

Adjuvant Chemotherapy of Non-Small Cell Lung Cancer

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Approximately 25-30% of patients with non-small cell lung cancer (NSCLC) present with early stage disease and undergo surgery with curative intent. Despite complete tumor resection, many of these patients will develop systemic relapses with or without local relapses and will eventually die from the disease. Systemic relapses occur due to the presence of micro-metastatic disease at the time of surgery. In order to treat these micro-metastases in an early stage, adjuvant chemotherapy following complete tumor resection has been studied. A meta-analysis of early trials indicated a trend towards improved survival for adjuvant platinum-based chemotherapy (1) and led to re-evaluation of adjuvant chemotherapy in clinical trials on large patient populations (2-8). Several of these trials demonstrated that adjuvant chemotherapy improves survival (3-6). The survival benefit was then further confirmed in a meta-analysis that included all five cisplatin-based trials (9). Thus adjuvant chemotherapy has been established for patients with stages II and III. Here we summarize the current status of adjuvant chemotherapy in patients with completely resected NSCLC.

Meta-analysis of early trials

A meta-analysis of early adjuvant chemotherapy trials suggested an increase in the 5-year survival rate of absolute 5% by cisplatin-based chemotherapy but this difference did not reach statistical significance (1). Based on this potential benefit, large randomized trials re-evaluated the impact of adjuvant chemotherapy with platinum-based chemotherapy in patients with completely resected NSCLC (Table) (2-8).

Recent adjuvant chemotherapy trials

ALPI-EORTC study

The ALPI-EORTC study failed to demonstrate a significant survival benefit of adjuvant chemotherapy with mitomycin C, vindesine and cisplatin (2). However, this protocol has been associated with enhanced toxicity and poor patient compliance and, therefore, is not in clinical use anymore.

Table. Adjuvant chemotherapy of completely resected NSCLC

	N	Stage	Chemo	5-year survival (%)		HR (95%CI)	P
				Chemo	Control		
ALPI-EORTC	1088	I-III A	MVP	49	48	0.96 (0.81-1.13)	NS
IALT	1867	I-III	Cis/Vinca	44.5	40.4	0.86 (0.76-0.98)	<0.03
JBR.10	482	IB-II	Cis/Vino	69	54	0.69 (0.52-0.91)	0.04
ANITA	840	IB-III A	Cis/Vino	51.2	42.6	0.80 (0.66-0.96)	0.02
CALGB	344	IB	Carbo/Pacl	57	5	0.80 (0.60-1.07)	0.1
BLT	381					1.0	NS
LACE meta-analysis	4584	I-III A	Cisplatin-based	48.8	43.5	0.89 (0.82-0.96)	0.004

IALT (International Adjuvant Lung Cancer Trial)

IALT was the first trial that demonstrated a statistically significant improvement in overall survival by adjuvant cisplatin-based chemotherapy (3). IALT enrolled 1,867 patients: median age 59 yrs, 80% males, WHO Performance Status 0-1 and 2 in 93% and 7%, respectively; stage I 35.5%, 24.2% stage II, 39.3% III; 47% squamous cell carcinomas, 40% adenocarcinomas, 13% large cell carcinomas and others; 64% lobectomy, 35% pneumonectomy, <1% segment resection. Patients were treated with 3-4 cycles of cisplatin (cumulative dose at least 240 mg/m² in 74% of the patients) plus either etoposide (56%), vinorelbine (27%), vinblastine (11%) or vindesine (6%).

Adjuvant chemotherapy increased overall survival. The hazard ratio was 0.86 (95% CI 0.76-0.98; $p < 0.03$) and the 5-year survival rates were 44.5% versus 40.4%. Disease-free survival was also improved with a hazard ratio of 0.83 (95% CI 0.74-0.94). The observed benefit was independent of gender, tumor histology and tumor stage. Chemotherapy-associated mortality was 0.8%.

The update of the trial was consistent with the initial results (4). The results of IALT were consistent with those of the previously published meta-analysis and led to the increasing clinical use of adjuvant chemotherapy in patients with completely resected NSCLC.

JBR.10 study

The JBR.10 study also demonstrated a survival benefit for adjuvant chemotherapy with cisplatin plus vinorelbine (5). This trial enrolled 482 patients (median age 61 yrs; 65% male) with completely resected NSCLC (53% adenocarcinomas; 45% stage IB, 55% stage II).

Patients were planned to receive cisplatin (50 mg/m² on days 1 and 8 every 4 weeks for 4 cycles) plus vinorelbine (25 mg/m² weekly for 16 weeks). The median number of cycles was three and 58% of the patients received 3 or more cycles of cisplatin. Seventy-seven percent required at least one dose reduction or omission.

Adjuvant chemotherapy increased survival. The hazard ratio was 0.69 (95% CI 0.52-0.91). Median survival times

were 94 months versus 73 months and 5-year survival rates were 69% versus 54%. Relapse-free survival was also increased. Side effects 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 from acceptable toxicity (11). Adjuvant chemotherapy was also considered to be cost effective (12).

ANITA study

The ANITA trial (6) enrolled 840 patients with the following characteristics: median age 59 yrs, 86% male, 35% stage IB, 30% stage II, 35% stage III; 58% lobectomy, 37% pneumonectomy. Chemotherapy consisted of cisplatin 100 mg/m² on days 1, 29, 57 and 85 plus vinorelbine 30 mg/m² weekly for a maximum of 16 doses. Adjuvant chemotherapy improved survival. Five-year survival rates were 51% versus 42.6% and 7-year survival rates were 45.2% versus 36.8%.

Side effects included neutropenia (92% of the patients), febrile neutropenia (9%) and nausea/vomiting (27% grade 3-4). Chemotherapy-associated mortality was 2% and, therefore, slightly higher than the rate in other trials which might be explained by the higher drug doses used in the ANITA trial. Fifty percent of the patients completed the planned four cycles. The dose intensities were 18 mg/m² per week for vinorelbine and 22 mg/m² per week for cisplatin. Therefore, the authors suggested slightly lower doses for clinical practice than the doses used in the ANITA trial.

CALGB study

The CALGB study randomized 344 patients (median age 61 yrs, 64% male) with completely resected stage IB NSCLC to 4 cycles of paclitaxel 200 mg/m² plus carboplatin AUC 6 every 3 weeks or observation only (7). Chemotherapy did not significantly improve overall

survival. The hazard ratio was 0.8 (95% CI 0.6-1.07) and the 5-year survival rates were 59% versus 57%. Patients with tumors larger than 4 cm, however, did not experience a survival benefit. Chemotherapy was well tolerated and did not result in treatment-related deaths. However, the CALGB study suffered from insufficient statistical power and a suboptimal chemotherapy because carboplatin-based protocols were shown to be inferior to cisplatin-based protocols in advanced disease (13).

Other adjuvant chemotherapy trials

The Big Lung Trial failed to demonstrate a survival benefit for adjuvant chemotherapy, which is not unexpected based on its low statistical power (8). A positive benefit of adjuvant uracil-tegafur has been reported for patients with stage IB NSCLC (14).

Lung Adjuvant Cisplatin Evaluation meta-analysis

The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis included a total of 4,584 patients from the five cisplatin-based chemotherapy trials (ALPI-EORTC, IALT, JBR.10, ANITA, Big Lung Trial) (9). The analysis demonstrated a hazard ratio of 0.89 (95% CI 0.82-0.96; $p=0.004$) which translated into a survival benefit of $5.3\% \pm 1.6\%$ at 5 years by adjuvant chemotherapy. Disease-free survival was also prolonged by adjuvant chemotherapy with a hazard ratio of 0.8 (95% CI 0.78-0.9; $p<0.001$).

Impact on clinical practice

Adjuvant chemotherapy improves outcome in patients with completely resected NSCLC as demonstrated in several trials and the LACE meta-analysis. In the positive trials, the 5-year survival rates increased by absolute 4% to 15% and the hazard ratios for death ranged from 0.69 to 0.86 (3-6). Cisplatin plus vinorelbine was the most widely used chemotherapy protocol. It was used in the JBR.10 trial as well as ANITA trial and in 27% of patients in IALT. The chemotherapy-associated mortality was 1-2 %.

Adjuvant chemotherapy after complete resection of NSCLC stages II and III is now considered as standard of

care in patients with good performance status, rapid postoperative recovery, adequate organ function and informed consent. Patients should receive 4 cycles of a cisplatin-based doublet, preferably cisplatin plus vinorelbine. The chemotherapy should start 4-8 weeks after surgery.

Role of adjuvant chemotherapy in stage I NSCLC

Adjuvant chemotherapy can be considered for selected patients with stage I disease (15). Factors supporting adjuvant chemotherapy are younger age, good performance status, patient preference, large tumors, visceral pleural invasion and inadequate staging. Lack of ERCC1 and p27 expression in tumors might also favor the use of adjuvant chemotherapy (16, 17).

Perspectives of adjuvant therapy

Strategies to improve outcome of adjuvant chemotherapy are characterization of predictive biomarkers and integration of targeted therapies as well as vaccines in the overall therapeutic management of patients with completely resected NSCLC.

Biomarkers

Potential biomarkers for the selection of patients for adjuvant chemotherapy are DNA repair enzymes, drug transporters, apoptosis parameters and cell cycle regulators. Patients with an enhanced DNA repair capacity, due to an increased tumoral expression of excision repair cross complementation group-1 (ERCC1) or ribonucleotide reductase subunit M1 (RRM1), benefit less from cisplatin- or gemcitabine-based chemotherapy, respectively.

The International Adjuvant Lung Cancer Trial Biologic Program (IALT-Bio) aims at characterizing predictive biomarkers from patients who were enrolled in IALT. Patients without ERCC1 expression in their tumors did not benefit from adjuvant chemotherapy, whereas those with ERCC1 expression did (16). Similarly, lack of p27 expression predicted benefit from adjuvant chemotherapy

(17). The predictive value could be further enhanced by the combination of both ERCC1 and p27. In contrast, multidrug resistance protein expression was without predictive value (18).

Translational research of the JBR-10 trial indicated that 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 receiving adjuvant chemotherapy (19). 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. Over-expression of p53 protein was associated with shorter survival but predicted a greater benefit from adjuvant chemotherapy (20). Lower haemoglobin levels at baseline were associated with a trend for shorter overall survival (21).

BRCA1 mRNA expression levels might impact on the sensitivity to cisplatin and antimicrotubule drugs. Thus the Spanish Lung Cancer Group investigates adjuvant chemotherapy customized according to BRCA1 mRNA levels in a randomized trial (GECF-SCAT).

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 Tyrosine Kinase Inhibitors 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 (22). An ongoing multi-center, randomized, double-blind, placebo-controlled, phase III trial, compares single-agent erlotinib with placebo following complete tumor resection with or without adjuvant chemotherapy in patients with stage IB-III A NSCLC who have EGFR-positive tumors based on FISH and/or

immunohistochemistry (RADIANT). Cetuximab is another drug that might be studied in combination with adjuvant chemotherapy in patients with EGFR-positive tumors in the near future because of its efficacy in combination with palliative chemotherapy in patients with advanced NSCLC and high EGFR expression in their tumors (24, 25).

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 III A NSCLC will be randomized to receive adjuvant cisplatin-based chemotherapy either alone or in combination with bevacizumab.

Vaccination

Another strategy to improve outcome of completely resected NSCLC is the use of Antigen-Specific Cancer Immunotherapeutics which should stimulate the immune system to recognize and eliminate cancer cells in a highly specific manner. An interesting tumor-specific antigen is MAGE-A3 which can be detected in about 35% of early-stage NSCLC but not in normal cells. 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% (26). These encouraging results led to the currently ongoing phase III trial (MAGRIT) comparing vaccination with observation alone in patients with completely resected NSCLC.

CONCLUSION

Adjuvant cisplatin-based chemotherapy is now a standard of care for patients with completely resected NSCLC stage II-III and in selected patients with stage I NSCLC. Further improvements of adjuvant treatment for early-stage NSCLC patients are expected by the implementation of customized chemotherapy, the integration of targeted therapies and cancer immunotherapy.

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