Current and future immunotherapy approaches in ovarian cancer

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Abstract: Ovarian cancer (OC) is the major cause of gynecologic cancer deaths and relapse is common despite advances in surgery and systemic chemotherapy. Therefore, novel treatments are required to improve long-term outcomes of the disease. Efficacy of immunotherapy was demonstrated in many tumors and it has been since incorporated into clinical practice for them. Although early data form preclinical studies imply that OC has an immunogenic microenvironment, immune checkpoint inhibitors (ICIs) did not produce favorable results in clinical trials to date. This review will highlight data from clinical studies regarding immunotherapy in OC and its combination with other agents as well as immunologic prospects which could strengthen the therapeutic armament against the disease in the future.

Keywords: Immune checkpoint inhibitors (ICIs); immunotherapy; ovarian cancer (OC)

Introduction

Ovarian cancer (OC) is the second most common gynecologic cancer in developed countries and the leading cause of gynecologic cancer mortality (1,2). Epithelial ovarian cancer (EOC) accounts for the majority of the disease which is primarily treated with debulking surgery and neoadjuvant or adjuvant platinum-based chemotherapy. Despite this approach, most patients eventually experience relapse and receive systemic chemotherapy depending on platinum sensitivity.

Evidence from studies in the last decades suggest that OC may be an immunogenic tumor. Zhang *et al.* demonstrated that presence of intratumoral CD3+ T cells was associated with longer survival in advanced OC while Schlienger *et al.* reported anti-tumor immune response in the form of interferon-γ (IFN-γ) secretion by T cells in peripheral blood or ascites of OC patients (3,4). Although restoration of immunity against OC seems rational on this basis, early studies investigating the strategy using cytokines yielded conflicting results. IFN-γ, an anti-viral protein known to enhance antigen presentation to T cells, had modest efficacy when administered intraperitoneally in OC patients and negative impact on survival when its subcutaneous form was added to carboplatin/paclitaxel regimen in first-line treatment of advanced OC (5,6). Interleukins (ILs) are other immunostimulatory cytokines,

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Table 1 Immune checkpoint inhibitor monotherapy trials in ovarian cancer

Reference	Study characteristics	Treatment	ORR (%)	mPFS (months)	mOS (months)
Hamanishi et al. (15)	Phase II, PTR-EOC; n=20, ≥2 lines of CT (100%)	Nivolumab 1 or 3 mg/kg q2w	15	3.5	20
Liu et al. (16)	Phase Ib, EOC, n=12; ≥2 lines of CT (92%)	Atezolizumab 15 mg/kg q3w	22.2	2.9	11.3
Disis et al. (17) (JAVELIN Solid Tumor)	Phase Ib, PTR-EOC; n=125, ≥3 lines of CT (65%)	Avelumab 10 mg/kg q2w	9.6	2.6	11.2
Varga et al. (18) (KEYNOTE-028)	Phase Ib, EOC; n=26, ≥2 lines of CT (88%)	Pembrolizumab 10 mg/kg q3w	11.5	1.9	13.8
Matulonis et al. (19) (KEYNOTE-100)	Phase II, EOC; Cohort A (n=285): 1–3 prior lines, PFI =3–12 months	Pembrolizumab 200 mg q3w	A: 7.4	2.1 for both	A: NR
	Cohort B (n=91): 4–6 prior lines, PFI: ≥3 months		B: 9.9		B: 17.6
Hodi et al. (20)	Phase I, EOC; n=9, previous vaccination with GM-CSF	Ipilimumab 3 mg/kg up to 11 infusions	11.1	NR	NR
NCT01611558 (21)	Phase II, recurrent PTS-OC, n=40, 1–4 prior lines of CT	Ipilimumab 10 mg/kg q3w ×4 followed by 10 mg/kg q12w	10.3	NR	NR

CT, chemotherapy; EOC, epithelial ovarian cancer; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; ORR, objective response rate; PFI, platinum-free interval; PTR-EOC, platinum-resistant epithelial ovarian cancer; PTS-OC, platinum-sensitive ovarian cancer.

among which IL-2 and IL-18 demonstrated some activity in various OC settings but data is limited to phase I or II trials (7-9). Additional prospective research is thus warranted to integrate this type of immunotherapy to OC management.

Immune checkpoint inhibitors (ICIs) are novel agents which exert immunostimulatory effects by antagonizing programmed cell death receptor 1 (PD-1), its ligand PD-L1 or cytotoxic T lymphocyte antigen 4 (CTLA-4). ICIs have become an established treatment option in many malignancies like advanced lung cancer and malign melanoma but for OC there is no specific immunotherapeutic agent approved yet. Nevertheless, immune checkpoints may be potential targets for activating anti-tumor immunity in OC. Hamanishi et al. reported high PD-L1 expression in 68% of tissue samples from 70 OC patients whereas Maine et al. revealed that monocytes derived from peripheral blood and ascites of OC patients had significantly higher PD-L1 expression compared to benign or borderline over tumors (10,11). Among EOC subtypes, high grade serous ovarian cancer (HGSOC) is most common and it showed higher PD-L1 positivity and more CD8+ tumor infiltrating lymphocytes (TILs) than less common histologies (12,13). These findings altogether

support the rationale that ICIs may be a promising treatment strategy for EOC and in particular, HGSOC cases.

This review will summarize data from clinical trials evaluating ICIs in OC and also address future aspects of immunologic therapy for the disease.

ICI monotherapy

Blockade of PD-1 or PD-L1 is one major mechanism by which immunotherapy acts. PD-1 is a cell surface protein that interacts with PD-L1 expressed by tumor cells. This interaction stimulates exhaustion of peripheral effector T cells and conversion of effector T (T_{eff}) cells to regulatory T (T_{reg}) cells, thereby limiting immune response (14). Nivolumab and pembrolizumab are anti-PD-1 monoclonal antibodies while atezolizumab, avelumab and durvalumab inhibit PD-L1.

Single-agent PD-1/PD-L1 inhibitors were evaluated in phase I or II clinical trials including heavily pretreated EOC patients and generally produced overall response rates (ORRs) of 10–15%, median progression-free survival (PFS) of 2–3 months and median overall survival (OS) of 11–20 months (*Table 1*). When analysed according

to biomarker status, PD-L1 positivity (2+ in immunohistochemistry) did not predict objective response in nivolumab trial while objective response to atezolizumab was observed in 2 of 8 patients who had ≥5% PD-L1 expression in immune cells (IC2/3) but not in the patient whose PD-L1 expression was <5% (IC0/1) (15,16). In the avelumab study, ORRs in PD-L1 positive and negative cohorts were 11.8% and 7.9%, respectively, when cut-off for PD-L1 positivity was set at 1% (17). With a PD-L1 cut-off of 5%, ORRs were 12.5% and 9.8%, respectively. The KEYNOTE-100 trial was the largest study on ICI monotherapy in OC where PD-L1 expression was measured as combined positive score (CPS), defined as the ratio of PD-L1 positive cells (lymphocytes, macrophages and tumor cells) to viable tumor cells (19). Here, ORR to pembrolizumab was reported as 5.0% for CPS <1, 10.2% for CPS ≥1 and 17.1% for CPS ≥10.

Another target of immunotherapeutics is CTLA-4. CTLA-4 is present on T lymphocytes and suppresses T cell activation by competing for ligands CD80 (B7-1) and CD86 (B7-2) which are expressed by antigen-presenting cells (22). Ipilimumab, a monoclonal antibody against CTLA-4, was administered to 9 advanced OC patients after immunization with granulocyte-macrophage colony-stimulating factor (GM-CSF) and only one patient had a partial response (20). In a phase II trial 40 recurrent platinum-sensitive OC patients were treated with ipilimumab 10 mg/kg every three weeks for 4 doses and then the same dose every 12 weeks (21). ORR in this study was reported as 10.3%.

Efficacy data from these trials suggest that EOC does not seem to respond well to anti PD-1/PD-L1 or anti-CTLA monotherapy. This can be possibly explained by the fact that only a small proportion of OCs have high tumor mutational burden (TMB), which is defined as the total number of mutations in a tumor specimen and emerged as a novel predictive biomarker for immunotherapy (23). Further limitations in monotherapy trials may be that the majority of patients had received multiple lines of chemotherapy and patient numbers were relatively small in some studies. Although ORR to ICIs was numerically better in PD-L1 positive tumors in some of the trials, the difference could not be statistically proven and optimal predictive cut-off value of PD-L1 is also not clear. It is apparent that better characterization of tumor microenvironment and validated biomarkers are required to select OC patients who may

benefit from ICI monotherapy.

Combination of ICIs with other agents

Chemotherapy

A reasonable approach for increasing tumor immunogenicity and enhancing efficacy of ICIs may be combining them with cytotoxic agents. Chemotherapy can cause release of tumor antigens upon cell death and facilitate phagocytosis by dendritic cells (DCs) which is mediated by damage-associated molecules and augments antigen presentation to T cells (24). Cell death can also stimulate type 1 interferon (IFN) secretion by tumor cells via toll-like receptor 3 (TLR3) which leads to production of the chemokine CXCL10 (25). Immunomodulatory effects of chemotherapeutics include various processes like promoting cell lysis, impairing T_{reg} activity and increasing DC activation (26).

Combination of ICIs with chemotherapy is an active area of research in OC and one of the largest trials based on this design is the phase III JAVELIN Ovarian 200 trial. It included 566 platinum-resistant or platinum-refractory EOC patients who had received up to 3 lines of treatment (27) (*Table 2*). In this study, addition of avelumab to pegylated liposomal doxorubicin (PLD) did not prolong PFS and OS significantly overall but in PD-L1 positive (≥1% of tumor cells or ≥5% of immune cells) subgroup an improvement in survival was reported [hazard ratio (HR) =0.72, P=0.11 for PFS and HR =0.59, P=0.005 for OS]. The Avelumab in Previously Untreated Patients With Epithelial Ovarian Cancer (JAVELIN OVARIAN 100, NCT02718417) trial aimed to assess efficacy of avelumab as maintenance therapy following carboplatin/paclitaxel or carboplatin/paclitaxel/ avelumab in 998 treatment-naive advanced EOC patients. The study was discontinued because of futile efficacy in interim analysis.

Anti-angiogenic therapy

Angiogenesis, defined as formation of new blood vessels, plays a critical role in tumor proliferation and metastasis. It is induced by vascular endothelial growth factor A (VEGF-A) which is secreted by tumor cells and stimulates proliferation of endothelial cells by binding to the receptors VEGFR-1 and VEGFR-2. VEGF-A also

Table 2 Trials evaluating combinations of immune checkpoint inhibitors with other therapies and dual immune checkpoint blockade in ovarian cancer

Reference	Study characteristics	Treatment	ORR (%)	mPFS (months)	mOS (months)
Pujade-Lauraine et al. (27) (JAVELIN Ovarian 200)	Phase III, PRROC; n=566, ≤3 lines of CT; no previous treatment for PTS disease	Arm A: Ave 10 mg/kg q2w (n=188)	3.7	1.9	11.8
		Arm B: Ave + PLD 40 mg/m² q4w (n=188)	13.3	3.7	15.7
		Arm C: PLD (n=190)	4.2	3.5	13.1
Liu et al. (28)	Phase II, recurrent EOC; n=38, PTS: n=20, PTR: n=18; ≤3 lines of CT	Nivolumab 240 mg + bevacizumab 10 mg/kg q2w	All: 28.9	All: 8.1	NR
			PTS: 40.0	PTS: 9.4	
			PTR: 16.7	PTR: 5.3	
Lee et al. (29)	Phase I, recurrent EOC; n=19, PTS: n=9, PTR: n=10; ≥5 lines of CT (53%)	Cohort A: Durvalumab 1,500 mg q4w + olaparib 300 mg bid†	Cohort A: 17	NR	NR
		Cohort B: Durvalumab 1,500 mg q4w + cediranib 20 mg (5 days on/2 days off)†	Cohort B: 50		
Drew et al. (30) (MEDIOLA)	Phase II, PTS-OC; BRCA1/2 mutant; n=32, ≥1 line of platinum-based CT	Olaparib 300 mg bid for 4 weeks followed by durvalumab 1,500 mg q4w + olaparib 300 mg bid	71.9	11.1	NR
Konstantinopoulos et al. (31) (TOPACIO/ Keynote-162)	Phase I/II, recurrent OC; n=62, PTR: 64%; ≤5 lines of CT	Pembrolizumab 200 mg q3w + niraparib 200 mg/day	Overall: 25	NR	NR
			BRCA-mutant: 45		
Zamarin et al. (32)	Phase II, recurrent EOC; n=100, PFI <12 months; 1–3 lines of CT	Arm 1: Nivo 3 mg/kg q2w	12.2	2	NR
		Arm 2: Nivo 3 mg/kg + ipi 1 mg/kg q3w ×4 doses, followed by nivo 3 mg/kg q2w	31.4	3.9	

†, final dose levels. Ave, avelumab; Nivo, nivolumab; ipi, ipilimumab CT, chemotherapy; EOC, epithelial ovarian cancer; mOS, median overall survival; mPFS, median progression-free survival; NR, not reported; OC, ovarian cancer; ORR, objective response rate; PFI, platinum-free interval; PLD, pegylated liposomal doxorubicin; PRROC, platinum-resistant and -refractory epithelial ovarian cancer; PTR, platinum-resistant; PTS, platinum-sensitive; PTS-OC, platinum-sensitive ovarian cancer.

causes immunosupression by blocking DC maturation and consequently decreasing antigen presentation to T cells (33). Other mechanisms of angiogenesis-directed immune tolerance are accumulation of immunoregulatory cells (T$_{reg}$ cells, myeloid-derived suppressor cells) and inhibition of T cell production and functions (34-37). Therefore, combination with VEGF blockade is another potential method to increase anti-tumor activity of immunotherapy.

Efficacy of nivolumab combined with bevacizumab, an anti-VEGF monoclonal antibody, was investigated in a phase II trial which enrolled 38 relapsed EOC patients (28) (Table 2). Outcomes of this trial revealed clinical activity of the combination, with an ORR of 28.9% and PFS of 8.1 months, which improved to 40% and 9.4 months, respectively, in platinum-sensitive subgroup (patients whose

disease progressed within 6-12 months after platinum-based chemotherapy). In patients with positive (≥1%) PD-L1 expression ORR was 14.3% whereas patients with negative (≤1%) PD-L1 expression had an ORR of 45.5%. This result suggests that predictive value of PD-L1 expression for ICI activity in OC is still controversial and future validated studies are necessary in this field.

There are ongoing randomized phase III trials investigating addition of atezolizumab to chemotherapy and/or bevacizumab in different OC settings (Table 3). In IMagyn050 (NCT03038100), previously untreated stage III or IV EOC patients will be randomized in 1:1 design to carboplatin/paclitaxel/bevacizumab plus placebo or atezolizumab arms and co-primary endpoints will be investigator-assessed PFS and OS. The ATALANTE

Table 3 Ongoing trials investigating immune checkpoint inhibitors combined with other agents, from which no results have been reported so far

Trial	Phase	Setting	Treatment	Primary endpoints
ENGOT OV-39/GOG 3015/ IMagyn050 (NCT03038100)	III	Frontline	CP + Bev + Atezo or placebo	PFS, OS
ENGOT OV-29/ATALANTE (NCT02891824)	III	PTS relapse (PFI >6 months); 1 or 2 previous CT lines	CP + Bev + Atezo or placebo, followed by Bev + Atezo or placebo	PFS
NRG-GY009 (NCT02839707)	III	PTR relapse (PFI <6 months); 1 or 2 CT previous lines	PLD + Bev and/or Atezo	PFS, OS, DLT
ENGOT-OV43/ KEYLYNK-001 (NCT03740165)	III	Frontline	CP + Pembro, followed by Olap; CP + Pembro, followed by placebo; CP + placebo, followed by placebo	PFS, OS
ENGOT OV-46/DUO-O (NCT03737643)	III	Frontline	Non-tBRCAm: CP + Bev+ placebo, followed by Bev + placebo; CP + Bev + Durva, followed by Bev + Durva; CP + Bev + Durva, followed by Bev + Durva + Olap; tBRCAm: CP + Durva, followed by Durva + Olap	PFS
ENGOT-OV44/FIRST (NCT03602859)	III	Frontline	CP + placebo, followed by placebo; CP + placebo, followed by niraparib + placebo; CP + dostarlimab (TSR-042), followed by niraparib + dostarlimab	PFS
ENGOT OV-45/GOG3020/ ATHENA (NCT03522246)	III	Maintenance following frontline	Rucaparib + nivolumab; rucaparib + placebo; nivolumab + placebo; placebo + placebo	PFS
ENGOT-OV41/ GEICO-69-O/ANITA (NCT03598270)	III	PTS relapse (PFI >6 months); 1 or 2 previous CT lines	CT[†] + Atezo or placebo, followed by niraparib + Atezo or placebo	PFS
NCT04034927	II	PTS relapse (PFI >6 months)	Olap; Olap + tremelimumab	PFS, DLT, RECIST 1.1 response

[†], carboplatin plus paclitaxel, gemcitabine or pegylated liposomal doxorubicin. Atezo, atezolizumab; Bev, bevacizumab; CP, carboplatin + paclitaxel; CT, chemotherapy; DLT, dose-limiting toxicity; Durva, durvalumab; Olap, olaparib; OS, overall survival; Pembro, pembrolizumab; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PTR, platinum-resistant; PTS, platinum-sensitive; tBRCAm, tumor BRCA mutation.

trial (NCT02891824) will assess efficacy of atezolizumab combined with platinum-based chemotherapy/bevacizumab and maintenance bevacizumab in 405 EOC patients who have platinum-sensitive relapse (>6 months). Finally, the NRG-GY009 study (NCT02839707) will evaluate activity of atezolizumab combined with PLD or PLD/bevacizumab in recurrent and platinum-resistant EOC patients who had received one or two previous lines.

PARP inhibitors

Poly ADP-ribose polymerase (PARP) is a nuclear enzyme which, as a response to DNA damage, synthesizes poly ADP-ribose (PAR) chains to recruit DNA repair proteins. The BRCA1/2 proteins are significant elements of DNA repair as well and participate in the homologous recombination (HR) pathway to interfere with double strand breaks (38). Clinical activity of PARP inhibitor (PARPi) therapy in various cancers including OC was demonstrated, especially in BRCA-mutant and also non-BRCA mutant HR-deficient cases. US Food and Drug Administration (FDA)-approved PARP inhibitors include olaparib, rucaparib, and niraparib, while veliparib is in the late stage of clinical development (39). Talazoparib inhibits PARP catalytic activity, trapping PARP1/2 on damaged DNA, and it has been approved by the US FDA for the treatment of metastatic germline BRCA1/2 mutated breast cancers in October 2018 (40). PARPi could potentiate immunotherapeutic activity in many ways. First, they are thought to increase neoantigen burden through DNA

damage (35). Presence of HR deficiencies like BRCA1/2 mutations cause amplification of TMB and contribute to ICI sensitivity (41,42). Second, PARPi-induced DNA damage could promote recruitment of T cells via the stimulator of interferon genes (STING) pathway and type I IFN (43). Third, upregulation of PD-L1 expression is a possible effect of PARP inhibition (44). Fourth, PARPi can lead to acute inflammation, remodeling of tumor microenvironment and thus enhancement of immune response (45).

A phase I dose-escalation study including heavily pretreated and recurrent EOC patients assessed clinical activity of durvalumab in combination with olaparib, an oral PARPi, or cediranib, an oral VEGF inhibitor (43). ORR in this study was 17% for olaparib and 50% for cediranib combination. In three patients with 3+ TIL infiltration (>50% of tumor area) in immunohistochemistry, median duration of response was 14.5 months but PD-L1 positivity (≥5%) was not associated with treatment response. Efficacy of durvalumab and olaparib combination was demonstrated in the phase II MEDIOLA trial which enrolled 32 BRCA-mutated platinum-sensitive OC patients (30). Updated results from this trial revealed an ORR of 71.9% and median PFS of 11.1 months while median OS was not reached at that time. TOPACIO/Keynote-162 is a phase I/II study investigating combination of pembrolizumab with niraparib, an oral PARPi, in recurrent OC (31). Interim analysis of the study reported that ORR was 25% in the overall cohort and 45% in BRCA-mutated patients. The phase III JAVELIN OVARIAN PARP100 trial was conducted to evaluate chemotherapy plus avelumab combination followed by maintenance avelumab plus talazoparib, an oral PARPi, in previously untreated and advanced OC. This trial was stopped because no benefit was observed with avelumab. The novel combination strategy of olaparib with the CTLA-4-antagonist tremelimumab is under investigation and early ongoing studies are certainly encouraging (46).

Several ongoing studies are exploring ICI/PARPi combinations in various settings of OC and their details are summarized in *Table 3*.

Other combinations

ICI monotherapies did not work well in OC so far, as mentioned above, but combination of two ICIs is a promising method aiming to potentiate anti-tumor activity. Preclinical and clinical studies reported that anti-CTLA-4 plus anti-PD-1 blockade enhanced immune response by increasing effector-to-suppressor cell ratios, leading to production of proinflammatory cytokines and modulating peripheral B cell populations (47,48). In a phase II study which enrolled 100 patients with recurrent or persistent OC, nivolumab plus ipilimumab followed by maintenance nivolumab was compared with nivolumab (32) (*Table 2*). Here, the combination improved response rate significantly (31.4% *vs.* 12.2%, P=0.034) and reduced the risk of disease progression by 47%. Response was not associated with PD-L1 expression in both arms. Efficacy data from this study emphasize the nivolumab/ipilimumab combination as an encouraging option in recurrent OC but future studies comparing it with standard chemotherapy are required to establish its role.

Radiotherapy is another modality which may cooperate with immunotherapy. Radiation-induced immunosensitization occurs mainly through DNA damage and immunologic cell death as well as upregulation of MHC class I molecules and enhancing presentation of tumor associated antigens (49-51). In a phase I study 73 patients with progressive metastatic solid tumors, including 9 with OC/fallopian tube cancer, received fractionated stereotactic body radiation therapy (SBRT) to 2–4 metastatic sites and then pembrolizumab which was started within 7 days after completion of SBRT (52). The regimen was well tolerated and had clinical activity, with 9 patients having objective response and 21 having stable disease. Nonetheless, it is clear that more specific trials are needed before recommending radioimmunotherapy in OC.

Future directions

Cancer vaccines

Tumor-specific immune response could be achieved with vaccination using various antigens. Tumor antigens reported to be present in EOC include New York oesophageal-1 (NY-ESO-1) of the cancer-testis (CT) antigen family and mucin 1 (MUC-1) (53). Epigenetic modulation of CT antigen genes through DNA hypomethylation can increase antigen expression and potential of vaccine efficacy (54). NY-ESO-1 vaccine along with PLD and decitabine, a DNA methyltransferase inhibitor, was administered to recurrent OC patients in a phase I study based on this rationale (55). In this study, disease control rate was 60% and median duration of response was around 6 months. A randomized phase II trial, which compared a DC vaccine (CVac) targeting MUC-1 with standard-of-care in advanced

OC, reported a significantly prolonged PFS in patients with complete remission after second-line chemotherapy (>13 *vs.* 5 months, HR =0.32) (56). With further research on identification of possible targets, tumor vaccines may emerge as a personalized immunologic treatment for OC.

Oncolytic viruses

An oncolytic virus (OV) infects tumor cells, causes their lysis and then spreads to adjacent tumor cells and metastases; it can also promote indirect cell death by the host immune system (57). OVs can be administered intratumoral, intraperitoneal or intravenously. Several OVs have been studied in OC. Oncolytic herpes simplex virus expressing interleukin-12 (IL-12) was shown to kill murine and human OC cell lines, control OC metastases and improve survival when administered to omentum and peritoneal cavity in a mouse model (58). Other phase I or II trials are investigating adenovirus, measles virus, vaccinia virus and reovirus in OC; anti-tumor activity was reported in some of them. A promising modification of OV therapy is to combine it with ICIs because OVs can augment immune infiltration in tumors. Combination of intratumoral Newcastle disease virus therapy with anti-CTLA-4 blockade has shown a therapeutic effect in animal models, as suggested by rejection of tumors and improvement in survival (59). Despite these developments, further clinical research is needed to clarify the role of OVs in OC and before approving them for treatment.

Cellular therapy

Adoptive cell therapy (ACT) is one of the promising immunologic prospects in oncology. It uses autologous or allogeneic lymphocytes isolated from tumor or peripheral blood through leukopheresis. These are cultured and activated *ex vivo* and then re-infused to the patient with recombinant interleukin-2 (rIL-2) after lymphodepleting chemotherapy (60). Early data regarding ACT in OC came from a phase I trial of Fujita *et al.* who treated 13 EOC patients with adoptive TIL therapy following surgery and cisplatin-based chemotherapy (61). They observed a 3-year survival of 100% in these patients versus 67.5% in the control group which did not receive TILs. In a second phase I trial, autologous vaccine-primed CD3/CD28-co-stimulated T lymphocytes were transferred to recurrent EOC patients following DC-based autologous vaccination and lymphodepletion (62). Treatment was well tolerated and anti-tumor response along with clinical benefit was reported.

A major drawback of ACT is that tumor-specific lymphocytes are difficult to obtain. To overcome this, T cells can be genetically modified by T-cell receptors (TCRs) and chimeric antigen receptors (CARs). Introduction of TCRs targeting the NY-ESO-1 antigen, which is expressed in OC, can enable harvesting tumor-specific T cells in large numbers (63). On the other hand, T cells can be engineered by CARs to recognize tumor antigens in an MHC-independent manner (64). CARs relevant to OC have been investigated so far and include folate receptor-α (FR-α), human epidermal growth factor receptor 2 (HER-2) and mesothelin (65-67). A phase I trial of Tanyi *et al.* demonstrated detectable T cells in peripheral blood of OC patients with mesothelin-expressing tumors after infusion of autologous T cells transduced to express a CAR directed against mesothelin (68). Ongoing clinical trials are evaluating TCR- or CAR-redirected T cells against NY-ESO-1 and mesothelin in OC.

Conclusions

Preclinical studies revealed immunogenicity of OC and activation of anti-cancer immunity is hence a reasonable therapeutic maneuver for the disease which commonly recurs. Early efforts on this approach evaluated cytokine treatment in OC but failed to present convincing phase III data. On the other hand, ICIs have emerged as significant immunostimulatory agents with increasing use in oncology and immunologic properties of OC provides the basis for introducing them to disease management. However, ICIs as monotherapy brought only modest efficacy when assessed in pretreated OC patients, necessitating additional methods for potentialization. Following this, several strategies aimed to sensitize OC to immunotherapy by combining it with chemotherapy, anti-angiogenetics, PARPi, radiotherapy and by dual immune checkpoint blockade. There are numerous ongoing trials investigating these approaches and some results reported so far indicate better outcomes than ICI monotherapy, especially in terms of response rate. A major concern hereby would be definition of optimal predictive biomarkers to better identify candidates for ICI treatment. Finally, current translational research focuses on other promising immunologic therapies including cancer vaccines, virotherapy and cellular therapy which showed clinical activity in some studies and may emerge as treatment options for OC in the future.

Footnote

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