Adjuvant Therapy in Patients With Completely Resected Non–small-cell Lung Cancer: Current Status and Perspectives

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Abstract

Patients with early-stage non–small-cell lung cancer undergo surgery with curative intent. Many of these patients relapse and, therefore, adjuvant therapies are important for improving survival of these patients. Adjuvant chemotherapy has been established and increases the 5-year survival rate. Here, we discuss systemic treatment strategies for further improving outcome of patients with completely resected non–small-cell lung cancer.

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Introduction

Approximately 30% of patients with non–small-cell lung cancer (NSCLC) are diagnosed with early stage disease and undergo surgery with curative intent. The prognosis of these patients greatly depends on the pathologic tumor stage at the time of surgery. According to the eighth edition of the TNM classification for lung cancer, the 5-year survival rates range from 41% among patients with stage IIIA to 90% among those with stage IA1.[1] Owing to the presence of systemic micro-metastases at the time of surgery, many patients will relapse, with systemic relapses in the majority of relapsed patients. Thus adjuvant therapies are important strategies to improve overall survival, including cure rates of these patients. Here, we summarize the current status of adjuvant chemotherapy and outline therapeutic perspectives for patients with completely resected NSCLC.

Establishment of Adjuvant Chemotherapy

A meta-analysis of randomized trials published in 1995 suggested that adjuvant cisplatin-based chemotherapy increases the survival rate by 5% at 5 years.[2] This led to the reevaluation of adjuvant chemotherapy with platinum-based regimens within randomized phase III trials on large patient populations.[3-9] Three trials then proved the survival benefit for adjuvant cisplatin-based chemotherapy.[3-6] Although 2 other trials failed to confirm a statistically significant survival benefit, their clinical relevance was limited because of an already outdated chemotherapy protocol at the time of trial analysis or low statistical power owing to insufficient patient numbers.[7,8]

Among the 3 positive trials, the hazard ratios for death were 0.86 (95% confidence interval [CI], 0.76-0.98; $P < .03$) in IALT (International Adjuvant Lung Cancer Trial); 0.80 (95% CI, 0.66-0.96) in ANITA (Adjuvant Navelbine International Trialist Association), and 0.69 (95% CI, 0.52-0.91) in the JBR.10 trial (Table 1). The increase in the 5-year survival rates ranged from 4.1% in IALT to 15% in the JBR.10 trial. An update of IALT after longer follow-up of the patients confirmed the survival benefit from adjuvant chemotherapy up to 5 years but also suggested that the mortality of patients of the chemotherapy arm may be increased after 5 years.[4] Disease-free and relapse-free survival times were also improved in the 3 trials.

Based on the sixth edition of the TNM classification for lung cancer, IALT enrolled patients with tumor stages I to III, JBR.10 those with tumor stages IB to II, and ANITA those with tumor stages IB to III.[3-6] Patients of all 3 trials were planned to receive 4 cycles of cisplatin-based chemotherapy. IALT patients received cisplatin plus either etoposide (56%), vinorelbine (27%), vinblastine, or vindesine. A cumulative cisplatin dose of at least 240 mg/m^2 was achieved in 74% of the IALT patients. Patients enrolled into JBR.10 or ANITA were treated with cisplatin plus vinorelbine. Fifty-eight percent of the JBR.10 patients received 3 or more cycles of cisplatin, and 50% of the ANITA patients completed the planned 4 cycles. Side effects of chemotherapy included neutropenia, febrile neutropenia (<10%), fatigue, nausea, vomiting, neuropathy, and constipation. Chemotherapy-associated mortality ranged from 0.8% to 2%.

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Table 1 Adjuvant Chemotherapy With Cisplatin-based Protocols

Trials	No. Patients	Stage	Chemotherapy	Overall Survival				Ref.
				5-Year Survival, %		Hazard Ratio (95% CI)	P Value	
				Chemotherapy	Control			
IALT	1867	I-III	Cis/Vinca	44.5	40.4	0.86 (0.76-0.98)	< .03	3
JBR.10	482	IB-II	Cis/Vino	69	54	0.69 (0.52-0.91)	.04	5
ANITA	840	IB-IIIA	Cis/Vino	51.2	42.6	0.80 (0.66-0.96)	.02	6
LACE meta-analysis	4584	I-IIIA	Cisplatin-based	48.8	43.5	0.89 (0.82-0.96)	.004	10

Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association; CI = confidence interval; Cis = cisplatin; IALT = International Adjuvant Lung Cancer Trial; LACE = Lung Adjuvant Cisplatin Evaluation; Ref. = reference; Vinca = Vinca Alkaloid; Vino = vinorelbine.

Two trials failed to demonstrate a survival benefit for adjuvant chemotherapy.[7,8] Possible explanations for lack of benefit are a toxic chemotherapy protocol (cisplatin, mitomycin C plus vindesine) in case of the ALPI-EORTC trial and insufficient statistical power in the case of the Big Lung Trial.[7,8] The CALGB (Cancer and Leukemia Group B) study failed to demonstrate a survival benefit for adjuvant chemotherapy with paclitaxel plus carboplatin in patients with stage IB. A subgroup analysis of this trial, however, suggested a benefit for patients with tumors larger than 4 cm.[9] Patients with tumors greater than 4 cm are now classified as at least stage IIA according to the eighth edition of the TNM classification. A benefit of adjuvant therapy with uracil-tegafur has been reported for Japanese patients with stage IB NSCLC.[11] However, this drug is not widely used in Western countries.

In order to better define the impact of adjuvant chemotherapy with cisplatin-based protocols on survival of patients, the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis was performed.[10] This meta-analysis, which included 4584 patients from all 5 randomized trials (ALPI-EORTC, IALT, JBR.10, ANITA, Big Lung Trial), confirmed the benefit of adjuvant cisplatin-based chemotherapy (Table 1). Adjuvant chemotherapy resulted in a hazard ratio of 0.89 (95% CI, 0.82-0.96; $P = .004$) and increased the 5-year survival rate by 5.3%. Among patients treated with cisplatin plus vinorelbine (LACE-vinorelbine cohort), the hazard ratio was 0.8 (95% CI, 0.70-0.91) and the 5-year survival rate increased by 8.9%.[12] Disease-free survival was also increased by adjuvant chemotherapy.

Because of the clinically meaningful benefits in overall survival seen within the positive trials and confirmed by the meta-analyses of all cisplatin-based trials,[3-6,10,12] adjuvant chemotherapy became standard treatment for patients with completely resected NSCLC with pathologic tumor stages II and III (according to the eighth edition of the TNM classification). Tumors greater than 4 cm, which benefitted from adjuvant chemotherapy based on a subgroup analysis of the CALGB trial,[9] have been classified as stage IB in the sixth edition but as stage IIA (or higher) in the eighth edition of the TNM classification.[1] Patient requirements for adjuvant chemotherapy are good performance status, rapid postoperative recovery, adequate organ functions, and informed consent. Whether elderly patients should also undergo adjuvant chemotherapy has to be judged on an individual basis. Chemotherapy should start 4 to 8 weeks after surgery and consist of a cisplatin-based doublet. Cisplatin plus vinorelbine was the most widely used chemotherapy protocol within the positive clinical trials because all patients of the JBR.10 trial and the ANITA trial, as well as 27% of IALT patients, were treated with this regimen.

Perspectives of Systemic Adjuvant Therapy

Strategies to improve outcome of patients with completely resected NSCLC are urgently needed because systemic chemotherapy as the current only established adjuvant therapy will benefit only a fraction of these patients. Strategies for improvement continue to focus on customized chemotherapy, targeted therapies, and immunotherapy.

Customized Chemotherapy

Translational research has focussed on the characterization of biomarkers for the selection of patients for adjuvant chemotherapy. In this context, predictive biomarkers are of greater clinical relevance than prognostic biomarkers because they allow characterizing those patients who will benefit from adjuvant therapy. Molecular tumor features involved in tumor growth or action of anticancer drugs have been studied for their ability to serve as potential predictive biomarkers. These parameters have included DNA repair enzymes, drug transporters, apoptosis parameters, cell cycle regulators, and other factors.

The International Adjuvant Lung Cancer Trial Biologic Program (IALT-Bio) has aimed at characterizing predictive biomarkers based on patients enrolled into IALT. The subsequent LACE-Bio project then attempted to validate some of these biomarkers among patients who had been part of the LACE meta-analysis.[10] Many molecular tumor factors have been studied. A systematic review of the findings of both research projects would be beyond the scale of the present article and, therefore, only few examples are provided here. Patients with low ERCC1 expression in their tumors were shown to benefit from adjuvant chemotherapy, whereas those with high ERCC1 expression did not.[13] Similarly, patients without p27 expression in their tumors did benefit from adjuvant chemotherapy compared with those with P27 expression.[14] In contrast, multidrug resistance protein expression was without predictive value.[15] However, neither ERCC1 nor p27 could be validated as predicted biomarkers in the LACE-Bio project. The lack of validation of ERCC1 as a predictive biomarker has been explained by changes in the anti-ERCC1 antibody over time.[16] Overall, these research projects clearly demonstrated the difficulties in characterizing and validating clinically relevant predictive biomarkers for adjuvant chemotherapy. The reasons for these difficulties include the complexity and heterogeneity of lung cancer as well as other factors.

Table 2 Adjuvant Therapy With Targeted Drugs

Trial	No. Patients	Stage	Drug	Hazard Ratio (95% CI)	Ref.
ECOG 1505	1501	IB-IIIA	CT ± bevacizmab	OS 0.99 (0.82-1.19)	24
NCIC CTG BR19	503	IB-IIIA	Gefitinib vs. placebo	OS 1.24 (0.94-1.64)	25
RADIANT	973	IB-IIIA	Erlotinib vs. placebo	DFS 0.90 (0.74-1.10)	26
ADJUVANT	483	II-IIIA	Gefitinib vs. placebo	DFS 0.60 (0.42-0.87)	27
MAGRIT	2312	IB-II	MAGE-A3 vs. placebo OS	1.04 (0.86-1.24)	28

Abbreviations: CI = confidence interval; CT = chemotherapy; DFS = disease-free survival; ECOG = Eastern Cooperative Oncology Group; OS = overall survival; Ref. = reference.

Translational research of the JBR-10 trial also focussed on the characterization of biomarkers.[17-19] High class III beta tubulin expression of tumors 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.[17] The survival benefit of adjuvant chemotherapy, however, was greater in patients with high tubulin expression compared with those with low tubulin expression, although this interaction between tubulin expression and chemotherapy effect did not reach statistical significance.[17] Similarly, patients with overexpression of p53 protein in their tumors had shorter survival but greater benefit from adjuvant chemotherapy than patients without p53 overexpression of p53.[18] Lower hemoglobin levels at baseline were associated with a trend for shorter overall survival.[19]

Chemotherapy customized according to molecular tumor characteristics has also been studied within randomized clinical trials. The Spanish Lung Cancer Group failed to show a benefit for adjuvant chemotherapy guided by BRCA1 levels in patients with resected node-positive NSCLC.[20] Another trial assessing chemotherapy customized according to BRCA1/RAP80 expression trial was prematurely closed because of lack of clinical benefit in the customized chemotherapy arm.[21] The ongoing ITACA trial evaluates customized chemotherapy based on ERCC1 and thymidylate synthase levels.[22] Until its clinical usefulness will have been proven, customized adjuvant chemotherapy remains experimental.

Integration of Targeted Therapies

Based on their efficacy in the palliative treatment of patients with advanced NSCLC (for review, see reference [23]), targeted drugs have been studied for their ability to improve outcome of patients with resected NSCLC. Trials have focused on bevacizumab and tyrosine kinase inhibitors targeting the epidermal growth factor receptor (EGFR). Phase III trials with targeted drugs in the adjuvant setting are summarized in Table 2.

Bevacizumab. Because of its efficacy and approval in combination with first-line platinum-based chemotherapy in patients with advanced NSCLC, bevacizumab was studied in combination with adjuvant chemotherapy in patients with completely resected NSCLC. The North American Intergroup Adjuvant Chemotherapy Trial ECOG 1505 evaluated adjuvant cisplatin-based chemotherapy either alone or in combination with bevacizumab in patients with resected NSCLC stages IB (>4 cm) to IIIA.[24] A total of 1501 patients were randomized to chemotherapy doublet with or without bevacizumab. Chemotherapy consisted of 4 cycles of cisplatin (75 mg/m^2 on day 1) in combination with vinorelbine, docetaxel, gemcitabine, or pemetrexed. Bevacizumab was administered at a dose of 15 mg/kg intravenously every 3 weeks for 1 year. The trial failed to show any improvement in overall or disease-free survival for the addition of bevacizumab to adjuvant chemotherapy in patients with resected early-stage NSCLC. The corresponding hazard ratios were 0.99 (95% CI, 0.82-1.19) and 0.99 (95% CI, 0.86-1.15), respectively. The median survival times were 85.8 months with bevacizumab and not reached without bevacizumab. These survival times did surpass those reported in previous adjuvant chemotherapy trials. The authors concluded that, first, the use of bevacizumab as part of adjuvant regimens is not advised, and, second, the overall survival of patients was improved compared with historical controls.[24]

EGFR-targeted Therapies. EGFR is often deregulated through gene amplification, gene mutation, or protein overexpression in patients with NSCLC and, therefore, has been an interested therapeutic target in these patients. EGFR blockade by monoclonal antibodies or tyrosine kinase inhibitors has been shown to improve outcome of patients with advanced NSCLC (for review, see references [29-31]). Cetuximab added to first-line chemotherapy improved overall survival,[32,33] and the magnitude of the benefit increased with increasing EGFR expression.[34] In another trial, the benefit from cetuximab was associated with EGFR positivity of tumors determined by fluorescence in situ hybridization (FISH).[35] This association led to the SWOG S0819 trial, which aimed at validating EGFR FISH positivity as predictive biomarker.[36] In the intent-to-treat population, the predictive value was not confirmed. Among patients with FISH-positive squamous cell carcinomas, however, chemotherapy plus cetuximab increased survival compared with chemotherapy alone, with a hazard ratio of 0.58 (95% CI, 0.39-0.86) and median survival times of 11.8 and 6.1 months, respectively. A similar benefit with a hazard ratio of 0.62 was shown for chemotherapy plus cetuximab compared with chemotherapy among patients with squamous cell NSCLC and high EGFR expression.[34] Necitumumab added to a platinum plus gemcitabine improved overall survival in patients with advanced squamous cell NSCLC, and this benefit appears to be greater among patients with EGFR FISH positivity of their tumors.[37,38] Thus, EGFR FISH positivity or high EGFR expression can be recommended for selecting patients with advanced squamous cell NSCLC for combining first-line chemotherapy with EGFR-directed monoclonal antibodies.[39]

Chang et al report an association of EGFR gene amplification of tumors with worse survival of patients with resected NSCLC.[40] This worse prognosis in the adjuvant setting is consistent with

Table 3 Immune Checkpoint Inhibitors as Adjuvant Therapy: Phase III Trials

Trials	Drug	No. Patients	Stage	Primary Endpoint	NCT Number	Ref.
PEARLS	Pembrolizumab	1380	IB-IIIA	DFS	NCT02504372	49
BR31	Durvalumab	1360	IB-IIIA	DFS	NCT02273375	50
IMpower010	Atezolizumab	1127	IB-IIIA	DFS	NCT02486718	51
ANVIL	Nivolumab	714	IB-IIIA	OS/DFS	NCT02595944	52

Abbreviations: DFS = disease-free survival; NCT = National Clinical Trials; OS = overall survival; Ref. = reference.

findings in advanced NSCLC where increasing EGFR expression levels of tumors were associated with increasingly shorter overall survival of patients.[34]

Based on the worse prognosis of patients with EGFR gene amplification together with the proven efficacy of combined treatment in advanced NSCLC, adjuvant chemotherapy combined with EGFR monoclonal antibodies could also improve survival among patients whose tumors are EGFR FISH-positive or have high EGFR expression. This possibility is also supported by recent findings on chemoradiotherapy with or without cetuximab in patients with locally advanced NSCLC.[41] Cetuximab was associated with longer overall survival among patients with high EGFR expression in their tumors, whereas it did not improve outcome in the total study population. Therefore, adjuvant studies on these patient populations are warranted. Every strategy that holds promise to improve outcome of patients with resected NSCLC should be pursued, particularly also because of their high numbers.

In contrast to monoclonal antibodies, EGFR tyrosine kinase inhibitors have already been studied as adjuvant therapy in phase III trials (Table 2).[25-27] These trials were done in either patients unselected for EGFR status (NCIC CTG BR19 study), patients with EGFR-positive tumors (RADIANT), or patients with EGFR-mutation-positive NSCLC (ADJUVANT). Two of these trials failed to improve disease-free survival or overall survival compared with placebo in the intent-to-treat population.[25,26] In the RADIANT trial, however, disease-free survival was prolonged among patients with EGFR mutation-positive NSCLC, although this difference might have been caused by imbalances in prognostic factors between the 2 treatment arms.[26] In a Chinese study among patients with EGFR mutation-positive NSCLC, adjuvant treatment with gefitinib improved progression-free survival compared with chemotherapy with cisplatin plus vinorelbine.[27] The hazard ratio was 0.60 (95% CI, 0.42-0.87), and the median disease-free survival times were 28.7 and 18 months, respectively. However, the clinical relevance of the findings of this study is limited because, first, patients did not receive adjuvant chemotherapy and, second, data on overall survival have not been reported. Thus adjuvant therapy with gefitinib is not a standard treatment among patients with resected EGFR mutation-positive NSCLC, although it may be considered for selected patients. Further studies among patients with mutation-positive NSCLC are ongoing and hopefully will clarify the role of EGFR tyrosine kinase inhibitors as adjuvant therapy in these patients.

Immunotherapy

Immune therapy is a very promising strategy for improving overall survival, including the cure rate of patients with completely resected NSCLC. This promise is based on, first, the remarkable efficacy of immune checkpoint inhibitors in patients with advanced NSCLC, and, second, the belief that immune therapies will particularly be effective in clinical settings of low tumor load, such as in patients with resected NSCLC.

Immune therapy has initially focused on tumor vaccines. The MAGE-A3 antigen was of particular interest as target for a vaccination strategy. This antigen is detected in about 35% of early-stage NSCLC. In a randomized phase II trial, vaccination with MAGE-A3 immunotherapeutic demonstrated a reduction in the relative risk of recurrence in MAGE-A3-positive patients with stage IB or II NSCLC.[42] To confirm this promising efficacy, the MAGRIT phase III trial was performed.[28] This trial screened 13,849 patients for MAGE-A3 expression and then randomized 2312 positive patients to vaccination with either the immunotherapeutic or placebo. The trial, however, failed to demonstrate improvements in disease-free survival or overall survival for patients treated with the MAGE-A3 immunotherapeutic compared with patients treated with placebo. Hazard ratios were 1.02 (95% CI, 0.89-1.18) for disease-free survival and 1.04 (95% CI, 0.86-1.24) for overall survival. The median disease-free survival times were 60.5 and 57.9 months, respectively. The median survival times were not reached in both treatment arms. These disappointing results led to the discontinuation of further clinical development of the MAGE-A3 immunotherapeutic.

Immune checkpoint inhibitors targeting programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) have improved survival of patients with advanced NSCLC in the first-line setting when administered either as single agent or in combination with platinum-based chemotherapy.[43-47] Durvalumab also improved progression-free survival compared with active surveillance in patients with unresectable stage III NSCLC who had not progressed following standard platinum-based chemotherapy concurrent with radiation therapy.[48] Based on these positive trials, current clinical trials are evaluating immune checkpoint inhibitors as adjuvant treatment in patients with resected NSCLC (Table 3).[49-52] Within these trials, patients receive adjuvant chemotherapy and immune checkpoint inhibitors. Immune checkpoint inhibitors are usually planned to be administered for up to 1 year. An important issue is whether immune checkpoint inhibitors should be administered as consolidation therapy after completion of adjuvant chemotherapy or whether they should be combined with adjuvant chemotherapy and continued as consolidation therapy. Whenever possible, these clinical trials should be accompanied by translational research on potential predictive biomarkers. Candidate biomarkers include PD-1/PD-L1 expression and tumor-mutation burden.[53-55]

Based on their remarkable efficacy in the palliative treatment of patients with advanced NSCLC, the expectations for these drugs to improve outcome of patients with completely resected NSCLC are high. It is hoped that immune checkpoint inhibitors will have a greater impact on the cure rate of these patients than adjuvant chemotherapy has been able to achieve.

Conclusion

Adjuvant chemotherapy with a cisplatin-based doublet has been established as a standard for patients with completely resected NSCLC. Customized chemotherapy based on molecular tumor features remains experimental. The addition of bevacizumab to adjuvant chemotherapy did not improve outcome. EGFR tyrosine kinase inhibitors failed to improve outcome, except gefitinib among Chinese patients with EGFR mutation-positive NSCLC. Immune checkpoint inhibitors are currently being evaluated in phase III trials.

Disclosure

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