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Cost–utility analysis for platinum-sensitive recurrent ovarian cancer therapy in South Korea: results of the polyethylene glycolated liposomal doxorubicin/carboplatin sequencing model

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Objective: We performed a cost–utility analysis to assess the cost-effectiveness of a chemotherapy sequence including a combination of polyethylene glycolated liposomal doxorubicin (PLD)/carboplatin versus paclitaxel/carboplatin as a second-line treatment in women with platinum-sensitive ovarian cancer.

Methods: A Markov model was constructed with a 10-year time horizon. The treatment sequence consisted of first- to sixth-line chemotherapies and best supportive care (BSC) before death. Cycle length, a time interval for efficacy evaluation of chemotherapy, was 9 weeks. The model consisted of four health states: responsive, progressive, clinical remission, and death. At any given time, a patient may have remained on a current therapy or made a transition to the next therapy or death. Median time to progressions and overall survivals data were obtained through a systematic literature review and were pooled using a meta-analytical approach. If unavailable, this was elicited from an expert panel (eg, BSC). These outcomes were converted to transition probabilities using an appropriate formula. Direct costs included drug-acquisition costs for chemotherapies, premedication, adverse-event treatment and monitoring, efficacy evaluation, BSC, drug administration, and follow-up tests during remission. Indirect costs were transportation expenses. Utilities were also derived from the literature. Costs and utilities were discounted at an annual rate of 5% per cycle.

Results: PLD/carboplatin combination as the second line in the sequence is more effective and costly than paclitaxel/carboplatin combination, showing an additional US$21,658 per quality-adjusted life years. This result was robust in a deterministic sensitivity analysis except when median time to progression of second-line therapies and administration cost of PLD/carboplatin per administration cycle were varied. The probability of cost-effectiveness for PLD/carboplatin combination was 49.4% at a willingness to pay $20,000.

Conclusion: A PLD/carboplatin combination is an economically valuable option as second-line chemotherapy for the treatment of platinum-sensitive ovarian cancer in South Korea.

Keywords: cost, utility, Markov modeling, ovarian cancer, chemotherapy

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Introduction

Ovarian cancer is the third-commonest type of cancer of the female reproductive system, after breast cancer and cervical cancer in Korea. It has a high mortality and a low 5-year survival rate (around 30%).[1]

Epithelial ovarian cancer is often diagnosed at advanced stages or misdiagnosed as other diseases, because patients don't show specific symptoms until the illness

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progresses to advanced stages, at which point the response to surgery and chemotherapy is poor.[2,3]

The European Society of Medical Oncology[4] and Korean practice guidelines for ovarian cancer[5] recommend performing a primary optimal debulking surgery first, before the start of chemotherapy. Taxane/platinum (especially carboplatin) is recommended as a first-line chemotherapy, with dosing frequency varying depending on the stage of the cancer. In the case of recurrence after first-line chemotherapy, a different strategy should be applied depending on whether the recurrence occurs within 6 months since the first-line therapy. Patients who relapse within 6 months, ie, "platinum-resistant" patients change to another chemotherapy option, while patients who relapse after 6 months since the first-line therapy, ie, "platinum-sensitive" patients, receive the platinum-based therapy once more.[5,6]

Korean practice guidelines for ovarian cancer recommend topotecan, gemcitabine, vinorelbine, and liposomal doxorubicin as the second-line therapy for platinum-resistant patients, and topotecan is used dominantly among these drugs. For platinum-sensitive patients who relapse after 6 months, paclitaxel/carboplatin, the same chemotherapy as the first-line therapy, is administered as the second-line therapy.

The active ingredient of polyethylene glycolated liposomal doxorubicin (PLD) is PLD hydrochloride, which passes through the target cell and suppresses ligation of a nucleotide strand, DNA replication, and ultimately protein synthesis. It results in an altered kinetic profile, extending the half-life to 74 hours. In addition, it increases the efficacy and decreases many of the side effects by improving the specificity of delivery to the tumors, reducing absorption by normal tissues, compared to doxorubicin.[7]

PLD can be used for both platinum-resistant and platinum-sensitive patients.[8] It was proven in a head-to-head randomized controlled trial (RCT) that PLD was equal in efficacy and superior in safety profile to topotecan in platinum-resistant patients.[9] In addition, PLD/carboplatin also showed superior efficacy as the second-line therapy in platinum-sensitive patients, extending progression-free survival (PFS) 2 months longer than paclitaxel/carboplatin, which was statistically significant in a head-to-head RCT (hazard ratio 0.821, 95% confidence interval 0.72–0.94; $P = 0.005$) (CALYPSO study).[10]

Based on the clinical trial that proved parity of clinical efficacy of PLD with topotecan, cost-minimization analyses for platinum-resistant patients have been performed in many countries, such as Spain, Italy, the US, and the UK, showing that PLD can save costs compared to topotecan.[11,12] To date, however, there has been no study that has evaluated the cost-effectiveness of PLD for platinum-sensitive patients. Thus, we developed a sequence model for an economic evaluation of PLD/carboplatin as second-line therapy, in which the treatment protocol of ovarian cancer in the real world was reflected, and explored the long-term clinical and economic impact of PLD/carboplatin in platinum-sensitive recurrent ovarian cancer patients. This study is the first, both internationally and domestically, to evaluate the cost-effectiveness of treatment sequences in women with recurrent ovarian cancer.[13]

Methods

Model structure

A Markov cohort simulation model was developed using a Microsoft Excel spreadsheet to estimate the costs and health outcomes in terms of life years gained (LYGs) and quality adjusted life years (QALYs) for the full range of relevant treatment strategies. The model consisted of four health states, ie, response and progress to each separate line of therapy, clinical remission, and death, so that the two cohorts of identical patients receiving a series of six different chemotherapies and best supportive care (BSC) could be compared (Figure 1, Table 1). BSC means palliative therapy without active treatment, due to treatment toxicity, patient frailty, or lack of benefit.

There is a need to define a confoundable term beforehand. Generally, chemotherapy for cancer treatment is administered at intervals of 3 or 4 weeks, which is termed a "cycle." In the absence of unacceptable toxicity or disease progression, patients are supposed to receive a total of six cycles of chemotherapy and then enter the withdrawal period, which is considered "clinical remission" in this model (Figure 1). On the other hand, the length of time during which a patient can move to another health state in the model is also called a cycle in the field of modeling of economic analysis. This cycle

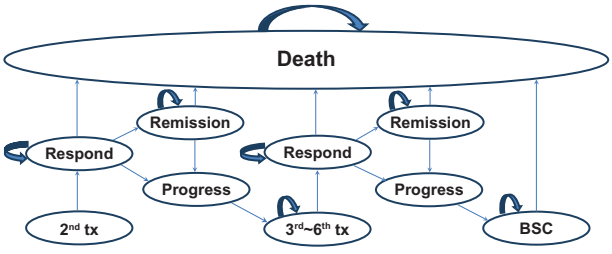

Figure 1 Structure of Markov model.
Notes: The different compartments are mutually exclusive health states. Arrows represent allowed transitions between states. "Progress/stable" state is "tunnel" state.
Abbrebiations: tx, treatment; BSC, best supportive care.

Table 1 Treatment sequence for cohort A vs cohort B

	Cohort A	Cohort B
Chemotherapy	PLD/carboplatin	Paclitaxel/carboplatin
	↓	↓
	Topotecan or belotecan	Topotecan or belotecan
	↓	↓
	Docetaxel	Docetaxel
	↓	↓
	Etoposide	Etoposide
	↓	↓
	Carboplatin or cisplatin	Carboplatin or cisplatin
Best supportive care	In-home service	In-home service
	↓	↓
	Hospice service	Hospice service

Abbreviation: PLD, polyethylene glycolated liposomal doxorubicin.

in the model can be confused with the aforementioned cycle of chemotherapy administration. Therefore, the latter shall be termed "Markov cycle," while the former shall be termed "administration cycle."

Patients are assumed to receive six lines of chemotherapy on average after diagnosis of ovarian cancer until death, according to an expert group composed of five clinical gynecologists in South Korea. So the model reflected this. Cohort A and B included the combination therapy of PLD/carboplatin and paclitaxel/carboplatin, respectively, as the second-line therapy in the treatment sequence. The third- to sixth-line therapies were common to the two cohorts (Table 1).

Patients remained on the same therapy for six administration cycles (18 weeks), at maximum, if they responded to the drug. If patients did not progress or show any serious side effects after six administration cycles, they would enter a clinical remission state, withdrawing from the drug. If the disease progressed during the treatment, patients would transit to the next line of therapy. "Progress" is a tunnel state. In other words, patients have to pass through the "progress" state to enter the subsequent line of therapy and cannot revert to an earlier line of therapy. Death could occur at any point during the Markov cycle (Figure 1).

The overall clinical validity of the model was confirmed by an expert group. Information on the chemotherapies most commonly used from the third to the sixth line in the treatment sequence of ovarian cancer, average median time to progression (TTP) of BSC, overall protocols related with drug administration, and the treatment of adverse events due to each therapy was also obtained from them.

The length of the Markov cycle defines the period of transition between the health states within the Markov model and depends on the characteristics of the disease. The length of the model cycle in this analysis was determined as 9 weeks for the following reason. Most chemotherapies are administered at 3-week intervals (one administration cycle). After three administration cycles, ie, 9 weeks, a series of tests for evaluating responsiveness to chemotherapy administered are performed, and according to the test result, it is determined whether the patient will move to the next line of therapy or stay on the current one. A cycle length of 9 weeks was determined to reflect this clinical practice in the real world.

Transition probabilities to the next line of therapies and death were drawn from the treatment-specific median TTP or PFS and over survival (OS) data obtained from clinical trials.

The time horizon should be enough to observe the long-term efficacy of intervention. Because the ultimate aim of an anticancer drug is to prolong patients' lives, the time horizon was set as 10 years in this analysis, at which 99% of the cohorts died.

Assumptions

- Patients received six lines of chemotherapy, on average, from the diagnosis of ovarian cancer until death.
- All patients experiencing disease progression received the next line of chemotherapy with no other treatment options, such as radiotherapy.
- All patients experiencing disease progression on BSC died.
- Chemotherapies were performed on the basis of ambulatory visits.
- Cisplatin and carboplatin as a sixth-line therapy were used on a fifty–fifty basis among patients.
- PLD/carboplatin is supposed to be administered at 4-week intervals, while the others are administered at 3-week intervals, according to the approved drug indication. However, it was assumed that all chemotherapies were administered at 3-week intervals, which is the assumption conservative to PLD.
- If patients showed progression to the sixth line of therapy, they would receive just BSC without any medical treatment. Patients on BSC used mainly in-home service and hospice service. Hospice service was used only for the last week before death.
- The model started from the second-line therapy.

Model estimates: transition probability distributions

Transition probabilities to the next line of therapy and death were calculated from the treatment-specific median TTP and OS data, using the equation below.[14]

$$tp_l = 1 - (1 - tp_t)^{1/t}$$

tp_l: yearly transition probability

tp_t: the overall probability over time t

For this, RCTs and other experimental studies published in English and Korean from January 1990 to January 2012 were searched using PubMed and the Cochrane database by a systematic review. Information where several different terms may be used for the same concept, such as ovarian cancer and TTP, was retrieved using Medical Subject Headings (MeSH). Systematic literature reviews were also included. After checking individual RCTs referenced in the systematic literature reviews, ones not overlapping with other RCTS in our search list were included.

In total, 808 papers were identified. After two reviewers independently reviewed the titles and abstracts primarily to identify the studies meeting the inclusion/exclusion criteria, 641 papers were excluded. Then, the full texts of the remaining 108 papers were reviewed, and 18 papers and one proceeding remained. All these procedures were cross-checked between the two reviewers.

Medial TTP and OS data obtained from the literature were merged using a weighted average based on the sample size (Table 2). Outcomes of the second-line chemotherapies in the base-case analysis were extracted from only head-to-head RCTs, even though there were other non-head-to-head trials meeting inclusion criteria. This was because the second-line drugs were the main target of this analysis. Outcomes of third-line chemotherapy were extracted from two studies,[15,] fourth-line from one,[16] fifth-line from one,[17] and sixth-line from three.[18–20] The median TTP of BSC was obtained from opinions of clinical experts.

Model estimates: cost

Since the analysis was carried out from the societal perspective, both nonmedical and medical costs associated with treatments were included. However, indirect costs, such as costs incurred by productivity loss of patient and informal caregivers, were excluded, because not only there are possibilities such as double-counting and overestimation but also there is no agreed methodology for measurement.

Direct medical cost includes cost associated with drug administration (ie, cost for drug acquisition, tests for monitoring adverse events, evaluation of responsiveness to chemotherapy, treatment of adverse events occurring during each chemotherapy, and service for drug administration), BSC, and follow-up tests during clinical remission. Cost items not reimbursed by insurance couldn't be identified because of a lack of data. Therefore, the mean proportion of cost incurred by nonreimbursement items in cancer patients was applied. Direct nonmedical costs include round-trip transportation costs for every ambulatory visit.

Most of the costs, except for nonreimbursement cost and hospice service, were estimated based on microcosting. Information concerning the proportion of cost not covered by insurance was retrieved from the report by the National Health Insurance Corporation (NHIC) in 2009.[21] However, this did not report ovarian cancer patient-specific data, but rather overall cancer patients' data. Therefore, data of the overall cancer patients was put into the model. Hospice service cost was from the literature.[22] Since PLD has not been listed on reimbursement yet, the price of PLD estimated by the manufacturer was put into the base-case analysis. Acquisition costs of other drugs were obtained from the ceiling price paid by insurance.

Cost items and frequencies of service use were estimated based on the current domestic and foreign clinical practice guidelines, literature, and expert opinions. Fee of service for drug administration, tests, and treatments of adverse events were drawn from the Korean fee schedule. Because the model starts from the second line, the cost of

Table 2 Clinical parameters of chemotherapies

Line	Therapy	Median TTP (month)	Probability	Median OS (month)	Probability
2nd	PLD/carboplatin	11.30	0.8804	30.70	0.0458
	Paclitaxel/carboplatin	9.40	0.8580	33.00	0.0427
3rd	Topotecan	6.34	0.7968	18.28	0.0758
4th	Docetaxel	4.60	0.7313	13.70	0.0997
5th	Etoposide	6.30	0.7957	16.50	0.0836
6th	Carboplatin or cisplatin	12.71	0.8929	20.45	0.0680
BSC		4.50	0.7262	4.50	1

Abbreviations: TTP, time to progression; OS, overall survival; PLD, polyethylene glycolated liposomal doxorubicin; BSC, best supportive care.

initial diagnosis for ovarian cancer was excluded. It was assumed that all the chemotherapies were performed on ambulatory visits and patients experienced adverse events only once since starting each chemotherapy treatment. The costs for drug acquisition, administration, and treatment of adverse event per Markov cycle (9 weeks) are presented in Table 3.

In-home service costs include costs for paracentesis and pain management. The costs for hospice service were calculated as weighted average with costs by the types of hospice facility and proportion of use. The cost for follow-up tests during clinical remission and BSC is also presented in Table 3.

All costs were converted to 2011 value and expressed in both Korean won (₩) and US dollars. An exchange rate of ₩1130 to $1 was applied (official exchange rate as of March 22, 2012).

Model estimates: utility

The final outcome measures used to evaluate the efficacy in this model were LYGs and QALYs. Because there are no QALY data of Korean ovarian cancer patients, they were drawn from foreign literature searched by systematic review, using PubMed CRD[23] and the utility registry home database of Tufts Medical Center in Boston.[24] There was only one study in which QALYs appropriate for health states defined in this model were surveyed, targeting both ovarian cancer patients and the general public.[25] Although utility values were reported by the adverse-event grades in the literature, they could not be used, as it is impossible to know the incidence rate of each adverse event by toxicity grades from clinical trials. Therefore, the proportion of grades 1–2 to 3–4 was assumed to be 50:50. Uncertainty surrounding this assumption was investigated in a sensitivity analysis.

There is one more thing to note. This study reported two results measured by both time trade-off (TTO) and visual analog scale (VAS). However, the result measured by TTO in this study was somewhat counterintuitive. It was reported in this study that QALYs of higher-grade adverse events were higher than those of lower-grade adverse events. This is presumed to be a mere input error, as it is natural that the higher the grade of adverse event, the lower the QALY figure will be. However, it does not affect the result, because the mean utility of grade 1–2 and 3–4 toxicity was the input in our model. Because TTO is a more recommendable method considering its reliability and consistency, the result measured by TTO was used in the base-case analysis (Table 4).

Results

Base-case analysis

The base-case analysis compares two cohorts composed of 1000 recurrent ovarian cancer patients, each receiving different treatment sequences, including PLD/carboplatin (cohort A) and paclitaxel/carboplatin (cohort B) as the second line.

In Figure 2, which shows the number of patients starting each line of therapy, fewer patients would eventually receive BSC in cohort A than in cohort B. This is because more patients exited the model due to death in cohort A than in cohort B.

Table 5 summarizes the expected total costs of two cohorts during each separate line of therapy and the difference in the

Table 3 Cost associated with drug administration and treatment of adverse events in each line of chemotherapy, follow-up test, and BSC

Chemotherapy	Line of treatment	Drug acquisition cost, US$ (Korean won)	Cost of drug administration per model cycle, US$ (Korean won)	Cost for treatment of adverse event US$ (Korean won)
PLD/carboplatin	2	1025 (1,158,600)	4357 (4,185,052)	94 (106,484)
Paclitaxel/carboplatin	2	656 (740,958)	3053 (2,932,126)	103 (116,326)
Topotecan	3	1743 (1,969,445)	6875 (6,603,593)	199 (225,084)
Docetaxel	4	874 (987,600)	3732 (3,584,956)	211 (239,218)
Etoposide	5	26 (29,088)	720 (691,144)	123 (127,135)
Carboplatin or cisplatin	6	113 (127,651)	1137 (1,092,205)	27 (30,185)
Item		**Cost, US$ (Korean won)**		
Cost for follow-up test		99 (111,313)		
BSC cost				
In-home service		2498 (2,823,152)		
Hospice cost		1180 (1,333,699)		

Notes: Drug acquisition cost includes dilute solution; cost of drug administration comprised of drug-acquisition cost, monitoring tests of adverse events, evaluation tests for response to chemotherapy, service for drug administration, remission, and nonreimbursement cost.
Abbreviations: PLD, polyethylene glycolated liposomal doxorubicin; BSC, best supportive care.

Table 4 Utility values for different health states

Health state	TTO	TTO (mean)	VAS	VAS (mean)
Ovarian cancer: clinical remission	0.83	0.83	0.72	0.72
Recurrent ovarian cancer: responding to chemotherapy/ grade 1–2 toxicity	0.5	0.56	0.44	0.42
Recurrent ovarian cancer: responding to chemotherapy/ grade 3–4 toxicity	0.61		0.4	
Recurrent ovarian cancer: progressive/grade 1–2 toxicity	0.4	0.435	0.36	0.315
Recurrent ovarian cancer: progressive/grade 3–4 toxicity	0.47		0.27	
End-stage ovarian cancer	0.16	0.16	0.16	0.16

Abbreviations: TTO, time trade-off; VAS, visual analog scale.

base-case analysis. Net costs per patient are also presented. Costs in each line of therapy are higher in cohort B than in cohort A, except for the second line of therapy. The reason for the difference in the cost of the third line is that more patients in cohort B progress from the second line to the third line therapy earlier than in cohort A. Yet the same transition probability is applied to both cohorts when progressing from third-line to fourth-line therapy. In other words, patients stay longer on third-line therapy in cohort B than do those in cohort A. Net cost per patient is a little higher in cohort A than cohort B. The two cohorts have comparable but distinct net costs per patient ($21,732 vs $20,838) and the mean OS (34.92 months vs 33.97 months). The treatment sequence including PLD/carboplatin gained 0.041 QALYs per patient and incurred $894 on average more than the treatment sequence including paclitaxel/carboplatin. Overall, the resulting incremental cost effectiveness ratio (ICER) was $21,658 per QALY and $67,761 per LYG.

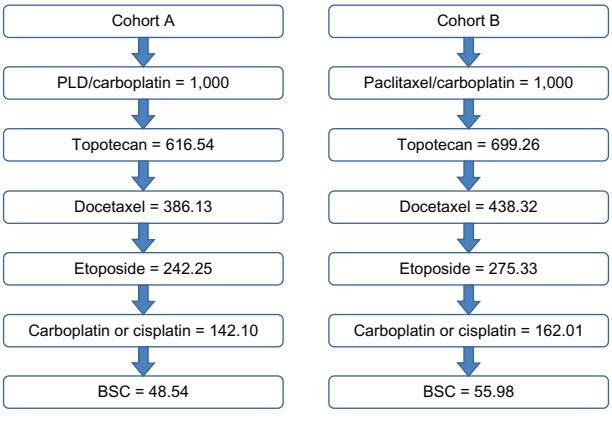

Figure 2 Number of patients starting each line of therapy.
Abbreviations: PLD, polyethylene glycolated liposomal doxorubicin; BSC, best supportive care.

One-way sensitivity analysis

To investigate the uncertainty, key parameters were varied in a one-way sensitivity analysis, and results are summarized in Table 6. Appropriate ranges of variation in parameters were determined based on clinical and economical perspectives. Two variables (ie, administration cost of PLD and clinical parameters of second-line therapies) had the biggest impact on the result. Except for these two parameters, ICERs were in the range of ₩16,781,475 ($14,851) to ₩32,166,198 ($28,466), which is within the acceptable range considering GDP per capita in Korea.

Variation in price of PLD

There is some uncertainty surrounding the price of PLD, because PLD has not yet been listed for reimbursement in Korea. In the base-case analysis, the price for a 50 mg (25 mL) pack of PLD is assumed to be ₩890,603 ($788), which is the price suggested by the manufacturer. When the price of PLD was varied within the range of ±5%, ICER changed between ₩16,781,475 ($14,851) and ₩32,166,198 ($28,466).

Variation in PLD administration cost

As mentioned before, PLD/carboplatin in the second line and carboplatin in the sixth line are supposed to be administered at 4-week intervals, according to the indication approved by the Korea Food and Drug Administration, while all the other chemotherapies are administered at 3-week intervals. However, the model cannot reflect this difference in administration interval. To fit our model specification, PLD/carboplatin and carboplatin were assumed to be given at 3-week intervals in the base-case analysis. Because carboplatin is included commonly in both treatment sequences, assumption of 3-week intervals of carboplatin turned out not to significantly impact the final ICER. However, PLD/carboplatin could cause some difference in the final result because it is a key subject of interest in this analysis.

The assumption of administration interval of PLD/carboplatin of 3 weeks is a very conservative one, in that PLD cost is likely to be overestimated. In order to adjust the potential cost overestimation, PLD/carboplatin administration costs was varied to 3/4 and 7/8 of the cost of 4-week intervals of PLD/carboplatin, respectively, for ICER calculation. One-way sensitivity analysis, based on these cost variations, now showed ICER estimates less than zero in both cases, which means that PLD/carboplatin dominates paclitaxel/carboplatin.

Table 5 Result of base-case analysis

Line	Cohort A, US$ (Korean won)	Cohort B, US$ (Korean won)	Difference
2nd	8,243,645 (9,315,318,744)	5,948,851 (6,722,201,396)	2,294,794 (2,593,117,348)
3rd	7,623,297 (8,614,325,333)	8,640,799 (9,764,102,974)	–1,017,502 (–1,149,777,642)
4th	2,617,252 (2,957,494,436)	2,995,857 (3,385,206,829)	–378,507 (–427,712,393)
5th	452,732 (511,587,701)	460,259 (520,092,811)	–7,527 (–8,505,110)
6th	385,854 (436,015,528)	437,552 (494,434,201)	–51,698 (–58,418,673)
BSC	654,985 (740,132,580)	743,578 (840,243,590)	–88,594 (–100,111,009)
Net cost per patient	21,732 (24,557,344)	20,838 (23,547,138)	894 (1,010,206)
Mean survival (months)	34.92	33.97	0.95
LYs per patient	2.603	2.590	0.013
QALYs per patient	1.864	1.823	0.041
Cost per LY	8325 (9,406,876)	8026 (9,069,346)	299 (337,530)
Cost per QALY	11,626 (13,137,763)	11,402 (12,884,545)	224 (253,218)
Incremental cost per QALY gained	21,658 (24,473,836)		
Incremental cost per LY gained	67,761 (76,569,719)		

Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; LY, life year.

Variation in clinical parameter of second-line therapies

There is only one RCT that directly compared PLD/carboplatin with paclitaxel/carboplatin as second-line therapy for platinum-sensitive recurrent ovarian cancer, and the results of this head-to-head RCT were used in the base-case analysis.[11]

In a sensitivity analysis, the weighted average of data from all relevant literature comparing PLD/carboplatin or paclitaxel/carboplatin with other comparators was put into the model instead of the result of the head-to-head RCT. As a result, ICER increased to ₩53,335,223 ($47,199), which is about twice the base-case result.

Table 6 Result of one-way sensitivity analysis

Parameter varied	Value in base case	Variation of value	Result, US$ (Korean won)
Price of PLD, US$ (Korean won)	788.15 (890,604)	5% reduction: 748.74 (846,073)	14,851 (16,781,475)
		5% increase: 827.55 (935,133)	28,466 (32,166,198)
Discount rate	Costs 5%	Costs 0% and benefits 0%	17,131 (19,357,641)
	Benefit 5%	Costs 3% and benefits 3%	19,754 (22,321,891)
		Costs 7.5% and benefits 7.5%	24,207 (27,354,258)
Administration cost of PLD/carboplatin per administration cycle	4-week cost	3/4 of 4-week cost	–31,515 (–35,611,603)
		7/8 of 4-week cost	–4,928 (–5,568,897)
Median TTP of BSC	4.5 months	3 months	21,984 (24,841,745)
		6 months	21,337 (24,111,272)
Clinical parameter of 2nd-line therapy	Parameters from CALYPSO study	Weighted average of median TTP drawn from all literature chosen	47,199 (53,335,223)
Utility	TTO	VAS	21,836 (24,674,656)
Sequence	Topotecan → docetaxel → etoposide → (carboplatin or cisplatin)	Docetaxel → topotecan → etoposide → (cisplatin or carboplatin)	19,254 (21,757,519)
		Docetaxel → topotecan → (cisplatin or carboplatin) → etoposide	20,602 (23,280,195)
Proportion of grade 1/2:3/4 of adverse events	50%:50%	40%:60%	22,087 (24,958,164)
		70%:30%	20,849 (23,559,466)
Time horizon	10 years	15.5 years (time point at which all cohorts die)	20,937 (23,658,389)
Proportion of nonreimbursement cost	Proportion of nonreimbursement cost of ambulatory services in all types of cancers: 15%	Proportion of nonreimbursement cost of all services in all types of cancers: 26.70%	25,115 (28,380,301)
		Assumed that there is no reimbursement: 0%	18,410 (20,862,761)

Abbreviations: PLD, polyethylene glycolated liposomal doxorubicin; TTP, time to progression; BSC, best supportive care; TTO, time trade-off; VAS, visual analog scale.

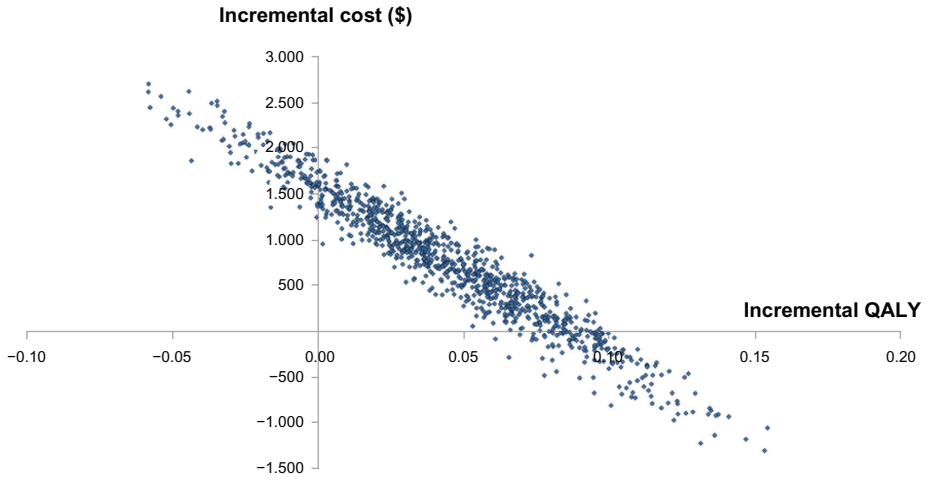

Figure 3 Cost-effectiveness plane.
Abbreviation: QALY, quality-adjusted life year.

Variation in proportion of nonreimbursement cost

In the base-case analysis, the average proportion of the costs not reimbursed by insurance among ambulatory care costs in treatment of all types of cancers was applied, which was drawn from the report by the NHIC, since there were no ovarian cancer-specific data available.

When the nonreimbursement proportion of overall services (ie, ambulatory care and hospitalization) was applied in the sensitivity analysis, ICER increased to ₩28,380,301 ($25,115). In addition, when it was assumed that all cost items were covered by insurance, ICER decreased to ₩20,862,761 ($18,410).

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA), involving 1000 random simulations of median TTPs of each chemotherapy, cost of hospice service, and utilities according to each health state, was performed in order to quantify the uncertainty surrounding the parameters used in the model.

PSA is a technique for testing the robustness of the result by investigating how cost-effectiveness changes when multiple parameters are varied simultaneously. The 1000 results from the PSA were plotted onto a cost-effectiveness plane (Figure 3). Most of the results of the 1000 simulations lie on the first quadrant, which means that PLD/carboplatin increases both QALYs and costs more than paclitaxel/carboplatin.

Figure 4 shows the cost-effectiveness acceptability curve, presenting the probability that the treatment sequence including PLD/carboplatin is cost-effective compared with the alternative sequence for a range of maximum monetary values that a decision-maker might be willing to pay for 1 QALY gained. We can see that PLD/carboplatin is cost-effective in nearly 49.4% of samples at a willingness to pay

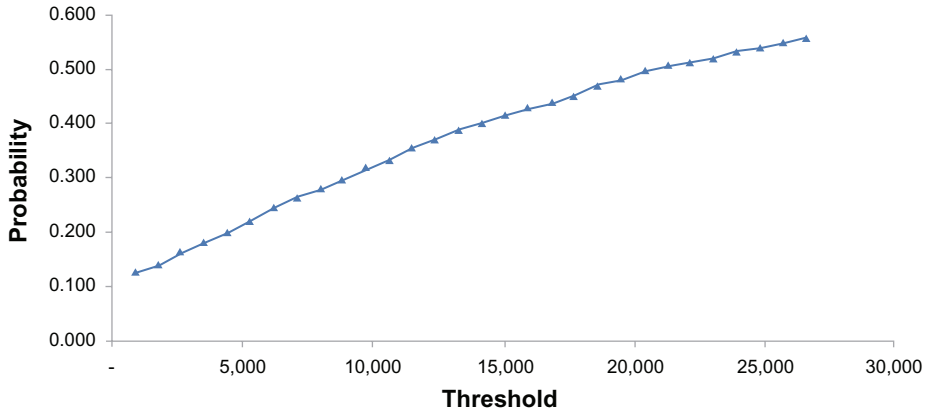

Figure 4 Cost-effectiveness acceptability curve.

a threshold of $20,000, which is close to the GDP per capita of Korea.

Discussion

The CALYPSO study comparing PLD/carboplatin directly with paclitaxel/carboplatin as second-line therapy in platinum-sensitive recurrent ovarian cancer patients showed superiority in PFS and a better therapeutic index of PLD/carboplatin over a standard paclitaxel/carboplatin regimen.[1] However, value for money of PLD/carboplatin in platinum-sensitive patients has not yet been proven.

The main objective of this analysis was to estimate the long-term clinical impact and cost-effectiveness of PLD/carboplatin in platinum-sensitive recurrent ovarian cancer in Korea. Efficacy such as PFS or OS might be important factors for decisions concerning drug selection for cancer patients in the clinical setting. However, straight comparison of efficacy outcomes can be misleading, because quality of life can be more valuable to cancer patients than mere extension of life. Some drugs have low tolerance, low compliance, or more adverse effects while prolonging PFS or OS, but efficacy measures can't capture these aspects. Utility can combine this efficacy and quality of life into a single measure.[26] Accordingly, a cost–utility analysis was applied in this analysis to this end.

Analysis was performed through decision-modeling because the treatment sequences after second-line therapies in the trial were not presented clearly and were different between the two arms. The treatment-sequence model of ovarian cancer patients, including PLD/carboplatin and paclitaxel/carboplatin as a second line, was constructed to reflect clinical protocol for patients receiving series of chemotherapies, depending on responsiveness to drugs.

PLD is a kind of improved formulation of conventional doxorubicin and surrounded by fatty coating called liposome, which enables doxorubicin to remain longer inside the body. This means that more of the doxorubicin can be delivered to the target cancer cell, while having fewer side effects on healthy tissue. In fact, PLD/carboplatin can be used for metastatic breast cancer, Kaposi's sarcoma, and ovarian cancer.[27]

The average median OS estimated by the model was 29.15 and 29.26 months in the PLD/carboplatin and paclitaxel/carboplatin arms, respectively. There was about a 3-month gap between OS of paclitaxel/carboplatin in the RCT and the one estimated by modeling, while OS of PLD/carboplatin in the RCT was similar to the one estimated by modeling. The reason for this is that OS in the RCT was not entirely due to the effect of PLD/carboplatin and paclitaxel/carboplatin, because the types of treatments after second-line therapy in the RCT were not controlled identically in both arms.

Predicted ICER under the base-case assumption was ₩24,473,836 ($21,658) per QALY. It was not considered that there was a need to perform additional subgroup analysis, because the target of the base-case analysis, ie, platinum-sensitive recurrent ovarian cancer patients, was already narrowed down. One-way sensitivity analysis showed that when key parameters were varied, ICERs (QALYs) lay in the range of ₩16,781,475 ($14,851) to ₩32,166,198 ($28,466), except when administration cost of PLD/carboplatin and source of clinical parameters of second-line therapies were varied. Probability sensitivity analysis revealed that there is sufficient uncertainty surrounding the baseline ICER. The cost-effectiveness acceptability curve demonstrated that there is about 49.4% probability of cost-effectiveness in the treatment sequence including PLD/carboplatin when decision-makers have the willingness to pay the threshold of $20,000, which was the GDP per capita of Korea in 2010.

When considering clinical superiority, cost-effectiveness of PLD, and current limited therapeutic options in platinum-sensitive recurrent ovarian cancer, overall, PLD/carboplatin can be said to be a valuable treatment option in these patients.

Although this economic analysis was performed according to the current methodological guidelines recommended, there are a few caveats. Firstly, although the administration cycle of PLD/carboplatin and carboplatin is 4 weeks, it was assumed to be 3 weeks because other chemotherapies, except for PLD/carboplatin and carboplatin, are administered every 3 weeks, and the model cannot reflect this difference in the administration interval. ICER was very sensitive to the variation of administration cost of PLD/carboplatin. However, we can guess that this is a conservative assumption for PLD/carboplatin, because the cost of PLD/carboplatin was put into the model more frequently than it should have been under this assumption. PLD/carboplatin would become even more cost-effective if the administration cycle of PLD/carboplatin could be reflected precisely.

Secondly, indirect costs incurred by patients and informal caregivers, such as cost of productivity loss, were not included. Incorporation of these societal costs would further decrease ICER to an even lower level.

Finally, we used OS data of the CALYPSO study, reported in proceedings because it has not been published yet. In addition, chemotherapies administered after PLD/carboplatin and paclitaxel/carboplatin until death were not controlled identically between the two groups in the

trial, because it was not OS but median TTP which was the main key outcome. Therefore, it cannot be said that the OS result was entirely due to the effect of PLD/carboplatin and paclitaxel/carboplatin. Nevertheless, OS in the CALYPSO study was used, because there were no other data that were more reliable.

In conclusion, PLD/carboplatin as a second therapeutic option in patients with platinum-sensitive recurrent ovarian cancer is cost-effective compared to the standard paclitaxel/carboplatin regimen, based on clinical and economical perspectives. These data can provide an objective basis for local decision-making on the possible economic impact of use of this intervention if different variables between the countries can be incorporated accordingly.

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