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Applicability of the Histoculture Drug Response Assay to Predict Platinum Sensitivity and Prognosis in Ovarian Cancer

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Abstract. *Background/Aim: To retrospectively analyze the results of histoculture drug response assays (HDRAs) to determine whether the results could predict platinum sensitivity and prognosis in ovarian cancer. Patients and Methods: One hundred thirty-nine patients with ovarian cancer were reviewed. HDRAs were conducted for platinum and taxane agents. Platinum resistance and sensitivity occurred in 21 and 118 patients, respectively. To analyze the relationship between the inhibition rates (IRs) of tumor growth caused by the platinum agent and clinical outcomes, Student's t-test and linear regression analysis were used. Results: We found that the average IRs of the platinum and taxane agent were not statistically significant between the platinum-sensitive and -resistant groups. There was no statistical significance for overall survival, progression-free survival, or platinum-free interval. Conclusion: The HDRA is not useful for predicting platinum sensitivity and survival outcomes.*

Globally, the incidence and mortality rates of ovarian cancer are the eighth highest among malignant tumors in women (1). It also bears one of the worst prognoses (2). Additionally, the recurrence rate of advanced ovarian cancer relapses is currently 70%. In 2020, the National Comprehensive Cancer Network (NCCN) recommended optimal debulking surgery with adjuvant chemotherapy for surgical candidates and neoadjuvant therapy for patients who are poor candidates for surgery. For the primary chemotherapy regimens, they recommended platinum-based drugs (3). Most gynecologists and oncologists agree with this recommendation and often administer platinum agents in combination with taxane agents. Many researchers are searching for better regimens to improve the prognosis of ovarian cancer. The histoculture drug response assay (HDRA) was introduced to achieve this purpose (4-12). The HDRA is an *in vitro* test that measures how much a particular antitumor drug inhibits tumor tissue growth. A few reports have suggested the possibility of applying the HDRA to ovarian and colorectal cancer (13-15); however, this test had a limitation wherein it can help decide only one regimen at a time (16). The integrative tumor response assay was introduced and applied in ovarian cancer to overcome this challenge (17). This new test can determine the two most powerful regimens, enabling physicians to decide on the first and second regimens simultaneously; however, it is not widely applied in gynecologic surgical fields.

The 5-year survival rate of advanced epithelial ovarian cancer is only about 31% (18); it has changed little since platinum-based treatment was introduced more than 30 years ago (19-22). Platinum resistance is a prognostic factor in ovarian cancer. The median survival was reported to be 9-12 months, and the response to subsequent treatment was less than 15%, if it occurred (23). If physicians can predict platinum resistance in ovarian cancer earlier, they could decide to use another regimen as first-line chemotherapy. More specifically, they could exclude platinum-based drugs.

In this respect, we speculated about whether HDRA results correlated with platinum sensitivity and prognosis in the real world for Korean patients with ovarian cancer.

Patients and Methods

Patients. We retrospectively reviewed HDRA results from 163 consenting patients with ovarian cancer from February 2011 to January 2021 at Kyungpook National University Chilgok Hospital (KNUCH). The stage of each patient was evaluated on the scale of I to IV, using the International Federation of Gynecology and Obstetrics (FIGO) guidelines (24). Criteria of diagnoses for patient selection included primary ovarian cancer, primary tubal cancer, and primary peritoneal cancer. One hundred thirty-nine participants remained, and twenty-one were excluded according to the criteria. Five patients were found not to have ovarian cancer by permanent biopsy. Two patients were excluded because they came to our clinic after primary surgery at other institutions. Six were excluded because they refused adjuvant chemotherapy. One was excluded because she

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Key Words: Chemotherapy, histoculture drug response assay, *in vitro* tumor response assay, ovarian cancer, platinum resistance, platinum sensitivity.

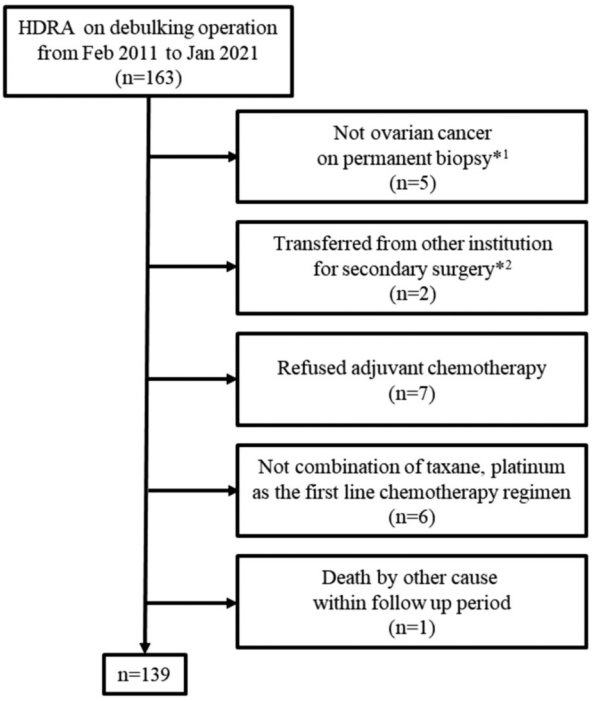

Figure 1. *Flow diagram for patient selection. *1They included benign, borderline malignancy, and other primary malignancies, such as endometrial cancer or colon cancer, *2They underwent re-staging surgery at our institution.*

Table I. *Patient characteristics and clinical factors.*

	Platinum sensitive (n=118)	Platinum resistant (n=21)	*p*-Value
Age, years	56.41±11.12	55.33±7.93	0.67*
FIGO stage, n (%)			
I	24 (20.3%)	4 (19.0%)	0.96†
II	8 (6.8%)	1 (4.8%)	
III	72 (61.0%)	13 (61.9%)	
IV	14 (11.9%)	3 (14.3%)	
Histological subtype, n (%)			
Epithelial	117 (99.2%)	21 (100%)	0.55†
Serous	81 (68.6%)	14 (66.7%)	
Endometrioid	12 (10.2%)	3 (14.3%)	
Clear cell	10 (8.5%)	4 (19.0%)	
Mucinous	4 (2.5%)	0	
Mixed	10 (8.5%)	0	
Non-epithelial	1 (0.8%)	0	
Timing of surgery, n (%)			
Primary	98 (83.1%)	16 (76.2%)	0.54†
Interval	20 (16.9%)	5 (23.8%)	
Residual tumor (n)			
Optimal	84 (71.2%)	13 (61.9%)	0.24†
Suboptimal	34 (28.8%)	8 (38.1%)	
Preoperative CA-125, U/ml	763.89±1315.31	660.52±1197.21	0.50*

Data are presented as means±SDs or numbers. *Student's *t*-test or Mann–Whitney *U*-test. †Chi-square test or Fisher's exact test.

died in a traffic accident (Figure 1). The Institutional Review Board of KNUCH approved this study (KNUH 2021-07-048).

Surgery. Surgery included total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, omentectomy, and removal of metastatic lesions. Optimal debulking surgery was achieved if the size of the residual tumor was less than 1 cm (25). Some patients underwent interval debulking surgery (IDS) after neoadjuvant chemotherapy due to their general condition or stage.

Chemotherapy. The first adjuvant chemotherapy began within 4 weeks post-surgery. All patients were administered either paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) and carboplatin (AUC 5) as the first-line regimen. For neoadjuvant chemotherapy, the regimen was a combination of paclitaxel or docetaxel and carboplatin for 3-6 cycles. Some patients could not complete six cycles of first-line chemotherapy due to various reasons, such as poor general condition or severe bone marrow suppression.

Platinum resistance and disease progression. We divided the patients into the platinum-resistant (R group) and platinum-sensitive groups (S group) according to the following criteria: if the disease progressed during the administration of the platinum agent or recurred within 6 months of the last administration, the case was considered platinum-resistant (16). Disease progression was confirmed by imaging studies, such as computed tomography (CT), magnetic resonance imaging, or positron emission tomography (PET)/CT (26).

Table II. *The results of HDRA and clinical outcomes.*

	Platinum sensitive (n=118)	Platinum resistant (n=21)	*p*-Value
Inhibition rate (IR) on HDRA			
Platinum agent (%)	44.25±17.07	46.29±20.67	0.63*
Taxane agent (%)	41.19±17.60	38.90±21.37	0.60*
Death, n (%)	9 (7.6%)	8 (38.1%)	<0.01†
Overall survival, months	51.92±18.53	35.33±25.54	<0.01*
Progression-free survival, months	39.97±21.03	6.05±3.12	<0.01*
Platinum-free interval, months	20.48±12.00	1.33±2.08	<0.01*

Data are presented as means±SDs or numbers. *Student's *t*-test or Mann–Whitney *U*-test. †Chi-square test.

Histoculture drug response assay. Ovarian cancer tissue harvested during debulking surgery was transported to the laboratory in 4˚C Hank's balanced salt solution (HBSS; GIBCO, Gaithersburg, MD, USA) within 24 h of collection. After the tissue was sectioned into

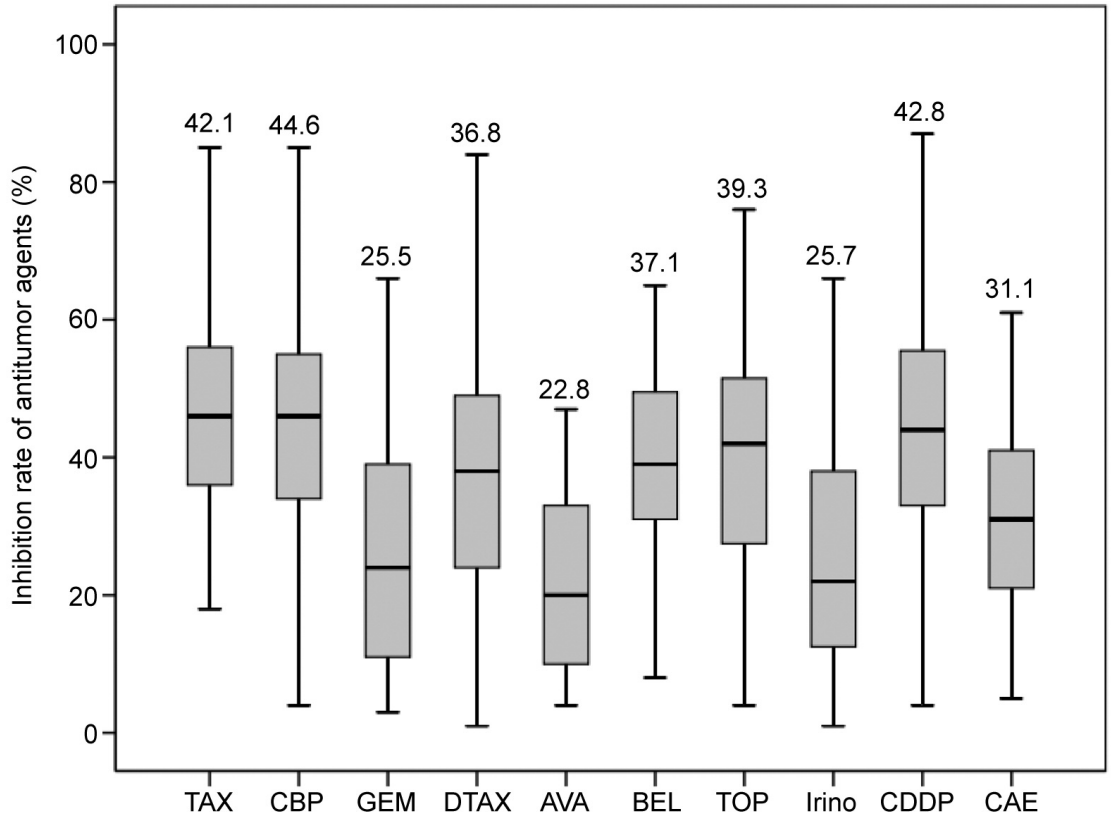

Figure 2. *Mean inhibition rates (IRs) of antitumor agents on the histoculture drug response assays for 139 patients with ovarian cancer. TAX: Paclitaxel; CBP: carboplatin; GEM: gemcitabine; DTAX: docetaxel; BEV: bevacizumab; BEL: belotecan; TOP: topotecan; IRINO: irinotecan; CDDP: cisplatin; CAE: liposomal doxorubicin. Data are shown as means±SD. The bold number is the mean IR of each antitumor agent.*

10-15-mg pieces of 0.5 mm diameter, viable samples were selected by specific staining. These were placed into 24 wells on the collagen sponge gel (Gel Foam; Pharmacia & Upjohn Ltd., Crawley, UK) and incubated with media (RPMI 1640 medium, 20% FCS; Sigma–Aldrich, St. Louis, MO, USA) for 1 day. Then, these samples were incubated for 72 h after the second day after the addition of the chemotherapeutic medicine. The control group was incubated with phosphate-buffered saline (PBS) (27).

Statistical analysis. All information about age, stage, histology, surgery, chemotherapy, and IR values determined by HDRA was collected from medical records. Overall survival (OS) and progression-free survival (PFS) were defined as the periods following the date of primary operation. Platinum-free interval (PFI) was evaluated from the last date of carboplatin administration. To analyze statistical significance, Student's *t*-test was used to compare the IRs of carboplatin and taxane determined by the HDRA. Chi-square or Fisher's exact test were used to evaluate correlations between histology, timing of surgery, residual tumor, conduction of HDRA, and death in the follow-up period. To determine the relationships between the IRs of antitumor agents and OS, PFS, and PFIs, simple linear regression analysis was used. All statistical analyses were performed using SPSS (version 26; IBM Corp., Armonk, NY, USA).

Results

Of the 139 patients, 118 (84.9%) were in the S group, and 21 (15.1%) were in the R group. No significant difference was found between the two groups regarding age, stage, histology, and other clinical factors (Table I).

The mean IRs of the platinum agent and taxane in both groups showed no significant differences [44.25±17.07 in S group *vs*. 46.29±20.67 in R group (%), 41.19±17.60 *vs*. 38.90±21.37 (%)]. In the follow-up period, nine patients (7.6%) in the S group and eight patients (38.1%) in the R group died. The mean OS in the S and R groups were 51.92±18.53 and 35.33±25.54 months, respectively. The mean PFS was 39.97±21.03 months in the S group and 6.05±3.12 months in the R group. The mean PFIs were 20.48±12.00 and 1.33±2.08 months in the S and R groups, respectively. For all three clinical outcomes, the correlations were statistically significant (Table II).

Ten types of antitumor agents were used for the HDRA. Of all drugs, the mean IRs of carboplatin, cisplatin, and paclitaxel were the highest (Figure 2). The IRs of platinum

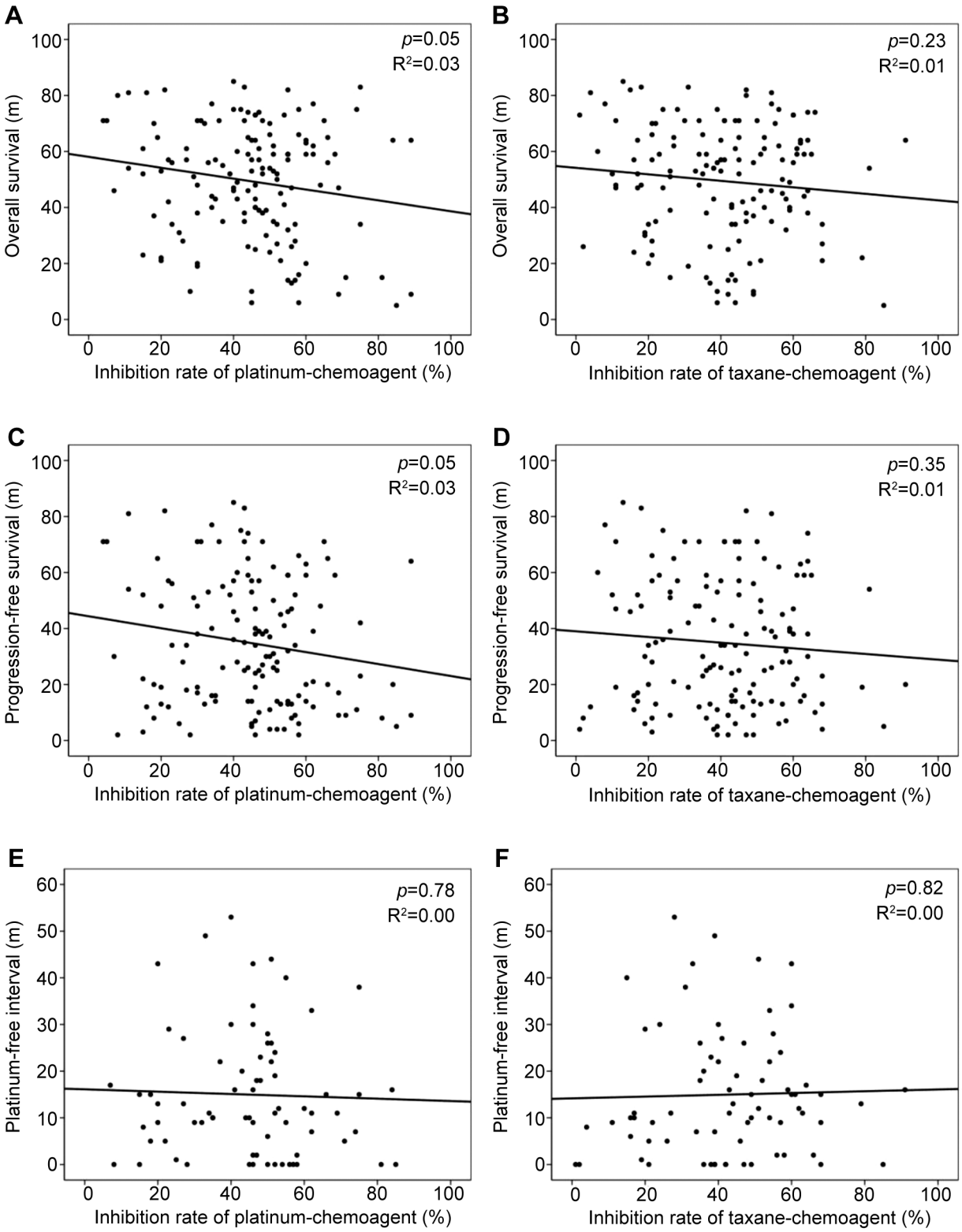

Figure 3. *Regression analysis for the relationship of the histoculture drug response assays results with OS, PFS, and PFI for 139 patients with ovarian cancer. A: OS and IR of platinum antitumor agent. B: OS and IR of taxane antitumor agent. C: PFS and IR of platinum antitumor agent. D: PFS and IR of taxane antitumor agent. E: PFI and IR of platinum antitumor agent. F: PFI and taxane IR of antitumor agent. OS: Overall survival; PFS: progression-free survival; IR: inhibition rate; PFI: platinum-free interval.*

and taxane antitumor agents did not significantly affect OS, PFS, or PFI (Figure 3).

Discussion

The R group showed significantly worse prognostic outcomes than expected, according to previous studies. The R group did show higher IRs of antitumor agents on the HDRA than the S group, although not significant.

We considered three possible reasons for this discrepancy. First, the *in vitro* HDRA has an evident limitation arising from differences with *in vivo* conditions. Second, ovarian cancer is highly heterogeneous in genetic and histological aspects (19, 28-30). Each part of the bulky tumor or each metastatic nodule arising from the same origin might respond differently to the same drug. Several tiny pieces of tumor tissue used in the HDRA could not reflect all characteristics of the ovarian cancer of a patient. Each sample might even have shown different IRs against a given antitumor agent. Finally, some procedures of the test were vulnerable to misinterpretation in some conditions. For example, normal tissue, not only tumor tissue, could be included in samples. The cut-off value of the IR on the HDRA is 30% compared with controls, according to the testing laboratory. This means that a high IR over 30% does not guarantee better effect according to the score itself. For example, an antitumor agent with an IR of 60% cannot be considered twice as effective as one with 30%. With these limitations, the HDRA alone is insufficient to determine optimal chemotherapy regimens.

In our study, platinum and paclitaxel antitumor agents showed the highest IRs of 10 drugs tested by the HDRA. This result was similar to that of a previous study in Korea (13), and supports the current combination of paclitaxel and carboplatin as the standard chemotherapy for ovarian cancer.

This study had three limitations. First, this study is a retrospective study based on data from a single center. Second, the small cohort size to compare platinum resistance; we found only 21 patients who met this criterion. Finally, it included 25 patients who were treated with neoadjuvant chemotherapy with a taxane and carboplatin combination. We obtained their tumor tissue during IDS. These tumor tissues may have developed drug resistance, and this may have been reflected in the IR determined by the HDRA.

In conclusion, the *in vitro* HDRA is not useful for predicting platinum sensitivity and survival outcomes. such as OS, PFS, and PFI.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

DG HONG conceived of the presented idea and supervised the study. J LEE performed the analytic calculations. Both DG HONG and J LEE contributed to the draft of the manuscript. J LEE and JM KIM processed the clinical data. YH LEE designed the figures. GO CHONG helped supervise the study. All Authors discussed the results and contributed to the final manuscript.

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