The impact of practice guidelines and funding policies on the use of new drugs in advanced non-small cell lung cancer*

George Dranitsaris M.Pharm FCSHP, William K. Evans MD FRCPC, Debbie Milliken BScPhm and Brent Zanke MD PhD FRCPC

1Consultant Pharmacist, Cancer Care Ontario, Ontario, Canada
2Chief Medical Officer and Provincial Vice President, Cancer Care Ontario, Ontario; and Professor, University of Toronto, Toronto, Canada
3Director, Provincial Drug Reimbursement Programs, Toronto, Canada
4Provincial Head Systemic Therapy, Cancer Care Ontario, Ontario; and Associate Professor, University of Toronto, Toronto, Canada

Abstract

Background Cancer Care Ontario’s (CCO) Program in Evidence-based Care has provided a credible basis for policy development and the funding of new and expensive anticancer drugs in the province of Ontario. In November 1997, vinorelbine was approved for the first-line treatment of advanced non-small cell lung cancer (NSCLC) on the basis of evidence-based practice guidelines generated by the Provincial Lung Disease Site Group. In June 1998, gemcitabine was approved as an alternative to vinorelbine for use in selected patients (e.g. significant venous access problems, peripheral neuropathy, severe toxicity to vinorelbine). A provincial drug database was used to determine the impact that these new policies had on the rate of vinorelbine and gemcitabine uptake within the CCO new drug funding programme. Methods Drug utilization data for vinorelbine and gemcitabine from October 1997 to June 1999 were obtained from the CCO drug database. Individual patient data consisted of age, gender, first-line agent used, number of treatments, duration of therapy, treatment location (regional cancer centre vs. other) and total cost. Demographic and drug utilization data were analysed descriptively as means, medians, or proportions. Multivariable logistic regression analysis was then used to identify factors associated with the selection of gemcitabine over vinorelbine, as a first-line therapy. Results Following the approval of the first policy in November 1997, there was a rapid adoption of vinorelbine use in new NSCLC patients. When the gemcitabine policy was approved in June 1998, there was a rapid uptake in its use reaching a stable plateau of approximately 15% of all NSCLC patients within 9 months. The logistic regression analysis identified patient age greater than 65 years [odds ratio (OR) = 1.90, \( P = 0.001 \)] and treatment in a non-regional cancer setting (OR = 1.71, \( P = 0.008 \)) as significant predictors of gemcitabine utilization. Overall, the mean drug cost per patient treated with first-line gemcitabine was significantly higher than vinorelbine ($Can2590 vs. $Can1030, \( P < 0.001 \)). Conclusions The new funding policies were associated with a rapid increase in drug utilization reaching a stable plateau within 9 months. Factors contributing to the usage of these new drugs for NSCLC included patient characteristics, such as age and treatment location.

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Introduction

In the past 10 years, considerable resources have been committed to the development of clinical practice guidelines for the optimal use of drugs. In oncology alone, a medline search over the past 5 years with keywords ‘oncology AND practice guidelines’ identified 118 guidelines that have been published in peer reviewed journals. However, current evidence suggests that physicians’ practice is only modestly affected by practice guidelines (Oxman et al. 1995; Bero et al. 1998). One approach to ensure implementation of evidence-based practice would be to link drug reimbursement to prescribing according to practice guidelines. Given the differences between cytotoxic agents in terms of efficacy, toxicity and cost, it is difficult to predict how rapid the uptake of specific anticancer drugs would be under these conditions. Nevertheless, this information would be of value to oncology formulary committees in establishing future budgets based on proposed new drug reimbursement policies. Fortunately, the process developed under the new drug funding programme in the province of Ontario, Canada provided insight into this important question.

In the province of Ontario, Cancer Care Ontario’s (CCO) Program in Evidence-based Care has provided a credible basis for policy development and the funding of new and expensive cytotoxic drugs. The programme is designed to develop evidence-based guidelines for drugs and other therapeutic movements. These guidelines undergo extensive internal and external review and are then connected to reimbursement through the provincial ‘new drug funding program’ (Fig. 1).

Vinorelbine and gemcitabine for the treatment of advanced non-small cell lung cancer (NSCLC) were among the first agents evaluated by the Program in Evidence-based Care. A well-designed randomized trial demonstrated that vinorelbine in combination with cisplatin provided a survival advantage compared to vindesine with cisplatin and vinorelbine alone (LeChevalier et al. 1994). Gemcitabine was the second agent reviewed for reimbursement under the new drug funding programme. However, at the time of the evaluation, the evidence supporting its use was only from phase II trials. (Evans et al. 1999) Additional evidence and indirect comparison across phase III trials suggest that first-line gemcitabine is clinically comparable to vinorelbine in terms of objective tumour response and overall survival (Kelly et al. 2001; Schiller et al. 2002). The drug cost per cycle of gemcitabine is higher than vinorelbine, but each agent has a unique side-effect profile (Berthelot et al. 2000).

In November 1997, vinorelbine was approved for the first-line treatment of advanced NSCLC on the basis of evidence-based practice guidelines generated by the Provincial Lung Disease Site Group. In June 1998, gemcitabine was approved as an alternative to vinorelbine in patients with significant venous access problems, peripheral neuropathy, serious bowel dysfunction or other severe toxicities. In November 2002, a new policy was approved which essentially removed the gemcitabine-prescribing restrictions and allowed oncologists open access to gemcitabine. A contributing factor to this change was the report of drug delivery problems with vinorelbine, particularly venous complications in older patients. The development of these three new polices over a 5-year period provided an attractive
opportunity to determine the rate of uptake of expensive drugs, following the development of evidence-based guidelines that were linked to reimbursement. In this study, a provincial drug utilization database was used to determine the impact that new funding policies had on the rate of vinorelbine and gemcitabine utilization within the province of Ontario and to identify factors that were associated with the preferential use of gemcitabine over vinorelbine.

Methods

Drug utilization data for vinorelbine and gemcitabine from October 1997 to March 2003 were obtained from the CCO drug database, which directly links reimbursement to each chemotherapy prescription. Individual patient data consisted of age, gender, first-line agent used, number of treatments, duration of therapy, treatment location (regional cancer centre vs. other) and total drug cost.

Demographic and drug utilization data were analysed descriptively as means, medians, or proportions. Parametric and non-parametric inferential statistics were used in an exploratory analysis to compare mean duration of therapy, number of treatments and total drug cost between patients treated with vinorelbine or gemcitabine.

A main-effects-only multivariate logistic regression model was initially developed to identify factors associated with the selection of gemcitabine over vinorelbine, as a first-line therapy for advanced NSCLC Kleinbaum 1994. To identify patient subgroups where gemcitabine would be used to a greater degree than vinorelbine, a multivariable regression model with interaction effects was also developed. Interaction effects are one method that can be used to identify relevant patient subgroups (Kleinbaum 1994). During any statistical analysis, one must be aware that multiple comparisons of subgroups (performed through interaction effects) within a large database can increase the likelihood of identifying significant differences by chance alone. To limit this risk, subgroup analyses should only be performed when there is evidence in the literature of a true difference between patient subgroups. Therefore, the interaction effects evaluated in the current study were based on hypotheses developed during the literature review and after discussions with oncologists (a priori). All of the statistical analyses were performed using Stata, release 7.0 (Stata Corp., College Station, Texas, USA).

Results

From October 1997 to June 1999, 1361 patients were treated with vinorelbine and 143 received gemcitabine under CCO’s new drug funding programme. Following the approval of the first policy in November 1997, there was a rapid adoption of vinorelbine use in new advanced-stage NSCLC patients at the expense of other agents such as etoposide, vincristine and vinblastine. When the restricted gemcitabine policy was approved in June 1998, there was also an immediate uptake of the drug. Within 9 months of the new policy, a plateau was reached where gemcitabine was the drug of choice in 15% of all new NSCLC patients treated under the new drug funding programme (Fig. 2).

Under CCO’s direction, there are eight regional cancer centres (RCCs) within the province. Non-RCCs consist of tertiary care centres and community hospitals. A closer examination of the patient data revealed that patients treated with gemcitabine tended to be older and a higher proportion received therapy in a non-RCC setting (72.7% vs. 62.5%; \( P = 0.016 \)). A comparison of mean duration of therapy and median number of drug administrations did not reveal any major differences between drugs...
Despite this, the mean total drug cost per patient was significantly higher with gemcitabine ($Can2590 vs. $Can1030; \ P < 0.001). Overall, this translated to a steady increase in expenditures over time (Fig. 3). For the first full year, a budget–impact analysis determined from actual consumption data estimated an incremental annualized drug cost of approximately $Can235 000 onto the CCO drug budget.

Logistic regression was then applied to identify factors associated with the use of gemcitabine over vinorelbine. The dependent variable in the model was the likelihood of using gemcitabine over vinorelbine. The initial main-effects-only model identified patient age above 65 (OR = 1.90; \ P = 0.001) and treatment within a non-RCC (OR = 1.71; \ P = 0.008) as being significantly associated with the use of gemcitabine (full regression results not shown). However, when the interaction between ‘patient age and treatment setting’ was added to the model, it generated a statistically significant odds ratio of 2.25, with age above 65 and treatment within a non-RCC no longer being significant (Table 2). This interaction effect is interpreted as follows: patients older than 65 years of age who are receiving treatment within a non-RCC setting were approximately twice as likely (OR = 2.25; \ P = 0.045) to receive gemcitabine over vinorelbine. The other variable of interest was the time variable ‘quarter’, which accounted for changes in gemcitabine usage for every 3-month interval (Table 2). The logistic regression analysis confirmed the observation that the use of gemcitabine significantly increased over time (Figs 2 & 3).

With the existing policies, approximately 15% of advanced-stage NSCLC patients were being treated with gemcitabine under the CCO new drug funding programme (Fig. 2). When the restrictions on gemcitabine usage were removed in November 2002, there was an immediate increase in drug use. By the end of the first quarter of 2003, 50% of new patients were being treated with gemcitabine, 48% were receiving vinorelbine and paclitaxel was used in 2% of new cases (Fig. 4). Using the incremental expenditure for the first quarter of 2003, the budget–impact analysis projected an incremental annualized drug cost of approximately $Can1.6 million onto the CCO drug budget (Fig. 5).

### Table 1 Comparative data of patients treated with vinorelbine and gemcitabine

<table>
<thead>
<tr>
<th>Variable (SE)*</th>
<th>Vinorelbine (n = 1361)</th>
<th>Gemcitabine (n = 143)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean patient age</td>
<td>63.0 (0.29)</td>
<td>66.2 (0.97)</td>
<td>0.002</td>
</tr>
<tr>
<td>Patient gender (males percentage)</td>
<td>57.3%</td>
<td>57.2%</td>
<td>0.97</td>
</tr>
<tr>
<td>Treatment within RCC†</td>
<td>37.5%</td>
<td>27.3%</td>
<td>0.016</td>
</tr>
<tr>
<td>Mean duration of therapy in months</td>
<td>3.15 (0.11)</td>
<td>3.70 (0.47)</td>
<td>0.25</td>
</tr>
<tr>
<td>Median number of drug administrations‡</td>
<td>5 (0.15)</td>
<td>4 (0.45)</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean drug cost of overall therapy</td>
<td>$Can1030</td>
<td>$Can2590</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SE, standard error of the mean.

*Detailed utilization data obtained from October 1997 to June 1999.

†RCC, regional cancer centre. During the evaluation periods, there were eight regional cancer centres. Non-RCCs include tertiary health care centres and community hospitals.

‡Common protocol of drugs under evaluation in the current study: gemcitabine 1000 mg m\(^{-2}\) day 1, 8, 15 + cisplatin 100 mg m\(^{-2}\) day 1. Vinorelbine 30 mg m\(^{-2}\) weekly + cisplatin 120 mg m\(^{-2}\) day 1 and 29.
Table 2 Factors associated with gemcitabine usage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>SEM</th>
<th>P-Value</th>
<th>Impact on gemcitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>1.06</td>
<td>0.36</td>
<td>0.86</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.86</td>
<td>0.16</td>
<td>0.42</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of therapy (months)</td>
<td>1.03</td>
<td>0.018</td>
<td>0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment in non-RCC vs. RCC*</td>
<td>1.04</td>
<td>0.31</td>
<td>0.90</td>
<td>NS</td>
</tr>
<tr>
<td>Quarterly interval†</td>
<td>1.39</td>
<td>0.07</td>
<td>&lt;0.001</td>
<td>39% increase over time</td>
</tr>
<tr>
<td>Age &gt; 65 × non-RCC‡</td>
<td>2.25</td>
<td>0.91</td>
<td>0.045</td>
<td>Twofold more usage in patients &gt;65 treated in Non-RCC</td>
</tr>
</tbody>
</table>

Dependent variable: Use of gemcitabine over vinorelbine.

*RCC, regional cancer centre. During the evaluation periods, there were eight regional cancer centres.

†From October 1997 to June 1999, the time period was broken down into seven quarterly intervals. Gemcitabine uptake relative to vinorelbine was evaluated for each successive quarter from when the new gemcitabine policy was introduced.

‡Evaluation of subgroups through the testing of interaction effects. In this case, the analysis suggested that gemcitabine was used approximately twice as much in patients >65 that received treatment in a non-regional cancer centre setting.

NS, not significant; SEM, standard error of the mean.

Discussion

There have been several large randomized trials comparing vinorelbine, paclitaxel, docetaxel and gemcitabine, all in combination with a platinum analogue for the first-line treatment of advanced-stage NSCLC (LeChevalier et al. 1994; Kelly et al. 2001; Schiller et al. 2002; Fossella et al. 2003). The overall response rates and survival between the various combinations were comparable with no one protocol standing out as being clinically superior. The major differences between regimens appeared to be in toxicity. The incidences of grade IV thrombocytopenia and decreased renal function were the highest with gemcitabine/cisplatin. In contrast, the gemcitabine arm had a lower risk of grade III/IV febrile neutropenia than the paclitaxel/cisplatin and docetaxel/cisplatin protocols (Schiller et al. 2002). In the Kelly et al. trial which compared vinorelbine/cisplatin to paclitaxel/carboplatin, there were differences in grade III/IV toxicity rates between groups with neutropenia, nausea and vomiting being significantly higher with vinorelbine/cisplatin and sensory neuropathy being more prevalent in the paclitaxel regimen. In addition, more patients discontinued therapy in the vinorelbine arm because of toxicity (28% vs.
15%, \( P = 0.001 \)}. However, there was no difference in quality of life and the paclitaxel regimen was significantly more costly (Ramsey et al. 2002).

Given the available data, the Provincial Lung Disease Site Group developed clinical practice guidelines for the use of vinorelbine and gemcitabine. The Policy Advisory Committee of CCO used these guidelines to initially approve the open use of vinorelbine and then the restricted use of gemcitabine in patients who met predefined criteria. The uptake of vinorelbine after the initial funding policy was virtually immediate, possibly reflecting a pent-up demand for the agent and substantial existing use. On introduction of a restrictive funding policy for gemcitabine, usage increased to about 15% of all patients and reached a plateau within 9 months. Therefore, these data support the hypothesis that evidence-based practice can be promoted by linking drug reimbursement to practice guidelines.

Prescribing gemcitabine within CCO guidelines was further reinforced by the findings of the regression analysis. The results suggested that patients older than 65 receiving treatment within a non-RCC were more likely to receive gemcitabine. As vinorelbine is associated with a higher risk of venous access complications, the underlying hypothesis is that older patients, who typically have poorer venous access than younger patients would be more likely to receive gemcitabine. There have been anecdotal reports from community oncologists that placement of a central venous access device in patients being treated in non-RCCs is frequently delayed for weeks if not months. To avoid the potential for venous access complications with vinorelbine, many community oncologists in non-RCCs may be opting to use gemcitabine to avoid the possible need for a venous access device in high-risk patients. Hence, the statistically significant interaction effect in our regression model implies that at least part of the gemcitabine usage is within CCO guidelines.

Despite this finding, it is important to recall that the first gemcitabine funding policy was associated with an incremental annualized cost of approximately $Can235 000. Therefore, reducing the risk of central venous access complications with gemcitabine in our elderly patients appears to be achieved at a high cost. A review of the literature revealed that the prevalence of grade II/III phlebitis with vinorelbine is between 10% and 36%, but can be successfully prevented in 76% of patients with cimetidine 200 mg IV prior to the vinorelbine infusion (Rittenberg et al. 1995; Vassilomanolakis et al. 2001). A 3-month duration of gemcitabine therapy is approximately $Can1560 more costly than vinorelbine over a similar duration. Cimetidine 200 mg IV is available at a cost of $Can1.00 per dose. Therefore, the use of vinorelbine + cimetidine as an alternative to gemcitabine in patients at risk of venous access complications could be a cost-saving strategy by avoiding at least part of the incremental annualized cost of $Can235 000. To help contain increasing drug costs, especially since the approval of the most recent funding policy, which removed the restrictions over gemcitabine, CCO oncologists should be encouraged to use cimetidine prophylaxis with vinorelbine as an alternative to gemcitabine in high-risk patients. The higher-cost gemcitabine can be reserved for those patients who develop severe phlebitis despite cimetidine or other serious toxicities from vinorelbine.

There are a number of limitations in the current study that have to be addressed. The analysis relied on the accuracy of the CCO drug use database. However, the extent of data entry errors is unknown. Data for the use of each drug were obtained from an electronic database and detailed patient data (e.g. performance status) were not available. Therefore, there are likely to be other important factors contributing to the rapid uptake of gemcitabine. The economic comparison only included direct drug costs and other relevant expenditures for side-effects management or for the placement of a central venous access device to deliver vinorelbine in high-risk patients was not available. A recent economic analysis suggested that the cost of toxicity with vinorelbine and cisplatin is almost two fold higher than with gemcitabine and cisplatin (Schiller et al. 2004). Therefore, the incremental drug cost of gemcitabine may be overestimated.

In conclusion, drug utilization increases quickly after the introduction of guidelines associated with funding policies for new drugs in NSCLC. The restrictive policies for the use of gemcitabine lead to a modest incremental cost to the CCO drug budget. However, the liberalization of the policy has had a substantial cost impact, in the order of $Can1.6 million. As a result, low-cost strategies such as...
Cimetidine prophylaxis with vinorelbine should be considered to help contain the costs associated with the rapid growth in gemcitabine utilization.

References


