JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Survival Advantage and Prognostic Factors Associated With Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study

Devansu Tewari, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog, Bradley J. Monk, and John K. Chan

See accompanying editorial doi: 10.1200/JCO.2014.60.2797

Devansu Tewari, Kaiser Permanente Irvine Medical Center, Irvine; John K. Chan, California Pacific/Palo Alto Medical Foundation/Sutter Research Institute, San Francisco, CA; James J. Java, Gynecologic Oncology Group Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY; Ritu Salani, Wexner Medical Center, Ohio State University, Columbus; Thomas Herzog, University of Cincinnati, Cincinnati, OH; Deborah K. Armstrong, Sidney Kimmel Comprehensive Cancer Center, John Hopkins University School of Medicine, Baltimore, MD; Maurie Markman, Eastern Regional Medical Center, Cancer Treatment Centers of America, Philadelphia, PA; Bradley J. Monk, Creighton University School of Medicine, Phoenix, AZ.

Published online ahead of print at www.jco.org on March 23, 2015.

Supported by National Cancer Institute Grants No. CA 27469 to the Gynecologic Oncology Group Administrative Office and No. CA 37517 to the Gynecologic Oncology Group Statistical and Data Center and by a Gynecologic Oncology Group Young Investigator Award (D.T.) and John A. Kerner Denise & Prentis Cobb Hale Research Award (J.K.C.).

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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

Corresponding author: John K. Chan, MD, Gynecologic Oncology, California Pacific/Palo Alto Medical Foundation/Sutter Research Institute, 3838 California St #410, San Francisco, CA 94115; e-mail: chanjohn@sutterhealth.org.

0732-183X/15/3399-1/$20.00

DOI: 10.1200/JCO.2014.55.9898

ABSTRACT

Purpose
To determine long-term survival and associated prognostic factors after intraperitoneal (IP) chemotherapy in patients with advanced ovarian cancer.

Patients and Methods
Data from Gynecologic Oncology Group protocols 114 and 172 were retrospectively analyzed. Cox proportional hazards regression models were used for statistical analyses.

Results
In 876 patients, median follow-up was 10.7 years. Median survival with IP therapy was 61.8 months (95% CI, 55.5 to 69.5), compared with 51.4 months (95% CI, 46.0 to 58.2) for intravenous therapy. IP therapy was associated with a 23% decreased risk of death (adjusted hazard ratio [AHR], 0.77; 95% CI, 0.65 to 0.90; $P = .002$). IP therapy improved survival of those with gross residual (≤ 1 cm) disease (AHR, 0.75; 95% CI, 0.62 to 0.92; $P = .006$). Risk of death decreased by 12% for each cycle of IP chemotherapy completed (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). Factors associated with poorer survival included: clear/mucinous versus serous histology (AHR, 2.79; 95% CI, 1.83 to 4.24; $P < .001$), gross residual versus no visible disease (AHR, 1.89; 95% CI, 1.48 to 2.43; $P < .001$), and fewer versus more cycles of IP chemotherapy (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). Younger patients were more likely to complete the IP regimen, with a 5% decrease in probability of completion with each year of age (odds ratio, 0.95; 95% CI, 0.93 to 0.96; $P < .001$).

Conclusion
The advantage of IP over intravenous chemotherapy extends beyond 10 years. IP therapy enhanced survival of those with gross residual disease. Survival improved with increasing number of IP cycles.

J Clin Oncol 33. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Epithelial ovarian carcinoma is the leading cause of gynecologic cancer mortality in the United States, with an associated 15,500 deaths in 2012.[1,2] Most patients with advanced-stage cancer will eventually experience recurrence and die as a result of the disease.[3] Therefore, more effective therapies are needed in the treatment of this aggressive cancer.

The peritoneum serves as the primary site of spread and failure in most cases of advanced cancers. Even in the relapsed setting, the disease is typically confined to the peritoneal cavity. Thus, this region provides a sanctuary site for developing local therapies. Prior studies have reported on the pharmacologic advantage of delivering cisplatin intraperitoneally (IP), with a 20-fold higher concentration in the IP space compared with that measured in plasma after intravenous (IV) administration.[4-6] Likewise, IP paclitaxel can achieve a 1,000-fold greater concentration compared with IV administration.[7-12] In addition, IP therapy allows for continuous and prolonged exposure of high drug concentrations with lower peak plasma levels over time.[13]

Three intergroup trials have demonstrated the survival benefit associated with IP over IV therapy in advanced, low-volume ovarian cancer.[14-16] Despite the positive clinical trial results and a subsequent

National Cancer Institute alert, IP treatment has not been widely accepted as the standard of care in the United States and is infrequently used in Europe.[13,17] The hesitancy of clinicians to use IP therapy is likely attributed to higher toxicity, inconvenience, catheter complications, and uncertain long-term benefits.[18] In the most recent trial, the majority of patients did not complete the proposed experimental IP regimen because of toxicity and other related complications.[14] Thus, it is unclear if a therapeutic advantage to increasing the number of IP cycles exists. Conversely, it is not known if there is a minimum number of cycles of IP treatment needed to achieve the pharmacologic advantage and thus avoid unnecessary toxicity. In addition, there are no studies that have identified demographic and clinicopathologic characteristics of patients who may not tolerate or benefit from IP therapy, such as older patients with poor performance status or those with macroscopic residual disease. Most importantly, it is uncertain if the benefit of IP therapy persists over an extended period.

As such, we report this exploratory analysis of two Gynecologic Oncology Group (GOG) randomized phase III clinical trials to investigate the 10-year survival outcomes of those who underwent IP versus IV chemotherapy. We also evaluated factors associated with survival after IP therapy, including the extent of residual disease and number of cycles of IP therapy.

PATIENTS AND METHODS

Our study was a posthoc analysis using pooled data from all patients enrolled onto GOG protocols 114 and 172 (Fig 1).[15,16] Eligibility criteria included stage III epithelial ovarian or peritoneal carcinoma with no residual disease >1 cm in diameter after surgery. All patients had a GOG performance status of 0 to 2. Patients enrolled onto GOG 114 were randomly assigned to two different treatment arms. Patients received either IV paclitaxel 135 mg/m^2 followed by IV cisplatin 75 mg/m^2 for six courses or the study arm of IV carboplatin for two courses followed by IV paclitaxel 135 mg/m^2 on day 1 and IP cisplatin 100 mg/m^2 on day 8 for six courses. IV cisplatin was substituted for IP cisplatin for catheter-related malfunctions. In GOG 172, patients received 135 mg/m^2 IV paclitaxel followed by either 75 mg/m^2 IV cisplatin on day 2 (IV group) or 100 mg/m^2 of IP cisplatin on day 2 and 60 mg/m^2 of IP paclitaxel on day 8 (IP group) for six cycles. If IP cisplatin could not be administered secondary to toxicity or catheter-related issues, substitution with IV carboplatin was permitted. Patients who were treated provided signed informed consent consistent with all regulatory requirements.

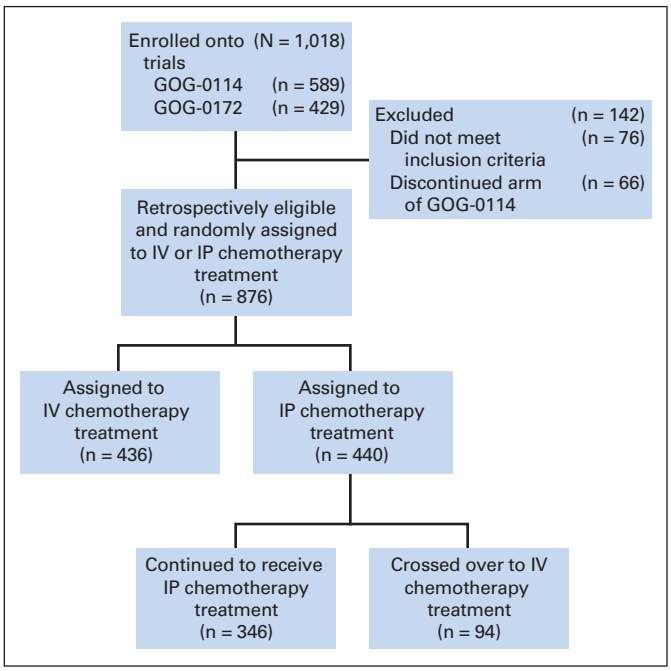

Fig 1. CONSORT diagram. GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous.

We compared baseline patient characteristics within and between the GOG studies using Pearson's χ^2 test to examine relationships between categorical variables and the Wilcoxon Mann-Whitney test for continuous variables.[19,20] Potential heterogeneity in treatment effect by prognostic factor subgroups was evaluated using likelihood ratio tests of subgroup-by-treatment interaction in models fitted to both the subgroups themselves and to the entire population. Kaplan-Meier estimates of survival functions included all-cause mortality and were compared using a two-sided log-rank test.[21] Hazard ratios (HRs) and CIs were estimated with Cox proportional hazards regression models to assess the relationship of treatment modality and survival outcomes adjusted for baseline demographic and clinicopathologic factors.[22,23] Overall significance of factors included in the Cox models was evaluated with Wald tests.[24] The number of total deaths resulting from nondisease causes was low for the patient sample (44 [5%] of 876). As a preliminary step in deciding whether competing-risk analyses were warranted, we censored nondisease deaths in the multivariable Cox models. Because results of the disease-specific models were not appreciably different from those of the all-cause models, competing-risk analyses were not performed. In addition, because this analysis was exploratory and hypothesis generating, no adjustments for multiple comparisons were made. All statistical analyses were performed with R software (version 2.14.2; http://www.r-project.org).

RESULTS

Characteristics of 876 patients included in the study are listed in Table 1. Demographic and clinicopathologic characteristics of patients in the two protocols were similar (Appendix Table A1, online only). Overall median follow-up was 10.7 years (GOG 114: median, 13.8 years; GOG 172: median, 9.7 years). In the overall study group, median progression-free survival (PFS) was 25 and 20 months for the IP and IV arms ($P = .019$), with corresponding overall survival (OS) of 61.8 versus 51.4 months, respectively ($P = .042$; Table 2; Fig 2). More specifically, IP therapy was associated with a 21% decreased risk of progression (adjusted HR [AHR], 0.79; 95% CI, 0.67 to 0.92; $P = .003$) and 23% decreased risk of death, with an AHR of 0.77 (95% CI, 0.65 to 0.90; $P = .002$) after adjusting for age, performance status, cell type, tumor grade, and residual disease (Table 2). Long-term survival rates after IV versus IP therapy based on protocols 114 and 172 are listed in Appendix Table A2 and Fig A1 (online only). We evaluated factors associated with long-term survival after IP therapy (Table 3). Clear-cell/mucinous versus serous histology (AHR, 2.79; 95% CI, 1.83 to 4.24; $P < .001$), gross residual (≤ 1 cm) versus no visible disease (AHR, 1.89; 95% CI, 1.48 to 2.43; $P < .001$), and fewer cycles of IP chemotherapy with crossover to IV therapy (AHR, 1.43; 95% CI, 1.02 to 2.01; $P = .041$) were prognostic factors associated with poorer long-term survival after IP therapy.

We then evaluated surgical factors that may predict for more benefit associated with IP therapy. Specifically, we proposed to determine whether IP therapy benefits those with gross residual disease (≤ 1 cm) in addition to those with no visible disease. Our data showed that IP therapy also improved the survival of those with gross residual

Table 1. Overall Patient Characteristics (N = 876)

Characteristic	No.	%
Age, years		
Median	48.6	
Range	48.6-65.6	
≤ 55.0	391	44.6
≥ 55.0	485	55.4
Race/ethnicity		
White	790	90.2
Black	41	4.7
Hispanic	28	3.2
Asian	16	1.8
Other	1	0.1
BMI, kg/m^2		
Median	24.7	
Range	21.8-29.1	
Performance status		
Normal, asymptomatic	387	44.2
Symptomatic, ambulatory	419	47.8
Symptomatic, in bed ≤ 50%	70	8.0
FIGO stage III	876	100
Tumor grade		
1	100	11.4
2	336	38.4
3	440	50.2
Histology		
Serous	635	72.5
Endometrioid	83	9.5
Clear cell	35	4.0
Mucinous	16	1.8
Other	107	12.2
Gross residual disease (≤ 1 cm)		
No	316	36.1
Yes	560	63.9
Treatment		
Intravenous	436	49.8
Intraperitoneal	440	50.2
GOG protocol		
114	462	52.7
172	414	47.3

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group.

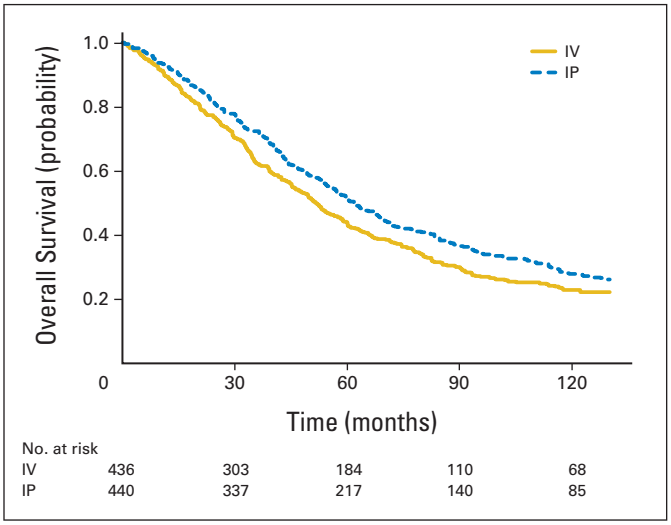

Fig 2. Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy ($P = .04$).

disease (AHR, 0.75; 95% CI, 0.62 to 0.92; $P = .006$; Fig 3). Nevertheless, it is important to note that those with gross residual disease had a 1.89-fold increase in risk of death (95% CI, 1.48 to 2.43; $P < .001$) compared with patients with no visible disease.

The overall study group of both trials showed 50% of patients in the IP arm completed six cycles of IP therapy required by the protocols. Because only a fraction of patients was able to complete the planned treatment, we considered the effect of treatment completion on survival. To account for the changing risk associated with chemotherapy over time, the number of cycles of chemotherapy completed was entered into the Cox proportional hazards model as a time-varying covariate. In our analysis, risk of death decreased by 12% for each cycle of IP chemotherapy completed by any patient (AHR, 0.88; 95% CI, 0.83 to 0.94; $P < .001$). The survival rates of subgroups of patients in GOG 0172 who completed all six cycles of chemotherapy are shown in Figure 4. Of these patients, completion of six cycles of IP chemotherapy was associated with better survival compared with three cycles of IP followed by three cycles of IV treatment ($P = .032$).

Because those who completed more cycles of IP therapy had a lower risk of death, we also evaluated the demographic and clinicopathologic factors associated with completing all six cycles of IP chemotherapy and found that younger age was associated with a higher likelihood of completing IP therapy. More specifically, the odds of completing IP therapy decreased approximately 5% for each increasing year of age at enrollment (odds ratio, 0.95; 95% CI, 0.93 to 0.96; $P < .001$). Other demographic and clinicopathologic factors, including performance status, were not prognostic of completing IP therapy.

Table 2. Long-Term PFS and OS of Patients After IV Versus IP Therapy (N = 876)

	PFS					OS				
Therapy Type	Median (months)	Range (months)	AHR	95% CI	*P*	Median (months)	Range (months)	AHR	95% CI	*P*
IV	20	17.7-23.5	Referent		—	51.4	46.0-58.2	Referent		—
IP	25	23.0-29.0	0.79	0.67 to 0.92	.003*	61.8	55.5-69.5	0.76	0.65 to 0.90	.002*
All	23	21.8-24.5	—		.019†	56.3	52.4-60.7	—		.042†

Abbreviations: AHR, adjusted hazard ratio; IP, intraperitoneal; IV, intravenous; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
†Wald test.

Table 3. Factors Associated With Long-Term Survival After IP Therapy

Factor	AHR	95% CI	*P*
Age, years	1.01	1.00 to 1.02	.137
GOG performance status			
0 (normal, asymptomatic)	1.00	Referent	—
1 (symptomatic, ambulatory)	0.96	0.76 to 1.22	.761
2 (symptomatic, in bed ≤ 50%)	1.20	0.80 to 1.81	.371
Histology			
Serous, other	1.00	Referent	—
Clear cell or mucinous	2.79	1.83 to 4.24	< .001
Tumor grade			
1	1.00	Referent	—
2	1.68	1.10 to 2.58	.017
3	1.49	0.99 to 2.25	.056
Gross residual disease*			
No	1.00	Referent	—
Yes	1.89	1.48 to 2.43	< .001
Cycles of IP chemotherapy (zero to six)	0.88	0.83 to 0.94	< .001
IV crossover†			
No	1.00	Referent	—
Yes	1.43	1.02 to 2.01	.041

Abbreviations: AHR, adjusted hazard ratio; GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous.
*Defined as ≤ 1 cm.
†IV crossover defined as those who stopped IP chemotherapy and crossed over to IV chemotherapy.

DISCUSSION

Despite trials showing survival benefit, IP therapy has not been widely adopted. GOG protocol 104 did show an IP survival advantage; however, cyclophosphamide was used rather than paclitaxel.[15] In GOG 114, investigators used paclitaxel, but OS was not statistically significant, and the IP arm included intensive IV carboplatin, which may have confounded the results.[16] The GOG 172 trial demonstrated that IV paclitaxel plus IP cisplatin and IP paclitaxel improved survival over IV paclitaxel and IV cisplatin. However, nearly half of the patients did not complete the IP regimen because of reported toxicity or associated complications. Furthermore, inferential data using cross-trial comparisons suggested that IV carboplatin may be slightly better than IV cisplatin, and the weekly schedule in the IP arm may have partially explained the survival advantage. This suggests that the magnitude of clinical benefit with IP therapy may not have been as prominent if the control arm of GOG 172 had included carboplatin and/or weekly dosing. On the contrary, two large meta-analyses combining multiple randomized trials showed the incorporation of an IP cisplatin regimen improved the survival of patients with advanced ovarian cancer.[25,26]

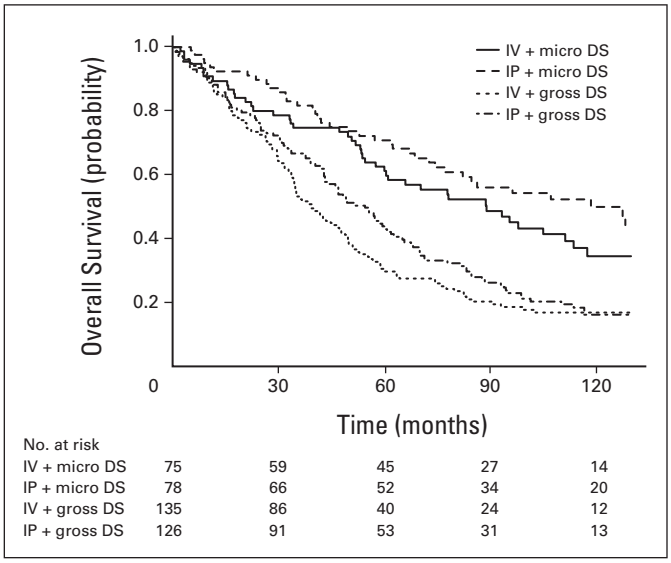

Fig 3. Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy based on extent of residual disease (DS; $P < .001$). NOTE. Gross residual defined as ≤ 1 cm; micro residual defined as no visible disease.

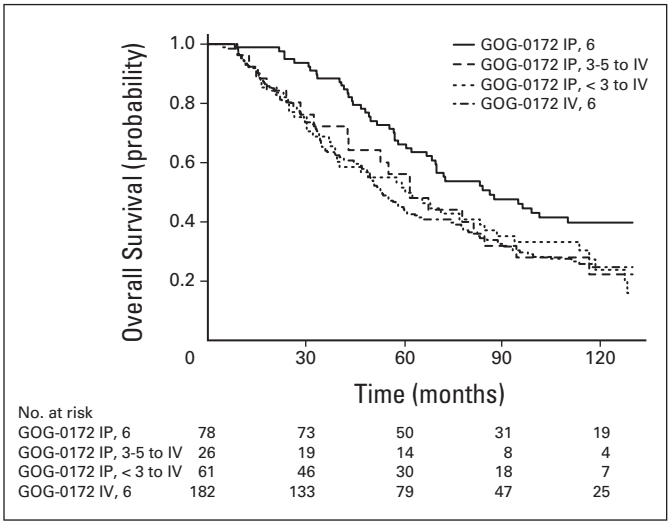

Fig 4. Long-term overall survival based on number of cycles of intraperitoneal (IP) therapy ($P = .03$). Analysis restricted to patients in Gynecologic Oncology Group (GOG) -0172 who completed all six cycles of chemotherapy (both IP and intravenous [IV] arms).

Additional concerns regarding IP therapy include: increased toxicity, multiday scheduling, lack of familiarity with catheter placement, and IP drug administration. More importantly, because median duration of follow-up was < 4.5 years in GOG 172, it is unknown if these results are sustainable after extended follow-up > 10 years. Our report provides 10-year data demonstrating the long-term survival advantage of IP over IV therapy. More specifically, IP treatment was associated with a 23% decreased risk of death that remained consistent after adjusting for age, performance status, cell type, tumor grade, and residual disease.

Additional advantages of IP therapy relate to a several-fold increase in drug concentration in the abdominopelvic cavity compared with systemic administration.[27,28] Despite this regional advantage, penetration into larger tumor burden may be limited; early animal studies showed that the penetration of IP drugs was limited to the superficial cell layer. Thus, IP therapy may not provide any advantage over IV treatment in patients with macroscopic residual disease.[10,11] Most clinical investigations of IP therapy have been confined to small-volume residual disease.[12,29-32] However, others have shown that prolonged drug exposure resulting from slow absorption from the peritoneum may contribute to an IP advantage. However, it is unclear if this pharmacokinetic advantage would benefit those with gross residual disease. In our analysis, we showed a survival advantage of IP

over IV therapy in patients with both gross residual (≤ 1 cm) and no visible disease. In a prior phase II trial, investigators evaluated the efficacy of IP therapy in women with large-volume residual disease and found a PFS of 25 months versus 20 months in IP- versus IV-treated patients.[33] A potential explanation for why IP therapy is effective even in large-volume residual disease is that multiple regimens of both IV and IP chemotherapies are administered over time. It is possible that the first few cycles of treatment depend on the delivery of platinum via capillary flow to reduce the size of larger residual tumors.[16,34] Subsequent IP treatments delivered regionally are more effective in small residual tumors.

These data are reassuring, because the most recent IP trial, GOG 252 (ClinicalTrials.gov identifier, NCT00951496), allowed for the enrollment of patients with larger-volume residual disease. If the long-term results from our report are confirmed, more patients might be candidates for IP treatment. It is important to note that those with gross residual disease had a 1.89-fold increase in risk of death compared with those with no visible residual disease. Our data confirmed a prior report on GOG trials 111, 132, 152, and 162 showing that those with microscopic residual disease or no gross residual disease had superior outcomes.[35-38] Our results confirm reports using data from two large prospective randomized trials and highlight the importance of complete cytoreductive surgery while suggesting a clinical benefit of IP therapy among those with gross residual disease.

Given that fewer than half of patients in the GOG 172 IP arm completed the proposed therapy, and yet there was an OS advantage, some may suggest that it is not necessary to complete all six cycles of IP therapy. However, there are no studies that have evaluated the number of cycles of therapy needed to obtain the IP advantage. Our data showed that those who completed more cycles of IP therapy had superior survival. Recent studies have shown that dose-dense therapy is associated with improved outcomes. The Japanese GOG study found that dose-dense therapy with paclitaxel improved OS, with a median follow-up of 6.4 years.[39] In contrast, a prior GOG study showed that doubling the dose of IV cisplatin and cyclophosphamide did not improve survival.[40] In fact, the strategy of increasing the dose density or dose-intensity of IV platinum agents resulted in significant nonhematologic toxicity related to cisplatin and thrombocytopenia resulting from carboplatin. The data from our report suggest that those who complete up to six cycles of IP therapy experience the most benefit. To achieve this, collaboration with a team of gynecologic oncologists, medical oncologists, and nursing professionals experienced in IP therapy may be required. We acknowledge that these findings may be confounded by the selection of patients who had better prognostic factors, leading to a higher likelihood of completing six cycles of chemotherapy with better outcomes. Nevertheless, these data on improved outcome associated with more cycles of IP chemotherapy remained significant after adjusting for demographic and clinical factors including age and performance status using multivariable analysis.

Because our data showed that it is important to receive six cycles of IP therapy, we performed an analysis to identify factors associated with completing the IP regimen. These findings may allow the clinician to better individualize IP therapy for those who will most likely complete and benefit from IP treatment and prevent unnecessary toxicity for those who will not tolerate this intensive regimen. Our data suggest that younger patients are more likely to complete six cycles of treatment. Prior studies have also shown that although younger patients are more likely to tolerate more intensive treatment, they also have better survival compared with older women after adjusting for extent of cytoreductive surgery and cycles of chemotherapy.[41]

The long-term results of these trials are encouraging and provide additional support on the benefit of IP therapy while demonstrating that long-term survival end points are achievable in advanced ovarian cancer. Clinical trial investigators suggest it is challenging to demonstrate long-term survival in cancers with an extended survival after progression. This may be explained by the significant treatment advances in salvage therapies, where variability in survival after progression dilutes the OS comparison for the initial treatment.[42] Some investigators have suggested that OS not be used as a primary end point when median survival after progression is > 12 months, but long-term OS results reported in our analysis suggest the contrary. We performed additional analyses in an attempt to determine the reason why IP chemotherapy prolonged OS. It is possible that IP therapy may not only extend the time to initial recurrence but also enhance response to subsequent treatment on relapse, resulting in better long-term survival. In our exploratory analyses, we found both an extension in PFS with updated follow-up data and longer survival after treatment for recurrence in the IP compared with IV patients. However, given the exploratory nature of this subset analysis, with a lower number of patients remaining in follow-up beyond 5 to 10 years after censoring, these findings should be interpreted with caution. Furthermore, it is possible that long-term survival results may have been affected by the differences in treatment of recurrent disease, which were not controlled for in these patients.

In conclusion, to our knowledge, this report provides the first updated results of GOG IP chemotherapy trials, showing long-term survival benefit extending beyond 10 years. Future results of the fourth phase III trial in GOG 252 will yield additional information regarding the incorporation of different approaches to IP therapy, including: dose-dense paclitaxel, antivascular targeted therapy, and maintenance therapy. Converting IP therapy into clinical practice based on the results of positive clinical trials is challenging. The long-term survival benefits described in this report may encourage more clinicians to adopt IP chemotherapy in the community. In addition, IP therapy may be implemented as a quality measure at institutions with the expertise and support teams necessary to administer IP treatment. Clinicians should support patients through the IP regimen, particularly if there are no significant or excessive toxicities. Lastly, the ability to better select patients who are more likely to complete IP therapy with better outcomes and less toxicity warrants further investigation as we move toward individualizing therapies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** Thomas J. Herzog, Johnson & Johnson, Genentech, AstraZeneca **Research Funding:** None

Expert Testimony: None **Patents, Royalties, and Licenses:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Devansu Tewari, Bradley J. Monk, John K. Chan

Provision of study materials or patients: Bradley J. Monk
Collection and assembly of data: Devansu Tewari, James J. Java, Deborah K. Armstrong, John K. Chan
Data analysis and interpretation: Devansu Tewari, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas J. Herzog, John K. Chan
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Siegel R, Naishadham D, Jemal A: Cancer statistics, 2013. CA Cancer J Clin 63:11-30, 2013
2. American Cancer Society: Cancer facts and figures 2012. http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf
3. Chan JK, Cheung MK, Husain A, et al: Patterns and progress in ovarian cancer over 14 years. Obstet Gynecol 108:521-528, 2006
4. Lopez JA, Krikorian JG, Reich SD, et al: Clinical pharmacology of intraperitoneal cisplatin. Gynecol Oncol 20:1-9, 1985
5. Pretorius RG, Hacker NF, Berek JS, et al: Pharmacokinetics of IP cisplatin in refractory ovarian carcinoma. Cancer Treat Rep 67:1085-1092, 1983
6. Howell SF, Pfeifle CE, Wung WE, et al: Intraperitoneal cis-diamminedichloroplatinum with systemic thiosulfate protection. Cancer Res 43: 1426-1431, 1983
7. Francis P, Rowinsky E, Schneider J, et al: Phase I feasibility and pharmacologic study of weekly intraperitoneal paclitaxel: A Gynecologic Oncology Group pilot study. J Clin Oncol 13:2961-2967, 1995
8. Markman M, Rowinsky E, Hakes T, et al: Phase I trial of intraperitoneal taxol: A Gynecoloic Oncology Group study. J Clin Oncol 10:1485-1491, 1992
9. Dedrick RL, Myers CE, Bungay PM, et al: Pharmacokinetic rationale for peritoneal drug administration in the treatment of ovarian cancer. Cancer Treat Rep 62:1-11, 1978
10. Los G, Mutsaers PH, van der Vijgh WJ, et al: Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: A comparison with systemic chemotherapy. Cancer Res 49:3380-3384, 1989
11. Los G, Mutsaers PH, Lenglet WJ, et al: Platinum distribution in intraperitoneal tumors after intraperitoneal cisplatin treatment. Cancer Chemother Pharmaco 25:389-394,1990
12. Howell SB, Zimm S, Markman M, et al: Long-term survival of advanced refractory ovarian carcinoma patients with small-volume disease treated with intraperitoneal chemotherapy. J Clin Oncol 5:1607-1612, 1987
13. Tummala MK, Alagarsamy S, McGuire WP: Intraperitoneal chemotherapy: Standard of care for patients with minimal residual stage III ovarian cancer? Expert Rev Anticancer Ther 8:1135-1147, 1987
14. Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354:34-43, 2006
15. 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
16. 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
17. Trimble EL, Christian MC: Intraperitoneal chemotherapy for women with advanced epithelial ovarian carcinoma. Gynecol Oncol 100:3-4, 2006
18. Walker JL, Armstrong DK, Huang HQ, et al: Intraperitoneal catheter outcomes in a phase III trial of intravenous versus intraperitoneal chemotherapy in optimal stage III ovarian and primary peritoneal cancer: A Gynecologic Oncology Group Study. Gynecol Oncol 100:27-32, 2006
19. Pearson K: On the criterion that a given system of deviations from the probable in the case of a correlated system of variables is such that it can be reasonably supposed to have arisen from random sampling. Philosophical Magazine Series 5 50:157-175, 1900
20. Mann HB, Whitney DR: On a test of whether one of two random variables is stochastically larger than the other. Ann Math Stat 18:50-60, 1947
21. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
22. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966
23. Cox DR: Regression models and life-tables. J R Stat Soc B 34:187-220, 1972
24. Wald A: Tests of statistical hypotheses concerning several parameters when the number of observations is large. Trans Am Math Soc 54:426-482, 1943
25. Jaaback K, Johnson N, Lawrie TA: Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 11:CD005340, 2011
26. Hess LM, Benham-Hutchins M, Herzog TJ, et al: A meta-analysis of the efficacy of intraperitoneal cisplatin for the front-line treatment of ovarian cancer. Int J Gynecol Cancer 17:561-570, 2007
27. Cannistra SA: Cancer of the ovary. N Engl J Med 351:2519-2529, 2004
28. Thigpen T: First-line therapy for ovarian carcinoma: What's next? Cancer Invest 22:21-28, 2004 (suppl 2)
29. Kirmani S, Lucas WE, Kim S, et al: A phase II trial of intraperitoneal cisplatin and etoposide as salvage treatment for minimal residual ovarian carcinoma. J Clin Oncol 9:649-657, 1991
30. Barakat RR, Sabbatini P, Bhaskaran D, et al: Intraperitoneal chemotherapy for ovarian carcinoma: Results of long-term follow-up. J Clin Oncol 20:694-698, 2002
31. Markman M, Brady MF, Spirtos NM, et al: Phase II trial of intraperitoneal paclitaxel in carcinoma of the ovary, tube, and peritoneum: A Gynecologic Oncology Group study. J Clin Oncol 16: 2620-2624, 1998
32. Rothenberg ML, Liu PY, Braly PS, et al: Combined intraperitoneal and intravenous chemotherapy for women with optimally debulked ovarian cancer: Results from an intergroup phase II trial. J Clin Oncol 21:1313-1319, 2003
33. Fujiwara K, Nagao S, Kigawa J, et al: Comparative phase II study of intraperitoneal (IP) vs intravenous (IV) carboplatin administration with IV paclitaxel in patients with bulky residual disease after primary debulking surgery for epithelial ovarian or primary peritoneal cancer: A Sankai Gynecology Study Group (SGSG) study. J Clin Oncol 25:294s, 2007 (suppl; abstr 5584)
34. Shapiro F, Schneider J, Markman M, et al: High-intensity intravenous cyclophosphamide and cisplatin, interim surgical debulking, and intraperitoneal cisplatin in advanced ovarian carcinoma: A pilot trial with ten-year follow-up. Gynecol Oncol 67:39-45, 1997
35. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin versus paclitaxel and cisplatin: A phase III randomized trial in patients with suboptimal stage III/IV ovarian cancer (from the Gynecologic Oncology Group). Semin Oncol 23:40-47, 1996 (suppl 12)
36. Muggia FM, Braly PS, Brady MF, et al: Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: A gynecologic oncology group study. J Clin Oncol 18:106-115, 2000
37. Rose PG, Nerenstone S, Brady MF, et al: Secondary surgical cytoreduction for advanced ovarian carcinoma. N Engl J Med 351:2489-2497, 2004
38. Winter WE 3rd, Maxwell GL, Tian C, et al: Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 26:83-89, 2008
39. Katsumata N, Yasuda M, Takahashi F, et al: Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: A phase 3, open-label, randomised controlled trial. Lancet 374:1331-1338, 2009
40. McGuire WP, Hoskins WJ, Brady MF, et al: Assessment of dose-intensive therapy in suboptimally debulked ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 13:1589-1599, 1995
41. Chan JK, Loizzi V, Lin YG, et al: Stages III and IV invasive epithelial ovarian carcinoma in younger versus older women: What prognostic factors are important? Obstet Gynecol 102:156-161, 2003
42. Broglio KR, Barry DA: Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 101:1642-1649, 2009

GLOSSARY TERMS

maintenance therapy: therapy intended to prolong the benefit (eg, disease remission) experienced by a patient from a prior primary treatment (eg, chemotherapy).

overall survival: the duration between random assignment and death.

progression-free survival: time from random assignment until death or first documented relapse, categorized as either locoregional (primary site or regional nodes) failure or distant metastasis or death.

Acknowledgment

Presented in abstract form at the Society of Gynecologic Oncology Annual Meeting, Los Angeles, CA, March 9-12, 2013.

Appendix

The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Alabama at Birmingham, Oregon Health Sciences University, Duke University Medical Center, Abington Memorial Hospital, University of Rochester Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, University of Southern California at Los Angeles, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group, University of California at Los Angeles, University of Washington, University of Pennsylvania Cancer Center, University of Miami School of Medicine, Milton S. Hershey Medical Center, Georgetown University Hospital, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, Albany Medical College, University of California Medical Center at Irvine, Tufts-New England Medical Center, Rush-Presbyterian-St Luke's Medical Center, University of Kentucky, Eastern Virginia Medical School, Cleveland Clinic Foundation, Johns Hopkins Oncology Center, State University of New York at Stony Brook, Eastern Pennsylvania GYN/ONC Center, Southwestern Oncology Group, Washington University School of Medicine, Memorial Sloan-Kettering Cancer Center, Columbus Cancer Council, University of Massachusetts Medical School, Fox Chase Cancer Center, Medical University of South Carolina, Women's Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, University of Arizona Health Science Center, Tacoma General Hospital, Eastern Collaborative Oncology Group, Thomas Jefferson University Hospital, Case Western Reserve University, Tampa Bay Cancer Consortium, North Shore University Hospital, Gynecologic Oncology Network, Ellis Fischel Cancer Center, and Fletcher Allen Health Care.

Table A1. Demographic and Clinicopathologic Characteristics of Patients in GOG Protocols 114 and 172 (N = 876)

Characteristic	GOG 114 (n = 462) No.	GOG 114 (n = 462) %	GOG 172 (n = 172) No.	GOG 172 (n = 172) %	*P*
Age, years					.047*
Median	56.6		57.5		
Range	47.4-64.9		49.5-66.8		
Age, years					
< 55.0	214	46.3	177	42.8	.289†
≥ 55.0	248	53.7	237	57.2	
Race/ethnicity					.003†
White	418	90.5	372	89.9	
Black	30	6.5	11	2.7	
Hispanic	10	2.2	18	4.3	
Asian	4	0.9	12	2.9	
Other	0	0.0	1	0.2	
BMI, kg/m^2‡					.445*
Median	24.5		25		
Range	21.7-28.8		21.9-29.3		
Performance status					.027†
Normal, asymptomatic	206	44.6	181	43.7	
Symptomatic, ambulatory	209	45.2	210	50.7	
Symptomatic, in bed < 50%	47	10.2	23	5.6	
Tumor grade (differentiation)					.417†
1	57	12.3	43	10.4	
2	182	39.4	154	37.2	
3	223	48.3	217	52.4	
Histology					< .001†
Serous	308	66.7	327	79.0	
Endometrioid	54	11.7	29	7.0	
Mucinous	13	2.8	3	0.7	
Clear cell	15	3.2	20	4.8	
Other	72	15.6	35	8.5	
Gross residual disease					.606†
No	163	35.3	153	37.0	
Yes	299	64.7	261	63.0	
Treatment					.593†
IV	226	48.9	210	50.7	
IP	236	51.1	204	49.3	

Abbreviations: BMI, body mass index; GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous.
*Wilcoxon test;
†Pearson's test.
‡Because of missing values, n = 873.

Table A2. Long-Term PFS and OS After IV Versus IP Therapy for Patients in GOG Protocols 114 and 172

GOG Protocol Arm	No. of Patients	PFS No. of Events	PFS Median (months)	PFS Range (months)	PFS *P**	PFS AHR	PFS 95% CI	PFS *P*†	OS No. of Events	OS Median (months)	OS Range (months)	OS *P**	OS AHR	OS 95% CI	OS *P*†
114-IV	226	191	22.2	17.8-25.1	.131	Referent		—	174	52.4	45.1-63.8	.216	Referent		—
172-IV	210	173	18.3	15.6-23.3		1.09	0.88 to 1.34	0.44	155	50.4	43.2-58.6		1.07	0.85 to 1.33	0.57
114-IP	236	197	27.3	23.4-30.7		0.83	0.68 to 1.01	0.06	176	59.6	52.3-69.5		0.87	0.71 to 1.08	0.21
172-IP	204	160	23.8	20.7-29.0		0.87	0.70 to 1.07	0.18	141	65.6	57.1-81.4		0.83	0.66 to 1.04	0.10

Abbreviations: AHR, adjusted hazard ratio; GOG, Gynecologic Oncology Group; IP, intraperitoneal; IV, intravenous; OS, overall survival; PFS, progression-free survival.
*Log-rank test.
†Wald test.

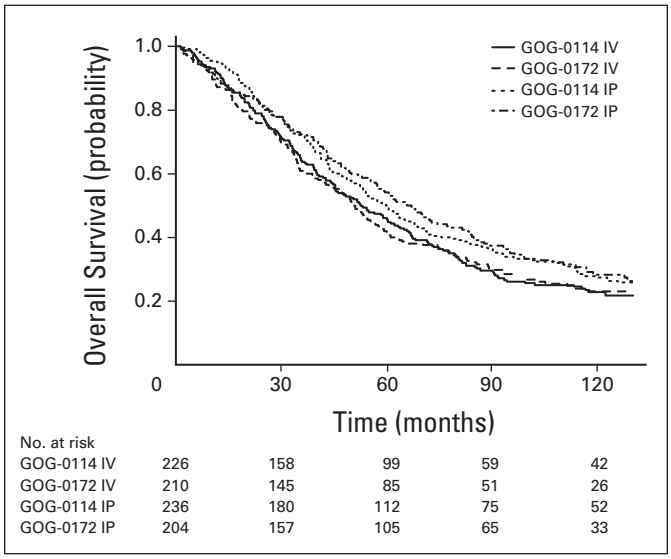

Fig A1. Long-term overall survival after intravenous (IV) versus intraperitoneal (IP) therapy based on Gynecologic Oncology Group (GOG) protocols 0114 and 0172.

