Review

New Chemotherapeutic Agents Prolong Survival and Improve Quality of Life in Non-Small Cell Lung Cancer: A Review of the Literature and Future Directions

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Abstract
In past years, there has been considerable pessimism over the role of chemotherapy in non-small cell lung cancers. The pessimism was largely derived from the fact that alkylating agent-based therapies shortened survival and produced severe side effects. This was especially important because the vast majority of patients (~85%) develop metastatic disease during their course. Randomized trials from the 1980s showed that cisplatin-based chemotherapy improved patient survival, improved quality of life as assessed by the patients, and relieved symptoms in the majority of symptomatic patients. When chemotherapy was administered on an outpatient basis, it actually lowered the total patient care costs for advanced stage patients. In the 1990s, five new agents, including two taxanes (paclitaxel, docetaxel), gemcitabine, navelbine, and irinotecan, were shown to produce higher response rates and longer survival in Phase II trials compared to cisplatin or carboplatin. In randomized trials, combinations of paclitaxel, gemcitabine, and vinorelbine with cisplatin improved the survival of advanced stage patients compared to cisplatin alone or in combination with etoposide. The toxicity profile of the new agents is also favorable compared to cisplatin-based therapy. Preliminary results in earlier stages are also encouraging. Thus, currently available chemotherapy given to non-small cell lung cancer patients with good performance status can improve survival to a similar extent as other solid tumors, such as small cell lung cancer and breast cancer.

Introduction
It is widely accepted that patients with SCLC should receive chemotherapy, because it relieves symptoms and improves survival (1). It is also widely accepted that breast cancer patients with positive lymph nodes at the time of diagnosis should receive systemic adjuvant therapy, because it decreases recurrences and leads to a slight increase in 5-year survival (2). It is not widely accepted that NSCLC patients should be offered systemic chemotherapy in these settings. In the past few years, four new active drugs (vinorelbine, paclitaxel, docetaxel, and gemcitabine) have been shown to improve survival and relieve symptoms in stage IIB and IV NSCLC patients. In addition, cisplatin-based chemotherapy has been shown to improve survival in resectable, node-positive NSCLC patients to a degree similar to that of chemotherapy for breast cancer. Thus, the attitude of oncologists should be changed to reflect the improvements afforded by currently available chemotherapy for NSCLC patients.

Lung cancer is the most common cause of cancer death in both men and women in the United States (3). It was expected that in 1997, there would be 160,400 deaths from lung cancer, which represents 29% of all cancer deaths (3). The overall cure rate is a dismal 14%, largely because the disease has metastasized by the time of diagnosis and because chemotherapy has not been sufficiently active to cure metastatic disease. Thus, there has been great pessimism among oncologists for treating lung cancer patients with chemotherapy. During the 1970s and 1980s, considerable enthusiasm was developed in the treatment of SCLC, when it was shown that chemotherapy increased survival of extensive-stage patients from 4 to 10 months and of limited-stage patients from 6 to 14-18 months when combined with chest radiotherapy (1). In breast cancer, the adjuvant use of chemotherapy decreased recurrence by about 20% and increased 5-10-year survival rates by 5-10% (2). Early studies of alkylating agents in lung cancer showed that they actually impaired survival, and no single agent was found to produce a response rate exceeding 20% in stage IV NSCLC (4, 5). This created considerable pessimism for treating NSCLC patients with chemotherapy. Recent studies indicate that newer chemotherapeutic agents prolong survival and alleviate symptoms in all stages of lung cancer, such that all NSCLC patients, with the exception of those with stage T1N0 and poor performance (PS 3-4), should be offered modern chemotherapy. This article will review the results of new chemotherapeutic agents in NSCLC and show how the appropriate use of chemotherapy can increase survival in NSCLC patients.

Cisplatin-based Chemotherapy Improves Survival and Quality of Life in Advanced NSCLC
The survival of patients with advanced (stage IV) NSCLC is extremely poor. Best supportive care measures, including palliative radiotherapy, produce median survivals of 16-17 weeks, and only 10-15% of patients are alive at 1 year (5-7). Prior to the 1990s, no single drug or drug com-
Combination had been proven to improve survival or quality of life in advanced NSCLC patients. During the 1980s, cisplatin and carboplatin emerged as the drugs most likely to improve survival and quality of life in advanced NSCLC, even though they produce objective responses in fewer than 20% of patients (4, 8, 9).

Multiple randomized trials were conducted in the 1980s and early 1990s that compared best supportive care to chemotherapy with cisplatin-based combinations. Meta-analyses of these trials proved that the cisplatin-based therapy improved the survival of these patients, although the benefits were modest (5–7). On average, the median survival of the cisplatin-treated patients improved by 10 weeks (from 16 to 26 weeks), and the 1-year survival rate improved by 10% (from 15 to 25%). Randomized trials also showed that cisplatin combinations were superior to single-drug therapy. For example, a French trial showed that patients treated with cisplatin plus Navelbine had a superior survival compared to patients receiving Navelbine alone (10).

Although there are fewer randomized trials that included quality of life analyses, the completed randomized trials showed that cisplatin-based combinations also improve quality of life. The randomized studies from the United Kingdom evaluating quality of life analyses, the completed randomized trials showed that cisplatin combinations were 1-year survival rates were 10%, and the 1-year survival was improved to only 20–30% in cisplatin combination studies.

**Table 1.** Randomized studies of quality of life in advanced NSCLC (11)*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Median survival (mo)</th>
<th>Survival rates</th>
<th>QOL</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>Chest radiotherapy</td>
<td>224</td>
<td>9.9</td>
<td>44% 18% 4% 394</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Chest radiotherapy + MIC</td>
<td>223</td>
<td>13</td>
<td>53% 24% 10% 287</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>BSC</td>
<td>176</td>
<td>4.8</td>
<td>18% 4% 589d</td>
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<td></td>
</tr>
<tr>
<td>IV</td>
<td>BSC + MIC</td>
<td>174</td>
<td>6.9</td>
<td>28% 6% 504</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* MIC, mitomycin C, ifosfamide, and cisplatin; BSC, best supportive care; QOL, quality of life score.

**New Single Agents for the Treatment of Advanced NSCLC**

The low response rates and modest survival gains from cisplatin-based therapy made the discovery of more effective agents imperative.

Table 2 summarizes the Phase I and II studies of six new chemotherapeutic agents that have been approved by the FDA for various indications over the past 2 years. These agents include two taxanes, paclitaxel and docetaxel; two topoisomerase 1 inhibitors, irinotecan and topotecan; a novel antimetabolite, gemcitabine; and a novel Vinca alkaloid, vinorelbine. Of the six, only vinorelbine (Navelbine) has been approved specifically for lung cancer to date in the United States, although approvals for paclitaxel and gemcitabine are likely in the near future. As shown in Table 2, five of the new agents, with the exception of topotecan, produced an objective response rate of 20% or higher, and at least 100 patients were available for response analysis. These studies were conducted in patients with good PS only. The median survival in these studies averaged about 40 weeks, which is longer than with any previously reported single agent and longer than with the best previously reported cisplatin combinations. In many instances, the percentage of patients alive at 1 year was greater than 40%. In prior studies, in which best supportive care was the only treatment, the median survival was 16–17 weeks, the 1-year survival rates were 10%, and 1-year survival was improved to only 20–30% in cisplatin combination studies.

**Vinorelbine (Navelbine).** The first new drug to be studied and approved by the FDA for NSCLC was vinorelbine (Navelbine). In Phase II and III studies, vinorelbine produced an objective response rate of 20% (10, 14–18). In large, multicenter randomized trials, the response rates were lower (10, 14) than in Phase II studies. A large, multicenter trial in the United States compared vinorelbine to the combination of 5FU and leucovorin (14). Vinorelbine produced a significantly higher response rate (13 versus 7%) and significantly longer survival.

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(median, 8.1 versus 5.4 months; 1-year survival, 25 versus 15%). In the French study, shown in Table 3, single-agent vinorelbine produced an objective response rate of 14%, a median survival of 31 weeks, and a 1-year survival rate of 25% (10). The 1-year survival rate with single-agent vinorelbine in these large, multicenter randomized trials is very similar to that found in many studies of cisplatin combinations (19). A comparison of single-agent vinorelbine to cisplatin in Table 3 shows that survival was somewhat better with vinorelbine (1-year survival rate of 25%, versus 12% for cisplatin). However, comparisons such as this must be interpreted with caution, because prognostic factors may vary between studies.

**Paclitaxel (Taxol).** Paclitaxel was the second of these new agents to be approved by the FDA for ovarian and breast cancers. The first two paclitaxel studies in NSCLC used a long, 24-h infusion schedule due to the original concern over possible hypersensitivity reactions with rapid infusions (20, 21). These long-infusion studies reported response rates of 21 and 24%, which established the activity of paclitaxel. Most impressive was the 1-year survival rate of 40% in both studies, which was the highest reported at the time. The ECOG trial was a randomized Phase II study with 1-year survivals of 20% in the other two arms, suggesting that the excellent survival results were not due to patient selection. Subsequent studies (shown in Table 2) with both long (24 h) and short (1–3 h) paclitaxel infusions confirmed the high response rate (average, 26% among 10 studies), long median survival (average, 37.3 weeks among 6 studies reporting survival), and high 1-year survival rates (average, 41% among 7 studies; Refs. 20–29). These single-agent results were superior to those reported for most cisplatin combination studies.

**Docetaxel (Taxotere).** Docetaxel, the other taxane that is active in NSCLC, has been approved by the FDA for breast cancer but not yet for lung cancer. The results of Phase II studies are summarized in Table 2 (30–37). As shown in Table 2, the 26% overall response rate is similar to the 26% rate reported in the paclitaxel studies. The survival data also appear similar, with median survivals ranging from 27 to 48 weeks (average, 41 weeks) and 1-year survival percentages ranging from 41 to 71% (average, 52%). This 1-year survival rate is higher than that reported with the best combinations in extensive-stage SCLC and considerably longer than that reported for the best prior cisplatin combinations in advanced NSCLC.

Docetaxel was studied in doses ranging from 60 to 100 mg/m². The higher doses were associated with considerably more toxicity, especially high rates of grade 4 myelosuppression (about 80%), and fluid accumulation. Patients with liver toxicity before therapy had significant morbidity and mortality and should not receive these doses of docetaxel. The efficacy results showed response rates of 29% for the 100 mg/m² dose and 23% for the 60 mg/m² dose. No published randomized trials have compared the two dose regimens. Until such randomized studies are conducted, it is probably best to use the least toxic dose schedule (60 mg/m²), particularly in combination with other agents.

**Gemcitabine.** Previous antimetabolites had little activity in NSCLC. For example, in a randomized trial of vinorelbine versus 5FU and leucovorin, the response rate to 5FU and leucovorin was only 8%, the median survival was only 5.5 months, and the 1-year survival was only 12% (14). Gemcitabine is a new antimetabolite that was developed because of its prolonged retention time in tumor cells and a high rate of activity against solid tumor cell lines in vitro and in vivo. Most Phase I studies used a weekly schedule with 30 min of i.v. administration each week for 3 out of 4 weeks (38). Doses as high as 2800 mg/m² could be given using this schedule (39). As summarized in Table 2, response rates in Phase II studies averaged 21% among 572 patients studied (38–44). There was remarkably little variation in response rates around the world. It is not clear that high doses (such as those over 2000 mg/m²) were superior to doses of 1000–2000 mg/m², but response rates were sometimes lower at doses less than 800 mg/m² (44). The survival of gemcitabine-treated patients was also remarkably long, with median survival ranging from 31 to 49 weeks (average, 41 weeks) and with 39% of patients alive at 1 year. Gemcitabine was also remarkably well tolerated, with few toxicities other than myelosuppression, which was less common than with other agents. There was less alopecia than with most chemotherapeutic agents.

Because the results with gemcitabine appeared to be as good as or better than those obtained with standard therapies such as the combination of etoposide and cisplatin, two random-
izes trials were conducted comparing single-agent gemcitabine to the combination of etoposide and cisplatin (45, 46). The results of these studies are summarized in Table 4. The response rates of gemcitabine (18% and 19%) were as high as those with the combination of etoposide and cisplatin (15% and 21%) and were similar to response rates of gemcitabine in Phase II studies. There were no significant differences in time to progression or survival. Not surprisingly, gemcitabine had fewer toxicities than the etoposide and cisplatin combination and was far more convenient. Quality of life analysis favored single-agent gemcitabine. On the basis of these studies, single-agent gemcitabine may be preferred over the prior standard combination.

**Irinotecan (CPT-11).** Irinotecan was developed as a camptothecin derivative that inhibits tumor cell growth by inhibition of topoisomerase 1. Topotecan has the same mechanism of action. Responses in patients with both SCLC and NSCLC were observed in Phase I trials of irinotecan in Japan. This led to Phase II trials in which responses were again seen in both SCLC and NSCLC. Table 2 summarizes the results of the studies in NSCLC patients (47–51). Overall, an objective response rate of 27% was reported among 138 treated patients. The survival data from these studies were not as impressive as those of some of the other new agents, but they appear superior to those obtained with single-agent cisplatin, with an average median survival of 35 weeks (range, 27–42 weeks). Additional studies with more survival information from various parts of the world are needed to confirm the role of irinotecan in NSCLC patients.

**Topotecan.** Topotecan has received the least study of any of the six new agents. As shown in Table 2, Phase I or II results in 119 patients reported an objective response in 13% of patients (52–56). The survival results, with a median survival of 38 weeks, were similar to those with irinotecan, yet the response rates were much lower. The reasons for these differences are unclear. The M. D. Anderson group has reported a higher response rate in squamous carcinoma than in adenocarcinoma (56). Certainly, more patients will need to be studied to define the ultimate role of topotecan in NSCLC patients. The 5-day schedule of administration is somewhat more inconvenient than schedules for the other new agents.

**Combination Chemotherapy with New Agents for Advanced NSCLC**

The activity of these new agents made it logical to combine them with other standard therapies, especially the platinum compounds. In all instances, the combination of one of these new agents with cisplatin or carboplatin led to higher response rates than those reported for either agent alone. In addition, median and 1-year survival rates were generally higher. Table 5 summarizes the results of Phase II trials combining these new agents with cisplatin and carboplatin.

**Vinorelbine + Cisplatin or Carboplatin.** Phase II studies summarized in Table 5 showed that full-dose vinorelbine could be combined with full-dose cisplatin and full-dose carboplatin. The response rates in these studies were higher than those reported with single-agent vinorelbine (10, 57–65). The survival data were also encouraging. These data led to randomized trials comparing the combination of vinorelbine and cisplatin to single-agent vinorelbine and single-agent cisplatin, the results of which are shown in Table 3.

These studies confirmed the superiority of two-drug combinations compared to either drug alone. Subsequent to these studies, the SWOG is conducting a Phase III randomized trial in which their vinorelbine + cisplatin regimen is compared to a paclitaxel (225 mg/m²/3 h) + carboplatin (area under the curve = 6 mg/ml/min) regimen.

**Paclitaxel + Cisplatin.** Phase I studies showed that full-dose paclitaxel could be combined with full-dose cisplatin. When a 24-h infusion of paclitaxel was combined with cisplatin, the schedule was extremely important, with considerably more toxicity when the cisplatin preceded the paclitaxel. When a short-infusion paclitaxel schedule is used, the sequence is less important. Phase II studies with the paclitaxel + cisplatin combination are summarized in Table 5 (66–73). The combination produced response rates of 31–56%, with an average of 42%, which are higher than those observed with paclitaxel or cisplatin alone. The few studies reporting survival found it to be only slightly superior to paclitaxel alone (median survival of 44 weeks and a 1-year survival rate of 38%). Survival was far superior to older cisplatin combinations.

The excellent results reported in the paclitaxel + cisplatin studies made it logical to compare paclitaxel + cisplatin to older cisplatin combinations. The first randomized studies comparing paclitaxel and cisplatin combinations to older podophyllotoxin and cisplatin combinations are summarized in Table 6 (74, 75). The ECOG study compared the results from 24-h infusions of paclitaxel given in a high dose (250 mg/m²) with G-CSF to

### Table 3 Randomized trials of single-agent Navelbine or cisplatin versus Navelbine + cisplatin

<table>
<thead>
<tr>
<th>IGR (10)</th>
<th>SWOG (57)</th>
</tr>
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<tbody>
<tr>
<td>VNB + CDDP</td>
<td>VNB + CDDP</td>
</tr>
<tr>
<td>No. of patients</td>
<td>208</td>
</tr>
<tr>
<td>% response</td>
<td>14</td>
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<tr>
<td>Median survival (weeks)</td>
<td>31</td>
</tr>
<tr>
<td>% 1-year survival</td>
<td>25</td>
</tr>
</tbody>
</table>

*IGR, Institute Goustave Roussy; VNB, vinorelbine (Navelbine); CDDP, cisplatin.

### Table 4 Randomized trials of gemcitabine versus etoposide + cisplatin

<table>
<thead>
<tr>
<th>Perng et al. (45)</th>
<th>Manegold et al. (46)</th>
</tr>
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<tbody>
<tr>
<td>Gemcitabine EP</td>
<td>Gemcitabine EP</td>
</tr>
<tr>
<td>No. of patients</td>
<td>26</td>
</tr>
<tr>
<td>% CR + PR</td>
<td>19%</td>
</tr>
<tr>
<td>Median survival (weeks)</td>
<td>37</td>
</tr>
<tr>
<td>1-year survival</td>
<td>40%</td>
</tr>
<tr>
<td>% GR 4 WBC</td>
<td>0</td>
</tr>
<tr>
<td>% GR 3-4 N, V</td>
<td>4</td>
</tr>
</tbody>
</table>

*EP, etoposide + cisplatin; CR, complete response; PR, partial response; % GR 4 WBC, percentage of patients with grade 4 leukopenia; % GR 3-4 N, V, percentage of patients with grade 3 or 4 nausea and vomiting; NR, not reported.
those from a standard dose (135 mg/m²) without G-CSF combined with 75 mg/m² of cisplatin (74). The control arm consisted of an etoposide and cisplatin regimen used in many prior ECOG studies. The two paclitaxel regimens produced significantly higher response rates (27–32% versus 12%) and significantly longer survival (median, 41–43 weeks versus 32 weeks) compared to the etoposide + cisplatin combination. The 1-year survival rates in the two paclitaxel arms were 40 and 37%, confirming the improved survival compared to older regimens without paclitaxel. Severe neutropenia occurred with similar frequency in each of the arms, but thrombocytopenia and neuropathy were more frequent on the high-dose paclitaxel arm.

The EORTC study compared a short infusion (3 h) paclitaxel + cisplatin regimen to a combination of teniposide + cisplatin, which the group had studied previously (75, 76). The paclitaxel arm showed a significantly higher response rate (47 versus 29%, respectively). The median survival was 41 weeks on the paclitaxel + cisplatin arm and 42 weeks on the teniposide + cisplatin arm. The survival results in the paclitaxel arm were quite similar to the results in the ECOG paclitaxel arms and higher than those reported in most other cooperative group studies for unclear reasons. The survival results in the teniposide + cisplatin arm were better than the group had reported in earlier studies (75, 76). Major toxicities including myelosuppression were significantly more common in the teniposide arm. Quality of life analysis favored the paclitaxel arm, and the authors concluded that the paclitaxel + cisplatin regimen is superior to the teniposide + cisplatin regimens.

**Paclitaxel + Carboplatin.** Carboplatin is as effective as cisplatin in NSCLC and is considerably more convenient and less toxic (9). Thus, it was logical to combine carboplatin with paclitaxel. Results of studies evaluating the combination of paclitaxel with carboplatin are summarized in Table 5 (77–84). Some of these studies used a 24-h paclitaxel schedule (77–79), whereas more recent studies used the more convenient 1–3-h infusion schedule (75–79). The response rates and survival data were similar with either schedule, with response rates of about 46%, median survivals of about 39 weeks, and 1-year survival rates of 40–45%. Both thrombocytopenia and peripheral neuropathy were less frequent with this combination compared to the paclitaxel + cisplatin combination. Because of these results, the ECOG, the SWOG, and the CALGB elected to compare the short-infusion paclitaxel + carboplatin combination to other combinations and to single-agent paclitaxel. The SWOG is comparing the paclitaxel + carboplatin combination to the standard vinorelbine + cisplatin combination. The CALGB is comparing single-agent paclitaxel to paclitaxel + cisplatin.

**Docetaxel + Cisplatin.** The results of Phase II studies of the combination of docetaxel and cisplatin are summarized in Table 5 (85–89). Among 255 patients, the response rate was 35%, and the average median survival was 35 weeks. These response and survival rates were slightly inferior to those reported with paclitaxel + cisplatin or carboplatin. Toxicity of the combination was considerable, especially when high doses (100 mg/m²) of docetaxel and cisplatin were used. The poor survival may have been due to the high toxicity. Lower doses of docetaxel (60–75 mg/m²) can be combined more easily. To determine whether there are any true differences between this combination and others, the ECOG is conducting the four-arm randomized study described above.

**Gemcitabine + Cisplatin.** The high response rates, long survival, and low toxicity observed with gemcitabine made it logical to combine it with cisplatin. In addition, in vitro studies showed considerable synergy between cisplatin and gemcitabine (90). Phase II studies of the gemcitabine + cisplatin combination are summarized in Table 5 (91–96). Overall, the 47% response rate is higher than with either drug alone and is higher than the 35–46% response rates reported with paclitaxel or docetaxel + cisplatin or carboplatin. The survival results are also very favorable, with an average median survival of 57 weeks in five studies and an average 1-year survival rate of 48%. These results compare very favorably with the results of other combinations shown in Table 4, accounting for the design of the ongoing ECOG trial described above. It is possible that the combination of gemcitabine with carboplatin or with paclitaxel will prove to be superior in efficacy or less toxic than the gemcitabine with cisplatin. Phase I and II studies of these gemcitabine combinations are in progress.
In most studies, objective response rates vary from 20 to 45%, whereas relief of symptoms occurs in the majority of patients. Therapy for NSCLC leads to considerable toxicity associated with several of the new chemotherapeutic agents (107, 108). The Canadian study, the costs associated with best supportive care averaged $8,595 (1984 Canadian dollars). These patients had a median survival of 17 weeks. The costs for the patients receiving chemotherapy were $7,645 and $12,232 in the two cisplatin arms. The median survival in the higher-costing vindesine + cisplatin arm was 33 weeks. Thus, the extra costs were $3,637 for 16 weeks of added life. This calculates to $11,820 per year of added life.

Cost analyses have also been completed for Navelbine and gemcitabine in NSCLC (107, 108). In addition, cost analyses for paclitaxel in ovarian cancer were recently reported (109, 110). Smith et al. (107) evaluated the costs of vinorelbine + cisplatin based on the randomized French trial shown in Table 1. They calculated that the cost effectiveness per year gained was $17,7000. Similar results were seen using paclitaxel in ovarian cancer, in which the costs per year of life gained were about $20,000 in the United States (110). Copley-Merriman et al. (108) compared the costs of treating advanced NSCLC patients with gemcitabine alone versus the combination of etoposide + cisplatin. They reported that gemcitabine treatment was less expensive, with cost savings of $1,500-$7,000 per cycle.

No formal cost comparisons of paclitaxel + cisplatin versus etoposide + cisplatin or best supportive care have been performed. However, advanced NSCLC patients receive a median of four cycles of paclitaxel + cisplatin, because half of the patients fail to respond and receive only one or two cycles, and the responders usually receive six cycles. Compared to the 16- or 17-week median survival of patients who receive best supportive care, patients treated with new agents alone or in combination have median survival of about 39–48 weeks, a gain of about 26 weeks. Currently, new therapies may cost as much as $2,500 (United States dollars) per cycle or $10,000 per four cycles. This equates to $20,000 per added year of life. Thus, the costs of therapy for advanced NSCLC are well within the range of other accepted medical therapies and will be lowered considerably when generic agents become available.

### Advanced NSCLC: Conclusions

Randomized trials and meta-analyses of these randomized trials established that chemotherapy significantly improves survival and quality of life in advanced NSCLC patients with good PS. The survival results with new drugs and new drug combinations are very similar to those obtained with the best combinations in advanced SCLC and are contrasted in Table 7. In extensive-stage SCLC patients, recent Southeast Cancer Study Group and Japanese Study Group trials comparing etoposide + cisplatin versus cyclophosphamide + doxorubicin + vincristine versus the alteration of the two combinations reported median survivals of 37 and 36 weeks (111, 112). The 1-year survival

### Table 6 Randomized trials of paclitaxel/cisplatin versus podophyllotoxin/cisplatin

<table>
<thead>
<tr>
<th>ECOG (74)</th>
<th>EORTC (75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EP</td>
<td>PPG</td>
</tr>
<tr>
<td>No. of patients</td>
<td>200</td>
</tr>
<tr>
<td>% CR + PR</td>
<td>124</td>
</tr>
<tr>
<td>Median survival (weeks)</td>
<td>32d</td>
</tr>
<tr>
<td>% 1-year survival</td>
<td>31</td>
</tr>
</tbody>
</table>

- EP, etoposide + cisplatin; PPG, paclitaxel (250 mg/m² over 24 h) + cisplatin; PP, paclitaxel (135 mg/m² over 24 h) + cisplatin; TP, tenoposide + cisplatin; PP2, paclitaxel (175 mg/m² over 3 h) + cisplatin; CR, complete response; PR, partial response; NR, not reported.
- The responses for PPG and PP were significantly higher than for EP (P < 0.001).
- Statistical data are not provided in reference, but by our analysis, the response rates are statistically different (P = 0.0098), whereas survival differences are not.
- The minimal P for the survival differences were: EP versus PP, P = 0.119; EP versus PPG, P = 0.091; and PPG versus PP, P = 0.829.
rates were 30% in both studies. In advanced NSCLC, the paclitaxel + cisplatin combination produced median survivals of 43 and 40 weeks in the two large, multicenter, randomized Phase III studies of the ECOG and EORTC, respectively (74, 75). The 1-year survival rate was 40% in both studies. These survival results are equivalent or superior to those reported in the SCLC studies. Thus, it is logical to conclude that advanced-stage NSCLC patients, like advanced-stage SCLC patients, should be offered chemotherapy.

Combined Modality Therapy for Stage IIIb NSCLC Improves Survival

Recent meta-analyses of multiple randomized studies comparing combined modality chemoradiotherapy to radiotherapy alone in stage IIIb NSCLC patients showed a significant survival advantage for the combined approach (6, 113). The combined therapy improved the median as well as the long-term survival. The 5-year survival was increased by as much as 3-fold. There are several randomized trials that showed that the combined approach is superior to chemotherapy alone. For example, Kubota et al. (114) reported a 4-year survival of 25% in patients receiving combined modality compared to 3% for those receiving chemotherapy alone.

In unresectable stage III patients, combined modality results are similar between SCLC and NSCLC. Table 7 compares the results of recent cooperative group randomized trials in limited-stage SCLC and NSCLC. The survival of patients in the SWOG and the ECOG studies with etoposide + cisplatin + chest radiotherapy in limited-stage SCLC (115, 116) were similar to the SWOG results with etoposide + cisplatin + chest radiotherapy followed by surgery and to the CALGB results with vinblastine + cisplatin followed by standard chest radiotherapy in stage III NSCLC (105, 117).

Optimal Means of Combining Chemotherapy and Radiotherapy

The dose and schedule of both chemotherapy and radiotherapy delivered in these studies varied considerably, and the optimal methods of combining the two modalities is unknown. A sequential approach was used in the CALGB study cited above, with two cycles of chemotherapy prior to the full-dose radiotherapy (117). The two cycles of induction vinblastine + cisplatin improved survival and decreased distant recurrence, but both distant and local recurrences remained high.

In an effort to take advantage of radiosensitizing properties of cisplatin chemotherapy, many studies gave concurrent chemotherapy daily or weekly, with radiotherapy. For example, the EORTC randomized stage IIIb NSCLC patients to receive radiotherapy alone, radiotherapy with weekly cisplatin, or radiotherapy with daily cisplatin (118). The two chemotherapy arms had significantly superior survival. The best results were in the daily cisplatin arm. The combined modality arms had a significantly reduced local failure rate, suggesting that there was a radiosensitizing effect, but there was no effect on distant relapse. Other groups reported similar results. For example, Jeremic et al. (119) reported that the two-drug combination of carboplatin and etoposide given daily, every other week, or daily with concurrent radiotherapy provided superior survival compared to radiotherapy alone. The daily drug administration produced the best results. The SWOG reported excellent results with daily cisplatin combined with daily radiotherapy, and the University of Colorado reported a 3-year survival rate of 40% using daily carboplatin combined with twice daily radiotherapy (120, 121). This study also gave several cycles of full-dose chemotherapy at 3-week intervals after the combined therapy to increase cytoreduction and to reduce distant relapse. The response rate increased after the postinduction chemotherapy, and there was long survival, suggesting that these goals were accomplished.

Other studies gave standard chemotherapy in full doses in 3-week schedules concurrently with the chest radiotherapy. The two-drug combination of etoposide and cisplatin has been given concurrently with radiotherapy in this manner in both SCLC and NSCLC. The SWOG studies shown in Table 6 delivered the combined therapy in this manner.

Recently, the results of one randomized trial comparing a concurrent to a sequential approach was reported by a Japanese study group (122). The chemotherapy consisted of mitomycin C, vinblastine, and cisplatin. The response rate and survival were statistically superior in the concurrent arm. Not surprisingly, the hematological toxicity was also greater in this arm but was felt to be acceptable. The authors concluded the concurrent

<table>
<thead>
<tr>
<th>Table 7</th>
<th>Comparison of results of Phase III trials with SCLC and NSCLC</th>
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<tbody>
<tr>
<td>Extensive stage</td>
<td>Limited stage</td>
</tr>
<tr>
<td></td>
<td>SCLC</td>
</tr>
<tr>
<td></td>
<td>SECSG</td>
</tr>
<tr>
<td>No. of patients</td>
<td>(112)</td>
</tr>
<tr>
<td>Median survival</td>
<td>140</td>
</tr>
<tr>
<td>% 1-year survival</td>
<td>37</td>
</tr>
<tr>
<td>% 4-year survival</td>
<td>30</td>
</tr>
</tbody>
</table>

*SECSG, Southeast Cancer Study Group.*  
*JSG, Japanese Study Group.*  
*In weeks.*  
*In months.*  
*NR, not reported.*  
*Two-year survival percentages.*
approach was favored. Other studies, evaluating altered fractionation schemes, increased dose with decreased volume, and other factors, are being conducted.

Radio sensitizing Properties of the New Agents for NSCLC

Most of the studies showing a benefit for combined chemoradiotherapy have used cisplatin- or carboplatin-based combinations. Both cisplatin and carboplatin have radiosensitizing properties. There are multiple studies that suggest that paclitaxel, docetaxel, gemcitabine, and irinotecan have radiosensitizing properties (123–125). Phase I and II studies combining these agents with radiotherapy are mostly preliminary. The largest clinical experience has been reported with paclitaxel (126–128). In these studies, the paclitaxel has been given both weekly and every 3 weeks. The weekly schedules used short infusions, whereas both long and short infusions were used in the triweekly programs. These studies suggest that full-dose paclitaxel can be given concurrently with the radiotherapy. In the weekly regimens, 60 mg/m² paclitaxel given alone or with weekly carboplatin did not produce excessive toxicity. In the regimens given every 3 weeks, a 3-h infusion of paclitaxel at a dose of 175 mg/m² alone or with carboplatin appeared to be safe. High response rates were reported in these preliminary studies, but there are no published, randomized trials comparing these combinations to non-paclitaxel-based combinations. There are also no randomized trials in which paclitaxel-based combination chemotherapy is given before or before and with radiotherapy. On the basis of the experience in stage IV NSCLC, it would be surprising if the survival advantage afforded by chemotherapy were not even greater in stage III.

Gemcitabine is a more potent radiosensitizer than other previously reported nucleosides and antimetabolites (129). This affords the opportunity for greater antitumor effect as well as increased normal tissue toxicities. Several studies reported severe normal tissue toxicity to the esophagus and lungs when standard doses of gemcitabine (800–1000 mg/m²/week) were given concurrently with chest radiotherapy, and in one study, four of the first eight patients died from the toxicity (130). Subsequent studies are starting at low doses such as 200 mg/m²/week. Studies with combined gemcitabine and radiotherapy in head and neck cancer also showed a high rate of complete response with a high rate of normal tissue toxicity even with a gemcitabine dose of 300 mg/m²/week (129). Clinical studies combining Navelbine, docetaxel, irinotecan, and topotecan with chest radiotherapy or before radiotherapy in stage IIIB NSCLC are in progress, but few results have been reported to date.

Chemotherapy for Stage IIIA N₂ NSCLC

The therapy for N₂ disease has been controversial. Surgical therapy provides 5-year survival rates of 10–15%. Because of the low survival rates, the group from the Memorial Sloan-Kettering Cancer Center conducted a study in which “neoadjuvant” cisplatin-based chemotherapy was given before surgery. The 5-year survival in this study exceeded 20% (131). This led to a series of Phase II neoadjuvant studies using chemotherapy alone or combined chemotherapy and radiotherapy prior to surgery and to randomized studies comparing neoadjuvant cisplatin-based chemotherapy plus surgery to surgery alone.

The Phase II neoadjuvant studies showed that response rates to induction chemotherapy or induction chemoradiotherapy were higher than response rates to the same therapy in stage IV disease (132). Response rates of 60–66% were routinely reported. However, there were wide variations in the rates of surgical resection and surgical mortality. In some series, nearly all patients underwent surgical resection after induction therapy, whereas in other series, the resection rate was below 50%. Operative mortality rates ranged from less than 5% to more than 50%. It is likely that the wide range in resection and operative mortality rates was related in part to patient selection and experience of the thoracic surgeon in operating after induction therapy. The dose of preoperative radiotherapy may also have played a role. In the experience of the Lung Cancer Study Group, operative mortality rates were higher after radiotherapy doses of 60 Gy compared to radiotherapy doses of 45 Gy, when given with or without chemotherapy (133).

There was considerable variability in the 5-year survival rates following neoadjuvant therapy, which may not be surprising, given the range of TNM subsets and the range of therapies in the various studies. The optimal induction therapy remains to be defined, and the value of using all three modalities is also undefined. In most series, the status of the mediastinal lymph nodes at the time of resection is the major determinant of survival time after surgery (105). Patients with negative mediastinal nodes at the time of surgery have a far superior survival compared to patients with positive mediastinal nodes. In large, cooperative-group, Phase II neoadjuvant studies, such as those conducted by the SWOG or the CALGB, the 5-year survival rates were about 20% (105, 134). Both groups reported similar 5-year survival rates in stage III patients treated with chemoradiotherapy alone (105, 134). Thus, it is unclear whether all three modalities will cure more patients than chemoradiotherapy alone. An Intergroup-randomized Phase III trial in the United States is currently addressing this issue. Stage IIIA N₂ patients are randomized to receive etoposide-cisplatin-radiotherapy alone or etoposide-cisplatin-radiotherapy followed by surgery. The radiotherapy dose is 60 Gy in patients receiving chemoradiotherapy alone and 45 Gy in patients randomized to surgery after induction chemoradiotherapy.

In the past 2 years, the results of two randomized Phase III trials comparing surgery alone to surgery plus neoadjuvant cisplatin-based chemotherapy given before and after surgery in stage IIIA (predominantly N₂) NSCLC patients were reported (135, 136). In both studies, there was a significant improvement in the relapse-free and the overall survival favoring the chemotherapy arms. Table 8 summarizes the results of these two studies. The reduction in recurrence and the improvement in the median and 1-year survival were of greater magnitude in these node-positive lung cancer patients than the improvements afforded by chemotherapy in node-positive breast cancer patients. For example, the 4-year survival rates were about 29 and 40% in the chemotherapy groups in both studies, whereas the 4-year survival rates were below 15% in both series with surgery alone. This indicates that the cisplatin-based chemotherapy used in these studies (which is inferior to paclitaxel-, Navelbine-, or gemcitabine-based therapy in stage IV disease) decreased the...
There are several theoretical reasons why preoperative, neoadjuvant chemotherapy might be superior to postoperative adjuvant chemotherapy, including the fact that full doses are more likely to be delivered, and tumor shrinkage may downstage the patient, make the surgery more complete, and lessen the likelihood of tumor dissemination at the time of surgery. The two recent randomized studies examining the role of pre- and postoperative chemotherapy with cisplatin-based regimens in stage IIIA NSCLC described above (135, 136) suggest that this approach should be considered in stages IB, IIA, and IIB NSCLC as well. Preliminary results with preoperative paclitaxel + carboplatin chemotherapy are just being reported. In one study, 83% of patients were downstaged and had a complete resection (139). Such studies have great promise to improve the dismally low cure rates observed with surgery alone or surgery and radiotherapy in operable stages of NSCLC.

Conclusions

Chemotherapy with cisplatin-based combinations improves survival and quality of life in advanced NSCLC patients with good PS as shown by randomized trials and meta-analyses of such trials. Chemotherapy with new agents for NSCLC is superior to chemotherapy with older agents and increases survival to the same extent as chemotherapy improves survival in SCLC and breast cancer. In extensive-stage SCLC, chemotherapy improves median survival from 2 months to 9–10 months, but fewer than 20% are alive at 2 years, and 5-year survival rates are about 1%. In NSCLC, new agent-based chemotherapy improves survival from 4 months to about 10 months, 1-year survival from 10% to 40–50%, and 2-year survival to 20%. At the same time, these therapies improve quality of life, and their cost is similar to that of other accepted medical therapies. Thus, it is reasonable to offer chemotherapy to advanced NSCLC patients with good PS.

In stage III NSCLC patients with good PS, randomized trials and meta-analyses showed that chemotherapy improves survival in both stage IIB patients when added to radiotherapy and stage IIIA patients when added to surgery. Currently, randomized trials are in progress comparing new two-drug regimens combining a new agent with cisplatin or carboplatin. The results of these trials should be available within 2–3 years. Current Phase III studies are evaluating new two-drug regimens without cisplatin (e.g., paclitaxel and gemcitabine), new three-drug combinations such as paclitaxel + gemcitabine + carboplatin, and alternating or sequential two-drug combinations. These new approaches will need to be compared to the best two-drug combinations in future randomized trials. The magnitude of the survival advantage provided by chemotherapy in stage III NSCLC is as great as chemotherapy provides in limited-stage SCLC patients. Combined modality therapy is associated with 14–18-month median survival in both NSCLC and SCLC. With respect to long-term survival, about 5–10% of SCLC patients survive 5 years, whereas 5-year survival rates are 15–20% in stage IIB NSCLC. There is a consensus that all limited-stage SCLC patients should be offered chemotherapy with radiotherapy, and the data justify the same conclusion in stage IIB NSCLC patients with good PS.

In patients with stage IIIA N2, single-modality therapy with
surgery or radiotherapy provides inferior results compared to chemotherapy and surgery or chemotherapy and radiotherapy. Ongoing randomized studies will determine whether all three modalities are superior to two modalities. Future randomized trials will need to determine whether the best new drug combinations provide additional survival benefit to the best combination of two or three modalities.

In patients with resectable stage IB, IIA, or IIB NSCLC, older cisplatin-based chemotherapy regimens produced a modest survival advantage. Preliminary trials with newer chemotherapy-based regimens are producing encouraging results, and it is likely that the magnitude of the ultimate survival advantage will be as great as or greater than that observed in breast and colon cancer patients treated with adjuvant chemotherapy. Currently, a randomized trial is evaluating the value of postoperative vinorelbine and cisplatin in completely resected patients. Several Phase II studies of neoadjuvant carboplatin and paclitaxel have shown promising results, and randomized trials with such combinations are planned.

It is time to end the pessimism over the role of chemotherapy in lung cancer patients. Currently available chemotherapy should be offered to lung cancer patients as we continue to search for and develop more effective agents and as we work to decrease the proportion of smokers.

References


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