PD-L1 expression following neoadjuvant chemotherapy is upregulated and serves as a prognostic factor in patients with advanced high-grade serous ovarian carcinoma

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BACKGROUND

Ovarian high-grade serous carcinoma (OHGSC) is the most frequent histological subtype of ovarian cancer and the leading cause of death due to cancer of the female genital tract. Typically, OHGSC respond well to platinum-based chemotherapy, which is a standard regimen for OHGSC. However, OHGSCs frequently recur and gradually acquire resistance to standard chemotherapy regimens. Recently, poly ADP-ribose polymerase (PARP) inhibitors have improved the clinical outcomes of patients with ovarian cancer with BRCA mutations or homologous recombination deficiency. Nonetheless, more effective treatment strategies for advanced OHGSC are required. Immune checkpoint inhibitors via programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 have caused breakthroughs in treatment strategies for various cancers. In our previous study on ovarian cancer, PD-L1 expression was positively correlated with histone deacetylase (HDAC) 6 expression, and HDAC6 upregulation led to a poor prognosis [1,2]. HDAC6 increases deacetylated α-tubulin levels, which upregulate cancer cell growth by enhancing microtubule dynamics. HDAC6 upregulation leads to platinum resistance, and HDAC6 downregulation enhances platinum agent-induced DNA damage and apoptosis. HDAC6 is also an immunomodulator, and the co-suppression of HDAC6 and PD-L1 has a synergistic anti-tumor effect on ovarian cancer [3]. In this study, we compared the immunohistochemical expressions of HDAC6 and PD-L1 before and after chemotherapy and verified whether their expression affects chemotherapy resistance and patient prognosis in OHGSC.

REFERENCES

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The authors declare no competing interests.

MATERIALS and METHODS

We identified 57 patients with OHGSC who were histologically diagnosed and received neoadjuvant chemotherapy between 2007 and 2015 at Saitama Medical University International Medical Center. Tumor samples were acquired before and after chemotherapy in all patients. Based on the results of an omental examination, chemotherapy response score (CRS) was used to classify patients as follows: patients with CRS3 had a complete/near-complete response, those with CRS2 had a partial response, and those with CRS1 had no or minimal response. The surgical status was classified as complete resection (R0) or incomplete resection (R1).

Immunohistochemical expressions of PD-L1 and HDAC6 (monoclonal rabbit anti-PD-L1, 1:100, 28-8 pharmDx, Dako North America, CA, USA; polyclonal rabbit anti-HDAC6, 1:500, ab1440, Abcam, Cambridge, UK) were analyzed using formalin-fixed paraffin-embedded tumor samples from both pre- and post-chemotherapy.

PD-L1 positivity was defined as staining in ≥ 5% of carcinoma cells. PD-L1 expression was also analyzed in a semiquantitative manner by scoring the proportion of stained carcinoma cells over the total number of carcinoma cells, ranging from 5% to 100% in 5% increments. High expression of HDAC6 was defined as staining in ≥ 50% of carcinoma cells.

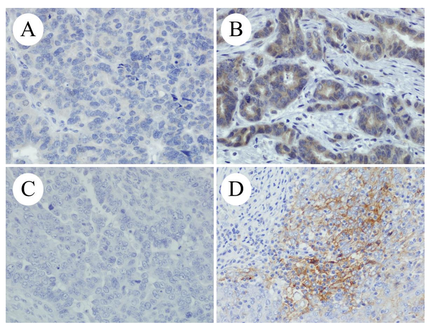

Figure 1. Immunohistochemical expressions of histone deacetylase 6 (A, before neoadjuvant chemotherapy [NAC]; B, after NAC) and programmed death ligand-1 (C, before NAC; D, after NAC).

RESULTS

Table 1. Patient background

Valuables	N
Age	
Median (range)	58.0 (41-79)
≤60	34
>60	23
CA125 (U/mL)	
Median (range)	3517 (73-24,200)
≤1,000	23
>1,000	34
Treatment	
NAC+IDS	55
NAC+Biopsy	2
FIGO stage	
III	43
IV	14
Surgical status	
R0	37
R1	20
CRS (omentum)	
1=resistant	9
2=intermediate	16
3=sensitive	29
Not available	3
Recurrence	
Yes	50
No	7
Death	
Yes	25
No	32

Table 2. HDAC6 and PD-L1 expressions before and after NAC

Valuables		Before NAC	After NAC	p value
HDAC6	High	4	13	**0.019**
	Low	53	44	
PD-L1	Positive	5	8	0.252
	Negative	52	49	
PD-L1 (%, average)		0.68	3.88	**0.045**

Table 3. Correlation between clinicopathological characteristics and expressions of HDAC6 and PD-L1

	HDAC6 (after NAC)			PD-L1 (after NAC)		
Valuables	Low	High	p value	Negative	Positive	p value
Age						
≤60	25	9	0.320	29	5	0.532
>60	19	4		19	4	
FIGO stage						
III	33	10	0.602	36	7	0.180
IV	11	3		12	2	
Surgical status						
R0	28	9	0.491	30	7	0.369
R1	16	4		18	2	
CRS (n=54)						
1/2	19	6	0.622	24	1	**0.042**
3	22	7		22	7	
Recurrence						
Yes	39	11	0.508	42	8	0.696
No	5	2		6	1	
Death						
Yes	24	8	0.452	27	5	0.624
No	20	5		21	4	

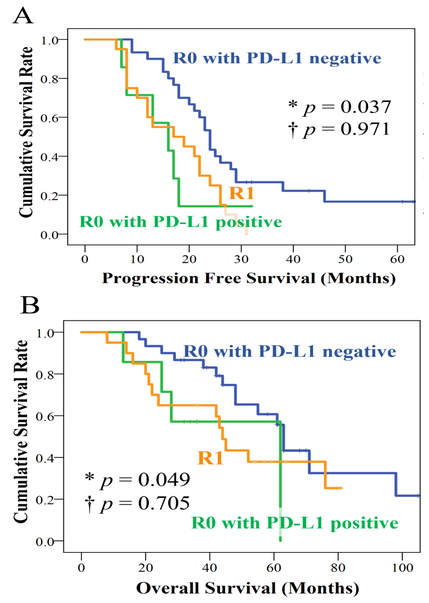

Fig 2. Kaplan–Meier survival analysis (A, PFS; B, OS). Asterisks indicate the p-values for comparing R0 with PD-L1 negative to R0 with PD-L1 positive, and daggers indicate the p-values for R0 with PD-L1 positive to R1.

CONCLUSIONS

Residual tumors of OHGSC after NAC show enhanced expressions of HDAC6 and PD-L1, which are associated with tumor immunity, cell proliferation, and chemoresistance. PD-L1 expression also correlates with patient prognosis. These results suggest that HDAC6 and PD-L1 may be therapeutic targets and prognostic factors for residual tumors after standard chemotherapy in OHGSC.