In vitro chemosensitivity assay of ascites in epithelial ovarian cancer

X. Xu[1,2*], H. Dai[3*], Y. Zhao[2,4], Y. Wang[5], X. Xu[2,5], Z. Qian[1,2], X. Chen[2,4,6]

[1]Department of Chemotherapy, Jiangsu Institute of Cancer Research, Nanjing
[2]Nanjing Medical University, Nanjing; [3]Medical School of Yangzhou University, Yangzhou
[4]Department of Gynecology Oncology, Jiangsu Institute of Cancer Research, Nanjing
[5]Department of Pathology, Jiangsu Hospital of Integrated Traditional and Western Medicine, Nanjing
[6]Department of Pathology, Jiangsu Institute of Cancer Research, Nanjing
[7]State Key Laboratory of Bioelectronics, South University, Nanjing (China)

Summary

Objective: This study aimed to investigate the predictive value of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay for chemosensitivity test in ascites. *Materials and Methods:* The relationship of the in vitro sensitivity results and the clinicopathological characteristics, objective response rates (ORRs) of chemotherapy, and time to progression (TTP) were retrospectively analyzed in 120 epithelial ovarian cancer (EOC) patients. The clinical response criterion was based on the Response Evaluation Criteria in Solid Tumors (RECIST) standard. The log-rank test and Kaplan-Meier curve were used to estimate TTP. *Results:* MTT assays revealed that tumor cells from ascites of primary and type II EOC were more sensitive to paclitaxel (PTX) and carboplatin (CBDCA) than relapse ($p = 0.01$ and $p < 0.01$, respectively) and type I ($p = 0.03$, $p = 0.02$, respectively) EOC. p53 positive expression and Ki67 high expression were associated with high PTX ($p = 0.01$ and $p < 0.01$, respectively) and CBDCA ($p = 0.03$ and $p < 0.01$, respectively) sensitivity. Ki67 weak positive immunostaining was associated with topotecan ($p < 0.01$), gemcitabine ($p < 0.01$), and doxorubicin ($p < 0.01$) resistance. Chemosensitivity to CBDCA/PTX was associated with the ORR of neo-adjuvant ($p = 0.03$) and adjuvant ($p = 0.02$) chemotherapy. The MTT assay results of ascites were consistent with the clinical response ($p = 0.04$) and TTP ($p = 0.04$) in patients with platinum-resistant relapse EOC tumors. *Conclusions:* Evaluation of the chemosensitivity of ascites in EOC by MTT can aid the establishment of individualized clinical chemotherapeutic plans for platinum-resistant relapse patients.

Key words: Epithelial ovarian cancer; Drug sensitivity assay; MTT, Ascites; Chemotherapy.

Introduction

The five-year survival rate of epithelial ovarian cancer (EOC) patients increased from 36% in 1977 to 44% in 2007 [1]. Nevertheless, more than 50% of EOC patients still relapse after their initial remission. Among them, 40%-60% acquire resistance to chemotherapeutic drugs and molecular target agents, which cause treatment failures [2]. The majorities of patients with EOC require chemotherapy in the course of their disease. Whether these patient's tumors are sensitive to a certain drug prior to chemotherapy initiation is uncertain. Chemotherapeutic regimens for ovarian cancer are usually based on clinical trials, which depend on the histological type of tumor rather than on the sensitivity of an individual's cancer cells to specific anti-cancer drugs [3]. Randomized trials comparing chemotherapeutic regimens or agents have contributed numerous pieces of evidence that cytotoxic treatment benefits ovarian cancer. However, given their heterogeneity, ovarian cancers respond differently to the same chemotherapeutic agent. A diagnostic assay that can predict the response of a given agent may help improve the clinical outcome of ovarian cancer patients. The premise of sensitivity-guided chemotherapy should be the consistency of in vitro sensitivity and in vivo response.

About 20%-40% objective response rates (ORRs) to single agents such as paclitaxel (PTX), carboplatin (CBDCA), epirubicin (EPI), cyclophosphamide (CTX), and cisplatin (CDDP) in ovarian cancer have been reported. The ORRs may be more than 70% for combinations of these agents [4, 5]. To date, apart from CBDCA + PTX regimens in primary therapy [6], no particular regimen has been shown to be superior to others in terms of prolonging overall survival in primary or platinum-sensitive ovarian cancer. The sensitivities of individual patients to anti-cancer agents such as PTX and CBDCA in relapse or platinum-resistant ovarian cancer must be assessed.

Recent studies have grouped EOC into two broad categories: type I and type II. These types are based on distinct clinicopathological and molecular genetic features. Type I tumors commonly include low-grade, well-differentiated serous, endometrioid, mucinous, and clear cell carcinomas. Type II tumors include high-grade serous, high-grade endometrioid, and undifferentiated carcinomas, as well as malignant mixed mesodermal tumors (carcinosarcomas). Type I ovarian cancers slowly grow and infrequently respond to platinum-based therapy. Type II ovarian cancers, constitute approximately 75% of EOCs, and aggressively grow but commonly respond to platinum-based therapy.

**First co-authors contributed equally to the paper.*

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Tumor cells resistant to a single drug are difficult to identify in vivo, and the administration of a multidrug regimen is common. A cell culture drug-resistance assay can facilitate the isolation of a single drug-resistant cancer cell [7]. Numerous studies on chemosensitivity in vitro assays have been performed using established cell lines [4-6]. Clonogenic assays have successfully been used to predict the initial response of EOC patients to chemotherapy, but technical problems and long culture time have limited the clinical use of these assays [8]. Most of these assays are short-term total cell killing tests, where the cell isolation and culture procedures are essentially the same but the methods of determining viable cells are different. Typically, in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, the surviving cells can convert MTT into formazan, which can be directly quantified by spectrophotometry [9]. Compared with other in vitro chemosensitivity assays, the MTT test is short term (two to four days) and requires a very low amount of cells in suspension [10-12]. A significant correlation between in vitro results and in vivo outcomes for ovarian cancer ($p < 0.0001$), with an assay sensitivity of 81%, has been found in ovarian cancer [13, 14]. However, the MTT assay in tumor tissue has two major drawbacks; namely, sensitivity investigation results may 1) lag behind the requirement, and 2) be interfered with by the amounts of non-tumor cells.

To evaluate the chemosensitivity testing results, ORRs, and overall survival, chemosensitivity assay results must be verified in a large number of ovarian cancer patients. In the present study, the authors evaluated the results of chemosensitivity testing using highly purified tumor cells from ascites through an MTT assay in 120 cases of ovarian cancer. The results were assessed in terms of the correlation with clinicopathological findings, clinical response, and time to progression (TTP) by comparing with those of patients treated by experienced clinicians. The tumor cells from ascites excluded the major interference of non-tumor cells in the test. The MTT assay was consistent with the objective therapy response in some agents, which indicated the possibility of further optimized protocol on the chemosensitivity assay results in EOC patients.

Materials and Methods

Clinicopathological characteristics

This retrospective study was approved by the Institutional Review Board of Jiangsu Cancer Hospital. A total of 120 EOC patients confined in this hospital between January 1, 2005 and January 1, 2010 were recruited. Those who did not receive the standard primary treatment, mostly including chemotherapy and cytoreduction surgery, in the present hospital were excluded. Patients were monitored according to the routine follow-up protocol for EOC recommended by the MD Anderson Cancer Center, which included visits every three months for the first two years, every four months at year three, and every six months at years four and five after primary treatment.

Table 1. — *Patient characteristics of the present study population.*

Characteristics	n (%)/median (range)
Age (years)	59.7 years (292.4)
Baseline CA-125 level	801 U/ml (7-33439)
Grade, n = 120	
Low grade	28 (23.3%)
High grade	92 (76.7%)
Histology, n = 120	
Serous	71 (59.2%)
Endometrioid	18 (15.0%)
Clear cell	9 (7.5%)
Mucinous	5 (4.2%)
Transitional	2 (1.7%)
Undifferentiated	7 (5.8%)
MMMT	8 (6.7%)
FIGO Stage, n = 120	
I	12 (10.0%)
II	7 (5.8%)
III	63 (52.5%)
IV	36 (20.0%)
Unknown	2 (1.7%)
Adjuvant chemotherapy, n = 112	
Carboplatin/paclitaxel	103 (92.0%)
Other regimes	9 (8.0%)
n (%)	133 (26.8)

The authors evaluated the relationship between drug sensitivity and patients' clinicopathological data, including the histological type and grade of tumors, stage of disease as defined by the International Federation of Gynecology and Obstetrics, type of primary treatment, ascites volume, time of disease relapse, management of relapse disease, immunophenotyping (including CA-125, p53, Ki67, Her-2, EGFR, RP, and PR), and follow-up data (including TTP). Pathological diagnoses of EOC were blindly reviewed by two pathologists (Yan Wang and Xinyu Xu). Ascites and tissue samples of the original EOC were obtained from 120 patients in the Jiangsu Cancer Hospital (Table 1). An avidin-biotin peroxidase system was routinely performed for immunohistochemistry (IHC) staining. The primary antibodies were as follows: p53 (1:100, DO-7), Ki67 (1:100, clone MIB-1), ER (1:100, Dako ID5), and PR (1:100, Novocastra PGR-312). Negative and positive control slides were included in the present assay. For p53 immunoassay, nuclear staining in more than 10% of the neoplastic cells was deemed as a positive cutoff. Considering that Ki67 expression is commonly homogenous, Ki67 protein was scored by the percentage of positively stained cells with a 10% cutoff.

Chemotherapy was given every 21 or 28 days. A total of 82 patients received neo-adjuvant chemotherapy, including 56 patients with CBDCA (area under the curve (AUC) = 5) and PTX (185 mg/m^2); 22 with CDDP (75 mg/m^2) and PTX (185 mg/m^2); and four with CBDCA (350 mg/m^2) and CTX (600 mg/m^2). After primary surgery, 102 patients were treated with CBDCA (AUC = 5) and PTX (185 mg/m^2); 14 with CBDCA (350 mg/m^2) and CTX (600 mg/m^2); two with CDDP (75 mg/m^2) and PTX (185 mg/m^2); and two with CBDCA (AUC = 5) and DOC (100 mg/m^2). Clinical response to chemotherapy was assessed by clinical examination every three months. Computerized tomography (CT) scans were performed when necessary. The Response Evaluation Criteria in Solid Tumors (RECIST) and World Health Organization (WHO) criteria were used to assess tumor therapy response and clinical relapse [15-17]. The follow-up period ranged from 0.7 months to 67 months.

Drugs and ovarian cancer cell lines

Eight commonly used agents in EOC were used for in vitro chemosensitivity assay, including PTX, CBDCA, 5-fluorouracil (5-FU), TPT, etoposide (VP-16), PLD, and GEM. CBDCA and PTX are now preferentially prescribed to EOC as first-line agents, and the others are commonly administered to relapse patients in accordance with current clinical practice. In the present study, the drug concentrations for sensitivity test were chosen to mimic those in vivo [18, 19]. The SKOV3 cell line was used in the MTT assay and as blank controls. CBDCA was dissolved in distilled water, and other drugs including PTX were dissolved in saline. All drugs were further diluted with RPMI-1640. The SKOV3 cell line was obtained from the American Type Culture Collection.

Separation of cells and culture suspension

Ascites for sensitivity test were obtained from abdominocentesis or surgical procedures. Ascites were centrifuged at 3,000 rpm for 30 min before immersion in a complete medium containing collagenase (2 mg/ml, Type V-S) and DNase I (0.4 mg/ml). The cells were harvested after incubation for 40 min at 37°C, washed, and suspended in a complete medium. The single-cell suspension was then centrifuged at 400 × *g* for 30 min. The collected interface was suspended in a complete medium at 1×10^6 /ml density. Discontinuous gradients consisting of 10 ml of 100% and 15 ml of 75% Ficoll–Hypaque were applied for onto the cell layer. A tumor cell-rich fraction was then obtained from the 75% interface after centrifugation at 400 × *g* for 30 min. Discontinuous gradients comprising four ml each of 25%, 15%, and 10% Percoll were then applied onto the tumor cell-rich suspension layer. Tumor cells depleted of lymphoid cells were obtained from the bottom and at the 25% interface, and then suspended in a complete medium at a density of 1×10^6 /ml after centrifugation was performed at 25 × *g* for 7 min.

In vitro chemosensitivity assay

With different drug concentrations in RPMI, the cell suspension was incubated in a 96-well round-bottomed microculture plate. Blank and control tumor cells (SKOV3) were cultured in RPMI without any other reagent. Wrapped in cling film, the plates were incubated for 48 h at 37°C in humidified air containing 5% CO_2. After 48 h of incubation, 50 g of MTT in five mg/ml concentration was added to each well. The plates were then incubated for another five hours at 37°C and 5% CO_2. During exposure, yellow MTT was transformed by viable cells into purple formazan.

After dissolving in 100 µl of dimethylsulfoxide, the formazan crystals were quantified by a microplate spectrophotometer at 540 nm. The following equation was used to calculate the ovarian cancer cell viability: (OD value of drug exposed well/mean OD value of control wells) × 100%. The OD of blank wells was used to adjust the control and test wells.

Criterion of chemosensitivity assay results

For each single drug, the result of MTT chemosensitivity assay was determined to be sensitive (i.e., greater than the mean inhibition rate). Based on the chemotherapeutic regimen, patients were classified into three categories in accordance with the combination of two sensitivities. The sensitive (S) category was defined as being sensitive to both drugs, the intermediate (I) was sensitive to only one of them, and resistant (R) was sensitive to none. The primary chemotherapeutic regimen was mostly CBDCA/PTX in 87 patients receiving neo-adjuvant chemotherapy and 43 patients who did not obtain satisfactory cytoreduction surgery. Regimens other than CBDCA/PTX were evaluated in 87 platinum-resistant relapses patients.

Statistical analyses

The relationship between the MTT assay results and clinical characteristics was tested for statistical significance by the t-test, whereas the clinical responses were assessed using the chi-squared test. The Kaplan-Meier method was used to estimate the TTP distribution, and a log-rank test was used to analyze differences between groups. A p value less than 0.05 was considered significant. All analyses were performed using the SPSS 11.5 software package.

Results

Correlation of in vitro chemosensitivity results with clinical characteristics

During the study period, 188 pieces of ascites specimens with ovarian cancer from 120 patients were tested by MTT assay. A total of 182 specimens were considered to be suitable for evaluation (success rate = 96.8%). Table 2 shows the overall results of chemosensitivity for each drug. The inhibition rates of tumor cells for PTX and CBDCA were significantly higher than 5-FU, VP-16, and EPI ($p < 0.01$, respectively). The inhibition rate for PLD did not different from those for GEM ($p = 0.39$) and TPT ($p = 0.72$).

The correlation of the clinicopathological characteristics with in vitro chemosensitivity test results was investigated. The inhibition rates for PTX and CBDCA in the relapse ($p = 0.01$ and $p < 0.01$, respectively) and type I ($p = 0.03$ and $p = 0.02$, respectively) tumors were significantly lower than those in the primary and type II tumors, respectively. The authors also found that the inhibition rates for GEM and 5-FU in type I tumors ($p = 0.01$ and $p = 0.01$, respectively) were significantly higher than those in type II tumors. No statistical difference between the inhibition rates in FIGO stages was observed for all tested drugs (Table 2). The inhibition rates for VP-16 in serous tumor cases were higher than those in endometrioid and mucous tumor cases ($p < 0.01$ and $p < 0.01$, respectively). No statistical difference existed between the inhibition rates for other drugs, except in p53 and Ki67 expression (Table 3).

Correlation of in vitro chemosensitivity results with in vivo clinical response

The authors analyzed the in vitro chemosensitivity test results and patients' ORRs using these tested drugs in EOCs. Most patients who received CBDCA/PTX had a high ORR in the S and I categories than those in the S category both in neo-adjuvant and adjuvant chemotherapy (Table 4; $p = 0.03$ and $p = 0.02$, respectively). For platinum-resistant relapse patients, chemotherapeutic regimens in S and I categories were associated with a higher ORR (Table 5; $p = 0.04$).

Table 2. — *Comparison of chemosensitivity between clinicopathologic characteristics in ovarian cancer.*

Tumor type	Inhibition rate							
	5-Fu	PTX	CBDCA	TPT	EPI	VP-16	GEM	PLD
Primary	41.6 ± 9.2	50.5 ± 10.2	51.5 ± 7.2	48.7 ± 9.7	42.3 ± 9.1	40.7 ± 5.1	45.6 ± 9.5	45.3 ± 7.2
Relapse	28.7 ± 5.1	35.1 ± 6.8[a]	34.1 ± 4.7[b]	32.2 ± 5.2	30.9 ± 6.7	33.0 ± 3.7	30.8 ± 7.9	30.6 ± 4.4
Type I	36.9 ± 7.8	38.8 ± 7.4[c]	37.8 ± 5.0[d]	37.6 ± 6.8	32.8 ± 6.3	33.1 ± 3.9	42.1 ± 8.1	34.4 ± 5.2
Type II	31.3 ± 7.0e	46.7 ± 9.6	47.7 ± 5.8	44.7 ± 7.4	39.5 ± 8.6	38.4 ± 4.8	34.0 ± 8.4[f]	41.2 ± 6.6
Stage I	35.2 ± 8.2	44.3 ± 8.9	45.3 ± 5.9	43.2 ± 7.4	36.2 ± 7.9	36.3 ± 4.3	39.1 ± 8.8	40.5 ± 6.1
Stage II-IV	33.8 ± 7.4	40.4 ± 8.1	39.4 ± 5.1	38.9 ± 6.9	35.1 ± 7.5	35.0 ± 3.5	37.2 ± 8.4	36.0 ± 5.5
Total	34.2 ± 7.6	42.6 ± 8.5	42.3 ± 5.5	40.8 ± 7.1	35.5 ± 7.7	35.5 ± 4.1	38.0 ± 8.7	38.5 ± 5.9

[a]$p = 0.01$, [b]$p < 0.01$ compared between primary and relapse lesions, [c]$p = 0.03$, [d]p = 0.02, [e]$p = 0.01$, [f]$p = 0.01$ compared between type I and type II lesions.

Table 3. — *Comparison of chemosensitivity between IHC characteristics of ovarian cancer.*

Characteristic	Inhibition rate							
	5-Fu	PTX	CBDCA	TPT	EPI	VP-16	GEM	PLD
P53+	36.7 ± 7.7	45.3 ± 9.4[g]	46.1 ± 5.5[h]	44.9 ± 7.5	40.4 ± 8.8	38.9 ± 4.8	45.0 ± 9.4	42.1 ± 6.7
P53-	31.8 ± 7.2	39.2 ± 7.6	39.9 ± 5.2	37.0 ± 6.7	31.8 ± 6.2	32.8 ± 3.8	32.8 ± 8.1	32.8 ± 5.0
Ki67 strong	41.0 ± 9.1	52.5 ± 10.3[i]	52.5 ± 7.3[j]	49.8 ± 9.9[k]	43.2 ± 9.1	41.7 ± 5.2	43.3 ± 9.2l	46.3 ± 7.4[m]
Ki67 weak	29.6 ± 5.3	34.1 ± 6.7	33.8 ± 4.7	31.4 ± 5.1	30.1 ± 6.6	32.1 ± 3.5	32.1 ± 8.0	30.2 ± 4.3
ER+	32.5 ± 7.2	40.0 ± 8.1	38.4 ± 5.0	39.3 ± 6.9	35.2 ± 7.5	35.2 ± 3.7	37.6 ± 8.4	36.2 ± 5.5
ER-	35.4 ± 8.5	44.6 ± 8.9	47.6 ± 6.1	42.7 ± 7.3	36.0 ± 7.9	36.1 ± 4.3	38.7 ± 8.8	40.1 ± 6.1
PR+	34.2 ± 7.5	42.0 ± 8.3	41.7 ± 5.3	39.8 ± 6.9	34.6 ± 7.2	35.4 ± 3.9	37.1 ± 8.6	37.8 ± 5.9
PR-	36.1 ± 7.8	43.1 ± 8.8	43.7 ± 5.6	42.2 ± 7.5	36.9 ± 7.8	36.2 ± 4.3	39.2 ± 8.9	38.1 ± 6.9

[g]$p = 0.01$, [h]$p = 0.03$, compared between p53 immunostaining status, [i]$p < 0.01$, [j]$p < 0.01$, [k]$p < 0.01$, [l]$p < 0.01$, [m]$p < 0.01$, compared between Ki67 expression status.

Table 4. — *Chemosensitivity of carboplatin/paclitaxel regime and the objective response rate in ovarian cancer.*

Inhibition rates	NACT (n = 72)		CT (n = 43)	
	CR + PR	SD + PD	CR + PR	SD + PD
CP (S)	22[n]	7	12[o]	4
CP (I)	18	5	8	3
CP (R)	9	11	5	11

[n]$p = 0.03$, [o]$p = 0.02$ compared with the inhibition rate and objective response rate on carboplatin/paclitaxel regime.

Table 5. — *Comparison of chemosensitivity and objective response rate in platinum-resistant relapse ovarian cancer.*

Inhibition rates	CR + PR	SD + PD
CP (S)	22[p]	9
CP (I)	14	8
CP (R)	9	15

[p]$p = 0.04$, compared with the inhibition rate and objective response rate on second line regimes (n = 87).

Correlation of MTT sensitivity results with patient outcomes

The MTT sensitivity assay results of adjuvant chemotherapy were insignificantly correlated with the overall survival ($p = 0.33$). For platinum-resistant relapse EOC, the Kaplan–Meier survival analysis demonstrated that the patients in the S and I categories (95% confidence interval, median = 7.0 months, range = 5.0-9.0 months) with longer TTP than those in the R category (95% confidence interval, median = 7.0 months, range = 2.4-7.2 months) (Figure 1; $p = 0.043$).

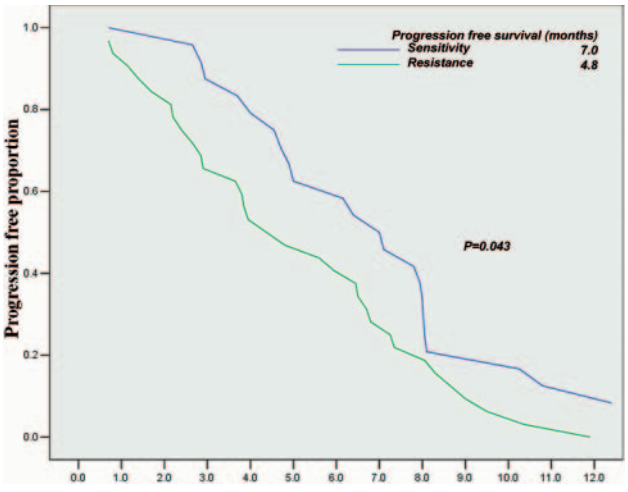

Figure 1. — TTP of the platinum-resistant relapse EOC in sensitive and intermediate categories was longer than those in the resistant category ($p = 0.04$).

Discussion

To the best of the authors' knowledge, the current study on in vitro chemosensitivity by MTT assay in 120 ovarian cancer patients is the largest retrospective study conducted so far [13, 14, 20-23). Based on the overall results, CBDCA and PTX showed higher sensitivities than PLD, TPT, EPI, and GEM in primary ovarian cancer, in agreement with clinical reports. Both CBDCA and PTX are presently first-line regimens for primary

and platinum-sensitive EOC [6, 24, 25]. On the other hand, 5-FU and VP-16 showed lower inhibition rates than the other drugs, suggesting that 5-FU and VP-16 alone were ineffective for most ovarian cancers. The authors found that the chemosensitivity of CBDCA and PTX were higher in primary, type II, and p53 immunostaining positive tissues than those in relapse, type I, and p53-negative ovarian cancer. This result suggested that the chemosensitivity testing results of primary tumor should not be referenced for second-line chemotherapy, and that the subtype of ovarian cancer should be a major agent selection factor. In relapse cases, tumor cells can acquire a tolerance for anti-cancer drugs that have been previously administered. Chemosensitivity test may play an important role in selecting a regimen of second-line chemotherapy and should be assessed as frequently as possible while tumors relapse. Ovarian cancer is not a single-disease entity but rather comprises many different subtypes with distinct clinicopathological characteristics [26, 27]. Type I ovarian cancer is apt to be less malignant without p53 mutation, and more resistant to CBDCA and PTX than type II. The present study revealed that Ki67, as a typical cell-proliferation and cell-cycle time marker, is associated with agents such as TPT, GEM, and so on. Thus, Ki67 may be an indicator of the effect of these agents on tumor metabolism and mitosis. Clinicopathological findings such as FIGO stage and ER/PR immunostaining were not correlated with chemosensitivity in all test agents.

Generally, chemotherapy benefits patients with platinum-sensitive relapse ovarian cancer, but the extent of this benefit is limited and no standard, universally accepted regimen exists for platinum-resistant patients. Anti-cancer drugs such as trabectedin [28], PLD, TPT, and GEM are already available and reportedly effective for ovarian cancer. However, the efficacy rates of these drugs are commonly < 30% and their adverse effects cannot be ignored. In the current work, the authors found by MTT assay that a higher inhibition rate in platinum-resistant ovarian cancer is associated with higher ORRs and prolonged TTP. To improve prognosis and avoid adverse effects in platinum-resistant relapse ovarian cancer patients, the chemotherapeutic regimen should be established in accordance with in vitro testing-based individualized chemosensitivity, which may enable personalized ovarian cancer treatment in the future.

The in vitro MTT tumor sensitivity assay had some inherent drawbacks. First, the tumor tissues for this assay were mostly obtained through biopsy, which is an invasive, surgical procedure. The drug sensitivity results were unavailable and may have been influenced by neoadjuvant chemotherapy. Second, the false positive and negative rates of MTT assay for clinical response were about 30%-50% and 5%-15% [29, 30]. Besides, the difference between the internal and external environments of tumor cells, non-tumor cells (such as lymphocytes and fiber cells), and interference also affect the accuracy of the results and drug sensitivity test in vitro. The authors recruited ascites by abdominocentesis for MTT assay, and the results were available within two to four days, which enabled quick application to patients in vivo. More importantly, MTT assay on ascites may partly avoid these interference factors.

In conclusion, patients have different sensitivities to anti-cancer drugs. Moreover, predicting the appropriate anti-cancer drug in accordance with the clinicopathological findings of tumors, including the difference between primary and relapse lesions, is difficult. Chemosensitivity testing is one of the most effective strategies for establishing an appropriate anti-cancer regimen, especially for platinum-resistant ovarian cancer, to improve patient outcomes. Chemotherapy based on the results of chemosensitivity testing can also help avoid potential adverse effects and be economical.

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Address reprint requests to:
X. CHEN, M.D.
Department of Gynecologic Oncology
Jiangsu Institute of Cancer Research,
Nanjing (China)
e-mail: cxxxxcyd@gmail.com