TBX2 expression is associated with platinum-sensitivity of ovarian serous carcinoma

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Abstract. The standard treatment for ovarian serous carcinoma comprises maximum debulking surgery and platinum-based chemotherapy. Despite the high response rate to chemotherapy, the majority of patients will be resistant to first-line agents and the prognosis for these patients is particularly poor. At present there are no reliable methods to determine or predict platinum resistance. T-box 2 (TBX2) is widely expressed in cancer cells and is involved in embryonic development and cell cycle regulation. TBX2 enables cells to bypass senescence through its ability to repress the cell cycle regulators p21 and $p14^{ARF}$; silencing TBX2 induces senescence. Ectopic expression of TBX2 is associated with conferred resistance to the DNA-damaging chemotherapeutic drugs cisplatin and doxorubicin. In the present study the association between TBX2 expression and platinum sensitivity was investigated. A total of 54 patients with ovarian serous carcinoma (FIGO stages III and IV) were treated at Osaka City University Hospital (Osaka, Japan) from January 2005 to December 2012. Patients were divided into platinum-sensitive (n=27) and resistant (n=27) groups, according to the platinum-free interval calculated from the last platinum administration to the time of recurrence. TBX2 expression in human ovarian serous carcinoma cells was inhibited by a TBX2-specific siRNA and changes in cisplatin and carboplatin sensitivity were determined. The TBX2-weighted score was significantly lower in the platinum-sensitive group than the platinum-resistant group (P=0.005) and the low TBX2 expression group was significantly more sensitive to platinum-based chemotherapy (P=0.004). Sensitivity to cisplatin and carboplatin significantly increased when TBX2 expression was inhibited in human ovarian serous carcinoma cells *in vitro* (P<0.05). TBX2 expression may serve as a predictive marker of the efficacy of platinum-based chemotherapy for patients with ovarian serous carcinoma.

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Introduction

Ovarian serous carcinoma is a common cause of cancer deaths of females worldwide. Patients are generally diagnosed at an advanced stage and consequently have a high mortality rate. The standard treatment comprises maximum debulking surgery and platinum-taxane combination therapy. Despite the high response rate to chemotherapy, the majority of patients will be resistant to first-line agents, and the prognosis of resistant patients is particularly poor. Upon recurrence, the probability of a response to retreatment with platinum-based chemotherapy depends on the platinum-free interval, defined as the duration from the last platinum administration to cancer recurrence (1). If the ovarian carcinoma recurs within 6 months from the last platinum administration, it is defined as 'platinum-resistant.' If the carcinoma recurs after 6 months from the last platinum administration, it is defined as 'platinum-sensitive' (2). Platinum-sensitivity or resistance is an independent prognostic factor for overall and progression-free survival of patients with ovarian carcinoma (3).

However, it is difficult to determine sensitivity to platinum-based chemotherapy at the first administration of chemotherapy and before the first recurrence. Therefore, 'platinum-resistant' patients are identified retrospectively after recurrence or unresponsiveness to initial platinum-based chemotherapy. Knowledge of the predictors of the response to platinum-based chemotherapy may allow selection of sensitive patients who are candidates for chemotherapy, as well as to avoid administering platinum-based chemotherapy to platinum-resistant patients. Further, customized treatment can be designed according to clinical stratification according to drug resistance.

Unfortunately, a reliable method is not available that determines or predicts platinum resistance. To improve the prognosis of platinum-resistant patients with ovarian serous carcinoma, we aimed here to identify new biomarkers with prognostic and predictive potential and to identify new therapeutic targets.

T-box 2 (TBX2) is a member of the T-box family of transcription factors that are involved in embryonic development, cell cycle regulation, and cancer (4,5). TBX2 allows cells to

bypass senescence through its ability to repress the activities of the cell cycle regulators p21 and $p14^{ARF}$, and silencing TBX2 expression induces senescence (5-8). Overexpression of *TBX2* occurs in breast cancer (7,9), melanoma (8) pancreatic cancer (10), gastric cancer (11), prostate cancer (12), laryngeal squamous cell carcinoma (13), and non-small cell lung cancer (14). The ectopic expression of TBX2 is associated with resistance to the DNA-damaging chemotherapeutic drugs cisplatin and doxorubicin (15,16). However, the mechanism of regulation of expression and the role of TBX2 in ovarian cancer remain to be determined.

Here we assessed the association between TBX2 expression and the sensitivity of ovarian serous carcinoma to platinum-based chemotherapy. We aimed to identify new biomarkers with prognostic and predictive potential and searched for new therapeutic targets to improve the prognosis of patients with platinum-resistant ovarian serous carcinoma.

Patients and methods

Patients and samples. We reviewed the records of 54 patients with ovarian serous carcinoma, stages III-IV, treated at our hospital from January 2005 to December 2013. Patients were allocated to the groups as follows: i) Platinum-sensitive group (n=27), subjected to maximum debulking surgery followed by platinum-based chemotherapy whose tumors did not recur within 6 months from the last platinum administration; ii) platinum-resistant group (n=27) subjected to maximum debulking surgery followed by platinum-based chemotherapy whose tumors recurred within 6 months. Written informed consent was obtained from all patients prior to treatment and the Institutional Review Board (IRB) of Osaka City University Hospital approved this study (IRB no. 3525).

Immunohistochemistry. TBX2 expression was determined by conducting immunohistochemical analysis of paraffin-embedded sections using a Dako LSAB2 Peroxidase kit (cat. no. K0675; Agilent Technologies, Inc., Santa Clara, CA, USA). Sections (4 μm-thick) were deparaffinized, rehydrated, and immersed in 3% hydrogen peroxide at room temperature for 10 min to block endogenous peroxidase activity. Antigen retrieval was performed by immersing sections in 10 mM citrate buffer (pH 6.0) and heating to 110˚C for 20 min in an autoclave. Tissue sections were then washed in phosphate-buffered saline (PBS) and incubated overnight at 4˚C with a 1:32 dilution of a rabbit polyclonal anti-TBX2 antibody (LS-C402301; LifeSpan BioSciences, Inc., Seattle, WA, USA). Next, sections were washed in PBS for 15 min and then incubated for 10 min with biotinylated goat immunoglobulin G secondary antibodies (Dako; Agilent Technologies, Inc.). Sections were then incubated with a streptavidin-peroxidase complex, and 3,3'-diaminobenzidine was used as the chromogen. Finally, tissue sections were counterstained with hematoxylin, and the specificity of the immunohistochemical reactions was verified by omitting the primary antibody.

TBX2 expression scores were calculated using the weighted score of Sinicrope *et al* (17). The percentage positivity was scored as: 0 (<5%), 1 (5-25%), 2 (25-50%), 3 (50-75%), and 4 (>75%). The staining intensity was scored as 0 (no staining), 1 (weak staining), 2 (moderate staining), or 3 (strong staining). The percentage positivity of cells and staining intensity were determined in a double-blinded manner. The TBX2 expression score was calculated by multiplying the percentage positivity score and the staining intensity score, which ranged from 0 to 12.

Cell culture. The human ovarian serous carcinoma cell line OVSAHO (cat no. JCRB1046; National Institutes of Biomedical Innovation, Health and Nutrition, Osaka, Japan) was cultured in RPMI medium (Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA) containing 10% fetal bovine serum (Gibco; Thermo Fisher Scientific, Inc.), penicillin (100 units/ml), and streptomycin (100 units/ml) at 37˚C in a humidified incubator containing an atmosphere of 5% CO_2. The medium was changed daily. For real-time PCR (RT-qPCR) analysis, cells were directly cryopreserved in a refrigerator at -20˚C.

Cell survival assay and siRNA procedures. OVSAHO cells were seeded into 96-well plates at 10,000 cells per well. We divided cells into a control group that was not transfected with the TBX2-specific siRNA (siTBX2) and an siTBX2 group that was transfected with siTBX2 for 24 h. The siTBX2 sequence was sense: 5'rCrCrArAUrGrArArCUrGrCrArGrArGrCrAUTT, antisense: 5'rAUrGrCUrCUrGrCrArGUUrCrAUUrGrGTT. Cells were transfected with siTBX2 using Lipofectamine RNAiMax (Invitrogen, Carlsbad, CA, USA) according to manufacturer's instructions. Twenty-four h after cell adhesion in the control group and 24 h after transfection with siTBX2 of the siTBX2 group, the medium was replaced with the fresh media containing 0, 1.0, 2.5, or 5.0 μM cisplatin or 0, 10, 50, or 100 μM carboplatin, and the cells were incubated for 48 h. Cells were prepared in six wells for each treatment and were incubated for 24 h prior to 48 h treatment with cisplatin or carboplatin. Cell viability was measured using a Cell Counting kit-8 (CCK-8; Dojindo Molecular Technologies, Inc., Kumamoto, Japan). Specifically, 10 μl CCK-8 and 100 μl RPMI1640 were added to each well and incubated for 2 h at 37˚C. Absorbance was measured at 450 nm using a microplate reader (Corona Electric Co., Ltd., Ibaraki, Japan). Dose-response curves were generated to determine the percentage of viable cells compared with that of control cells.

RT-qPCR. Total RNA was extracted from OVSAHO cells using an RNeasy mini kit (QIAGEN GmbH, Hilden, Germany) following manufacturer's instructions. RNA was reverse-transcribed using a High Capacity cDNA Reverse Transcription kit (Thermo Fisher Scientific, Inc.). Expression of TBX2 mRNA was performed using the TaqMan Gene Expression Assay (Applied Biosystems; Thermo Fisher Scientific, Inc.) with an ABI7500 Fast System. The mRNA levels were normalized to those of *GAPDH* mRNA. The RT-qPCR assays (Thermo Fisher Scientific, Inc.) employed TaqMan TBX2 (Hs00911929_m1) and GAPDH (Hs99999905_m1) assays.

Statistical analysis. The data are expressed as the mean ± standard deviation. Kaplan-Meier and log-rank

Table I. Characteristics of patients in the platinum-sensitive and platinum-resistant groups.

Characteristics	Platinum sensitive (n)	Platinum resistant (n)	P-value
No. of patients	27	27	
Age (years)			0.725[a]
Mean ± SD	61.0±12.2	60.0±10.0	
FIGO stage			0.277[b]
IIIA	1	0	
IIIB	3	1	
IIIC	21	19	
IVA	1	4	
IVB	1	3	
Tumor marker			0.374[a]
Mean CA125, U/ml	3,343.3	2,180.1	
Postoperative residual disease			0.004[b]
None	5	0	
<1 cm	10	4	
>1 cm	12	23	

[a]Student's t-test, [b]χ^2 test. FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

analyses were performed to evaluate prognosis. Weighted scores were compared using the Mann-Whitney test. The Student's t-test was performed to evaluate the significance of differences between the mean values of two groups, and the χ^2 test was performed to identify significant associations between the categorical variables of the two groups. SPSS software version 21.0 (IBM SPSS, Armonk, NY, USA) was used for all statistical analyses. P<0.05 indicates a statistically significant difference.

Results

Patients' characteristics. We investigated the associations of age, FIGO stage, CA125 levels, and postoperative residual disease. There was no significant difference between the former three variables. In contrast, the size of postoperative residual disease was significantly higher in the platinum-resistant group (P=0.004) (Table I).

Expression of TBX2 in ovarian serous carcinoma tissue. TBX2 was detected predominantly in the nucleus (Fig. 1). The mean weighted scores of the platinum-sensitive and platinum-resistant groups were 2.7 and 5.4, respectively. The mean weighted score for TBX2 expression was significantly lower in the platinum sensitive group (P=0.005) (Table II and Fig. 2). Next, we divided the patients into two groups according to their TBX2 expression scores as follows: Low TBX2 expression (weighted score ≤6, n=44) and high TBX2 expression (weighted score ≥8, n=10). Table III lists the characteristics of the high and low expression groups. There was no significant difference between them.

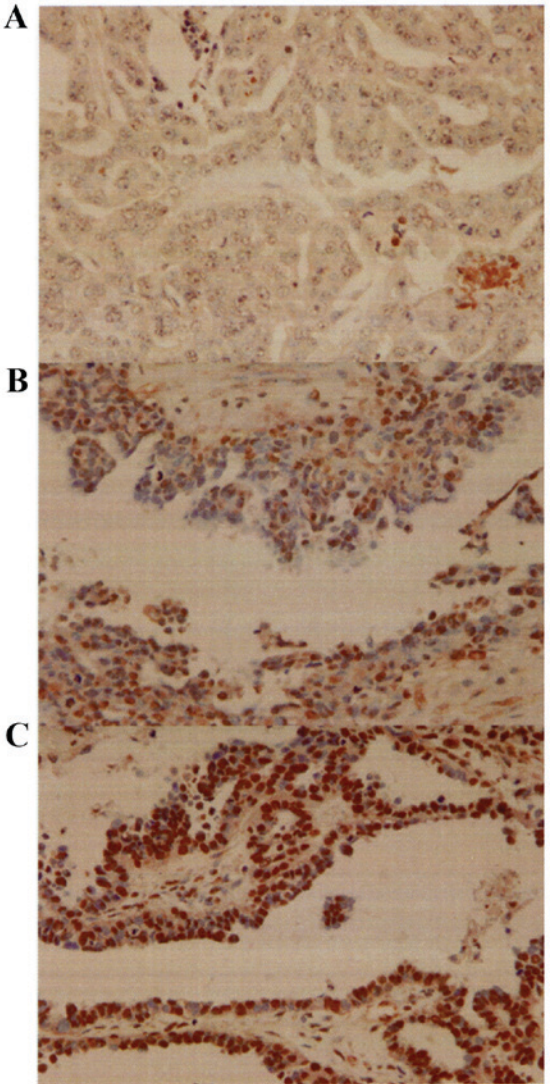

Figure 1. Immunohistochemical analysis of TBX2 expression in ovarian serous carcinoma. (A) Negative control without the primary antibody. (B and C) Scores of (B) 6 and (C) 12 were obtained using a primary antibody against TBX2. Hematoxylin staining (magnification, x400). TBX2, T-box 2.

Association of platinum sensitivity with TBX2 expression. In the low TBX2 expression group, there were 26 (59.1%) and 18 (40.9%) patients in the platinum-sensitive and platinum-resistant groups, respectively. In the high TBX2 expression group, one patient (10.0%) and nine (90%) patients were in the platinum-sensitive and platinum-resistant groups, respectively. The low TBX2 expression group was more sensitive to platinum-based chemotherapy compared with the high TBX2 expression group (P=0.004) (Table IV).

Survival. The overall survival (OS) of members of the low TBX2 expression group was significantly longer compared with that of the high TBX2 expression group (P=0.023) (Fig. 3).

siRNA-mediated silencing of TBX2 expression enhances the sensitivity of ovarian carcinoma cells to carboplatin. TBX2 mRNA expression by OVSAHO cells was suppressed 48 h after the cells were transfected with siTBX2 (Fig. 4), and cells transfected with siTBX2 were significantly more sensitive to cisplatin and carboplatin after 48 h (Fig. 5).

Table II. Weighted scores of TBX2 expression in the platinum-sensitive and platinum-resistant groups.

	No. of patients	
Weighted score	Platinum sensitive	Platinum resistant
0	3	1
1	9	4
2	4	5
3	1	2
4	3	4
6	6	2
8	1	4
9	0	1
12	0	4
Total	27	27
Mean	2.7	5.4

TBX2, T-box 2.

Table III. Characteristics of patients in the low and high TBX2 expression groups.

	No. of patients		
Characteristics	Low TBX2 expression (score ≤6)	High TBX2 expression (score ≥8)	P-value
No. of patients	44	10	
Age (years)			0.685[a]
Mean ± SD	60.2±11.4	61.8±10.0	
FIGO stage			0.649[b]
IIIA	1	0	
IIIB	4	0	
IIIC	31	9	
IVA	4	1	
IVB	4	0	
Tumor marker			0.593[a]
Mean CA125, U/ml	2,931.0	2,017.1	
Postoperative residual disease			0.419[b]
None	5	0	
<1 cm	12	2	
>1 cm	27	8	

[a]Student's t-test, [b]χ^2 test; TBX2, T-box 2; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

Discussion

The effective treatment of ovarian serous carcinoma remains a major challenge because of the recurrence of platinum-resistant tumors. The mechanism of platinum-resistance may involve decreased cellular uptake caused by abnormalities of transporters, intracellular cisplatin inactivation (e.g., caused by glutathione), and increased DNA repair (18). However, no available therapy prevents platinum-resistance.

TBX2 is overexpressed by numerous human cancers (7-14). TBX2 may serve as a prognostic factor of breast cancer (7,9), melanoma (8), gastric cancer (10), prostate cancer (11), laryngeal squamous cell carcinoma (12), and non-small cell lung cancer (14). TBX2 is associated with resistance to therapeutic drugs such as cisplatin and doxorubicin (15,16), and TBX2 therefore may serve as a therapeutic target.

One report shows that chromosome 17q12-q24 harbors strong candidates for ovarian tumorigenesis, such as LASP1 (17q12), TGF11 (17q21.32), MUL (17q23.2), TBX2 (17q23.2), AXIN2 (17q24.3), and GRB2 (17q25.1) (19). Further, TBX2 is upregulated in a subset of breast cancer cell lines, and breast tumors with mutations in BRCA1 and BRCA2 (7,20-22), which are strongly associated with ovarian serous carcinoma.

In the present study, the OS of the low TBX2 expression group was significantly longer compared with that of the high TBX2 expression group. Transfection with siTBX2 increased

Table IV. Number of patients with low and high TBX2 expression in the platinum-sensitive and platinum-resistant groups.

TBX2 expression	Platinum sensitive, number (%)	Platinum resistant, number (%)	P-value
Low expression (score ≤6)	26 (59.1)	18 (40.9)	0.004[a]
High expression (score ≥8)	1 (10.0)	9 (90.0)	

TBX2, T-box 2.

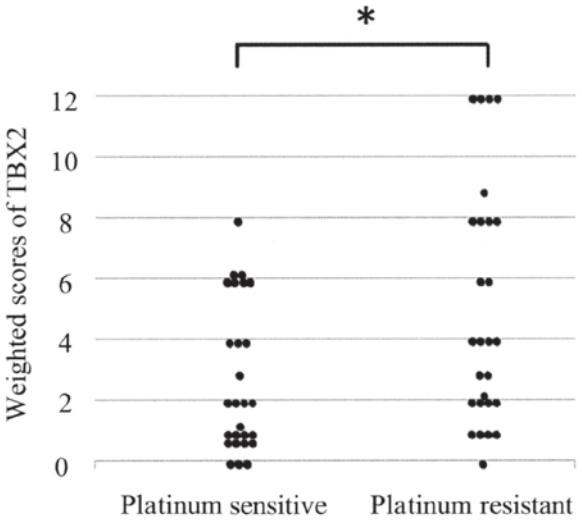

Figure 2. Weighted scores for TBX2 expression in tumor samples from patients with ovarian serous carcinoma. *P=0.005 (Mann-Whitney test). TBX2, T-box 2.

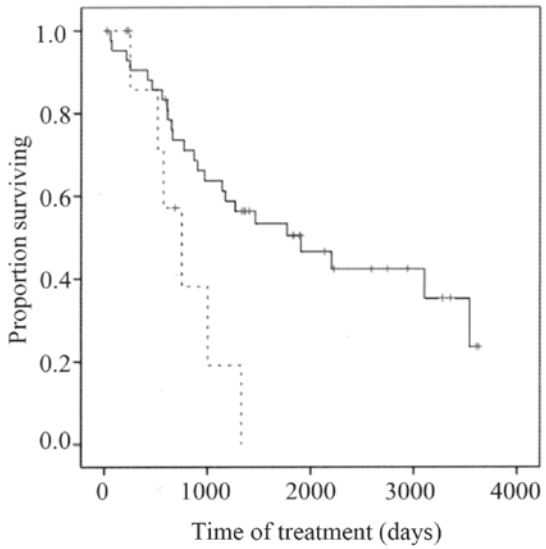

Figure 3. Overall survival of the low TBX2 (solid line, n=44) and high TBX2 (broken line, n=10) expression groups. P=0.023 (Kaplan-Meier and log-rank tests). TBX2, T-box 2.

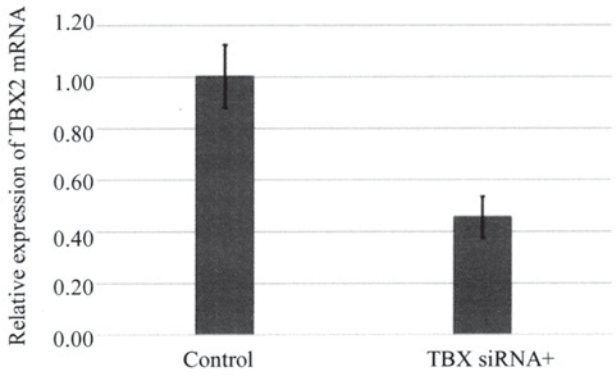

Figure 4. Relative expression of TBX2 mRNA in OVSAHO ovarian serous carcinoma cells, as confirmed by reverse transcription-quantified polymerase chain reaction analysis of TBX2. TBX2, T-box 2; siRNA, small interfering RNA.

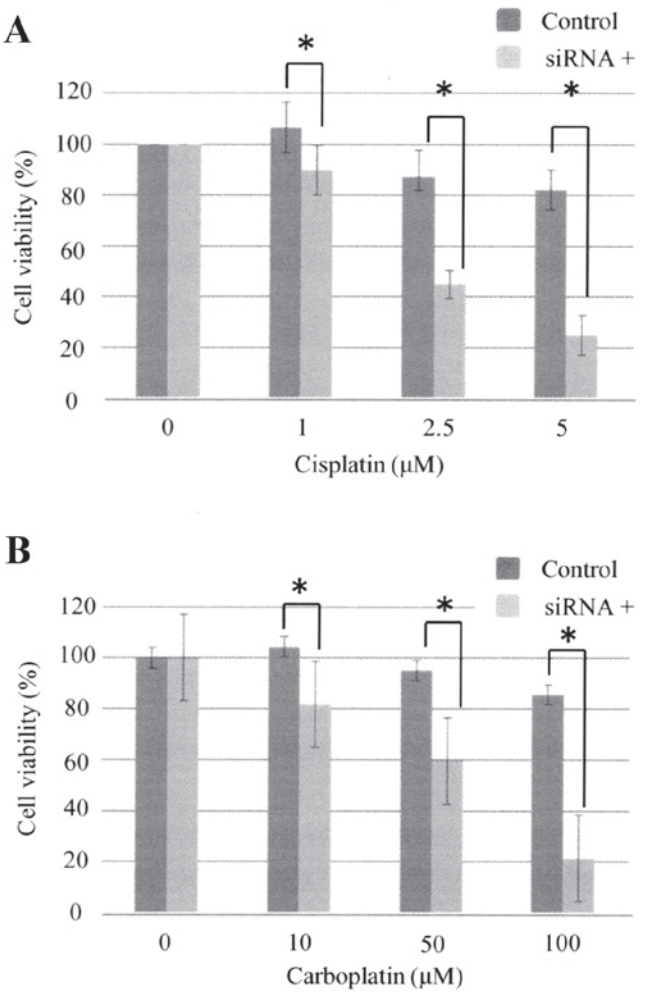

Figure 5. Sensitivities of OVSAHO cells to cisplatin (A) and carboplatin (B) in the presence or absence of an siRNA specific for TBX2. *P<0.05 (Student's t-test). TBX2, T-box 2; siRNA, small interfering RNA.

the sensitivity of OVSAHO cells to cisplatin and carboplatin. Wansleben *et al* found that breast cancer and melanoma cell lines are sensitive to cisplatin and undergo mitotic catastrophe in a cisplatin-resistant breast cancer cell line when TBX2 expression is knocked down (23), which is consistent with our present results.

Demay *et al* found that TBX2 has the potential to recognize mitotic chromatin and can interact with the histone H3 N-terminal tail (24). Further, Warfel *et al* indicated that p21 is frequently downregulated in human cancers, and its expression can either inhibit or promote carcinogenesis, depending on the cellular context (25). Huang *et al* reported that TBX2 is overexpressed, while p21 is expressed at relatively lower levels in laryngeal squamous cell cancer (13). Moreover, TBX2 binds and represses the p21 promoter in melanoma cells by recruiting histone deacetylase 1 (HDAC1) (8). In contrast, TBX2 and p21 protein levels increase simultaneously (24).

Another mechanism that accounts for poor prognosis associated with TBX2 involves the repression of E-cadherin by TBX2, leading to the epithelial-mesenchymal transition and subsequent invasion of adjacent tissues by tumor cells (26). Moreover, TBX2 inhibits the tumor suppressor PTEN by recruiting HDAC1 (27). Despite several studies showing the association of TBX2 with poor prognosis, the mechanism by which TBX2 induces resistance of chemotherapy is unknown. This study included only 54 patients. That small number is one of the limitations of this study. Further investigations with a larger number of cases are required to fill the critically important gap in our knowledge.

In conclusion, TBX2 expression may serve as a marker that predicts the efficacy of platinum-based chemotherapy administered to patients with ovarian serous carcinoma. To our knowledge, the present study is the first to report an association of TBX2 expression with platinum sensitivity. This knowledge will be helpful for efforts to improve the prognosis of patients with ovarian serous carcinoma.

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