Is Paclitaxel and Cisplatin a Cost-Effective First-Line Therapy for Advanced Ovarian Carcinoma?

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BACKGROUND. Paclitaxel and cisplatin use for the treatment of advanced ovarian carcinoma (AOC) has been shown to increase median survival duration. An evaluation was performed on the economic consequences of treating AOC patients with combined paclitaxel and cisplatin chemotherapy compared with current usual care, i.e., combined cyclophosphamide and cisplatin chemotherapy.

METHODS. Linear modeling techniques combined with retrospective chart analysis were used to predict the clinical progression and treatment of AOC patients until death. Cost-effectiveness analysis comparing paclitaxel and cisplatin and usual care was performed from a simplified Ministry of Health perspective.

RESULTS. Assuming a 50% increase in survival for paclitaxel and cisplatin patients, an assumption supported by recent clinical trial data, this treatment showed an average lifetime cost per patient of $50,054 Cdn compared with a cost of $36,837 Cdn for usual care. The incremental cost of the paclitaxel and cisplatin treatment over the usual treatment was $20,355 Cdn per life year gained. These results withstood extensive sensitivity analyses.

CONCLUSIONS. Paclitaxel, in combination with cisplatin, appears to be a cost-effective first-line treatment for AOC. A moderate increase in incremental cost compares favorably with other life-saving strategies currently in use. As more data become available for the use of paclitaxel, this pilot study will provide a basis for more extensive economic evaluation of paclitaxel. ***Cancer* 1996; 77:2086–91.**

KEYWORDS: advanced ovarian carcinoma, cisplatin, cyclophosphamide, paclitaxel, chemotherapy, economic analysis, cost-effectiveness.

According to statistics from the National Cancer Institute (NCI) of Canada there were an estimated 2200 new cases of ovarian cancer in Canada in 1995 of which 1,350 will result in death. Overall Canadian incidence is 11.9 per 100,000, with a death rate of 7.7 per 100,000.[1] As with other cancers, the cost of care is expected to increase with the progression of the disease.[2] The average cost of care is expected to be high as 70 to 85% of newly diagnosed ovarian carcinoma, are in advanced stages.[3,4] Previously, usual treatment for advanced ovarian cancer (AOC) included a cyclophosphamide and cisplatin regimen following debulking surgery.[5,6] Recent results from the Gynecologic Oncology Group study 111 (GOG-111) indicated that the use of paclitaxel and cisplatin increases median survival from 24.4 to 37.5 months (54%)[7] over usual care in the treatment of AOC.[8,9]

Although paclitaxel has shown significant promise in the treatment of AOC, its cost may have a negative effect on decisions concerning its inclusion in treatment regimens. In Canada, there has been no examination to date of resource utilization or cost implications of treating AOC. Therefore, the objectives of this study were to describe the cost-of-care

structure for previous usual care of AOC in Canada and to compare the economic outcomes of usual care with paclitaxel and cisplatin chemotherapy.

METHODS

An evaluation based on simple linear modelling techniques was performed to assess the cost and survival structures of AOC in Canada and to allow comparison of the cost-effectiveness of usual care and paclitaxel and cisplatin (PC). Modelling was chosen because at the time of this study PC treatment was infrequently used in Canada except in clinical trials and insufficient primary data was available. The model was structured on the resource utilization patterns of usual care based on retrospective data collection from patient charts. The most previously widely accepted first-line therapy for AOC following debulking surgery is a combination of cyclophosphamide and cisplatin (CC) and this constituted usual care for this study.

Criteria for inclusion of patient chart data comprised: (1) diagnosis of Stage IIIC or IV AOC between 1988 and 1992; (2) minimum follow-up of 3 years after initial diagnosis and; (3) first-line chemotherapeutic treatment taking place at the Toronto-Sunnybrook Regional Cancer Center where this study was performed. Patients were excluded if they had any major comorbidities at time of diagnosis, if they were lost to follow-up within the 3-year period for any reason but death, or if they had participated in a clinical trial for initial chemotherapeutic treatment of AOC.

Four distinct treatment and disease progression phases were established as the basis for allocation of resource utilization and cost data for the purpose of economic evaluation. First, the initial treatment phase began with the first consultation following debulking surgery and lasted until the end of the initial course of chemotherapy. Initial surgery was not included in this phase. If treatment was modified due to toxicity, the patient was maintained in initial treatment. However, if modification occurred because of nonresponse or progression, then the patient was moved to the next treatment (relapse) phase.

Second, the follow-up phase followed any course of treatment (usually chemotherapy) and no aggressive treatment (chemotherapy or surgery) occurred. The patient was seen on a routine basis only for clinical monitoring purposes.

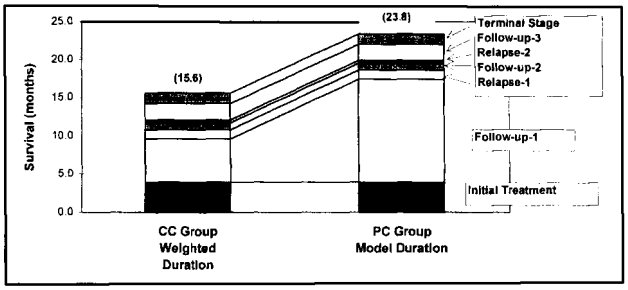
Third, the relapse phase started when a new therapeutic regimen was instituted due to clinical relapse. It may not have coincided precisely with clinical relapse. When no modification of treatment was instituted despite a clinical relapse, the patient remained in follow-up. More than one relapse was experienced by some of the patients.

Fourth, the terminal stage began the day after the final course of chemotherapy and continued until death. It measured the costs of palliative care.

The following assumptions were made in building the model. Specific practices derive either from those used in the GOG-111 study[9] or from recommended practice in Ontario at the time of the study.[10] (1) A 50% increase in average duration of survival time is achieved by PC treated patients. (2) The entire 50% increase in patient survival time occurs during the first follow-up phase after initial chemotherapy and all enhancement of survival is attributable to the treatment regimen. (3) Frequency of resource utilization other than initial chemotherapy is equivalent for all phases of both treatment regimens. (4) Paclitaxel is administered as a 3-hour infusion at a dose of 135 mg/m^2 body surface area (210 mg per cycle for a "standard" patient). (5) The proportion of in-patient chemotherapy is the same in each cohort (at the time of the study this was 25% of all cycles). (6) The PC regimen includes 5.5 cycles of chemotherapy during initial treatment and 5.4 cycles during the CC regimen. (7) The overhead cost of paclitaxel is a constant percentage of the acquisition cost in the pharmacy department of the center.

From primary data each patient's course of illness was broken down into these defined phases. Because all of the patients experienced one initial treatment and one terminal phase, but the number of follow-up and relapse phases varied, standard weighted days were calculated for each treatment phase of the model. Phase durations calculated for the CC group were used to estimate survival and phase intervals for the PC group. Fifty percent of the average survival of patients on the CC regimen was added to the weighted duration for the follow-up-1 phase to determine an average follow-up-1 phase for the PC regimen. For those patients with more than three relapses, all phases after the third follow-up were amalgamated and the data was incorporated into the follow-up-3 phase.

Clinical, economic, and sociodemographic data was recorded in standardized data collection forms. Hospitalization data included number of days of hospitalization in any hospital and transfers between departments at the center. All in-patient and out-patient data was recorded separately. Number and type of all medical consultations, medical procedures, laboratory tests, and drugs were recorded. Since the vast majority of care for AOC patients is provided by oncology departments, data collection was limited to hospital- and cancer clinic-based care at the center and days of hospitalization in any other hospital. This same data was also collected from the charts of four patients who had received PC treatment at the center. This data was not complete since all four patients were



CC= cyclophosphamide/cisplatin treatment regimen
PC= paclitaxel/cisplatin treatment regimen

FIGURE 1. Survival structure comparison of treatments for Advanced Ovarian Cancer with PC (model) and CC (treatment group).

still living, but was intended for comparison purposes with data obtained from the model for PC treatment.

A simplified Ontario Ministry of Health (MOH) perspective using only hospital-based in- and out-patient care was used, assuming that all other direct health care resource utilization will be comparable for both treatment groups. Costs were obtained from the Ontario Schedule of Benefits for information on physicians' fees for both in-patient and out-patient consultations and procedures, and from the Case Cost System of the Sunnybrook Center for the cost of nursing care, laboratory tests, procedures, and drugs. Standard daily costs for each phase of the model were calculated using resource utilization and cost data collected for usual care. All costs are presented in 1993 Cdn dollars. Discounting of future costs was not considered necessary due to the short survival time being assessed.

The robustness of these results was tested through a series of sensitivity analyses performed on the model for survival durations of +25% and +75%, for variations in hospital costs and drug consumption (±20% of mean cost) and for alternative chemotherapy procedures.

RESULTS

Findings presented in the tables are based on linear modelling of the consequences of PC treatment and retrospective chart analysis for the CC group (n = 18). In Figure 1, a comparison of survival structure for PC and CC treatment regimens is presented graphically to illustrate the duration of each phase of AOC in usual care and to highlight the two basic assumptions set out in the model for PC treatment, i.e., 50% augmentation of survival and prolongation of the first follow-up phase.

Health care utilization costs per patient are presented in Table 1 by medical resources consumed and by treatment phase. Total average lifetime cost per patient was $50,054 Cdn for PC treatment and $36,837 Cdn for CC treatment. As a consequence of the model, with the exception of the initial treatment and follow-up-1 phases, costs were identical for both treatment groups. During initial treatment phase, the significant difference in cost was attributable to the acquisition cost difference between paclitaxel and cyclophosphamide (a "drug effect") and during follow-up 1 to the augmented survival duration (a "duration effect").

TABLE 1
Lifetime Health Care Utilization Costs Hospital Inpatient and Outpatient Services (1993 $ Cdn per patient)

	PC group (model) Average cost	CC group (n = 18) Average cost
By medical resource		
Hospitalization (per diem)	27,617	25,454
Consultations (physician fees)	2,108	1,847
Procedures (hospital costs)	1,287	1,157
Procedures (physician fees)	1,840	1,566
Laboratory tests (hospital costs)	1,946	1,754
Drugs (hospital costs)	15,256	5,061
Chemotherapy	12,539	2,531
Other drugs	2,717	2,530
Total	**50,054**	**36,837**
By treatment phase		
Initial treatment	18,455	8,447
Follow-up 1	5,551	2,342
Relapse 1	5,642	5,642
Follow-up 2	2,298	2,298
Relapse 2	2,337	2,337
Follow-up 3G[a]	3,633	3,633
Terminal stage	12,139	12,139
Total	**50,054**	**36,837**

PC = paclitaxel/cisplatin treatment regimen; CC = cyclophosphamide/cisplatin treatment regimen.

The total average cost per patient for CC treatment was $36,837 Cdn. More than half of this expenditure occurs in the initial treatment and terminal stage phases. The main cost driver in the CC cohort was cost of hospitalization (69% of total average cost). The cost of drugs had the next greatest influence on costs (13.7%) and was evenly split between chemotherapeutic agents and others.

A total average lifetime cost of $50,054 Cdn per PC patient treated was derived from the model, 60% of which was incurred in the initial treatment and terminal stage phases. Again, hospitalization was the predominant cost driver, accounting for 55.2% of the total average cost, while the cost of drugs was the second largest variable (30.5%). In this case however, greater than 80% of the drug cost was attributable to the cost of paclitaxel.

When costs derived from patient chart review for four PC patients undergoing initial treatment (data not shown) were compared to those predicted by the PC model, the results are approximately 25% less in the model. This difference arose mainly because two of the four PC patients underwent interval debulking surgery while no one

TABLE 2
Incremental Analysis of Cost Per Life Year Gained Comparing CC Treatment Group and PC Model (+50% Survival)

	CC group (n = 18)	PC group (model)	Increment (PC-CC)
Average cost ($ Cdn)	36,837	50,054	13,217
Duration effect			3,209
Drug effect			10,008
Survival months	15.6	23.4	7.8
Cost/year of life gained (1993 $Cdn) per life year)			20,355

CC = cyclophosphamide/cisplatin treatment regimen; PC = paclitaxel/cisplatin treatment regimen.

TABLE 3
Sensitivity Analyses for the PC Model (1993 $ Cdn Per Life Year)

	Incremental cost per life year (PC-CC) Range of survivals		
	(+25%)	(−50%)	(+75%)
Basic assumptions	36,000	20,355	15,000
No duration effect	31,000	15,413	10,000
Survival divided over all follow-ups	42,000	26,765	22,000
Paclitaxel 24-hour infusion	46,000	25,317	19,000
−20% on cost of drugs	30,000	17,215	13,000
+20% on cost of drugs	42,000	23,495	17,000
−20% on cost of per diem	35,000	19,689	15,000
+20% on cost of per diem	37,000	21,022	16,000
No overhead on paclitaxel	28,000	16,271	13,000

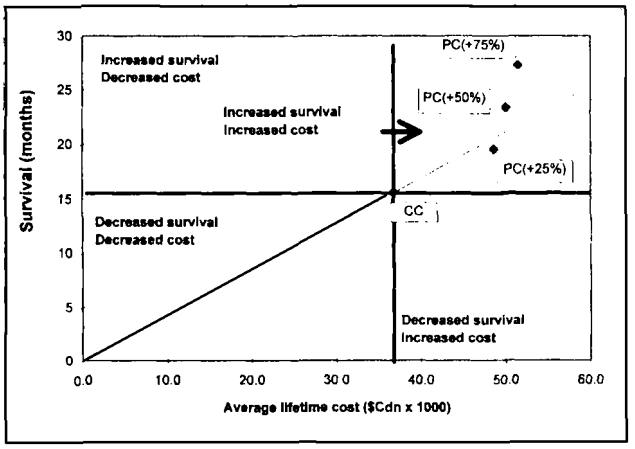
PC = paclitaxel/cisplatin treatment regimen; CC = cyclophosphamide/cisplatin treatment regimen.

in the CC cohort did. When the cost of this nonchemotherapy-related hospitalization is excluded, the average total cost of initial treatment for these 4 patients was $19,859 Cdn, compared with the $18,455 Cdn generated by the model.

The increment in cost (Table 2) between the 2 treatment groups is plus $13,217 Cdn for PC treatment. This was due in part to a longer follow-up-1 phase while keeping constant the frequency of resource utilization per day. The cost attributable solely to this "duration effect" is $3,209 Cdn. The higher cost of paclitaxel chemotherapy during initial treatment phase (the "drug effect") was responsible for the remaining difference in cost of $10,008 Cdn. Overall weighted survival was 7.8 months longer for the PC cohort. The incremental cost-effectiveness ratio was $20,355 Cdn per life year gained.

The robustness of these findings was tested by several sensitivity analyses and the results expressed as incremental cost per life year gained are shown in Table 3.

To examine the effect of survival on average and incremental cost of PC treatment, prolongation of duration of survival was examined at 25% and 75%. Results show the incremental cost-effectiveness ratio decreases as duration of survival increases with treatment. The average cost of treatment (Fig. 2) increases moderately as survival increases ($48,500 Cdn to $51,400 Cdn as survival increases from 25% to 75%) while there is a significant drop in the incremental cost per life year gained as survival increases ($36,000 Cdn for 25% vs. $15,000 Cdn for 75%).



CC= cyclophosphamide/cisplatin treatment regimen
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FIGURE 2. Average lifetime cost as a function of total survival time.

To remain conservative, the primary analysis was done with the same daily standard cost in both groups. For the PC, regimen this was reflected by an increase in cost of care in the initial follow-up phase. The data was analyzed without additional cost for this prolongation period and the cost per life year gained was $15,413 Cdn.

To estimate the consequence of the increase in survival occurring throughout the follow-up phases and not just in the first, the 50% increase was proportionately distributed to all 3 periods according to their weighted duration. In this case, the cost per life year gained was $26,765 Cdn for 50% increased survival.

The one study which demonstrated prolongation of median survival used a 24-hour infusion of paclitaxel, rather than the 3-hour infusion assumed in the model. To account for a higher incidence of neutropenia a conservative estimate of a 10% increase in hospitalization was made. When this possible scenario was evaluated, the cost per life year gained was $25,317 Cdn for the +50% survival assumption.

The main cost drivers (hospitalization and drugs) were varied by ±20%. This range was applied to reflect regional and temporal variations in resource utilization and costs. Results obtained ranged from $17,215 Cdn to $23,495 Cdn per life year gained.

Overhead costs for administration of both chemo-

therapy treatments were applied by the hospital as a percentage of the acquisition cost of the drug. This made overhead cost significantly higher for paclitaxel due to its greater acquisition cost. This overhead element was removed to test for possible distortion. The cost per life year gained (+50% survival) was $16,271 Cdn.

When the 50% increased survival assumption was considered, incremental costs ranged from $15,413 Cdn to $26,765 Cdn over the range of sensitivity analyses.

DISCUSSION

This study was implemented to evaluate the cost of care following debulking surgery for AOC in Canada and to assess the cost-effectiveness of PC treatment compared with usual care. Results indicate that total cost of care exclusive of surgery for usual treatment of AOC in Canada is $36,837 Cdn and that the main cost drivers are hospitalization and drugs.

Comparing CC and PC treatments, increased length of survival (the "duration effect") and greater drug-related costs of paclitaxel (the "drug effect") are the principal differences seen between treatment regimens. The cost of paclitaxel and its related overhead charges account for the greater cost of the PC regimen in the initial treatment phase. Enhanced survival or the "duration effect" accounts for the difference in follow-up-1.

Incremental analysis of cost-effectiveness showed an increase of $20,355 Cdn per year gained for PC compared with CC treatment, with a range of $15,413 Cdn to $26,765 per year gained for the +50% survival hypothesis after several sensitivity analyses.

The limitations of this study should be considered. Primary data was collected from a small number of CC patients. However, results reflect a cost structure which is consistent with published information for other types of advanced cancer. In a study on breast cancer, Richards et al. indicated that hospitalization accounted for 56% of total costs, cytotoxic drugs for 9%, laboratory and radiologic investigations for 13%.[2] Substantiation of results generated by the model was also obtained from the primary data from four patients in early phases of PC treatment.

The cost of initial debulking surgery was not included in this study. This would have the effect of lowering the total cost of care for AOC treatment but should not have any effect on treatment comparisons since all AOC patients receive this initial surgery.

Patterns of treatment are continually changing and this may have an impact on the cost of care for both treatment regimens. This would not, however, significantly affect cost-effectiveness analysis since the model assumed the same intensity of resource utilization for both groups.

To ensure the confidentiality of financial information obtained from the center, only total costs are reported here and not units of resource utilization. Thus, the external validity of this study extends primarily to the Canadian health care setting and should be reconsidered in situations where hospital accounting or practice patterns differ significantly.

Despite these limitations, this pilot study was based on primary data from naturalistic medical practices and on very conservative model hypotheses. Bias was always in favor of usual care where assumptions were made. It shows robust results which prevail under extensive and multiple sensitivity analyses.

The significance of differences in average costs for PC and CC treatment regimens may be examined graphically in Figure 2. By comparing average survival to average lifetime costs we have a basis of comparison for similar treatments and may work towards optimal treatment strategies. Any point on a line extrapolated from no survival, no cost (0,0) through a point representing usual care (CC) theoretically will have an equal cost-effectiveness ratio. With the CC or usual care point as a central co-ordinate, similar treatments may be compared. Those which fall on points above the line exhibit a lower cost-effectiveness ratio, i.e., are more cost-effective than usual care, those below the line a higher one, i.e., are less cost-effective. In evaluating new treatments, the points where they fall on this coordinate scale are important. Most desirable are treatments which fall into the upper left quadrant, but these are truly exceptional. Most new therapies are found in the upper right quadrant. These enhance survival (in this case) or other desirable effects but at an increased cost of treatment. For consideration as first-line treatment for AOC, PC treatment should demonstrate greater efficacy and a comparable or better cost-effectiveness ratio than usual treatment. This study was initially established on the assumption that there would be a longer survival time following initial treatment for those patients receiving paclitaxel and cisplatin, based on results from the GOG-111. Results suggest that not only does it represent a significantly better first-line treatment for AOC compared with usual care, but it exhibits a better cost-effectiveness ratio as well.

The incremental cost of any treatment provides decision-makers with a tool to optimize resource allocation within a health care system with limited resources. It provides a common denominator, i.e., cost per life years gained, by which cross-comparison of nonsimilar treatments can be made.

Tengs et al.[11] have compared 500 life-saving interventions and their incremental cost-effectiveness. Among these, the cost of postsurgical chemotherapy for premenopausal women with breast cancer is estimated to be $18,000 US per life year gained, or $22,000 US per life year gained for women age 60 years. Bone marrow

transplantation for breast cancer patients would add 1 life year at an approximate cost of $129,000 US. The use of beta-blockers for low risk myocardial infarct survivors was estimated to cost $16,897 US per life year gained; lovastatin treatment for males with heart disease between the age of 55 and 64 years $19,989 US; coronary artery bypass graft surgery (vs. medical management) up to $75,000 US depending on the number of vessels involved; heart transplantation for patients age 50 years with terminal disease, $104,226 US. Another study based on modelling of long term effects of zidovudine, found that low dose therapy for asymptomatic HIV infection had a cost per life year gained of between $6,553 US and $70,526 US depending on which epidemiologic model was used.[12] These figures are for treatment in the US and are expressed in US dollars. While not directly comparable, they are indicative of an acceptable cost to society of many life-saving medical strategies. Although patterns of practice are slightly different in Canada, an incremental cost of $20,355 Cdn per life year gained, which this study projects for the treatment of AOC patients with paclitaxel and cisplatin, compares favorably with these strategies.

Thus, from the perspective of the decision-makers, the incremental cost of treating AOC patients with a PC combination is in line with those for several other life-saving medical interventions currently in use.

Future work in this area should concentrate on gathering more extensive primary data on both costs and outcomes for larger samples of patients which could be developed into a more sophisticated economic model. However, the results of such studies are unlikely to lead to substantially different conclusions from those presented here since the magnitude of hospitalization cost and the significant impact of PC treatment on patient survival are the primary variables affecting cost-effectiveness of the PC regimen.

The methodology of this study has a much broader applicability.[13] As expensive new medical and pharmacologic interventions are developed, techniques are needed to assess their value and justify their adoption by decision-makers such as the MOH. When insufficient data is available or sample size is small, a model such as the one developed for this study using primary resource utilization data derived from the comparator can serve as a valuable tool for initial economic assessment of health care interventions.

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