Adjuvant Chemotherapy for Lung Cancer: Cisplatin Doublets Only?

Daniel Morgensztern, MD, and Ramaswamy Govindan, MD, St. Louis, Missouri

American Cancer Society estimated that 213,380 new cases of lung cancer would be diagnosed and 160,390 deaths would occur in the United States in 2007. Among patients with lung cancer, approximately 87% have non–small cell lung cancer (NSCLC).

Despite complete resection, a significant proportion of patients with NSCLC will die of distant metastases, with 5-year survival ranging from 67% in patients with pathologic stage IA disease to 23% in those with stage IIIA disease. Because most recurrences after resection occur in distant sites, a strong rationale exists for using chemotherapy after surgery to eradicate micrometastatic disease.

Historical Perspectives

Several studies conducted from 1965 to 1991 evaluated the role of adjuvant chemotherapy in patients with resected NSCLC. Because most trials were small, they had no power to detect a significant survival benefit. In 1995, the Non-Small Cell Lung Cancer Collaborative Group (NSCLCCG) performed a large meta-analysis to evaluate the role of chemotherapy in patients with NSCLC. Fourteen trials with 4357 patients addressed the role of adjuvant chemotherapy after curative surgery. The role of adjuvant chemotherapy in patients with stage I disease remains controversial. Although no clinical or molecular predictors of recurrent disease after surgical resection are reliable, encouraging preliminary data on gene expression studies suggest that identifying, and perhaps treating, only patients at high risk for relapse might be possible in the near future. Furthermore, molecular predictors of resistance may guide the selection of chemotherapy in this setting.

Lung cancer is the most commonly diagnosed malignancy and the leading cause of cancer-related mortality worldwide, with approximately 1.2 million new cases and 1.1 million deaths estimated for 2000. The American Cancer Society estimated that 213,380 new cases of lung cancer would be diagnosed and 160,390 deaths would occur in the United States in 2007. Among patients with lung cancer, approximately 87% have non–small cell lung cancer (NSCLC).

Despite complete resection, a significant proportion of patients with NSCLC will die of distant metastases, with 5-year survival ranging from 67% in patients with pathologic stage IA disease to 23% in those with stage IIIA disease. Because most recurrences after resection occur in distant sites, a strong rationale exists for using chemotherapy after surgery to eradicate micrometastatic disease.

Historical Perspectives

Several studies conducted from 1965 to 1991 evaluated the role of adjuvant chemotherapy in patients with resected NSCLC. Because most trials were small, they had no power to detect a significant survival benefit. In 1995, the Non-Small Cell Lung Cancer Collaborative Group (NSCLCCG) performed a large meta-analysis to evaluate the role of chemotherapy in patients with NSCLC. Fourteen trials with 4357 patients addressed the role of adjuvant chemotherapy after curative surgery. Five trials, involving 2145 patients, used long-term alkylating agents and showed a detriment in survival from chemotherapy, with an absolute decrease of 5% at 5 years (hazard ratio [HR], 1.15; 95% CI, 1.04–1.27; P = .05). However, a 5% absolute survival benefit was seen at 5 years from the 8 trials involving 1394 patients treated with surgery followed by observation or the use of adjuvant cisplatin-based regimens (HR, 0.87; 95% CI, 0.74–1.02; P = .08). This lack of statistical significance has been attributed to the small number of patients available for this subset analysis.
Randomized Clinical Trials Developed After the 1995 Meta-Analysis

The trend toward improved survival observed in the NSCLCCG led to several larger randomized studies with platinum-based chemotherapy (Table 1). In the Adjuvant Lung Project Italy (ALPI) trial, 41209 patients with completely resected NSCLC stages I to IIIA were randomized to observation or adjuvant MVP (mitomycin, 8 mg/m² on day 1, vindesine, 3 mg/m² on days 1 and 8, and cisplatin, 100 mg/m² on day 1) every 3 weeks for 3 cycles. Patients were able to undergo radiation therapy according to preferences of the individual participating centers. Thirteen patients were excluded from the analysis because of eligibility criteria violations, and because of concerns about data integrity, 108 patients from a single institution were excluded, leaving 1088 patients in the final analysis. With a median follow-up duration of 64.5 months, no significant difference was seen in overall survival (OS; HR, 0.96; 95% CI, 0.81–0.13; P = .589) or progression-free survival (HR, 0.89; 95% CI, 0.76–1.03; P = .128) between the groups. Median OS in the chemotherapy and observation arms was 55 and 48 months, respectively.

The Big Lung Trial (BLT) evaluated the role of adjuvant cisplatin-based chemotherapy in patients with completely resected NSCLC stages I to III. Radiation therapy was allowed and 3% of patients underwent chemotherapy before surgery. Patients randomized to chemotherapy received 3 cycles of adjuvant treatment with 4 choices of combination, including MIP (cisplatin, 50 mg/m², mitomycin, 6 mg/m², and ifosfamide, 3 g/m², all on day 1 every 3 weeks), MPV (cisplatin, 50 mg/m², mitomycin, 6 mg/m², and vinblastine, 6 mg/m², all on day 1 every 3 weeks), CN (cisplatin, 80 mg/m² on day 1, and vindesine, 30 mg/m² on days 1 and 8, every 3 weeks), or CV (cisplatin, 80 mg/m² on day 1, and vindesine, 3 mg/m² on days 1 and 8, every 3 weeks). Median OS and 2-year survival rates for patients treated with chemotherapy were 33.9 months and 58%, respectively, compared with 32.6 months and 60% in patients who did not undergo chemotherapy. Adjuvant chemotherapy showed no survival benefit (HR, 1.02; 95% CI, 0.77–1.35; P = .90).

The International Adjuvant Lung Cancer Trial (IALT) randomized 1867 patients with completely resected NSCLC stages I to III to observation or cisplatin-based adjuvant chemotherapy. The choices of chemotherapy included 3 or 4 cycles of cisplatin with doses ranging from 80 to 120 mg/m² (total adjuvant dose, 300–400 mg/m²) and a second drug consisting of vindesine, 3 mg/m² per day, from days 1 to 29 and then every 2 weeks after day 43 until the last dose of cisplatin; vinblastine, 4 mg/m² per day, from days 1 to 29 and every 2 weeks after day 43 until the last dose of cisplatin; vinorelbine, 30 mg/m², weekly starting on the first day of cisplatin; or etoposide, 100 mg/m², on days 1 to 3 with each cycle of cisplatin. Radiation therapy was allowed after the completion of chemotherapy. The combination of cisplatin 100 mg/m² for 3 to 4 cycles and etoposide was the most commonly used regimen, selected for 49.3% of patients. After a median follow-up of 56 months, patients assigned to chemotherapy had a significant increase in 5-year OS (44.5% vs. 40.4%; HR, 0.86; 95% CI, 0.76–0.98; P = .001).

### Table 1 Benefit From Adjuvant Chemotherapy in the NSCLCCG 1995 Meta-Analysis and Recent Large Randomized Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Stage</th>
<th>Chemotherapy</th>
<th>Hazard Ratio for Overall Survival (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLCCG</td>
<td>1394</td>
<td>I–III</td>
<td>Cisplatin-based</td>
<td>0.87 (0.74–1.02)</td>
<td>.08</td>
</tr>
<tr>
<td>ALPI</td>
<td>1209</td>
<td>I–IIIA</td>
<td>MPV</td>
<td>0.96 (0.81–1.13)</td>
<td>.589</td>
</tr>
<tr>
<td>BLT</td>
<td>381</td>
<td>I–IIIA</td>
<td>Cisplatin-based</td>
<td>1.02 (0.77–1.35)</td>
<td>.90</td>
</tr>
<tr>
<td>IALT</td>
<td>1867</td>
<td>I–IIIA</td>
<td>Cisplatin-based</td>
<td>0.86 (0.76–0.98)</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>JBR.10‡</td>
<td>482</td>
<td>II–II</td>
<td>Cisplatin-vinorelbine</td>
<td>0.69 (0.52–0.91)</td>
<td>.009</td>
</tr>
<tr>
<td>ANITA</td>
<td>840</td>
<td>II–IIIA</td>
<td>Cisplatin-vinorelbine</td>
<td>0.8 (0.66–0.96)</td>
<td>.017</td>
</tr>
<tr>
<td>CALGB 9633</td>
<td>344</td>
<td>IB</td>
<td>Carboplatin-paclitaxel</td>
<td>0.8 (0.60–1.07)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: ALPI, Adjuvant Lung Cancer Project Italy; ANITA, Adjuvant Navelbine International Trialist Association; BLT, Big Lung Trial; CALGB, Cancer and Leukemia Group B; IALT, International Adjuvant Lung Cancer Trial; MPV, cisplatin mitomycin vinblastine; NSCLCCG, Non-Small Cell Lung Cancer Collaborative Group.
Adjuvant Chemotherapy for Lung Cancer

P < .03) and disease-free survival (39.4% vs. 34.3%; HR, 0.83; 95% CI, 0.74–0.94; P < .003).

The National Cancer Institute of Canada Clinical Trials Group JBR.10 randomly assigned 482 patients with completely resected stage IB or II (excluding T3 N0) to 4 cycles of adjuvant cisplatin (50 mg/m² on days 1 and 8, every 4 weeks) and vinorelbine (25 mg/m² weekly for 16 weeks) or observation. No postoperative radiation was allowed. After a median follow-up of 3.3 years in the observation group and 5.1 years in the chemotherapy group, significant improvement was seen in both OS (94 vs. 73 months; HR, 0.69; 95% CI, 0.52–0.91; P = .009) and relapse-free survival (not reached vs. 46.7%; HR, 0.60; 95% CI, 0.45–0.79; P < .001). Five-year survival rates for adjuvant chemotherapy and observation were 69% and 54%, respectively (P = .03).

In the Adjuvant Navelbine International Trialist Association (ANITA) trial,12 840 patients with resected NSCLC stage IB to III were randomly assigned to observation or adjuvant chemotherapy with cisplatin (100 mg/m² on day 1 every 4 weeks) and vinorelbine (30 mg/m² weekly for a maximum of 16 doses). Radiation therapy was allowed but not mandatory or randomized. The median survival was significantly improved in patients treated with adjuvant chemotherapy (65.7 vs. 43.7 months; HR, 0.8; 95% CI, 0.66–0.96; P = .017). The absolute survival benefit in the adjuvant chemotherapy arm increased from 2.8% at 1 year to 8.4% at 7 years.

The CALGB trial 963314 randomized patients with completely resected NSCLC stage IB to observation or 4 cycles of adjuvant chemotherapy with carboplatin (area under the curve = 6 on day 1 every 3 weeks) and paclitaxel (200 mg/m², on day 1 every 3 weeks). No postoperative radiation was allowed. The preliminary results were reported in 2004 after a median follow-up of 34 months13 showing a significant improvement in the 4-year OS for the chemotherapy arm (71% vs. 59%; HR, 0.62; 95% CI, 0.41–0.95; P = .028). With more mature results at a median follow-up of 57 months, however, the difference in survival was no longer statistically significant (HR, 0.80; 95% CI, 0.60–1.07; P = .10).14 Median OS and 5-year survival were 95 months and 59% in the chemotherapy arm compared with 78 months and 57% in the observation group. In an unplanned subset analysis, a significant improvement was seen in both OS (HR, 0.66; 95% CI, 0.45–0.97; P = .04) and disease-free survival (HR, 0.62; 95% CI, 0.44–0.89; P = .01) for patients with tumors larger than 4 cm treated with adjuvant chemotherapy.

The Lung Adjuvant Cisplatin Evaluation

The Lung Adjuvant Cisplatin Evaluation (LACE)15 was a pooled analysis of individual patients enrolled into clinical trials of adjuvant cisplatin-based chemotherapy involving at least 300 patients. A total of 4584 patients were selected from 5 randomized clinical trials (ALPI, BLT, IALT, JBR.10, and ANITA). At a median follow-up of 5.1 years, a significant 5-year OS benefit favored chemotherapy (48.8% vs. 43.3%; HR, 0.89; 95% CI, 0.82–0.96; P = .004) with no significant heterogeneity. Although adjuvant chemotherapy was associated with survival improvement in patients with stage II or III disease (HR, 0.83; 95% CI, 0.73–0.95), the benefit was not statistically significant in patients with stage IB (HR, 0.92; 95% CI, 0.78–1.10) and the treatment may be detrimental for patients with stage IA disease (HR, 1.41; 95% CI, 0.96–2.09).

Issues Relevant for Clinical Practice

Treatment of Stage I NSCLC

Among the 6 large randomized clinical trials testing adjuvant chemotherapy in patients with completely resected stage IB NSCLC,6–11 none showed improved survival. In an unplanned subset analysis from the CALGB study,11 patients with tumors larger than 4 cm showed significant improvement in OS and disease-free survival. Furthermore, the earlier improvement in survival until 3 years after the surgery (3-year OS of 79% for chemotherapy vs. 71% for observation; P = .043) suggests that chemotherapy may delay tumor recurrence in this patient population. Therefore, the role of chemotherapy remains controversial in patients with stage IB disease but should still be considered in those with large tumors. However, the LACE analysis15 showed detriment in survival and provided no evidence to support the use of adjuvant platinum-based chemotherapy in stage IA disease.

An additional option in patients with stage I disease is the use of UFT, an oral fluorouracil (FU) derivative composed of tegafur (a prodrug of FU) and uracil (an inhibitor of dihydropyrimidine dehydrogenase, the enzyme responsible for the FU catabolism), in a molar ratio of 1:4. A recent meta-analysis16 evaluating the
efficacy of adjuvant UFT in 2003 patients from 6 randomized trials showed a significant benefit in the treatment arm, with increased 5-year survival from 77.2% in patients treated with surgery alone to 81.5% in patients undergoing adjuvant UFT ($P = .011$). In this meta-analysis, more than 95% of patients had pathologic stage IA or IB disease, and the benefit was statistically significant in patients with pathologic stage T1 (HR, 0.73; 95% CI, 0.56–0.93). Because of the wide variation in the CI, perhaps because of the lower number of patients, the survival benefit did not reach statistical significance in patients with pathologic stage T2 (HR, 0.78; 95% CI, 0.60–1.01). Despite these encouraging results in stage I disease, no confirmatory data exist outside Japan, and this agent is currently not available in the United States.

### Cisplatin Versus Carboplatin

CALGB 9633 is the only trial that used carboplatin. Although the survival benefit was not statistically significant for the chemotherapy arm, this study enrolled only patients with stage IB. Because the lack of survival benefit in patients with stage IB disease was also noted in most large randomized clinical trials and the LACE analysis, the impact of carboplatin is difficult to evaluate in this setting. Nevertheless, cisplatin has long been considered a slightly more effective drug than carboplatin in the metastatic setting. The recent meta-analysis comparing cisplatin with carboplatin (CISCA) in patients with advanced NSCLC evaluated 2968 patients from 9 trials. Cisplatin was associated with increased response rates (30% vs. 24%; $P < .001$), median survival (9.1 vs. 8.4 months), and 1-year survival (37% vs. 34%; $P = .1$). The patients from more recent trials treated only with platinum-based third-generation agents showed a significant survival improvement for cisplatin compared with carboplatin (HR, 1.11; 95% CI, 1.01–1.21). Patients with nonsquamous histology showed similar survival improvement from treatment with cisplatin (HR, 1.12; 95% CI, 1.01–1.23). The elimination of heterogeneity may explain the significant survival benefit in these particular patient subsets. A 2004 meta-analysis comparing the 2 platinum agents further supports the benefit of cisplatin compared with carboplatin in third-generation platinum doublets. Although the 1-year OS benefit from cisplatin-based therapy was only 5% and not statistically significant for the entire cohort, it increased to 11% in the 5 trials that included the use of new agents, such as taxanes and gemcitabine. Although this modest benefit in survival may not be very important in the palliative setting, it could be rather critical in the adjuvant setting, where cure is the ultimate goal and even small differences may matter.

### Chemotherapy Regimens

Chemotherapy regimens used in the cisplatin-based adjuvant trials can be broadly divided into 3 subgroups: cisplatin and vinorelbine; cisplatin and another drug; and cisplatin-based triplets. Three studies that showed improved survival in patients treated with adjuvant chemotherapy used a cisplatin-based doublet with either cisplatin or vinorelbine only (JBR.10, ANITA) or cisplatin combinations consisting mostly of cisplatin in combination with etoposide or vinorelbine (IALT). Two studies showing no survival benefit from adjuvant chemotherapy using cisplatin-based regimens used either MVP alone (ALPI) or mostly triplet therapy with MVP or MIP (BLT). Two possible explanations for the lack of improved survival in patients treated with cisplatin-based triplets are the increased toxicity associated with these regimens and decreased total dose of cisplatin; compliance with adjuvant chemotherapy was decreased in both studies.

In the ALPI trial, 69% of patients completed the treatment, with half requiring dose adjustments or omission of parts of the planned regimen. In addition, 22% of patients stopped treatment because of toxicity or personal choice and 9% never began therapy. The number of deaths within the first year after randomization was also greater in the chemotherapy arm, with 90 deaths in the MPV group and 69 deaths in the control.

In the BLT trial, 75% of the patients were treated with triplets (MVP or MIP) compared with 25% treated with platinum doublets. Among the 192 patients randomized to chemotherapy, 123 (64%) underwent the planned cycles, with 46 (40%) of these requiring dose modification, delays in therapy, or both. Compared with the trials using cisplatin-based doublets, 73.8% of patients in the IALT trial received at least 240 mg/m² of cisplatin, 58% of patients in the JBR.10 trial completed at least 3 cycles of chemotherapy with planned doses of cisplatin on days 1 and 8 (300 mg/m²), and 61% of patients in the ANITA trial received at least 3 cycles of cisplatin (300 mg/m²).

In the LACE analysis, cisplatin plus vinorelbine was the most commonly used combination and seemed to be the most effective regimen, showing a significant
Adjuvant Chemotherapy for Lung Cancer

survival benefit compared with observation (HR, 0.80; 95% CI, 0.70–0.91), cisplatin plus another drug (HR, 0.93; 95% CI, 0.8–1.07), and cisplatin-based triplets (HR, 9.98; 95% CI, 0.84–1.14). However, the total doses of cisplatin were significantly higher for patients treated with this combination, with most patients scheduled to receive 400 mg/m². In contrast, the group receiving cisplatin plus another drug received a more evenly distributed total cisplatin dose from 300 mg/m² to 400 mg/m², and most patients receiving cisplatin-based triplets were scheduled to receive a total cisplatin dose of 300 mg/m². Therefore, compliance and total cisplatin dose may be the most important factors in determining success of a particular regimen in the adjuvant setting.

In summary, 6 recent large, randomized adjuvant trials involved the use of platinum agents, with 3 showing survival advantage for chemotherapy and 3 showing no significant difference. A common feature of all positive studies was the use of cisplatin-based doublets, whereas the negative trials used carboplatin or a cisplatin-based triplet as either the only treatment option or the most commonly chosen regimen.

Role of Adjuvant Radiation Therapy

In contrast to the established benefit from adjuvant chemotherapy, the role for radiotherapy in this setting remains controversial. The postoperative radiotherapy (PORT) meta-analysis evaluated individual patient data from 9 randomized clinical trials comparing surgery alone and surgery followed by radiation therapy. The studies accrued 2128 patients between 1966 and 1994. With a median follow-up of 3.9 years for surviving patients, adjuvant radiation showed a significant adverse effect on survival, with a 21% relative increase in the risk for death (HR, 1.21; 95% CI, 1.08–1.34; P = .001). In a subset analysis, the detriment in survival was greater in stage I compared with stage II disease, and no clear survival disadvantage was seen for patients with stage III disease. Some criticisms of this meta-analysis include the use of outdated radiation modalities and inappropriately high doses, which may be associated with early deaths. None of the trials from the PORT analysis would be considered acceptable in the context of modern therapy. The most recent meta-analysis included 1 additional trial, increasing the total number of evaluated patients to 2232. The relative increase of death associated with adjuvant radiation therapy was 18%, clearly indicating a detriment effect for this treatment.

This adverse effect on survival was most evident in patients with early-stage disease and low nodal status. Nevertheless, whether adjuvant radiation is detrimental or beneficial for patients with stage III (HR, 0.97; 95% CI, 0.82–1.14) or N2 disease (HR, 0.96; 95% CI, 0.79–1.17) is unclear. Further support for the use of adjuvant radiation in patients with advanced-stage disease comes from a Survival, Epidemiology, and End Results (SEER) analysis involving 4013 patients diagnosed between 1988 and 1995. In this study, the use of adjuvant radiation was associated with a significant improvement in OS, from 16% to 22% (P = .001). Although the concurrent use of chemotherapy and radiation in the adjuvant setting allows the timely delivery of both modalities soon after the surgery, with potential additive or synergistic effects, this combination does not result in survival advantage. Therefore, radiation therapy has been commonly used in patients at high risk for local recurrence, including those with positive surgical margins, residual local disease, mediastinal lymph node involvement, and extracapsular extension. When indicated, radiation therapy should begin after the completed course of adjuvant chemotherapy.

Adjuvant Chemotherapy After 2 Months

Because patients enrolled into the large randomized clinical trials were started on chemotherapy between 4 and 6 weeks after surgery, no data is available on the use of adjuvant chemotherapy beyond 2 months from complete resection.

Molecular Predictors for Benefit From Adjuvant Cisplatin Chemotherapy

Because the benefits from adjuvant chemotherapy are limited to a small subgroup of patients with micrometastases who are sensitive to chemotherapy, significant interest has been shown in the development of predictive biomarkers to allow better selection of patients most likely to benefit from this treatment modality. Recent retrospective studies of large randomized clinical trials have evaluated the role for molecular predictors of benefit from adjuvant chemotherapy (Table 2).

Platinum compounds induce cell death through binding to DNA and forming bulky DNA adducts, which may lead to mutagenesis or apoptosis. In mammalian cells, the nucleotide excision repair (NER) is the major mechanism involved in removing damaged bases, including DNA adducts. Chemosensitive cells with low NER activity cannot repair the adducts and undergo
apoptosis, whereas chemoresistant cells with high NER activity may excise the adduct with DNA repair. Once the adduct is recognized, the proteins of the NER are assembled at the adduct site, with the rate-limiting step performed by the assembly of excision repair cross-complementary group 1 (ERCC1). In patients with NSCLC treated with cisplatin and gemcitabine, low ERCC1 expression has been correlated with improved response rates and survival. Furthermore, single nucleotide polymorphisms of the ERCC1 at codon 118 have been associated with increased response to chemotherapy and improved survival in patients with NSCLC, with better outcomes in patients with the C/C phenotype than in those with C/T or T/T.

The impact of ERCC1 as a predictor of benefit from chemotherapy in patients with completely resected NSCLC was recently evaluated in a retrospective analysis of patients treated in the IALT study (Table 2). In this analysis, immunohistochemistry showed that ERCC1 expression was positive in 335 (44%) among 761 tumors available for the study. Among patients with ERCC1-negative tumors, the median OS and 5-year survival for those who underwent chemotherapy were 56 months and 47%, respectively, versus 42 months and 39% for the observation groups (HR, 0.56; 95% CI, 0.50–0.86; P = .002). In contrast to the significant benefit seen in patients with ERCC1-positive tumors, adjuvant chemotherapy showed no survival benefit in patients with ERCC1-positive tumors; median OS and 5-year survivals for the chemotherapy group were 50 months and 40%, respectively, compared with 55 months and 46% for the observation group (HR, 1.14; 95% CI, 0.84–1.55; P = .40).

Filipits et al. evaluated the prognostic and predictive value of cell cycle regulators (p27, p16, cyclin D1, cyclin D3, cyclin E) and Ki-67 in 778 patients enrolled in the IALT study. The only biomarker that predicted benefit from adjuvant chemotherapy was p27, which immunohistochemistry analysis showed was expressed in approximately 50% of patients. Among patients with p27-negative tumors, the median OS and 5-year survival for patients treated with adjuvant chemotherapy were 58 months and 50%, respectively, versus 45 months and 41% for controls (HR, 0.66; 95% CI, 0.50–0.88; P = .006). In contrast, patients with p27-positive tumors had no significant benefit from adjuvant chemotherapy, with median OS and 5-year survival of 41 months and 37%, respectively, in the chemotherapy group versus 52 months and 42% in the control group (HR, 1.09; 95% CI, 0.82–1.45; P = .54).

In the JBR.10 trial, ras was mutated in 24% of patients randomized to chemotherapy or observation. Among patients with wild-type ras, the median survival was significantly improved with adjuvant chemotherapy (not reached vs. 74 months; HR, 0.69; 95% CI, 0.49–0.98; P = .03), whereas adjuvant chemotherapy did not provide significant benefit (HR, 0.95; 95% CI, 0.53–0.71; P = .87). In a second retrospective from the JBR.10 trial, β-tubulin III expression was evaluated as a predictor of outcome in patients with completely resected NSCLC. High β-tubulin III expression was present in approximately 50% of patients and was more common in women and patients with nonsquamous histology, ras mutations, and age younger than 60 years. Patients with low β-tubulin III showed no significant benefit in OS (HR, 1.0; 95% CI, 0.57–1.75; P = .99), whereas patients with high β-tubulin III expression experienced a significant improvement in relapse-free survival (HR, 0.45; 95% CI, 0.25–0.75; P = .002). The OS for patients with high β-tubulin III expression treated with chemotherapy, however, did not reach statistical significance (HR, 0.64; 95% CI, 0.39–1.04; P = .07).

Future Directions
Because of the survival benefit observed with epidermal growth factor receptor (EGFR) inhibitors and antiangiogenesis therapy in patients with advanced disease, ongoing clinical trials are evaluating the role of targeted therapies in the adjuvant setting.
The JBR.19 study planned to enroll 1200 patients with surgically resected stages IB to III NSCLC to receive 2 years of gefitinib or placebo after adjuvant chemotherapy. This study, however, was closed prematurely because of the results of the Iressa Survival Evaluation in Advanced Lung Cancer study, which failed to show a survival advantage for gefitinib compared with placebo in patients with advanced disease. Nevertheless, the survival advantage from erlotinib compared with placebo in patients with advanced NSCLC supported the development of the Randomized Double-blind Trial in Adjuvant NSCLC with Tarceva (RADIANT), a large phase III study evaluating the role of erlotinib in the adjuvant treatment of patients with resected stage IB to IIIA NSCLC. Only patients with EGFR-positive tumors, assessed with either fluorescence in situ hybridization or immunohistochemistry, will be randomized and may or may not undergo adjuvant chemotherapy before treatment with erlotinib, 150 mg daily, for 2 years. Antiangiogenesis in the adjuvant setting is currently being tested in a phase III trial in which patients will receive 4 cycles of cisplatin-based chemotherapy (cisplatin and gemcitabine, vinorelbine, or docetaxel), with or without the addition of bevacizumab, every 3 weeks for 1 year.

Conclusions
Strong evidence supports the use of adjuvant cisplatin-based chemotherapy after complete surgical resection in medically fit patients with stage II or III NSCLC. The recommended chemotherapy regimen is a cisplatin-based doublet, with the combination of cisplatin and vinorelbine being the most commonly studied. Carboplatin-based doublets may still be considered in patients with contraindication to cisplatin, given their similar efficacy in the metastatic setting, and survival benefit in patients with stage I tumors larger than 4 cm from the CALGB 9633 study. Nevertheless, given the absence of clinical data in stages II and III, the use of adjuvant carboplatin remains experimental. Although adjuvant treatment with UFT has shown some promise in treating patients with stage I disease, this agent is not currently available in the United States. Studies using cisplatin-based triplets did not show survival benefit. The role of adjuvant chemotherapy in patients with stage IB remains controversial. Retrospective studies have evaluated potential molecular predictors of benefit from adjuvant cisplatin chemotherapy, but the results must be validated in prospective trials before they are incorporated into clinical practice. The development of these molecular predictors may provide better guidance for patient selection. Furthermore, patients known to have reliable predictors for poor response to cisplatin may be considered for treatment with alternative regimens. Another area of research interest is the incorporation of targeted agents in the adjuvant setting, either concurrently with chemotherapy or as maintenance.

References


