with clinical outcome after gemcitabine-based chemotherapy in advanced NSCLC patients. PBMC samples were obtained from 62 stage IIIB and IV patients treated with gemcitabine-based chemotherapy. RRM1 mRNA expression levels were assessed by real-time PCR. Three RRM1 SNPs, –37C–>A, 2455A–>G and 2464G–>A were assessed by direct sequencing. RRM1 expression was detectable in 57 PBMC samples, and SNPs were sequenced in 56 samples. The overall response rate to gemcitabine was 18%; there was no significant association between RRM1 mRNA expression and response rate ($P = 0.56$). The median progression-free survival (PFS) was 23.3 weeks in the lower expression group and 26.9 weeks in the higher expression group ($P = 0.669$). For the –37C–>A polymorphism, the median PFS was 30.7 weeks in the C(–)37A group, 24.7 weeks in the A(–)37A group, and 23.3 weeks in the C(–)37C group ($P = 0.043$). No significant difference in PFS was observed for the SNP 2455A–>G or 2464G–>A. The investigators concluded that the RRM1 polymorphism –37C–>A correlated with PFS in NSCLC patients treated with gemcitabine-based chemotherapy whereas no significant correlation was found between PBMC RRM1 mRNA expression and the response to gemcitabine [22].

Kirsten rat sarcoma viral oncogene homolog

RAS is an enzyme that transmits growth signals by binding to and hydrolyzing guanosine triphosphate. RAS is downstream of the growth signal transmitted into a cell by the epidermal growth factor receptor (EGFR). Within RAS mutations, which are detectable in approximately 20% of lung cancers, Kirsten rat sarcoma viral oncogene homolog (KRAS) constitute 90% of all RAS mutations in NSCLC [23]. In the JBR-10 adjuvant trial (adjuvant vinorelbine and cisplatin vs. observation in patients with completely resected stage IB or stage II NSCLC) 482 patients were analyzed for RAS mutations and the mutation status was determined in 450 patients (93%) [2]. Among these patients, 24% harboured a RAS mutation in their tumor whereas 333 patients harboured a wild-type RAS (WT RAS). WT RAS was significantly associated with prolonged survival by adjuvant chemotherapy

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compared with observation-only cases (HR, 0.69; 95% CI, 0.49–0.97; $P = 0.03$). No survival benefit was recognized among patients with a RAS mutant tumor [2]. Although RAS was not an independent predictor of survival in this study, the trial suggests that patients with a RAS mutation should not be offered adjuvant cisplatin/vinorelbine [2].

Human epidermal growth factor receptor

EGFR is a signaling protein attached to the cell membrane that transmits growth signals into the cytoplasm through a tyrosine kinase that is activated when the receptor binds to growth factors. Mutations in the tyrosine kinase domain are strongly associated with sensitivity to erlotinib and gefinitib, which are both inhibitors of the EGFR tyrosine kinase [24–26]. It should be noted that mutations in KRAS and EGFR are mutually exclusive. The presence of a KRAS mutation predicts a lack of benefit from the TKI [27,28]. Therefore, patients whose tumors harbor a KRAS mutation need not be screened for an EGFR mutation. EGFR mutations are almost never found in squamous cell NSCLC but occur in up to 16.6% of adenocarcinomas [29]. Moreover, these mutations are significantly associated with a history of never smoking, whereas KRAS mutations were associated with smoking ($P < 0.005$). Independently of treatment, patients with an EGFR mutant tumor live longer than those with an EGFR WT. Within different types of EGFR mutations, patients whose tumors bear an exon 19 deletion had significantly longer median survival than those with mutations in exon 21 (exon 19 vs. exon 21, 34 vs. 8 months, $P = 0.01$) [27,30].

There are numerous, prospective, single-arm clinical trials that suggest that the TKIs, erlotinib and gefitinib, are highly active for patients bearing an EGFR mutation. The Iressa Pan Asian Study study is a phase III, open-label study, which randomly assigned untreated patients earlier with advanced pulmonary adenocarcinoma and who were nonsmokers or former light smokers to receive gefitinib or carboplatin and paclitaxel. The primary end point was PFS. The 1-year rates of PFS were 24.9% with gefitinib and 6.7% with carboplatin/paclitaxel. The study met its primary objective of showing the noninferiority of gefitinib and also showed its superiority, as compared with carboplatin–paclitaxel, with respect to PFS in the intention-to-treat population (HR, 0.74; 95% CI, 0.65–0.85; $P < 0.001$). In the subgroup of 261 patients harboring an EGFR mutation, PFS was significantly longer among those who received gefitinib than among those who received carboplatin–paclitaxel (HR, 0.48; 95% CI, 0.36–0.64; $P < 0.001$), whereas in those with a WT EGFR ($n = 176$) PFS was significantly longer among those who received carboplatin–paclitaxel [31].

Currently, there are no data from a randomized trial in early-stage NSCLC. The ongoing RADIANT trial is a multicenter, randomized, double-blind, placebo-controlled, phase III study which investigates single-agent erlotinib after complete tumor resection with or without adjuvant chemotherapy in patients with stage IB-IIIA NSCLC who have EGFR-positive tumors (*ClinicalTrials.gov* Identifier NCT00373425).

Class III β-tubulin

Tubulins constitute a family of proteins that make up microtubules in cells. They are vital for cell structure, movement, mitosis, and metabolism. High expression of β-Tub III correlates with poor response rates and inferior survival to treatment consisting of antimicrotubule agents (e.g. vinca-alkaloids, taxanes). In the earlier mentioned JBR-10 adjuvant trial (adjuvant vinorelbine and cisplatin vs. observation in patients with completely resected stage IB or stage II NSCLC) tumor tissues of resected specimens were collected from 265 out of 482 patients and were analyzed for β-Tub III expression by immunohistochemicalIHC staining [2]. High β-Tub III expression was associated with a poor relapse-free survival and a trend toward a shorter survival. However, patients with high β-Tub III expression ($n = 133$) appear to benefit from adjuvant cisplatin-based chemotherapy compared with those in the observation-only group (relapse-free survival: HR, 0.45; 95% CI, 0.27–0.75; $P = 0.002$; shorter survival: HR, 0.64; 95% CI, 0.39–1.04; $P = 0.007$) [2].

Gene expression profiling

Gene expression profiling is useful for classifying tumors and formulating a prognosis for patients with various types of cancer. Nevertheless, the use of microarrays in clinical practice is limited, however, by the large number of genes used in gene profiling, the need for complicated methods, and the lack of both reproducibility and independent validation. The genes selected for profiling in studies of NSCLC have varied considerably, with only a few genes that have been consistently included [32]. This suggests that several different gene expression signatures are capable of predicting outcome. Moreover, none of the studies of NSCLC gene signatures published to date inform choice of chemotherapy. Experiments using lung cancer cell lines with variable sensitivity to different drugs and validation of this approach in patients with metastatic disease, in whom efficacy is immediately apparent, is required before such an approach can be applied in the adjuvant setting [23,32].

Conclusion

Several biomarkers were retrospectively evaluated using samples obtained in large adjuvant chemotherapy trials of NSCLC (Table 1). The current retrospective data are by no means sufficient to support the routine use of molecular markers to guide adjuvant therapy for NSCLC outside a clinical trial. Before their routine practice, validation and standardized laboratory techniques must be established. For example, there are still differing opinions regarding the most efficient and accurate

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method for detecting EGFR mutations. A molecularly tailored adjuvant therapy strategy for resected NSCLC requires prospective trials. Such trials are conducted as, for example, the pilot program at MSKCC. Patients are offered enrollment in clinical trials of adjuvant therapies based on their molecular phenotype, which included determination of ERCC1 expression (by IHC), presence of an EGFR and/or KRAS mutation status (WT vs. mutant) [23].

There are strong retrospective data to suggest that patients with high ERCC1 expression should not be offered cisplatin-based adjuvant chemotherapy. Validation of platinum-free regimens in those patients is sorely needed. An ongoing European phase III study, the ITACA trial will explore the impact of pharmacogenomically driven adjuvant chemotherapy in resected NSCLC (Fig. 1). The control arm consists of standard cisplatin-based (cisplatin/vinorelbine, cisplatin/docetaxel, or cisplatin/gemcitabine) adjuvant chemotherapy selected based on investigator preference. In the test arm, the expression levels of ERCC1 and TS will define the chemotherapy regimen selected. Patients with high ERCC1 and high TS will be treated with a single agent, paclitaxel; high ERCC1 and low TS with a single agent pemetrexed; low ERCC1 and high TS with cisplatin/ gemcitabine; and low ERCC1 and low TS with cisplatin/pemetrexed.

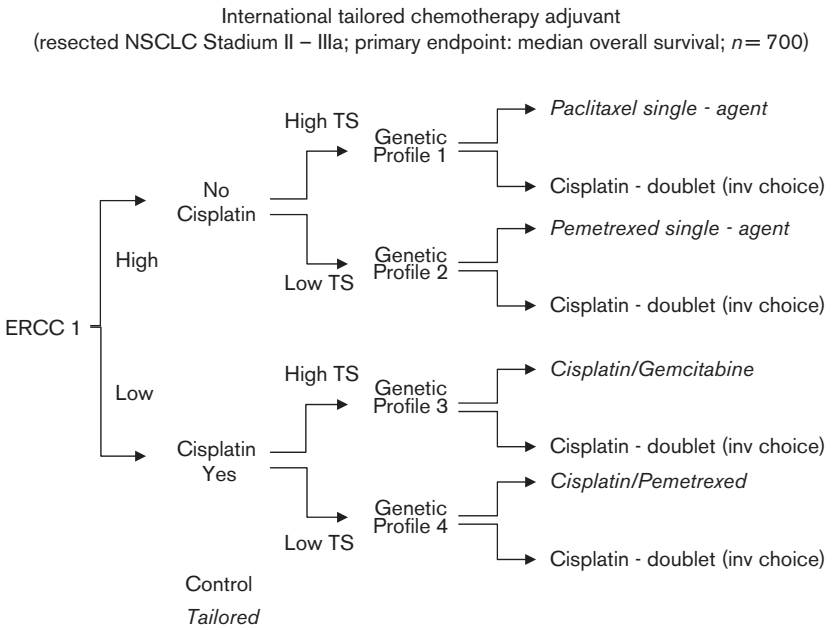
In conclusion, biomarkers seemed to be helpful for the selection of individuals with poor prognoses for adjuvant chemotherapy. In addition, biomarkers that enable selection of the most effective chemotherapeutic agent or regimen to an individual patient are also highly desirable.

Table 1 Biomarkers, prognostic relevance and drug sensitivity

Biomarker	ERCC1		TS		RRM1		βTubIII		KRAS		EGFR	
Expression or Mutation	↑	↓	↑	↓	↑	↓	↑	↓	WT	mut	WT	mut
Prognosis	Good				Good			Poor				Good
Sensitivity to												
CDDP		+							+			
Antimicrotubule agents							+		+			
GEM						+						
PEM			–									
TKI												+

–, decreased drug sensitivity; +, increased drug sensitivity; CDDP, cisplatin; EGFR, epidermal growth factor receptor; ERCC1, excision repair cross-complementation group 1; GEM, gemcitabine; mut, mutant; KRAS, Kirsten rat sarcoma viral oncogene homolog; PEM, pemetrexed; RRM1, ribonucleotide reductase M1; TS, thymidilate synthase; TKI, tyrosin kinase inhibitor; WT, wild-type.

Fig. 1



Study design ITACA trial. ERCC1, excision repair cross-complementation group 1; TS, thymidylate synthase.

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The avoidance of chemotherapy in good prognostic subsets and the consequent relief from toxicity is another attractive effect of such a biomarker-based approach. Finally, the economic impact of such tailored adjuvant cheotherapy strategies could be substantial.

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