Chemotherapeutic Management of Stage IV Non-small Cell Lung Cancer*

Mark A. Socinski, MD, FCCP; David E. Morris, MD; Gregory A. Masters, MD, FCCP; and Rogerio Lilenbaum, MD

Stage IV non-small cell lung cancer (NSCLC) denotes the presence of metastatic disease and is largely incurable using present-day therapies. Chemotherapy remains a therapeutic option in this patient population, and there are many pertinent issues surrounding its use in patients with stage IV NSCLC. Eleven questions were framed by the American College of Chest Physicians Lung Cancer Guidelines Committee, and these were addressed by a systematic search of the available literature. The issues addressed included the identification of prognostic factors in selecting patients for chemotherapy and a critical analysis of the survival benefit provided by chemotherapy. Given the development of several new chemotherapeutic agents over the past decade, the impact that these agents have made was addressed as well as the definition of a standard of care regarding chemotherapeutic regimens. Given the fact that chemotherapy does not represent a curative option, other issues addressed were the optimal duration of treatment as well as its impact on symptom relief and quality of life, the role of second-line therapy, and the outcomes expectations from both first-line and second-line chemotherapy. The question of what specialty delivered the chemotherapy also was addressed. Once the data were identified, a critical analysis was undertaken attempting to objectively portray the data in support of answers for each of the questions posed. We believe the data support the fact that properly selected patients benefit from chemotherapy with regard to survival and palliation in both first-line and second-line settings. It appears that in trials addressing the duration of first-line therapy, this survival and palliative benefit occurs early, and prolonged therapy is not indicated. Therapy in this setting is cost-effective, and there are several regimens that can be considered to be “standard-of-care” options. Physicians involved in the diagnosis of these patients should be aware of the potential benefits of chemotherapy, allowing them to give recommendations to patients that are based on data derived from clinical trials. In addition, this awareness will allow them to make referrals, when appropriate, to physicians who are trained in the administration of chemotherapy and the management of patients undergoing such therapy.

Key words: chemotherapy; evidence-based medicine; guidelines; non-small cell lung cancer

Abbreviations: BSC = best supportive care; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ELVIS = Elderly Lung Cancer Vinorelbine Italian Study; EORTC = European Organization for Research and Treatment of Cancer; FACT-L = functional assessment of cancer therapy-lung cancer; HR = hazard ratio; NSCLC = non-small cell lung cancer; OR = odds ratio; PS = performance status; QOL = quality of life; RR = relative risk; TOI = trial outcome index; TRT = thoracic radiation therapy; V/I = vinorelbine or ifosfamide

Lung cancer remains the leading cause of cancer-related death in the United States.1 Approximately 169,400 new cases will be diagnosed in the year 2002 with an estimated 154,900 deaths expected from this disease.1 The vast majority of these patients have non-small cell lung cancer (NSCLC), which comprises approximately 80% of all new cases.2 In early-stage NSCLC, surgical resection remains the standard of care in fit patients. Ongoing trials in this setting are addressing the role of both adjuvant and neoadjuvant chemotherapy. In fit patients with unresectable, locally advanced, stage III NSCLC, chemotherapy in combination with thoracic radiation therapy (TRT) is the standard of care. Controversy exists regarding the optimal strategy in combining these two modalities (ie, sequential therapy, concurrent therapy, or both) as well as regarding the optimal chemotherapeutic agents and optimal dose

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and schedule of TRT. In these two groups of patients, cure remains the goal in fit patients, and local modalities (ie, surgery and TRT) remain a cornerstone of therapy.

Stage IV NSCLC denotes the presence of metastatic disease. The more common sites of metastatic disease include the liver, bones, adrenal, brain, and contralateral lung. In the 1997 revision of the staging system, a separate tumor nodule in the ipsilateral nonprimary tumor lobe was also classified as metastatic disease, although the possibility of multiple primary lung cancers should be considered in selected cases. In addition, there are subsets of patients with stage IIIIB disease who are not appropriate for combined therapeutic modality approaches, such as those patients with a malignant pleural/pericardial effusion and certain patients with advanced palpable supraclavicular adenopathy. These patients are typically included with stage IV patients when the benefit of systemic chemotherapy is considered and have been included in most clinical trials addressing this issue, as the prognosis of these patients is similar to that of patients with stage IV NSCLC. Where possible, we have clearly indicated the percentage of stage IV patients in each of the trials included in this analysis.

The purpose of this section is to review the evidence supporting the role of systemic chemotherapy in the management of stage IV NSCLC. As noted above, most trials have included selected patients with stage IIIIB NSCLC in whom a systemic therapeutic approach is appropriate. The 5-year survival rate of this group of patients is 1%, and therefore these patients are generally considered to be incurable. Despite this, the important issues to address include which patients are appropriate for chemotherapy, the survival and palliative impact of chemotherapy, the optimal chemotherapeutic approach, and its toxicity and outcomes expectations. To accomplish this, we sought to identify the evidence addressing these issues from primary data sources that have been published in the existing English literature. Eleven questions regarding the role of chemotherapy in treating patients with stage IV NSCLC were framed by the American College of Chest Physicians Lung Cancer Guidelines Committee. A list of MEDLINE search terms that were used to identify the primary evidence addressing these 11 questions is shown in the Appendix. In addition, the primary evidence was supplemented by the authors if data sources were identified outside the MEDLINE search mechanism. Once appropriate data sources were identified, a comprehensive review was undertaken. The evidence addressing each question is presented in detail followed by a summary statement. All attempts to eliminate bias were made by objective presentation of the evidence as it exists in the primary data source.

**ARE THERE IDENTIFIABLE PROGNOSTIC FACTORS THAT SHOULD BE USED WHEN SELECTING PATIENTS FOR SYSTEMIC CHEMOTHERAPY?**

The prognosis of patients with advanced NSCLC is poor. Most large phase III trials have shown a median survival time of 8 to 10 months and a 1-year survival rate of 30 to 35%. Given the consistent improvement in the survival of patients who have been treated with chemotherapy over those receiving supportive care alone, clinicians struggle to stratify these patients into different prognostic groups. One would like to identify those patients who are the most likely to benefit from aggressive chemotherapy and to tolerate its side effects, and to identify another group of patients who are unlikely to obtain any meaningful advantage from such therapy. Ideally, prognostic groups could help to stratify patients in order to apply different approaches or levels of aggression. This also could allow an appropriate focus on quality of life (QOL) as a major end point.

Individual patient characteristics seem to influence survival in patients with advanced NSCLC. The most important factor across all studies is performance status (PS). Patients with stage IV NSCLC who are compromised by their disease have poorer survival compared to patients who are less compromised. Two commonly used PS scales are shown in Table 1. At least 10 trials evaluating prognostic factors in patients with advanced NSCLC have clearly identified PS at the time of diagnosis to be a powerful predictor of survival. In a landmark analysis of 893 patients with stage IV NSCLC, Finkelstein et al documented the impact that PS had on survival. In that study, the 1-year survival rate was 36% for PS level 0 patients, 16% for PS level 1 patients, and 9% for PS level 2 patients (p < 0.001).

Pretreatment weight loss is generally regarded as a negative prognostic factor, but not all trials have reliably corroborated this. The sex of NSCLC patients also has been described as an important prognostic variable, with most trials suggesting improved survival for women. Differences in survival based on patient sex have generally been small, usually ≤ 1 to 2 months.

Age may be a predictor of survival, with some studies suggesting that elderly patients with advanced NSCLC have poor outcomes. Other studies looking at this variable have failed to confirm this or have suggested that older patients have a similar or even superior survival.
Table 1—Performance Status Scales

<table>
<thead>
<tr>
<th>Status Scales</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>100</td>
</tr>
<tr>
<td>Fatigue without significant decrease</td>
<td>90</td>
</tr>
<tr>
<td>or bedrest</td>
<td>80</td>
</tr>
<tr>
<td>Fatigue with significant impairment</td>
<td>70</td>
</tr>
<tr>
<td>or bedrest &lt; 50% of waking hours</td>
<td>60</td>
</tr>
<tr>
<td>Bedrest &gt; 50% of waking hours</td>
<td>50</td>
</tr>
<tr>
<td>Bedridden or unable to care for self</td>
<td>40</td>
</tr>
<tr>
<td>Karnofsky</td>
<td></td>
</tr>
<tr>
<td>Normal, no complaints</td>
<td>100</td>
</tr>
<tr>
<td>Normal activity, minor signs of symptom disease</td>
<td>90</td>
</tr>
<tr>
<td>Normal activity with effort</td>
<td>80</td>
</tr>
<tr>
<td>Cares for self in daily activities, but unable to carry on normal activity or work</td>
<td>70</td>
</tr>
<tr>
<td>Requires occasional assistance but able to care for most needs</td>
<td>60</td>
</tr>
<tr>
<td>Requires considerable assistance and frequent medical care</td>
<td>50</td>
</tr>
<tr>
<td>Disabled; requires special care and assistance</td>
<td>40</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>30</td>
</tr>
<tr>
<td>Very sick; hospitalization necessary; active supportive treatment necessary</td>
<td>20</td>
</tr>
<tr>
<td>Moribund</td>
<td>10</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>

pective review,14 no difference in survival was seen for patients < 40 years of age compared with a matched group of patients who were > 50 years of age. Therefore, it is difficult to say that age is a reliable independent prognostic factor for these patients.

A large Eastern Cooperative Oncology Group (ECOG) trial15 in the United States (ECOG 5592) showed that QOL scores, as measured by the functional assessment of cancer therapy-lung cancer (FACT-L), were important predictive factors. This study also showed that the absence of change in cough or hoarseness, the absence of bone pain, the absence of other symptoms from metastases, and the absence of anorexia were all independent favorable prognostic factors. Another retrospective study16 showed pain level to correlate inversely with survival. QOL, however, was not a predictive factor in this analysis.

Pretreatment stage, even among those patients with advanced NSCLC is prognostic, with stage IIIB patients generally having a better survival rate than those with overt metastatic or stage IV disease.4,17 The total number of metastatic sites may influence the prognosis.4–10,12,13 Several nonrandomized trials have suggested that patients with a solitary site of metastasis may have superior outcomes and that more aggressive therapy (including surgical resection of the primary tumor and metastatic site) may provide up to 20 to 30% of patients with long-term survival. Studies also have suggested that specific sites of metastatic disease may change the prognosis in patients with advanced NSCLC. Specifically, patients with disease confined to the lungs may have superior outcomes. Those with brain metastases may have poorer outcomes,4 but this conclusion is controversial.18,19 The presence of bone or liver metastases has been found to confer a poor prognosis in the retrospective analysis previously.15

Histologic subtype does not reliably provide prognostic importance in patients with advanced NSCLC, despite the different clinical manifestations of adenocarcinoma compared to squamous histology.4–6,10,11 Normal levels of serum lactate dehydrogenase, high levels of albumin, and low levels of alkaline phosphatase all have, however, been associated with a better prognosis in patients with advanced NSCLC.6,13,20

The expression of neuroendocrine markers may predict survival in patients with NSCLC. In one study,21 responding patients with two or more positive markers survived longer. Another study22 found that tumors containing > 50% positively staining cells were associated with shorter survival times. Currently, neuroendocrine markers cannot be used to reliably predict survival in patients with advanced NSCLC.

Perhaps the most important prognostic factor, and the one most clearly proven in randomized trials, is whether patients receive chemotherapy.23–32 Numerous randomized trials and several meta-analyses have confirmed an improvement in the median survival time of 6 to 8 weeks, translating to a 10% improvement in the 1-year survival rate for those advanced NSCLC patients who are receiving platinum-based chemotherapy.

Recommendation 1

1. When selecting patients for systemic chemotherapy, PS at the time of diagnosis should be used because it is a consistent prognostic factor for survival. Patients with a PS of ECOG level 0 or 1 should be offered chemotherapy. Level of evidence, good; benefit, substantial; grade of recommendation, A

2. Data are not yet sufficient to routinely recommend chemotherapy to patients with a PS of ECOG level 2. Level of evidence, poor; benefit, small/weak; grade of recommendation, I

3. Patients with a PS of ECOG level 3 or 4 should not receive chemotherapy. Level of evidence, fair; benefit, moderate; grade of recommendation, B

4. Other patient-related factors (eg, gender, age, sites of metastases, and histology) have not been consistent prognostic factors for survival. Level of evidence, poor; benefit, small/weak; grade of recommendation, I
Ten randomized clinical trials have been published comparing platinum-based chemotherapy to best supportive care (BSC) [Table 2]. It should be noted that BSC in these trials included aggressive symptom management (eg, antitussive agents, supplemental oxygen, and nonnarcotic and narcotic analgesic agents) as well as palliative radiotherapy when indicated. In all 10 trials, the median survival time of the treated patients was numerically superior to that of patients receiving BSC. The median survival time of patients receiving BSC was 3.6 months (range, 2.4 to 4.9 months) in these 10 trials, providing a benchmark for survival in patients with untreated, advanced NSCLC. The median survival time of the treated patients was 6.5 months (range, 4.7 to 8.5 months). The numeric survival advantage seen in all 10 trials was statistically significant in 6 of these trials.

Four meta-analyses have been published examining the effect of treatment vs BSC in patients with advanced NSCLC. The studies have differed in how trials were selected for review, in the number of trials included, in the use of group or individual patient data in the analysis, and in the statistical methodology used (Table 3). Despite this, these four meta-analyses were consistent in their conclusions. The majority of trials included in these four studies used cisplatin-based regimens. Souquet et al included seven trials, of which six were cisplatin-based. The other three trials used long-term alkylating agents or vinca alkaloids and etoposide. Although a survival advantage for chemotherapy was documented over BSC, there was a difference between cisplatin-based trials and non-cisplatin-based trials. In fact, the long-term administration of alkylating agents actually had a negative impact on survival compared to BSC. When evaluating trials employing only cisplatin-based regimens, there was a 27% reduction in the risk of death (hazard ratio, 0.73; 95% CI, 0.63 to 0.85; p = 0.0001) with chemotherapy vs BSC (Fig 1).

Table 4 summarizes the recommendations from several guidelines addressing this issue. As can be seen, the organizations represent national as well as international guidelines. The end point analyzed was the number of deaths at 3-month intervals up to 18 months. There was a significant reduction in mortality for up to 6 months for chemotherapy vs BSC. The odds ratio (OR) at 6 months was approximately 0.6 in favor of chemotherapy. Grilli et al analyzed six trials (of which five were cisplatin-based) in terms of relative risk (RR). The overall RR for death for chemotherapy vs BSC was 0.76 (95% confidence interval [CI], 0.66 to 0.87). Marino et al included eight trials (of which six were cisplatin-based) and determined the individual and pooled odd ratios for death at 6 months. The OR for death was 0.44 (95% CI, 0.32 to 0.50) in favor of chemotherapy.

What Is the Evidence That Platinum-Based Chemotherapy Improves Survival?

Table 2—Randomized Clinical Trials of Platinum-Based Chemotherapy vs BSC in Advanced NSCLC*

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Patients, No.</th>
<th>Age, yr†</th>
<th>Stage IV, %</th>
<th>Chemotherapy Regimen</th>
<th>Survival Time, mo‡</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapp et al 1988</td>
<td>198 T 53 BSC 56</td>
<td>53 T 58</td>
<td>CAP</td>
<td>5.7 3.9 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganz et al 1989</td>
<td>22 T 6 BSC (54% &lt; 60 yr) 85</td>
<td>90 100</td>
<td>VdP</td>
<td>7.5 3.9 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woods et al 1990</td>
<td>97 T 61 BSC 61</td>
<td>73 82</td>
<td>VdP</td>
<td>6.2 3.9 NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quoix et al 1991</td>
<td>24 T 69 (36-74) 62 T 52-73</td>
<td>72 93</td>
<td>VdP</td>
<td>6.5 2.4 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellerino et al 1992</td>
<td>62 T 59 (33-70) 62 T 45-72</td>
<td>63 97</td>
<td>CErP → Mx ECC</td>
<td>7.9 4.9 NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaasa et al 1991</td>
<td>44 T 43 BSC 62</td>
<td>49</td>
<td>EP</td>
<td>5.0 3.7 NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cartei et al 1993</td>
<td>52 T 56 (39-73) 57 (39-71)</td>
<td>72</td>
<td>MCP</td>
<td>8.5 4.0 0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Helsing et al 1998</td>
<td>22 T 61 (36-72) 65 (44-78)</td>
<td>65 90</td>
<td>EC</td>
<td>6.7 2.6 0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thongprasert et al 1999</td>
<td>189 T 58 (36-73) 60 (28-73)</td>
<td>NR NR</td>
<td>IErP/MVbP</td>
<td>6.0 2.5 0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cullen et al 1999</td>
<td>175 T 62 (56-69) 64 (59-69)</td>
<td>62 72</td>
<td>MIP</td>
<td>6.7 4.8 0.03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* T = treated; CAP = cyclophosphamide, Adriamycin, cisplatin; VdP = vindesine, cisplatin; CErP = cyclophosphamide, epirubicin, cisplatin; MVbP = mitomycin, vinblastine, cisplatin; MCP = mitomycin, cyclophosphamide, cisplatin; EC = etoposide, carboplatin; IErP = ifosfamide, epirubicin, cisplatin; MIP = mitomycin, ifosfamide, cisplatin; NS = not significant; NR = not reported.
† Values given as median (range).
‡ Values given as median.
§ Percentage of patients with either ECOG PS 0–1 or Karnofsky PS ≥ 70.

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international societies from the United States, Canada, and Europe. The guidelines are either evidence-based or consensus guidelines and represent an analysis of the cisplatin-based literature. All of these organizations recommend chemotherapy in patients with advanced stage IV NSCLC.

It is difficult to portray to patients the magnitude of the survival effect in this setting. Table 2 shows the differences in median survival times in trials comparing platinum-based regimens to BSC. Stage IV NSCLC still is a disease with a steeply downsloping survival curve, making median survival a less meaningful end point. In general, investigators in this area have focused on the 1-year survival percentage. To evaluate this end point, the last four trials published in which the 1-year survival percentage was reported and that included a BSC control were analyzed. Fig 2 shows the percentage of patients who are alive at 1 year as well as the absolute number of patients who are alive in the United States, comparing BSC to chemotherapy. The data suggest a doubling of the 1-year survival rate and approximately 10,000 more patients surviving beyond 1 year as a result of chemotherapy.

In conclusion, the evidence from both randomized clinical trials and four separate meta-analyses support the fact that platinum-based chemotherapy improves survival in patients with advanced stage IV NSCLC.

**Recommendation 2**

Patients with a good PS (ie, ECOG level 0 or 1) should be considered for a platinum-based chemotherapy regimen based on the survival advantage provided over BSC. Level of evidence, good; benefit, substantial; grade of recommendation, A

**DO “NEW AGENTS” IMPROVE SURVIVAL AS SINGLE AGENTS COMPARED TO BSC?**

Since 1990, several new agents with significant single-agent activity in NSCLC have been developed including paclitaxel, docetaxel, vinorelbine, gemcitabine, and irinotecan. These agents are commonly referred to as third-generation agents. Several randomized trials have been reported in which these new agents were tested against BSC using survival as the primary end point (Table 5). Both taxanes (ie, paclitaxel and docetaxel) have been compared to BSC in a randomized trial. Survival was superior for patients who received both taxanes compared to BSC (Table 5). The magnitude of the benefit measured either as an increase in median survival or as 1-year survival is similar to the benefit seen with cisplatin-based chemotherapy regimens. Vinorelbine has been compared to BSC in the elderly (defined as persons ≥ 70 years of age) in the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS). In this select population of patients, a survival advantage was seen with the estimated relative hazard of death for patients receiving vinorelbine compared to BSC being 0.65 (95% CI, 0.45 to 0.93). In addition to

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Trials/Platinum-Based Trials, No.</th>
<th>Patients, No.</th>
<th>End Point</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Souquet et al 1993</td>
<td>7/6</td>
<td>706</td>
<td>No. of deaths at 3, 6, 9, 12, and 18 mo</td>
<td>Statistically significant reduction of mortality for up to 6 mo</td>
</tr>
<tr>
<td>Grilli et al 1993</td>
<td>6/5</td>
<td>635</td>
<td>RR of death at 3, 6, 9, and 12 mo</td>
<td>24% (95% CI, 13–34%) reduction in probability of death for chemotherapy vs BSC</td>
</tr>
<tr>
<td>Marino et al 1994</td>
<td>8/6</td>
<td>712</td>
<td>OR of death at 6 mo</td>
<td>OR = 0.44 (95% CI, 0.32–0.50; p &lt; 0.05) favored chemotherapy</td>
</tr>
<tr>
<td>NSCLC Collaborative Group 1995</td>
<td>11/8</td>
<td>1190</td>
<td>HR in death</td>
<td>For cisplatin-based chemotherapy HR = 0.73 (95% CI, 0.63–0.85; p &lt; 0.0001) vs BSC</td>
</tr>
</tbody>
</table>

**Figure 1.** Survival in trials employing cisplatin-based regimens vs BSC only. Reprinted with permission from the Non-Small Cell Lung Cancer Collaborative Group.
these three studies, further evidence of an impact of the new agents comes from the randomized trial by Crawford and colleagues.\(^{40}\) In that study, vinorelbine was compared to fluorouracil and leucovorin rather than BSC. The selection of fluorouracil and leucovorin as the control arm of the study was arbitrary, and this combination had not been tested previously in patients with advanced NSCLC. The response rate to fluorouracil and leucovorin was only 3%, the median survival time was 5.1 months, and the 1-year survival rate was 16%. These survival outcomes are almost identical to the BSC arms of the other three trials shown in Table 5, suggesting that fluorouracil and leucovorin had no impact on the natural course of advanced NSCLC. The outcomes associated with vinorelbine on the study were a response rate of 12%, a median survival time of 7.0 months, and a 1-year survival rate of 25% (\(p = 0.03\) [compared to fluorouracil and leucovorin]). Thus, this trial suggested a benefit to patients receiving vinorelbine that was similar to that in the ELVIS.\(^{38}\) This study is not included in Table 5 only because patients in the control arm of the study received “ineffective” chemotherapy rather than BSC. Another trial\(^{41}\) compared the use of single-agent gemcitabine to BSC but was designed to show a palliative benefit. Since survival was not the end point, this trial also is not included in Table 5.

The magnitude of the survival benefit from these single agents is similar to that obtained with platinum-based regimens. Whether the new active single-agents yield survival outcomes that are similar to the platinum-based regimens is not known. Several ongoing randomized clinical trials are addressing this issue.

**Recommendation 3**

Although the new agents demonstrate improved survival compared to BSC (level of evidence, good; benefit, moderate; grade of recommendation, B) in elderly as well as nonelderly patients with advanced NSCLC, the data are not yet sufficient to compare the new single agents to platinum-based combinations. Level of evidence, poor; benefit, small/weak; grade of recommendation, I

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*Table 4—Summary of Recommendations From Other Guidelines in Stage IV NSCLC Patients*

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year of Publication</th>
<th>Recommendation</th>
<th>Grade of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Society of Clinical Oncology</td>
<td>1997</td>
<td>Chemotherapy is recommended for good PS (0–1) and possibly PS 2</td>
<td>A</td>
</tr>
<tr>
<td>British Thoracic Society</td>
<td>1998</td>
<td>Patients with NSCLC referred to pulmonologist or oncologist for chemotherapy</td>
<td>C</td>
</tr>
<tr>
<td>National Cancer Guidance Group, NHS Executive</td>
<td>1998</td>
<td>In advanced disease, platinum-based chemotherapy indicated</td>
<td>A</td>
</tr>
<tr>
<td>ACCC</td>
<td>2000</td>
<td>Chemotherapy for PS 0–2 NSCLC patients</td>
<td>C</td>
</tr>
<tr>
<td>Lopez—CCOPGI</td>
<td>2000</td>
<td>Chemotherapy indicated for survival and symptom control/QOL</td>
<td>A</td>
</tr>
<tr>
<td>NCCN</td>
<td>2000</td>
<td>Chemotherapy indicated for PS 0–2 NSCLC patients</td>
<td>C</td>
</tr>
<tr>
<td>PDQ Adult Treatment Editorial Board</td>
<td>2001</td>
<td>Chemotherapy indicated in stage IV NSCLC</td>
<td>C</td>
</tr>
</tbody>
</table>

*C = consensus guidelines; ACCC = Association of Community Cancer Centers; CCOPGI = Cancer Care Ontario Practice Guidelines Initiative; NCCN = National Comprehensive Cancer Network.

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**Figure 2.** Estimated 1-year survival rates and absolute no. of patients who are alive at 1 year in the United States.\(^{31,32,37,39}\) CT = chemotherapy. Numbers on the right abscissa represent thousands.

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*Do the New Agents in Combination With the Platinum-Based Agents Improve Survival Over Second-Generation Platinum-Based Regimens?*

As noted above, a number of new chemotherapy agents (ie, paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan) have been identified over the last 10 years as having documented activity in patients with advanced NSCLC. These third-genera-
tion agents have been incorporated into clinical trials and have been reported to have an improved toxicity profile, but is there proof that these new drugs also improve survival compared to older standard therapies? The first of the new drugs to be studied in randomized trials was vinorelbine. A large French trial compared the European standard regimen of cisplatin and vindesine to vinorelbine alone or vinorelbine in combination with cisplatin. This study showed a significant improvement in patient survival for the new drug combination of cisplatin/vinorelbine, with a median survival of 40 weeks vs 32 weeks for cisplatin-vindesine. Survival for patients receiving vinorelbine alone was not significantly different from that for patients in the standard treatment arm. A Southwest Oncology Group trial showed an advantage for patients receiving cisplatin with vinorelbine over those receiving cisplatin alone. The median survival time for the patients receiving cisplatin and vinorelbine was 8 months compared to 6 months for those receiving cisplatin alone.

Other new drugs have been studied in randomized trials as well. A trial from ECOG showed improved survival for patients receiving cisplatin and paclitaxel (at lower or higher doses with granulocyte colony-stimulating factor support) over the older combination of cisplatin and etoposide. In this study, patients receiving the combination of cisplatin and paclitaxel showed a median survival time of 9.6 and 10 months, respectively, for the lower and higher doses, compared to 7.7 months for the cisplatin and etoposide combination. A trial by Belani and colleagues failed to show a survival advantage for patients receiving carboplatin and paclitaxel over those receiving cisplatin and etoposide. This trial did slow some of the momentum for the new drug combinations but did not dampen the enthusiasm for these agents, since the study suggested an improved QOL for patients receiving paclitaxel and carboplatin over the older combination of cisplatin and etoposide. A trial comparing patients receiving cisplatin alone to those receiving cisplatin plus paclitaxel failed to show a survival advantage. Another trial showed equivalent survival in a trial comparing patients receiving cisplatin and paclitaxel vs those receiving cisplatin plus teniposide.

Gemcitabine is another of the new agents studied in randomized trials. A trial showed a survival advantage for patients receiving cisplatin and gemcitabine over those receiving cisplatin alone. This study showed a median survival time of 9.1 months for patients receiving the two-drug combination compared to 7.6 months for patients receiving the older drug alone. No survival advantage was shown for patients receiving the combination of cisplatin and gemcitabine compared to those receiving mitomycin, ifosfamide, and cisplatin or cisplatin and etoposide in two trials from Europe. Two trials showed equivalent survival for patients receiving gemcitabine as a single agent to those receiving cisplatin and etoposide. Both studies also found significantly less toxicity for the new drug compared to the older combination.

Two trials from Japan have compared a standard regimen of cisplatin and vindesine to the new combination of cisplatin and irinotecan. One such study found a median survival time of 52 weeks for patients receiving the new regimen vs 47 weeks for patients receiving the older standard (difference not significant), with a trend in the 1-year survival rate favoring the newer regimen at 49% compared to 40%. The other trial did not show significant differences between the two arms. A subset analysis including only stage IV patients suggested a significant survival advantage for patients receiving cisplatin/irinotecan compared to those receiving cisplatin/vindesine.

Despite these positive trial results, over the last 20 years there still has been evidence that the progress is slow in improving the treatment for patients with advanced NSCLC. A retrospective study from the Dana Farber Cancer Institute looked at outcomes in North American randomized chemotherapy trials.
and found slow progress in improving survival in the studies they reviewed. Of 33 randomized phase III trials of chemotherapy for advanced NSCLC between 1973 and 1994, only 5 showed a significant difference in survival. There was a median prolongation of survival time of 2 months in these positive trial results. It is important to note, however, that this review omitted most of the trials with the newer drugs, which were introduced in the early 1990s. Baggstrom and colleagues have performed a meta-analysis of the published literature comparing platinum-based regimens including a third-generation agent to older standard platinum-based regimens. Eight trials published since 1994 were identified, which included 3,296 patients. In an analysis of heterogeneity, the results of the trials were thought to be consistent, allowing a summary analysis. When examining the impact on 1-year survival, the new third-generation regimens increased patient survival compared to the older regimens (RR, 1.14; 95% CI, 1.01 to 1.29). There was an absolute increase in the 1-year survival rate of 4% using the newer combination regimens compared to the older regimens (p = 0.04). Also, patient response rates were improved with the newer regimens (RR, 1.50; 95% CI, 1.51 to 2.15) with an absolute increase of 13%. There was no difference in the rates of treatment-related deaths comparing the newer regimens to the older platinum-based regimens. This analysis suggests that there has been a significant, albeit small, improvement in survival with the use of the newer third-generation regimens compared to the older standard regimens.

In conclusion, the data suggest that progress is being made in the management of patients with advanced NSCLC through newer and more effective chemotherapy. The magnitude of improvement, however, is small. This emphasizes the importance of continuing active clinical research into new treatments. We need to identify more effective treatment options that have less toxicity, including targeted and biological agents, for this disease.

Recommendation 4

Combination chemotherapy regimens incorporating the new single agents with a platinum-based agent should be considered the standard of care. Level of evidence, fair; benefit, moderate; grade of recommendation, B

IS THERE A STANDARD OF CARE REGARDING THE CHOICE OF CHEMOTHERAPY IN THE FIRST-LINE SETTING?

Two large randomized trials that were reported within the last 2 years compared several of the new-generation regimens in the treatment of patients with advanced NSCLC. The first trial, conducted by the Southwest Oncology Group, compared the use of cisplatin-vinorelbine with carboplatin-paclitaxel. There was no difference in objective response, median survival time, or 1-year survival rates between patients receiving the two combinations. The second trial, by ECOG, compared cisplatin-paclitaxel as the standard regimen to the following three new combinations: cisplatin-gemcitabine; cisplatin-docetaxel; and carboplatin-paclitaxel. No significant difference in response rates or survival was observed among the four arms. There was a small, but statistically significant, difference in progression-free survival in favor of patients receiving the cisplatin-gemcitabine combination. Both of these trials also included a comprehensive analysis of toxicity. In the first trial, the combination of cisplatin-vinorelbine produced more nausea and hematologic toxicity. Carboplatin-paclitaxel produced more alopecia and peripheral neuropathy. A formal QOL analysis was undertaken and demonstrated comparable parameters between the two regimens. In the second trial, the combination of cisplatin-gemcitabine caused more thrombocytopenia, whereas the cisplatin-docetaxel combination produced more neutropenia. Overall, patients receiving carboplatin-paclitaxel had the lowest incidence of life-threatening or lethal toxicities. Platinum-based combination regimens that have been tested and reported in published phase III trials are shown in Table 6.

Given the number of active agents available, non-platinum-containing combination regimens have been evaluated in many phase I and II trials. A randomized trial comparing patients receiving the combination of cisplatin-docetaxel to those receiving gemcitabine-docetaxel has been published.

Table 6—Platinum-Based Combination Regimens Tested in Published Phase III Trial and Considered Standard of Care*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Doses</th>
<th>Schedule</th>
<th>References</th>
</tr>
</thead>
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<tr>
<td>Cisplatin</td>
<td>75–80 mg/m² day 1</td>
<td></td>
<td>44, 47</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m²/24 day 1</td>
<td>Every 21 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>175 mg/m²/3 h day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC = 6 day 1</td>
<td></td>
<td>45, 58, 59</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>225 mg/m² day 1</td>
<td>Every 21 d</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m² day 1</td>
<td></td>
<td>42, 43, 58</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>25 mg/m²/wk</td>
<td>Every 28 d</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m² day 1</td>
<td></td>
<td>48, 49, 59</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1,000 mg/m²/wk</td>
<td>Every 28 d</td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75 mg/m² day 1</td>
<td></td>
<td>59</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75 mg/m² day 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AUC = area under the concentration curve.
was no significant difference in response or survival rates. The toxicity profile was slightly more favorable for patients receiving gemcitabine-docetaxel, with less neutropenia, nausea, and diarrhea. No other trial that has been published to date addresses the issue of nonplatinum doublets in stage IV NSCLC.

**Recommendation 5**

No one regimen has been demonstrated to be superior in the first-line therapy for patients with advanced NSCLC. A cisplatin-based or carboplatin-based combination regimen that includes one of the new agents remains the standard of care for first-line therapy in patients with stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A

**IS THERE AN OPTIMAL DURATION OF CHEMOTHERAPY?**

Given the noncurative nature of stage IV NSCLC, the duration of chemotherapy must be weighed against the toxicity it engenders. Until recently, few trials addressed this issue, and chemotherapy would be administered for six or more cycles. In the 1997 guideline issued by the American Society of Clinical Oncology, the lack of data pertaining to this issue was cited. The consensus of the expert panel was that chemotherapy should be administered for no more than eight cycles in patients with stage IV NSCLC. The only trial referenced in that guideline was reported in 1989 by Buccheri and colleagues. This controlled trial used a non-cisplatin-based chemotherapy regimen and randomized patients with stable disease after two or three cycles of chemotherapy to continued treatment or BSC. No survival benefit was seen with continuous treatment in this subset of patients with stable disease.

In 2001, Smith and colleagues reported a randomized trial of three cycles vs six cycles of mitomycin, vinblastine, and cisplatin in 308 patients with advanced NSCLC, of whom 54% had stage IV disease. Of the patients randomized to three cycles, 72% completed therapy, while only 31% of the patients randomized to six cycles completed therapy. The median survival times and 1-year survival rates were similar for patients in both study arms, with no advantage seen for the longer duration of therapy. In addition, the median duration of symptom relief was similar in both study arms. QOL parameters were the same or were improved in patients receiving three cycles of therapy as less fatigue, nausea, and vomiting (typical cumulative toxicities of cisplatin) was reported compared to patients receiving the longer duration (six cycles) of therapy.

Another trial randomized 230 patients with stage IIIB/IV NSCLC to either four cycles of carboplatin-paclitaxel or to continuous treatment until they experienced objective progression of the disease. Survival and QOL were the primary end points of this trial. Of interest is the fact that in the continuous-treatment arm of that trial, a median of only four cycles of treatment was administered. No benefit was seen in survival, QOL, or response rates between the two arms of that randomized trial. An increasing rate of peripheral neuropathy (a known cumulative toxicity of the regimen used) was seen in patients receiving more than four cycles of therapy with no significant increase in survival rates.

The results of these two randomized trials suggest that the survival and palliative benefit that patients receive from chemotherapy occurs in the first 3 to 4 cycles. Prolonged therapy may increase cumulative toxicities that are specific to the regimen used without increasing survival, thereby decreasing the therapeutic benefit of therapy.

**Recommendation 6**

The duration of first-line therapy in patients with stage IV NSCLC should be brief, consisting of three to four cycles or fewer if there are signs of progressive disease. Level of evidence, good; benefit, substantial; grade of recommendation, A

**DOES SECOND-LINE CHEMOTHERAPY IMPROVE SURVIVAL?**

Since the first-line therapy used in patients with stage IV NSCLC is not curative, patients will eventually experience disease progression unless they develop another fatal comorbid illness. Once the disease progresses, the median survival time is approximately 3 months. The proportion of patients receiving second-line therapy following disease progression after receiving first-line platinum-based therapy has not been well-described but is generally < 50%. Many of these patients retain a good PS at the time of disease progression and are motivated to receive further therapy.

Two randomized clinical trials have been reported that addressed the issue of second-line treatment in patients with advanced NSCLC that progresses after they have received first-line platinum-based chemotherapy. Both trials used docetaxel because this agent had shown significant activity in this patient population in single-arm phase II trials. The eligibility requirements for both trials were also very similar, resulting in similar groups of patients being entered into each trial. Patients could have received more than one previous chemotherapy regi-
immen, but 65 to 77% of the patients entered into these studies had received only one regimen. In the trial of Shepherd et al., previous treatment with a taxane was also an exclusion criterion. The majority of patients had a good PS (ECOG level 0 to 1 in 75 to 85% of patients), had stage IV NSCLC (80 to 90%), and were men (72 to 82%).

The first trial compared two doses of docetaxel (100 mg/m² and 75 mg/m² every 3 weeks) to BSC in patients who were taxane-naïve but had previously been treated with a platinum-based regimen. The original design was a two-arm trial comparing docetaxel, 100 mg/m², to BSC. The trial was halted when a 6% death rate was noted in 49 patients secondary to febrile neutropenia. Also, a median of only two cycles of therapy was delivered. The dose of docetaxel was subsequently reduced to 75 mg/m². At this dose, the median number of cycles delivered was four, and no febrile neutropenic deaths occurred. In an analysis of all patients, both the median survival times (chemotherapy arm, 7.0 months; BSC arm, 4.6 months) and the 1-year survival rates (chemotherapy arm, 29%; BSC arm, 19%) were significantly better for patients receiving second-line docetaxel vs those receiving BSC (p = 0.047 [log rank test]). The median survival time and the 1-year survival rate for the patients treated with docetaxel, 75 mg/m², were 7.5 months and 37%, respectively (p = 0.003 compared to BSC). The overall response rate was 7.1%, with 42.7% of patients having disease stabilization on treatment. Clinical benefit was shown in a QOL study in which all QOL parameters favored the docetaxel-treated patients. Specifically, a significant reduction in pain and fatigue scale scores among the docetaxel-treated patients and a reduction in the need for narcotics, nonmorphine analgesic agents, and radiotherapy were documented in this group of patients.

The second trial randomized 373 patients who had previously received platinum-containing chemotherapy to one of the three following arms: docetaxel, 100 mg/m²; docetaxel, 75 mg/m²; or a control regimen of either vinorelbine or ifosfamide (V/I). The overall response rates were 6.7 to 10.8% among patients in the two docetaxel arms vs 0.8% among patients in the V/I arm (p < 0.05). The time to progression and the progression-free survival at 26 weeks also significantly favored patients in the two docetaxel arms. Although the median survival time was not significantly different between the groups, the 1-year survival rate was significantly greater with docetaxel, 75 mg/m², (32%) compared to V/I (19%; p = 0.025). The 1-year survival rate for patients receiving docetaxel at 100 mg/m² was 21%.

Several of the other new agents have been studied in the second-line setting, including paclitaxel, gemcitabine, irinotecan, and vinorelbine. In general, these trials have included small numbers of patients with variable results. Response rates have ranged from 0 to 20% and median survival rates (when reported) of 4 to 8 months. No randomized trials including these other agents exist with the exception of vinorelbine, as noted above.

**Recommendation 7**

Patients with a good PS who are experiencing disease progression after receiving platinum-based chemotherapy should be offered second-line chemotherapy. Level of evidence, good; benefit, moderate; grade of recommendation, B.

**Is There Evidence To Support the Use of Chemotherapy To Relieve Symptoms and Improve QOL?**

The majority of patients with advanced NSCLC are symptomatic at some point as a result of their disease. Symptoms may be either disease-specific (eg, cough, hemoptysis, chest pain, or dyspnea) or disease-nonspecific (eg, weight loss, malaise, or declining PS).

At least seven studies have documented palliation of symptoms by chemotherapy in patients with advanced NSCLC (Table 7). These phase II studies generally have reported percentages of patients with a specific symptom in whom any improvement was noted. A substantial percentage of patients derived symptomatic benefit from treatment for both disease-specific and organ-specific symptoms. The rate of symptom relief appears to be higher than the objective response rates in all the studies reported, suggesting that palliation can be achieved with tumor shrinkage that does not meet the standard criteria for objective responses.

The duration of symptom relief has not been reported consistently but ranges from 1.5 to 3.5 months. The review by Thatcher et al. examining the palliative impact of gemcitabine, suggested that some symptoms may be more effectively palliated than others (ie, median relief of 3 to 5 months for dyspnea, cough, and chest pain, and median relief of 2 to 3 months for anorexia and hemoptysis). When the median duration of symptom relief is compared with the median survival time of this population, symptom relief can be achieved for approximately 25 to 50% of the patient’s life span. It is important to provide patients with this information regarding the relief of symptoms.

In addition to symptom relief, the impact of chemotherapy on the patient’s overall PS also has been reported. Eight nonrandomized trials involving...
770 patients were reported in a review by Thatcher et al. These trials included chemotherapy regimens consisting of platinum combinations, nonplatinum single agents, and combinations. Almost all of the trials excluded patients with a PS of 2. The response rates to the chemotherapy regimens ranged from 20 to 59%, and the median survival time ranged from 5 to 13 months. Approximately one third of patients experienced an improvement in PS (range, 4 to 52%), and another one third of patients had a stable PS while receiving treatment (range, 30 to 67%). Two other trials have confirmed these findings. The duration of improvement has not been reported consistently. However, when it has been reported, improvement typically lasted from 4 to 6 months.

A randomized phase III trial comparing gemcitabine with BSC has been reported and highlights the palliative aspect of chemotherapy on disease-related symptoms. Symptom control was the primary end point of this study, which involved 299 symptomatic patients with advanced or metastatic NSCLC. Improvements were noted in terms of the need for palliative radiotherapy for progressive symptoms. At 2 months, 42.3% of patients in the BSC arm required radiotherapy compared with 7.3% of patients in the gemcitabine arm. Also, the median time before radiotherapy was needed was 7 months for patients receiving gemcitabine vs 1 month for those receiving BSC (p < 0.0001). QOL questionnaires and a patient-assessed symptom scale noted improvements significantly favoring the gemcitabine arm of the study. The overall response rate for gemcitabine was 17%. No difference in survival was noted; however, this was not the end point of the study.

QOL is an important aspect of treatment that differs from symptom relief or assessment of PS. QOL attempts to define the patient’s perception of how the disease and its treatment affect his or her well-being in all of life’s domains (ie, functional, social, psychological, spiritual, disease-related symptoms, and treatment side effects). Several questionnaires have been developed and validated for clinical use. In the past, it has been difficult to obtain carefully conducted serial QOL measurements in patients receiving chemotherapy. This may be due to the deterioration of the patient’s condition and to the unwillingness or inability of the patient to complete the questionnaires. One of the early QOL instruments developed was the functional living index-cancer. Using this instrument, two reports suggested that initial functional living index-cancer QOL scores were more predictive of survival than were other parameters. This suggests that QOL measurements could further refine the assessment of PS, as has been suggested in breast cancer patients.

Three randomized studies demonstrated improved QOL with chemotherapy compared with BSC. In one study, single-agent vinorelbine was compared with BSC in patients > 70 years of age. The QOL instrument used was the European Organization for Research and Treatment of Cancer (EORTC) questionnaire and its lung cancer-specific module. Although longitudinal compliance was not optimal, EORTC functional scales were consistently better for the patients receiving vinorelbine than for control patients. Also, symptom improvement scores were clearly better for some lung cancer-specific items (ie, pain and dyspnea), which was consistent with the results of the trial of gemcitabine vs BSC that was discussed above. In the other two trials, cisplatin-based combination chemotherapy improved QOL compared with BSC.

Cella et al suggested that prognosis can be

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**Table 7—Relief of Symptoms by Chemotherapy in Advanced NSCLC**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Ellis et al72 (n = 120)</th>
<th>Cullen et al73 (n = 74)</th>
<th>Osoba et al74 (n = 53)</th>
<th>Tummarrello et al75 (n = 46)</th>
<th>Fernandez et al76 (n = 31)</th>
<th>Hardy et al77 (n = 24)</th>
<th>Thatcher et al78 (NR)</th>
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<tr>
<td>Regimen used</td>
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<td>MIP</td>
<td>BEP</td>
<td>MVbP</td>
<td>PVbMVI</td>
<td>MVbP</td>
<td>Gemcitabine</td>
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<td>Objective response rate</td>
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<td>44</td>
<td>33</td>
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<td>Median survival time, mo</td>
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<td>Symptom improvement†</td>
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<td></td>
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<td>62</td>
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</table>

*Values given as %, unless otherwise indicated. BEP = bleomycin, etoposide, and platinum; PVbMVI = platinum, vinblastine, mitomycin, vincristine, and ifosfamide. See Table 2 for abbreviations not used in the text.
†Percentage of patients with a specific symptom who had relief or improvement in this symptom with treatment.
predicted from baseline QOL as well as from early changes in a patient’s QOL. Using the FACT-L, baseline, 6-week, 12-week, and 6-month QOL measurements were obtained for 571 patients who were enrolled in a three-arm, randomized, phase III trial comparing a cisplatin-etoposide regimen with two different schedules of cisplatin-paclitaxel. The study showed a survival advantage for patients in the paclitaxel-containing arms.\textsuperscript{44} There were no differences in any of the QOL scores among patients in the three arms of the study. The FACT-L physical well-being emerged second (p < 0.01) behind treatment with a paclitaxel regimen (p < 0.01) in predicting a response to treatment in a model that considered multiple clinical factors (ie, disease stage, PS, weight loss, comorbidity, presence of symptoms, and FACT-L scores). The baseline trial outcome index (TOI), which combines physical, functional, and lung cancer symptom scores, correlated highly with survival, but a change from baseline to subsequent assessment proved to be more important. The following four groups of patients were identified: (1) those with a high baseline TOI who improved at 6 weeks; (2) those with a high baseline TOI who did not improve at 6 weeks; (3) those with a low baseline TOI who improved at 6 weeks; and (4) those with a low baseline TOI who did not improve at 6 weeks. The median survival times for the four groups were 16, 11, 11, and 5 months, respectively. The authors suggested that a change in QOL may be able to predict survival and may aid in decisions that are made during the course of chemotherapy. Compliance with the collection of QOL data was not reported, but one has to wonder how this may have influenced outcomes. Although interesting, these findings need corroboration in future studies.

There may be differences in QOL among patients receiving various treatment regimens. An EORTC study\textsuperscript{47} randomized patients with advanced disease to receive either cisplatin-teniposide or cisplatin-paclitaxel. The response rates were 28% for patients receiving cisplatin-teniposide vs 41% for those receiving cisplatin-paclitaxel. However, the 1-year survival rate was the same. Using the EORTC instrument, QOL measurements favored patients in the paclitaxel-containing arm. In another study\textsuperscript{45} comparing a cisplatin-etoposide regimen with a carboplatin-paclitaxel regimen, the QOL using the FACT-L significantly favored patients receiving the carboplatin-paclitaxel regimen during the first 6 weeks of treatment. Patients in the carboplatin-paclitaxel arm also had a significantly higher response rate. In two other phase III studies\textsuperscript{49,49} comparing cisplatin-gemcitabine regimens, either with mitomycin-ifosfamide-cisplatin or with cisplatin alone, no difference in global QOL was reported between the two arms, despite a significantly higher response rate in the cisplatin-gemcitabine arm in both studies.

Baseline QOL appears to be an important prognostic factor, and differences in QOL may occur during treatment with different chemotherapy regimens. More data are needed regarding the longitudinal measurement of QOL during chemotherapy to ascertain how this correlates with baseline PS measurements and response rates.\textsuperscript{87} Also, further refinement and simplification of QOL instruments will help to capture data on the chronic toxicity of chemotherapy and its impact on the patient’s QOL.

**Recommendation 8**

Data from case series and randomized trials show that chemotherapy can have a palliative effect on disease-related symptoms and can improve QOL compared to BSC in stage IV NSCLC patients who are deemed suitable for treatment. Level of evidence, good; benefit, moderate; grade of recommendation, B

**What Are Patients’ Preferences and Attitudes Toward Chemotherapeutic Treatment Options for Advanced NSCLC?**

Two descriptive studies utilizing cancer patients who previously had been treated addressed the issue of patient preferences and attitudes toward receiving palliative cisplatin-based chemotherapy compared to BSC for survival and/or QOL benefit. Using a time-tradeoff technique, 60 patients were interviewed to address attitudes toward the improved median survivaltime and 1-year survival rate for the addition of cisplatin chemotherapy and BSC compared to BSC alone. Attitudes ranged from willingness to choose more toxic treatment with no survival advantage to declining chemotherapy regardless of the survival benefit. Over half of the participants (57%) would choose chemotherapy if it improved the 1-year survival rate by > 10%.\textsuperscript{69} A second descriptive study of 81 patients with advanced NSCLC who previously had been treated with a cisplatin-based chemotherapy regimen was performed to measure the survival threshold that patients would be willing to accept for receiving chemotherapy.\textsuperscript{90} As in the prior study, the response varied between a survival benefit of 1 week to not accepting treatment even if survival were to be improved by 24 months. A median survival threshold for accepting chemotherapy with mild toxicity was 4.5 months, and for severe toxicity it was 9 months. Only 22% of patients would be willing to choose chemotherapy for a survival benefit of 3 months. However, over half (65%) would choose chemotherapy if it substantially improved QOL.
No study has been able to demonstrate or predict a necessary minimum threshold improvement in survival or QOL based on age, sex, education, PS, or role in the treatment decision making. One study has suggested that patients with cancer are much more likely to opt for radical treatment that could prolong life and relieve symptoms with minimal chance for benefit than people who do not have cancer, including health professionals. Therefore, the different attitudes of health professionals toward the benefits of chemotherapy for the patient need to be considered.

**Recommendation 9**

Patient preferences need to be considered and respected with regard to the decision to treat with chemotherapy. Most patients would not choose chemotherapy for a likely survival time of 3 months or a < 10% improvement in the 1-year survival rate unless there was an improvement in QOL. No patient variables have been identified to determine an individual patient’s minimum threshold to accept chemotherapy, and therefore the decision to treat with chemotherapy needs to be discussed with each patient individually. Level of evidence, fair; benefit, moderate; grade of recommendation, B

**IS THERE ANY EVIDENCE THAT WOULD SUPPORT WHO ADMINISTERED THE CHEMOTHERAPY MADE A DIFFERENCE?**

The MEDLINE search addressing this issue yielded no citations that were relevant with regard to addressing this question. Since the evaluation of NSCLC patients for chemotherapy requires an understanding of its indication as well as the proper selection of patients, physicians performing these duties should have experience and specialized training. This specialized training also should include experience with the proper administration of chemotherapy protocols as well as a working knowledge of the toxicity (both acute and chronic) of all chemotherapeutic agents used in this disease setting. In addition, physicians should have the proper infrastructure necessary for the administration of commonly used chemotherapeutic agents/regimens and the management of the common complications of these agents. Although no data exist on this issue, it seems intuitive that patients who are potential candidates for chemotherapy should be referred to physicians with specialized training in its administration and with experience in the management of such patients.

**Recommendation 10**

Patients with stage IV NSCLC should be referred to a physician with specialized training in oncology. If chemotherapy is considered to be appropriate, adequate resources to administer chemotherapy safely must be available. Level of evidence, poor; benefit, substantial; grade of recommendation, C

**WHAT ARE THE OUTCOME EXPECTATIONS AND ADVERSE EFFECTS SEEN WITH CHEMOTHERAPY AND HOW DO THEY COMPARE WITH THE NATURAL HISTORY?**

The natural history of untreated stage IV NSCLC is best documented in the randomized trials of chemotherapy vs BSC (Tables 2 and 5). The impact that chemotherapy has on survival is significant and has been discussed in the previous sections. When QOL has been examined, patients receiving chemotherapy report better scores compared to patients receiving only BSC, supporting the contention that the disease is worse than the treatment. The expectations regarding survival and toxicity when using modern chemotherapy regimens are shown in Table 8. The trials shown in Table 8 predominantly include patients with good PS with stage IV disease who have been studied in large phase III trials that have been published in peer-reviewed journals. Only platinum-based regimens are described as those regimens represent the standard of care in patients with good PS and stage IV NSCLC. As is shown in Table 8, the median survival time and the 1-year survival rate expectations are 8.0 to 9.9 months and 30 to 43%, respectively. The major toxicities are hematologic, with neutropenia being the predominant adverse effect. Despite this, the clinical consequences of severe neutropenia (ie, sepsis) occur in < 10% of patients, and the treatment-related death rates in these studies ranged from 0 to 4%. Severe anemia occurs in 7 to 30% of patients. Severe thrombocytopenia varies depending on the regimen used as well as on the dose and schedule of the agents in the regimen. However, bleeding complications are unusual. Nonhematologic toxicity consists mainly of nausea/vomiting, fatigue, and alopecia. In the more recent trials employing modern antiemetic regimens or using carboplatin rather than cisplatin, the rates of severe nausea/vomiting range from 7 to 20%. The toxicity profiles of single agents are somewhat less than those of combination regimens and can be found in the individual references provided. It should also be noted that the risk of toxicity increases in patients with PS 2.

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Combination platinum-based chemotherapy can be administered safely with acceptable and manageable toxicity profiles in patients with good PS who have stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A

Conclusion

Chemotherapy improves survival and palliates symptoms, thereby improving QOL in patients with stage IV NSCLC in both the first-line and second-line setting. Selecting patients based on PS is important as patients significantly compromised by their disease may not benefit from therapy and may experience excessive toxicity. Both platinum-based regimens as well as individual single-agent regimens have an impact on survival. However, platinum-based combination regimens using the new third-generation agents represent standard-of-care regimens. The impact that chemotherapy has on patient survival probably occurs early in the treatment, and the prolonged administration of therapy is not indicated. Physicians involved in the evaluation and management of patients with stage IV NSCLC should be aware of the potential benefits of chemotherapy, allowing them to make appropriate recommendations for patients under their care.

Summary of Recommendations

1. When selecting patients for systemic chemotherapy, PS at the time of diagnosis should be used because it is a consistent prognostic factor for survival. Patients with a PS (PS) of ECOG 0 or 1 should be offered chemotherapy (level of evidence, good; benefit, substantial; grade of recommendation, A). Data are not yet sufficient to routinely recommend chemotherapy to patients with a PS of ECOG level 2 (level of evidence, poor; benefit, small/weak; grade of recommendation, I). Patients with a PS of ECOG level 3 or 4 should not receive chemotherapy (level of evidence, fair; benefit, moderate; grade of recommendation, B).

2. Patients with good PS (ie, ECOG level 0 or 1) should be considered for a platinum-based chemotherapy regimen based on the survival advantage provided over BSC. Level of evidence, good; benefit, substantial; grade of recommendation, A

3. Although new agents demonstrate improved survival compared to BSC (level of evidence, good; benefit, moderate; grade of recommendation, B) in elderly patients as well as in nonelderly patients with advanced NSCLC, the data are not yet sufficient to compare the new single agents to platinum-based combination therapies. Level of evidence, poor; benefit, small/weak; grade of recommendation, I

4. Combination chemotherapy regimens incorporating the new single agents with a platinum...
agent should be considered the standard of care. Level of evidence, fair; benefit, moderate; grade of recommendation, B

5. No one regimen has been demonstrated to be superior in the first-line therapy for patients with advanced NSCLC. A cisplatin-based or carboplatin-based combination regimen that includes one of the new agents remains the standard of care for first-line therapy in patients with stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A

6. The duration of first-line therapy in patients with stage IV NSCLC should be brief, consisting of 3 to 4 cycles or fewer if there are signs of progressive disease. Level of evidence, good; benefit, substantial; grade of recommendation, A

7. Patients with a good PS in whom disease progresses after receiving platinum-based chemotherapy should be offered second-line chemotherapy. Level of evidence, good; benefit, moderate; grade of recommendation, B

8. Data from case series and randomized trials show that chemotherapy can have a palliative effect on disease-related symptoms and can improve QOL compared to BSC in stage IV NSCLC patients who are deemed suitable for treatment. Level of evidence, good; benefit, moderate; grade of recommendation, B

9. Patient preferences need to be considered and respected with regard to the decision to treat with chemotherapy. Most patients would not choose chemotherapy for a likely survival of 3 months or a <10% improvement in the 1-year survival rate unless there was an improvement in QOL. No patient variables have been identified to determine an individual patient’s minimum threshold to accept chemotherapy, and therefore the decision to treat with chemotherapy needs to be discussed with each patient individually. Level of evidence, fair; benefit, moderate; grade of recommendation, B

10. Patients with stage IV NSCLC should be referred to a physician with specialized training in oncology. If chemotherapy is considered to be appropriate, adequate resources to administer chemotherapy safely must be available. Level of evidence, poor; benefit, substantial; grade of recommendation, C

11. Combination platinum-based chemotherapy can be administered safely and with acceptable and manageable toxicity profiles in patients with good PS who have stage IV NSCLC. Level of evidence, good; benefit, substantial; grade of recommendation, A

ACKNOWLEDGMENT: Thanks to Lenka Cook for the creation of Figure 2.

APPENDIX

The following search terms were used in the study: age and lung cancer; antineoplastic agents, combined; carcinoma, non-small cell lung; carcinoma, non-small cell lung/drug therapy; carcinoma, non-small cell lung/therapy; chemotherapy; clinical trials; combination chemotherapy; duration of therapy; lung neoplasms; lung neoplasms/drug therapy; lung neoplasms/therapy; outcomes; performance status and lung cancer; prognosis factors and lung cancer; prognosis and lung cancer; prognosis and non-small cell lung cancer; quality of life and lung cancer; randomized trials; sex and lung cancer; stage IV non-small cell lung cancer; weight loss and lung cancer.

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