Adjuvant chemotherapy of completely resected early stage non-small cell lung cancer (NSCLC)

Ying Liang[1], Heather A. Wakelee[2]

[1]Department of Medical Oncology, Cancer Center, Sun Yat-sen University, Guangzhou 510060, China; [2]Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA, USA

Corresponding to: Heather A. Wakelee. Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University, 875 Blake Wilbur Drive, Stanford, CA 94305-5826, USA. Email: hwakelee@stanford.edu.

Abstract: Surgery is regarded as the primary treatment modality for early stage non-small cell lung cancer (NSCLC), but even after complete resection, a substantial percentage of these patients eventually develop local recurrence or distant metastases. Therefore more effective treatment strategies to reduce lung cancer mortality and recurrence rate are needed. Only recently has the use of adjuvant chemotherapy become standard in early stage NSCLC, at least for stage II and resected IIIA NSCLC. Controversies remain about the benefit for stage I patients. Five-year survival improvements of 5% to 10% have been reported with cisplatin-based adjuvant chemotherapy from multiple large randomized phase III clinical trials and meta-analyses. Questions remain as to which patients benefit and which regimens are best. In this paper, important clinical research in the field of adjuvant chemotherapy of NSCLC is reviewed.

Key Words: Non-small cell lung cancer (NSCLC); adjuvant chemotherapy; elderly patient

Although surgery is regarded as the primary treatment modality for non-small cell lung cancer (NSCLC), only 20-25% of tumors are suitable for potentially curative resection (1) and even after resection, a substantial percentage of these patients eventually develop local recurrences or distant metastasis. Consequently, 5-year survival rates after surgery are disappointingly low, ranging from 58% to 73% in stage I, 36% to 46% in stage II, and only 19% to 24% in patients with stage IIIA tumors (2).

Therefore more effective treatment strategies to reduce lung cancer mortality and recurrence rate are needed. High expectations for post-operative (adjuvant) chemotherapy were based on the fact that this is a standard treatment after complete resection in malignancies such as breast (3) and colon (4). But only recently has adjuvant chemotherapy become standard in early stage NSCLC. Questions remain as to which patients benefit and which regimens are best. In this paper, important clinical research in the field of adjuvant chemotherapy of NSCLC is reviewed, in order

to provide a reference for further clinical practice. Data with pre-operative (neo-adjuvant) therapy, alternatives to chemotherapy, and prognostic or predictive biomarkers are discussed elsewhere.

Early trials of adjuvant chemotherapy with regimens consisting of alkylating agents and older chemotherapy did not show any clear impact on survival. In 1995 an individual patient data-based meta-analysis (5) from 52 randomized trials and 9,387 patients was initiated by the British Medical Research Council's Cancer Trials Office, Cambridge; the Institut Gustave Roussy, Villejuif, France; and the Istituto Mario Negri, Milan, Italy, and was carried out on behalf of the Non-small Cell Lung Cancer Collaborative Group (NSCLCCG). Data were available from 14 trials (4,357 patients and 2,574 deaths) for evaluating surgery versus surgery plus chemotherapy. The trials included platinum-based and non-platinum based regimens. The overall hazard ratio of 0.87; 95% CI, 0.74 to 1.02; (P=0.08), or 13% reduction in the risk of death, suggested an absolute benefit from

chemotherapy, but it was not statistically significant. This ignited the interest of study groups for NSCLC adjuvant chemotherapy after surgery and led to multiple large randomized trials, which have subsequently proven the benefit suggested by the original 1995 meta-analysis. The standard of care has now become adjuvant chemotherapy for resected non-small cell lung cancer.

The Adjuvant Lung Project Italy (ALPI) trial (6) was the first large, prospective adjuvant study designed to detect small differences in survival that were in the range detected by the NSCLCCG meta-analysis. This trial was a randomized controlled study to evaluate the Mitomycin C, Vindesine, Cisplatin (MVP) regimen in patients with radically resected stages I-IIIA non small-cell NSCLC. A total of 1,209 patients (1,086 from the Italian centers and 123 from EORTC-LCCG centers) were enrolled in this study. Patients were randomly assigned to the MVP arm or the control arm and received adjuvant radiotherapy according to the policy of the individual participating center. In total, 69% of patients on the experimental arm completed the planned 3 cycles of MVP treatment. Sixty-five percent of patients received radiotherapy in the MVP arm, and 82% in the control arm. Treatment-related deaths were documented in 10 patients (three patients in the MVP arm and seven patients in the control arm), respectively. After median duration of follow-up for 64.5 months (52.1-79.6 months), no significant difference in overall survival (OS) was seen with an OS HR of 0.96 (95% CI, 0.81-1.13; P=0.589), nor in progression-free survival (HR=0.89, 95% CI, 0.76-1.03; P=0.128). Median overall survival was 55 months in the MVP arm and 48 months in the control arm. One possible reason for this result may be low compliance with chemotherapy, or the regimen utilized. In the multivariable analysis, only disease stage and sex were associated with survival (P<0.001 for stage II or III versus stage I and P=0.034 for male versus female, respectively). Another theory about the lack of benefit seen with adjuvant chemotherapy in this NSCLC population is that the health of patients who have undergone a major thoracic surgical procedure is very often compromised by the procedure itself, and these patients usually require a long time to fully recover.

Investigators in the United Kingdom (UK) reported a randomized trial (Big Lung Trial-BLT) (7) evaluating cisplatin-based adjuvant chemotherapy in patients with completely resected stage I-IIIA NSCLC. Between November 1995 and November 2001 a total of 381 patients were enrolled into the trial from 52 UK and 4 non-UK

centers. One hundred ninety-two patients were randomized to receive chemotherapy(C), and 189 to no chemotherapy (NoC). Twenty-seven percent of patients had stage I disease, 38% stage II, and 26% stage IIIA, respectively. Fifty-two (14%) patients received radiotherapy as part of their planned primary treatment. In the chemotherapy arm the patients were prescribed three cycles of 3-weekly cisplatin-based chemotherapy, primarily doublet regimens. Only 64% of patients finished all three cycles of the chemotherapy as planned, with the rest requiring dose reductions or delays. There were 6 treatment related deaths and 30% of patients experienced grade 3/4 toxicity. With a median-follow time of 34.6 months, the median survival was 33.9 months for Chemotherapy patients, and 32.6 months for No-chemotherapy patients. The overall survival hazard ratio was 1.02 (95% CI, 0.77-1.35, P=0.90) and PFS hazard ratio was 0.97 (95% CI, 0.74-1.26, P=0.81). The results of ALPI and this trial taken together cast doubt on the utility of adjuvant chemotherapy.

More recent trials, however, have been positive and have led to a change in the standard of care. The International Adjuvant Lung Cancer Trial (IALT) (8) was the largest prospective, randomized trial to test the hypothesis from the NSCLCCG Meta-analysis (5). From February 1995 to December 31, 2000, 1,867 completely resected stage I-III NSCLC patients were recruited by 148 centers in 33 countries. They were randomized to adjuvant chemotherapy or best supportive care. Each participating center could determine the pathological stages of disease to include, the dose of cisplatin given per cycle, the drug that was combined with cisplatin, and the postoperative radiotherapy policy. Adjuvant chemotherapy regimens included cisplatin combined with etoposide, vindesine or vinblastine. In the chemotherapy group, 73.8 percent of patients received at least 240 mg/m^2 of cisplatin. Twenty-seven percent of patients received postoperative radiotherapy. The median follow-up was 56 months. A total of 22.6% of the patients had at least one episode of grade 4 toxic effect and seven patients (0.8%) died of toxic effects of chemotherapy. The disease-free survival rate was significantly higher in the chemotherapy group (HR=0.83, 95% CI, 0.74-0.94, P<0.003). The overall survival rate was also significantly higher in the chemotherapy group (HR=0.86, 95% CI, 0.76-0.98, P<0.03); the five-year survival rates were 44.5% *vs.* 40.4%. The absolute five-year benefit in overall survival was 4.1 percent, a value that is concordant with the estimation from the chemotherapy meta-analysis (5). However, in 2009, the long-term follow-up results with a median follow-

up 7.5 years was reported (9), and while the results still showed potential benefit, the significance was lost with an overall survival HR=0.91 (95% CI, 0.81-1.02; P=0.10), but a persistently significant benefit on disease-free survival (HR, 0.88; 95% CI, 0.78-0.98; P=0.02). The results of overall survival were significantly different before and after 5 years of follow-up (HR, 0.86; 95% CI, 0.76-0.97; P=0 .01 *vs.* HR, 1.45; 95% CI, 1.02-2.07; P=0 .04). The reasons behind this are not clear. The non-lung cancer deaths analysis showed a HR of 1.34 (95% CI, 0.99-1.81; P=0.06). The second malignancies were not significantly different (8-year rate of approximately 10%) between the arms. Although absolute 5-year survival benefits of 4% are fairly modest, and the long-term benefit is not as robust, on a global scale the use of cisplatin based adjuvant chemotherapy could potentially help keep approximately 10,000 more NSCLC patients alive at 5 years. The positive results of this study and others that matured around the same time, laid the foundation for the routine use of adjuvant chemotherapy and future trials.

Most of the earlier trials have used a variety of chemotherapy combination regimens, including toxic triplet regimens, but the National Cancer Institute of Canada Clinical Trials Group JBR.10 trial in patients with completely resected stage IB or stage II non-small-cell lung cancer utilized a regimen of vinorelbine (VNR) plus cisplatin (DDP) as adjuvant chemotherapy (10). This study was a North American intergroup, phase III, randomized trial and between 1994-2001 it enrolled 482 patients who were randomly assigned to observation or vinorelbine plus cisplatin chemotherapy. No patients received adjuvant radiotherapy. Fifty-eight percent of the patients received three or more cycles of cisplatin, 77% had at least one dose reduction or omission, and 55% required one dose delay or more, most related to neutropenia at the expected time of vinorelbine administration on day 15 (cycle week 3). Seventy-three percent of patients had grade 3 or 4 neutropenia. With median follow-up of just over 5 years, five-year survival rate was 69% in the vinorelbine-cisplatin group and 54% in the observation alone (P=0.03). In subgroup analysis there was no statistically significant improvement in overall survival among patients with stage IB disease. In the quality-of-life (QOL) analyses (11), despite toxicity, the decline in function and symptom-related domains during chemotherapy in this trial was limited and resolved rapidly (within three months after completion of therapy). In 2010, an updated survival analysis (12) with a median follow-up of 9.3 years was published. Patients in the adjuvant chemotherapy arm continued to show a significant

survival advantage compared with observation (HR, 0.78; 95% CI, 0.61-0.99; P=0.04). The absolute benefit for 5-year survival was 11% (67% chemotherapy *vs.* 56% observation). For patients without lymph node involvement, patients with tumors 4 cm or larger in size derived clinically meaningful benefit from chemotherapy (HR, 0.66; 95% CI, 0.39-1.14; P=0.13), while those with tumors smaller than 4 cm did not (HR, 1.73; 95% CI, 0.98-3.04; P=0.06). Seventy-three percent of patients died of disease or complications of treatment of their NSCLC and 10.6% patients developed second malignancies. This was the first clinical trial in which all patients on chemotherapy received third-generation chemotherapy drugs in an adjuvant setting for completely resected NSCLC, and has the best reported outcomes.

The Adjuvant Navelbine International Trialist Association (ANITA) reported positive results from their phase III randomized trial in patients with completely resected stage IB, II, and IIIA NSCLC (13). From December 1994, to December 2000, 840 patients were enrolled and randomly assigned to vinorelbine plus cisplatin or to observation (control). Postoperative radiotherapy was optional, decided by every participating center, and was to be decided before patients were included into the trial. Among the patients, 37% underwent pneumonectomy and 39% had stage IIIA disease. Fifty percent of patients completed the planned four cycles. Grade 3-4 neutropenia was seen in 85% patients in the chemotherapy arm and there were seven (2%) treatment-related deaths in the chemotherapy group. Median survival was 65.7 months (95% CI, 47.9-88.5) for the chemotherapy group and 43.7 months (35.7-52.3 months) for controls [hazard ratio 0.80 (0.66-0.96), P=0.017]. The absolute overall survival benefit for patients receiving chemotherapy compared with controls was 8.6% at 5 years. Relapse was lower in the chemotherapy group than in the observation group (local relapse, 12% of patients *vs.* 18% of patients, P=0.025). Subgroup analysis indicated that the benefit is seen in patients with stage II and IIIA disease. Postoperative radiotherapy was delivered to 232 (28%) patients (> N0) with improved 5-year survival in patients with N2 disease who received PORT from both groups. This trial showed survival benefits of the vinorelbine-cisplatin combination in the adjuvant setting and confirmed the JBR.10 (10) findings in patients with stage II disease; and also provided new data for patients with stage IIIA NSCLC.

Paclitaxel/carboplatin remains one of the most widely used regimens in the United States for advanced stage

NSCLC, partly due to a favorable toxicity profile. There has only been one large randomized trial to explore this regimen in the adjuvant setting, CALGB9633, which randomly assigned completely resected stage IB (T2N0) patients to four postoperative cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC =6) chemotherapy versus surgery alone. The trial started in September 1996 and was closed in November 2003 by the Data and Safety Monitoring Board after a planned interim analysis following accrual of 344 patients. Chemotherapy was well tolerated, and there were no treatment-related toxic deaths. The predominant toxicity was grade 3 to 4 neutropenia, which was observed in 35%. Fifty-seven percent (77 of 136) of patients received four cycles of chemotherapy at full dose. This trial was initially presented at ASCO 2004 (14) as positive (HR: 0.62; 95% CI, 0.44-0.89; P=0.014) with median follow-up of 34 months. However in the final publication of the mature results with median follow-up of 74 months, the survival gain lost statistical significance in OS (HR, 0.83; 90% CI, 0.64-1.08; P=0.125), and DFS (HR, 0.80; 90% CI, 0.62-1.02; P=0.065); respectively. In the subgroup of tumor size ≥4.0 cm in diameter though, there were significant advantages in OS (HR, 0.69; 90% CI, 0.48 to 0.99; P=0.043) and DFS (HR, 0.69; 90% CI, 0.49 to 0.97; P=0.035) for patients who received chemotherapy. Results of CALGB 9633 (and confirmatory findings from NCIC-CTG-JBR-10) support consideration for adjuvant chemotherapy in stage IB patients who have tumors ≥4.0 cm in diameter. However, the routine use of carboplatin/paclitaxel as an adjuvant regimen is discouraged based on the results of this trial.

The Lung Adjuvant Cisplatin Evaluation (LACE) analysis (15) collected and pooled data on 4,584 patients from the 5 randomized adjuvant cisplatin-based chemotherapy trials which were conducted after the NSCLCCG 1995 meta-analysis (5) and whose cohorts were larger than 300 patients: ALPI (6), IALT (8), ANITA (13), BR.10 (10), BLT (7). With a median follow-up of 5.1 years (3.1-5.9 years) the result showed there was a statistically significant benefit (HR: 0.89; 95% CI, 0.82-0.96; P=0.005) in OS for the chemotherapy group compared with the control group corresponding to an 11% reduction in the risk of death and absolute survival benefits of 3.9% and 5.4% at 3 and 5 years, respectively. The benefit varied with stage (test for trend, P=0.046) with an HR of 1.41 (0.96-2.09) for stage IA, 0.93 (0.78-1.10) for stage IB, 0.83 (0.73-0.95) for stage II, and 0.83 (0.73-0.95) for stage III. The rate of overall grade 3 to 4 toxicity was 66% and the most common toxicity was neutropenia (9% grade 3 and 28% grade 4).

This analysis clearly confirmed that cisplatin-based adjuvant chemotherapy is of benefit for completely resected NSCLC and further supports its use in routine clinical practice. Of note, 59% of patients received at least 240 mg/m^2 of cisplatin.

Results from LACE were very closely mirrored by the results of the updated NSCLC Meta-analyses Collaborative Group (16) which conducted a meta-analysis to assess the effectiveness of adjuvant chemotherapy in patients with NSCLC from randomized trials starting from Jan 1, 1965. The individual data was from 11,107 patients from 47 comparisons in 33 trials, which is more than three times that available in 1995. The comparison of surgery plus chemotherapy versus surgery alone was based on 34 trial comparisons and 8,447 patients (3,323 deaths) and showed a benefit of adding chemotherapy after surgery [hazard ratio (HR) 0.86, 95% CI, 0.81-0.92, P<0.0001], with an absolute increase in survival of 4% (95% CI, 3-6%) at 5 years (from 60% to 64%). Results for recurrence-free survival (HR 0.83, 95% CI, 0.77-0.90, P<0.0001), time to locoregional recurrence (0.75, 0.66-0.85, P<0.0001), and time to distant recurrence (0.80, 0.72-0.89, P=0.0007) all significantly favored chemotherapy. Another comparison of surgery plus radiotherapy and chemotherapy versus surgery plus radiotherapy was based on 13 trial comparisons and 2,660 patients (1,909 deaths) and showed a benefit of adding chemotherapy to surgery plus radiotherapy (HR 0.88, 95% CI, 0.81-0.97, P=0.009), representing an absolute improvement in survival of 4% (95% CI, 1-8%) at 5 years (from 29% to 33%).

The largest proportion of patients randomized to date to adjuvant chemotherapy have received cisplatin/vinorelbine (CVb, 41%) (17), which also was the most homogeneous subgroup in terms of drug doses and eligibility. As shown in a LACE meta-analysis subgroup analysis (17), the cisplatin/vinorelbine combination was associated with a substantially superior survival benefit compared with other cisplatin-based regimens. However, toxicity has been a critical issue in platinum-based adjuvant protocols with neutropenia in up to 85% and febrile neutropenia in up to 9% reported. Further points of concern are incomplete treatment delivery in up to 50% of the patients, mainly due to toxicity and patient refusal (18). In a phase III trial (19) in advanced stage NSCLC, the combination of cisplatin and pemetrexed (CPx), a multi-target folate antimetabolite, showed a good safety profile and convenient administration schedule and also OS superiority in adenocarcinoma (HR=0.84, P=0.03) and large cell (HR=0.67, P=0.03), both separately and

grouped together as "nonsquamous" (HR=0.81, P=0.005) when compared with gemcitabine combined with cisplatin. The question of whether this regimen could be used in the adjuvant setting was addressed in the TREAT study (20), a prospective, open-label, randomized phase 2 trial conducted in 16 centers in Germany and Belgium. A total of 132 patients with completely resected IB, IIA, IIB orT3N1 NSCLC were randomly assigned to cisplatin/pemetrexed (CPx) or cisplatin/vinorelbine (CVb). Postoperative radiotherapy was not allowed. The primary objective was the clinical feasibility rate. The results showed that the feasibility rate differed significantly and was higher in CPx than CVb [95.5% (95% CI, 87.5-99.1%) *vs.* 75.4% (95% CI, 63.1-85.2%), P=0.0010]. However, for efficacy data, the limitations of the size of a phase II trial, and of a large proportion of patients with stage IB or with squamous cell carcinoma, have to be taken into account. Further results of adjuvant cisplatin combined with pemetrexed are expected from the ITACA (EudraCT #: 2008-001764-36) and the ECOG E1505 (NCT00324805) trials. Although there is a lack of level 1 data regarding the utility of cisplatin/pemetrexed in an adjuvant setting, the NCCN guidelines (21) still recommend it as an option for non-squamous histology adjuvant chemotherapy. In addition to cisplatin/vinorelbine and cisplatin/pemetrexed, other regimens included on the E1505 trial, which closed to accrual in September 2013, include cisplatin/gemcitabine and cisplatin/docetaxed, which are also included as options per the NCCN. In interim data presented on E1505 (22), all 4 options have been selected on a fairly equal basis for patient enrolled onto the trial.

The treatment of lung cancer in the elderly bears special consideration. Between 2003 and 2007, 68% of cases of lung cancer were diagnosed in patients more than 65 years old and approximately 37% in patients over age 75 in the United States (23). However, although the incidence of NSCLC in elderly patients is high, they are underrepresented in clinical trials frequently (24). In a retrospective subgroup analysis of the JBR.10 trial (25), there were in total 155 patients (nearly 1/3 of the total) aged 65 years or older and the eldest patient was 82 years old, and in this subgroup adjuvant chemotherapy significantly prolonged overall survival (HR 0.61; 95% CI, 0.38-0.98; P=0.04). In a pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy in the LACE meta-analysis (26), patient and treatment characteristics, overall and event-free survival, delivery, chemotherapy toxicity and cause-specific mortality were compared among different age groups. There are 414 patients (9%) age

70 years or older. A trend toward survival benefit with adjuvant chemotherapy in elderly patients was shown (HR 0.90; 95% CI, 0.70-1.16; P=0.29), and no differences in severe toxicity rates were observed. This pooled analysis concluded that adjuvant cisplatin-based chemotherapy should not be withheld from elderly patients with NSCLC purely on the basis of age. These findings improved the probability of chemotherapy administration in the elderly in North America. A population based study based on the Ontario Cancer Registry (27) demonstrated that the percentage of patients aged at least 70 years of age who received adjuvant chemotherapy increased from 3.3% (2001 to 2003) to 16.2% (2004 to 2006). Twenty-eight percent of patients received carboplatin-based and 70% of patients received cisplatin-based regimens. In the Ontario analysis, the four-year survival of elderly patients increased significantly (47.1% for patients diagnosed from 2001 to 2003; 49.9% for patients diagnosed from 2004 to 2006; P=0.01). Survival improved in all subgroups except patients age ≥80 years. In US 16,420 patients >65 years with resected stage IB-IIIA NSCLC diagnosed between 1992 and 2007 were identified from the SEER-Medicare database (28). Among these patients, 1,803 (11%) received platinum-base adjuvant chemotherapy and this was associated with improved OS. However, 83% of the treated patients received carboplatin-based adjuvant chemotherapy and had a comparable OS advantage, and more favorable toxicity profile when compared with cisplatin-based adjuvant chemotherapy. In clinical practice, biologic age instead of chronologic age should be considered.

The combination of uracil and tegafur (also referred to as UFT, a pro-drug of 5FU) is an oral anticancer agent with good absorption in the small intestine (29). The West Japan Study Group for Lung Cancer Surgery reported that survival was significantly longer in patients assigned to adjuvant treatment with uracil-tegafur than in patients assigned to observation alone after complete resection of stage I, II, or III non–small-cell lung cancer. The five-year survival rate was 64 percent in the uracil-tegafur group and 49 percent in the control group (P=0.02). In a subgroup analysis, there was no significant difference in overall survival between the UFT group and the control group among patients with squamous-cell carcinoma (P=0.24) (30). Another Japanese Phase III randomized trial enrolled 979 patients with stage I (T1N0M0 or T2N0M0) adenocarcinoma of the lung and randomized them to receive either UFT 250 mg/m^2 for 2 years or observation. With median follow-up for 73 months, the difference in overall

survival between the two groups was statistically significant in favor of the UFT group (P=0.04). In subgroup analysis, the survival rate among patients with T2 disease in the UFT group was significantly higher than that in the control group, whereas among patients with T1 disease, there was no significant difference in survival between the UFT and control groups (31). A meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer (32) showed that postoperative adjuvant chemotherapy with UFT improved 5- and 7-year survival in a Japanese patient population composed primarily of stage I adenocarcinoma patients. Now in Japan, UFT is used as the standard postoperative adjuvant chemotherapy for stage I NSCLC patients with a tumor larger than 2 cm (33). S-1 is an orally active combination of tegafur and gimeracil [an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil)] (34). Tsuchiya *et al.* (35) reported a phase II trial that included 51 curatively resected pathologic stage IB-IIIA non-small-cell lung cancer patients who received 8 courses (4-week administration, 2-week withdrawal) of S-1 at 80-120 mg per day. Postoperative 1-year administration of S-1 seems feasible as an oral adjuvant chemotherapy for lung cancer and further trials are ongoing. The Japanese WJOG4107 trial enrolled 200 patients with completely resected stage II and IIIA (excluded multi-station N2 cases) NSCLC who were randomized to receive either oral S-1 (40 mg/m^2 twice per day) for consecutive 2 weeks repeated every 3 weeks for 1 year or cisplatin (60 mg/m^2 day1) plus oral S-1 (40 mg/m^2 twice per day) for consecutive 2 weeks repeated every 3 weeks for 4 cycles. Relapse free survival rate on 2 years was 65.6% (95% confidence interval, 55.3-74.0%) in the S-1 arm and 58.1% (95% confidence interval, 47.7-67.2%) in the cisplatin plus S-1 arm. OS data was not mature.

In summary, adjuvant therapy for NSCLC has reached a new era, but continued progress must be made. At this time, the role of adjuvant cisplatin-based chemotherapy has been established by multiple large randomized phase III trials for resected stage II and IIIA NSCLC, but it is controversial in high risk stage IB patients and is not recommended for those with resected stage IA disease. The majority of the adjuvant chemotherapy data is with cisplatin/vinorelbine but other cisplatin/based regimens are commonly utilized and are included in ongoing clinical trials. The carboplatin/paclitaxel regimen is only recommended if patients have comorbidities and are not able to tolerate cisplatin.

Acknowledgements

References

1. Datta D, Lahiri B. Preoperative evaluation of patients undergoing lung resection surgery. Chest 2003;123:2096-103.

2. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-14.

3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.

4. André T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-51.

5. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899-909.

6. Scagliotti GV, Fossati R, Torri V, et al. Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. J Natl Cancer Inst 2003;95:1453-61.

7. Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004;26:173-82.

8. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.

9. Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010;28:35-42.

10. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell

lung cancer. N Engl J Med 2005;352:2589-97.

11. Bezjak A, Lee CW, Ding K, et al. Quality-of-life outcomes for adjuvant chemotherapy in early-stage non-small-cell lung cancer: results from a randomized trial, JBR.10. J Clin Oncol 2008;26:5052-9.

12. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010;28:29-34.

13. Douillard JY, Rosell R, Delena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27.

14. Strauss GM, Herndon JE 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.

15. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.

16. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.

17. Douillard JY, Tribodet H, Aubert D, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol 2010;5:220-8.

18. Alam N, Shepherd FA, Winton T, et al. Compliance with post-operative adjuvant chemotherapy in non-small cell lung cancer. An analysis of National Cancer Institute of Canada and intergroup trial JBR.10 and a review of the literature. Lung Cancer 2005;47:385-94.

19. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.

20. Kreuter M, Vansteenkiste J, Fischer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed

versus cisplatin and vinorelbine: the TREAT study. Ann Oncol 2013;24:986-92.

21. NCCN Guildlines: Non-small-cell Lung Cancer. Available online: http://www.nccn.org/ professionals/ physician_gls/ f_guidelines.asp#site

22. Wakelee HA, Dahlberg SE, Keller SM, et al. Interim report of on-study demographics and toxicity from E1505, a phase III randomized trial of adjuvant (adj) chemotherapy (chemo) with or without bevacizumab (B) for completely resected early-stage non-small cell lung cancer (NSCLC). J Clin Oncol 2011;29:abstr 7013.

23. Altekruse SF, Kosary CL, Krapcho M, et al. eds. SEER Cancer Statistics Review, 1975-2007. Available online: http://seer.cancer.gov/csr/1975_2007, Accessed October 25, 2010.

24. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341:2061-7.

25. Pepe C, Hasan B, Winton T, et al. Adjuvant chemotherapy in elderly patients: An analysis of National Cancer Institute of Canada Clinical Trials Group and Intergroup BR.10. J Clin Oncol 2006;24:366s.

26. Früh M, Rolland E, Pignon JP, et al. Pooled analysis of the effect of age on adjuvant cisplatin-based chemotherapy for completely resected non-small-cell lung cancer. J Clin Oncol 2008;26:3573-81.

27. Cuffe S, Booth CM, Peng Y, et al. Adjuvant chemotherapy for non-small-cell lung cancer in the elderly: a population-based study in Ontario, Canada. J Clin Oncol 2012;30:1813-21.

28. Gu F, Wisnivesky JP, Mhango G, et al. Carboplatin versus cisplatin-based adjuvant chemotherapy in elderly patients with stages IB, II, and IIIA non-small cell lung cancer in the community setting. Proc Am Soc Clin Oncol 2013:31;abstr 7533.

29. Fujii S, Kitano S, Ikenaka K, et al. Effect of coadministration of uracil or cytosine on the anti-tumor activity of clinical doses of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. Gann 1979;70:209-14.

30. Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. West Japan Study Group for Lung Cancer Surgery. J Clin Oncol 1996;14:1048-54.

31. Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. N Engl J Med 2004;350:1713-21.

32. Hamada C, Tanaka F, Ohta M, et al. Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. J Clin Oncol 2005;23:4999-5006.

33. Nakagawa K, Kondo H. Lung cancer. Gan To Kagaku Ryoho 2011;38:1412-5.

34. Shirasaka T, Shimamato Y, Ohshimo H, et al. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 1996;7:548-57.

35. Tsuchiya T, Nagayasu T, Yamasaki N, et al. A multicenter phase II study of adjuvant chemotherapy with oral fluoropyrimidine S-1 for non-small-cell lung cancer: high completion and survival rates. Clin Lung Cancer 2012;13:464-9.