PD-1 and PD-L1 expression in 1599 gynecological malignancies – implications for immunotherapy

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Abstract

Objectives: T-cell suppression via PD-1/PD-L1 interactions plays a central role in cancer progression and survival, making PD-1/PD-L1 attractive therapeutic targets. Clinical trials involving PD-1/PD-L1-targeted immunotherapies have demonstrated marked success in solid tumors including melanoma, non-small cell lung carcinoma (NSCLC), and renal cell carcinoma, and studies indicate PD-L1 expression may identify patients who are more likely to benefit from immunotherapies. These agents and biomarkers could revolutionize management of gynecological malignancies that have developed resistance to standard chemotherapies. The purpose of this study is to identify gynecological malignancies that may benefit from this new class of targeted therapy.
Methods: 1599 cases encompassing all gynecological malignancies (e.g. cervical, uterine, ovarian, vaginal, vulvar) were evaluated at a central laboratory (Caris Life Sciences) for the presence of PD-1 (NAT105) and PD-L1 (B7-H1 antibody) expressing cells. Intraepithelial PD-1-positive lymphocytes (IEL) and aberrantly expressed PD-L1 on carcinoma cells were considered specific.
Results: Overall, positive PD-1 expression was 67.9% (1086/1599) and PD-L1 expression was 19.6% (313/1598). Analysis showed the highest PD-1 expression in the following tumor types: endometrial cancer (337/450, 74.9%), epithelial ovarian cancer (622/930, 66.9%), and cervical cancer (53/84, 63.1%). Furthermore, the highest PD-L1 expression rates were in the following tumor types: ovarian sex cord – stromal tumors (24/32, 75.0%), uterine sarcoma (40/86, 46.5%), endometrial cancer (112/450, 24.9%). In terms of histology, the highest PD-1 expression rates were in carcinosarcomas of the endometrium and ovary (80.0% and 74.2%, respectively) while the highest PD-L1 expression rates occurred in granulosa cell tumors (77.8%) and endometrioid endometrial cancer (39.7%). Amongst the highest PD-1/PD-L1 co-expression rate was in endometrioid endometrial cancer (35.3%).
Conclusions: Subsets of gynecological cancer preferentially express PD-1 and PD-L1, implying potential application of a new set of agents in the treatment of gynecological cancers. As no predictive standard exists, biomarker studies will be necessary to elucidate which patients derive the most benefit from novel immunotherapies.

Background

T-cell suppression via PD-1/PD-L1 interactions plays a central role in cancer progression and survival, making PD-1/PD-L1 attractive therapeutic targets. Clinical trials involving PD-1/PD-L1-targeted immunotherapies have demonstrated marked success in solid tumors including melanoma, NSCLC, and renal cell carcinoma, and studies indicate PD-L1 expression may identify patients who are more likely to benefit from immunotherapies. These agents and biomarkers could revolutionize management of gynecological malignancies that have developed resistance to standard chemotherapies.

Background (cont.)

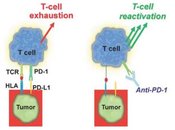


Illustration 1. Mechanism of action for PD-1 antibodies. PD-1 = programmed death 1, PD-L1 = programmed death ligand 1, HLA = human leukocyte antigen, TCR = T-cell receptor. Adapted from *http://www.medscape.com/viewarticle/812990_10*.

Methods

1599 cases encompassing all gynecological malignancies (e.g. cervical, uterine, ovarian, vaginal, vulvar) were evaluated at a CLIA-certified central laboratory (Caris Life Sciences) for the presence of PD-1 (NAT105 mouse monoclonal antibody, Ventana, positive when 1+ or greater intensity) and PD-L1 (B7-H1 antibody, positive when 2+ or 3+ in at least 5% cells). Intraepithelial PD-1-positive lymphocytes (IEL) and aberrantly expressed PD-L1 on carcinoma cells were considered specific.

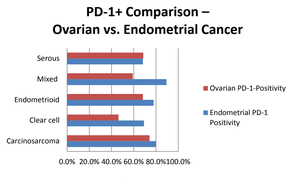
Results

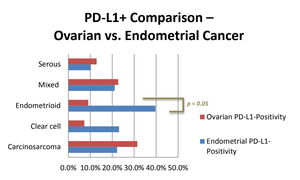
Gynecologic cancer	PD-1 Expression	PD-L1 Expression	PD-1/PD-L1 Co-expression
Cervical cancer	63.1% (53/84)	11.0% (9/82)	11.0% (9/82)
Endometrial cancer	74.9% (337/450)	24.9% (112/450)	22.2% (100/450)
Ovarian cancer - epithelial	66.9% (622/930)	13.5% (126/930)	10.4% (97/929)
Ovarian cancer – germ cell tumors	60.0% (3/5)	0.0% (0/5)	0.0% (0/5)
Ovarian cancers – sex cord-stromal tumors	37.5% (12/32)	75.0% (24/32)	34.4% (11/32)
Uterine sarcoma	57.0% (51/85)	46.5% (40/86)	25.9% (22/85)
Vaginal cancer	66.7% (4/6)	33.3% (2/6)	16.7% (1/6)
Vulvar cancer	57.1% (4/7)	0.0% (0/7)	0.0% (0/7)

Figure 1 – Overall distribution of PD-1, PD-L1 in gynecologic cancer (listed alphabetically). The overall PD-1 expression rate was 67.9% (1086/1599) the PD-L1 expression rate was 19.6% (313/1598). The co-expression rate was 15.0% (240/1596). The highest co-expression rates of PD-1 and PD-L1 are in sex-cord/stromal tumors and endometrial cancer. Ovarian sarcomas, arising from mesenchymal tissue, also have high co-expression of PD-1/PD-L1. Lower rates are seen in HPV-associated cancers of the distal genital female tract (e.g. cervical, vaginal and vulvar cancer). However, numbers are low in vaginal and vulvar cancer, so caution is necessary when interpreting those numbers.

Cancer, Histology	PD-1 Expression	PD-L1 Expression	PD-1/PD-L1 Co-Expression
Cervical cancer			
Adenocarcinoma	37.5% (9/24)	0.0% (0/24)	0.0% (0/24)
Squamous cell	77.3% (34/44)	16.7% (7/42)	16.7% (7/42)
Endometrial cancer			
Carcinosarcoma	80.0% (36/45)	22.2% (10/45)	22.2% (10/45)
Clear cell	69.2% (9/13)	23.1% (3/13)	23.1% (3/13)
Endometrioid	77.9% (106/136)	39.7% (54/136)	35.3% (48/136)
Mixed	89.5% (17/19)	21.1% (4/19)	21.1% (4/19)
Serous	68.2% (60/88)	10.2% (9/88)	8.0% (7/88)
Ovarian cancer - epithelial			
Carcinosarcoma	74.2% (26/35)	31.4% (11/35)	25.7% (9/35)
Clear cell	46.3% (19/41)	7.3% (3/41)	4.9% (2/41)
Endometrioid	68.2% (15/22)	9.1% (2/22)	9.1% (2/22)
Mixed	59.1% (13/22)	22.7% (5/22)	22.7% (5/22)
Mucinous	30.4% (7/23)	8.7% (2/23)	4.3% (1/23)
Serous	68.6% (394/574)	12.9% (74/573)	9.6% (55/573)
Ovarian cancer – sex-cord stromal tumor			
Granulosa cell tumor	33.3% (9/27)	77.8% (21/27)	33.3% (9/27)
Uterine sarcoma			
Endometrial stromal sarcoma	64.3% (9/14)	64.3% (9/14)	42.9% (6/14)
Leiomyosarcoma	46.9% (23/49)	36.0% (18/50)	8.2% (4/49)

Figure 2 – Overall distribution of PD-1, PD-L1 based on gynecologic cancer histology (listed alphabetically). Shown above are histologic subtypes where at least ten specimens had been tested for PD-1 and PD-L1. Mucinous endometrial carcinomas, Sertoli-Leydig tumor, dysgerminoma, PNET, and yolk sac tumors were tested fewer than five times (each) and, therefore, are not shown.





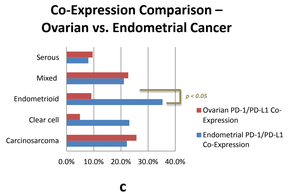


Figure 3a-c. Analyzing differences between endometrial and ovarian carcinomas with similar histology. These figures compare PD-1 and PD-L1 expression alone or together, focusing on histologies shared by endometrial and ovarian cancer. In most comparisons, no statistically significant difference was noted. However, statistically significant differences ($p < 0.05$) were noted in PD-L1 expression and PD-1/PD-L1 co-expression of endometrioid ovarian and endometrial carcinomas.

Conclusions

- PD-1 expression is found in all gynecologic malignancies independent of histology. By contrast, PD-L1 expression is variable across malignancies and histologies. Since current, published data suggests PD-L1 may have predictive utility, PD-L1 should be prioritized when deciding what cancer(s) be considered for immunotherapy.
- Co-expression of PD-1 and PD-L1 was highest in endometrioid endometrial cancer which suggests this histology be considered for immunotherapies like pembrolizumab, nivolumab, MPDL3280A, and other agents targeting the PD-1/PD-L1 axis. Our data suggests the HPV-associated cancers of the lower gynecologic tract (e.g. carcinomas of the cervix, vagina and vulva), may derive less benefit based on absence of PD-L1.
- Comparison of histologies independent of the tumor primary showed few statistically significant differences between specific histologic subtypes of endometrial and ovarian cancer. However, endometrioid endometrial carcinoma was noticeably different from endometrioid ovarian carcinoma, again making the case for immunotherapy in this disease.

References

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