Cost Effectiveness of Intraperitoneal Compared With Intravenous Chemotherapy for Women With Optimally Resected Stage III Ovarian Cancer: A Gynecologic Oncology Group Study

Laura J. Havrilesky, Angeles Alvarez Secord, Kathleen M. Darcy, Deborah K. Armstrong, and Shalini Kulasingam

ABSTRACT

Purpose

To determine the cost effectiveness of intraperitoneal versus intravenous regimens for adjuvant treatment of optimally resected stage III ovarian cancer.

Patients and Methods

A decision model was developed to compare the cost effectiveness at 7-, 11.5-, and 35-year horizons of intravenous carboplatin and paclitaxel (IV-CARBO/PAC), intravenous cisplatin and paclitaxel (IV-CIS/PAC), or intravenous paclitaxel followed by intraperitoneal cisplatin and paclitaxel (IP-CIS/PAC). Survival data were from women participating in representative Gynecologic Oncology Group (GOG) protocols. Medicare reimbursement rates and the Agency for Healthcare Research and Quality Database were used to estimate costs for treatment regimens and grade 3 to 4 adverse effects, respectively.

Results

Median predicted survival was 66, 57, 51, and 48 months for IP-CIS/PAC, IV-CARBO/PAC, IV-CIS/PAC (GOG 172), or IV-CIS/PAC (GOG 158), respectively. Across a range of analyses, IV-CIS/PAC was more costly and had lower life expectancy than IV-CARBO/PAC. Compared with IV-CARBO/PAC, IP-CIS/PAC had an incremental cost-effectiveness ratio (ICER) of \$180,022 per quality-adjusted life year (QALY) saved at a 7-year time horizon, \$71,835/QALY at 11.5 years, and \$32,053/QALY over a lifetime. Extending the survival advantage of IP-CIS/PAC over 11.5 years and a lifetime results in ICERs of \$26,249 and \$23,973, respectively. Assuming IP-CIS/PAC and IV-CIS/PAC were equally effective when administered on an outpatient basis, the ICER of IP-CIS/PAC compared with IV-CARBO/PAC was \$26,311.

Conclusion

Inpatient IP-CIS/PAC, while not cost effective compared with IV-CARBO/PAC at 7 years, becomes cost effective if a longer time horizon is modeled and/or a survival benefit can be assumed to persist longer than currently available data. Outpatient IP-CIS/PAC may also be cost effective compared with IV-CARBO/PAC if proven as effective as inpatient IP-CIS/PAC.

J Clin Oncol 26:4144-4150. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Three phase III clinical trials have identified advantages to the use of intraperitoneal chemotherapy for adjuvant treatment of stage III ovarian cancer after surgical cytoreduction.¹⁻³ Recently, a randomized controlled trial demonstrated a significant survival advantage to a regimen combining intraperitoneal cisplatin and paclitaxel with intravenous paclitaxel, compared with a regimen of intravenous cisplatin and paclitaxel.³ The overall survival (OS) advantage of 16 months in the intraperitoneal arm was achieved at the expense of significantly higher rates

of adverse events in the short term including fatigue, pain, hematologic, gastrointestinal, metabolic, and neurologic toxicity,⁴ resulting in a significant reduction in quality of life (QOL) during treatment. This study has generated much discussion about whether platinum and taxane-based chemotherapy administered via the intraperitoneal route should constitute the standard of care for women with optimally resected stage III epithelial ovarian cancer.⁵

While survival and QOL are of utmost importance, the cost of treatment is also relevant to the chemotherapy regimen chosen. In order to inform this discussion, we performed a cost-effectiveness

From the Division of Gynecologic Oncology and Division of Clinical and Epidemiological Research, Department of Obstetrics and Gynecology, and Duke Center for Clinical Health Policy Research, Duke University Medical Center, Durham, NC; Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo NY; and the Johns Hopkins Kimmel Cancer Center, Baltimore, MD.

Submitted June 29, 2007; accepted May 1, 2008.

Supported by a grant from the American Board of Obstetrics and Gynecology/American Association of Obstetricians and Gynecologists Foundation, and the National Cancer Institute grants from the Gynecologic Oncology Group Administrative Office along with the GOG Tissue Bank (CA 27469) and the Gynecologic Oncology Group Statistical and Data Center (CA 37517).

Presented at the 37th Annual Meeting of the Society of Gynecologic Oncologists, San Diego, CA, March 3-7, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Laura J. Havrilesky, MD, Box 3079, Duke University Medical Center, Durham, NC, 27710; e-mail: havri001@mc.duke.edu.

© 2008 by American Society of Clinical Oncology

0732-183X/08/2625-4144/\$20.00

DOI: 10.1200/JCO.2007.13.1961

Fig 1. Decision tree structure with intravenous (IV) cisplatin and paclitaxel treatment node expanded to reveal entire subtree.

analysis of three currently available chemotherapy strategies for women with optimally resected, stage III ovarian cancer.

METHODS

Model Structure

A Markov state transition model was constructed using commercially available software (TreeAge Inc, Williamstown, MA). Treatment regimens were compared as defined in Gynecologic Oncology Group (GOG) 172³ and GOG-158⁶ studies (Fig 1): 135 mg/m² intravenous paclitaxel over 24 hours day 1, 75 mg/m² intravenous cisplatin day 2 of a 21-day cycle (treatment arms for identical regimens from GOG-172 and GOG-158 modeled independently; IV-CIS/PAC); 135 mg/m² intravenous paclitaxel over 24 hours day 1, followed by 100 mg/m² intraperitoneal cisplatin day 2, 60 mg/m² intraperitoneal paclitaxel day eight of a 21-day cycle (IP-CIS/PAC; GOG-172); and: 175 mg/m² paclitaxel over 3 hours, carboplatin (AUC 7.5) day 1 of a 21-day cycle (IV-CARBO/PAC; GOG-158).

Markov states were active primary chemotherapy treatment, completed primary chemotherapy, and dead. A cohort of women was assumed to enter the model at age 60, based on median ages of patients enrolled in GOG trials. Cycle length for the model was 6 months. All patients were assumed to be treated during the first 6 months (active treatment state). Patients surviving the first cycle based on GOG survival data were transitioned to completed primary chemotherapy. Thereafter, the number of patients transitioning to dead during each cycle was determined directly from survival data in 6-month increments. To account for effects of toxicity on QOL, global QOL-related health utility scores were obtained from GOG trials and applied to months 1 to 5 and 6 to 12 as previously described by Bristow et al.^{7,8} Time horizon for analysis was 7 years based on length of follow-up for GOG-172, with additional time horizons of 11.5 years and 35 years (corresponding to a lifetime) analyzed to determine whether extending survival curves for IP-CIS/PAC had an impact on cost effectiveness. Assumption that the survival benefit existing at 7 years would apply over these extended time horizons was examined in sensitivity analyses. Costs and outcomes were discounted at 3% yearly.⁹ A societal perspective was used; results are presented using costs per QALY. Sensitivity analyses were performed to account for uncertainty in assumptions and inputs.

Chemotherapy regimens were compared with regard to costs and life expectancy using incremental cost-effectiveness ratio (ICER). Key assumptions for construction of the model are listed under each component below.

Baseline Model and Estimates

Survival. Survival distributions were generated for women randomly assigned to one of three treatment regimens (IV-CARBO/PAC, IV-CIS/PAC, or IP-CIS/PAC) as reported by Armstrong et al¹ (GOG-172) and Ozols et al⁵ (GOG-158). Key assumptions: we assumed that survival curves from two studies could be compared since baseline characteristics for the two groups were almost identical, but confirmed this assumption by incorporating IV-CIS/PAC arms from GOG-172 and GOG-158 into analyses. GOG-172 allowed enrollment of patients with primary peritoneal carcinomas, while

GOG-158 did not. Duration of follow-up was unequal between GOG-158 (median for IV-CARBO/PAC arm, 8.8 years) and GOG-172 (median for IP-CIS/PAC arm, 6.4 years; median for IV-CIS/PAC arm, 6.5 years). Because follow-up data from GOG-172 was complete to 7 years, we made this the primary time horizon. To evaluate time horizons beyond length of follow-up for GOG-172 and to minimize bias, we used data from the 24-hour paclitaxel/cisplatin (IV-CIS/PAC) arm of GOG-114 (median follow-up, 11.5 years), a previous randomized trial for optimally cytoreduced ovarian cancer with similar eligibility criteria, to model survival in all four arms between 7 and 11.5 years. Beyond 11.5 years, survival in all arms was modeled based on United States life-tables.¹⁰ The assumption of no further deaths from ovarian cancer after 11.5 years is based on observed plateauing of survival curves after 10 years follow-up in two prior GOG trials of optimally cytoreduced ovarian cancer treated with platinum-based regimens (unpublished long-term data, GOG-52 and -114, GOG Statistical and Data Center, Buffalo, NY) and limited survival data with long-term follow-up reported in retrospective studies of patients with advanced ovarian cancer.^{11,12}

Toxicity. Rates of treatment-related toxicities for each arm were obtained from the GOG Statistical and Data Center. Toxicities were classified between 0 and 5 as defined by GOG Common Toxicity Criteria. Grade 3 to 5 adverse effects included were gastrointestinal, genitourinary, neurologic, fever, infection, pain, metabolic, and hematologic (hematologic toxicities evaluated in sensitivity analysis only). Key assumptions: toxicities were assumed to occur during the first 6 months of treatment.

Costs. Costs of treatment and adverse events are presented in Table 1. Each treatment regimen consisted of six cycles of treatment lasting 21 days each and included laboratory work (weekly CBC during treatment, metabolic panel every 3 weeks). Caregiver costs were incorporated as reported previously.⁷ For IP-CIS/PAC, costs of port placement during first hospital admission for chemotherapy and outpatient port removal were incorporated. Costs for each treatment modality were estimated using 2006 national Medicare reimbursement data.¹³

Median charges associated with each severe adverse event were obtained from 2003 national database of the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project Nationwide Inpatient Sample¹⁴ as follows. Searches were performed for primary diagnoses by *International Classification of Diseases, ninth revision* codes to correlate to adverse events of interest: gastrointestinal—nausea with vomiting 787.01 and intestinal obstruction 560.9; genitourinary—renal failure 586; neurologic—neuropathy due to drugs 357.6; fever—fever 780.6; infection—septicemia 038.9; pain—abdominal pain site unspecified 789.0; metabolic—hypokalemia 276.8 and hypomagnesemia 275.2; thrombocytopenia—secondary thrombocytopenia 287.4. The mean of the charges was calculated whenever there were two primary diagnoses. Costs were estimated as 60% of charges.¹⁵

Key assumptions. Costs were applied to grade 3 to 4 adverse events whose rates were significantly different between treatment arms. Based on GOG Common Toxicity Criteria, we made the assumption that a hospital stay would be needed for the following grades of adverse events: gastrointestinal, 3 to 4; genitourinary, 3 to 4; fever, 3 to 4; infection, 3 to 4; neurologic, 4; pain, 4; metabolic, 4. Although rates of granulocyte colony-stimulating factor use were not reported in either study, the cost of this treatment for grade 4 neutropenia

Table 1. Costs and Ranges

Parameter	No. of Cycles	Length of Stay	Charges	Unit Cost	Units	Subtotal (\$)	Total Cost (\$)	Cost (\$)	Range (\$)
Intravenous carboplatin/paclitaxel	6	Outpatient							
MD evaluation				115.29	6	692			
Outpatient infusion charge				309.81	6	1,859			
Medication				435.12	6	1,988			
Laboratory work				126	6	757	5,295		4,000-7,000
Intravenous cisplatin/paclitaxel	6	Inpatient							
MD evaluation		Inpatient		221	6	1,326			
Laboratory work				126	6	757			
Inpatient hospital DRG (includes medications, infusion charges)		1 night		7,748	6	46,488	48,571		40,000-60,000
Intraperitoneal cisplatin/paclitaxel	6	Inpatient and outpatient							
Medication		Day 8 outpatient		94.36	6	566			
IP chemotherapy administration charges		Day 8 outpatient		68.37	6	410			
Laboratory work				126	6	757			
Inpatient hospital DRG				7,748	6	46,488			
IP port placement (professional charges only)		Inpatient, during first chemotherapy admission		570	1	570			
IP port removal		Outpatient		1,766	1	1,766	51,883		40,000-60,000
Intravenous cisplatin/paclitaxel	6	Outpatient							
MD evaluation				115.29	6	692			
Infusion charges		Outpatient		309.81	6	1,859			
Medication				127.84	6	767			
Laboratory work				126	6	757	4,075		4,000-6,000
Intraperitoneal cisplatin/paclitaxel	6	Outpatient							
MD evaluation				115.29	6	692			
Infusion charges		Outpatient		667.09	6	4,002			
Medication				178.16	6	1,068			
Laboratory work				126	6	757	6,519		4,500-7,500
Caregiver support									
Intravenous regimen	6		NA					492	250-1,000
Intraperitoneal regimen	6		NA					860	400-1,700
Hospitalization for									
Gastrointestinal toxicity			9,569					5,741	2,500-10,000
Genitourinary toxicity			9,347					5,608	2,500-10,000
Neurologic toxicity			13,492					8,095	4,000-16,000
Fever			7,851					4,711	2,500-10,000
Infection			17,282					10,369	5,000-20,000
Pain			8,702					5,221	2,500-10,000
Metabolic toxicity			8,727					5,236	2,500-10,000
Thrombocytopenia, grade 4			15,200					9,120	5,000-15,000
Pegfilgrastim for prevention of leukopenia	3		NA					6,513	3,000-13,000
Platelet transfusion		Outpatient	NA					841	400-1,000
Treatment grade 4 thrombocytopenia*			NA					841	400-15,000
Salvage chemotherapy IV carboplatin/paclitaxel	6		NA					5,295	4,000-22,000
Palliative care, 3 months			NA					13,370	10,000-20,000

Abbreviations: MD, medical doctor; DRG, diagnosis-related group; IP, intraperitoneal; IV, intravenous; IP, intraperitoneal; NA, not applicable.

*Outpatient treatment estimate with range for sensitivity analysis incorporating possibilities of both outpatient and inpatient treatments.

was incorporated into the base case. Costs of outpatient platelet transfusion and of pegfilgrastim injections following up to five cycles chemotherapy were included for the base case. Hospitalization for grade 4 thrombocytopenia was incorporated into the range of costs for sensitivity analysis. To incorporate additional costs of cancer recurrence, a simplifying assumption was made. Patients who died during the first 5 years after diagnosis were assumed to incur the cost of six cycles outpatient carboplatin and paclitaxel and costs of 3 months palliative care. For the latter we used information from Brumley et al.¹⁶ Patients with recurrent disease often receive multiple chemotherapy regimens and different degrees of palliative care, however, for purposes of the analysis we

assigned this arbitrary type and number of chemotherapy cycles to incorporate the cost of earlier recurrence and death, with cost ranges extended for sensitivity analysis to account for uncertainty in choice of salvage regimens. Costs were inflated to 2006 dollars using the medical care component of Consumer Price Index.¹⁷

Sensitivity Analyses

Sensitivity analyses were performed at three time horizons: 7 years (reflecting available follow-up data for GOG-172), 11.5 years, and 35 years (reflecting hypothetical lifetime follow-up). We examined a scenario in which

we assumed that the survival advantage that existed at 7 years would apply over these extended time horizons. To evaluate the validity of comparing treatment arms from two separate randomized clinical trials, we incorporated both IV-CIS/PAC from GOG-172 and the identical arm from GOG-158 as separate regimens in the model, with survival and toxicity modeled. We performed sensitivity analyses on adverse event rates by varying these rates over ranges established by prior GOG phase III trials (Table 2).¹⁸⁻²¹ If toxicity rates were not previously well established in GOG trials, clinically reasonable ranges encompassing true event rates were selected for sensitivity analysis (Table 2).

For the base case, we incorporated costs of each regimen by assigning the cost of six cycles of the assigned regimen to each patient. For sensitivity analysis, we incorporated costs of each regimen based on treatment completion rates reported in GOG-172 and GOG-158,³ as previously reported.^{6,12} Finally, we varied costs of chemotherapy treatment regimens represented in GOG-172 (IP-CIS/PAC and IV-CIS/PAC) by assuming that outpatient regimens could be conducted equally effectively (Table 1).

Probabilistic sensitivity analysis was performed with Monte Carlo simulation with 10,000 repetitions. Triangular distributions were assumed for costs and adverse effects and beta distributions were used for survival.

RESULTS

Base Case

The model estimated median overall survival of 66 months for IP-CIS/PAC, 57 months for IV-CARBO/PAC, 51 months for IV-CIS/PAC (GOG-172), and 48 months for IP-CIS/PAC (GOG-158), compared to 65.6 months, 57.4 months, 49.7 months, and 48.7 months, respectively, observed in corresponding randomized clinical trials (Fig 2). IV-CIS/PAC was more costly and had lower average life expectancy compared with IV-CARBO/PAC (online-only Appendix Table A1). Using a 7-year time horizon, IP-CIS/PAC had an ICER of \$180,022 per QALY compared with IV-CARBO/PAC (Table A1). When the time horizon was extended to 11.5 years, the ICER of IP-CIS/PAC compared with IV-CARBO/PAC was reduced to \$71,835 per QALY. Over a lifetime, the ICER of IP-CIS/PAC compared with IV-CARBO/PAC was \$32,053 per QALY.

The IV-CIS/PAC regimen modeled from GOG-172 behaved almost identically to the similar arm from GOG-158; both regimens were more costly and less effective than IV-CARBO/PAC at 7 years (Table A1). At a lifetime time horizon, the IV-CIS/PAC regimen from GOG-158 was dominated by IV-CARBO/PAC while the

Fig 2. Model simulation of overall survival associated with chemotherapy regimens (intravenous cisplatin and paclitaxel [IV-CIS/PAC; GOG 172] v IV-CIS/PAC [GOG 158] v intravenous carboplatin and paclitaxel [IV-CARBO/PAC] v intraperitoneal [IP]-CIS/PAC) for the treatment of patients with stage III ovarian cancer after optimal cytoreduction (< 1 cm residual disease). GOG, Gynecologic Oncology Group.

identical regimen from GOG-172 was more costly and less effective than a theoretical combination of IV-CARBO/PAC and IP-CIS/PAC (weakly dominated).

Sensitivity Analyses

Robustness of results was assessed in sensitivity analyses. If survival advantage at 7 years was assumed to persist over 11.5 years, the ICER for IP-CIS/PAC compared with IV-CARBO/PAC was \$26,249 at a lifetime. If the survival advantage at 7 years was assumed to persist over a lifetime, the ICER for IP-CIS/PAC compared with IV-CARBO/PAC was \$23,973 per QALY.

None of the conclusions of the model significantly changed when rates of severe adverse effects were altered within published or estimated ranges (Tables 2 and 3). In the base case at 7 years, IV-CIS/PAC was dominated and IP-CIS/PAC retained an ICER greater than \$168,000 per QALY compared with IV-CARBO/PAC in all analyses. Over a lifetime, IP-CIS/PAC retained an ICER below \$34,000 per QALY when compared with IV-CARBO/PAC in all analyses.

Results were insensitive to variations in the cost of each chemotherapy regimen and to variations in costs associated with adverse

Table 2. Severe Adverse Event Estimates for Base Case and Ranges for Sensitivity Analysis^{6,18-21}

Adverse Event	Regimen							
	GOG 158				GOG 172			
	IV-CARBO/PAC		IV-CIS/PAC		IV-CIS/PAC		IP-CIS/PAC	
	%	Range	%	Range	%	Range	%	Range
Leukopenia grade 4	6	4-66	12	9-20	15	9-20	32	10-45
Thrombocytopenia grade 4	20	12-25	2	0-4	2	0-4	5	3-15
Gastrointestinal grade 3-4	10	7.5-15	22	4-30	24	4-30	45	30-50
Genitourinary/renal grade 3-4	0.8	0-3	3	0-4	2	0-4	7	0-10
Peripheral neurologic grade 4	0	0-1	0.2	0-1	0	0-1	1	0-3
Fever grade 3-4	0.8	0-10	1.5	1-6	4	1-6	9	5-12
Infection grade 3-4	2	0-10	3	1-10	6	1-10	16	10-20
Pain grade 4	0.3	0-1	0.25	0-2	0	0-2	1.5	1-5
Metabolic grade 4	0.8	0-3	2	1-4	3	1-4	9	3-12

Abbreviations: GOG, Gynecologic Oncology Group; IV-CARBO-PAC, intravenous carboplatin and paclitaxel; IV-CIS/PAC, intravenous cisplatin and paclitaxel.

Table 3. Effect of Selected One-Way Sensitivity Analyses on ICER Comparing IP-CIS/PAC to IV-CARBO/PAC, 7-Year Time Horizon

Parameter	Range	Incremental Cost Effectiveness Ratio (Cost in \$)/QALY	
		Low	High
Cost of IP-CIS/PAC, \$	40,000-60,000	136,061	211,893
Cost of treatment for grade 3-4 GI toxicity, \$	2,500-10,000	175,990	184,437
Probability of grade 3-4 GI toxicity, IP-CIS/PAC	0.3-0.5	177,423	181,879
Probability of grade 4 thrombocytopenia, IV-CARBO/PAC	0.12-0.25	178,822	181,423
Cost of treatment for grade 4 thrombocytopenia, \$	400-15,000	175,983	182,135
QOL-related health utility score, IP-CIS/PAC, months 1-5	0.50-0.80	140,571	265,030

Abbreviations: ICER, incremental cost-effectiveness ratio; IV-CIS/PAC, intravenous cisplatin and paclitaxel; IV-CARBO-PAC, intravenous carboplatin and paclitaxel; QALY, quality-adjusted life year.

events over specified ranges (Table 1). Costs associated with death (defined here as the cost of six cycles of salvage outpatient chemotherapy plus palliative care) were varied from \$14,000 to \$42,000 with no change in results. Results were insensitive to variation of cost-to-charge ratio from 0.4 to 0.8.

A previously described method of calculating the cost of each chemotherapy regimen based on the actual number of cycles received was evaluated.¹² Using this method, the ICER of IP-CIS/PAC compared with IV-CARBO/PAC was \$117,305, \$46,809, and \$20,886 per QALY at 7 years, 11.5 years, and a lifetime, respectively.

Finally, the costs of IP-CIS/PAC and IV-CIS/PAC were varied to represent the costs of administering similar outpatient regimens with shortening of paclitaxel infusion from 24 hours to 3 hours (\$9,982 and \$4,262, respectively). When the costs of IP-CIS/PAC and IV-CIS/PAC were assumed to be the costs incurred for a similar outpatient regimen and efficacy held equivalent, IV-CIS/PAC became the least expensive strategy. The ICER for IV-CARBO/PAC was \$4,215 per QALY compared with IV-CIS/PAC, while the ICER of IP-CIS/PAC compared with IV-CARBO/PAC was \$26,311. At a lifetime under outpatient cost assumptions, IP-CIS/PAC had an ICER of \$5,522 per QALY compared with IV-CIS/PAC.

Monte Carlo simulation with 10,000 repetitions was performed for the 7-year time horizon; results are presented in a cost-effectiveness scatterplot (Fig 3). This analysis revealed some overlap with respect to the effectiveness of each strategy but no overlap with respect to cost. The ICER based on the probabilistic sensitivity analysis for IP CIS/PAC compared with IV-CARBO/PAC was \$180,294 per QALY (95% CI, \$146,336 to \$252,124).

DISCUSSION

Although the survival advantage of intraperitoneal chemotherapy observed in GOG protocol 172 was consistent with the results of two previous phase III trials, intraperitoneal administration was associated with more severe adverse events and lower QOL during treatment, raising serious concerns.³⁻⁵ Our study suggests that when compared with standard outpatient carboplatin and paclitaxel, the costs and effects on QOL of inpatient intraperitoneal chemotherapy also need to be considered. We found that extending the survival curves over a longer time horizon (11.5 years and over a lifetime) improved the cost effectiveness of IP-CIS/PAC compared with IV-CARBO/PAC. However, incorporation of time horizons beyond 7 years required use of

data from GOG-114 and United States life-tables, with inherent uncertainty in such projections. As expected, if the survival benefit that existed at 7 years was assumed to persist over these extended time horizons, IP-CIS/PAC retained a more favorable cost effectiveness profile.

A recently published cost-effectiveness analysis reported that IP-CIS/PAC was potentially cost effective compared with IV-CARBO/PAC, with an ICER of \$37,454 per QALY.⁷ This is considerably lower than our estimate of \$180,022 at a 7-year time horizon. While the prior study used median survival times, we used a Markov model and obtained survival from trial data at 6-month intervals, with calculation of mean survival times as a measure of effectiveness. The Markov model format allowed us to evaluate the economic impact of the chemotherapy regimens at several time horizons. Unlike the prior study, we obtained costs from Medicare reimbursement data and a large national database rather than local hospital charges. The prior study calculated the costs of each chemotherapy regimen based on the number of patients who completed intended cycles of treatments; patients not completing six cycles of intraperitoneal treatment were assigned costs of outpatient IV regimens to fill the balance of chemotherapy cycles.^{7,8} This results in a lower cost estimate for the intraperitoneal regimen. We assigned each patient the full cost of six cycles of

Fig 3. Monte Carlo simulation probabilistic sensitivity analysis comparing intravenous cisplatin and paclitaxel (IV-Cis/Pac) with intravenous carboplatin and paclitaxel (IV-Carbo/Pac), 7-year time horizon. GOG, Gynecologic Oncology Group.

the assigned chemotherapy regimen. To assess for bias, we performed the alternative method of chemotherapy cost calculations without significant change in results. Finally, we incorporated the costs of all severe toxicities whose rates differed significantly between regimens, incorporating both inpatient and outpatient costs in cases of hematologic toxicity.

The relatively high ICER of \$180,022 for IP-CIS/PAC compared with IV-CARBO/PAC at 7 years appears to be driven by the higher costs of inpatient chemotherapy. Many oncologists who administer intraperitoneal chemotherapy may choose to modify IV paclitaxel to a 3-hour infusion, which is now standard practice for outpatient IV-CARBO/PAC. In our sensitivity analysis, IP-CIS/PAC administered outpatient had a favorable ICER compared with IV-CARBO/PAC. However, acceptance of the cost effectiveness of outpatient IP-CIS/PAC with costs adjusted as such requires the assumption that 3-hour and 24-hour paclitaxel infusions result in regimens of equivalent effectiveness. While the effectiveness of paclitaxel infusions of different durations is likely similar, there is relatively limited phase III data to support the assumption that they are equivalent.^{22,23}

One potential limitation of our study is the use of survival data from two separate phase III trials. When comparing the raw survival data from both GOG-158 and GOG-172, we incorporated the IV-CIS/PAC arm data from each trial with nearly identical results and no difference in the ordering of strategies, suggesting that regimens from the two trials can be compared.

We used estimates for QOL-related utilities to compare chemotherapy regimens using QALYs. Women in the intraperitoneal arm of GOG-172 had significantly lower FACT-O QOL, pain, and neurotoxicity scores during treatment and 6 weeks post-treatment; neurotoxicity scores remained lower 1 year after treatment.^{3,4} As there is no validated method to directly convert the FACT-O score into a utility ratio to apply to the model,²⁴ we applied a method for calculation of utilities from QOL scores reported by Bristow et al to report results in QALYs.^{11,12} This may introduce error but does allow us to account for the impact of QOL on cost-effectiveness assessments. Further vali-

dated sets of ovarian cancer-specific utilities are needed to accurately assess the impact of treatments.

The treatment of patients with advanced ovarian cancer requires consideration of both the likelihood that each therapy will be effective and the patient's expected QOL during and after treatment. While it is attractive to suppose that the treatment resulting in the highest survival should become the gold standard, the costs of treatment and adverse events, both in dollars spent and in treatment-related reduction in QOL, must be taken into account. Our study suggests that an intraperitoneal inpatient chemotherapy regimen is only cost effective over a longer time horizon or if we assume that a survival advantage persists. If intraperitoneal chemotherapy can be conducted on an outpatient basis with a comparable and lasting survival advantage, this regimen has an attractive ICER compared with IV carboplatin and paclitaxel. Consideration should be given to a two-arm clinical trial of inpatient IP-CIS/PAC versus an outpatient intraperitoneal platinum-taxane chemotherapy regimen to identify the most effective treatment with the most acceptable adverse effects and costs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Laura J. Havrilesky, Angeles Alvarez Secord, Shalini Kulasingam

Provision of study materials or patients: Deborah K. Armstrong

Collection and assembly of data: Laura J. Havrilesky,

Kathleen M. Darcy, Deborah K. Armstrong

Data analysis and interpretation: Laura J. Havrilesky,

Angeles Alvarez Secord, Kathleen M. Darcy, Shalini Kulasingam

Manuscript writing: Laura J. Havrilesky, Angeles Alvarez Secord,

Kathleen M. Darcy, Shalini Kulasingam

Final approval of manuscript: Laura J. Havrilesky, Angeles Alvarez

Secord, Kathleen M. Darcy, Deborah K. Armstrong, Shalini Kulasingam

REFERENCES

- Alberts DS, Liu PY, Hannigan EV, et al: Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *N Engl J Med* 335:1950-1955, 1996
- Markman M, Bundy BN, Alberts DS, et al: Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group *J Clin Oncol* 19:1001-1007, 2001
- Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med* 354:34-43, 2006
- Wenzel LB, Huang H, Armstrong D, et al: Quality of life (QOL) results of a randomized study of intravenous (IV) paclitaxel and cisplatin vs IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer: A Gynecologic Oncology Group trial. *J Clin Oncol* 22:454s, 2004 (abstr 5026)
- Ozols RF, Bookman MA, du Bois A, et al: Intraperitoneal cisplatin therapy in ovarian cancer: Comparison with standard intravenous carboplatin and paclitaxel. *Gynecol Oncol* 103:1-6, 2006
- Ozols RF, Bundy BN, Greer BE, et al: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. *J Clin Oncol* 21:3194-3200, 2003
- Bristow RE, Santillan A, Salani R, et al: Intraperitoneal cisplatin and paclitaxel versus intravenous carboplatin and paclitaxel chemotherapy for stage III ovarian cancer: A cost-effectiveness analysis. *Gynecol Oncol* 106:476-481, 2007
- Bristow RE, Santillan A, Diaz-Montes TP, et al: Centralization of care for patients with advanced-stage ovarian cancer: A cost-effectiveness analysis. *Cancer* 109:1513-1522, 2007
- Gold M, Russell L, Weinstein M: *Cost-Effectiveness in Health and Medicine*. New York, NY, Oxford University Press, 1996
- Arias E: United States life tables, 2003. *Natl Vital Stat Rep* 54:1-40, 2006
- Baker TR, Piver MS, Hempling RE: Long term survival by cytoreductive surgery to less than 1 cm, induction weekly cisplatin and monthly cisplatin, doxorubicin, and cyclophosphamide therapy in advanced ovarian adenocarcinoma. *Cancer* 74:656-663, 1994
- Hoskins PJ, O'Reilly SE, Swenerton KD, et al: Ten-year outcome of patients with advanced epithelial ovarian carcinoma treated with cisplatin-based multimodality therapy. *J Clin Oncol* 10:1561-1568, 1992
- American Medical Association. www.ama-assn.org
- Agency for Healthcare Research and Quality. www.hcup.ahrq.gov
- Rocconi RP, Case AS, Straughn JM Jr, et al: Role of chemotherapy for patients with recurrent platinum-resistant advanced epithelial ovarian cancer: A cost-effectiveness analysis. *Cancer* 107:536-543, 2006
- Brumley RD: Future of end-of-life care: The managed care organization perspective. *J Palliat Med* 5:263-270, 2002
- US Department of Labor: Archived news releases for consumer price index. http://www.bls.gov/schedule/archives/cpi_nr.htm

18. Bell J, Brady MF, Young RC, et al: Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: A Gynecologic Oncology Group study. *Gynecol Oncol* 102:432-439, 2006

19. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 334:1-6, 1996

20. Muggia FM, Braly PS, Brady MF, et al: Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with sub-optimal stage III or IV ovarian cancer: A gynecologic oncology group study. *J Clin Oncol* 18:106-115, 2000

21. Rose PG, Nerenstone S, Brady MF, et al: Secondary surgical cytoreduction for advanced ovarian carcinoma. *N Engl J Med* 351:2489-97, 2004

22. Williams C, Collingwood M, Simera I, et al: Short versus long duration infusions of paclitaxel

for any advanced adenocarcinoma. *Cochrane Database Syst Rev* 4:CD00391, 2002

23. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al: European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: High-dose versus low-dose and long versus short infusion. *J Clin Oncol* 12:2654-2666, 1994

24. Basen-Engguist K, Bodurka-Bervers D, Fitzgerald MA, et al: Reliability and validity of the functional assessment of cancer therapy-ovarian. *J Clin Oncol* 19:1809-1817, 2001

Acknowledgment

We thank Caroline Folger for assistance in assembling cost data and Kim Blaser for manuscript preparation.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).