Adjuvant chemotherapy in patients with completely resected non-small cell lung cancer

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Abstract: Adjuvant chemotherapy has been established as a standard for patients with completely resected non-small cell lung cancer (NSCLC). Adjuvant chemotherapy increased the 5-year survival rates by 4% to 15% within randomized trials and, based on a meta-analysis of five cisplatin-based trials, by 5.4%. Adjuvant chemotherapy consists of a cisplatin-based doublet, preferentially cisplatin plus vinorelbine. Future improvements in outcome of adjuvant therapy are expected by customized chemotherapy and the integration of targeted therapies or immunotherapy.

Keywords: Adjuvant; chemotherapy; non-small cell lung cancer (NSCLC); resection

Introduction

Approximately 25-30% of patients with non-small cell lung cancer (NSCLC) present with localized disease at the time of diagnosis and undergo surgery with curative intent. Despite complete tumor resection, however, many patients will develop systemic relapses with or without local relapses and will eventually die from their disease. Thus adjuvant chemotherapy was studied as a strategy to increase survival of patients with completely resected NSCLC. A meta-analysis of early trials revealed a statistically non-significant survival gain of 5% at 5 years by adjuvant cisplatin-based chemotherapy (1). These results then led to re-evaluation of adjuvant chemotherapy with modern platinum-based regimens within randomized phase III trials on large patient populations (2-8). Three trials and the meta-analysis of cisplatin-based trials then proved the survival benefit for cisplatin-based chemotherapy (2-5,9). These results then established adjuvant chemotherapy as standard treatment for patients with completely resected NSCLC. The present paper summarizes the pivotal trials, describes the current status of adjuvant chemotherapy, and also outlines future strategies to improve outcome of adjuvant therapy in patients with completely resected NSCLC.

Phase III trials

The meta-analysis of early adjuvant chemotherapy trials suggested a survival benefit for adjuvant chemotherapy and led to re-evaluation of adjuvant cisplatin-based chemotherapy with better chemotherapy regimens and/or better supportive care within large phase III trials in patients with completely resected NSCLC (2-8). The results of these trials are summarized in *Table 1*.

International adjuvant lung cancer trial (IALT)

IALT was the first trial that demonstrated a statistically significant improvement in overall survival by adjuvant cisplatin-based chemotherapy (2). The trial enrolled 1,867 patients and, therefore, was the largest adjuvant chemotherapy trial. The patients had the following baseline characteristics: median age 59; 80% males; WHO performance status 0-1 and 2 in 93% and 7%; 36.5% stage I, 24.2% stage II, 39.3% stage III; 47% squamous cell carcinomas, 40% adenocarcinomas, 13% large cell carcinomas and others; 64% lobectomy, 35% pneumonectomy, <1% segment resection. Patients of the chemotherapy arm received 3-4 cycles of a cisplatin-based doublet. The cumulative dose of cisplatin

Table 1 Adjuvant chemotherapy of completely resected NSCLC

	N	Stage	Chemo	5-year survival (%)		HR (95% CI)	P
				Chemo	Control		
ALPI-EORTC	1,088	I-IIIA	MVP	49.0	48.0	0.96 (0.81-1.13)	NS
IALT	1,867	I-III	Cis/Vinca	44.5	40.4	0.86 (0.76-0.98)	<0.03
JBR.10	482	IB-II	Cis/Vino	69.0	54.0	0.69 (0.52-0.91)	0.04
ANITA	840	IB-IIIA	Cis/Vino	51.2	42.6	0.80 (0.66-0.96)	0.02
CALGB	344	IB	Carbo/Pacl	57.0	59.0	0.80 (0.60-1.07)	0.1
BLT	381	I-III	Cis-based	NR	NR	1.0	NS
LACE meta-analysis	4,584	I-IIIA	Cis-based	48.8	43.5	0.89 (0.82-0.96)	0.004

NR, not reported; NS, not significant; NSCLC, non-small cell lung cancer.

was at least 240 mg/m^2 in 74% of the patients. Cisplatin was combined with either etoposide (56%), vinorelbine (27%), vinblastine (11%) or vindesine (6%).

Adjuvant chemotherapy increased overall survival of the patients. The hazard ratio was 0.86 (95% CI, 0.76-0.98; P<0.03). The 5-year survival rates were 44.5% and 40.4% in the chemotherapy arm and control arm, respectively. Disease-free survival was also improved with a hazard ratio of 0.83 (95% CI, 0.74-0.94). The survival benefit was independent of gender, tumor histology and tumor stage. Chemotherapy-associated mortality was 0.8%. An update of the study after longer-follow-up of the patients confirmed the survival benefit from adjuvant chemotherapy up to 5 years but also indicated that the mortality of patients of the chemotherapy arm may be increased after 5 years (3). The results of IALT were consistent with those of the meta-analysis of early trials and led to the clinical implementation of adjuvant chemotherapy in patients with completely resected NSCLC.

JBR.10 trial

The JBR.10 trial (4) enrolled 482 patients with the following baseline characteristics: median age 61; 65% male; 53% adenocarcinomas; 45% stage IB, 55% stage II. Patients of the chemotherapy arm were planned to receive cisplatin (50 mg/m^2 on days 1 and 8 every 4 weeks for four cycles) plus vinorelbine (25 mg/m^2 weekly for 16 weeks). Fifty-eight percent of the patients received three or more cycles of cisplatin. Seventy-seven percent of patients required at least one dose reduction or omission.

Adjuvant chemotherapy increased overall survival of the patients. The hazard ratio was 0.69 (95% CI, 0.52-0.91). Five-year survival rates were 69% and 54% in the

chemotherapy arm and control arm, respectively. Relapse-free survival was also increased. Side effects of chemotherapy included neutropenia (88% of the patients), febrile neutropenia (7%), fatigue (81%), nausea (80%), anorexia (55%), vomiting (48%), neuropathy (48%) and constipation (47%). Chemotherapy-associated mortality was 0.8%.

Patients who had undergone pneumonectomy were more likely to discontinue therapy due to toxicity (10). Elderly patients did also benefit at acceptable toxicity (11). Adjuvant chemotherapy was also considered to be cost effective (12).

ANITA trial

The ANITA trial (5) enrolled 840 patients with the following baseline characteristics: median age 59, 86% male, 35% stage IB, 30% stage II, 35% stage III; 58% lobectomy, 37% pneumonectomy. Patients of the chemotherapy arm were planned to receive cisplatin 100 mg/m^2 on days 1, 29, 57 and 85 plus vinorelbine 30 mg/m^2 weekly for a maximum of 16 doses. Fifty percent of the patients completed the planned four cycles. The dose intensities were 22 mg/m^2 per week for cisplatin and 18 mg/m^2 per week for vinorelbine.

Adjuvant chemotherapy improved survival of the patients. The hazard ratio was 0.80 (95% CI, 0.66-0.96). Five-year survival rates were 51% and 42.6%, and 7-year survival rates were 45.2% and 36.8% in the chemotherapy arm and control arm, respectively. Side effects of chemotherapy included neutropenia (92% of the patients), febrile neutropenia (9%) and nausea/vomiting (27% grade 3-4). Chemotherapy-associated mortality was 2%. This higher percentage compared to other trials can be explained by the higher drug doses used in the ANITA trial. Therefore, the authors suggested slightly lower drug doses for clinical practice than those of the ANITA trial.

Other adjuvant chemotherapy trials

The ALPI-EORTC failed to demonstrate a survival benefit for adjuvant chemotherapy with cisplatin, mitomycin C and vindesine (6). The toxicity of the in the meantime outdated chemotherapy protocol might have contributed to the failure of the trial. The Big Lung Trial had insufficient statistical power to prove or exclude the benefit of adjuvant chemotherapy (7).

The CALGB study enrolled 344 patients with completely resected stage IB NSCLC (8). Patients of the chemotherapy arm received paclitaxel plus carboplatin. Chemotherapy did not significantly increase overall survival. The hazard ratio was 0.8 (95% CI, 0.6-1.07). The 5-year survival rates were 59% and 57% in the chemotherapy arm and control arm, respectively. A subgroup analysis revealed that patients with tumors larger than 4 cm may derive a survival benefit from adjuvant chemotherapy. Chemotherapy did not result in treatment-related deaths.

A benefit of adjuvant therapy with uracil-tegafur has been reported for Japanese patients with stage IB NSCLC (13).

Meta-analyses

The lung adjuvant cisplatin evaluation (LACE) meta-analysis (9) included a total of 4,584 patients from the following five trials: ALPI-EORTC, IALT, JBR.10, ANITA and the Big Lung Trial. The analysis demonstrated a survival benefit for adjuvant cisplatin-based chemotherapy. The hazard ratio was 0.89 (95% CI, 0.82-0.96; P=0.004). The 5-year survival rate was increased by 5.3%. Disease-free survival was also increased by adjuvant chemotherapy with a hazard ratio of 0.8 (95% CI, 0.78-0.9; P<0.001).

When only patients who had been treated with cisplatin plus vinorelbine were analyzed (LACE-vinorelbine cohort), the hazard ratio was 0.8 (95% CI, 0.70-0.91) and the increase in the 5-year survival rate was 8.9% (14).

Impact on clinical practice

Adjuvant chemotherapy increased survival of patients with completely resected NSCLC in three phase III trials (2-5). Within these trials, adjuvant chemotherapy resulted in an absolute increase in the 5-year survival rates ranging from 4% to 15% and in hazard ratios for death ranging from 0.69 to 0.86 (2-5). Cisplatin plus vinorelbine was the most widely used chemotherapy protocol. All patients of the JBR.10 trial and the ANITA trial and 27% of IALT patients were

treated with this regimen in the chemotherapy arm. The chemotherapy-associated mortality was 1-2%.

The survival benefit was then confirmed by the LACE meta-analysis (9). Based on these phase III trials and the meta-analysis, adjuvant chemotherapy after complete resection of NSCLC stages II and III has been established as standard of care in patients with good performance status, rapid postoperative recovery, adequate organ function and informed consent. Patients should receive four cycles of a cisplatin-based doublet, preferably cisplatin plus vinorelbine. The chemotherapy should start 4-8 weeks after surgery.

Adjuvant chemotherapy can also be considered for selected patients with stage IB (sixth TNM classification) (15). Factors supporting adjuvant chemotherapy in these patients are younger age, good performance status, patient preference, large tumors, visceral pleural invasion and inadequate staging.

Perspectives of adjuvant therapy

Three major strategies are investigated for improving outcome of adjuvant therapy in patients with completely resected NSCLC. The first strategy focuses on characterization of predictive biomarkers and customized chemotherapy. The second strategy assesses the integration of targeted therapies. The third strategy evaluates tumor vaccines.

Predictive biomarkers and customized chemotherapy

Translational research has focussed on the characterization of biomarkers for the selection of patients for adjuvant chemotherapy. Predictive biomarkers for characterizing patients benefiting from adjuvant therapy are of greater interest than prognostic biomarkers. The focus has been on molecular tumor features which are involved in either tumor growth or mechanisms of action of anticancer drugs. In particular, DNA repair enzymes, drug transporters, apoptosis parameters and cell cycle regulators have been studied as potential biomarkers.

The IALT biologic program (IALT-Bio) has attempted to characterize predictive biomarkers from IALT. Many molecular tumor factors have been studied for their potential role as biomarkers. Patients with low ERCC1 expression in their tumors were shown to benefit from adjuvant chemotherapy, whereas those with high ERCC1 expression did not (16). Similarly, patients without p27 expression in their tumors did benefit from adjuvant

chemotherapy (17). In contrast to ERCC1 and p27, multidrug resistance protein expression was without predictive value (18). However, neither ERCC1 nor p27 could be validated as predicted biomarkers in the LACE-Bio project. The lack of validation of ERCC1 as predictive biomarker might be due to changes in the anti-ERCC antibody over time (19).

Translational research of the JBR.10 trial also focussed on the characterization of biomarkers (20-22). High class III beta tubulin expression was associated with shorter relapse-free and overall survival in patients treated with surgery alone but not in patients treated with surgery plus adjuvant chemotherapy (20). The survival benefit of adjuvant chemotherapy was greater in patients with high compared to those with low tubulin expression in their tumors. However, the interaction between tubulin expression and chemotherapy treatment did not reach statistical significance (20). Patients with overexpression of p53 protein in their tumors had shorter survival but greater benefit from adjuvant chemotherapy than patients without overexpression of p53 (21). Lower haemoglobin levels at baseline were associated with a trend for shorter overall survival (22).

Customized chemotherapy based on molecular tumor characteristics is currently evaluated within phase III trials. The Spanish lung cancer group investigates adjuvant chemotherapy customized according to BRCA1 mRNA levels. The ITACA trial studies customized chemotherapy based on ERCC1 and thymidylate synthase levels. Until its clinical usefulness will have been proven in these or other trials, customized chemotherapy will remain experimental.

Integration of targeted therapies

The second strategy to improve outcome of adjuvant chemotherapy studies the integration of targeted therapies. EGFR-directed therapies and angiogenesis inhibitors are of primary interest because of their efficacy in patients with advanced NSCLC.

EGFR-directed TKIs as single agents have shown efficacy in patients previously treated with chemotherapy, in the maintenance setting and in patients with EGFR-activating mutations independent of treatment line (23). A multi-center, randomized, double-blind, placebo-controlled, phase III trial (RADIANT) compared single-agent erlotinib with placebo following complete tumor resection with or without adjuvant chemotherapy in patients with stage IB-IIIA NSCLC who have EGFR-positive tumors based

on FISH and/or immunohistochemistry (24). However, disease-free survival and overall survival were not different between the erlotinib and the placebo arm. Among patients with EGFR mutation-positive NSCLC, disease-free survival was better in the erlotinib arm compared to the placebo arm but this difference might have been caused by imbalances in prognostic factors between the two arms. Similarly, adjuvant therapy with gefitinib failed to improve disease-free survival or overall survival in another trial (25). Trials with adjuvant gefitinib in patients with EGFR mutation-positive tumors are currently ongoing. Cetuximab has shown efficacy in patients with advanced NSCLC, particularly in those with high EGFR levels in their tumors (26,27). Despite these findings, no anti-EGFR monoclonal antibody is currently evaluated in the adjuvant setting.

Bevacizumab added to adjuvant chemotherapy is currently evaluated in the North American Intergroup Adjuvant Chemotherapy Trial ECOG 1505 in patients with early-stage NSCLC. In this trial, patients with stage IB (>4 cm), II or IIIA NSCLC will be randomized to receive adjuvant cisplatin-based chemotherapy either alone or in combination with bevacizumab.

Vaccines

The third strategy to improve outcome of completely resected NSCLC focuses on immunological approaches. MAGE-A3 is an interesting target for such an approach because it can be detected in about 35% of early-stage NSCLC but not in normal cells. Results from adjuvant trials with a MAGE-A3 vaccine have recently been reported (28-30). A randomized, placebo-controlled phase II trial indicated that vaccination with MAGE-A3 vaccine in MAGE-A3 positive patients with stage IB or II NSCLC reduces the relative risk of recurrence by 27% (28). In addition, a gene signature allowed characterizing those patients who will derive a benefit from the vaccine (29). According to a press release (30), however, the phase III trial (MAGRIT) failed to demonstrate an improvement in disease-free survival for the vaccine compared to placebo.

Conclusions

Adjuvant chemotherapy, preferentially with four cycles of cisplatin plus vinorelbine, has been established as a standard for patients with completely resected NSCLC. Clinical trials currently study bevacizumab added to adjuvant chemotherapy, gefitinib in patients with EGFR mutation-

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positive tumors, and customized chemotherapy based on molecular tumor features.

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