

The Present Status of Postoperative Adjuvant Chemotherapy for Completely Resected Non-Small Cell Lung Cancer

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Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancers, with patients having a poor prognosis. Approximately one third of NSCLC patients present with early-stage disease in which potentially curative resection and multi-modality therapy. Although adjuvant chemotherapy is the standard practice for patients with stages I–III breast and colorectal cancer, the therapeutic efficacy of adjuvant chemotherapy, following complete surgical resection of early stage NSCLC, has not been fully established. Several prospective randomized trials for patients with early stage NSCLC (stages I–IIIA) have confirmed a survival benefit with cisplatin-based adjuvant chemotherapy, as demonstrated in the 1995 meta-analysis performed by the NSCLC Collaborative Group. Studies from Japan have reported that adjuvant therapy with uracil-tegafur (UFT) afforded an improvement of 4% in the 5-year survival rate and a relative risk reduction of 26% in mortality at 5 years among patients with T1-2N0 (stage I) disease. In particular, the Japan Lung Cancer Research Group has demonstrated an improvement in the 5-year survival rate of 11%, favoring chemotherapy with UFT in the subset of patients with T2N0 (stage IB) disease. Two published meta-analyses based on abstracts have estimated a relative risk reduction in mortality of 11–13% at 5 years. The Lung Adjuvant Cisplatin Evaluation (LACE), which was based on a pooled analysis of five randomized trials, has demonstrated that cisplatin-based adjuvant chemotherapy improved survival in patients with completely resected NSCLC. This benefit depended on stage, being greatest in patients with stage II or IIIA disease. This analysis has suggested that platinum-based adjuvant chemotherapy may have no benefit for patients with stage IA and only a marginal benefit for patients with stage IB. Thus, the information available at the current time supports the administration of adjuvant chemotherapy for patients who have undergone complete resection of stages IB–IIIA NSCLC. Further research is needed to define the role of adjuvant platinum-based chemotherapy and its use, in conjunction with chest radiotherapy as the treatment for patients with resected stages IB and IIIA NSCLC. (*Ann Thorac Cardiovasc Surg* 2007; 13: 73–7)

Key words: non-small cell lung cancer, surgery, adjuvant chemotherapy, complete resection, postoperative treatment, meta-analysis

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Received August 29, 2006; accepted for publication March 13, 2007.

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Introduction

The most effective treatment for early stages (IA–IIIA) non-small cell lung cancer (NSCLC) is surgical resection. However, up to 60% of patients with IB to IIIA NSCLC relapse after surgery and die.^{1,2)} The presence of micrometastatic disease at the time of resection is the most

likely cause of recurrence occurring even after complete surgical removal of all macroscopically recognizable disease. Micrometastases in patients with radiologically localized lung cancer can be detected by immunohistochemistry and polymerase chain resection assays. If micrometastases are indeed responsible for disease recurrence, adjuvant chemotherapy would be a rational treatment, and this hypothesis has led to attempts to reduce the risk of relapse and death from lung cancer by giving adjuvant chemotherapy to patients with complete surgical resection.³⁾ This approach has been successful in patients with breast and colorectal cancer where in clinical practice some patients with stage I–III cancer are routinely given adjuvant hormonal therapy (in the case of breast cancer), or chemotherapy or the both as the combination of both.

A meta-analysis of small randomized trials of patients with early stage NSCLC in the preceding 30 years was performed in 1995.³⁾ This analysis revealed a 5% survival advantage at 5 years for patients with surgically resected early stage NSCLC treated with cisplatin-based chemotherapy, compared to those patients only followed up after resection. This led to the planning and execution of multiple national and international trials that were granted enough statistical power to detect a small benefit of even only 5% at 5 years. The results of these trials have been reported in the last 4 years. The seven trials included in this review are those which recruited more than 150 patients with completely resected stages I–IIIA NSCLC per arm. Those seven trials used different regimens of chemotherapy, included different proportions of stages IA–IIIA NSCLC, and used different methods of reporting their results.

The purpose of this article is to provide a general overview of the evolution of adjuvant chemotherapy for early-stage NSCLC, with special emphasis on recent reports on the randomized trials and meta-analyses which have evaluated improvements in survival and reductions in cancer death by the administration of adjuvant chemotherapy.

The Results of Recent Phase III Studies

Adjuvant Lung Project Italy (ALPI): Mitomycin, vindesine and cisplatin adjuvant trial for patients with pathological stages I to IIIA NSCLC⁴⁾

This trial randomized 1,209 patients with completely resected stage I to IIIA disease either to three cycles of mitomycin, vindesine, and cisplatin every 3 weeks or to

observation. The control arm was no postoperative treatment. Stratification categories included tumor size, lymph node involvement, center and intended radiotherapy. After a 64.5 month median follow-up, there was no difference between the two arms in survival time or recurrence. The main toxicity was grade 3 neutropenia, observed in 16% of the patients and grade neutropenia in 12% of the patients. Only one third of patients received all three intended cycles of chemotherapy, while radiotherapy was completed in only 65% of the 176 scheduled patients receiving chemotherapy vs 82% of the 152 scheduled patients in the control arm.

The Big Lung Trial (BLT): Cisplatin-based adjuvant trial for patients with potentially respectable NSCLC⁵⁾

This trial randomly allocated a total of 381 patients to three courses of cisplatin-based chemotherapy (for which each center could choose one from the following four combinations: vinorelbine/cisplatin, vindesine/cisplatin, mitomycin/ifosfamide/cisplatin, or mitomycin/vinblastine/cisplatin) before or after surgery, or to observation. Approximately one third of the patients had clinical stage IIIA or greater disease, and the remaining two thirds of the patients had stage I–II disease. The result indicated no improvement in overall survival rate or disease-free survival rate. Regarding safety, there were six treatment-related deaths in the study, and 30% of patients experienced grade 3 or worse toxic events which consisted mainly hematologic toxicity.

The International Adjuvant Lung Cancer Collaborative Group Trial (IALT): Cisplatin-based adjuvant trial for patients with resected stages I–IIIA NSCLC⁶⁾

This is the largest study of adjuvant chemotherapy ever conducted to this date, which had a planned accrual of 3,300 patients, and was designed to have sufficient statistical power to confirm a 5% absolute survival benefit for chemotherapy at 5 years (from 50 to 55%). Patients were randomly assigned after surgery to receive either 3–4 cycles of cisplatin-based chemotherapy or to observation. Due to slow accrual, the study closed after the enrollment of 1,867 patients. Of those, 74% received at least 240 mg/m² of cisplatin; and in more than half of these patients, this regimen was combined with etoposide (56.5%) or vinorelbine (26.8%). Seven patients (0.8%) died of chemotherapy-induced toxic events. After the median follow-up period of 56 months, there was a sta-

tistically significant improvement in overall survival shown as an absolute difference of 4.1% at 5 years favoring adjuvant chemotherapy.

Vinorelbine cisplatin adjuvant trial for patients with resected stages IB and II (excluding T3N0) NSCLC (JBR10)⁷

This trial was conducted by the National Cancer Institute of Canada Clinical Trials Group (NCI-CTG). A total of 482 patients were randomized to either observation or to four cycles of chemotherapy with vinorelbine and spirit-scheduled cisplatin. The patients were stratified by nodal status (ie, N0 vs N1) and ras mutation status (ie, present vs absent vs unknown). Notable toxicity was grade 4 neutropenia, including febrile neutropenia in 7% of the patients receiving vinorelbine at 30 mg/m², which prompted a dose reduction to 25 mg/m² shortly after the study started. Two patients died of therapy-related toxicity (febrile neutropenia in one patient and pulmonary fibrosis in the other patient). There was a significant improvement in median survival time for patients in the adjuvant chemotherapy arm from 73 to 94 months. There was also a 15% improvement in 5 year survival in the adjuvant chemotherapy arm (HR: 0.7). In subset analysis, no benefit was noted for patients with stage IB disease.

Paclitaxel carboplatin adjuvant trial for patients with resected stage IB NSCLC (CALGB9633)^{8,9}

This trial, conducted by the Cancer and Leukemia Group B, recruited a total of 344 patients with stage IB (T2N0) disease in which the absence of lymph node metastasis was proven by mediastinoscopy or thoracotomy. Patients were randomised within 4–8 weeks after undergoing complete surgical resection to observation only or to four cycles of chemotherapy with paclitaxel (200 mg/m²) and carboplatin (area under the curve = AUC, 6) administered on day 1 every 3 weeks. The regimen was well-tolerated with no treatment-related deaths. The most common toxicity observed was grade 3 or 4 neutropenia, in a total of 36% of the patients. Preliminary results of this study released in 2004 provided compelling evidence that adjuvant chemotherapy with paclitaxel and carboplatin significantly improved disease-free and overall survival in resected stage IB NSCLC at a median follow-up time of 34 months.⁸ Indeed, the study was closed early by the DSMB after an initially planned interim analysis demonstrated a *p* value for overall survival being less than a prespecified stopping boundary. However, the updated but “preliminary” analysis of this trial in 2006 no longer

showed a significant advantage in overall survival for adjuvant chemotherapy for stage IB NSCLC at a median follow-up time of 57 months.⁹ It is important to note, however, that the re-designed study lacked adequate power to detect small differences in overall survival that might actually be clinically significant. The initial accrual target was 500 patients, but it was reduced to 384 patients in 2000 because of slow accrual and then further reduced when the early closure of the trial was decided because of the positive results of interim analysis. It must be noted that if a statistically significant hazard ratio were determined to be 0.8, the trial would have required more than 1,000 patients. Although the observed advantages in disease-free survival and 3 year survival may suggest further consideration of adjuvant chemotherapy with carboplatin and paclitaxel in stage IB NSCLC, the latest 2006 update results do not.

Adjuvant Navelbine International Trialist Association (ANITA): vinorelbine cisplatin adjuvant trial for patients with resected stages IB–IIIA NSCLC¹⁰

A total of 840 patients were randomized either to observation or to four cycles of chemotherapy with vinorelbine and cisplatin. The two arms were nearly equally balanced in terms of stage (IB/II/IIIA). Although the chemotherapy arm showed a 9% survival advantage at 5 years (the hazard rate: 0.79), in the subset analysis no benefit was found for the patients with stage IB disease. Three patients (1.7%) died of therapy-related toxicity.

The Japan Lung Cancer Research Group (JLCRG): Uracil-tegafur adjuvant trial for patients with completely resected stage I (T1-2N0) adenocarcinoma of the lung¹¹

After undergoing complete surgical resection, 999 patients with stage I (T1-2N0) adenocarcinoma disease were randomized within 4–6 weeks to observation only or to the oral combined chemotherapy of tegafur plus uracil, with tegafur at a dose of 250 mg/m² (as in the form of capsules containing 100 mg of tegafur and 224 mg of uracil), given each day for 2 years. This trial is the largest study ever performed targeting patients with stage I lung adenocarcinoma. The subgroup analysis of patients with T2N0 disease demonstrated that the UFT therapy significantly improved the 5-year survival rate by 11%. Despite minimal toxicity, the treatment compliance dropped from 80% at 6 months to 62% at 24 months. Two recent meta-analyses confirmed a survival benefit favoring postoperative UFT therapy, with a 17% risk reduction for mor-

tality at 5 years. The hazard ratio for UFT in a meta-analysis of six trials recruiting just over 2,000 patients altogether was 0.74 ($p=0.001$).¹² The benefit was limited to those with a tumor size of 2 cm or more. In Japanese clinical practice, adjuvant chemotherapy with UFT for patients with stage IB adenocarcinoma of the lung is recommended standard care. While one study has suggested that the pharmacokinetics of tegafur is similar in Japanese and Western patients, differences in body size between different populations may play an important role.^{13,14} Thus, it would be helpful to confirm the adjuvant benefits of tegafur in other populations before it is introduced in adjuvant regimens elsewhere outside Japan.

Discussion

Result of seven large adjuvant trials enrolling 150 patients or more with stages I–IIIA NSCLC on each arm have been released over the last 4 years. Three of the seven randomized trials have confirmed a survival benefit with adjuvant cisplatin-based chemotherapy provided some information about subsets of patients who would benefit most from adjuvant chemotherapy following complete surgical resection of early stage NSCLC. Two recent meta-analyses based on abstract of trials published since 1995 have reported a consistent relative risk reduction of 11% in mortality at 5 years after postoperative platinum-based chemotherapy.^{15,16} Most information deals with disease stage, but some looks into the impact of gender, age, histology, type of chemotherapy, and chest radiotherapy on the benefit of adjuvant chemotherapy treatment.

The Lung Adjuvant Cisplatin Evaluation (LACE) study was based on a pooled meta-analysis of individual patient data from the five largest randomized trials (ALPI, ANITA, BLT, IALT and JBR10), conducted after the NSCLC meta-analysis.¹⁷ This study may help to put some critical findings into perspective. With a median follow-up of 5.1 years, the overall hazard ratio of death was 0.89 (95% C.I.; 0.82–0.96; $p<0.005$) which corresponds to a 5-year absolute benefit of 4.2% with chemotherapy. The benefit varied with stage (test for interaction, $p=0.046$) as the hazard ratio for stage IA was 1.41 (95% C.I.; 0.96–2.09), stage IB; 0.93 (95% C.I.; 0.78–1.10), stage II 0.83 (95% C.I.; 0.73–0.95) and stage III; 0.83 (95% C.I.; 0.73–0.95). These analyses indicated that adjuvant cisplatin-based chemotherapy improved survival in patients with completely resected NSCLC especially in stages II and III. In other words, according to this analysis patients with

stage IA might not benefit from platinum-based adjuvant chemotherapy and patients with stage IB might gain only a marginal advantage. As of 2004, benefit from adjuvant chemotherapy seemed to be observed most consistently in patients with resected stage IB to II NSCLC. However, the mature and follow-up results of JBR10 and CALGB9633 presented in 2006 does not consistently exhibit a benefit of adjuvant chemotherapy to patients with surgically resected stage IB NSCLC. It seems that gender, age, and histology do not have a major impact and there is no complete information to suggest that these factors should be used to select patients. The management of patients with resected stage IB NSCLC still remains unclear, and further research is needed to appropriately define the roles of postoperative radiotherapy and chemotherapy in patients with stage III NSCLC.

On the other hand, the Japanese adjuvant trials with UFT are currently the only studies showing a survival benefit with adjuvant chemotherapy in stage IB NSCLC. However, UFT, which was not available in North America at that time for the treatment of lung cancer, was used in a very different manner. It was used mainly to prolong daily maintenance. Future trials may include molecular targeted agents, for example, as maintenance after adjuvant chemotherapy, provided that they demonstrate activity in patients with advanced NSCLC. The use of orally administered drugs with potentially lower toxicity in an attractive option. This is particularly true from the patient's perspective as patients generally favor oral medications as long as drug efficacy is not sacrificed in return for the ease of administration. For example, the NCIC-CTG BR19 study, which was already closed in 2005, was intended to assess the value of adjuvant gefitinib in patients with completely resected stages IB, II or III A NSCLC.¹⁸ A similar phase III trials is now planned for erlotinib, in which patients with completely resected stages IB–IIIA NSCLC will be randomised to receive erlotinib for adjuvant maintenance treatment or to observation alone. Studies of vascular endothelial growth factor inhibitor, such as the ECOG trial (E1505) with bevacizumab, are also being considered.

Conclusion

Adjuvant chemotherapy after resection of stages II–IIIA NSCLC is now the standard of care based on the results of three large-scale phase III trials, using cisplatin-based regimens, such as IALT, JBR10 and ANITA studies, and the recent individual patient meta-analysis; LACE. The

role of adjuvant chemotherapy for stage IB disease remains controversial, now even more so as the update results from CALGB9633 are statistically negative. However, based on the data of the largest adjuvant trial and meta-analysis with UFT, adjuvant chemotherapy with UFT for patients with stage IB adenocarcinoma of the lung is recommended as standard care in Japanese clinical practice. A new era of adjuvant chemotherapy for completely resected NSCLC is evolving, but continued progress and further insight into the role of adjuvant chemotherapy must be achieved.

Acknowledgment

The authors thank Professor J.P. Barron, International Medical Communications Center, Tokyo Medical University, for his support in reviewing this manuscript.

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