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Gynecologic Cancers (RJ Morgan, Section Editor)

Immunotherapy for Ovarian Cancer

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Opinion statement

All work referenced herein relates to treatment of epithelial ovarian carcinomas, as their treatment differs from ovarian germ cell cancers and other rare ovarian cancers, the treatments of which are addressed elsewhere. Fallopian tube cancers and primary peritoneal adenocarcinomatosis are also generally treated as epithelial ovarian cancers. The standard of care initial treatment of advanced stage epithelial ovarian cancer is optimal debulking surgery as feasible plus chemotherapy with a platinum plus a taxane agent. If this front-line approach fails, as it too often the case, several FDA-approved agents are available for salvage therapy. However, because no second-line therapy for advanced-stage epithelial ovarian cancer is typically curative, we prefer referral to clinical trials as logistically feasible, even if it means referring patients outside our system. Immune therapy

has a sound theoretical basis for treating carcinomas generally, and for treating ovarian cancer in particular. Advances in understanding the immunopathogenic basis of ovarian cancer, and the immunopathologic basis for prior failures of immunotherapy for it and other carcinomas promises to afford novel treatment approaches with potential for significant efficacy, and reduced toxicities compared with cytotoxic agents. Thus, referral to early phase immunotherapy trials for ovarian cancer patients that fail conventional treatment merits consideration.

Introduction

Ovarian cancer (OC) is considered to arise from epithelial cells encapsulating ovaries, stromal cells, or ova, although recent evidence suggests origins in Fallopian tubes and other sites as well [1]. The great majority of OC is epithelial carcinomas and often presents with advanced or metastatic disease. Although chemotherapy and surgical debulking can eliminate clinically apparent cancer, patients often succumb to chemotherapy-resistant tumor relapse within several years after initial remission. Immunotherapy for OC could be effective [2–8, 9••] as OC cells express immunogenic tumor-associated antigens that elicit detectable, specific immune responses [10–19]. The positive correlation between OC survival and tumor infiltration with CD8+ T cells is compelling evidence that antitumor immune surveillance is a critical dictate of clinical outcomes in OC [20••]. Despite abundant evidence that anti-tumor immunity in OC could be effective, immune-based OC therapies have generally been only modestly successful, at best. The first immunotherapy for OC used intraperitoneal injections of anti-human milk fat globulin-1 antibodies in 1987 [21], which was also among the very first uses of monoclonal antibodies as cancer immunotherapy. Additional antibody approaches followed, most notably with failure of the anti-CA-125 antibody oregovomab. Although there have been anecdotal reports of good clinical responses to newer immunotherapy approaches, there is no FDA-approved OC immunotherapy, as exists for other cancers. Nonetheless, recent data suggest that effective, tolerable OC immunotherapy could be developed in the near future. Recent advances in the understanding of OC immunopathogenesis, including understanding the immunopathogenic role of regulatory T cell, immature myeloid cells and dysfunctional immune co-signaling, help identify potentially more effective immunotherapy approaches. Combination immunotherapies appear more promising than individual immunotherapy agents, and immunotherapy could be combined with cytotoxic agents, small molecule inhibitors, radiation therapy, or surgery based on rational concepts.

Treatment

- Standard of care treatment for advanced stage OC includes optimal surgical debulking combined with chemotherapy with a platinum plus taxane agent.
- Immunotherapies include passive cell transfers, active vaccinations, or cytokine, toxin, or antibody infusions to stimulate antitumor immunity.
- Newer experimental approaches include combinations of immunoactive agents or combining immunotherapy with cytotoxic agents, small molecule inhibitors, surgery, or radiation therapy.

Surgery

- Standard of care front-line surgery consists of optimal tumor debulking where feasible, or debulking as much primary tumor as possible.
- Surgery is also used in recurrences and salvage settings, occasionally with curative intent, but more often for patient comfort or to preserve organ function.
- Surgical debulking as an adjunct to immunotherapy is in the exploratory phase.

Interventional procedures

Radiotherapy

- External beam irradiation is not typically front-line OC therapy, but is used to reduce surgically inaccessible tumors or for palliation.
- The efficacy of combined external beam irradiation with immunotherapy is under investigation in other cancers [22] but has not yet been reported in OC.

Pharmacologic treatment

Chemotherapy as immunotherapy

This review of OC immunotherapy will not detail front-line and salvage chemotherapeutic agents, which are discussed in detail elsewhere [23••]. Chemotherapy can serve as an adjunct to immune therapies through the reduction of immune suppressive factors or by increasing immune surveillance. Fludarabine [24] or cyclophosphamide [25] can deplete immunopathogenic regulatory T cells. 5-fluorouracil can deplete cancer-promoting myeloid-derived suppressor cells in preclinical models [26]. Anthracyclines can increase the immunogenicity of tumors through the uncovering of tumor-associated antigens by tumor lysis or release of danger signals, such as high-mobility group box 1 [27••]. There is a clear rationale to combine certain cytotoxic agents with immune therapies.

Monoclonal antibodies

Anti-milk fat globulin-1

The first therapeutic antibodies to treat human OC were anti-human milk fat globulin-1 antibodies radiolabeled and injected into the peritoneum, reported 27 years ago [21]. Treatment responses were positively correlated with irradiation doses and inversely correlated with tumor volumes. Additional antibodies continued to highlight the relative safety of intraperitoneal antibody injections, and produced occasional long-term clinical

responses [28]. However, a phase II trial of ^{90}yttrium-labeled anti-human milk fat globulin-1 antibodies did not show significant clinical benefits in 25 patients. Further dose-escalations produced myelosuppression [29], limiting the approach.
A phase I/II trial using ^{90}yttrium-labeled anti-human milk fat globulin-1 in 52 patients tested standard-of-care surgery plus chemotherapy at initial OC diagnosis, followed by intraperitoneal antibody [30]. Treatment was well tolerated and 21 of 52 patients had no detectable disease at the end of therapy. At 35 months median follow-up, survival was potentially better than historical controls, suggesting possible efficacy, which was corroborated by a longer-term survival analysis in 2000 [31]. More recent trials of intraperitoneal ^{90}yttrium-labeled anti- human milk fat globulin-1 suggest that whereas it can control local (intraperitoneal) disease, distant relapses could offset any overall survival benefits. Nonetheless, further study could be warranted [32].

Farletuzumab

Folate receptor-α is overexpressed in most OCs. Farletuzumab is a humanized anti-folate receptor-α antibody thought to function not through blocking folate transport but through antibody dependent cellular cytotoxicity. Safety and activity was demonstrated in phase I and II trials at doses from 12.5–400 mg/m^2 in OC patients in platinum-resistant relapse [33, 34]. Grade 1–2 adverse events were noted in 80 % of patients, with grade 3 fatigue reported in 2. The most common side effects were hypersensitivity, fatigue, diarrhea, and cough/dyspnea. Ultimately, farletuzumab failed to meet its endpoint of improving progression-free survival in a recent phase III trial of 1100 platinum-resistant OC patients (http://www.eisai.com/news/news201305.html) although a post hoc analysis suggested a trend toward improved progression free survival in OC subsets, prompting additional analyses. In another trial [33], 54 OC patients received weekly farletuzumab alone or combined with carboplatin (AUC 5-6) plus paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2). Cytotoxics were given every 21 days for 6 cycles, followed by weekly farletuzumab until progression. 28 patients with asymptomatic CA-125 relapse got farletuzumab alone and were eligible for carboplatinum/taxane plus farletuzumab if they progressed on farletuzumab alone. 26 patients with symptomatic relapse initially got cytotoxics plus farletuzumab and 21 additional patients had cytotoxics added after initial farletuzumab. Farletuzumab alone was well-tolerated and did not augment toxicities of cytotoxics. In the 47 patients on farletuzumab plus chemotherapy, 38 (80.9 %) normalized CA-125. Complete or partial response rates were 75 % with farletuzumab plus cytotoxics. Thus, farletuzumab alone might be poorly effective, but combination with carboplatin plus a taxane could merit additional consideration in platinum sensitive first relapse.

Catumaxomab

Catumaxomab is a trifunctional antibody that kills EpCAM-expressing tumor cells, the primary cause of malignant ascites. It is approved to treat malignant ascites in Europe but not the United States. It is administered as 4 3-hour intraperitoneal infusions. One case report describes complete

remission in an OC patient that received 4 infusions of catumaxomab alone. The most frequent adverse effects are fever, nausea, vomiting, and abdominal pain. In a phase IIIb study, 25 mg prednisolone reduced catumaxomab-related adverse events in OC patients receiving it for malignant ascites. There were nonsignificant trends for prednisolone to reduce time between paracenteses and for catumaxomab alone to increase overall survival, but the main finding was that prednisolone did not reduce catumaxomab-related adverse events [35].

Ipilimumab

Immune checkpoint blockade with antibodies is emerging as potentially effective immunotherapy in many cancers [36••]. Ipilimumab and tremelimumab are fully human IgG1 or IgG2 antibodies, respectively, that antagonize the CTLA-4 immune checkpoint. Ipilimumab is FDA-approved to treat metastatic or unresectable melanoma and is the first standard-of-care immune checkpoint inhibitor. Anecdotal reports of OC responses to ipilimumab and preclinical findings prompted an ongoing phase II trial of ipilimumab for platinum-resistant OC (NCT01611558). Ipilimumab can cause significant autoimmune side effects. Tremelimumab (in phase III trials for melanoma) could have similar efficacy with reduced toxicities.

Anti-PD-L1

Various clinical and preclinical studies support PD-L1 as a cancer treatment target [37]. BMS-936559 is a fully human IgG4 monoclonal antibody that blocks PD-L1 from binding its 2 known receptors PD-1 and CD80 (http://www.onclive.com/web-exclusives/the-role-of-anti-pd-l1-immunotherapy-in-cancer/6#sthash.NSf1zUJC.dpuf). It was safe in a phase I trial that included 17 OC patients [37] in doses of 0.3–10 mg/kg by intravenous infusion. Adverse events of any grade were reported in 91 % of 207 patients. Only 12 patients (6 %) discontinued therapy for treatment-related adverse events. Common side effects included fatigue, infusion reactions, diarrhea, arthralgia, pruritis, rash, nausea, and headache. Potential immune adverse events (rash, hypothyroidism, hepatitis, sarcoidosis, diabetes mellitus, endophthalmitis, myasthenia gravis) were observed in 81 patients (39 %). Only OC patients at the 10 mg/kg dose achieved objective responses: 1 (6 %) with a partial response and 3 (18 %) with stable disease lasting ≥ 24 weeks.

Oregovomab

CA-125 is a tumor-associated antigen used to monitor OC treatment responses. CA-125 was targeted in vivo by the murine IgG1 monoclonal antibody oregovomab. Antigen-antibody complexes prime dendritic cells [38] to activate T cells [39]. In a pivotal phase III study of 373 OC patients [40], oregovomab maintenance was used after front-line therapy. No difference in clinical outcome was identified, although treatment was well tolerated. The future for this monoclonal antibody was uncertain although interest remained. It is currently in a phase II randomized study (NCT01616303) in combination with first-line chemotherapy consisting of carboplatin plus paclitaxel vs carboplatin plus paclitaxel alone in advanced

	OC. As prior work suggested immune boosting effects [38–40], this trial will study anti-CA-125 immunity in addition to clinical end points.
Abagovomab	
	Abagovomab is an anti-idiotypic CA-125 murine monoclonal antibody [41] that induces anti-CA-125 antibodies. In a phase I trial, 42 OC patients were randomized to abagovomab vaccination with 2 or 0.2 mg by intramuscular vs subcutaneous vaccination 4 times every 2 weeks, plus 2 additional monthly vaccinations. The most common adverse events were minor injection site pain, myalgia, and fever. No >grade 2 immunization-related toxicities were noted. Human anti-mouse antibodies were elicited in all patients in addition to anti-CA-125 antibodies, which were unrelated to vaccine dose or administration route [42], prompting additional study. In a recently completed phase III trial of abagovomab maintenance therapy (the MIMOSA study) in 888 patients with stage III or IV OC [43] in complete clinical remission after front-line surgery plus platinum/taxane-based chemotherapy, patients were randomized to abagovomab 2 mg or placebo every 2 weeks for 6 weeks as induction, followed by maintenance vaccinations every 4 weeks until recurrence. Patients were treated a mean of 450 days. Side effects were similar to the phase I trial. Vaccinations induced robust anti-CA-125 antibodies, but unfortunately without increase in recurrence-free or overall survival.
Volociximab	
	Volociximab is a chimeric IgG4 monoclonal antibody against AAB1, a component of $\alpha 5\beta 1$ integrin that is anti-angiogenic [44]. A phase II study of weekly volociximab was conducted in 16 patients with platinum-resistant, advanced epithelial OC or primary peritoneal cancer [45]. Volociximab 15 mg/kg intravenously was given weekly until disease progression or treatment intolerance. One patient had stable disease at 8 weeks whereas the others progressed. Common adverse events included headache and fatigue in 75 % of patients. Possible study-related serious adverse events in 3 patients were reversible posterior leukoencephalopathy syndrome, pulmonary embolism, and hyponatremia. This trial has prompted further assessments.
Amatuximab	
	Mesothelin is a tumor differentiation antigen over-expressed in certain cancers including those of ovary, pancreas and mesothelium [46]. MORAb-009 (amatuximab) is a chimeric anti-mesothelin monoclonal antibody that was tested in a phase I trial of 24 patients with mesothelin-expressing tumors including patients with OC [47]. Eleven subjects experienced stable disease prompting an ongoing phase II trial in mesothelioma patients.
Siltuximab	
	IL-6 in an important immunopathologic cytokine in distinct tumors [48] and plays diverse immunopathogenic roles in OC [49, 50]. Siltuximab is an anti-IL-6 antibody being tested as treatment for various carcinomas, hematologic malignancies and tumor cachexia [51].
Tocilizumab	
	Tocilizumab is a humanized anti-IL-6 receptor antibody being tested for cancer cachexia [52] and is used to mitigate cytokine release symptoms in

adoptive T cell therapy [53]. In vitro studies of tocilizumab have been reported with human OC cells but there are no reported clinical trials. Additional anti-IL-6 and anti-IL-6 receptor antibodies are in trials, including for cancer.

Anti-CD137

CD137 (4-1BB) is a stimulatory T cell co-receptor that enhances T cell proliferation and cytolytic activity. In mouse OC models, combining anti-CD137 plus anti-Tim3 [54•] or anti-PD-1 [55•] improved immune and clinical responses. Anti-CD137 has moved into phase I human clinical trials that include patients with OC [56].
For additional information on antibody therapy for cancer, see a recent review [57••].

Additional approaches

We recently reported that the fusion toxin denileukin diftitox reduces regulatory T cells in human cancer and improves anti-tumor immunity, including OC, and induced a significant partial response in 1 patient with metastatic OC in a phase I trial. We tested denileukin diftitox 12 μg/kg every 3–4 weeks in a phase II trial of 28 OC patients. It was well-tolerated with no more than grade 2 toxicities (most commonly fatigue, fever, myalgias) but failed clinically [58•]. Our recent preclinical findings that immune checkpoint blockade greatly enhances denileukin diftitox clinical efficacy, including in OC [59] has prompted additional ongoing studies of combination strategies. In other preclinical studies we showed that anti-CD73 improves clinical effects of adoptive T cell transfer in OC [60] and demonstrated that age [61] and sex [62] alter immunotherapy outcomes, factors generally not taken into account in immunotherapy trial design.

Cytokines

Interferon-α

Type I interferons (primarily interferons α, β, and ω) were originally identified as anti-viral proteins [63]. Soon after their discovery, they were found to block malignant cell proliferation. Interferon-α is the principal type I interferon tested for human anti-cancer activity. Studies have focused on high doses that directly inhibit tumor cell replication, but these high doses elicit significant toxicities that limit clinical applications [64]. Intraperitoneal interferon-α to treat OC was first assessed in the early 1980s, with only modest efficacy [65, 66]. A phase II study of 14 patients showed that interferon-α could be administered intraperitoneally in combination with cis-platinum as OC salvage therapy when optimal surgical debulking was not achieved. The approach was tolerable with hints of clinical efficacy [67]. Intraperitoneal interferon-α is ineffective against malignant OC ascites [68].
In a mouse OC model, interferon-α improved paclitaxel clinical efficacy [69]. Interferon-α upregulates OC cell human leukocyte antigen class I in vitro [70] suggesting possible beneficial immune modulation. However,

interferon-α down-regulated molecules HMFG1 and HMFG2, antigens that could be OC immune therapy targets. These results illustrate the concept that treatments effects can be multi-faceted, which must be taken into account when designing combination therapies.

We found that interferon-α at low immune modulating doses improved the immune and clinical efficacy of denileukin diftitox used to deplete regulatory T cells in a mouse OC model, and in 2 of 3 OC patients with manageable toxicities [71•], prompting ongoing studies. Gene therapy with adenoviruses engineered to express interferon-β was used in an early phase clinical trial that included 2 OC patients [72]. One of the 2 had stable disease 2 months after treatment ended, but both died within 5 months of treatment. Interferon-β levels decreased after the second adenovirus infusion, because neutralizing anti-adenovirus antibodies developed, a well-known limitation of repeated adenovirus administrations. Nonetheless, anti-tumor antibodies were also generated. Finally, interferon-α reduces proliferation in human OC stem cells [73], suggesting additional mechanisms of action.

Interferon-γ

Interferon-γ was used to treat OC by 1992 [74], and by 1996, intraperitoneal interferon-γ elicited some encouraging preliminary results [75]. Interferon-γ plus front-line chemotherapy improved OC survival [76]. Interleukin-2 plus interferon-γ was studied with infusion of tumor filtrating lymphocytes in OC. Interferon-γ either alone or combined with interleukin-2 upregulated tumor cell human leukocyte antigen class I and class II expression [77], suggesting augmented tumor immunogenicity. Of the 22 OC patients receiving cytokine treatments, 2 also received tumor infiltrating lymphocyte adoptive transfer after ex vivo expansion. One of these 2 had disease stabilization >6 months. Interferon-γ plus IL-2 therapy activated $CD8^+$ T cells but also induced potentially immunosuppressive IL-10 and TGF-β.

In a phase I trial, 25 potentially chemotherapy-sensitive OC patients with recurrent measurable disease got subcutaneous GM-CSF (starting at 400 μg/day) for 7 days plus subcutaneous IFN-γ (100 μg) on days 5 and 7 in attempts to boost antibody dependent cellular cytotoxicity, before and after carboplatin (AUC 5, intravenous). Levels ofactivated monocytes increased but without clear effects on antibody dependent cellular cytotoxicity [78].

In mouse xenograft models, interferon-γ treatment significantly improved survival of OC tumor-challenged mice. Carboplatin did not enhance the survival benefit of interferon-γ, whereas survival was enhanced by the matrix metalloprotease inhibitor batimastat [79]. In 4 human OC lines studied in vitro, interferon-γ downregulated Her2 and impeded cell proliferation [80]. In another in vitro study, interferon-γ rendered OC cells more susceptible to cytotoxicity mediated by $CD8^+$ CA-125 (tumor)-specific T cells [81].

Interleukin-2

Interleukin (IL)-2 a T cell growth and activator factor, exerts modest anti-cancer activity in melanoma and renal cell carcinoma, among

other cancers [82]. IL-2 at low doses was combined with retinoic acid in an OC trial [83]. Five-year progression-free survival and overall survival rates were 29 % and 38 %, respectively, in 65 evaluable OC patients. Immune effects included decreased vascular endothelial growth factor and statistically significant increases in lymphocytes and natural killer cells. In a phase II trial of 31 OC patients with platinum-resistant or platinum-refractory disease [84], intraperitoneal IL-2 elicited hints of clinical efficacy in addition to being relatively well tolerated. In 24 patients so assessed, there were 4 complete responses and 2 partial responses. Survival was positively correlated with total and interferon-γ^+CD8^+ T cell numbers.
IL-2 plus erythropoietin was tested in peripheral blood stem cell transplants for breast cancer and OC. Myeloid cell recovery was improved but there were no significant immune benefits [85]. Therapeutic IL-2 infusions modulate Treg numbers and trafficking in OC [86], but the clinical significance is uncertain. However, because IL-2 is a Treg growth and differentiation factor, combining IL-2 with Treg depletion could be useful.

Tumor necrosis factor-α

Tumor necrosis factor (TNF)-α can directly induce apoptosis of cancer cells and promote anticancer immune responses. TNF-α fused to the tri-peptide asparagine-glycine-arginine (NGR-hTNF) binds selectively to CD13, which is overexpressed on tumor blood vessels. Preclinical studies showed that NGR-hTNF exhibits higher potency than native TNF-α and circumvents its toxicities. 37 patients with platinum-resistant OC were given a median of 4 cycles of NGR-hTNF [87]. Partial responses were observed in 8 (23 %) and stable disease in 15 (43 %). Weakness, anemia, leukopenia, nausea, neutropenia, vomiting, chills, and constipation were the most common side effects. Febrile neutropenia was observed in 1 patient (3 %). However, <10 % of adverse events were attributable to NGR-hTNF.

IL-18

Recombinant IL-18 (SB-485232) is an immunostimulatory cytokine that boosts antitumor immunity in combination with pegylated liposomal doxorubicin in mouse models. In a phase I study, SB-485232 was combined with pegylated liposomal doxorubicin in patients with recurrent OC. 16 patients received 4 cycles of pegylated liposomal doxorubicin (40 mg/m^2) every 28 days, plus dose-escalated SB-485232 on days 2 and 9 of each cycle plus additional discretionary pegylated liposomal doxorubicin monotherapy. Most patients (82 %) were platinum-resistant or refractory, and heavily pretreated. SB-485232 up to 100 μg/kg was well-tolerated. Pegylated liposomal doxorubicin did not alter SB-485232 biologic activity and SB-485232 did not affect doxorubicin toxicities. Ten of 16 subjects (63 %) completed study and 5 (31 %) progressed on treatment. 6 % had a partial response, and 38 % had stable disease [88].
A summary of recent clinical trials using antibodies, immunotoxins, or cytokines is summarized in Table 1.

Table 1. Selected recent clinical trials in OC that use antibodies/immunotoxins or cytokines

Clinical trial approach	Clinical trial	# OC patients	Objective responses	Reference or trial ID
Antibodies and immunotoxins	Phase II trial of farletuzumab (anti-folate receptor) ± carboplatin or a taxane, 2013	54	44 – CR/PR 10 – PD or NA	33
	Phase I trial of farletuzumab, 2010	25	9 – SD 15 – PD 1 – N/A	34
	Phase II trial of ipilimumab (anti-CTLA-4) ongoing	N/A	N/A	NCT01611558
	Phase I trial of BMS-936559 (anti-PD-L1), 2012	17	1 – PR 3 – SD 13 – PD	37
	Phase II trial of oregovomab ± paclitaxel or paclitaxel/carboplatin, ongoing	N/A	N/A	NCT01616303
	Phase III trial of abagovomab (anti-CA-125 idiotype), 2013	888	No change in recurrence free or overall survival	43
	Phase II trial of volociximab (anti-α5β1 integrin), 2011	16	1 – SD 15 – PD	45
	Phase I trial of amatuximab (MORAb-009, anti-mesothelin), 2010	4	0 – CR/PR	47
	Phase 0/I trial of denileukin diftitox (IL-2/diphtheria fusion toxin), 2005	4	1 PR (trial did not have therapeutic intent and other patients were not evaluated for clinical endpoints)	58
	Phase II trial of denileukin diftitox, 2011	28	26 – PD 2 – SD	58
	Phase I trial of siltuximab (anti-IL-6 receptor), ongoing	N/A	N/A	NCT00841191
Cytokines	Phase II trial of NGR-hTNF + doxorubicin, 2012	35	8 – PR 15 – SD 7 – PD	87
	Phase I trial of IL-18 + pegylated liposomal doxorubicin, 2013	15	1 – PR 6 – SD 8 – PD	88
	Phase II trial of denileukin diftitox plus subcutaneous pegylated interferon-α, 2011	3	2 – SD 1 – PD	71

CCR continued clinical response, *CR* complete response, *IR* initial response, *N/A* not available, *NED* no evidence of disease, *NR* no response, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease

Other treatments

Peptide vaccines

Many OC patients have easily detectable numbers of functional tumor antigen specific T cells, suggesting that augmenting tumor-specific immunity could lead to improved clinical benefits. A number of tumor-associated antigens have been detected in OC, any of which potentially could help elicit beneficial anti-tumor immunity. These tumor-associated antigens include HER2/neu [5], MUC1 [10], NY-ESO-1 [11], membrane folate receptor r [12], folate binding protein (gp38) [13], TAG-72 [14], mesothelin [15, 16], sialyl-Tn [17, 18], milk fat globulin-1 [21], and OA3 [19].

Peptide vaccines help to define the magnitude and kinetics of specific immune responses, but are limited clinically in that they are generally recognized by a single major histocompatibility complex molecule as they are relatively short in length. Peptide library vaccines could help overcome this shortcoming [89] but have not specifically been tested in OC to our knowledge.

NY-ESO-1

NY-ESO-1 is highly expressed in OC. It was expressed in vaccinia or fowlpox viruses and tested in 22 patients with advanced OC in clinical remission [90]. Patients were given 1 intradermal dose of NY-ESO-1-vaccinia vector followed by monthly subcutaneous NY-ESO-1-fowlpox vector. Vaccination increased NY-ESO-1 specific antibodies, or $CD4^+$ or $CD8^+$ T cells. The median duration of progression-free survival was 21 months and median overall survival was 4 years. No adverse events higher than grade 2 were observed and the most common side effect was injection site pain.

A phase I trial used decitabine as an epigenetic modifier for NY-ESO-1 vaccine and liposomal doxorubicin liposome in 12 patients with relapsed OC. The regimen was safe with manageable toxicities. Vaccination increased NY-ESO-1-specific antibodies and T cells and antibodies to additional tumor antigens were elicited. Stable disease or partial clinical response was noted in 6/10 evaluable patients [91], prompting additional studies.

P53

p53 overexpression is common in many distinct cancers, including OC. Vaccination with p53 peptide plus IL-2, GM-CSF and montanide adjuvant was tested in patients with stage III, IV, or recurrent p53-overexpressing OC without evidence of disease at vaccination. Subcutaneous vaccination improved anti-p53 immunity (interferon-γ production and p53-containing MHC tetramers) in 9 of 13 patients [92]. Subcutaneous vaccination was compared with intravenous infusion of p53-pulsed dendritic cells using IL-2 as an adjuvant/T cell enhancer. Both strategies elicited comparable immunity [92]. Thus, the logistically simpler subcutaneous approach could be the best path forward, according to study investigators. OC recurrence and survival data were not reported. IL-2 administration increased blood Treg numbers significantly, which could impede anticancer immunity, an issue that requires further investigation. Another phase II trial tested a synthetic long p53 peptide in patients with recurrent OC and found that it induced

antigen-specific T cells, but did not improve clinical outcomes as a stand-alone approach, or when tested with secondary chemotherapy [93].

Natural cancer peptides

DPX-0907 (DepoVax) is an oil-based peptide adjuvant. In a phase I trial of patients with advanced-stage cancers of breast, ovary, or prostate, a vaccine of DPX-0907 plus naturally occurring HLA A2-expressed cancer peptides derived from cell lines was well-tolerated and immunogenic [94]. Injection site reactions were the most common adverse event. Vaccination induced polyfunctional T cells, including in OC patients, prompting additional studies.

Carcinoembryonic antigen glypican-3 (GPC3)

A phase II trial tested a GPC3-derived peptide vaccine in incomplete Freund's adjuvant. OC patients received vaccination biweekly for 6 injections and then every 6 weeks until disease progression. Two OC patients with chemotherapy-refractory disease achieved partial clinical responses in this ongoing trial [95].

Carcinoembryonic antigen (CEA) and MUC1

CEA and MUC-1 are overexpressed many carcinomas. 25 patients were primed with a vaccinia virus expressing CEA and MUC-1 plus the costimulatory molecules CD80, intercellular adhesion molecule 1, and lymphocyte function-associated antigen 3, PANVAC-V) and boosted with fowlpox expressing these molecules (PANVAC-F). Vaccination was well tolerated with no grade 2 toxicity in more than 2 % of the cycles, except local vaccine reactions. MUC-1 and/or CEA-specific immunity was generated in 9 of 16 patients. One patient with clear cell OC had a durable (18-month) clinical response [96•].

In a follow-up study [97], 26 patients were vaccinated with PANVAC monthly. Side effects were largely injection-site reactions. Of the 14 OC patients, median time to progression was 2 months (range 1–6) and median overall survival was 15.0 months. Patients with limited tumor burden and minimal prior chemotherapy seemed to derive the most benefit from the vaccine. An OC patient from the prior trial cited above [96•] progressed after 38 months. Additional studies are underway.

Adoptive cell transfers

Dendritic cells (DC)

The role of DC in cancer therapy has been reviewed [98]. Adoptive transfer of tumor antigen-pulsed DC increases antitumor immunity by activating anti-tumor T cells. In a phase I/II trial, 11 advanced-stage OC patients received DC loaded with Her2/neu, telomerase, and pan T helper cell stimulating (PADRE) peptides ± low dose cyclophosphamide to deplete Tregs [99]. Cell infusions were well tolerated and the most common side effects were low-

grade hypersensitivity reactions with no treatment-related grade 3 events. Only modest immunity was elicited by the vaccine (antigen-specific T cell cytokines or tetramer labeling). However, of 11 patients, only 1 died within 3 years of vaccination. Of the remaining 10, 3 experienced chemotherapy-responsive recurrences and the rest remained disease-free. Another recent trial used autologous whole tumor lysate-pulsed DC plus bevacizumab, cyclophosphamide, and autologous tumor lysate-primed T cells in recurrent OC patients [100]. Transfusions were well tolerated with no grade 3 or higher events. Two of 6 patients experienced partial responses, and 2 exhibited stable disease. There were reduced circulating Tregs and increased tumor-specific T cells at study end in the 4 patients that experienced clinical benefit. Very recently, a phase II trial of 10 OC patients with minimal residual disease tested subcutaneous autologous DC pulsed with tumor lysate and keyhole limpet hemocyanin as an adjuvant plus adjuvant low-dose IL-2 [101]. Three of 10 patients maintained complete remissions for 38–83 months and a third with complete remission relapsed after 50 months. In patients that experienced clinical benefit, multiple measures of antitumor immunity increased, such as natural killer cell activity, interferon-γ^+ T cells, T_H1-stimulating IL-12, and immunosuppressive TGF-β declined.

DC/tumor cell fusions

Reinfusion of autologous DC fused to OC cells could induce more efficient presentation of the wide array of tumor antigens vs tumor alone. DC/tumor cell fusion has been tested in various preclinical models [102, 103], but not in human OC trials.

T cells

The goal of adoptive T cell transfer in cancer immunotherapy is to increase numbers of activated, cancer-specific cytotoxic or helper T cells. Recent technologies have been reviewed [104••]. In a pilot study, 7 subjects with recurrent local OC were given multiple cycles of intraperitoneal infusions of autologous MUC1 peptide-stimulated cytotoxic T lymphocytes [105]. Infusions were well tolerated, multiple infusions did not offer greater benefit over one, and clinical benefit was seen in only 1 patient who was disease free >12 years.

Most recent adoptive T cell transfers use T cell receptor (TCR) transgenic or chimeric antigen receptor (CAR) T cells. Recombinant TCRs give a T cell fixed MHC-dependent specificity. CAR T cells express tumor-antigen specific antibody fragments on their surface, fused to intracellular activation proteins (eg, CD3ζ, 4-1BB, OX40) and recognize antigen independent of MHC. A preclinical study showed NKG2D-specific CAR T cells provide protection and establish memory against distinct OC tumors where only 7 % of cells express NKG2D [106]. Despite inducing complete remissions in leukemia patients, the efficacy of CAR T cells in solid tumors has been more limited because of inefficient tumor homing. However, folate receptor-α-specific CAR T cells expressing CD3ζ plus CD137 costimulatory domains protected against established OC in immunodeficient mice, underscoring the importance of the intracellular activation proteins. A phase 1 trial of OC patients with recurrent OC used autologous folate receptor-α –specific CAR (CD3ζ-CD137) T cells is planned [107].

Oncolytic viruses

Myxoma virus is nonpathogenic in humans but infects human cancer cells and exhibits oncolytic activity in preclinical models, reviewed elsewhere [108]. Myxoma virus possesses oncolytic activity against ascites-derived human OC cells in vitro [109]. However, there are currently no reported OC clinical trials

Table 2. Selected clinical trials in OC that use vaccines, adoptive cell transfers or oncolytic viruses

Clinical trial approach	Clinical trial	# OC patients	Objective responses	Reference or trial ID
Vaccines	Phase II trial of recombinant vaccinia and fowlpox vaccines expressing NY-ESO-1, 2012	22	21 mo PFS 4 y OS	90
	Phase II trial of subcutaneous p53 peptide vaccination, 2012	13	4.2 mo PFS 41 mo OS	92
	Phase I trial of p53-synthetic long peptide vaccine, 2012	20	No increase in OS	93
Adoptive cell transfers	Phase II trial of p53-pulsed dendritic cells vaccine, 2012	6	8.7 mo PFS 29.6 mo OS	92
	Phase I/II vaccination trial of Her2/neu, telomerase, PADRE peptide-pulsed DCs ± cyclophosphamide, 2012	11	90 % 3 y OS NED in 6 pts at 3 y	99
	Phase I trial of autologous tumor lysate-pulsed dendritic cells + bevacizumab, cyclophosphamide, autologous tumor lysate-primed T cells, 2013	6	2 – PR 2 – SD 2 – PD	100
	Pilot study of MUC1-primed cytotoxic T lymphocyte transfer, 2012	7	1 – CR 6 – PD	105
	Phase I trial of anti-mesothelin CAR T cells, ongoing	N/A	N/A	NCT02159716
	Phase I trial of anti-mesothelin CAR T cells + chemotherapy, ongoing	N/A	N/A	NCT01583686
	Phase I trial of anti-VEGFR2 $CD8^+$ CAR T cells + chemotherapy, ongoing	N/A	N/A	NCT01218867
Oncolytic viruses	Phase I trial of CA-125- or Na/I symporter-expressing measles virus, ongoing	N/A	N/A	NCT00408590
	Phase I/II trial of Na/I symporter-expressing measles virus infected mesenchymal stem cells, ongoing	N/A	N/A	NCT02068794
	Phase II trial of thymidine kinase-inactivated vaccinia virus, ongoing	N/A	N/A	NCT02017678
	Phase I/II trial of oncolytic adenovirus, ongoing	N/A	N/A	NCT02028117
	Phase II trial of oncolytic reovirus, ongoing	N/A	N/A	NCT02028117

CCR continued clinical response, *CR* complete response, *IR* initial response, *N/A* not available, *NED* no evidence of disease, *NR* no response, *OS* overall survival, *PD* progressive disease, *PFS* progression-free survival, *PR* partial response, *SD* stable disease

with myxoma virus. Reovirus is also oncolytic against human OC cells in vitro [110]. Neutralizing antibodies in malignant ascites can inactivate reovirus oncolytic activity, which can be overcome by loading reovirus onto immature DCs or lymphokine-activated killer cells [111]. A phase I trial of reovirus in platinum-resistant OC patients is ongoing (NCT00602277).

A summary of recent clinical trials using vaccines, adoptive cell transfers, and oncolytic viruses is summarized in Table 2.

Conclusions

Recent advances in understanding cancer immunotherapy and in developing novel agents has led to significant improvements in immunotherapy, most notably in malignant melanoma, but also in other cancers. There is currently no FDA-approved immunotherapy for OC, but there is much promise from leads developed in ongoing trials in OC and other cancers. Over the next several years, we expect that important advances in OC immunotherapy will be made, leading to important phase II and III trials. Because of a lack of curative salvage treatment options for relapsed or refractory OC, clinicians should consider referrals to early phase clinical trials, including OC immunotherapy trials.

Compliance with Ethics Guidelines

Conflict of interest

Justin M. Drerup, Yang Liu, Alvaro Padron, Vincent Hurez, and Bin Zhang declare no conflict of interest. Tyler J. Curiel has received research support and consulting fees from Eisai.

Human and Animal Rights and Informed Consent

This article does not contain any primary animal or human studies.

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