Induction Therapy for Early-Stage Non-Small-Cell Lung Cancer

Review Article [1] | July 01, 2004
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Data from adjuvant trials clearly indicate that one of the most important problems in patients with resected non-small-cell lung cancer (NSCLC) is compliance to chemotherapy. In the postoperative setting, significant comorbidities and incomplete recovery after surgery often make it difficult for patients to tolerate or comply with systemic therapy. Therefore, it may be preferable to deliver chemotherapy before surgery as "neoadjuvant" or "induction" chemotherapy. The rationale for using induction chemotherapy is based on evidence that chemotherapy might reduce tumor burden and possess activity against micrometastases, resulting in improved results by surgery, radiotherapy, or a combination. Moreover, induction therapy facilitates in vivo assessment of tumor response or resistance. Potential drawbacks include the risk of perioperative complications, and the possibility that the tumor mass may become unresectable due to disease progression. During the past decade, four phase III randomized trials evaluated the role of induction chemotherapy in stage IIIA NSCLC. The first three studies consistently showed that induction chemotherapy improves survival compared with surgery alone. More recently, a large phase III trial performed by French investigators suggested a survival benefit in stage I/II patients, but not stage IIIA. The high activity of new platinum-based chemotherapy-based on response rate and 1-year survival in advanced disease-reinforces the rationale for the use of these new combinations in early-stage NSCLC, especially for a subset of patients traditionally treated with surgery alone. Several phase III trials are currently evaluating the role of new doublets as induction chemotherapy; these are discussed in the article. The results of these ongoing phase III trials should help clarify the role of induction chemotherapy in early-stage disease.

Despite advances in therapy combined with smoking-cessation programs, lung cancer continues to be the leading cause of cancer death in the United States with an estimated 173,770 new patients diagnosed and 160,440 deaths in 2004.[1] For patients with non-small-cell lung cancer (NSCLC), tumor staging is the most important prognostic factor and largely determines treatment. Radical surgery alone is the treatment of choice of early-stage NSCLC. Nevertheless, after surgical resection for stage I and II NSCLC, the 5-year survival rate without recurrence is approximately 50% in stage I disease and 35% in stage II. The vast majority of patients with stage IIIA disease that is resected for cure relapse, and the majority of these develop systemic spread. In recent years, clinical trials have attempted to determine whether postoperative therapy improves the results obtained with surgery alone. The first generation of adjuvant trials (ie, those carried out in the 1960s through the 1970s) used long-term alkylating agents; the trials with the largest patient populations were those of the Medical Research Council[2] and the Veterans Administration.[3,4] Starting in the late 1970s, most trials incorporated cisplatin-containing chemotherapy regimens into their study designs.[5,6] Chemotherapy often included cyclophosphamide (Cytoxan, Neosar), doxorubicin, and cisplatin. Because of the limited number of patients, it was not possible to establish clearly the role of adjuvant chemotherapy in early-stage NSCLC. The Medical Research Council and Institut Gustave Roussy therefore conducted a large overview using updated individual data of all trials, whether published or unpublished.[7] More than 9,000 patients from 52 randomized trials fulfilled the selection criteria. In the group comparing surgery alone to surgery followed by adjuvant chemotherapy, 14 trials recorded an overall accrual of 4,357 patients.
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In the five trials using long-term alkylating agents, adjuvant chemotherapy showed a detrimental effect; in the eight trials that used a cisplatin-based regimen, there was a 13% reduction in the risk of death, suggesting an absolute benefit of 5% with adjuvant chemotherapy at 5 years. Chemotherapy was randomly added to surgery and radiotherapy in a total of 807 patients. This led to a 6% reduction in the risk of death, suggesting a 2% absolute benefit at 5 years. These findings constituted the rationale for the large-scale trials and several adjuvant studies worldwide using newer regimens that have been initiated. An important conclusion from the European meta-analysis is that survival benefits from chemotherapy are small, and trial sizes therefore must have large patient populations to demonstrate patient benefit. The results of four randomized multicentric trials have been presented recently (Table 1).[8-11] Although the results were controversial, these studies, particularly the Japanese study and the International Adjuvant Lung Cancer Trial (IALT), confirmed a small, statistically significant benefit in survival for patients receiving adjuvant chemotherapy.[10,11] Data from adjuvant trials clearly indicate that one of the most important problems in patients with resectable NSCLC is compliance to chemotherapy. In the postoperative setting, significant comorbidities and insufficient recovery following surgery often make it difficult for patients either to tolerate or comply with systemic therapy. Therefore, it might be preferable to deliver chemotherapy before surgery ("neoadjuvant" or "induction" chemotherapy). Induction chemotherapy offers several theoretical advantages: (1) immediate systemic therapy in patients at high risk for relapse with potential eradication of micrometastases, (2) avoidance of postoperative complications and comorbidities that might potentially compromise compliance or tolerance, (3) reduction of tumor burden with a potential for increases in resectability rates and ease of resection, and (4) in vivo assessment of tumor response or resistance. However, potential drawbacks include risk of perioperative complications and potential for the tumor to become unresectable due to disease progression.

**Induction Chemotherapy With Older-Generation Regimens**

Although complete resection for patients with stage IIIA disease is technically feasible, the 5-year survival is only 10%, primarily due to the development of distant metastases. Several phase II studies evaluated the role of induction chemotherapy in stage IIIA NSCLC.[12-15] These studies demonstrated that induction chemotherapy is feasible, with acceptable toxicity, and capable of inducing an average overall response rate ranging from 50% to 82%, with complete responses achieved in less than 10% of the treated patients. More than 60% of patients who responded underwent radical resection, and the combined-modality approach produced an overall median survival duration of approximately 19 months, with median survival of 27 to 29.7 months in patients undergoing complete resection. During the 1990s, four phase III randomized trials evaluated the role of induction chemotherapy in stage IIIA NSCLC (Table 2).[16-19] The first three studies consistently
demonstrated that induction chemotherapy improved survival compared with surgery alone.[16-18] Pass et al.[16] randomly assigned 27 stage IIIA NSCLC patients to receive cisplatin/etoposide chemotherapy followed by surgery or surgery alone. This small study reported a trend toward improved survival time in the chemotherapy group.[16] Rosell et al.[17] conducted a randomized phase III study comparing surgery alone with induction cisplatin/mitomycin (Mutamycin)/ifosfamide (Ifex) for three cycles followed by surgery. This study was prematurely closed based on an interim analysis that demonstrated a significant benefit in survival for the patients receiving induction chemotherapy.[17] Median survival was 26 months in the combined-modality arm compared to only 8 months in the surgery-only arm (P < .001); no patients were alive at 2 years in the surgery-only arm. Disease-free survival was 20 months in the combined modality arm as opposed to 5 months in surgery group (P < .001). Standard therapy yielded survival results much poorer than expected, based on historic data in patients with initially resectable stage III disease. (In fact, several retrospective studies showed that the 5-year survival for completely resected N2 patients is 20% to 30% without chemotherapy.) Moreover, the incidence of k-ras oncogene mutations was only 15% in the chemotherapy arm vs 42% in the surgery-only arm.[17] Roth et al.[18] randomly assigned patients with IIIA disease to undergo either surgery alone or induction chemotherapy (cyclophosphamide/cisplatin/etoposide) for three cycles followed by surgery and additional chemotherapy. Although the complete resection rates were similar in both arms, median survival was significantly increased in patients receiving induction therapy (64 vs 11 months, P < .008). The estimated 2- and 3-year survival percentages were 60% and 56% for the induction chemotherapy arm compared to 25% and 15%, respectively, for study patients undergoing surgery alone.[18] Similar to Rosell et al's decision in their study based on interim results,[17] this trial prematurely closed with only 60 patients accrued rather than the intended 130. Moreover, induction chemotherapy was highly toxic, with 80% encountering grade 3/4 neutropenia and 15% with neutropenic fever, with 70% of patients requiring dose reduction. These trials of Rosell et al and Roth and colleagues have demonstrated survival benefits for induction chemotherapy in patients with stage IIIA NSCLC. Notably, both trials closed early due to the overwhelming survival benefit in the experimental arms.[17,18] While these trials were encouraging, the number of accrued patients was small and contained a heterogeneous population. Moreover, potential, unintentional selection bias, such as the presence of a high percentage of k-ras mutations in the surgery-only arm of the Rosell trial,[17] and the very poor outcome of the standard-therapy arms, preclude a definitive conclusion regarding induction therapy.

Depierre et al.[19] recently conducted a randomized phase III trial that compared the survival benefit of NSCLC patients with stage I, II, and IIIA disease receiving two induction cycles of mitomycin/ifosfamide/cisplatin (the MIP regimen) before resection with patients undergoing surgical resection alone. For patients with stage IB through IIIA disease, a general 11-month improvement in median survival was recorded for patients receiving MIP chemotherapy. Importantly, this finding occurred after the first 5 months, and survival benefit also reached statistical significance only in stage I and II—not in stage IIIA disease. However, the lack of survival benefit in stage IIIA disease observed in the trial by Depierre and co-workers[19] contrasts with previous data[16-18] in which a survival benefit was reported for stage IIIA patients. A possible area of discrepancy might lie in the study design used by Depierre et al[19]: it was the first study to include a large number of patients, and possibly, chemotherapy could be less active on bulky disease. Moreover, a recent update of the data of Roth and co-workers reinforced an important difference in respective survival difference.
between the two arms. The investigators reanalyzed the study data with a median time from random allocation to analysis of 82 months, reporting that the increase in survival conferred by perioperative chemotherapy was maintained during the period of extended observation.[20] Another important finding in the study by Depierre et al[19] was that the benefits of preoperative induction chemotherapy with MIP were delayed for 5 months because of the high perioperative toxicity that was associated with the combination of chemotherapy and resection. Because this issue is potentially the most important finding from the trial, reducing perioperative toxicity should be addressed in future trials and treatment protocols. **Induction Chemotherapy With Newer-Generation Regimens**

During the 1990s, several trials evaluated the role of new cytotoxic drugs, such as the taxanes, gemcitabine (Gemzar), and vinorelbine (Navelbine), in combination with a platinum agent. These studies demonstrated that combinations of a new drug with a platinum derivative produced better response rates when compared with (1) a single agent, (2) an older two-drug combination, or (3) an older three-drug regimen.[21-30] Thus, the combination of either cisplatin or carboplatin (Paraplatin) with a new cytotoxic evolved into the standard treatment for patients with advanced NSCLC. Several large phase III trials recently compared these new doublets to determine the ideal treatment regimen for patients with advanced NSCLC. The trials similarly demonstrated a substantial equivalence of the new regimens in terms of efficacy and survival parameters, with differences only in toxicity profiles and economics.[31-33] Thus, in early-stage NSCLC, the new doublets are possibly more active and less toxic than older combinations, and these factors might contribute toward increased survival benefit.

### Table 3

<table>
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<tr>
<th>Study Group</th>
<th>Stage</th>
<th>Regimen</th>
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<tr>
<td>SWOG</td>
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<td>Carboplatin/paclitaxel</td>
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<tr>
<td>SLCG</td>
<td>I, II, IIIA</td>
<td>Carboplatin/paclitaxel</td>
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<td>MRC-LU22</td>
<td>IB, II, IIIA</td>
<td>Navelbine/cisplatin, Vindeosine/ifosfamide/cisplatin, Mitomycin/ifosfamide/cisplatin</td>
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<td>I, II, IIIA</td>
<td>Gemcitabine/cisplatin</td>
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<td>IB, II</td>
<td>Carboplatin/paclitaxel</td>
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<tr>
<td>IFCT</td>
<td>I, II</td>
<td>Carboplatin/paclitaxel, Gemcitabine/cisplatin</td>
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ChEST = Chemotherapy in Early Stage NSCLC; DLCSCG = Dutch Lung Cancer Study Group; EORTC = European Organisation for Research and Treatment of Cancer; IFCT = Intergroupe Francophone de Cancers du Thorax;}

**Gemcitabine** is one of the most active agents in the management of NSCLC. Phase II trials in patients with unfavorable stage IIIB or stage IV NSCLC demonstrated that the combination of gemcitabine and cisplatin achieved an objective response rate ranging of 52% to 54%.[34,35] Randomized phase III trials conducted in the patients with similar-stage disease showed that the gemcitabine/cisplatin combination was more active than cisplatin alone.[23] cisplatin and etoposide,[21] or the MIP regimen.[22] These pivotal data prompted Van Zandwijk and the European Organization for Research and Treatment of Cancer (EORTC) Lung Cancer Cooperative Group to initiate a phase II trial to define further the activity and toxicity of the gemcitabine/cisplatin combination as induction treatment in 47 stage IIIA NSCLC patients with N2, mediastinoscopy verified disease.[36] Patients received gemcitabine at 1,000 mg/m$^2$ given on days 1, 8, and 15, and cisplatin at 100 mg/m$^2$ on day
2, every 4 weeks. The response rate was 70%, with mediastinal downstaging in 53% of patients. Radical resection was feasible in 71% of the patients who underwent thoracotomy. Notably, the median survival was 18.9 months, and the 1-year survival rate was 69%. Grade 3/4 thrombocytopenia was the primary toxicity (reported in 60% of patients), and was commonly associated with the 4-week schedule of gemcitabine. Cappuzzo et al recently conducted a large phase II study (N = 129) that evaluated the safety and efficacy of gemcitabine/cisplatin in patients with unresectable stage IIIA/IIIB NSCLC.[37] Patients received gemcitabine at 1,000 mg/m$^2$ on days 1 and 8, and cisplatin at 70 mg/m$^2$ on day 2, every 3 weeks, as part of a combined-modality approach. The efficacy data from this trial indicated a 70.4% response rate with a 29% complete resectability rate. Importantly, using a 3-week treatment administration schedule, toxicity was generally mild, with grade 3/4 thrombocytopenia as the primary toxicity (27% of patients). The high activity and favorable toxicity profile of the gemcitabine/cisplatin combination, especially with the 3-week schedule, thus reinforced the rationale for testing this regimen in early-stage disease. The Chemotherapy in Early StAGE NSCLC (ChEST) study is an international, multicenter, randomized phase III trial of surgery alone vs preoperative chemotherapy followed by surgery in early-stage (I, II, IIIA) NSCLC. The experimental arm consists of three courses of gemcitabine at 1,250 mg/m$^2$ given on days 1 and 8 and cisplatin at 75 mg/m$^2$ day 2 (every- 3-week cycle) followed by surgery. Surgery alone is the standard arm. The primary end point of the study is progression-free survival, while secondary end points include overall survival, sites of relapse, perioperative toxicity, and response. The trial is ongoing and results will be available in the near future. Paclitaxel or docetaxel/platinum combination regimens are established strategies in the management of advanced NSCLC.[31,38] Docetaxel is one of the most effective drugs for the treatment of advanced NSCLC, and many also consider platinum/docetaxel combinations to be very active regimens in the advanced disease setting.[31,38] Mattson et al.[39] randomly assigned 274 patients with resectable stage IIIA/IIIB NSCLC to receive either induction therapy with docetaxel (n = 134) or no chemotherapy (n = 140) before surgery and curative intent radiotherapy. Patients received up to three 3-weekly cycles IV of docetaxel at 100 mg/m$^2$. Median survival was 14.8 months in the docetaxel group vs 12.6 months in the control group. Although this trend toward improved survival in the patients with potentially resectable NSCLC who received induction therapy was not statistically significant, this trial reported the excellent tolerability of induction chemotherapy with docetaxel. Betticher and colleagues[40] recently evaluated the activity of docetaxel/ cisplatin chemotherapy as induction therapy in NSCLC patients with previously untreated, potentially resectable stage IIIA mediastinoscopically pN2 disease (N = 90). Patients in the phase II trial received three cycles of docetaxel at 85 mg/m$^2$ given on day 1 plus cisplatin at 40 mg/m$^2$ on days 1 and 2, with subsequent surgical resection. The investigators reported an overall response rate of 66%, and pathologic complete responses in 19% of patients, demonstrating that the docetaxel/cisplatin combination was very active. Moreover, the incidence of perioperative mortality and morbidity was 3% and 17%, respectively. These encouraging data support the use of regimens including docetaxel in patients with early-stage disease. Pisters and the Bimodality Lung Oncology Team assessed the role of induction carboplatin/paclitaxel chemotherapy in mediastinoscopically negative early-stage NSCLC.[41] The chemotherapy regimen consisted of paclitaxel at 225 mg/m$^2$ given over 3 hours, and carboplatin at an area under the concentration-time curve (AUC) of 6, every 3 weeks. The initial 94 patients treated were to receive two preoperative and three postoperative chemotherapy cycles. A second cohort of 41 patients was then treated to evaluate a treatment strategy of three preoperative and two postoperative chemotherapy cycles. Data from the first 94 patients showed that induction therapy with carboplatin/paclitaxel was active and well tolerated in early-stage NSCLC. The overall response rate was 56%, and 86% of patients were fully resected. The 1-year survival percentage was reported to be 85%; median survival had not yet been reached at the time of publication. Importantly, 96% of patients received their planned induction chemotherapy, while postoperative chemotherapy was administered only in 45% of patients. No unexpected chemotherapy- or surgery- related morbidity occurred. Two large phase III trials are currently evaluating the role of induction chemotherapy with carboplatin/paclitaxel in early-stage NSCLC. The Southwest Oncology Group (SWOG trial 9900) is evaluating whether three cycles of induction chemotherapy with carboplatin/paclitaxel improve survival compared with surgery alone in previously untreated patients with clinical stage IB, II, and selected IIIA NSCLC disease. The Spanish Lung Cancer Group (SLCG) is conducting a large phase III study in which untreated NSCLC patients with stage I, II, IIIA (T3, N1) are randomly assigned to either surgery alone (standard arm) or two experimental arms, in which three courses of carboplatin/paclitaxel chemotherapy are given before (induction arm) or after (adjuvant arm) surgery. Other randomized trials of preoperative chemotherapy in earlystage disease are ongoing, including those conducted by
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Published on Physicians Practice (http://www.physicianspractice.com)

the Lung Cancer Group of the Medical Research Council (trial LU 22), the Dutch Lung Cancer Study Group, and the EORTC (Table 3). The Intergroupe Francophone de Cancerologie Thoracique will compare two different strategies of induction chemotherapy. After two cycles of neoadjuvant chemotherapy, responders will receive two additional cycles, either after surgery in one arm, or immediately after the first two cycles and before surgery in the other arm. This study design also compares two new regimens: paclitaxel/carboplatin and gemcitabine/cisplatin. The results of these ongoing trials will help clarify the role and the optimal scheduling of chemotherapy in the treatment of patients with early-stage NSCLC. **Conclusions** Despite an apparent complete resection of NSCLC in many patients, death occurs in the majority of patients who develop recurrent disease. Therapy aimed at eradicating micrometastatic disease has been the primary end point of adjuvant chemotherapy. Data from adjuvant trials indicate that significant comorbidities and insufficient recovery after surgery are often associated with the patients' inability to tolerate or comply with systemic therapy. Therefore, it might be preferable to deliver chemotherapy before surgery. For patients who present with locally advanced disease, induction chemotherapy followed by surgery and/or radiotherapy is a candidate for standard therapy. For patients with early-stage NSCLC, data from randomized phase III trials that have concluded have not yet produced sufficient evidence to consider induction chemotherapy as a standard treatment option. However, the published trials have generally included an induction chemotherapy regimen consisting of older-generation regimens, which many considered less active and more toxic than newer doublets. Large randomized studies are currently evaluating the role of newer-generation combinations in patients with resectable NSCLC. The results of these trials will be available in the future, and may further define the role of induction chemotherapy in the treatment of patients with early-stage disease.

**Disclosures:** The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**
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