Cost-effectiveness of chemotherapy for nonsmall-cell lung cancer

George Dranitsaris, MPharm,* Wayne Cottrell, BScPharm,* and William K. Evans, MD†

After decades of research into its prevention and treatment, lung cancer remains the leading cause of cancer death in North America and Europe. Approximately 75% of all new lung cancer diagnoses are of the nonsmall-cell subtype, and less than 25% of these patients are potentially operable upon first detection. First-generation cisplatin-based chemotherapy regimens for patients with metastatic disease achieved a median survival of 175 days, with 15 to 20% of patients alive at 1 year.

In recent years, vinorelbine, gemcitabine, paclitaxel, and docetaxel have emerged as promising agents in the treatment of advanced nonsmall-cell lung cancer. Evidence from randomized trials demonstrates that when these agents are combined with cisplatin, the objective tumor response is 25 to 40%, with a median overall survival approaching 300 days. In addition, recent studies have shown that single-agent docetaxel improves survival and quality of life in patients with platinum-refractory nonsmall-cell lung cancer. Since these modest but important improvements in the management of nonsmall-cell lung cancer are achieved at a significant cost, cost has emerged as a major consideration in health policy decision-making. This article reviews the pharmacoeconomic literature to provide guidance on the cost-effective use of chemotherapy in the treatment of advanced nonsmall-cell lung cancer.

Lung cancer continues to be the leading cause of cancer death in Europe and North America [1]. In Canada alone, there were more than 20,000 new cases with nearly 18,000 deaths from the disease in 2001 [2]. Forty percent of these deaths occurred in people younger than 65 years. Hence, there is a substantial societal loss and an economic burden to a health system that funds universal health care. Furthermore, it has been reported that over the course of their lives, smokers require additional health care resources compared with nonsmokers [3].

Approximately 75% of all new cases of lung cancer are of the nonsmall-cell lung cancer (NSCLC) subtype, which is less responsive to chemotherapy than small-cell carcinoma. Surgical resection may cure early-stage NSCLC, but less than 25% of patients seek treatment with stage I and II disease. The vast majority of newly diagnosed patients with NSCLC already have locally advanced or metastatic stage IV disease [4]; and surgical intervention is impractical and radiation therapy is predominantly palliative. Until a decade and a half ago, the impact of drugs such as cisplatin, mitomycin C, ifosfamide, etoposide, vinblastine, and vindesine on survival was uncertain, and therefore it was difficult to recommend incorporating chemotherapy into the standard care of patients with disseminated NSCLC [5].

The role of chemotherapy in advanced NSCLC became more clearly defined with the publication of four meta-analyses [6–9] that showed a prolongation of survival after chemotherapy compared with best supportive care (BSC). Cisplatin-based chemotherapy conferred a survival advantage with a hazard ratio of death of 0.73 (95% CI, 0.63–0.85) relative to BSC. Although the meta-analyses showed a small absolute increase of 10% in 1-year survival rate and a 1.5 month median extension of survival, LeChevalier [10] pointed out that these figures may represent as much as a 6-month increase in survival for the 20 to 30% of patients who demonstrated the best response.

When treatment cannot cure and survival times are short, the physical, emotional, philosophical, and spiritual dimensions of life require greater consideration and sensitivity when selecting therapy. Symptom control, quality of life, toxicity, convenience, and financial costs of treatment are important elements to consider [11].

The last element, cost, is usually one of the first elements considered by decision-makers charged with allo-
Cost, however, is a crude measure of the value of a new anticancer drug. A more comprehensive economic evaluation is warranted once a new agent becomes available for clinical use. There are four types of economic evaluations: (1) a cost-benefit analysis expresses years of life gained in monetary terms, (2) a cost-minimization analysis compares costs of competing strategies that yield the same clinical outcomes, (3) a cost-effectiveness analysis determines a ratio of cost to effectiveness and is expressed as dollars per outcome gained, and (4) a cost-utility analysis compares quality-adjusted life-years gained (LYGs) with incremental costs [12,13]. Schulman [14] has described the difficulties of meaningfully comparing cost-effectiveness literature among countries with differing health-care practice patterns, reimbursement structures, currencies, and relative prices. League tables are interesting and useful juxtapositions of relative costs and benefits of diverse treatments, although they must be interpreted with caution because the costs may not be calculated through comparable methodologic approaches. An acceptable cost-effectiveness ratio is commonly benchmarked against that of hemodialysis for end-stage renal disease (approximately US$50,000/LYG) [16]. Against this background, the literature on the cost-effectiveness of chemotherapy for advanced NSCLC is reviewed here.

Overview of major economic evaluations in nonsmall-cell lung cancer

Jaakkimainen et al. [17••] conducted what is now regarded as a landmark economic evaluation of a randomized clinical trial (BR5) of the National Cancer Institute of Canada. Patients were randomized to receive vindesine and cisplatin (VP), cyclophosphamide, doxorubicin, and cisplatin (CAP), or BSC. Median survival was 119 days for BSC, 173 days for CAP, and 228 days for VP (VP vs BSC, P = 0.012). Direct costs (chemotherapy, hospitalization, clinic visits, radiotherapy) in 1984 Canadian dollars were determined for each patient from entry into the trial until death based on these costs in Ontario-based institutions. Indirect costs (absorbed by third-party insurance carriers and by patients themselves) were not included in the analysis. Costs in the three arms were as follows: BSC, Can$8595; CAP, Can$7645; and VP, Can$12,232. Cost-effectiveness ratios were as follows: CAP versus BSC, Can$6200 cost savings per LYG; VP versus BSC, Can$14,800; and VP versus CAP, Can$49,700. The robustness of these data was maintained even after variation of unit costs by 25%. Hospitalization, not chemotherapy, was the principal driver of the care costs. The authors concluded that a policy of BSC consumes considerably more resources (higher hospitalization rates and more palliative radiotherapy treatments) and that chemotherapy may prolong survival at an acceptably higher cost and may even reduce costs.

Five years after Jaakkimainen et al. [17••] conducted their cost-effectiveness analysis, Kennedy et al. [18] re-examined the same BR5 data using cost data from the province of Quebec. Their cost-utility analysis suggested that BSC is, in fact, the most cost-effective alternative, largely because of the higher costs and reduced quality of life (QOL) secondary to the toxicities of chemotherapy. In this analysis, the survival gain with chemotherapy was counterbalanced by lower quality-adjusted survival and by greater expense. In interpreting the data, it must be borne in mind that, although both analyses were conducted in Canada, the clinical practices and unit costs differed between the two provinces. In addition, quality-adjusted survival rates were determined by incorporating the preferences of oncology physicians for the chemotherapy and BSC modalities. The use of patient surrogates for utility values and the reporting of absolute rather than incremental cost-utilities have been major criticisms of this study [12]. However, for some time, the Kennedy et al. [18] analysis created uncertainty about the economic value of chemotherapy.

The cost-effectiveness of combined modality approaches for stage III NSCLC was reported by Evans et al. [19] in 1993 Canadian dollars. Chemoradiotherapy for stage IIIb NSCLC was shown to cause a small incremental cost of Can$9800 but was very cost-effective at Can$3350/LYG. The use of neoadjuvant chemotherapy with or without radiotherapy for stage IIIa disease is more controversial because of weaker evidence. Economic analysis shows that it would be more expensive to treat stage IIIa patients with combined modality therapy by as much as Can$24,000 per case. However, based on the available survival data, it appears that such strategies would also be cost-effective. For combined modality therapy consisting of surgery and preoperative and postoperative chemotherapy, the cost-effectiveness would be in the range of Can$9500/LYG. If radiotherapy were added to preoperative and postoperative chemotherapy, the cost-effectiveness was estimated to be in the range of Can$15,000/LYG relative to standard radiotherapy for stage IIIa disease in Canada.

During the 1990s, the first-generation agents were progressively replaced by new, more active agents. In most cases, these new agents were better tolerated by patients; however, they were also substantially more expensive. For example, the European Organization for Research and Treatment of Cancer [20], in comparing cisplatin and carboplatin in combination with etoposide, detected no significant survival difference and reduced hematologic and gastrointestinal toxicity with carboplatin, but the newer agent cost approximately four times as much as cisplatin. It has become imperative that these new agents be evaluated for their cost-effectiveness.
Vinorelbine
LeChevalier et al. [21] compared vinorelbine and cisplatin (NVBP) versus VP versus vinorelbine alone. Median survival rates were 40 weeks for NVBP, 32 weeks for VP, and 31 weeks for vinorelbine. The survival rate for NVBP was superior to that of VP (P = 0.04) and vinorelbine alone (P = 0.01). Subsequently, the data from this European study were subjected to cost-effectiveness and cost-utility analyses by Smith et al. [22] using cost data from a single US oncology center. The incremental cost-effectiveness ratio was found to be US$17,700/LYG for NVBP compared with vinorelbine (an 8-week median survival increase), US$22,100/LYG for VP compared with vinorelbine (a 2.7-week median survival increase), and US$15,500/LYG for NVBP compared with VP. Survival benefit was least with vinorelbine alone, but this regimen was also found to be the least expensive. Physicians and nurses were then surveyed to estimate a quality preference for the survival gained, and costs per quality-adjusted LYG were determined. The cost per LYG of US$17,700 (NVBP vs vinorelbine) increased to US$241,300 per quality-adjusted LYG. Compared with VP, vinorelbine alone extended survival 18 days while saving US$29,000. NVBP, with a mean survival of 49.6 weeks, was considered the most effective of the three regimens [23]. Its cost-effectiveness was well within acceptable limits, a finding that has been reconfirmed elsewhere [24].

Evans and LeChevalier [25•] combined clinical and economic data from pre-existing European and Canadian trials [17,21,22,26•] to determine the cost-effectiveness of vinorelbine alone and NVBP compared with VP, etoposide and cisplatin (VP16P), vinblastine and cisplatin (VLBP), and BSC. The Population Health Model (PoHeM) [27•,28•] developed by Statistics Canada was used to model the cost of care per patient, the total economic burden to the Canadian health care system, and the cost-effectiveness of the chemotherapy regimens relative to BSC, expressed as the cost per LYG.

The model incorporates actual chemotherapy costs with other resource use information appropriate for stage of disease with survival to simulate a typical cohort of Canadians with NSCLC. PoHeM has enabled the development of a NSCLC chemotherapy treatment decision framework for ranking currently available regimens relative to their cost-effectiveness and cost-utility [29]. NVBP administered as an inpatient regimen did result in increased costs relative to BSC but was cost-effective at Can$5551/LYG. Furthermore, when administered as an outpatient regimen, NVBP would save Can$473 per patient and offer an average of 0.44 years increased survival.

The most cost-effective regimen relative to BSC was VLBP; average survival increased by 0.27 years, and there was a cost savings of Can$3265 per case. It must be noted that an assumption in PoHeM is that the number of terminal care hospital days is 23.6 for BSC compared with 17.1 for chemotherapy—a finding of the National Cancer Institute of Canada BR5 trial in 1984 that has not been reevaluated recently. In all, four out of the six chemotherapy regimens modestly increased survival and resulted in a total cost savings. The additional cost of chemotherapy was more than compensated for by a reduction in the number of days of terminal care hospitalization and associated palliative radiotherapy. When compared with the standard regimens of VP16P and VLBP, the outpatient administration of NVBP was determined to be cost-effective (Can$7902 and Can$16,404 per LYG, respectively). It was concluded that various regimens, among them outpatient NVBP, were cost-effective interventions in the management of advanced NSCLC.

Gemcitabine
Gemcitabine is a pyrimidine antimetabolite with broad-spectrum antitumor activity [30,31]. Its activity is attributable to its lipophilicity and increased cellular penetration, higher intracellular level of triphosphate, and longer intracellular residence of the active metabolite relative to the structurally-related compound, cytosine arabinoside [32]. It is attractive as a first-line therapy against advanced NSCLC because of its relatively mild, reversible toxicity profile, over a wide dose range [33–35]. Although the most frequent serious hematologic toxicity is neutropenia, serious infections requiring hospitalization are uncommon. Furthermore, nonhematologic toxicities are mild and manageable [36]. Administered as a single agent, performance status has been observed to improve in approximately one third of patients [33].

The phase II trials of single-agent gemcitabine produced tumor responses in approximately 20% of patients, with a median survival of from 7 to 9 months [37]. Improvement in cough, hemoptysis, and dyspnea paralleled that observed with radiation and standard combination chemotherapy regimens. However, QOL issues were examined as a primary outcome in a recent randomized trial [38].

Considering its activity and relatively mild toxicities, gemcitabine was a good candidate to combine with other agents, particularly cisplatin, and has been compared with the VP16P regimen in a Spanish phase III trial [39•]. Because there was no significant difference in survival between the two regimens, a cost minimization analysis was undertaken. Despite higher drug costs on the gemcitabine arm, total direct medical costs were similar. The difference in the number of hospitalization days (4.8 ± 6.2 for the gemcitabine arm vs 9.1 ± 14.2 for the etoposide arm), although not statistically significant,
resulted in a greater cost in the standard arm and counterbalanced the incremental cost of the new agent.

An average and incremental cost-effectiveness analysis was performed, using response rate and median time to progression as endpoints. This analysis resulted in a cost per additional tumor response and cost per progression-free year in favor of the gemcitabine arm. The authors of this prospective economic evaluation concluded that the combination of gemcitabine-cisplatin had a more favorable cost-effectiveness profile than that of VP16P [39•].

In 1997, Evans [40•] extracted survival data of single-agent gemcitabine-treated patients in an international phase II trial (EO-18) and compared these data with similar data of untreated patients from the BSC arm of the BR5 study. Expressed in 1993 Canadian dollars, the costs of BSC (diagnostic work-up to palliative care) were found to be approximately Can$28,617. When administered in a dosage of 1000 mg/m$^2$ weekly for 3 weeks, treatment with gemcitabine was only slightly more expensive, at Can$28,907. It was assumed that gemcitabine monotherapy would reduce the number of days of hospitalization associated with terminal care to the same extent noticed in the BR5 study. This treatment effect has been attributed to improved symptom control and possibly greater motivation on the part of the patient and the physician for the patient to remain more active. Considered from a health system perspective, this Can$290 additional cost of treating a patient with gemcitabine compared with BSC could potentially result in a total cost to the Canadian health care system of 141.8 million Canadian dollars.

An average survival advantage of 0.396 years in favor of gemcitabine was estimated as the difference between the survival curves of the gemcitabine trial arm and that of patients receiving BSC. This difference translated into a cost per LYG of Can$632. Because the patients of the EO-18 trial were selected for good performance status, a sensitivity analysis was performed. It showed that even when a 25% reduction in survival gain was modeled, the cost per LYG was Can$919, and at a 50% reduction in survival gain, the cost per LYG was Can$1578. An analysis of the cost components of care for patients with advanced NSCLC treated with gemcitabine showed that only 17.8% of the costs were attributable to chemotherapy, including the costs of drug administration, whereas 35.2% were attributable to hospitalization during the diagnostic phase and 40.6% for hospitalization during terminal care. Based on this analysis, it was concluded that gemcitabine monotherapy was cost-effective in stage IV NSCLC and was competitive with other established health-care practices.

The investigators acknowledged that the PoHeM model greatly overestimated the impact of gemcitabine on the total health care expenditure in Canada, because only a modest proportion of patients with stage IV NSCLC would be considered for treatment with the drug. Many patients are not suitable candidates because of age, performance status, and comorbid conditions. In addition, there are many physicians, including oncologists, who still have a conservative attitude in the treatment of advanced NSCLC. As a result, chemotherapy is not presented as an option to some patients. Because of these factors, PoHeM would be expected to overestimate the economic impact of gemcitabine on the Canadian health care system.

Paclitaxel

Paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ), alone or in combination, has been extensively studied as a first-line agent in patients with inoperable NSCLC. The large, phase III Eastern Cooperative Oncology Group trial by Bonomi et al. [41] compared VP16P, paclitaxel 250 mg/m$^2$ plus cisplatin with granulocyte colony-stimulating factor support, and paclitaxel 135 mg/m$^2$ plus cisplatin without growth factors. The response rates were statistically superior for both paclitaxel arms ($P < 0.001$) and 1-year survival increased from 20% with VP16P to 40% with paclitaxel and cisplatin.

One cost analysis of paclitaxel treatment in NSCLC, conducted by Earle and Evans [42•], incorporated a mean paclitaxel dose of 214 mg/m$^2$ from two phase II trials [43,44], a 3-week dosing schedule, a median of three treatment cycles, and data from the BSC arm of the National Cancer Institute of Canada BR5 study into the PoHeM model. The total cost of administering three cycles of chemotherapy in 1993 Canadian dollars was Can$8143 per patient. This figure represented a Can$3375 increase over that expected in the BSC strategy. However, based on an estimate of the difference in the area under the survival curves for the phase II studies versus BSC, the taxane cost per life-year saved (LYS) was calculated at Can$4778. This reasonable cost-effectiveness ratio has magnitude similar with that of vinorelbine compared with BSC (Evans and LeChevalier [25]). Even in the least favorable scenario of the sensitivity analysis (projecting five cycles at 50% survival gain), the paclitaxel cost rose to only Can$21,377 per LYS.

The investigators acknowledged several inherent weaknesses of this analysis. First, measures of QOL were not included. As a result, the adverse effects of paclitaxel on QOL were not incorporated into the economic analysis. Second, the patients included in these trials may have been selected for a better outcome by virtue of superior performance status, lower volume disease, or other characteristics predictive of a better prognosis. Third, the model assumed uncomplicated drug administration and no treatment-related hospital admissions.
Earle and Evans [45•] undertook a second cost-effectiveness comparison, this time based on the phase III Eastern Cooperative Oncology Group trial [41]. The cost estimates for paclitaxel administration were high because it was the practice in the Eastern Cooperative Oncology Group trial to administer paclitaxel over a period of 24 hours to inpatients. When modeled as an outpatient 3-hour infusion, paclitaxel and cisplatin cost Can$30,619/LYG.

**Docetaxel**

Docetaxel is another taxane active against NSCLC. One multicenter, randomized, phase III study [46] presented at the ASCO 2001 conference compared docetaxel plus cisplatin, docetaxel plus carboplatin, and NVBP in stages IIIb and IV NSCLC. An improved 2-year survival of docetaxel plus cisplatin over NVBP was observed: 21% versus 14%, respectively ($P = 0.035$). Survival comparisons between docetaxel plus carboplatin and NVBP were not significantly different. In addition, the incidence of grade III or IV nausea in the vinorelbine arm was roughly twice that of both docetaxel arms.

An economic analysis of docetaxel treatment has yet to be reported. However, docetaxel has a acquisition cost similar to that of paclitaxel, but can be infused over a period of 1 hour, compared with paclitaxel’s 3-hour infusion rate. Hence, it would be reasonable to predict a comparable cost-effectiveness ratio. A comparison of the cost-effectiveness of various first-line chemotherapy regimens is presented in Table 1 [47••].

**Second-line docetaxel in platinum-refractory nonsmall-cell lung cancer**

Platinum-refractory NSCLC is a difficult disease to treat, and only a small proportion of patients live beyond the first year. However, two randomized, phase III trials revealed significant 1-year survival benefits with single-agent docetaxel. In one of these trials, reported by Shepherd et al. [48], docetaxel 100 mg/m$^2$ and 75 mg/m$^2$ were compared with BSC. Patients receiving 75 mg/m$^2$ experienced a survival benefit over those receiving only BSC (7.5 mo vs 4.6 mo, and 37% vs 11% alive at 1 y). Requirements for analgesia and radiation therapy were also reduced in the chemotherapy arms.

An economic analysis of this study was reported by Leigl et al. [49]. Using cost data in 1999 Canadian dollars from the Princess Margaret Hospital, Toronto, Canada, the investigators demonstrated that docetaxel at a dose of 75 mg/m$^2$ was more expensive than BSC but relatively cost-effective at Can$31,777 per LYG. Cost-effectiveness ratios were most sensitive to changes in survival, ranging from Can$18,374 to Can$117,434 per LYG with a 20% variation in survival.

Gemcitabine has some activity as a second-line agent, but paclitaxel, vinorelbine, and irinotecan have been disappointing in this difficult to treat population [50]. An economic analyses of second-line gemcitabine therapy has yet to be undertaken. Given the reduced responsiveness of agents in this setting, the cost-effectiveness ratios of gemcitabine and other agents as second-line therapy are likely to be substantially higher than ratios for these agents as first-line therapy.

Now that BSC is no longer considered the standard of care for patients with advanced NSCLC, various chemotherapy regimens compete for dominance in the marketplace. Factors on which they compete are cost-effectiveness and cost-utility. An advanced decision framework that ranks the various treatment regimens on these factors has been reported by investigators from the Heath Analysis Modeling Division of Statistics Canada. Berthelot et al. [47••] applied the PoHeM model to compare the cost-effectiveness and cost-utility of various

**Table 1. Cost-effectiveness of various chemotherapy regimens compared to best supportive care for metastatic nonsmall-cell lung cancer**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Average cost per case, Can$</th>
<th>Average survival, y</th>
<th>Average years saved*</th>
<th>Cost per life-year saved, Can$†</th>
<th>Utility estimate‡</th>
<th>Cost per QALY gained, Can$§</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td>25,643</td>
<td>0.49</td>
<td>–</td>
<td>–</td>
<td>0.53</td>
<td>–</td>
</tr>
<tr>
<td>V + P</td>
<td>30,387</td>
<td>0.76</td>
<td>0.27</td>
<td>17,600</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>VLB + P</td>
<td>24,828</td>
<td>0.76</td>
<td>0.27</td>
<td>D</td>
<td>0.52</td>
<td>D</td>
</tr>
<tr>
<td>NVB</td>
<td>26,184</td>
<td>0.77</td>
<td>0.28</td>
<td>1900</td>
<td>0.60</td>
<td>2700</td>
</tr>
<tr>
<td>GEM</td>
<td>28,463</td>
<td>0.90</td>
<td>0.41</td>
<td>6800</td>
<td>0.65</td>
<td>8600</td>
</tr>
<tr>
<td>NVB + P</td>
<td>27,446</td>
<td>0.93</td>
<td>0.44</td>
<td>4100</td>
<td>0.60</td>
<td>6000</td>
</tr>
<tr>
<td>VP16 + P</td>
<td>27,654</td>
<td>0.76</td>
<td>0.27</td>
<td>7500</td>
<td>0.55</td>
<td>12,800</td>
</tr>
<tr>
<td>PC + P 135 mg/m$^2$</td>
<td>34,488</td>
<td>1.06</td>
<td>0.57</td>
<td>15,400</td>
<td>0.63</td>
<td>21,500</td>
</tr>
<tr>
<td>PC + P 200 mg/m$^2$</td>
<td>38,019</td>
<td>1.06</td>
<td>0.57</td>
<td>21,500</td>
<td>0.63</td>
<td>30,100</td>
</tr>
<tr>
<td>PC + P 250 mg/m$^2$</td>
<td>41,178</td>
<td>1.06</td>
<td>0.57</td>
<td>27,000</td>
<td>0.63</td>
<td>37,800</td>
</tr>
</tbody>
</table>

*Average years saved calculated as average survival for chemotherapy — average survival for BSC for each chemotherapy regimen. **Not calculated. †Cost per life-year saved calculated as (chemotherapy case cost – BSC case cost) / average years saved. ‡Utility estimate is an estimate of the health-related quality of life of patients for each intervention. §Cost per QALY gained calculated as (chemotherapy case cost – BSC case cost) / (average survival x utility for chemotherapy – average survival x utility for BSC). BSC, best supportive care; D, dominant strategy (ie, both less expensive and more effective than BSC); GEM, gemcitabine NVB, vinorelbine; P, cisplatin; PC, paclitaxel; QALY, quality-adjusted life-year; V, vindesine; VLB, vinblastine; VP16, etoposide. Reprinted with permission [47••].

Chemotherapy in nonsmall-cell lung cancer

Dranitsaris et al. 379
chemotherapy regimens (Table 2) [47••]. The regimens administered in the outpatient setting were ranked to optimize benefit below a range of cost-effectiveness thresholds (Table 3) [28•]. It was determined that only vinblastine plus cisplatin resulted in both improved survival and lower health care expenditures than BSC. The cost-effectiveness ratios of the other regimens relative to BSC were as follows: NVB, Can$4,100 per LYS; gemcitabine monotherapy, Can$6,800 per LYS; VP16P, Can$7,500 per LYS; and paclitaxel (200 mg/m² over a period of 3 h) plus cisplatin, Can$21,500 per LYS (Table 2).

Emerging therapies
Having reached a new plateau of cytotoxic effect with the currently available cytotoxic agents, efforts have turned to the study of proteins and genes involved in signal transduction pathways.

ZD1839 (Iressa), a low molecular weight inhibitor of the epidermal growth factor receptor overexpressed on the surface of NSCLC cells, is currently being investigated in an oral dosage form with the carboplatin plus paclitaxel and cisplatin plus gemcitabine regimens [51]. Another oral epidermal growth factor receptor antagonist, OSI-774, is being studied in combination with vinorelbine [52]. Farnesyltransferase inhibitors are being developed with the expectation of interrupting oncogenic signaling pathways. Early data suggest that these agents sensitize lung cancer cells to taxanes [53].

Similarly, the monoclonal antibody trastuzumab (Herceptin; Genentech, S. San Francisco, CA), a HER2 receptor inhibitor, has been observed to sensitize NSCLC cells to cytotoxic chemotherapy [54]. The antisense oligonucleotides, which target c-raf and protein kinase C, are also under investigation [55]. The intratumoral injection, or bronchoalveolar lavage, of functional p53 tumor suppressor protein by way of an adenoviral vector is being studied in patients treated with cisplatin [56]. Costs are unknown for these emerging therapies, but for those demonstrating efficacy, they are likely to be applied in combination with existing chemotherapy regimens, which are already costly. Therefore, the cost and cost-effectiveness of these new agents may prove critical to their adoption, and prospective economic analyses should accompany future randomized clinical trials.

Discussion
The estimated average lifetime cost of treating a patient with advanced NSCLC in Canada ranges from Can$25,822 for stage IV disease to Can$31,035 for stage IIIa disease. Approximately 5000 new metastatic NSCLC patients are diagnosed annually in Canada, im-

Table 2. Comparison of incremental cost per life-year saved and incremental cost per quality-adjusted life-year gained among various therapies for metastatic nonsmall-cell lung cancer

<table>
<thead>
<tr>
<th>Incremental cost per life-year saved, 1995 Can$</th>
<th>VB + P</th>
<th>BSC</th>
<th>VLB</th>
<th>VLB + P</th>
<th>VP16 + P</th>
<th>GEM</th>
<th>V + P</th>
<th>PC + P 135 mg/m²</th>
<th>PC + P 200 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVB</td>
<td>99,700</td>
<td>1900</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVB + P</td>
<td>15,200</td>
<td>4100</td>
<td>8000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VP16 + P</td>
<td>WD</td>
<td>7500</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM</td>
<td>25,200</td>
<td>6800</td>
<td>17,400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V + P</td>
<td>D</td>
<td>17,600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC + P 135 mg/m²</td>
<td>31,600</td>
<td>15,400</td>
<td>28,400</td>
<td>52,800</td>
<td>22,400</td>
<td>37,400</td>
<td>13,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC + P 200 mg/m²</td>
<td>43,200</td>
<td>21,500</td>
<td>40,500</td>
<td>79,800</td>
<td>33,900</td>
<td>59,200</td>
<td>25,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC + P 250 mg/m²</td>
<td>53,500</td>
<td>27,000</td>
<td>51,300</td>
<td>103,000</td>
<td>44,300</td>
<td>78,800</td>
<td>35,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incremental cost per quality-adjusted life-year gained, 1995 Can$</td>
<td>VB + P</td>
<td>BSC</td>
<td>VLB</td>
<td>VLB + P</td>
<td>VP16 + P</td>
<td>GEM</td>
<td>V + P</td>
<td>PC + P 135 mg/m²</td>
<td>PC + P 200 mg/m²</td>
</tr>
<tr>
<td>BSC</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVB</td>
<td>19,769</td>
<td>2658</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVB + P</td>
<td>15,982</td>
<td>6036</td>
<td>13,254</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VP16 + P</td>
<td>124,702</td>
<td>12,762</td>
<td>D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GEM</td>
<td>18,933</td>
<td>8626</td>
<td>18,468</td>
<td>36,083</td>
<td>4778</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC + P 135 mg/m²</td>
<td>35,048</td>
<td>21,545</td>
<td>40,110</td>
<td>62,982</td>
<td>27,016</td>
<td>72,048</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC + P 200 mg/m²</td>
<td>47,859</td>
<td>30,146</td>
<td>57,166</td>
<td>94,562</td>
<td>40,975</td>
<td>114,272</td>
<td>WD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC + P 250 mg/m²</td>
<td>59,320</td>
<td>37,841</td>
<td>72,424</td>
<td>122,815</td>
<td>53,463</td>
<td>152,048</td>
<td>WD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tables show the incremental cost per life-year saved and cost per quality-adjusted life-year gained of each regimen in the first column compared with the regimen in the top row. VP was not shown in the lower table because a utility value was not estimated. BSC, best supportive care; D, dominant strategy (ie, the therapy in the top row is both less expensive and more effective); GEM, gemcitabine; NVB, vinorelbine; P, cisplatin; PC, paclitaxel; V, vindesine; VLB, vinblastine; VP16, etoposide; WD, weakly dominant (ie, the therapy in the top row is less expensive with the same survival). Reprinted with permission [47••].
plying that the health care system requires an additional 130 million Canadian dollars each year to manage stage IV disease alone. The elements most responsible for these costs are hospitalization for the diagnosis and initial surgical treatment of patients (45.1%), and terminal care (38.5%). Obviously, shifting medical practice toward ambulatory diagnosis and treatment, and terminal care in the community, would be a cost-conscious approach.

The introduction of new and expensive chemotherapy drugs with only a modest survival benefit and, at times, questionable improvement in quality of life has been accompanied by some controversy because of concerns about cost. However, as has been shown, chemotherapy can be cost-effective and, in some instances, cost-saving compared with BSC. This finding underscores the need for well-designed cost-effectiveness analyses, rather than simple concern for the unit cost of a new drug.

However, new cost-effective agents will strain and perhaps overwhelm the budgets of health care systems. In considering the total economic impact of treating NSCLC, it is important to recognize that not all patients with advanced NSCLC will be treated with chemotherapy, in part because of the attitude of physicians within a country. For example, it has been acknowledged that Canadian oncologists are still relatively more conservative than their US counterparts in the treatment of NSCLC [56]. In addition, chemotherapy is not feasible because of poor performance status or concomitant illnesses in some patients. Because lung cancer is a disease that predominantly affects older people, clinicians may fear that the patient is too old to tolerate a chemotherapy regimen [57]. However, a recent report [58] demonstrated that older patients have an incidence of adverse effects, with the exception of leukopenia, similar to that of younger patients. Even when comorbidity is considered, Hebert-Croteau et al. [59] found that older patients are not offered more aggressive treatment, which could prolong survival.

It has been implied that the increased costs associated with chemotherapy for advanced NSCLC outweigh the limited survival benefits derived, particularly in this era of fiscal restraint. However, patients also experience subjective improvement in symptoms such as pain, cough, dyspnea, and hemoptysis. Furthermore, there have been improvements in the therapeutic index of current regimens. As an example, the serotonin antagonists have markedly reduced the incidence of nausea and vomiting, and alopecia is less common with the NVBP regimen. Patients have been reported with improved QOL, pain relief, and overall well being after receiving a docetaxel plus cisplatin regimen as opposed to NVBP [60]. Finally, reduction of the number of cycles to the number neces-

<table>
<thead>
<tr>
<th>Table 3. Ranking of various therapies by cost per life-year saved and per quality-adjusted life-year gained based on threshold Can$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank of chemotherapy regimens by cost per life-year saved</td>
</tr>
<tr>
<td>Regimen</td>
</tr>
<tr>
<td>VLB + P</td>
</tr>
<tr>
<td>BSC</td>
</tr>
<tr>
<td>NVB</td>
</tr>
<tr>
<td>NVB + P</td>
</tr>
<tr>
<td>VP16 + P</td>
</tr>
<tr>
<td>GEM</td>
</tr>
<tr>
<td>Y + P</td>
</tr>
<tr>
<td>PC + P 135 mg/m²</td>
</tr>
<tr>
<td>PC + P 200 mg/m²</td>
</tr>
<tr>
<td>PC + P 250 mg/m²</td>
</tr>
</tbody>
</table>

For each threshold value of the cost willing to be paid per life-year saved or cost per quality-adjusted life-year gained, this table shows the ranking of chemotherapy regimens that would maximize survival. V + P was not shown in the lower table because a utility value was not estimated. BSC, best supportive care; GEM, gemcitabine; NVB, vinorelbine; P, cisplatin; PC, paclitaxel; V, vindesine; VLB, vinblastine; VP16, etoposide. Reprinted with permission [28].
sary for symptom control and meaningful survival (as low as three) should increase the cost-effectiveness of chemotherapy for advanced NSCLC [61].

Conclusions

Non-small-cell lung cancer is often a terminal illness that uses substantial health care resources to optimize patient survival and overall quality of life. Chemotherapy is typically used for locally advanced and metastatic lung cancer. Many in the medical community falsely assumed that the use of chemotherapy, particularly the newer agents vinorelbine, gemcitabine, and the taxanes, was not cost-effective. However, as highlighted in this review of the pharmacoeconomic literature, chemotherapy is not only cost-effective in NSCLC but also cost-saving in some cases. As a result, chemotherapy for NSCLC can provide a clinical benefit to patients while being a cost-effective use of limited oncology resources. Therefore, it should be offered to medically appropriate patients with NSCLC.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
• Of outstanding interest


