Adjuvant chemotherapy for surgically resected non–small cell lung cancer

Stephanie Heon, MD, and Bruce E. Johnson, MD

Despite surgical resection, patients with early-stage (I to IIIA) non–small cell lung cancer (NSCLC) are at considerable risk of recurrence and death from their lung cancer. In recent years, multiple, large, randomized trials assessing the efficacy of adjuvant chemotherapy for resected NSCLC have been reported. Three of 6 trials with 300 or more patients with early-stage NSCLC have demonstrated that adjuvant cisplatin-based chemotherapy can significantly improve 5-year survival in carefully selected patients with resected NSCLC. These benefits have been confirmed in a meta-analysis of modern cisplatin-based adjuvant trials. The most consistent benefit has been reported in patients with resected stage II and IIIA NSCLC. The benefit of adjuvant chemotherapy in patients with resected stage IB NSCLC is less concrete. Herein, we review the results of the major adjuvant chemotherapy trials and their implications for the treatment of patients with completely resected NSCLC. A future challenge will be to identify the subsets of patients who will derive the greatest benefit from adjuvant chemotherapy. Current trials are also underway to define the role of novel targeted therapies, such as inhibitors of the epidermal growth factor receptor and monoclonal antibodies, in adjuvant treatment strategies. (*J Thorac Cardiovasc Surg* 2012;144:S39-42)

The most effective treatment of early-stage (I to IIIA) non–small cell lung cancer (NSCLC) is surgical resection. Despite optimal surgery, a substantial percentage of patients with stage I to IIIA NSCLC subsequently relapse and die of their lung cancer.¹ Studies that suggested adjuvant chemotherapy could prolong survival for some patients with early-stage lung cancer began to emerge. A number of trials have since documented that the use of chemotherapy in the postoperative setting can prolong survival. The present review summarizes the evidence showing the benefit from adjuvant chemotherapy for specific subgroups of patients with early-stage NSCLC.

EVIDENCE FOR ADJUVANT CHEMOTHERAPY

Small randomized trials of patients with early-stage NSCLC performed during the past 30 years were jointly analyzed in an individual patient data meta-analysis published in 1995.² That analysis, involving more than 4300 patients, showed a strong trend toward improved survival of approximately 5% at 5 years for patients with resected early-stage NSCLC treated with adjuvant cisplatin-based chemotherapy compared with those on observation alone (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.74 to 1.02; $P =$

.08). These results prompted a new generation of larger randomized controlled trials to attempt to validate the observations made in the meta-analysis. The outcome information from the studies enrolling more than 300 patients and comparing surgery alone with surgery followed by chemotherapy is presented in [Table 1](#). This review does not address the use of postoperative tegafur and uracil. Although Japanese trials have demonstrated a survival benefit with adjuvant tegafur and uracil, no confirmatory trials have been performed in Western populations, and this agent is not presently available in the United States.³

Adjuvant Therapy Trials Showing Differences in Survival

Three of the six trials listed in [Table 1](#) reported a statistically significant survival advantage for the patients treated with chemotherapy after resection. In the initial study, referred to as the International Adjuvant Lung Trial (IALT), 1867 patients with stage I to IIIA NSCLC who underwent a complete resection of their tumor were randomly assigned to either observation or cisplatin given for 3 to 4 cycles combined with etoposide (56%), vinblastine (11%), vinorelbine (27%), or vindesine (6%).⁴ Radiotherapy was administered to 474 patients (25%). Although the study was terminated early because of slow accrual (3300 patients initially planned), there was a significant improvement in survival in favor of the chemotherapy arm (HR, 0.86; 95% CI, 0.76 to 0.98; $P < .03$), translating into an absolute gain of 4.1% at 5 years (from 40.4% to 44.5%). No significant interaction with pathologic stage was observed. An updated report after 7 years of follow-up, however, revealed that the overall survival advantage was no longer significant (HR, 0.91; 95% CI, 0.81 to 1.02; $P = .10$).⁵ This late loss of survival benefit appeared to be due to an excess of noncancer-related deaths in the chemotherapy arm.

From the Lowe Center for Thoracic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute; Department of Medicine, Harvard Medical School; and Department of Medicine, Brigham and Women's Hospital, Boston, Mass.

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Address for reprints: Bruce E. Johnson, MD, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, Dana Building 1234, Boston, MA 02215 (E-mail: bejohnson@partners.org).

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Abbreviations and Acronyms

ALPI	= Adjuvant Lung Project Italy
ANITA	= Adjuvant Navelbine International Trialist Association
BLT	= Big Lung Trial
CALGB	= Cancer and Leukemia Group B
CI	= confidence interval
HR	= hazard ratio
IALT	= International Adjuvant Lung Trial
LACE	= Lung Adjuvant Cisplatin Evaluation
NSCLC	= non-small cell lung cancer

The National Cancer Institute of Canada Clinical Trials Group reported another adjuvant chemotherapy trial (JBR.10), which showed a difference in patient outcome.⁶ In that trial, 482 patients with completely resected stage IB or II NSCLC were randomized to postoperative observation or vinorelbine and cisplatin for 4 cycles. No chest radiotherapy was administered. After a median follow-up of 5.1 years, overall survival was significantly prolonged for the patients treated with surgery plus chemotherapy compared with those treated with surgical resection alone (HR for death, 0.69; 95% CI, 0.52 to 0.91; $P = .04$). The corresponding 5-year survival rates were 69% and 54%. An updated survival analysis of the JBR.10 trial reported a persistent survival advantage for patients treated with adjuvant chemotherapy after more than 9 years of follow-up.⁷ In both these reports, the benefit was restricted to patients with resected stage II disease and was not seen in the subjects with stage I NSCLC.

The Adjuvant Navelbine International Trialist Association (ANITA) study also examined vinorelbine and cisplatin after resection of the participants' lung cancer.⁸ A total of 840 patients with stage IB-III NSCLC who had undergone successful surgical resection were randomly assigned to either observation or chemotherapy for 4 cycles. Postoperative radiotherapy was delivered to 282 patients (28%). Adjuvant chemotherapy was associated with significantly improved survival (HR, 0.80; 95% CI, 0.66 to 0.96; $P = .017$). This benefit was observed in patients with stage II and IIIA NSCLC. The 5-year survival rate for those with stage I, II, and IIIA was 62%, 52%, and 42% in the chemotherapy arm compared with 63%, 39%, and 26% in the observation arm, respectively.

Negative Adjuvant Therapy Trials

The benefits of postoperative chemotherapy were challenged by 3 other randomized trials completed after the 1995 meta-analysis, all of which failed to show a significant survival advantage for adjuvant chemotherapy. The Adjuvant Lung Project Italy (ALPI) studied patients with

resected stage I-III NSCLC by randomly allocating them to treatment with mitomycin, vindesine, and cisplatin every 3 weeks for 3 cycles or observation after complete surgical resection.⁹ Postoperative thoracic radiotherapy was allowed at the discretion of each participating site. A total of 1088 patients were analyzed after a median follow-up period of 64.5 months. In the chemotherapy arm, 69% of patients completed the mitomycin, vindesine, and cisplatin treatment and one half required dose modifications or omission of part of the planned regimen. No difference was found between the outcomes of patients treated with resection plus chemotherapy versus those treated with surgery alone (HR for death, 0.96; 95% CI 0.81 to 1.13; $P = .589$). The use of the chemotherapy regimen of mitomycin, vindesine, and cisplatin is considered inferior by today's standards and might have led to the high death rates during the first year after randomization and the poor compliance with chemotherapy, 2 strong criticisms of the study. Similarly, no benefit from adjuvant cisplatin-based chemotherapy was seen among 381 patients with stage I-III NSCLC in the Big Lung Trial (BLT).¹⁰ However, the trial was underpowered to detect the magnitude of difference in survival observed in the other trials, and a considerable proportion (15%) of patients had undergone microscopically incomplete surgical resection.

The Cancer and Leukemia Group B (CALGB) 9633 trial was unique in limiting enrollment to patients with resected stage IB NSCLC who were randomized to treatment with paclitaxel and carboplatin every 3 weeks for 4 cycles or to observation.¹¹ The study was terminated early when an interim analysis in 2004 suggested a significantly greater survival rate with adjuvant therapy. After a reanalysis of the data in 2006, the survival benefit still favored chemotherapy but was no longer significant (HR, 0.83; 90% CI, 0.64 to 1.08; $P = 0.12$). With 344 patients, CALGB 9633 might have lacked statistical power to detect small, but meaningful, improvements in survival in this relatively good risk population. Furthermore, the use of a carboplatin regimen instead of a cisplatin backbone might have affected the results, because a recent meta-analysis demonstrated cisplatin-based chemotherapy to be slightly superior to carboplatin regimens for advanced NSCLC.¹²

Meta-Analyses

A meta-analysis (Lung Adjuvant Cisplatin Evaluation [LACE]) combining individual patient data from 4584 patients from the 5 large adjuvant cisplatin-chemotherapy trials described earlier in the present review (ALPI, BLT, IALT, ANITA, and JBR.10) has been published.¹³ The analysis confirmed a statistically significant benefit in overall survival for chemotherapy compared with observation (HR, 0.89; 95% CI, 0.82 to 0.96; $P = .005$), corresponding to an absolute gain of 5.4% at 5 years. The benefits of

TABLE 1. Overview of adjuvant chemotherapy trials enrolling more than 300 patients published after 1995 non-small cell lung cancer meta-analysis

Trial	Patients (n)	Stage eligibility	Absolute difference in			
			5-year survival (%)	HR for death	95% CI	P value
IALT ⁴	1867	I-III	4.1	0.86	0.76–0.98	<.03
JBR.10 ⁶	482	IB-II	15	0.69	0.52–0.91	.04
ANITA ⁸	840	IB-III A	8.6	0.80	0.66–0.96	.017
ALPI ⁹	1088	I-III A	1	0.96	0.81–1.13	.589
BLT ¹⁰	381	I-III	NA	1.02	0.77–1.35	.9
CALGB 9633 ¹¹	344	IB	2	0.83	0.64–1.08	.125

HR, Hazard ratio; CI, confidence interval; IALT, International Adjuvant Lung Trial; ANITA, Adjuvant Navelbine International Trialist Association; ALPI, Adjuvant Lung Project Italy; BLT, Big Lung Trial; NA, not available; CALGB, Cancer and Leukemia Group B.

chemotherapy were confined to patients with resected stage II or III NSCLC. A suggestion of a worse outcome with adjuvant chemotherapy for the 347 patients with stage IA disease was found (HR, 1.40; 95% CI, 0.95 to 2.06). The LACE meta-analysis also found a trend for longer survival for the patients treated with cisplatin plus vinorelbine versus cisplatin plus 1 or 2 other drugs. However, the greater planned doses of cisplatin in the cisplatin- and vinorelbine-treated patients might have been responsible for the observations. Finally, an update of the 1995 meta-analysis presented at the 2007 Annual Meeting of the American Society of Clinical Oncology showed a consistent benefit with adjuvant chemotherapy for surgically resected NSCLC, with an overall benefit of 4% at 5 years.¹⁴

Thus, 3 randomized trials of postoperative cisplatin-based chemotherapy (IALT, JBR.10, and ANITA) and 2 large individual patient data meta-analyses have convincingly demonstrated that cisplatin-doublet adjuvant chemotherapy causes a statistically significant and clinically meaningful survival advantage for patients with resected early-stage NSCLC. The most consistent benefit has been reported for patients with surgically resected stage II and IIIA NSCLC. From this evidence, postoperative adjuvant cisplatin-based chemotherapy is now the standard of care for the management of completely resected stage II and IIIA NSCLC.¹⁵

Potential Candidates for Adjuvant Chemotherapy

Stage IB NSCLC with adverse prognostic factors. Evidence is not yet available from the randomized trials or the LACE meta-analysis to routinely recommend adjuvant chemotherapy for resected stage IB disease. The CALGB 9633 trial was composed exclusively of patients with stage IB NSCLC. The study design showed that patients given paclitaxel and carboplatin lived slightly longer but the difference did not reach significance for the overall population. However, in an unplanned subset analysis, the trial reported significant disease-free and overall survival benefits in favor of postoperative chemotherapy for patients with tumors 4 cm or greater in diameter (HR for death, 0.69; $P = .043$). In a similar exploratory subgroup analysis of the JBR.10 trial, patients with stage IB disease with tumors 4 cm or

greater showed a trend toward improved survival rates with adjuvant chemotherapy.⁷ However, there are currently no prospectively validated data supporting a survival benefit with adjuvant chemotherapy in patients with stage IB NSCLC and larger tumors. Likewise, the presence of visceral pleural invasion identifies a group of stage IB patients with poorer prognosis. In a large retrospective analysis of 9758 patients who underwent surgical resection of NSCLC, the Japanese Joint Committee for Cancer Registration demonstrated poorer survival of resected T2 tumors with visceral pleural invasion (5-year overall survival rate, 53.0%) compared with T2 tumors without visceral pleural invasion (61.6%; $P < .001$).¹⁶ However, no analyses have yet reported on the effect of adjuvant chemotherapy in node-negative T2 tumors according to visceral pleural involvement. Given the currently available information, we strongly recommend considering patients with stage IB disease and larger tumors (≥ 4 cm) for cisplatin-based adjuvant chemotherapy on an individualized basis. Similarly, postoperative chemotherapy might be an option for select patients with resected node-negative T2 tumors with visceral pleural invasion given their poorer prognosis for survival.

T3 with separate tumor nodules in the same lobe. Data are not specifically available to inform the use of adjuvant chemotherapy for patients with separate tumor nodules in the same lobe as the primary tumor, without lymph node involvement. Tumors with same-lobe nodules were reclassified as stage T3 instead of T4 on the basis of the similar survival rates in the 7th edition of the TNM staging system for lung cancer of the American Joint Committee on Cancer.¹ Our de facto practice is to consider these patients with T3 tumors with separate tumor nodules in the same lobe for cisplatin-based adjuvant chemotherapy because of their similar survival to patients with T3 tumors without satellite nodules and data supporting adjuvant systemic therapy for resected stage II NSCLC.

Resected oligometastatic NSCLC. Retrospective studies have suggested that highly selected patients with NSCLC and a solitary synchronous site of extrathoracic metastatic disease, usually brain or adrenal, can be effectively treated

by resection of all disease sites.¹⁷⁻¹⁹ No randomized trials have investigated the value of chemotherapy after surgical removal of the primary tumor and isolated metastasis. On the basis of the established benefit of adjuvant chemotherapy, it would seem reasonable to include chemotherapy in the treatment of patients who have undergone resection of an isolated metastasis and primary tumor with curative intent.

FUTURE STRATEGIES

Current research efforts aim at identifying subsets of patients who will derive the greatest benefit from adjuvant chemotherapy by using pharmacogenomic approaches and gene-expression profiling. Moreover, modern adjuvant therapy trials are attempting to integrate novel biological therapeutic agents, such as bevacizumab, into standard treatment paradigms. The addition of bevacizumab to paclitaxel and carboplatin has been successful in advanced NSCLC and is now being investigated in the early-stage setting within the context of a large Intergroup phase III randomized controlled trial (E1505/NCT00324805). In that trial, patients with resected stage IB (≥ 4 cm), II, and IIIA NSCLC are randomized to receive adjuvant cisplatin-based doublet chemotherapy, with or without bevacizumab. The optimal adjuvant therapy for patients whose tumors harbor activating mutations of the epidermal growth factor receptor is also being studied. Subjects with resected NSCLC and epidermal growth factor receptor mutations are being treated with adjuvant chemotherapy with or without a tyrosine kinase inhibitor of the epidermal growth factor receptor (NCT00567359). Whether these approaches will improve on the current standard of adjuvant cisplatin-based doublet chemotherapy remains to be determined.

CONCLUSIONS

The treatment of early-stage NSCLC has undergone a paradigm shift during the past 7 to 8 years with the addition of systemic therapy to local therapy. Several large randomized controlled trials and 2 meta-analyses have demonstrated a survival advantage for patients with stage II and IIIA NSCLC treated with adjuvant chemotherapy compared with those who underwent observation. Adjuvant platinum-based chemotherapy is now considered the standard of care for patients with stage II and IIIA NSCLC and can be considered an option for select patients with stage IB disease and adverse prognostic factors (primary tumor ≥ 4 cm, T2 tumor with visceral pleural invasion), patients with T3 tumors with same-lobe nodules, and those with resected oligometastatic disease. In this era of personalized targeted therapy, research is ongoing to individualize systemic therapy for early-stage NSCLC and to integrate novel biological therapeutic agents into the treatment paradigm.

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