Genetic characteristics of platinum-sensitive ovarian clear cell carcinoma

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Abstract

Background

Most ovarian clear cell carcinomas (OCCCs) are resistant to platinum-based chemotherapy, while a small subset shows a positive response. The aim of this study was to clarify the clinical, pathological, and genetic characteristics of platinum-sensitive OCCCs.

Methods

The study included 53 patients with stage III–IV OCCC who had residual tumors after primary surgery and received platinum-based therapy between 2009 and 2018. A retrospective examination of platinum sensitivity was performed using the criterion of ≥6 months from the last day of first-line platinum therapy until recurrence/progression. Cases determined to be platinum-sensitive were subjected to immunohistochemical staining, genomic analyses using target sequencing (i.e., NCC Oncopanel) and homologous recombination deficiency (HRD) (myChoice® HRD Plus) assays.

Results

Of the 53 stage III–IV OCCC cases, 11 (21%) were platinum-sensitive. These cases showed better progression-free and overall survival than platinum-resistant cases (hazard ratio = 0.16, $P < 0.001$). Among the seven sensitive cases whose tumor tissues were available for molecular profiling, five were pure OCCC based on pathological and genetic features, whereas the remaining two cases were re-diagnosed as HGSOC (high-grade serous ovarian carcinoma). The pure OCCCs lacked *BRCA1* and *BRCA2* mutations, consistent with the absence of the HRD phenotype, whereas two cases (40%) had *ATM* mutations. By contrast, the two HGSOC cases had *BRCA1* or *BRCA2* mutations associated with the HRD phenotype.

Conclusions

The subset of platinum-sensitive OCCCs includes a majority with pure OCCC features that lack the HRD phenotype.

1. Background

Ovarian clear cell carcinoma (OCCC) is a histological subtype of epithelial ovarian cancer with a higher incidence rate in East Asian countries (15–25% of all ovarian cancers) than in North America and Europe (< 10%) [1–3]. The biological, genetic, and clinical characteristics of OCCC are distinct from those of other epithelial ovarian cancer subtypes such as high-grade serous ovarian carcinoma (HGSOC), which is the most prevalent histological subtype [2, 4–7]. OCCC is characterized by typical clear or hobnail cells arranged in a papillary, solid, or tubulocystic pattern, and often associated with endometriosis and adenofibroma [4, 8]. Advanced OCCCs are routinely treated with platinum-based regimens after surgery; however, most (63–89%) cases are resistant to treatment and often recur or progress within 6 months [9–12]. By contrast, platinum-based therapy is effective in approximately 70–80% of in HGSOC cases [11, 13]. The response of HGSOC to treatment is associated with the homologous recombination deficiency (HRD) phenotype of tumor cells, which is caused by loss-of function (LoF) mutations of *BRCA1*, *BRCA2*, and other genes involved in homologous recombination [14–16]. HGSOCs also respond well to molecular targeted therapy using poly (ADP-ribose) polymerase (PARP) inhibitors. Because this response is also associated with HRD, the HRD phenotype is assessed in daily oncology using companion diagnostic tests such as myChoice® CDx and FoundationOne® CDx [17–19]. On the other hand, OCCCs rarely show LoF mutations of *BRCA1*, *BRCA2*, and other genes involved in homologous recombination [14, 20], which is consistent with their resistance to platinum-based chemotherapy.

Despite the ubiquitous resistance of OCCC to platinum-based therapy, a small fraction of OCCC cases responds to platinum-based therapy [9–12], suggesting that OCCCs include two biological types, minor platinum-sensitive and major platinum-resistant tumors. However, because of the small fraction of OCCC among all ovarian carcinomas, particularly in North America and Europe, our understanding of the characteristics of platinum-sensitive OCCC is limited. Here, we performed a retrospective study including a Japanese OCCC cohort of 418 cases to examine platinum-sensitive OCCCs and their underlying clinical, pathological, and genetic characteristics.

2. Methods

2.1. Patients

A cohort of 418 patients who underwent surgery and were diagnosed with OCCC at the National Cancer Center Hospital (NCCH) or the Jikei University Hospital (JUH) in Tokyo, Japan between 2009 and 2018 was analyzed. Pathological diagnosis and pathological staging were performed using resected specimens according to the WHO classification and the International Federation of Gynecology and Obstetrics (FIGO) classification (2014). Most patients received surgical resection of primary tumors, and > 90% of patients received platinum-based adjuvant chemotherapy. Clinical data including age at diagnosis, FIGO stage, size of residual tumors, therapeutic regimens, and serum CA125 levels were collected retrospectively by reviewing medical records. Response and progression after treatment were retrospectively evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1). The platinum-free interval (PFI) was defined as the time between the date of the last platinum dose and the date of disease progression or recurrence. Progression-free survival (PFS) was defined as the time interval between the date of surgery and the date of disease progression or recurrence. Overall survival (OS) was defined as the time interval between surgery and the date of last contact or death.

Fifty-three patients with stage III–IV OCCC who had residual tumors after surgery and received adjuvant chemotherapy with a platinum-based regimen were followed-up for a mean period of 23 months. Sensitivity to platinum-based chemotherapy was assessed according to the criteria established by the Fifth Ovarian Cancer Consensus Conference [21], i.e., “platinum-sensitive” was defined as > 6 months from the last platinum dose until recurrence/progression, whereas “platinum-resistant” was defined as within 6 months from the last platinum dose until recurrence/progression. This study was approved by the

Institutional Review Board of the National Cancer Center [2017 – 190] and the Jikei University [30–446 (9467)], and informed consent was obtained from all patients. This study was conducted according to the criteria set by the Declaration of Helsinki.

2.2. Chemotherapeutic regimens

The chemotherapeutic regimens used for the first-line treatment of stage III and IV OCCC were the standard regimens used for epithelial ovarian cancer [22–25]: TC (paclitaxel plus carboplatin), DC (docetaxel plus carboplatin), ddTC (dose dense TC), and TC + Bev (TC plus bevacizumab). A few patients received other regimens, including TC + Tem (TC plus temsirolimus), CPT-P (irinotecan plus cisplatin), weekly-TC, ddTCip (paclitaxel plus intraperitoneal carboplatin), and TC + Avelumab (TC plus avelumab). Other regimens were used for second- and later line treatments, including PLD + CBDCA (pegylated liposomal doxorubicin plus carboplatin) and GEM (gemcitabine single-agent chemotherapy).

2.3. Pathological study

Tumors from platinum-sensitive cases were re-reviewed by two of the authors (H. Yoshida and T. Kiyokawa) to define the pathological characteristics using formalin-fixed, paraffin-embedded (FFPE) tumor samples obtained at surgery. The samples were also deparaffinized and subjected to immunohistochemical (IHC) analysis of OCCC markers such as HNF1β (clone C-20; 1:200 dilution; Santa Cruz Biotechnology, Dallas, TX, USA) and Napsin A (clone IP64; 1:400 dilution; Leica Biosystems, Newcastle Upon Tyne, England), and a HGSOC marker, WT1 (clone 6F-H2; prediluted; Dako, Glostrup, Denmark). IHC detection of p53 (clone DO7; prediluted; Dako, Glostrup, Denmark) and ARID1A (polyclonal rabbit; 1:2000 dilution; Sigma, St. Louis, MO, USA) was also performed. For analysis of HNF1β, Napsin A, ARID1A, and WT1 cases were diagnosed as “focal-positive” if 1–50% of tumor cell nuclei exhibited unequivocal staining, and “diffuse-positive” if > 50% of tumor cell nuclei stained positive. For analysis of p53, cases were defined as “overexpression” if > 90% of tumor cell nuclei showed at least moderate-to-strong staining. A weak and heterogeneous staining pattern of tumor cells was classified as the wild-type pattern.

2.4. Molecular profiling

Mutation, amplification, fusion, and homozygous deletions of all coding regions of 114 cancer-related genes were examined using the NCC Oncopanel test (ver. 4), a hybridization capture-based next-generation sequencing (NGS) assay, according to the method previously described [26]. This test is approved as OncoGuide™ NCC Oncopanel System by the Pharmaceuticals and Medical Devices Agency and reimbursed by the National Health Insurance System in Japan. Briefly, genomic DNA extracted from FFPE samples was subjected to sequencing library construction using a KAPA Hyper Prep Kit (KAPA Biosystems, Wilmington, MA, USA) and sequenced on the Illumina NextSeq (Illumina, San Diego, CA, USA) with 150 bp paired-end reads. The significance of detected mutations was annotated using OncoKB [27]. The FFPE tissues were also subjected to the myChoice® HRD Plus test [28], another NGS assay to assess HRD [calculated as genomic instability score (GIS)], tumor mutational burden (TMB; number of mutations/Mb) and alterations in 15 genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D*, and *RAD54L*) (Myriad Genetic Laboratories, USA). A GIS ≥ 42 was defined as HRD-positive.

2.5. Statistical methods

Patient survival was analyzed using the Kaplan–Meier method. The significance of the survival distribution in each group was tested using a generalized Wilcoxon test and the log-rank test. The χ^2-test and Student’s t-test for unpaired data were used for statistical analyses. A P-value of < 0.05 was considered statistically significant. Stat View software SPSS statistics version 24.0 (IBM Japan, Ltd., Tokyo, Japan) was used for data analysis.

3. Results

3.1. Selection of platinum-sensitive OCCCs

Among the 418 OCCC cases in the cohort, 136 had stage II–IV diseases, and 131 of these received adjuvant chemotherapy after surgery. Among the 131 cases, prognosis was associated with FIGO stage and residual disease, but not with chemotherapeutic regimen (**Fig. S1**). Stage III and IV cases (n = 105) showed a similarly poor prognosis and a high frequency of residual disease (51%) (Table 1). Most stage III and IV cases (88%) received adjuvant chemotherapy using standard regimens, which mainly consisted of TC/DC, ddTC, and TC + Bev. Thus, the stages III–IV cases were included in the analysis of platinum sensitivity.

Table 1
Characteristics of Stage III and IV patients with ovarian clear cell carcinoma

	N	All		Stage III		Stage IV		P-value
								III vs. IV
Age	105			87		18		
Median [range]		55.5	[38–79]	56.0	[38–78]	53.5	[39–71]	0.324 [a]
FIGO (N, %)	105							
III		87	, 82.9	87	, 100.0			
IV		18	, 17.1			18	, 100.0	
Lymph node metastasis (N, %)	105							0.281 [b]
Positive		47	, 44.8	43	, 65.2	4	, 44.4	
Negative		58	, 55.2	23	, 34.8	5	, 55.6	
Unknown		30	, -	21	, -	9	, -	
Ascites cytology (N, %)	105							0.116 [b]
Positive		71	, 83.5	57	, 80.3	14	, 100.0	
Negative		14	, 16.5	14	, 19.7	0	, 0.0	
Unknown		20	, -	16	, -	4	, -	
Residual disease (N, %)	105							0.006 [b]
0 cm		51	, 48.6	46	, 52.9	5	, 27.8	
0–1 cm		20	, 19.0	19	, 21.8	1	, 5.6	
≥ 1 cm		34	, 32.4	22	, 25.3	12	, 66.7	
Postoperative therapy (N, %)	92			80		12		0.103 [b]
TC/ DC		28	, 30.4	24	, 30.0	4	, 33.3	
ddTC		33	, 35.9	28	, 35.0	5	, 41.7	
TC + Bev		12	, 13.0	11	, 13.8	1	, 8.3	
Others		19	, 20.7	17	, 21.3	2	, 16.7	

P-value calculated using [a] Mann-Whitney U test or [b] Fisher's exact test.

TC: paclitaxel plus carboplatin; DC: docetaxel plus carboplatin; ddTC: dose dense TC; Bev: bevacizumab.

To identify platinum-sensitive cases, we focused on the 54 stage III and IV cases with residual disease after surgery (Fig. 1A). Of 53 patients treated with platinum-based chemotherapy, 11 (20%) were considered platinum-sensitive according to the criteria proposed by the Fifth Ovarian Cancer Consensus Conference [21]. These cases showed longer PFS (after surgery) and longer OS than platinum-resistant cases (hazard ratio = 0.16), indicating that the response to platinum therapy is strongly associated with the prognosis of OCCC patients (Fig. 1B).

3.2. Clinical characteristics of platinum-sensitive OCCCs

There was no statistically significant difference between platinum-sensitive and platinum-resistant cases regarding the therapeutic regimens or clinical factors affecting prognosis, such as FIGO stage, size of residual tumors, lymph node metastasis, positive ascites cytology, and pre- or post-operative serum CA125 levels (Table 2). Detailed examination of the clinical characteristics of the 11 platinum-sensitive OCCCs (Table 3) showed a PFI of ≥ 8 months (cases 2, 3, 4, 6, 7, 9, and 10) or no recurrence > 3 years after platinum-based therapy (cases 1, 5, 8, and 11). Among the seven cases with recurrence, the recurrent tumors of two cases (cases 6 and 7) showed a complete response to second-line chemotherapy using platinum agents, suggesting the maintenance of the platinum-sensitive characteristics during therapy. The detailed therapeutic history of two representative cases is shown in Fig. 2. These two cases showed the typical pathological morphology of OCCC, as indicated by abundant clear cytoplasm of tumor cells. Case 6 responded to both ddTC (for residual tumors) and PLD + CBDCA (recurrent tumors) treatments, but progressed with the gemcitabine treatment. This suggested that the tumor was specifically sensitive to platinum agents. Case 11 showed a partial response to the CPT-P treatment of residual tumors and remained without recurrence for 10 years, indicating a strong therapeutic effect of platinum agents.

Table 2
Characteristics of platinum-sensitive and -resistant stage III and IV patients with ovarian clear cell carcinoma

	N	Platinum-sensitive (N = 11)		Platinum-resistant (N = 42)		P-value
Age	53					0.417 [a]
Median [range]		57.0	[54.0, 61.0]	56.0	[49.0, 62.0]	
FIGO stage (N, %)	53					0.421 [b]
III		10	90.9	31	73.8	
IV		1	9.1	11	26.2	
Lymph node metastasis (N, %)	25					> 0.999 [b]
Negative		2	33.3	5	26.3	
Positive		4	66.7	14	73.7	
Unknown		5	-	23	-	
Ascites cytology (N, %)	43					0.558 [b]
Negative		0	0.0	4	12.5	
Positive		11	100.0	28	87.5	
Unknown		0	-	9	-	
Residual disease (N, %)	53					0.079 [b]
0–1 cm		7	63.6	13	31.0	
> 1 cm		4	36.4	29	69.0	
Postoperative therapy (N, %)	44					> 0.999 [b]
TC/DC		4	36.4	11	26.2	
ddTC		4	36.4	13	31.0	
TC + Bev		0	0.0	1	2.4	
Others		3	27.3	8	19.0	
CA125 (Preoperative) (N, %)	44					0.250 [b]
< 35 U/mL		1	9.1	0	0.0	
≥ 35 U/mL		10	90.9	33	100.0	
CA125 (Postoperative) (N, %)	45					0.582 [b]
< 35 U/mL		2	18.2	3	8.8	
≥ 35 U/mL		9	81.8	31	91.2	

P-value calculated using [a] Mann-Whitney U test or [b] Fisher's exact test.

TC: paclitaxel plus carboplatin; DC: docetaxel plus carboplatin; ddTC: dose dense TC; Bev: bevacizumab.

Table 3
Clinical features of 11 platinum-sensitive cases of ovarian clear cell carcinoma

Case	Age	Stage	Pathology (Re-diagnosis)	Residual tumor Diameter (cm)/ site		1st line chemotherapy	Response	PFI	Recurrence/ site		2nd line therapy	Response	PFS
1	47	IIIB	OCCC	0–1 /	Peritoneum	ddTC	-	-	- /	-	-	-	3y 8m
2	71	IIIC	OCCC	0–1 /	Liver surface, Diaphragm	ddTC	-	1y3m	+ /	Lung, LN, Peritoneum	PLD + CBDCA	PD	1y 11r
3	57	IIIC	OCCC	0–1 /	Diaphragm	TC + Tem	-	1y3m	+ /	Liver, LN, Peritoneum	TC	PD	1y 8m
4	52	IIIC	OCCC	0–1 /	Peritoneum	ddTC ip	-	2y4m	+ /	Liver	TC	PD	2y 8m
5	73	IIIC	HGSOG	0–1 /	Peritoneum	TC	-	-	- /	-	-	-	7y 1m
6	54	IIIC	OCCC	0–1 /	Peritoneum Diaphragm	ddTC	-	9m	+ /	Peritoneum, LN	Tumorectomy →PLD + CBDCA	CR	1y 3m
7	58	IIIC	OCCC	0–1 /	Peritoneum	ddTC	-	4y1m	+ /	Liver, LN	TC + Bev	CR	4y 7m
8	59	IIIC	OCCC	1 < /	Peritoneum	TC	CR	-	- /	-	-	-	8y 5m
9	57	IIIC	HGSOG	1 < /	Peritoneum	TC	CR	2y5m	+ /	Brain	Tumorectomy →Radiation	CR	3y 0m
10	61	IIIC	OCCC	1 < /	Peritoneum	TC	SD	8m	+/	Peritoneum	DC	PD	1y 2m
11	56	IVB	OCCC	1 < /	LN, Intrathoracic	C-CPT	PR	-	- /	-	-	-	10y 7m

PFI: platinum-free interval; PFS: progression-free interval; OS: overall survival.

TC: paclitaxel plus carboplatin; ddTC: dose dense TC; Tem: temsirolimus; C-CPT: cisplatin plus irinotecan; PLD + CBDCA: pegylated liposomal doxorubicin plu DC: docetaxel plus carboplatin.

LN: lymph node; NED: no evidence of disease; DOD: dead of disease; AWD: alive with disease.

3.3. Molecular characteristics of platinum-sensitive OCCCs

Among the 11 platinum-sensitive cases, seven had available tumor tissues, which were subjected to molecular profiling (Fig. 3). For case 6 described above, both primary and recurrent (pelvic peritoneum) tumors were available. Five cases including case 6 were re-diagnosed as pure OCCC, as determined by characteristic morphology and IHC positivity of the OCCC markers HNF1β and Napsin A. The tumors of case 6 were associated with endometriosis, supporting that OCCC arises from endometriosis [4, 8]. The IHC results for the two representative cases are shown in **Figure S2**. By contrast, molecular profiling of the remaining two cases showed that they were both negative for the two OCCC markers but positive for the HGSOC marker WT1, a finding consistent with their HGSOC morphology. Thus, these two cases we re-diagnosed as HGSOC, consistent with the fact that differentiating OCCC from HGSOC with clear cell change is sometimes a diagnostic challenge [29]. The other four cases, which were not subjected to molecular profiling, also showed pure pathological OCCC morphology in the re-diagnosis. Therefore, platinum-sensitive cases were a minor fraction of OCCCs, and most of these were pathologically pure OCCC (9/11, 82%). Molecular profiling of the seven cases revealed that none of five pure OCCC cases had the HRD phenotype, consistent with the absence of pathogenic mutations in *BRCA1*, *BRCA2*, and other genes involved in homologous recombination. The accuracy of the pathological diagnosis as “pure OCCC” was supported by the fact that most (4/5, 80%) cases had mutations in SWI/SNF chromatin remodeling genes (i.e., *ARID1A* and *PBRM1*) and the *PIK3CA* gene, which are genetic alterations that distinguish OCCC from HGSOC [4–6, 16, 30]. The two pure OCCC cases (cases 6 and 11) had *ATM* mutations. Both residual and recurrent tumors of case 6 had the same pathogenic LoF *ATM* mutation, L1956H, whereas case 11 had an *ATM* mutation, R2151G, whose significance is undetermined. This case also contained a LoF mutation, S332fs*35 in *MLH1*, a mismatch repair gene, consistent with a high TMB (15 mutations per Mb of DNA). On the other hand, both the two re-diagnosed HGSOC cases showed the HRD phenotype associated with pathogenic LoF *BRCA1* or *BRCA2* mutations. One case (case 9) had a *JAKMIP3-NTRK2* fusion that would produce a fusion protein in which the N-terminal coiled-coil domain of JAKMIP3 is fused with the C-terminal NTRK kinase domain (**Fig. S3**).

4. Discussion

We investigated the characteristics of platinum-sensitive OCCCs, a relatively rare subtype of OCCC, which is characterized by platinum resistance and a poor prognosis. The present OCCC cohort of 418 cases treated between 2009 and 2018 showed a similar FIGO stage distribution and similar prognosis to previous cohorts that included patients treated between 1990 and 2006 [10, 11]. This suggests that the efficacy of treatments for OCCC has not improved in the last decades. Although inclusion of bevacizumab, an angiogenesis inhibitor, as a first-line platinum treatment has improved the prognosis of patients with advanced OCCC [31], the TC + Bev regimen did not significantly improve PFS/OS in the present cohort (**Fig. S1B**). However, the present study clearly demonstrates that the presence, and larger size, of residual tumors after surgery are associated with poor PFS/OS (**Fig. S1C**). Therefore, the results indicate that OCCC remains an intractable disease, and that design of precision medicine strategies according to the characteristics of each tumor is needed urgently to improve the prognosis of advanced OCCCs. Of 54 OCCCs with residual disease, 11 (20%) were defined as platinum-sensitive according to previously established criteria [21]. This fraction is consistent with that reported previously, i.e., 11–37% [10–12]. Both PFS (after surgery) and OS were better in platinum-sensitive than in platinum-resistant cases (Fig. 1B), supporting the existence of responders to platinum-based therapy who benefit from this treatment. Response to treatment was not associated with specific regimens, i.e., drugs combined with platinum agents, strongly indicating that these cases are sensitive to platinum agents.

Most cases (5/7, 71%) of platinum-sensitive OCCC were pathologically and genetically validated as pure OCCC. These cases did not show the HRD phenotype or LoF mutations in *BRCA1*, *BRCA2*, and other homologous recombination-related genes; however, two platinum-sensitive HGSOC cases showed the HRD phenotype associated with deleterious *BRCA1/2* mutations. This suggests that the factors underlying platinum sensitivity in pure OCCC differ from those in HGSOC, and that there are as-yet-undefined genetic factors that increase the sensitivity of these tumors to platinum agents. Since the number of platinum-sensitive pure OCCCs studied herein is highly limited (n = 5), definitive factors underlying sensitivity were not identified. However, it was notable that two cases showed *ATM* mutations, which are observed in < 10% of Japanese OCCC cases with stage III–IV disease [7, 32–34] (**Table S**). ATM protein is a key signaling factor involved in repair of DNA double strand breaks. ATM deficiency causes susceptibility to platinum and other DNA damaging agents [35], but does not cause the HRD phenotype [36, 37]. Therefore, *ATM* mutations are a potential cause of platinum sensitivity.

The results of molecular profiling also confirmed the presence of druggable genetic alterations in a subset of platinum-sensitive OCCCs, including deleterious *MLH1* mutation and *NTRK2* fusion, for which tumor-agnostic therapies consist of immune checkpoint and NTRK kinase inhibitors, respectively [38]. In addition, *ATM* mutations are a candidate biomarker of the response to PARP inhibitor therapy [39, 40]. Therefore, NGS-based molecular profiling will facilitate the design of precision medicine for OCCC.

The present study had several limitations. First, the proportion of platinum-sensitive OCCC cases was not definitely determined because of the small number of retrospective samples. Second, the molecular characteristics that can predict platinum sensitivity were not identified definitively, although *ATM* mutations are a potential candidate. Further prospective and/or retrospective studies including a larger cohort of OCCC cases are warranted to obtain definite results.

5. Conclusions

This study revealed that the majority of platinum-sensitive cases are pathologically and genetically diagnosed as pure OCCC and do not show the HRD phenotype, consistent with the absence of deleterious mutations in *BRCA1*, *BRCA2*, and other HR genes. Mutations in the ATM gene, which is involved in DNA double strand break repair, were detected in some platinum-sensitive cases.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the National Cancer Center [2017-190] and the Jikei University [30-446 (9467)], and informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

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Figures

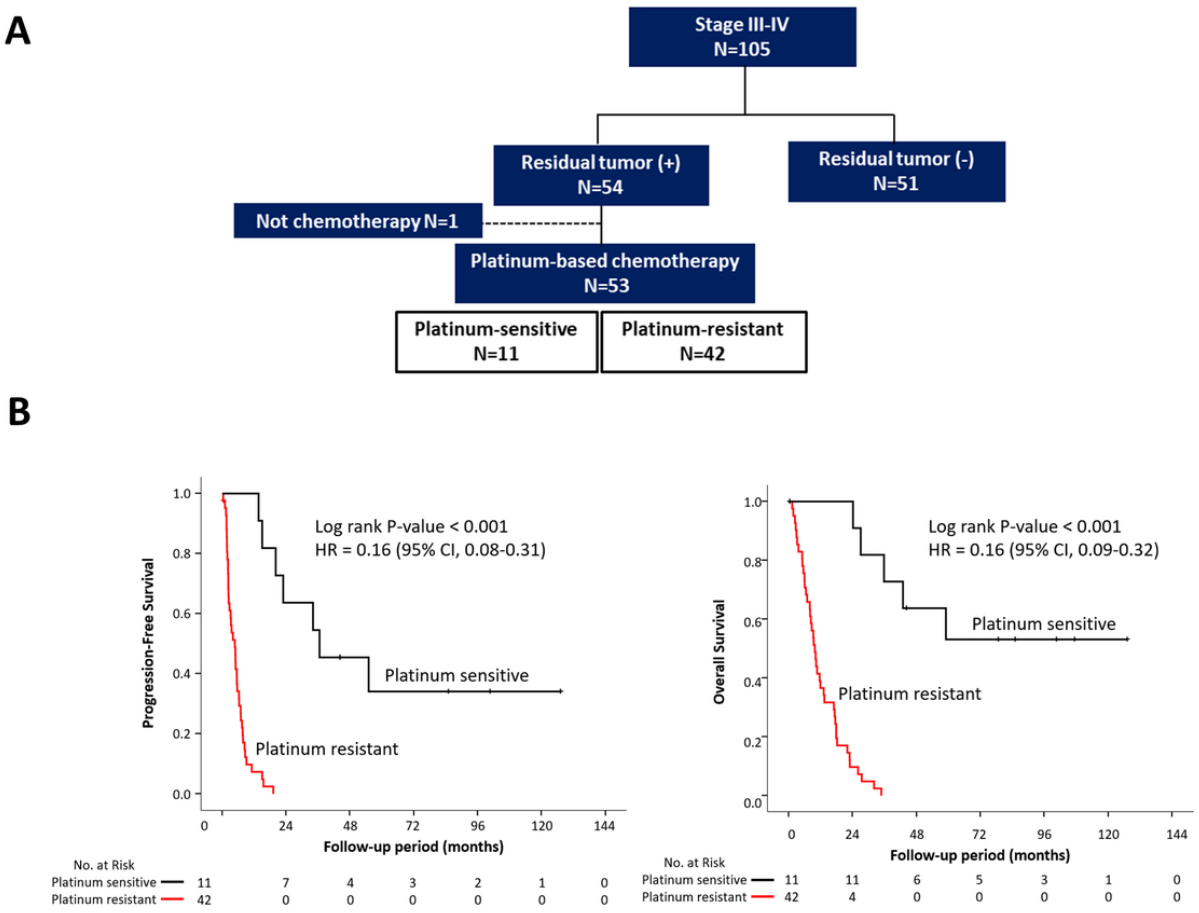

Figure 1

Selection of platinum-sensitive ovarian clear cell carcinomas

(A) Consort diagram for the selection of platinum-sensitive stage III–IV OCCCs. Of 54 cases with residual tumors, 53 received adjuvant chemotherapy. Eleven platinum-sensitive cases were selected according to the criteria of the Fifth Ovarian Cancer Consensus Conference [21], i.e., “platinum-sensitive” was defined as >6 months from the last day of the platinum dose until recurrence/progression.

(B) Progression-free survival (PFS) and overall survival (OS) of patients according to platinum sensitivity. Kaplan–Meier curves for PFS (left) and OS (right) of platinum-sensitive and -resistant patients are shown (*p < 0.001, each; log-rank test; HR: hazard ratio).

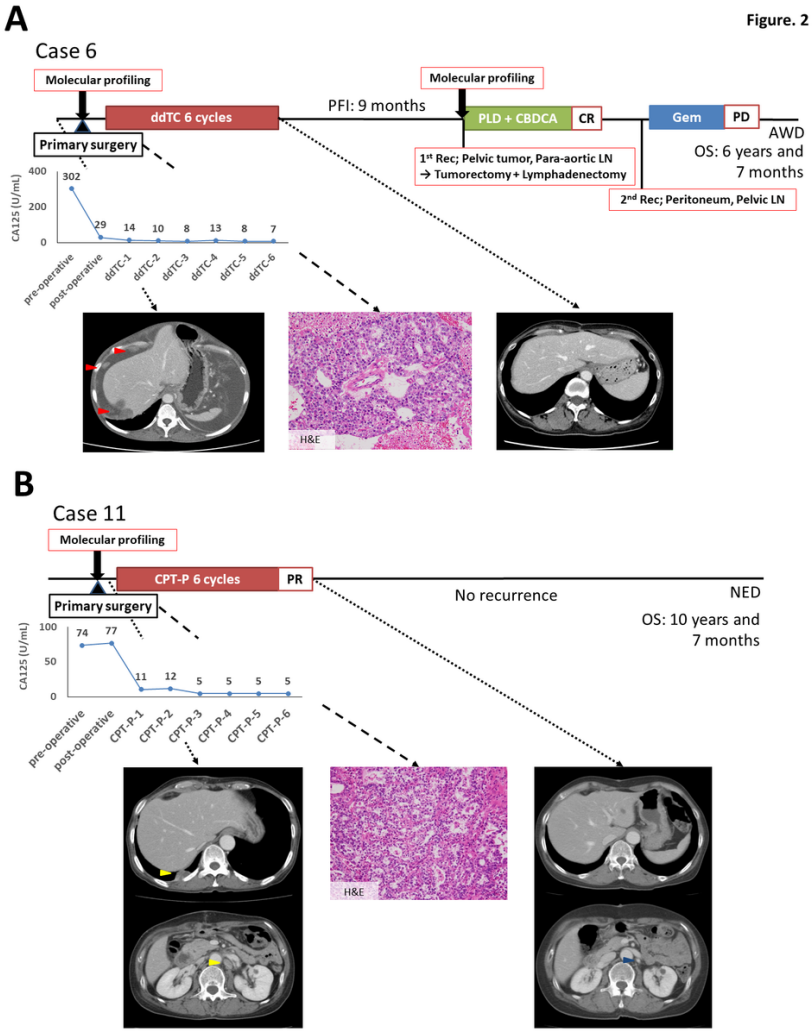

Figure. 2

Figure 2

Histology of two platinum-sensitive OCCC cases

(A) Case 6. Preoperative computed tomography (CT) detected multiple subdiaphragmatic disseminated lesions (red arrowheads) that persisted postoperatively. Resected tumors showed hobnail-like growth of carcinoma cells with a clear cytoplasm. Residual tumors showed complete response to the ddTC treatment. Recurrent tumors in the pelvic peritoneum also showed complete response to PLD+CBDCA but did not respond to subsequent gemcitabine treatment. Both the primary and recurrent tumors were subjected to molecular profiling.

(B) Case 11. Post-operative CT showed an intrathoracic metastatic tumor and enlarged para-aorta lymph nodes (yellow arrowhead). Resected tumors showed carcinoma cells with a clear cytoplasm. The intrathoracic tumor showed complete response to the CPT-P treatment, whereas the para-aortic lymph nodes (blue arrowhead) shrank and remained without recurrence for 10 years.

ddTC: dose dense TC; PLD+CBDCA: pegylated liposomal doxorubicin plus carboplatin; GEM: gemcitabine; C-CPT: cisplatin plus irinotecan

CR: complete response; PD: progressive disease; PR: partial response; AWD: alive with disease; NED: no evidence of disease; Rec: recurrence; LN: lymph node; H&E: hematoxylin eosin.

Figure. 3

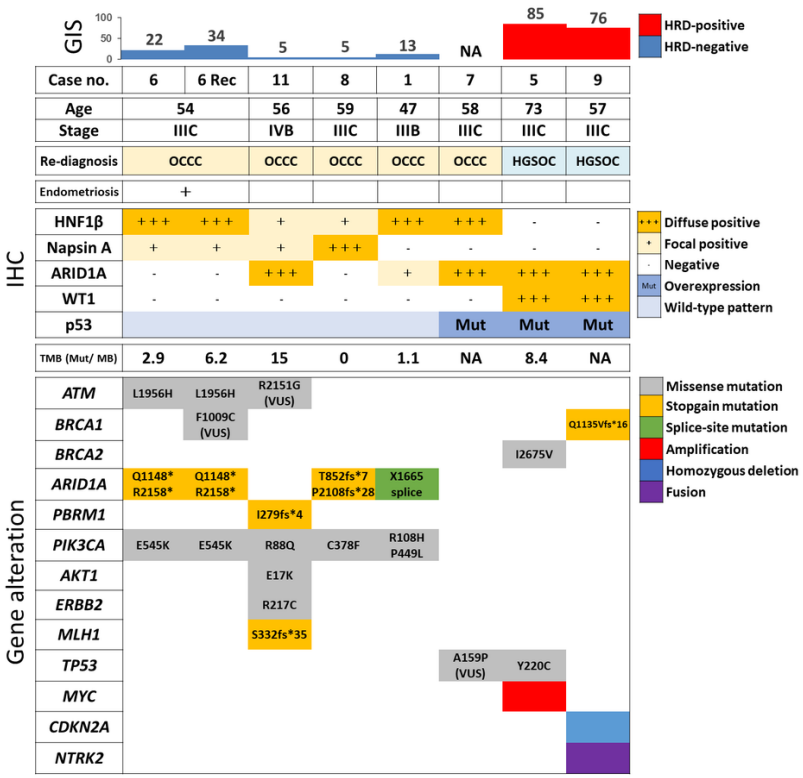

Figure 3

Molecular profiles of platinum-sensitive OCCCs

Pathological and genetic features are summarized. In case 6, both the residual and recurrent tumors (6 Rec) were subjected to profiling. Amino acid changes due to nonsynonymous mutations are shown. Oncogenic mutations annotated by OncoKB are listed. Mutations of unknown significance in the *ATM, BRCA1*, and *TP53* genes are also listed. GIS: genomic instability score; TMB: tumor mutational burden (number of mutations/Mb); VUS: variants of unknown significance; IHC: immunohistochemistry; NA: not available.

Supplementary Files

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