A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and the UK

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Background: Economic information is necessary for rational decision-making in health care. Many European countries require financial impact statements prior to drug approval, and many health care organizations in the USA consider cost-effectiveness when making formulary decisions. We report the findings and discuss the policy implications of an economic evaluation based on an international, randomized controlled trial of salvage therapy for epithelial ovarian cancer, wherein topotecan and pegylated liposomal doxorubicin (PLD) were found to have similar efficacy but differing toxicities.

Patients and methods: Direct costs to the payer were estimated for 235 North American and 239 European trial participants who had relapsed or failed platinum-based therapy. Unit costs were obtained from national sources or previously reported economic analyses. Sensitivity analyses were also performed.

Results: Total cost per person in the topotecan arm was $12,325 (95% CI $9,445 to $15,415; P > 0.05) higher in the USA-based analysis and $2,909 (95% CI $779 to $3,415; P < 0.05) higher in the UK-based analysis than for PLD. Pegylated liposomal doxorubicin was cost saving over a wide range of assumptions. The main differences (per person) in toxicity management following PLD compared with topotecan in Europe were for blood transfusions ($1,190 versus $181, respectively) and hospitalizations ($1,197 versus $280, respectively). In North America, differences were mainly for granulocyte colony stimulating factors ($1,936 versus $419 µg, respectively), erythropoietin ($3,493 versus $308, respectively) and blood transfusions ($1,346 versus $140, respectively).

Conclusions: Policy makers who evaluate pharmacoeconomic studies should consider international differences in health care delivery. Cost assessments based on information obtained from one country may not be relevant for policy makers in a different country.

Key words: cost, economic analysis, ovarian cancer, PLD, topotecan

Introduction

In deciding between therapeutic options for cancer care, consideration is given to effectiveness, toxicity, quality of life and cost [1–5]. In the USA, managed care programs play a large role in the delivery of cancer care, and they expect low cost and effective services [6]. In universal health care systems, the challenge is to adopt new technologies and maintain quality of care while staying within the constraints of fixed health care budgets. Policy makers in both North America and Europe have an increasing need for economic data on new agents. Only recently have organizations such as cooperative clinical trial groups sponsored by the National Cancer Institute (NCI) conducted economic analyses, because of concerns over funding, data manager burden, statistical center support and conflicts of interest [7–9]. In this paper, we evaluate the treatment-related costs of two alternative cancer treatments used in a recent internationally conducted phase III clinical trial.

The clinical trial evaluated an important malignancy, ovarian cancer, which is the most frequent cause of death due to gynecologic malignancy. Women with this cancer generally present with advanced disease, where standard care consists of surgical debulking followed by platinum-based therapy. Up to 30% of patients fail to respond to the paclitaxel and platinum therapy, and up to 75% of patients relapse [10]. Some of these patients are retreated with platinum regimens, but patients...
who do not respond or who relapse in <6 months are less likely to respond to subsequent platinum-based chemotherapy regimens. One of the most common second line agents is topotecan [11, 12]. Topotecan is an effective agent, but like all chemotherapeutic agents, it is not without toxicity, including neutropenia, thrombocytopenia, anemia, and asthenia. Recently, a clinical trial upon which this economic analysis is based showed that the use of liposomal doxorubicin versus topotecan for ovarian cancer patients who had failed platinum-based chemotherapy was associated with similar median time to progression, overall response rates, and mean survival durations, while serious toxicities occurred more frequently with topotecan [13]. The pegylated liposomal formulation of doxorubicin extends the half-life to 55 h and may improve specificity of delivery to tumors, while decreasing absorption by normal tissues and toxicity. However, its use is also associated with toxicity, primarily palmar-plantar erythrodysesthesia (PPE) and stomatitis.

In this study, we report on an assessment of the comparative costs and effects of topotecan versus pegylated liposomal doxorubicin (PLD) and discuss the implications of our findings for policy makers who work in fee-for-service or national health care systems. Our analyses are based on a recently reported clinical trial with 239 patients who were treated in Europe and 235 patients who were treated in North America [13]. This study represents one of the first cost analyses in oncology that accounts for marked international differences in the practice of cancer care.

Patients and methods

Data source

The study sample and clinical results have been described previously [13]. In brief, a total of 474 patients with ovarian cancer were enrolled, all of whom had failed or relapsed after first-line chemotherapy with a platinum-based regimen. The study was a randomized phase III trial with sites in Europe (49% from the UK, with eight other sites contributing <10% each) and North America (93% from the USA). Patients were stratified prospectively for platinum sensitivity and bulky disease. Study drug regimens consisted of either a 1-h intravenous infusion of PLD 50 mg/m² every 28 days, or topotecan 1.5 mg/m²/day as a 30-min infusion for 5 consecutive days every 21 days. The main clinical outcome measures for efficacy were progression-free survival and overall survival. Patients were followed for 1 year, or until death or disease progression.

Structure of the cost model

As the results from the trial indicated that PLD and topotecan had similar clinical efficacy and health-related quality of life results [13], we carried out a cost-minimization analysis based on the trial data, an appropriate method given the findings and equivalence design of the trial [14]. The perspective is that of the payer in both the USA and the UK. There were three main cost categories considered: study drug, drug administration, and management of adverse events.

The dosage of study drug was taken directly from the clinical trial data. Resources estimated in the administration of the study drugs include an ambulatory visit for each dose, pre-medication, and a specialist visit at the beginning of each cycle (UK only). Eight adverse events were evaluated: stomatitis/pharyngitis, PPE, nausea/vomiting, diarrhea, anemia, thrombocytopenia, neutropenia, and sepsis/fever. Other adverse events may also occur when these drugs are administered, but these were chosen because they are known to be associated with the two study drugs and have the potential for substantial health care resource consumption in their management. In the clinical trial, adverse events were recorded each time they occurred, regardless of whether or not other adverse events were coincident. Two approaches were taken to avoid potential double counting. First, when overlapping time periods were indicated for any combination of neutropenia, sepsis or fever, the single event with the most resource-intensive management was selected. In cases where several events were reported in sequential (unbroken) time periods, events were discarded if they would not have allowed enough time to complete the maximum estimated visits or hospital length of stay. Secondly, only one adverse event of each type per dosing cycle was included for each patient. In cases where more than one event of a particular type occurred during a cycle, the one with the greatest severity was selected.

We relied on the clinical trial data for the quantities of resources estimated to have been used in adverse event treatment. For treatments whose use is clearly tied to a particular adverse event, we were able to use the clinical trial data directly. These treatments were platelet transfusions for thrombocytopenia, erythropoietin and blood transfusions for anemia, and colony-stimulating factors for neutropenia. Other drug treatments and ambulatory visits were not collected in a manner that made it possible to calculate their use from the clinical trial data directly, so for these items estimates were obtained from a panel of oncologists from the USA and the UK. Estimates of hospital stays were obtained from the clinical trial database as part of reporting serious adverse events. Since adverse events could have overlapping time periods, a conservative approach for hospitalization counting was used, wherein, for each patient who developed a serious adverse event, only one hospitalization per cycle was assumed to have occurred. To account for potential protocol-induced resource use of hospitalizations, inpatient stay counting was restricted to those associated with serious adverse events of grade 3 and 4. As days of hospital stay were not captured by the trial, estimates of length of stay were used. The weighted average estimate for length of stay (weighted by the frequency of adverse event occurrence in the trial) was a mean of 2.3 days (range 1.6–4.9 days) in the USA and 5.5 days (range 3.5–7.9 days) in the UK.

Cost data

Table 1 shows the costs for individual resources used in the analysis according to the USA and UK sources. For comparability, UK costs are reported in US dollars (conversion rate of $1.4 = £1.0). Costs from the UK perspective come from the British National Formulary [15]. Costs of blood products come from the National Blood Authority, 2000 Tariff, and costs for inpatient stays (medical oncology) come from a national costing database of hospital trusts [16]. The cost of an intensive care unit (ICU) is based on literature from a UK trust that studied patients in ICU [17]. Costs of an outpatient clinic visit and a chemotherapy administration come from tariffs at a UK cancer center and were similar to costs at two other major cancer centers in England.

Costs from the USA perspective were obtained from sources that have been used in our prior studies of costs of cancer care in the USA [5]. Costs of physician services are based on the oncology outpatient Medicare reimbursement protocol, using 2000 Relative Value Units and the Primary Care Conversion Factor. The local Geographical Practice Cost Indices were not included in the calculations to maintain generalizability.
of the data. The resulting average Medicare fees are published by Yaki Technologies [medical diagnosis and procedure coding; www.eICD.com (last accessed 5 July 2001)]. Medication costs are based on 2000 US Average Wholesale Prices as listed in the Red Book [18]. Costs for hospital stay, supplies, laboratory fees and blood products were obtained from hospital fee lists at a major academic center. The hospital applied department-specific costs to charge ratios to compute item-specific costs, which have been published previously [5]. These cost estimates are comparable to those reported by other USA investigators [19].

Analysis

For consistency with the clinical trial reporting, costs of care for the UK-based analysis were estimated assuming that all the patients received care in Europe. Similarly, for the USA-based analysis, costs of care were estimated assuming that all the patients received care in North America. However, as there were marked treatment differences in supportive care between Europe and the USA, specifically with respect to cytokine use, resource use was extrapolated between local settings. For these resources collected from trial data (erythropoietin and colony-stimulating factor dosages, and number of transfusions and hospitalizations), an extrapolation was made from one setting to the other by using ordinary least squares regression models to predict the patient-specific amounts of these items that would have been used if, for example, those in North America had been treated in Europe (and vice-versa). Regressors in the equations included variables indicating the number and type of adverse events experienced, and final models were chosen using backward selection. Because the resulting patient-specific estimates are averages based on the regression parameters, some variation is lost; the impact of this was explored by including only local patients in a sensitivity analysis.

In the trial, 35 patients (7%) were censored (10% in PLD and 6% in topotecan); the timing of the losses was similar in the two groups. As has been done in other evaluations [20] that have small amounts of patient loss with similar timing of loss, we used the follow-up experience of all patients and imputed a zero cost from their time of censoring to the end of follow-up. We further assumed that those who experienced disease progression would have similar clinical and resource use consumption patterns following disease progression, regardless of treatment arm assignment.

Table 1. Estimates of resource cost (in US$)

<table>
<thead>
<tr>
<th>Resource Description</th>
<th>North America</th>
<th>Sensitivity analysis value</th>
<th>Europe</th>
<th>Sensitivity analysis value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegylated liposomal doxorubicin (per mg)</td>
<td>33</td>
<td>NV</td>
<td>29</td>
<td>NV</td>
</tr>
<tr>
<td>Topotecan (per mg)</td>
<td>151</td>
<td>NV</td>
<td>109</td>
<td>NV</td>
</tr>
<tr>
<td>Study drug administration (per dose + pre-meds)</td>
<td>295</td>
<td>136</td>
<td>185</td>
<td>139</td>
</tr>
<tr>
<td>Erythropoietin (per 10000 U)</td>
<td>120</td>
<td>NV</td>
<td>116</td>
<td>NV</td>
</tr>
<tr>
<td>Colony stimulating factors (per 300 µg)</td>
<td>165</td>
<td>NV</td>
<td>108</td>
<td>NV</td>
</tr>
<tr>
<td>Platelets (per unit)</td>
<td>601</td>
<td>NV</td>
<td>223</td>
<td>NV</td>
</tr>
<tr>
<td>Packed red cells (per unit)</td>
<td>79</td>
<td>NV</td>
<td>136</td>
<td>NV</td>
</tr>
<tr>
<td>Blood product administration</td>
<td>310</td>
<td>36</td>
<td>410</td>
<td>206</td>
</tr>
<tr>
<td>Hospital stays (per day)</td>
<td>1000</td>
<td>500</td>
<td>410</td>
<td>206</td>
</tr>
<tr>
<td>Oncologist office visit</td>
<td>140</td>
<td>70</td>
<td>126</td>
<td>63</td>
</tr>
</tbody>
</table>

NV, not varied in sensitivity analysis.

Statistical analysis

Clinical results were based on time-to-event analysis using Kaplan–Meier estimates and Cox regression models. In all cost analyses, to account for the right skewness in cost data, confidence intervals (95%) were calculated based on a normal distribution assumption and checked using the bootstrap method [21–23]. Much of the data in this study are taken directly from the clinical trial; the uncertainty in these trial-based data is reflected in the confidence interval estimates. Sensitivity analyses were performed on parameters where there was residual uncertainty or variability in our estimates, as well as according to geographic location (North America versus Europe). In the first sensitivity analysis, expert opinion and cost-of-care variations were addressed simultaneously. The range of expert opinion estimates was used to reflect uncertainty in parameters from expert opinion (days per hospitalization and outpatient visits). With regard to costs, important variation is seen in the UK, where one standard deviation from the mean reflects a 25% variation from the mean cost for gynecologic hospitalization; a similar pattern was observed for gynecologic chemotherapy administration [16, 24]. Similarly, in the USA substantial variation was found between Medicare fees (payments) and reported institutional costs. Because of this observed variability in costs, we varied the estimated cost of hospitalization, outpatient visits, and blood product and study drug infusions in our sensitivity analyses by using Medicare payments in the USA sensitivity analysis, and 25–50% reductions in the UK sensitivity analysis. A second sensitivity analysis restricted the cost estimates to patients treated only in North America compared with Europe.

Results

Clinical end points

The time to progression was 113 days in the PLD arm and 119 in the topotecan arm [hazard ratio (HR) = 1.176; 90% confidence interval (CI) 1.00–1.38; P = 0.10]. Although overall survival (HR = 1.12; 90% CI 0.92–1.36; P = 0.34) and overall response (19.7% in liposomal doxorubicin and 17% in the topotecan group) rates were similar for PLD- and topo-
tecan-treated patients, platinum-refractory patients had a 12.3% response in the PLD group compared with 6.5% in the topotecan group (\(P >0.05\)). Time and duration of response were a mean of 47 days in the PLD group and 40 days in the topotecan group. Differences were observed with regard to the toxicity profiles of the two agents (Figure 1). Pegylated liposomal doxorubicin patients had fewer episodes of grade 3 or 4 neutropenia (53 compared with 642), anemia (18 compared with 130), thrombocytopenia (three compared with 184) and sepsis (five compared with 23), and more episodes of PPE (62 compared with zero) and stomatitis/pharyngitis (31 compared with two) compared with topotecan.

### Cost analysis

Estimates of resource and costs of care were derived for North America and Europe, and are shown in Tables 2 and 3. While acquisition costs were higher for PLD than for topotecan ($2904 higher in North America and $4095 higher in Europe), differences in administration costs offset the higher acquisition cost. These administration cost differences were due to dosing frequency (every 28 days for liposomal doxorubicin and every 21 days for topotecan) as well as total number of doses per cycle (one for PLD and five for topotecan). Overall, the total cost per person of patients in the topotecan arm was estimated to be $12325 higher in North America and $2909 higher in Europe than those on liposomal doxorubicin (both with \(P <0.05\)). The majority of the cost savings in Europe were due to differences in the management of anemia and thrombocytopenia ($1243 higher in the topotecan arm), especially blood product transfusions and hospitalizations ($917 higher in the topotecan arm). In North America the main differences were management of anemia and thrombocytopenia ($4715 higher in the topotecan arm), especially erythropoietin, and management of neutropenia ($3259 higher in the topotecan arm).

### Resource utilization

Resources used to manage toxicities differed between the topotecan and PLD treatments, and also between locations as

### Table 2. North American cost analysis per person (in US$)

<table>
<thead>
<tr>
<th></th>
<th>Topotecan (T)</th>
<th>Pegylated liposomal doxorubicin (P)</th>
<th>Difference (P – T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study drug</td>
<td>10058</td>
<td>12962</td>
<td>2904</td>
</tr>
<tr>
<td>Administration</td>
<td>8377</td>
<td>1438</td>
<td>–6939</td>
</tr>
<tr>
<td>Total study drug + administration</td>
<td>18435</td>
<td>14 400</td>
<td>–4035</td>
</tr>
<tr>
<td>Stomatitis/pharyngitis</td>
<td>30</td>
<td>101</td>
<td>71</td>
</tr>
<tr>
<td>PPE</td>
<td>0</td>
<td>104</td>
<td>104</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>83</td>
<td>49</td>
<td>–34</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>58</td>
<td>34</td>
<td>–24</td>
</tr>
<tr>
<td>Colony stimulating factors</td>
<td>1936</td>
<td>419</td>
<td>–1517</td>
</tr>
<tr>
<td>Neutropenia office visits and other medication</td>
<td>1820</td>
<td>78</td>
<td>–1742</td>
</tr>
<tr>
<td>Total neutropenia</td>
<td>3756</td>
<td>497</td>
<td>–3259</td>
</tr>
<tr>
<td>Sepsis and fever</td>
<td>111</td>
<td>56</td>
<td>–55</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>3493</td>
<td>308</td>
<td>–3185</td>
</tr>
<tr>
<td>Transfusions</td>
<td>1346</td>
<td>140</td>
<td>–1206</td>
</tr>
<tr>
<td>Anemia and thrombocytopenia office visits and medication</td>
<td>342</td>
<td>18</td>
<td>–342</td>
</tr>
<tr>
<td>Total anemia and thrombocytopenia</td>
<td>5181</td>
<td>466</td>
<td>–4715</td>
</tr>
<tr>
<td>Hospital stays</td>
<td>566</td>
<td>188</td>
<td>–378</td>
</tr>
<tr>
<td>Total cost</td>
<td>28220</td>
<td>15895</td>
<td>–12325</td>
</tr>
<tr>
<td>95% CI on total cost</td>
<td>25 750 to 30 974</td>
<td>14 515 to 17 306</td>
<td>–9445 to –15 415</td>
</tr>
</tbody>
</table>

CI, confidence interval.
shown in Table 4. Among patients treated in North America, the toxicity management differences were associated with fewer cycles of granulocyte colony stimulating factor (762 µg compared with 3520 µg per person, respectively; \(P<0.05\)), erythropoietin (25670 U compared with 291091 U per person, respectively; \(P<0.05\)), red blood cell transfusions (0.26 U compared with 1.56 U per person, respectively; \(P<0.05\)) and office visits (4.6 compared with 12.7 visits per person, respectively; \(P<0.05\)). In Europe, the main differences in resources used for toxicity management following cycles of topotecan compared with PLD were for red blood cell transfusions (0.65 U compared with 4.15 U per person, respectively; \(P<0.05\)) and hospitalizations (0.12 compared with 0.53 stays per person, respectively; \(P<0.05\)).

Sensitivity analyses

Given the finding that PLD was less costly, a sensitivity analysis was performed such that assumptions were made in favor of topotecan (extreme analysis). This sensitivity analysis explores the ‘best case scenario’ for topotecan in order to examine the robustness of our main finding. In this analysis, the number of days per hospitalization is the minimum estim-
ate from the experts (1.6 days for the USA and 3.5 days for the UK). This favors the topotecan group, because there were three times as many hospitalizations in the topotecan group (87 topotecan hospital stays versus 28 for PLD). Likewise, the minimum number of outpatient visits estimated to be required for each level of adverse event was used. This favors the topotecan group, because using the minimum outpatient visit estimate yields 300 fewer net visits in the topotecan group in North America, and 234 fewer net visits in the topotecan group in Europe. Furthermore, the estimated cost of hospitalization, study drug infusion, blood product infusion and outpatient visits for adverse event treatment was decreased, as shown in Table 1. An analysis restricted to local patients (no extrapolation using regressions) was also done. Figure 2 shows the result of the sensitivity analysis for North America and Europe, displayed as a cumulative probability distribution of the cost difference (PLD minus topotecan) obtained by performing 1000 bootstrap replicates. In the North American sensitivity analyses, PLD is cost saving under all scenarios. In the European sensitivity analysis favoring topotecan, 93% of the replicates show PLD as cost saving; in the analysis restricted to local patients, 89% of the replicates show PLD as cost saving. These graphs indicate that in the analysis restricted to European patients, the cost saving decreases slightly, but increases when restricted to North American patients. This may be due in part to the increased proportion of patients with severe (grade 3 or 4) adverse events in North America compared with Europe for anemia (53 out of 235 and 32 out of 239 in North America and Europe, respectively), neutropenia (125 out of 239 and 84 out of 239, respectively) and thrombocytopenia (61 out of 235 and 22 out of 239, respectively).

**Discussion**

With increasing international concern over health care costs, clinical trials will need to provide information on costs, survival and quality of life [1]. In this clinical trial of second-line ovarian cancer treatments, PLD in comparison to topotecan was associated with similar clinical outcomes, different toxicity profiles, and higher acquisition costs, but lower toxicity management cost, leading to lower overall costs of care. Hematologic adverse events, noted more frequently with topotecan, were relatively expensive to treat. Adverse events of PLD, primarily stomatitis and PPE, were relatively less costly. The economic implications of these findings varied between the USA and Europe. Overall, care for women who received PLD was associated with $12,235 less cost than treatment with topotecan in a USA-based model and $2,909 less cost in a UK-based analysis.

The USA-based cost estimates for topotecan are higher than those reported in one prior cost-effectiveness study [5]. In both studies, USA estimates of costs of study drug and administration were about $14,000. USA toxicity costs in the model derived from this clinical trial were $9,277, while the prior results, based entirely on a modeling effort for USA patients, were $5,070. In both studies, the estimated rates of grade 3 or 4 neutropenia, thrombocytopenia and anemia were similar. Most of the estimated difference in toxicity costs was related to use of erythropoietin for the treatment of anemia during the phase III clinical trial (estimated cost of $3,493 per topotecan-treated patient) compared with no use of this cytokine in the literature-based model. It is interesting to note that the empirical finding during the clinical trial of the frequent use of erythropoietin as supportive care in the USA, but not in the UK, mirrors the results obtained from an international survey of oncologists [25]. Prior cost studies for PLD have been reported only for Kaposi’s sarcoma in the USA, where PLD was shown to be more cost-effective than liposomal daunorubicin [26]. No previous studies have reported on economic assessments of either drug from a European perspective.

While the NCI-sponsored cooperative clinical trials groups in the USA have formed task forces to evaluate the feasibility
The study reported herein uses a retrospective methodology that has been evaluated in three previous NCI-sponsored cooperative group clinical trials, and the previous international study with GM-CSF [7–9, 27]. The study methods are based upon recommendations from economists who have reported on the basic principles of pharmacoeconomic studies, primarily basing the retrospective modeling effort on costs and resource profiles that were derived for patients in the clinical trial [2, 28]. The clinical trials database was obtained directly from the sponsoring pharmaceutical company who developed the data for submission to the licensing authorities in Europe and the USA, thus minimizing data collection costs as well as data manager burden. The analyses were completed by teams of health policy experts from the USA and the UK, coordinating the economic study analysis with clinical trial investigators in both countries, and developing a multinational, multidisciplinary team. This approach allowed for efficient collaborations among an international team of economists, research analysts and clinical investigators.

The study results have important implications for policy makers in Europe and the USA. In Europe, countries that require an economic impact statement before deciding upon reimbursement policies for new drugs may base these decisions in a large part on the information that is included in the European cost model. In contrast, in the USA, many managed care organizations use economic analyses when they make formulary decisions. International differences in the policy implications of first-line treatments for ovarian cancer have also been reported. In economic models based on a phase III clinical trial conducted by the Gynecologic Oncology Group (GOG 111), paclitaxel and cisplatin compared with cyclophosphamide and cisplatin had an incremental cost-effectiveness of $21222 in the USA compared with $23617 in Canada [3, 4]. Paclitaxel use was viewed as cost-effective in a fee-for-service health care system, but not in a national health care system where the budgetary impact of the treatment on overall cancer costs would be very large [29].

The limitations of our study should be noted. First, expert opinion was used to supplement the data from the clinical trial, because complete economic data were not collected during the trial. Using expert opinion data instead of patient-level data can lead to underestimates of variability. However, >83% of the costs in the analysis are from data collected within the trial, and the remainder are based on actual events recorded within the trial, minimizing the potential bias. Furthermore, conservative methods of counting adverse events and hospitalizations were used to avoid double counting of events, and we investigated the impact of expert opinion ranges through sensitivity analysis.

Secondly, while the trial used the approved doses, lower doses may be used in practice. Lower doses may lead to a decreased frequency or severity of adverse events for either or both agents, thus potentially changing the relative costs of adverse event treatment. What effect this lowering of dose would have on efficacy or on the incremental cost difference is unknown, however.

Thirdly, the cost analyses were based on an assumption that all patients received care in either the USA (the ‘USA-based analysis’) or the UK (the ‘UK-based analysis’). As has been discussed by others, there is a difficulty when using data from international clinical trials in economic evaluations, because of the inherent trade-off between locally relevant data and the precision that is derived from using the complete dataset [30]. We have attempted to reflect both sides of this issue by showing sensitivity analyses for local patients. These local analyses indicate that when the economic model was limited to only the 235 patients in North America or 239 patients in Europe, clinical outcomes and cost savings were similar to our primary model. While in all sensitivity analyses, PLD remained the less costly treatment option, the magnitude of the estimated cost savings varied. Because the local UK analysis has patients from several European countries, it also has limitations. However, given the small numbers that arise upon breaking the data down by individual country in Europe, and the similarities in European health care delivery (and the common differences from the USA style of health care), aggregation of the European patient population was felt to be a reasonable alternative to a country-by-country analysis.

Finally, the framework of this study was a cost-minimization analysis and did not include indirect costs, such as out-of-pocket costs to the patient or costs for loss of productivity. It has recently been shown that among women with ovarian cancer, the total costs of chemotherapy-related neutropenia and thrombocytopenia were $11830 and $7550, with indirect costs accounting for 43% and 57% of the total costs of toxicity, respectively [31].

**Conclusion**

This study represents one of the first international collaborations in the design and analysis of economic assessments of a new cancer pharmaceutical. We have shown that the setting may be an important consideration in economic analyses of cancer care, and that cost assessments based on information obtained from one country may not be relevant for policy makers in a different country. Policy makers who evaluate
pharmacoeconomic studies should consider international differences in health care delivery.

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References