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SURVIVAL FOLLOWING SECOND-LINE INTRAPERITONEAL THERAPY FOR THE TREATMENT OF EPITHELIAL OVARIAN CANCER: THE GYNECOLOGIC ONCOLOGY GROUP EXPERIENCE

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Abstract

Objective—To assess the association between patient-disease characteristics and (OS) survival following second-line intraperitoneal (IP) treatment of ovarian cancer.

Methods—Data were aggregated from seven GOG phase II studies conducted between 1988 and 1995 to evaluate IP therapy of partially responsive or recurrent disease, but no tumor masses greater than 0.5 cm. Factors evaluated include: age, performance status, extent of residual disease, tumor grade and histology,

Results—432 eligible women were treated on one of the seven second-line phase II IP trials. The median OS was 2.4 years (individual study medians: 1.9–2.9 years). Relative to women with grade 1 cancers, those with grade 2 or grade 3 cancers experienced 1.82 (95% confidence interval (CI): 1.21 – 2.74) and 2.02 (95% CI: 1.35 – 3.03) times greater instantaneous death rates, respectively, and those with clear cell adenocarcinoma experienced death rates 6.00 (95% CI: 3.27 – 10.9) times greater. The extent of residual disease, surgically assessed prior to starting study treatment, was also associated with OS. Relative to those who had no evidence of gross disease, those with gross disease that was completely resected, or unresectable disease (not larger than 0.5 cm), experienced death rates 1.74 (95% CI: 1.25 – 2.42) and 2.26 (95% CI: 1.67 – 3.05) times greater, respectively.

Conclusions—There are patient and disease characteristics strongly associated with survival following second-line IP treatments. These factors are relevant to clinicians considering IP therapy outside the investigative setting and for the development of future studies in this area.

Keywords

Ovarian cancer; intraperitoneal chemotherapy; cisplatin; paclitaxel

INTRODUCTION

Over the past two decades much has been learned regarding both the potential clinical utility and limitations associated with intraperitoneal drug delivery as a management strategy for patients with ovarian cancer. The safety and pharmacokinetic advantage of regional treatment employing selected agents with known activity in this malignancy have been confirmed (1,2), as providing a modest improvement in survival (progression-free and overall), compared to intravenous delivery of the agent, as primary treatment of small volume residual advanced ovarian cancer (3–6).

The Gynecologic Oncology Group (GOG) had been a pioneer in the exploration of intraperitoneal drug delivery as a second-line management approach in women with residual or recurrent disease following primary platinum-based chemotherapy (7–13). In a series of phase II studies initiated in 1988, the GOG evaluated the clinical efficacy, and toxicity, of combination cisplatin-based regional therapy (with etoposide [7], thiotepa [8], 5-fluorouracil [9], and interferon [10,11]), as well as several non-platinum single-agent programs (interferon [12] and paclitaxel [13]).

Prior to entry into all of these studies, patients had to undergo a laparotomy to assess the extent of disease and, if possible, the gynecologic oncologist was to resect persistent macroscopic cancer where possible. Further, to evaluate response to the regional treatment programs, a reassessment surgical procedure was to be performed at the completion of therapy in all patients who were without evidence of clinical disease progression at this point in time. However, since reassessment laparotomy is a burdensome procedure for the patient, it is not an ideal trial endpoint. For this reason, progression-free survival (PFS) or overall survival (OS) may be preferable endpoints for future phase 2 trials. Therefore, the current study seeks to assess those factors related to the duration of OS in this patient population.

This historical series of GOG trials forms a rather unique experience, as the same group of investigators employing essentially identical entry criteria and evaluation procedures, conducted sequential intraperitoneal phase II studies where surgical documentation of the extent of disease was required. Further, with the passage of a number of years since the completion of the last such trial, it is now possible to look at the entire patient population, involving more than 400 women, and inquire regarding any general conclusions which can be developed from this large multi-institution non-randomized phase 2 trial experience.

Of particular interest is the OS (or PFS) of patients treated on these studies; specifically, to inquire if there is any evidence that one particular regimen, or sub-group of patients, may have experienced a more (or less) favorable outcome (14–17). This paper reports the results of this retrospective review of survival for patients entered into one of the seven GOG phase II second-line intraperitoneal treatment trials conducted between 1988 and 1995.

METHODS AND MATERIALS

Patient eligibility

Patients had to meet the following eligibility criteria to be eligible for entry into any of the GOG phase II intraperitoneal trials: (a) histologically documented invasive epithelial carcinoma of the ovary; (b) patients who had a partial or incomplete response to primary chemotherapy and who had documented residual disease (≤ 0.5 cm maximum tumor diameter) at the conclusion of a second-look laparotomy were eligible; (c) patients with a history of complete response followed by a recurrence with no residual nodule > 0.5 cm in diameter at the completion of surgical assessment were eligible; (d) patients with ≤ 0.5 cm residual disease in the intraperitoneal space were eligible regardless of whether or not a retroperitoneal biopsy

was done, if they met all other eligibility criteria; (e) patients were to have had no more than one prior chemotherapy regimen; however, for studies *not* containing platinum compounds, patients may have received one prior intravenous regimen and one prior intraperitoneal platinum program; (f) treatment must have started within 12 weeks after the second-look laparotomy; (g) white blood count $\geq 3,000/\text{mm}^3$, neutrophils $\geq 1,500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, serum creatinine $\leq 2.0 \text{ mg\%}$; (g) patients must have signed a local IRB approved informed consent document indicating they understood the investigational nature of the treatment programs.

Patients were *ineligible* for treatment on a GOG regional therapy trial if any of the following were present: (a) prior evidence of extraperitoneal metastasis, except for a pleural effusion which responded completely to previous intravenous therapy; (b) history of past or concomitant malignancy other than skin (excluding melanoma); (c) presence of serious infection, septicemia or pneumonia; (d) prior whole abdominal radiotherapy; (e) prior intraperitoneal cisplatin as primary chemotherapy (for programs including this drug); (f) GOG performance status 3 or 4; (f) < 3 weeks from the last treatment with chemotherapy or radiation therapy.

For the purposes of the current report, those patients who did not receive any of their study treatment, are not included in these analyses.

Drug delivery

The treatments were administered intraperitoneally through an implantable peritoneal dialysis catheter (e.g., Tenckhoff catheter), which in many patients was attached to an indwelling portal delivery system.

Each protocol included specific requirements for treatment duration and for the process of delivery of therapy, based on the drug(s) utilized. The details of each intraperitoneal regimen have previously been published (7–13).

Definition of survival

OS was defined as observed length of life from entry into the study until death due to any cause, or, for living patients, the date of last contact regardless of whether or not this contact was on a subsequent protocol.

Progression-free interval was defined as the date from entry onto the study to the date of first progression or death or for patients alive without progression the date of last contact. Persistent disease detected during reassessment surgery was not considered progression.

Statistical analysis

Descriptive summaries by treatment protocol in terms of mean, standard deviation or frequencies are presented. Unadjusted estimates of the survival probabilities and median survival for time to death and time to progression were calculated using the Kaplan-Meier procedure and the null hypothesis of equal distributions of failure times was assessed with a log-rank test. The adjusted hazard ratios for time to death were estimated using proportional hazards models. Covariates that were considered for inclusion in the proportional hazards models included: age (< 50 , 50–59, 60 – 69, > 70 years old), initial performance status (0-normal, 1-symptomatic, 2-partially bedridden), histologic cell type (papillary serous, endometrioid, clear cell, mucinous, mixed adenocarcinoma, adenocarcinoma not otherwise specified (NOS), and other histologies), grade of tumor (1, 2, 3 and clear cell which was not graded), and extent of residual disease at second-look surgery (no gross disease identified (microscopic disease only), gross disease completely resected during reassessment surgery, gross residual disease which could not be completely resected). These covariates were assessed

individually in separate models and collectively. A step-down procedure was used to construct the final model which included those covariates which were considered to be significantly ($p < 0.05$) associated with overall survival. A prognostic index is computed for each patient as the vector dot product of the patient's covariates and the estimated coefficients from the final model. Finally, treatment protocols (102B, 102C, 102E, 102F, 102G, 102N, 0151 – see Table 1) were compared adjusting for patients' prognostic indices.

RESULTS

A total of 432 eligible patients were enrolled and treated on one of the seven phase II GOG intraperitoneal trials. The mean ages of patients in each of the seven trials ranged from 54.8 years to 57.0 years. The proportion of patients with performance status 0 or 1 ranged from 86% to 98%. Papillary serous adenocarcinoma was the most common histology (60% – 80%) and the primary tumors were often either grade 2 or 3 (83% – 89%). Clear cell adenocarcinomas were not assigned grades since there is no universally accepted grading system for this cell type.

The PFS and OS for the seven individual phase II trials are shown in Figures 1 and 2 (Figure 2 available online), respectively. The combined median OS for the seven studies combined was 2.4 years and range from 1.9 years to 2.9 years across studies. An unadjusted log-rank test assessing equality of deaths rates across the seven treatment protocols was statistically significant ($p = 0.04$). The combined median PFS was 1.2 years ranging from 0.78 to 1.5 years across studies. Likewise, an unadjusted log-rank test assessing equivalence of the PFS across studies was also statistically significant ($p = 0.04$). One study, 102-F, had the both the smallest median time to progression and smallest median time to death. (See the multivariate assessment below for additional results.)

The unadjusted comparison of survival duration between age groups is significant ($p = 0.003$). However, this appears to be primarily due to slightly longer survival times among those patients younger than 50 years, whose median survival time was 3.1 years. For those 50 to 59, 60 to 69 and 70 years or older, the median times to death were 2.5, 1.9 and 2.8 years, respectively (Figure 3 – available online).

Figure 4 illustrates the distribution of the OS times for these patients classified by the extent of their disease at reassessment surgery. The median survival time was 3.6 years for those patients who had no gross disease identified during surgery. For those with gross residual disease, the median time to death was 2.5 years, if it was completely resected during surgery, but only 1.7 years if it was not resected. The unadjusted comparison of survival time distributions for these three groups is statistically significant ($p < 0.001$).

The estimated cumulative distribution of survival times is displayed in Figure 5 for all of the patients classified by the grade of their primary tumor. These grades were assessed on tissue specimens collected when the patient was initially diagnosed. Patients with grade 1 primary cancers tended to survive longer (median = 4.3 years) than those with grade 2 or 3 cancers (median = 2.3 years). However, the shortest survival times were observed among those women with clear cell adenocarcinoma, which were not assigned histologic grades. The median time to death for these patients was only 1.2 years. After adjusting for tumor grade there were no other noteworthy differences in the distribution of the survival times among the remaining cell types. However, the precision of these comparisons is limited due to many histologic subgroups involve only a small number of patients.

The estimated relative hazards from the final multivariate Cox regression model of survival are summarized in Table 2. This model includes age, extent of residual disease and primary tumor grade. Relative to those patients who were younger than 50 years old, the estimated

instantaneous death rates were 1.36, 1.57 and 1.38 times greater for those 50 – 59, 60 – 69 and ≥ 70 years old, respectively. That is, while those younger than 50 years tended to experience a lower death rate, the differences among the older age groups are less striking or consistent. Compared to those patients with grade 1 tumors, the instantaneous death rates were 1.82 and 2.02 times greater for those patients with grade 2 or 3 tumors, and the death rate for those with a clear cell adenocarcinoma was 6.00 (95% CI: 3.27 – 10.9) times greater. Finally, the adjusted death rates were greater among those patients who had residual disease discovered at their second-look assessment surgery. Relative to those who had no residual disease discovered, those with disease that was completely resected had a death rate 1.74 times greater, but those who had some unresectable disease exhibited death rates 2.26 times greater. The final model does not include initial performance status or histologic cell type because these factors did not attain the threshold level set for statistical significance (0.05).

The prognostic index for each patient was computed using the vector dot product of the estimated log-hazard ratios from the final model and the value each patient's covariates. The median score for all 432 patients is 1.54. The first three quartiles of these score for each treatment study are summarized in Table 1. There is a small amount of variability in these score between studies, but this is not statistically significant (Kruskal-Wallis rank test, $p=0.439$). The study with the least favorable distribution of prognostic scores (not statistically significant) was 102-F.

Table 3 summarizes the estimated treatment hazard ratios adjusted for each patient's prognostic score. These treatment hazard ratios are expressed relative to study 151, but they can be expressed relative to any of the other studies by simply dividing each estimate by the hazard ratio for preferred reference study. A test of the null hypothesis that these death rates are equivalent can be rejected at the 0.05 level ($p=0.034$). The study with the highest adjusted death rate is 102-F. After removing this study from the analysis, a test of this null hypothesis is no longer considered statistically significant ($p=0.547$).

DISCUSSION

In this retrospective review of more than 400 ovarian cancer patients treated on a phase II GOG trial employing second-line intraperitoneal therapy, we have observed several interesting findings relevant to clinicians considering this management approach outside the investigative setting, and for the development of future studies in this area.

First, there are a few factors which appear to be associated with the patient's prognosis. In particular, the prognosis is relatively more favorable for those with either no macroscopic disease or completely resected disease at the time the therapeutic program is initiated. Similar observations have been reported from other studies (14–18). Also, patients with well differentiated adenocarcinoma tend to experience longer survival than those with more anaplastic tumors and those with a clear cell histology. Finally, those younger than 50 years old tend to experience slightly longer survival than older patients.

Unfortunately, in the absence of data from a randomized phase III trial it remains unknown if the prolonged PFS and OS in this population is a direct result of the second-line intraperitoneal treatment strategy, or reflects the *natural history of the disease process* in a group of individuals with particularly favorable biological characteristics (e.g., lower tumor grade), or is a combination of these factors.

Second, there is no evidence from this analysis to suggest that one intraperitoneal platinum-based regimen is superior to another in the second-line setting. However, there was a noteworthy difference in OS between the regimens that contained either platinum or paclitaxel and the only regimen that did not (102-F). The reason for shorter survival in this specific

treatment group was not explained by the patient or disease factors evaluated in this study. Although not documented through the conduct of a phase III trial, these data support for the conclusion that intraperitoneal alpha-interferon is an inferior second-line treatment strategy, compared to either intraperitoneal cisplatin-based chemotherapy or intraperitoneal paclitaxel.

There is considerable data revealing a survival advantage attributable to intraperitoneal cisplatin when employed as first-line chemotherapy of small volume residual advanced ovarian cancer (3–5). In the most recent phase III trial, both cisplatin and paclitaxel were delivered by the intraperitoneal route.

However, there is currently little justification to employ second-line *combination* platinum-based regional drug delivery outside a clinical trial. In fact, based on currently available evidence, it may be more appropriate to argue for the use of single agent intraperitoneal cisplatin, which permits the increased tumor-drug interactions of this important drug without the additional toxicity of a second agent of unknown clinical utility. In this regard, it is important to note that while the GOG does not have current experience with the administration of second-line single-agent intraperitoneal carboplatin, other investigators have documented the tolerability and activity of this management strategy (19–22).

Finally, consideration might be given to using the data from these multi-institutional studies that involve patients who met documented eligibility criteria and were treated with prospectively well-defined regimens as an important “historical control” population for future studies examining novel management strategies (e.g., intraperitoneal drug delivery, intravenous chemotherapy followed by a “cancer vaccine”). In this rather extensive second-line treatment data base involving patients with small-volume residual ovarian cancer, it is even possible to specifically describe the outcome of populations with “platinum-sensitive” versus “platinum-resistant” disease (data not shown), which could be employed in such an analysis.

Comparisons to these data would allow investigators to obtain a preliminary assessment of whether *the survival* they observe following the investigational treatment of individuals is particularly promising, or appears to fall within “the range” of that associated with the previously reported trials.

For example, if the median survival in an intraperitoneal phase II trial of a novel cytotoxic or cytostatic agent is found to be substantially longer than noted in the current experience and not attributable to an over-representation of patients with more favorable clinical features (e.g., grade 1 cancers), then this might be considered sufficient evidence to warrant further evaluation of the regimen. The opposite survival outcome, such as that observed in the current series following treatment with intraperitoneal alpha-interferon, would also be informative in future decisions regarding development of a particular strategy.

In summary, several phase III studies have demonstrated that front-line cisplatin therapy for the treatment of women with advanced small volume ovarian cancer increases OS when it is delivered regionally rather than systemically (3–5). For women with large volume disease, surgical and medical debulking followed by a second-line intraperitoneal regimen may be a reasonable therapeutic approach. However, in order to assess this treatment strategy, effective and safe second-line intraperitoneal regimens are desperately needed. It would be inefficient to conduct randomized phase III clinical trials to assess the myriad of possible cytotoxic and cytostatic treatment combinations and doses. Rather, smaller phase 2 trials are currently needed to identify regimens that are promising. Investigators proposing single-arm investigations need a frame of reference. These data or the results from this study can be used for this purpose. Investigators proposing randomized phase II trials must consider the potential for confounding

between prognosis and treatment, since those trials are usually relatively small. This current study identifies some pre-treatment factors that should be considered as potential confounders.

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Figure 1.
Survival by Treatment Protocol.

Progression – Free Survival By Treatment Protocol

Figure 2.
Progression-Free Survival by Treatment Protocol.

Figure 3.
Survival by Age Group.

Figure 4.
Survival by Residual Disease at Reassessment Surgery

Figure 5.
Survival by Primary Tumor Grade

Table 1

Study, patient and disease characteristics

Study characteristics							
Study identifier	102-B	102-C	102-E	102-F	102-G	102-N	151
Date accrual initiated	Jan-1988	Aug-1988	Aug-1989	Jun-1989	Dec-1990	Feb-1992	Jul-1994
Date accrual terminated	Dec-1988	Aug-1989	Dec-1990	Mar-1994	Dec-1991	Mar-1994	Sep-1995
Number of patients	43	42	84	80	52	55	76
P agent(s)	Cisplatin + 5-FU	Cisplatin + α -interferon	Cisplatin + Etoposide	α -interferon	Cisplatin + Thiotepa	Cisplatin + α -2b interferon	Paclitaxel
Characteristics of evaluable patients							
Age (mean $\pm$ std dev)	56.3 $\pm$ 10.1	56.2 $\pm$ 10.4	56.1 $\pm$ 11.8	57.0 $\pm$ 10.9	56.4 $\pm$ 11.2	55.1 $\pm$ 11.0	54.8 $\pm$ 11.7
<50	23.3%	26.2%	32.1%	26.2%	30.8%	29.1%	32.9%
50-59	39.5%	40.5%	30.95%	30.0%	32.7%	40.0%	31.6%
60-69	27.9%	23.8%	26.2%	25.0%	25.0%	18.2%	28.9%
≥ 70	9.3%	9.5%	10.7%	11.5%	11.5%	12.7%	6.6%
Performance status							
0	58.1%	40.5%	45.2%	33.7%	46.1%	43.6%	46.0%
1	39.5%	40.5%	50.0%	52.5%	46.1%	52.7%	51.3%
2	2.3%	19.0%	4.8%	13.7%	7.7%	3.64%	2.6%
Residual disease at 2 nd look							
surgery							
No gross disease	25.6%	9.5%	13.1%	12.5%	19.2%	29.1%	25.0%
Disease comp. resected	13.9%	30.9%	39.3%	31.2%	32.7%	29.1%	22.4%
Unresectable disease	60.5%	59.5%	47.6%	56.2%	48.1%	41.8%	52.6%
Tumor Grade							
1	4.7%	16.7%	13.1%	8.7%	9.6%	7.3%	10.5%
2	37.2%	40.5%	50.0%	32.7%	32.7%	30.9%	53.9%
3	46.5%	35.7%	33.3%	53.8%	53.8%	56.4%	35.5%
No grade (clear cell)*	7.0%	7.1%	3.6%	3.8%	3.8%	5.4%	0.0%
Histology							
Papillary serous	60.5%	64.3%	70.2%	71.2%	67.3%	61.8%	80.3%
Endometrioid	16.3%	11.9%	14.3%	5.0%	19.2%	9.1%	7.9%
Clear cell	7.0%	7.1%	3.6%	5.0%	3.8%	5.4%	0.0%
Mucinous	2.3%	2.3%	1.2%	2.5%	1.9%	1.3%	1.8%
Mixed adenocarcinoma	4.6%	9.5%	3.6%	5.0%	1.9%	5.4%	3.9%
Adenocarcinoma NOS***	9.3%	4.8%	5.9%	7.5%	5.8%	9.1%	6.6%
Other	0.0%	0.0%	1.2%	3.7%	0.0%	7.3%	0.0%
Prognostic index***							
Median	1.60	1.49	1.52	1.62	1.54	1.52	1.52
1 st and 3 rd quartile	1.01-1.84	1.15-1.84	1.15-1.78	1.26-1.83	1.15-1.83	1.01-1.74	1.04-1.82

* Clear cell adenocarcinoma is not graded.

** NOS = Not otherwise specified.

*** Higher score indicates greater risk of death.

Table 2

Multivariate proportional hazards model of prognostics factors

Patient/Disease Characteristic	Relative Hazard	95% Conf. interval	p-value*
Age			
< 50	1.0		0.016
50–59	1.36	1.03 – 1.78	
60–69	1.57	1.18 – 2.08	
>70	1.38	0.937 – 2.05	
Residual disease at 2nd look surgery			
No gross disease	1.0		< 0.001
Completely resected	1.74	1.25 – 2.42	
Unresectable	2.26	1.67 – 3.05	
Tumor grade/histology			
1	1.0		< 0.001
2	1.82	1.21 – 2.74	
3	2.02	1.35 – 3.03	
Clear cell	6.00	3.27 – 10.9	

* A Wald test of the hypothesis that the death rates are equal within each patient/disease characteristic.

Table 3

Multivariate analysis of survival comparing study treatments adjusting for patient prognostic scores.

Covariate	Relative Hazard	95% Conf. Interval	p-value
Study ID			
151	1.0		0.034*
102-B	1.11	0.732 – 1.69	
102-C	1.19	0.780 – 1.83	
102-E	1.19	0.826 – 1.71	
102-F	1.69	1.20 – 2.39	
102-G	0.948	0.637 – 1.41	
102-N	1.35	0.925 – 1.98	
Prognostic score	2.76	2.20 – 3.46	<0.001**

* A test of the hypothesis, that the death rates are equivalent for all studies.

** A test of the hypothesis that the prognostic score is independent of survival duration.