Abstract. Background/Aim: To evaluate the role of serine protease inhibitor B11 (SERPINB11) expression as a prognostic biomarker in high-grade serous carcinoma (HGSC) and clear cell carcinoma of the ovary (CCC). Materials and Methods: We obtained tumor tissues from patients with HGSC (n=145) and CCC (n=59). We evaluated immunohistochemically the expression of SERPINB11 and investigated whether SERPINB11 expression affects platinum-resistance and the prognosis of HGSC and CCC. Results: High expression of SERPINB11 was more common in CCC than in HGSC (57.6% vs. 28.3%; p<0.01), and SERPINB11 expression did not correlate with platinum-resistance of HGSC and CCC. High expression of SERPINB11 was associated with worse progression-free survival and overall survival with marginal significance in HGSC; no relation between SERPINB11 expression and the prognosis of CCC was found. Conclusion: SERPINB11 expression maybe a prognostic biomarker for HGSC.

Epithelial ovarian cancer (EOC) is the most fatal among female genital tract malignancies due to the lack of effective screening methods for detecting early-stage disease (1). Among all histologic types, high-grade serous carcinoma (HGSC) is the most common histologic type and consists of 80% of EOC, whereas endometrioid, mucinous, and clear cell carcinoma (CCC) comprise the 10%, 5%, and 5% (2). Considering that histologic type is a well known prognostic factor for EOC (3), CCC reportedly showed the worst prognosis (4-6). Moreover, estrogen exposure is one of the well-known risk factors for EOC (7-9), and specific histologic types such as HGSC and CCC have been reported to be associated with prolonged exposure to estrogen (9, 10), suggesting that an imbalanced effect of estrogen could influence the tumorigenesis of HGSC and CCC (11, 12). On the other hand, the paradoxical finding that HGSC may show high levels of estrogen receptors, whereas CCC may show low levels of estrogen receptors has been suggested to be a prognostic factor affecting treatment response (13).

As a biomarker related to the hormone, serine protease inhibitors (serpins) belong to the family of protease inhibitors, and 36 types of serpins are known in humans, which are classified into nine clades (14). They are involved in various processes such as blood coagulation, angiogenesis, immune response, fibrinolysis, and most of them exist as secreted forms in plasma (14, 15). Clade B serpins (SERPINB) have no signal peptide, exist as cytoplasmic
proteins, and act through a non-inhibitory mechanism. Especially, SERPINB11 has been reported to show high expression in ovarian cancer lesions of hens and human ovarian cancer cell lines (13, 16). However, the prognostic role of SERPINB11 expression in EOC has not been elucidated. Previous studies on the effect of SERPINB11 expression on ovarian differentiation and carcinogenesis have only been reported to the extent which the balance of diethylstilbestrol, as a synthetic estrogen, was essential in the development and maintenance of oviduct in the avian model (17, 18), and the increased expression of SERPINB11 in a chicken ovarian cancer model was associated with exposure of the chicken oviduct to diethylstilbestrol (19).

In this study, we compared the immunohistochemical expression of SERPINB11 between HGSC and CCC using tissue microarray and evaluated the role of SERPINB11 expression as a prognostic biomarker for predicting platinum-resistance and survival in patients with HGSC and CCC, under the hypothesis that expression of SERPINB11 might be increased in human EOC tissues, and its pathogenesis might be associated with estrogen exposure.

Materials and Methods

We searched the data of patients with HGSC and CCC between July 2001 and November 2012 and obtained approval from the Institutional Review Board for the current study in advance (No. 1311-050-533). We included patients with the following criteria: those with HGSC or CCC; those who underwent cytoreductive surgery followed by adjuvant chemotherapy; those with an Eastern Cooperative Oncology Group performance status of 0-2; and those without underlying diseases affecting survival.

We collected the following data: the International Federation of Gynecology and Obstetrics (FIGO) stage, age, the extent of cytoreduction, platinum-resistance, progression-free survival (PFS), and overall survival (OS). In this study, we defined optimal cytoreduction as the maximal diameter of a residual tumor <1 cm, whereas suboptimal cytoreduction was defined as the maximal diameter of a residual tumor ≥1 cm after cytoreductive surgery. All patients received six cycles of adjuvant chemotherapy using paclitaxel (175 mg/m2) and carboplatin (AUC 5) every three weeks. Platinum-resistance was defined as a poor response to chemotherapy with a treatment-free interval of fewer than six months. PFS was defined as the time elapsed from the treatment start date to the date of disease recurrence, and OS was defined as the time from the treatment start date to the date of death or end of the study.

For immunohistochemistry, we took representative core tissue sections (2 mm diameter) from paraffin blocks and arranged them in new tissue microarray blocks using a trephine apparatus (SuperBioChips Laboratories, Seoul, Republic of Korea). Furthermore, expression of SERPINB11 was evaluated by immunohistochemistry using a primary antibody obtained from Santa Cruz Biotechnology (Santa Cruz, CA, USA), and the substitution of the primary antibody with purified non-immune mouse IgG was included at the same concentration for negative controls. Thereafter, one pathologist unaware of the clinicopathologic characteristics of patients interpreted the level of SERPINB11 expression semi-quantitatively based on the staining intensity (Intensity score; 1, weak; 2, moderate; 3, strong) and percentage of positive cells (Percentage score, 1, <25%; 2, 25-50%; 3, 51-75%; 4, >75%). The final immunoreactive score, which was calculated by the Intensity score multiplied by the Percentage score, ranging from 1 to 12, and the high expression of the gene was considered when the final immunoreactive score was six or more.

For evaluating the role of SERPINB11 expression in platinum-resistance, we used the Chi-square and Student’s t-tests, and logistic regression analysis to determine the odds ratio (OR) and 95% confidence interval (CI). For survival analysis, we used Kaplan-Meier analysis with the log-rank test and Cox proportional hazards analysis to estimate the hazard ratio (HR) and 95% CI. Statistical analysis and calculations were performed using SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). In this study, p-value <0.05 indicated statistically significant differences.
Results

A total of 204 patients with HGSC (n=145) and CCC (n=59) were included in this study. Figure 1 shows low and high expression levels of SERPINB11, and Table I shows the clinicopathologic characteristics of all patients. Older age, stage III-IV disease, and the use of neoadjuvant chemotherapy were more common in patients with HGSC than in those with CCC, whereas optimal cytoreduction and high expression of SERPINB11 were more frequent in those with CCC. Although the complete response rate was higher in patients with CCC with marginal significance, there was no difference in the frequency of platinum-resistance between HGSC and CCC patients.

Multivariate analyses showed that suboptimal cytoreduction was a factor associated with an increase in platinum-resistance in patients with HGSC (adjusted OR=3.469; 95%CI=1.475-8.155; p<0.01), whereas stage I-II disease was related to a decrease in platinum-resistance in those with CCC (adjusted OR=0.126; 95%CI=0.020-0.783; p=0.03). However, high expression of SERPINB11 did not affect platinum-resistance in both HGSC and CCC patients (adjusted ORs=0.623 and 0.293; 95% CIs=0.258-1.505 and 0.175-4.833; tables not shown).

In patients with HGSC, high expression of SERPINB11 showed worse PFS (median, 16.5 vs. 22.4 mons; p=0.052) and OS (mean, 61.6 vs. 90.5 mons; p=0.084) with marginal significance. However, there were no differences in PFS and OS between low and high expression of SERPINB11 in patients with CCC (mean, 78.7 vs. 100.8 mons, and 111.4 vs. 113.6 mons; p>0.05; Figure 2). In multivariate analyses, high expression of SERPINB11 was associated with poor PFS (adjusted HR=1.505; 95%CI=0.982-2.306; p=0.06) and OS (adjusted HR=1.697; 95%CI=0.977-2.948; p=0.06) with marginal significance in patients with HGSC (Table II). However, high expression levels of SERPINB11 were not associated with PFS and OS in those with CCC (adjusted HRs=0.844 and 1.073; 95% CIs=0.350-2.032 and 0.330-3.482; p>0.05; Table III).

Discussion

Up to now, the roles of SERPINB2, SERPINB3, SERPINB4, and SERPINB5 among the different subtypes of SERPIN have been elucidated in cancer cells. SERPINB2, which is the first known urokinase-type plasminogen activator, has been shown to have a role in the progression and metastasis of head and neck, breast, and lung cancers (20-22). SERPINB3 and SERPINB4 are known to be co-expressed in healthy human tissues such as the tongue, tonsil, uterine cervix, and respiratory tract epithelium (23), whereas their transition to squamous cell carcinoma may induce the excretion of SERPINB3 and SERPINB4 (24). Moreover, SERPINB5, which is known as Maspin, is over-expressed and localized in ovarian cancer tissues, which may play an essential role in inducing angiogenesis for tumor progression (25, 26).

Especially, SERPINB has been reported to have an inhibitory action on proteins related to tumor invasions, such as extracellular matrix degradation in human breast and ovarian cancers (27). On the contrary, we showed that high expression of SERPINB11 may be associated with poor prognosis of HGSC, not CCC. We thought that an estrogen-dependent mechanism might be involved in the association between high expression of SERPINB11 and poor prognosis of ovarian cancer. Previous studies on serpins have demonstrated that SERPINA6 acts as a corticosteroid-binding globulin (28), and the conformational change of SERPINA6 attributes to a corticosteroid transporter function (29). This means that serpins could affect hormone-dependent tumor growth and differentiation, which can be supported by our previous studies where the treatment of a chicken ovarian cancer model with estrogen showed significantly increased expression of SERPINB11 in the oviducts (19).

Moreover, the effect of high expression of SERPINB11 on prognosis was observed only in patients with HGSC in this study. This finding can be supported by a previous study where the down-regulation of SERPINB11 with eupatilin

Table I. Clinicopathologic characteristics of patients with high-grade serous carcinoma (HGSC) and clear cell carcinoma (CCC) of the ovary.

| Characteristics          | HGSC (n=145, %) | CCC (n=59, %) | p-Value |
|--------------------------|----------------|--------------|---------|
| Age (years)              |                |              | 0.03    |
| ≤52                      | 70 (48.3)      | 39 (66.1)    |         |
| >52                      | 75 (51.7)      | 20 (33.9)    |         |
| FIGO stage               |                |              | <0.01   |
| I-II                     | 10 (6.9)       | 39 (66.1)    |         |
| III-IV                   | 135 (93.1)     | 20 (33.9)    |         |
| Neoadjuvant chemotherapy |                |              |         |
| No                       | 126 (86.9)     | 58 (98.3)    |         |
| Yes                      | 19 (13.1)      | 1 (1.7)      |         |
| Residual tumor size (cm) |                |              | <0.01   |
| <1                       | 79 (54.5)      | 51 (86.4)    |         |
| ≥1                       | 66 (45.5)      | 8 (13.6)     |         |
| Platinum-resistance      |                |              | 0.35    |
| No                       | 34 (23.4)      | 49 (83.1)    |         |
| Yes                      | 111 (76.6)     | 10 (16.9)    |         |
| Response                 |                |              | 0.06    |
| Complete response        | 107 (73.9)     | 52 (88.1)    |         |
| Partial response         | 26 (17.9)      | 2 (3.4)      |         |
| Stable disease           | 6 (4.1)        | 2 (3.4)      |         |
| Progressive disease      | 6 (4.1)        | 3 (5.1)      |         |
| SERPINB11 expression     |                |              | <0.01   |
| Low                      | 104 (71.7)     | 25 (42.4)    |         |
| High                     | 41 (28.3)      | 34 (57.6)    |         |

FIGO: International Federation of Gynecology and Obstetrics.
enhanced the effect of conventional chemotherapeutic agents against ovarian cancer cell progression (30). This means that the hormonal action of SERPINB11 can depend on the distribution of hormonal receptors in ovarian cancer tissues. Previous studies have shown that 81% of the tumors of patients with HGSC were positive for estrogen receptors (13, 31), whereas CCC tissues and cell lines showed decreased or no expression of estrogen receptors (32-34). Especially,
Table III. Prognostic factors affecting survival in patients with clear cell carcinoma of the ovary.

| Characteristics                        | Univariate       | Multivariate       |
|----------------------------------------|------------------|-------------------|
|                                         | HR   | 95%CI     | p-Value   | Adjusted HR | 95%CI | p-Value   |
| Progression-free survival               |       |           |           |             |       |           |       |
| Age >52 y                               | 0.400 | 0.151-1.063 | 0.066     | 0.157       | 0.046-0.539 | 0.003 |
| FIGO stage III-IV                       | 12.625 | 5.054-31.536 | <0.001     | 10.272      | 3.482-30.302 | <0.001 |
| Suboptimal cytoreduction                | 7.395 | 3.075-17.780 | <0.001     | 4.619       | 1.432-14.894 | 0.010 |
| No neoadjuvant chemotherapy             | 7.531 | 0.926-61.235 | 0.059     | 4.447       | 0.430-45.950 | 0.210 |
| High-expression of SERPINB11            | 1.174 | 0.532-2.589 | 0.691     | 0.844       | 0.350-2.032 | 0.705 |
| Overall survival                        |       |           |           |             |       |           |       |
| Age >52 y                               | 0.138 | 0.018-1.048 | 0.056     | 0.052       | 0.034-3.286 | 0.094 |
| FIGO stage III-IV                       | 13.837 | 3.832-49.961 | <0.001     | 9.084       | 2.299-35.887 | 0.002 |
| Suboptimal cytoreduction                | 3.660 | 1.159-11.563 | 0.027     | 1.717       | 0.375-7.875 | 0.486 |
| No neoadjuvant chemotherapy             | 13.271 | 1.483-18.792 | 0.021     | 10.892      | 0.893-21.302 | 0.082 |
| High-expression of SERPINB11            | 1.167 | 0.415-3.280 | 0.769     | 1.073       | 0.330-3.482 | 0.907 |

HR, Hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

CCC has been shown to have a high proportion of negative expression of estrogen and progesterone receptor (81% and 92%), and their expression levels have been reported not to affect survival of CCC patients (13). To our best knowledge, this is the first study indicating that SERPINB11 may be a prognostic biomarker for patients with HGSC, suggesting that high expression of SERPINB11 might negatively affect survival of HGSC patients. However, this study has some limitations. We did not reveal the definite mechanism of how SERPINB11 can affect tumor progression in ovarian cancer, and the association between SERPINB11 expression and the distribution of hormonal receptors was not investigated. Thus, the potential of SERPINB11 as a biomarker should be further investigated in preclinical and clinical studies.

Conclusively, this study showed that high expression of SERPINB11 was associated with poor prognosis, suggesting the potential of SERPINB11 as a prognostic biomarker in patients with HGSC.

Conflicts of Interest

All Authors declare no conflicts of interest in relation to this study.

Authors’ Contributions

GS and HSK, designed this study. SJP, WL, SP, GS and HSK collected the data. SJP, WL, JM, HP, SP, HL, JK, EJL, GWY, NL, CL and HSK analyzed the results. SJP, WL, JWK, GS and HSK contributed to manuscript writing. All Authors read and approved the final manuscript.

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