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Intraperitoneal Chemotherapy after Interval Debulking Surgery for Advanced-Stage Ovarian Cancer: Feasibility and Outcomes at a Comprehensive Cancer Center

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Abstract

Objectives—Intraperitoneal (IP)-based chemotherapy following primary debulking surgery (PDS), although associated with substantial toxicity, is supported by a strong evidence base. We sought to determine feasibility and outcomes of IP chemotherapy after interval debulking surgery (IDS) among patients deemed ineligible for PDS.

Methods—We identified all patients with high-grade, stage III/IV ovarian cancer treated at our institution with neoadjuvant chemotherapy (NACT) followed by IDS and postoperative chemotherapy from 1/2008–5/2013. IP and intravenous (IV) regimens were defined; demographic and clinical data were analyzed using appropriate statistics.

Results—Of 128 evaluable patients, 118 (92%) achieved 1cm residual disease at IDS and 74 (58%) achieved a complete gross resection (CGR). An IP port was placed in 54/128 patients (42%), with 89% port utilization. Forty-eight (38%) of 128 patients received IP chemotherapy, 17 (13%) weekly IV paclitaxel/q3week carboplatin, and 63 (49%) q3week IV carboplatin/paclitaxel. Patients completed a median of 3 IP cycles (range, 2–6), with 3 (5.5%) of 54 ports removed due to

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Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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complications. Overall survival (OS) for patients with a CGR treated with IP and weekly IV chemotherapy was 53.2 months (range, 24.7-NE), and 44.2 months (range, 30.2-NE) with any visible residual disease ($p<0.001$). Median OS was 53.2 months (range, 44.5-NE) for IP-, not reached for weekly IV-, and 34.2 months (range, 27.5–49.8) for q3week IV-treated patients ($p=0.1$).

Conclusions—Patients administered IP after IDS had a high rate of successful port utilization, with few regimen switches. Oncologic outcomes were optimal in patients with a CGR at IDS, regardless of chemotherapy used.

Introduction

The majority of epithelial ovarian, fallopian tube, and primary peritoneal cancers present at an advanced stage [1]. This is largely due to ineffective screening methods for women at an average risk for developing ovarian cancer [2–4]. The current treatment standard for advanced-stage ovarian cancer is primary debulking surgery (PDS) for those medically fit for surgery and in whom disease is deemed resectable by the treating surgeon [5, 6]. Although more recent efforts have focused on cytoreduction to microscopic residual disease, retrospective series demonstrate that cytoreduction to residual disease of 1 cm or less in greatest diameter affords women similar survival benefits as complete cytoreduction following neoadjuvant chemotherapy (NACT) [7–11]. Thus, optimal cytoreductive surgery to 1 cm or less remains an acceptable outcome in the primary surgical setting.

For women who undergo PDS and are cytoreduced to microscopic or minimal residual disease, combined intravenous (IV) with intraperitoneal (IP) platinum plus paclitaxel chemotherapy affords them superior survival over an every-3-week (q3week) IV regimen. This has been shown in multiple prospective clinical trials, which led to an NCI clinical announcement supporting its use in 2006 [12–14]. Despite the demonstrated benefits of IP chemotherapy, administration and regimen tolerance have proven challenging [15]. Similar improvements in survival outcomes have been seen with IV carboplatin plus weekly paclitaxel chemotherapy in a prospective trial randomizing women to a q3week IV carboplatin/paclitaxel regimen versus weekly paclitaxel following optimal primary cytoreductive surgery, but with apparently superior regimen tolerability [16].

Although optimal primary cytoreductive surgery followed by chemotherapy remains the preferred standard in the management of newly diagnosed advanced ovarian cancer, not all patients are candidates for upfront surgery. Data from literature supporting the use of IP or weekly paclitaxel-containing IV regimens rather than q3week IV chemotherapy following PDS have been extrapolated to make decisions regarding postoperative chemotherapy following interval debulking surgery (IDS). IP and weekly paclitaxel-containing chemotherapy regimens following IDS surgery have undergone only limited study. Prospective studies evaluating the use of NACT followed by IDS versus PDS followed by chemotherapy have used the q3week IV chemotherapeutic regimen [17, 18].

Given the challenge of IP administration reported in the literature, we sought to determine the rates of IP port placement, port utilization, and IP treatment tolerability in an IDS population. We sought to determine, within our comprehensive cancer center, whether or not

IP and IV weekly paclitaxel regimens offer a survival advantage when administered after IDS. We chose a time period that encompassed influential publications, specifically, the publication of the findings of the European Organization for Research and Treatment of Cancer-Gynaecological Cancer Group (EORTC) trial examining NACT versus upfront surgical debulking and the collaborative work from other high-volume cancer centers that helped refine selection criteria for the use of NACT [17, 19].

Methods

We obtained institutional review board approval to conduct a retrospective analysis at Memorial Sloan Kettering Cancer Center. All consecutive patients with a diagnosis of epithelial ovarian, fallopian tube, or primary peritoneal cancer treated at our institution from January 1, 2008 to May 1, 2013 were reviewed for eligibility.

We included all newly diagnosed patients with stage III or IV disease, designated as such based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging criteria, who underwent NACT followed by an interval cytoreductive surgery at our institution [20]. We included all high-grade histologic subtypes. We excluded patients who had undergone PDS, had tumor of borderline or low-grade histology, had stage I or II disease, or had completed NACT and IDS prior to presentation at our institution. Stage IV disease was assigned in cases with extensive pulmonary or infiltrative hepatic lesions on initial imaging, malignant pleural cytology or biopsy at the time of video-assisted thoracic surgery (VATS). Patients who had previously undergone an open surgery with cytoreductive intent were excluded. During the study time period, diagnostic laparoscopy to evaluate for resectability was performed at the surgeon's discretion, and was not formal practice. A patient in whom diagnostic laparoscopy was performed and the attending surgeon opted not to proceed with cytoreductive surgery was considered a NACT case. A patient who had prior surgery for non-oncologic reasons at which time the index malignancy was discovered (i.e., acute abdomen or bowel obstruction) was also considered a NACT case.

The type of post-IDS chemotherapeutic regimen used and the decision for IP port placement was determined by the healthcare team. Institutional criteria for IP port placement during the study period included age younger than 75 years, overall good performance status, adequate renal function, and optimal cytoreductive surgery.

We defined the date of diagnosis for NACT cases as the first pathologic confirmation of malignancy. Acceptable specimens included core biopsy or fine-needle aspirate of solid tumor, pleural or peritoneal fluid cytology. IDS was defined as any debulking surgery performed after initial platinum-based chemotherapy. IP chemotherapy was defined as one or more cycles of an IP regimen administered after IDS. Weekly IV chemotherapy (wklyIV) was defined as no IP chemotherapy and one or more cycles of weekly IV paclitaxel plus q3week IV carboplatin following IDS. Every-3-week chemotherapy (3wkIV) was defined as an exclusive day 1 IV platinum and taxane-based regimen repeated every 3 weeks following IDS. Our IP regimen during this time period was a modified Gynecologic Oncology Group (GOG) trial 172 outpatient regimen of day 1 IV paclitaxel (135 mg/m^2), day 2 IP cisplatin (75 mg/m^2), and day 8 IP paclitaxel (60 mg/m^2) repeated every 3 weeks [21, 22]. Our

weekly paclitaxel regimen was based on Japanese Gynecologic Oncology Group (JGOG) trial 3016 and included day 1 carboplatin (area under the curve [AUC] 6) plus IV paclitaxel (80 mg/m²) on days 1, 8, and 15 repeated every 3 weeks [16]. The 3wkIV regimen included day 1 IV carboplatin (AUC 6) plus IV paclitaxel (175 mg/m²) repeated every 3 weeks. Surviving patients were censored at date of death or last date of contact.

Clinical variables collected from the medical record included body mass index (BMI), serum CA-125 and albumin levels, comorbidities, number of surgeries prior to diagnosis, computed tomography (CT) scan evidence of carcinomatosis, pathology and cytoreductive outcomes, and documentation of IP port placement. Indications for IP port removal and adverse events related to IP port placement or use were captured via review of the clinical and procedural medical record.

Optimal debulking was defined as residual disease ≤ 1 cm in greatest dimension; suboptimal debulking as any residual disease >1 cm in greatest dimension; and complete gross resection as no visible residual disease at the completion of IDS.

Statistical analysis

Descriptive statistics such as median, range, frequency, and percent are provided for continuous and categorical variables. The comparisons of clinical factors among the different treatment groups (i.e., IP, wklyIV, and 3wkIV) were performed using Kruskal-Wallis test for continuous variables and the Fisher exact test for categorical variables. All tests were two sided, and a $p < 0.05$ was considered statistically significant.

Progression-free survival (PFS) was calculated from the date of IDS until recurrence, death, or date of last follow-up; and OS was calculated from the date of IDS until death or date of last follow-up. Recurrence and death were considered an event in PFS. Death was considered an event in OS. Due to the small number of patients in the weekly IV group, wklyIV-treated patients were combined with the IP group when examining survival based on prior data demonstrating wklyIV treatment was superior to q3wkIV in the upfront setting [16].

Due to the time-dependent nature of adjuvant treatment after IDS, the landmark methodology was used to report PFS and OS for cases grouped by adjuvant treatment regimen. This methodology was chosen in order to account for the variation in time to initiation of a chemotherapy regimen after IDS across all groups. A landmark time of 3.4 months after IDS surgery was chosen based on the longest recorded delay to initiating adjuvant treatment from the interval surgery date among the entire cohort. Eight patients were excluded from this landmark analysis due to early recurrence before the 3.4 months. The Kaplan-Meier method was used to report the median PFS and OS; the Cox-proportional hazards model was applied to obtain the hazard ratio; and the log-rank test was used to report the p value. All analyses were performed using SAS 9.4.

Results

Five of 154 patients selected for NACT progressed on initial treatment and did not undergo IDS and were therefore excluded from this analysis. Of the remaining 149 patients selected for NACT over the study period, 128 (86%) met inclusion criteria and were evaluated. Twenty-one (14%) of 149 patients were excluded based on receipt of a post-IDS chemotherapeutic regimen that did not conform to any of our aforementioned regimens. Among the entire cohort of 128 patients, the median age was 65 years (range, 34–86 years) and the median BMI was 25.3 kg/m² (range, 17.4–49.8 kg/m²). Sixty patients (47%) had stage IV disease, and 126 (98%) had disease of high-grade serous histology. One patient had disease of clear cell histology and one had a carcinosarcoma. Median CA-125 at the time of diagnosis was 723 U/mL (range, 6–16,923 U/mL), median serum albumin was 3.9 g/dL (range, 1.7–4.8 g/dL), and carcinomatosis was evident on CT scan in 109 patients (85%). The median number of NACT cycles administered was 4 (range, 1–7 cycles). Three patients (2%) received 2 or fewer cycles of NACT, with the remaining 125 (98%) receiving 3 or more cycles of NACT. Patient characteristics in the total cohort are listed in Table 1.

Post IDS chemotherapeutic regimens

Forty-eight patients (38%) were treated with IP, 17 (13%) with wklyIV, and 63 (49%) with 3wkIV chemotherapy. Median ages were 60 years (range, 34–76 years), 64 years (range, 36–80 years), and 66 years (range, 38–86 years), respectively ($p<0.001$). Twelve (25%) of 48 IP patients, 9 (53%) of 17 wklyIV patients, and 39 (62%) of 63 3wkIV patients had stage IV disease ($p<0.001$). Median CA-125 at time of diagnosis was 927 U/mL (range, 12–8,143 U/mL), 1,410 U/mL (range, 98–10,514 U/mL), and 370 U/mL (range, 6–16,923 U/mL), respectively ($p<0.001$). No patients received IP chemotherapy with concurrent bevacizumab. Patient characteristics for each of the three treatment groups are listed in Table 2.

Residual disease after IDS

In patients who underwent IDS, 120 (94%) of 128 were optimally debulked, 74 (58%) achieved a complete gross resection, and 8 (6%) were suboptimally debulked. Forty-seven (98%) of 48 IP patients were optimally cytoreduced to less than 1 cm, 28 (58%) achieved a complete gross resection, and 1 (2%) was suboptimally cytoreduced. Sixteen (94%) of 17 wklyIV patients were optimally cytoreduced, 10 (59%) achieved a complete gross resection, and 1 (6%) was suboptimally cytoreduced. Fifty-seven (90%) of 63 3wkIV patients were optimally cytoreduced, 36 (57%) achieved a complete gross resection, and 6 (10%) were suboptimally cytoreduced ($p=0.6$). Resection rates by treatment group are listed in Table 3.

IP port utilization

Fifty-four (42%) of 128 patients underwent IP port placement at the time of IDS. Forty-eight (89%) of these 54 patients subsequently received at least one cycle of IP chemotherapy. The median number of IP chemotherapy cycles was 3 (range, 2–6 cycles), with 71% completing at least 3 cycles. Six patients who underwent IP port placement did not receive IP chemotherapy, and all 6 received a 3wkIV regimen. The reasons for not pursuing IP treatment were as follows; baseline neuropathy (3), prolonged postoperative recovery (2), and age/comorbidities (1). Port-related complications in 3 (5.5%) of 54 IP ports placed

necessitated transition to IV-only chemotherapy. Port infection was the documented reason for 1 IP-treated patient and 1 patient in the 3wkIV treatment group. Small bowel obstruction precluding IP treatment was the documented reason in the remaining IP-treated patient. All three ports were subsequently removed.

Grade 2–3 neuropathy that necessitated a regimen switch was noted in 4% of the entire cohort; 1 (2%) of 48 IP patients, 0 of 17 wklyIV patients, and 4 (6%) of 63 3wkIV patients ($p=0.4$). Documentation of platinum hypersensitivity was noted in 0 of 48 IP patients, 1 (6%) of 17 wklyIV patients, and 1 (2%) of 63 3wkIV patients (Table 4). There were no 30-day postoperative deaths.

Survival by treatment group

Median follow-up for the 18 patients surviving without recurrence was 45.3 months (range, 12.5–71.9 months). The median PFS for the entire cohort was 11.8 months (95% CI, 9.4–13.4 months). PFS was reported for each treatment group using the landmark method, which accounts for post-debulking treatment regimen as a time-dependent variable. The median PFS was 9.9 months (95% CI, 7.4–13.9) in the IP-treated group, 7.3 months (95% CI, 3.6–11.2) in the wklyIV group, and 7.2 months (95% CI, 4.3–12.6) in the 3wkIV group ($p=0.3$). The median PFS for patients with stage IV disease was 11.1 months (95% CI, 8.5–15.6 months). The median PFS for stage IV patients was 9.1 months (95% CI, 3.7–33.3) in the IP-treated group, 7.3 months (95% CI, 3.6–12.9) in the wklyIV group, and 10 months (95% CI, 4.7–13) in the 3wkIV group ($p=0.7$). Figure 1A depicts the PFS Kaplan-Meier curves for the entire cohort grouped by treatment regimen.

The median OS for the entire cohort was 42.6 months (95% CI, 34.9–57.5 months). The median OS was 53.2 months (95% CI, 44.5–NE) in the IP group, not yet reached (NR) in the wklyIV group, and 34.2 months (95% CI, 27.5–49.8 months) in the 3wkIV group ($p=0.1$). When grouping the IP- and wklyIV-treated patients and comparing them to patients treated with the 3wkIV regimen, OS was 34.2 months (95% CI, 27.5–49.8 months) versus 53.2 months (95% CI, 44.5–NE) ($p=0.04$). The median OS for patients with stage IV disease was 57.5 months (95% CI, 34.9–68.2 months). The median OS for stage IV patients was NR in the IP or wklyIV group, and 35.1 months (95% CI, 25.4–62.9) in the 3wkIV group ($p=0.1$). Figure 1B depicts the OS Kaplan-Meier curves for the entire cohort grouped by treatment regimen.

We examined PFS according to residual disease, either no residual disease or any visible residual disease, in order to obtain an adequate number of patients for comparison between each group. The median PFS for patients with no residual disease treated with IP or wklyIV chemotherapy was 12.5 months (95% CI, 8.6–17.1 months), and 7.4 months (95% CI, 5.2–9.4) for patients with any visible residual disease. The median PFS for patients with no residual disease treated with 3wkIV chemotherapy was 14.3 months (95% CI, 5.7–18.3 months), and 3.8 months (95% CI, 2.8–4.7 months) for patients with any visible residual disease.

The median OS for patients with no residual disease treated with IP or wklyIV chemotherapy was 53.2 months (95% CI, 24.7–NE), and 44.2 months (95% CI, 30.2–NE) for

patients with any visible residual disease. The median OS for patients with no residual disease treated with 3wkIV chemotherapy was 62.9 months (95% CI, 31.5-NE), and 24 months (95% CI, 14.7–35.1 months) for patients with any visible residual disease. Median PFS and OS stratified by residual disease and treatment group are depicted in Figures 2A and 2B.

Discussion

This study analyzes a large cohort of patients with advanced ovarian cancer treated with NACT followed by IDS and post-IDS chemotherapy at a comprehensive cancer center. All patients underwent primary evaluation and treatment by our group of specialized gynecologic oncologists. Our results are hypothesis generating and support the feasibility of administering IP and wklyIV chemotherapy regimens after IDS. Our results also support efforts to achieve microscopic residual disease at the time of IDS to maximally improve disease related outcomes.

There are limited publications examining chemotherapy regimens in an IDS population (Supplemental Table 1 [23–25]). The two prospective trials published by Vergote et al and Kehoe et al randomized patients to PDS versus NACT and IDS, with all patients receiving a q3week IV chemotherapy regimen, resulting in non-inferior outcomes between treatment arms [17, 18]. Findings from a small retrospective study by Al Mutairi et al failed to show any improvement in PFS or OS in the 16 patients who received IP chemotherapy after optimal IDS compared with 47 patients who received 3wkIV [23]. Le et al published their retrospective experience of 17 patients treated with IP chemotherapy after IDS compared with 54 patients treated with 3wkIV chemotherapy, which did not demonstrate improvements in PFS or OS. The authors concluded the benefits of IP chemotherapy may not translate to the post-IDS setting [24].

The Southwestern Oncology Group sponsored a phase II clinical trial examining 58 patients after IDS. Optimally debulked patients received 6 cycles of IV/IP chemotherapy [25]. The median PFS and OS for the 26 patients who were eligible for the protocol were 29 and 34 months, respectively. The PFS and OS for the entire cohort of 58 patients were 21 and 32 months, respectively. The authors noted these outcomes were similar to those of prior publications of primary suboptimally debulked patients. Less than 50% of the cohort completed the intended treatment, IP carboplatin rather than cisplatin was used, and was administered every 28 days rather than every 21 days with a relatively limited follow-up time of 21 months. Comparing these results to our patient population are therefore limited.

Thirty-eight percent of the patients included in our analysis received IP chemotherapy following IDS, which represents a significant portion of the cohort. Trials showing IP chemotherapy after PDS conferred superior survival outcomes compared with IV chemotherapy provided the rationale for choosing IP regimens during this time period. The toxicity of IP chemotherapy can be substantial, yet patients were able to complete a median number of 3 IP cycles following IDS, with minimal complications. These data support IP chemotherapy as a feasible option in pretreated IDS patients. Our use of a modified GOG

172 regimen [21], as well as improved experience with placing and using IP ports, is a possible reason for the high treatment completion rate [15].

Thirteen percent of our cohort received wklyIV chemotherapy following IDS as an extrapolation of JGOG 3016 to the post-IDS setting. The results of GOG 262, which is a prospective trial that randomized patients to receive a q3week IV chemotherapy regimen versus a weekly IV regimen after either PDS or IDS, were recently published. Eighty-four percent of patients in each treatment arm also received bevacizumab. The trial did not show any survival benefit in the weekly IV regimen over the q3week regimen. In the patients who received either treatment arm without bevacizumab, survival outcomes favored the weekly paclitaxel regimen [26]. The study authors noted 13% of the study cohort included patients who opted to receive NACT followed by IDS. No subgroup analysis looking at survival outcomes for these patients was performed. In our study cohort, OS was longest in patients receiving either wklyIV or IP chemotherapy after IDS in whom a complete gross resection was achieved, although median OS rates were comparably high across all groups.

There was no statistically significant PFS advantage across the three chemotherapy regimens, although a 2-month improvement in PFS was noted in the IP-treated group, which is clinically interesting. However, 75% of the IP-treated patients had stage III disease, compared with 38% of the 3wkIV group. Additionally, the median age of patients in the IP group was significantly younger. These factors likely contributed to the perceived improvement in PFS in the IP group.

Our data do not demonstrate superiority of IP chemotherapy over 3wkIV or wklyIV chemotherapy regimens after IDS, and emerging data in the frontline setting question the most appropriate role for IP therapy following PDS. The preliminary results of GOG 252 were presented at the 2016 Society for Gynecologic Oncology annual meeting. The study randomized patients after optimal PDS to receive: day 1 carboplatin (AUC 6) plus day 1, 8, and 15 IV paclitaxel at 80 mg/m² (Arm 1) versus day 1 IP carboplatin (AUC 6) plus day 1, 8, and 15 IV paclitaxel at 80 mg/m² (Arm 2) versus day 1 IV paclitaxel at 135 mg/m², day 2 IP cisplatin at 75 mg/m² plus day 8 IP paclitaxel at 60 mg/m² (Arm 3). All treatment arms received bevacizumab, and as part of an exploratory analysis, 7% were suboptimally debulked and 5% were stage IV. The preliminary results show no PFS advantage for IP chemotherapy after PDS, with no significant difference in PFS across all three treatment arms [27]. It is premature to utilize GOG 252 to redefine the standard of care in the upfront setting, as further analysis is underway, and some limitations of this study include the addition of bevacizumab to each arm; the reduced dose of the IP cisplatin regimen; all three arms received weekly paclitaxel, which may have influenced the equivalent outcomes; and some have argued that the more frequent radiologic surveillance to detect recurrence could contribute to a shortened PFS rate.

The trials that support the use of IP chemotherapy in the frontline setting have been extrapolated to treat patients with IP chemotherapy after IDS. In our study, patients did not experience improved oncologic outcomes with IP chemotherapy, and thus, it is no longer our practice to administer IP chemotherapy following IDS. It is our institutional strategy to offer PDS as a standard of care, unless a patient is medically unfit for surgery or disease is

considered unresectable in the primary setting. This strategy results in a consolidated NACT patient group who may not be prime IP candidates; we have previously shown that patients who receive NACT at our institution tend to be older, with more stage IV disease, lower serum albumin, higher rates of carcinomatosis on CT scan, and higher CA-125 levels at the time of diagnosis [10]. These factors are reflective of our cohort of patients who underwent NACT/IDS during this time period. Although the notion of IP chemotherapy after IDS remains relevant and interesting, the results of our study do not support its use.

At the recent 2016 American Society of Clinical Oncology (ASCO) annual meeting, the Gynecologic Cancer Intergroup (GCIg) presented the results of OV21, a randomized study examining IV- versus IP-based chemotherapeutic regimens in women who received NACT followed by optimal IDS for advanced ovarian cancer. Patients were randomized to receive an IV-based regimen versus an IP cisplatin- or IP carboplatin-based regimen. On Arm 1, patients were given IV carboplatin (AUC 5/6) followed by IV paclitaxel 135 mg/m² on day 1 plus IV paclitaxel 60 mg/m² on day 8 every 21 days for 3 cycles. On Arm 2, patients were given IP cisplatin 75 mg/m² followed by IV paclitaxel 135 mg/m² on day 1 and IP paclitaxel 60 mg/m² on day 8 every 21 days for 3 cycles. On Arm 3, patients were given IP carboplatin (AUC5/6) followed by IV paclitaxel 135 mg/m² on day 1 and IP paclitaxel 60 mg/m² on day 8 every 21 days for 3 cycles. Arm 2 with IP cisplatin was closed early due to toxicity. Due to low trial accrual and funding issues, the trial was modified from a phase III to a phase II study, and the primary endpoint was changed from PFS to a 9-month progression of disease (PD) rate. PFS and OS became secondary endpoints. The study demonstrated a statistically significant improvement in the 9-month PD rate of 42% in Arm 1 (IV arm) versus 23% in Arm 3 (IP carboplatin arm). PFS was 11.3 versus 12.5 months between Arms 1 and 3 (p=0.27), and OS was 38.1 versus 59.3 months between Arms 1 and 3 (p=0.40). Both treatment arms were well tolerated, with no difference in quality of life outcomes. Though considered a positive trial based on an improvement in the 9-month PD rate, accrual was poor, requiring a change in endpoint, and there was no statistically significant survival benefit to IP chemotherapy; the role of IP chemotherapy in this setting remains a subject of debate [28].

In conclusion, the current study demonstrates that IV/IP chemotherapy is feasible and safe in an IDS population. Improved oncologic outcomes are seen in patients after complete gross resection regardless of the post-IDS chemotherapy regimen, and the current data do not support routine IP cisplatin following IDS. In our experience, patients with visible residual disease at the time of IDS experience shorter PFS and OS compared with patients resected to no visible residual disease.

Selecting an optimal, evidence-based treatment strategy after IDS is of crucial importance. As we await the results of additional prospective trials examining alternative chemotherapy regimens after IDS [29], we must work toward optimal patient selection for IP and weekly paclitaxel-based chemotherapy strategies to refine best practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research Highlights

- IP-based chemo after optimal IDS in advanced ovarian cancer is feasible and safe
- Survival outcomes are comparable between IV- and IP-based chemo after IDS
- Complete gross resection at the time of IDS optimizes oncologic outcomes

Figure 1A.

Figure 1B.

Figure 1.

Figure 1A. Kaplan-Meier curve showing PFS in the total cohort by treatment group (landmark analysis applied).

Figure 1B. Kaplan-Meier curve showing OS in the total cohort by treatment group (landmark analysis applied).

Figure 2A.

Figure 2B.

Figure 2.

Figure 2A. Kaplan-Meier curves showing PFS in the total cohort stratified by treatment group and residual disease (landmark analysis applied).

Figure 2B. Kaplan-Meier curves showing OS in the total cohort stratified by treatment group and residual disease (landmark analysis applied).

Table 1

Overall Patient Characteristics at time of diagnosis (N=128)

Characteristic	No. of Patients	%
Median age, years	65	
Range	34–86	
BMI, kg/m ²		
Median	25.3	
Range	17.4–49.8	
Preoperative CA-125, units/mL		
Median	723	
Range	6–16,923	
Preoperative albumin, g/dL		
Median	3.9	
Range	1.7–4.8	
Preoperative carcinomatosis on CT	109	85
Presence of comorbidity		
Hypertension	46	36
Diabetes	12	9
Pulmonary	24	19
Coronary Artery Disease	6	5
Stroke	1	1
Congestive Heart Failure	0	0
Renal	2	2
Hypothyroid	16	13
Hyperthyroid	1	1
Dementia	0	0
Hepatic	2	2
Peripheral Vascular Disease	2	2
Prior Laparotomies		
0	81	63
1	33	26
2	9	7
3 or greater	5	4
Histology		
Serous	126	98
Other	2	2
FIGO Stage		
III	68	53

Characteristic	No. of Patients	%
IV	60	47

BMI, body mass index; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics

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Table 2

Patient characteristics at time of diagnosis grouped by treatment regimen

	IP Chemotherapy (N=48)			wkly IV Chemotherapy (N=17)			3wkIV Chemotherapy (N=63)		
	No.	%		No.	%		No.	%	p
Median age, years	60		64			66			<0.001
Range	34–76		36–80			38–86			
BMI, kg/m ²									<0.001
Median	25.1		24.4			25.7			
Range	17.4–40		18.9–34.3			18.9–49.8			<0.001
Preoperative CA-125, units/mL									
Median	927		1,410			370			<0.001
Range	12–8,143		98–10,514			6–16,923			
Preoperative albumin									<0.001
Median	4		3.8			3.9			
Range	2.1–4.5		2.8–4.5			1.7–4.8			0.6
Preoperative carcinomatosis on CT	41	85		16	94	52	83		
Presence of comorbidity									
Hypertension	15	31		6	35	25	40		0.7
Diabetes	3	6		1	6	8	13		0.6
Pulmonary	7	15		6	35	11	18		0.2
Coronary Artery	2	4		1	6	3	5		1
Disease	1	2		0	0	0	0		
Stroke									
Prior Laparotomies									0.1
0	31	65		11	65	39	62		
1	12	25		2	12	19	30		
2	2	4		4	24	3	5		

	IP Chemotherapy (N=48)		wkly IV Chemotherapy (N=17)		3wkIV Chemotherapy (N=63)		p
	No.	%	No.	%	No.	%	
3 or more	3	6	0	0	2	3	
Histology							
Serous	48	100	17	100	61	97	
Other	0	0	0	0	2	3	
FIGO Stage							<0.001
III	36	75	8	47	24	38	
IV	12	25	9	53	39	62	

BMI, body mass index; CT, computed tomography; FIGO, International Federation of Gynecology and Obstetrics; BMI, body mass index

Table 3

Resection rates for patients after IDS grouped by treatment regimen

	IP Chemo (N=48)		wklyIV Chemo (N=17)		3wkIV Chemo (N=63)		Total (N=128)	p
	No. (%)		No. (%)		No. (%)		No. (%)	
Complete gross resection (no residual disease)	28 (58)		10 (59)		36 (57)		74 (58)	0.6
Optimal visible residual (≤ 1 cm)	19 (40)		6 (35)		21 (33)		46 (36)	
Suboptimal (>1 cm)	1 (2)		1 (6)		6 (10)		8 (6)	

p values were calculated using the Fisher exact test

IDS, interval debulking surgery

Table 4
Number of chemotherapy cycles and chemotherapy related complications based on treatment group

	IP Chemo (N=48)		wkly IV Chemo (N=17)		3wk IV Chemo (N=63)		p
	No.	%	No.	%	No.	%	
Median NACT cycles	4		3		4		<0.001
Range	2-7		1-7		3-7		
Median post-IDS chemotherapy Cycles	3		3		3		
Range	2-6		2-6		1-6		
IP port placement	48	100	0	0	6	10	
Neuropathy requiring regimen switch	1	2	0	0	4	6	0.4
Platinum hypersensitivity	0	0	1	6	1	2	

NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; IP, intraperitoneal