Management Issues for Stage IV Non-Small-Cell Lung Cancer
Craig C. Earle, MD, FRCPC, and William K. Evans, MD, FRCPC

Systemic chemotherapy offers modest improvement in survival and quality of life for patients with metastatic NSCLC, and does so at a reasonable cost, but it can be associated with toxicity.

**Background:** The management of stage IV non-small-cell lung cancer (NSCLC) has been a controversial subject over the past several decades. Data from randomized trials and from phase II trials on new cancer agents are changing physician attitudes and treatment practices.

**Methods:** The literature on the management of metastatic lung cancer was reviewed and interpreted.

**Results:** There is good evidence from randomized controlled trials and meta-analyses that chemotherapy provides a modest survival benefit in stage IV NSCLC. There is indirect evidence of improvement in quality of life, as systemic chemotherapy palliates cancer-related symptoms in the majority of patients. New drug combinations are likely to improve recent treatment results with less morbidity than older chemotherapy regimens. Despite the relatively high cost of these treatments, chemotherapy is cost effective in the Canadian health care environment relative to other accepted medical interventions.

**Conclusions:** Chemotherapy will play an increasing role in the management of patients with advanced NSCLC.

**Introduction**

Lung cancer is the leading cause of cancer death in North America, and non-small-cell lung cancer (NSCLC) -- squamous, adenocarcinoma, and large-cell carcinoma -- is the dominant histology, being responsible for 75% to 80% of all lung malignancies. Approximately 40% to 50% of those patients present with incurable metastatic (stage IV) disease. Because of early hematogenous spread, most of those presenting with earlier-stage disease will eventually develop metastases and become candidates for systemic therapy.

The addition of chemotherapy to the supportive, symptomatic care of patients with metastatic NSCLC remains controversial. Despite decades of clinical investigation, the treatment of stage IV NSCLC remains unsatisfactory. There is no treatment with curative potential, and even the most active regimens have complete response rates of less than 5%. While systemic chemotherapy offers the possibility of temporary disease control, an improvement in quality of life, and a modest increase in survival, many clinicians have concerns that these limited benefits do not justify the toxicity and expense associated with treatment. Most of the currently used chemotherapy regimens are based on cisplatin, usually in combination with a plant alkaloid such as etoposide or a vinca. However, several new agents with promising activity against NSCLC have recently been added to the therapeutic armamentarium against NSCLC that yield higher response rates, improved one-year survival rates, and lower toxicity.

**Improving Survival in Stage IV NSCLC**

The only therapeutic modality that can consistently cure a subset of patients with NSCLC is surgery. In metastatic disease, the role of surgery is restricted to the management of solitary metastases. Resection of either noncontiguous synchronous or metachronous lung metastases, as well as synchronous solitary adrenal lesions, has been reported to cure a minority of patients. The brain will be the only site of recurrence in approximately 6% of patients with completely resected NSCLC. Nearly half of these metastases will be solitary. Compared with radiation alone, surgical excision of brain metastases followed by radiation prolongs median survival from 3.4 months to 9.2 months and provides a better quality of life.

There have been no reports of long-term survival after removal of liver, bone, or skin metastases, as these usually are not solitary metastatic foci. Several studies have attempted to define those prognostic features that are important for survival in advanced NSCLC. Good performance status, female gender, and absence of extrathoracic disease consistently have been associated with a more favorable outcome. Some studies have shown that poor prognostic features are weight loss, particular metastatic sites such as the brain, or the overall number of metastatic sites. Histologic subtype, on the other hand, does not appear to significantly affect prognosis.

As previously noted, approximately half of all NSCLC patients present with metastatic disease. Furthermore, when patients relapse following complete surgical resection, it is as distant metastases in 75% of cases. Effective systemic therapies are necessary to improve current surgical results in NSCLC. Active agents in NSCLC achieve major tumor regression in only 15% to 25% of patients (Table 1). They virtually never induce complete remissions (CRs), and single agents have little...
or no impact on overall survival. Therefore, it is not surprising that empiric combinations of these drugs produce only modest antitumor activity and that no specific combination has emerged as the clear standard of practice. The current best combinations cause partial regressions in 30% to 40% of patients with stage IV disease (Table 2), a rare CR, a fairly consistent median survival time of six to nine months, and survival at one year of approximately 20% to 30%. Given this degree of activity, some clinicians have argued against using cytotoxic agents in metastatic NSCLC. Recent data, however, suggest that a position of therapeutic nihilism is inappropriate.

Table 1: Agents With Consistent Response Rates of 15% or Greater

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>29</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>33</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>29</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>17</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>29</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>22</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>25</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>9</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>28</td>
</tr>
<tr>
<td>VP-16</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 2: Selected Chemotherapy Regimens in Advanced NSCLC

- Cisplatin plus etoposide: Cisplatin 75 mg/m² IV day 1 then q 3 wks Etoposide 100 mg/m² IV days 1-3 then q 3 wks
- Cisplatin plus etoposide: Cisplatin 100 mg/m² IV days 1 then q 3 wks Vinorelbine 60 mg/m² IV weekly
- Cisplatin plus etoposide: Cisplatin 75 mg/m² IV days 1 then q 3 wks Etoposide 100 mg/m² IV days 1-3 then q 3 wks
- Carboplatin 150 mg/m² IV q 3 wks
- Paclitaxel 175 mg/m² IV (24 h) day 1 q 3 wks
- Paclitaxel 175 mg/m² IV (24 h) day 1 q 3 wks

Published randomized trials of polychemotherapy vs supportive care in advanced NSCLC have produced a literature of conflicting small trials. Several attempts have been made to summarize this evidence by meta-analysis. Four such meta-analyses addressed the question of whether chemotherapy increases survival in advanced NSCLC, and all showed a benefit with chemotherapy.

The largest, by the Non-Small-Cell Lung Cancer Collaborative Group (NSCLCCG), incorporated individual updated data in 11 trials of 1,190 patients with stage IIIB or IV disease. The NSCLCCG found a pooled hazard ratio of death of 0.73 (95% CI [confidence interval] = 0.63 to 0.85) at one year for patients treated with cisplatin-containing chemotherapy regimens compared with those managed with supportive care only (Fig 1). The absolute survival benefit at one year was 10% (95% CI = 5% to 15%), increasing from 16% to 26% (PLEASE SEE HARD COPY OF JOURNAL FOR FIGURE 2). The gain in median survival was 1.5 months (95% CI = 1 to 2.5 months). No additional survival advantage was seen after six months. The use of long-term alkylating agents actually had a negative effect on survival. Although authors have interpreted the clinical significance of this difference to argue both for and against the use of chemotherapy in NSCLC, it is nonetheless proof that chemotherapy produces a biologic effect. Furthermore, as noted by Le Chevalier, an increase in median survival of one to two months may represent as much as a six-month increase in survival for the 20% to 30% of patients who have the best response. If these patients could be identified, treatment could be targeted more effectively.

Subgroup analysis of the NSCLCCG meta-analysis was unable to identify groups of patients less likely to benefit from treatment based on age, sex, histology, performance status, or stage of disease (metastatic vs nonmetastatic). When the survival results were divided into six-month periods, a significant risk reduction was seen in only the first six-month period. All trials excluded patients with poor performance status (Eastern Cooperative Oncology Group status = >2; Karnofsky index = <50) as they have historically had extremely short survival and virtually never respond to chemotherapy.

The other three meta-analyses showed similar results. These studies did not use individual patient data, however, and were therefore unable to separate stage IIIB patients from stage IV patients. Marino and colleagues included eight randomized trials and found that median survival increased from 3.9 to 6.7 months for the chemotherapy-treated group over best supportive care alone. Their endpoint was the odds ratio of death at six months, which was 0.44 (95% CI = 0.32 to 0.59). Souquet et al analyzed seven studies to derive a relative risk of death of 0.91 at one year. Grilli et al demonstrated a relative risk of one-year mortality of 0.76 (95% CI = 0.66 to 0.87) and a six-week average prolongation of survival with analysis restricted to six trials.

Although meta-analyses can achieve significant power, they must be viewed with caution. They are prone to publication bias toward positive results as well as to any other biases contained in the originally published data. There have been several recent unsettling examples of meta-analyses that were later refuted by large randomized trials. In the analyses described above, the variable inclusion of stage IIIB patients in some trials has resulted in an inhomogeneity of the study population that may confound the results, as stage IIIB patients often have better responses to systemic therapy. Furthermore, for several trials, the one-year survival had to be extracted from published survival curves, which may have decreased the accuracy of the data. Lastly, several different chemotherapy regimens were grouped together for comparison with supportive care, making it difficult to draw conclusions about the effectiveness of any one regimen. Large, definitive randomized trials are needed but are difficult to organize.

Palliation of Metastatic NSCLC

Most patients with metastatic NSCLC have disease-related symptoms at the time of diagnosis. Table 3 shows the frequency of common symptoms of lung cancer in patients with advanced NSCLC. Fatigue and decreased activity are the most common complaints, followed by cough and dyspnea. Symptoms in an individual patient...
Surgical palliation of symptoms includes drainage and pleurodesis of malignant pleural and pericardial effusions, as well as occasional endobronchial stenting of an obstructing lesion or removal of a tumor that causes persistent, serious hemoptysis. Resection in this situation is usually kept to the minimum needed for relief. Bronchoscopic techniques such as laser resection are employed where possible. Surgical fixation of bone followed by irradiation is necessary to manage pathologic fractures.

Radiation can be effective in palliating bone pain, hemoptysis, or symptomatic brain metastases. Furthermore, it can be used if complications occur (eg, spinal cord compression, superior vena cava obstruction, or obstructive lobar collapse). There is randomized evidence that radiation therapy can effectively palliate symptoms and improve performance status. Also, intraluminal brachytherapy, with or without endoluminal laser treatment, has shown benefit in selected cases with hemoptysis or dyspnea related to the primary tumor.

Those who oppose systemic treatment for patients with metastatic NSCLC claim that the survival benefits are too small to justify its use. While this may be true for many patients, it is paternalistic for physicians to make this decision unilaterally for patients. There is ample evidence that a survival benefit of several months may be valued much more by a patient with only a few months to live than by health professionals or by healthy members of the general population. A 1995 survey of Canadian oncologists reported that 79% of physicians would suggest no specific treatment for stage IV NSCLC. The respondents generally underestimated the value of chemotherapy while overestimating the benefits of radiotherapy. These results were essentially unchanged from a previous survey in 1986.

The effect of chemotherapy on quality of life has rarely been formally addressed; however, there is indirect evidence of benefit. Chemotherapy reduces symptoms such as pain, cough, hemoptysis, and dyspnea in approximately 70% of patients (Table 4), and improvements in performance status and weight gain have been reported. Such symptomatic improvement can occur in the absence of objective response.

The average duration of symptom control is short, with benefit lasting an average of six to eight weeks. Nevertheless, a large Canadian trial showed that chemotherapy-treated patients were hospitalized fewer days than those who received supportive care alone (17.1 vs 23.6 days, respectively) and required less palliative radiotherapy. These observations suggest that chemotherapy results in fewer clinical symptoms and possible improved quality of life. Studies are needed that formally assess the quality of life of lung cancer patients who are undergoing chemotherapy. Attempts to capture this in clinical trials have been hindered by the rapid deterioration of many patients who are either unable or unwilling to complete the questionnaires on quality of life after one or two treatment cycles. This has led some to contend that chemotherapy causes deterioration in quality of life. However, a clinical trial from Norway that succeeded in comparing the quality of life of lung cancer patients randomized between chemotherapy and radiotherapy found no difference between the two groups. Other uncontrolled studies have also found relatively preserved quality of life in NSCLC patients who were being treated with chemotherapy. Another difficulty in measuring quality of life is its inherent subjectivity. Physicians may be overly optimistic about the positive effects of medical treatment on quality of life. Several instruments to measure quality of life have been developed specifically for lung cancer, such as the Functional Assessment of Cancer Therapy (FACT-L), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-LC13), and the Lung Cancer Symptom Scale (LCSS).

Chemotherapy can palliate symptoms for patients with NSCLC but at the expense of nontrivial toxicity. Approximately 35% to 50% of patients in randomized chemotherapy trials experience some form of severe side effect, and the overall risk of lethal toxicity is 1%. Advances in supportive care, such as the use of serotonin antagonist antiemetics and hematopoietic growth factors, have markedly reduced the side effects of treatment and have improved the therapeutic index. Furthermore, current chemotherapy regimens are less toxic than previous ones. For example, the lack of hair loss associated with the vinorelbine-cisplatin combination has made this therapy more acceptable among patients. As a result, the quality of life of many patients probably improves despite treatment-related toxicity. However, this impression requires objective confirmation.

Lastly, the psychologic benefit from undergoing an active treatment as opposed to being told to "get your affairs in order" or "take a vacation" should not be discounted. Recurrent suggestions in the literature indicate that patients with a "fighting spirit" seem to fare better than those who do not have this characteristic. Physician attitude and a concrete treatment plan may contribute to this positive mental state.
Lung cancer is a relatively inexpensive disease to manage. Because of its prevalence, however, it constitutes a significant proportion of total health care expenditures. The University of Ottawa and Statistics Canada have collaborated to determine the direct costs of lung cancer diagnosis and treatment by disease stage and cell type in Canada. The cost of managing a patient with stage IV lung cancer with supportive care alone from diagnosis to death was approximately $28,000 in 1995 Canadian dollars. Since approximately 5,000 patients will present with metastatic NSCLC each year in Canada (and about 10 times as many in the United States), the total cost to the Canadian health care system of managing stage IV disease is approximately $150 million. Not surprisingly, the majority of this cost, $132 million, is spent in the first year of illness after diagnosis. Hospitalization during the initial diagnostic workup constitutes approximately one third of the total cost. Terminal care accounts for about half of the total cost whether a patient receives chemotherapy or not. As a result, continuing present trends toward ambulatory diagnostic assessment and treatment, as well as optimizing community-based terminal care, will have the greatest impact on reducing costs.

In a time of increasing fiscal restraint in health care budgets, the appropriateness of offering relatively expensive cytotoxic agents with limited impact on survival and quality of life presents an understandable concern. However, a cost analysis performed by the National Cancer Institute of Canada (NCIC) on a multicenter randomized trial comparing chemotherapy with best supportive care showed that chemotherapy can be cost effective -- and can even lead to a net savings -- by reducing both the palliative measures and the length of terminal hospitalization. When the cost of introducing some of the newer, more expensive therapeutically agents is considered, treatment can still be cost effective.

We compared the costs of several new drugs with the survival advantage they appear to provide from phase II studies. For example, for life-year gained, gemcitabine costs between $3,000 and $6,000 Canadian dollars, paclitaxel costs $4,778, and vinorelbine with cisplatin costs $5,551. Assuming quality of life is reasonable while on treatment, this falls well within accepted guidelines for cost effectiveness and compares favorably with many accepted but expensive medical treatments.

Despite being cost effective, chemotherapy treatment for all stage IV NSCLC patients would create a significant burden on both finances and manpower by virtue of its frequency. As advances in cancer research provide more cost-effective treatments, we are forced to question how many cost-effective treatments we can afford. Oncologists in Canada are still relatively more conservative in their management of advanced NSCLC than their American colleagues. Also, many patients are not candidates for systemic therapy due to biologic age, performance status, or comorbid conditions. As a result, the actual impact of a new treatment on health budgets is likely to be less than might otherwise be projected.

In Canada, universal health coverage is threatened by its rapidly increasing societal cost. To guide the expenditure of public money, evidence-based medicine and practice guidelines are being developed. The Ontario Cancer Treatment Practice Guidelines Initiative, a multidisciplinary group developing evidence-based guidelines sponsored in part by the Ontario Ministry of Health, has recommended that it is “reasonable to offer cisplatin-based chemotherapy to medically suitable patients as a treatment option”; for survival, symptom control, and outcomes of quality of life in metastatic NSCLC patients. In the United States, managed care is playing an increasingly powerful role in treatment decisions. While health maintenance organizations (HMOs) have been successful in controlling costs, there is concern that some of this success comes from a philosophy of denying patients access to expensive treatments that might not be beneficial. Primary care physicians acting as gatekeepers are forced into a conflict of trying to serve both the interests of their patients and those of their employers when deciding whether a patient should even see an oncologist. Thus, establishing the cost effectiveness of a new treatment is important in both countries.

**Treatment Issues**

Patients must be carefully selected for chemotherapy. Response to treatment and prognosis are most closely related to performance status. Patients with even moderately impaired ambulation, for example, have reduced survival and greatly increased toxicity when compared with more mobile patients. Therefore, therapy should be offered only to patients in relatively good physical condition.

Next, a chemotherapy regimen must be selected. There is little evidence that establishes the superiority of one commonly used combination over another. Cisplatin has emerged as the most important component of current NSCLC chemotherapy regimens. Optimal platinum dosages or combinations, however, cannot be determined from the present literature. There is evidence that protocols delivering cisplatin at doses of 100 mg/m² produce higher response rates than less intensive regimens, although survival is not prolonged.

Cisplatin with vinorelbine has become a popular combination over the past several years because of its favorable toxicity profile. Specifically, the lesser degree of hair loss with these drugs has been an important factor in patient acceptance. Table 2 shows a commonly used schedule. Randomized studies have demonstrated that vinorelbine with cisplatin can produce superior response and survival outcomes when compared with cisplatin alone, vindesine plus cisplatin, and vinorelbine alone.

A three-arm phase III study by the Eastern Cooperative Oncology Group was published in abstract form in the 1996 Proceedings of the American Society of Clinical Oncology. This study compared cisplatin plus etoposide vs cisplatin plus paclitaxel at two different dose levels, either with or without granulocyte colony-stimulating factor (G-CSF). The response rates were higher in the paclitaxel-containing regimens: 27% without G-CSF and 32% with G-CSF vs 12% for the etoposide/cisplatin regimen. There was a trend towards improved one-year survival: 39% of patients treated with paclitaxel plus cisplatin with G-CSF were alive at one year vs 32% of those receiving etoposide plus cisplatin. Another randomized trial is underway comparing 200 mg/m² of paclitaxel with supportive care alone in patients with inoperable NSCLC.

A similar regimen using carboplatin is also being used. Since carboplatin does not significantly add to paclitaxel’s neurotoxicity, a combination of these two drugs has been successful. Response rates of 27% to 62% have been reported, including some complete responses. The median survival of patients in these trials ranged from 8.7 to 12.5 months, and the one-year survival ranged from 37% to 54%.

Most protocols give paclitaxel as a continuous infusion over three or 24 hours. Because longer infusions consume more resources, we recently performed a phase II study of paclitaxel and carboplatin with paclitaxel given as a one-hour infusion at an average dose of 188 mg/m². Although it was extremely well tolerated and yielded some impressive responses (Fig 3), we observed a response rate of only 29%, suggesting that shorter infusions may not be as efficacious as longer infusions.

The optimal duration of treatment with any of these regimens is not clear. The usual practice is to treat for two to three cycles to determine tolerance and to evaluate response. If there is evidence of response, treatment is continued for six to eight cycles. If there is no evidence of a response, treatment is commonly stopped or the regimen is changed. However, abandoning treatment due to lack of response after a few cycles may deprive some patients of a useful treatment. There is randomized evidence that NSCLC patients with stable disease on chemotherapy have similar survival to those with objective responses. Furthermore, Finkelstein et al found that patients who responded very slowly fared as well or better than those who responded quickly. Similar phenomena have been observed in multiple myeloma and lymphoma. The taxanes in particular have been noted to cause late responses in patients with lung cancer or breast cancer. As a result, minimally responding regimens are changed. However, abandoning treatment due to lack of response after a few cycles may deprive some patients of a useful treatment. There is randomized evidence that NSCLC patients with stable disease on chemotherapy have similar survival to those with objective responses. Furthermore, Finkelstein et al found that patients who responded very slowly fared as well or better than those who responded quickly. Similar phenomena have been observed in multiple myeloma and lymphoma. The taxanes in particular have been noted to cause late responses in patients with lung cancer or breast cancer.
These observations suggest that a treatment resulting in stability in a disease that is usually rapidly progressive may have significant antitumor activity. Furthermore, experience with neoadjuvant chemotherapy in earlier-stage disease has taught us that at the time of surgery, an unshrinking tumor mass may consist of mostly fibrosis or necrotic debris that would not be evident with noninvasive imaging.57

Whether to continue treatment beyond six months in responding patients is the next question to be answered. In the meta-analyses described previously, the survival advantage in the treatment arm was lost after six months. With a median survival of approximately six months in the treated group, this is not a surprising finding. In addition, many of the trials used chemotherapy protocols that did not allow treatment to continue beyond six cycles.9 Whether patients who are doing well on chemotherapy after six cycles benefit from continuing until there is a reason to stop has not been tested. Presently, clinicians must use their own judgment and the values of their patients to decide in each specific situation.

While few oncologists offer a second-line regimen if a patient fails first-line treatment, we now have an agent, docetaxel, that has shown an encouraging 17% response rate in patients who were resistant to platinum-based chemotherapy.58 However, patients who have been refractory to first-line agents generally are unlikely to benefit from second-line treatment.

**New Chemotherapeutic Agents**

Optimism about improving the results of treatment for NSCLC is high among physicians who treat patients with this disease. An unprecedented number of new agents are in clinical trials with single-agent response rates over 15%.59 These agents have arguably less toxicity, and many appear to have higher response rates compared with current drugs.5

The taxanes have shown impressive activity in a number of human cancers, including NSCLC.60 Both paclitaxel and its semisynthetic analogue, docetaxel, have shown response rates above 20% in uncontrolled trials.61-63 Paclitaxel is particularly interesting because of reported survival rates of 40% at one year.51,64 The major toxicities of paclitaxel are myelosuppression, peripheral neuropathy, alopecia, and myalgias. Allergic reactions to the castor oil diluant are common but can be prevented by prophylaxis with corticosteroids and histamine antagonists. Docetaxel has a similar toxicity profile, with the addition of a capillary leak syndrome that also can be prevented with corticosteroids. As described above, it may have useful action as a second-line agent.

Irinotecan (CPT-11), a camptothecin, has shown promising results in phase II trials, both alone (where response rates over 30% have been seen65 and in combination with other agents.66 The dose-limiting toxicity is severe diarrhea. A related compound, topotecan, has shown less impressive activity.67 Gemcitabine, the pyrimidine antimetabolite, also has demonstrated response rates of over 20% in phase II studies.68 Response rates of 30% to 58% have been reported when gemcitabine is combined with agents such as cisplatin.69

All of these results must be viewed with caution, however, as there is a poor correlation between tumor response and subsequent survival, especially when generalizing to a larger population with less favorable prognostic factors than the phase II study population.13

Eligible patients with metastatic NSCLC should be encouraged to participate in clinical trials where possible. Currently, only 1% of all patients with NSCLC in the United States are enrolled in clinical trials.70 With careful observation of the efficacy and toxicity of new regimens, we will be able to more effectively manage this major public health problem. Whether it is ethical to include a no-treatment arm has been a subject of considerable debate.11 The equipoise between chemotherapy and supportive care alone varies considerably among investigators.

**Future Treatment Modalities**

In addition to new chemotherapeutic agents, several biologic strategies are being investigated. Gene therapy attempts either to insert an antioncogene into tumor cells to suppress an active oncogene or to insert a wild-type gene where tumor suppressor genes have been inactivated.90 Antisense oligonucleotides and antisense RNA have been shown to inhibit tumor growth both in vitro and in animal models.71 Unfortunately, delivery and uptake of the antisense product are difficult. Methods have included viral vectors, liposomes, and direct injection72; however, catabolism is rapid in vivo.73

Matrix metalloproteinases are enzymes secreted by cancer cells to digest connective tissue. These enzymes are required for a metastatic cell to implant. Several agents have been developed that inhibit these enzymes and limit invasion by malignant cells in vivo and in animal models.74 Differentiating agents, antioxidants, and angiogenesis inhibitors are other strategies that hold promise for the future.59

**Conclusions**

Patients with stage IV NSCLC and good performance status may realize a modest improvement in survival with cisplatin-based chemotherapy. While the chances of improving specific symptoms are good, the effect on overall quality of life is unclear when treatment-related toxicity is considered. The decision to use chemotherapy must incorporate physician judgment and patient values on a case-by-case basis. Chemotherapy should at least be offered as an option to all eligible patients. The cost-effectiveness of treatment for NSCLC is comparable to that of many other accepted medical therapies, and cost should not be considered a barrier. Since the degree of benefit from current therapies is small, it is appropriate to consider previously untreated patients for trials of investigational agents. Randomized trials of new chemotherapy regimens that also assess quality of life are needed to define the future practice standard.

**References**


