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Opportunities in immunotherapy of ovarian cancer

G. Coukos[1], J. Tanyi[2] & L. E. Kandalaft[1,2*]

[1]*Ludwig Institute for Cancer Research at the University of Lausanne, Department of Oncology, University Hospital of Lausanne, Lausanne, Switzerland;* [2]*Ovarian Cancer Research Center, University of Pennsylvania, Philadelphia, USA*

Ovarian cancer (OC) is the most important cause of gynecological cancer-related mortality, with the majority of women presenting with advanced disease. Although surgery and chemotherapy can improve survival, the 5-year survival rates remain ominously low at 45%. Novel therapies are urgently needed. The presence of T cells in the OC tumor microenvironment is correlated with improved progression-free and overall survival, while the presence of regulatory T cells and expression of T-cell inhibitory molecules is correlated with a poor prognosis. These data indicate that immunotherapy could hold promise in improving the treatment of OC. In this review, we will discuss the rational of immunotherapy, highlight current results with cancer vaccines, adoptive T-cell therapy and immunomodulatory agents and summarize the immune effects of selected chemotherapeutic and radiotherapeutic agents.

Key words: immunotherapy, vaccines, ovarian cancer

introduction

Despite a global effort to reduce mortality, ovarian cancer (OC) remains the most common cause of gynecological cancer-associated death among women with 21 290 American women reported to be diagnosed with OC, and 14 180 that died of this disease in 2015 [1]. Major efforts have been put in clinical trials studying different cytotoxic and targeted agents with different routes of delivery and new schedules [2–8]; with no major improvement in cure rates [9], leaving surgery and platinum-based chemotherapy the basis of OC treatment. This sobering reality warrants an urgent need for novel alternative treatments to increase the response rate and survival of this patient population.

Evidence developed over the last decade has shown that OC is an immunogenic tumor that can be recognized by the host immune system [10]. Spontaneous anti-tumor immune response can be detected in peripheral blood, tumors and ascites of OC patients in the form of tumor-reactive T cells and antibodies [11, 12]. Tumor-derived or peripheral blood T cells recognize autologous tumor-associated antigens (TAAs) including testis differentiation antigens, universal TAAs and possibly private non-synonymous somatic mutations. However, spontaneous anti-tumor immune response has only been demonstrated in ~55% of patients with OC whose tumors are rich with T-cell infiltrates [13]. Others and we reported that patients with T-cell-rich tumors experience longer progression-free and overall survival [10, 14–16], whereas immune evasion mechanisms in this patient population correlate with poor survival [17–22]. The relationship of T-cell infiltrates with prolonged survival, as well as the association of immune escape mechanisms with poor survival suggest that OC patients could respond to immunotherapy approaches. These approaches can be vaccines, adoptive T-cell therapy or immunomodulatory drug-based such as interleukin-2 (IL-2), or antibodies against cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed cell death 1 (PD-1) co-inhibitory immune receptors. Standard chemotherapeutic agents and radiotherapy (RT) approaches may also have immunomodulatory properties. Here, we discuss OC immunotherapy, highlighting emerging therapeutic opportunities that can harness the immune system to improve clinical outcomes.

cancer vaccines

Therapeutic cancer vaccines have been investigated since the 1920s and they are the most studied immunotherapeutic strategy in OC [23]. Contrasting to chemotherapy, RT, or surgery, an immune response induced by a vaccine could establish immunological memory, which can persist for long periods of time even after a tumor is cleared. Consistent with other tumors [24], vaccines have demonstrated limited efficacy in patients with advanced recurrent disease; however, some results are promising and provide the basis for further optimization. Various phase I studies have shown the induction of antigen-specific T-cell and humoral immunity and improved survival in advanced OC patients who were vaccinated with different vaccines including peptide, protein, viral, bacterial, tumor and dendritic cell (DC)-based or anti-idiotypic vaccines. Some of those vaccines have targeted a single antigen such as a CA-125, MUC-1, Her2, p53 and NY-ESO-1 (reviewed in [25]), while others used multiple peptides from various antigens or a whole tumor antigen approach created with tumor cells, autologous tumor lysate or tumor-derived RNA [26–28]. Recent advances in immunotherapy suggest that 'personalized', private antigens (that arise from

*Correspondence to: Dr Lana E. Kandalaft, Center of Experimental Therapeutics, Ludwig Center for Cancer Research at the University of Lausanne, Department of Oncology, University Hospital of Lausanne, Rue du Bugnon 46-BH09-709, Case Postale 5, 1011 Lausanne, Switzerland. E-mail: lana.kandalaft@chuv.ch

mutations) could also be expected to induce rapid and strong secondary immune responses (reviewed in [29]). Prolongation of progression-free and overall survival rates were demonstrated in various studies where patients were vaccinated against single antigens [30, 31]. Objective responses were also reported in recurrent advanced OC patients vaccinated with a DC-based whole tumor vaccine [32, 33], autologous tumor cells infected with Newcastle disease virus [34] or viral oncolysate vaccine generated from OC cell lines infected with influenza-A virus [35, 36].

adoptive T-cell therapy

Another cell-based approach is adoptive T-cell therapy which has shown promise in a variety of cancers [37]. This approach utilizes autologous or allogeneic lymphocytes to induce cancer regression. Lymphocytes are isolated through leukapheresis, cultured, activated and expanded *ex vivo* before reinfusion into cancer patients following lymphodepleting chemotherapy, which prepares the host by creating space, eliminating immunosuppressive cells and inducing cytokines which support the *in vivo* survival and expansion of transferred T cells [38].

Adoptive T-cell therapy was used in advanced-stage OC patients with no evidence of disease following surgical resection and cisplatin chemotherapy in a non-randomized phase I trial, where consecutive patients received autologous tumor-infiltrating lymphocytes (TILs) with chemotherapy, while others received chemotherapy alone. The 3-year overall survival rates were shown to be 100% and 67.5%, respectively [39]. Additionally, TILs were shown to induce objective cancer regressions when administered in patients with advanced or recurrent platinum-resistant ovarian disease [39]. Recently, Svane and colleagues opened a new clinical study where TILs will be administered in recurrent metastatic OC patients post-lymphodepletion and followed by interleukin 2 (IL-2) administration (NCT02482090). We have also recently reported a phase I study of a combinatorial approach encompassing DC-based autologous whole tumor vaccination followed by the adoptive transfer of autologous vaccine-primed CD3/CD28-co-stimulated lymphocytes [32], demonstrating that clinical benefit was correlated with vaccine-induced restoration of anti-tumor immunity.

The adoptive T-cell therapy approach is however limited, by the availability of tumor-specific lymphocytes. It can become more effective and powerful by genetically engineering patients' lymphocytes endowing them with more tumor specificity. Genes used to modify T cells include those encoding T-cell receptors (TCRs) and chimeric antigen receptors (CARs). TCR-based engineering represents a compelling strategy for OC therapy as TCRs that recognize HLA-A2 restricted epitopes from known OC antigens such as NY-ESO-1, p53 and others. [40]. Engineering T cells with redirected specificity to recognize antigens in an MHC-unrestricted fashion can be achieved through the use of CARs. In this case, T cells are transduced with fusion genes encoding an extracellular domain that specifically binds to tumor epitopes through a single-chain variable fragment (scFv) antibody, linked to intracellular signaling modules that mediate T-cell activation [41]. Some of the generated CARs, which have been investigated and are relevant to OC, are folate receptor-α (FRα), human epidermal growth factor receptor 2 (Her-2) [42] and mesothelin [43, 44]. The first study of adoptive transfer of FRα CARs in OC showed no clinical response because of low expression of the transgenic CAR and poor persistence of the transferred T cells [45]. Preliminary data from another ongoing phase I study utilizing mesothelin-specific CAR T cells detected the presence of these T cells in tumor biopsies post-infusion in five patients with recurrent disease whose tumors expressed mesothelin [46]. Clinical studies utilizing T cells redirected through a recombinant TCR against NYESO-1, a cancer testis antigen (NCT01567891) and CAR-transduced T cells redirected against mesothelin (NCT02159716; NCT01583686) are currently ongoing. Most recently, a new phase I study was opened to test activated T cells that have been coated with bi-specific antibodies against the T-cell surface marker cluster of differentiation (CD3) and the tumor surface marker Her-2, combined with low-dose IL-2 and recombinant granulocyte macrophage colony-stimulating factor (GM-CSF), in stage III–IV patients with refractory or recurrent ovarian, fallopian tube or primary peritoneal cancer (NCT02470559).

drug-based immunotherapeutic strategies

immune checkpoint inhibitors

Monoclonal antibodies (MAbs) targeting immune inhibitory checkpoints such as CTLA-4 (binding to CD80/86), PD-1 or the PD ligand 1 (PD-L1) and other inhibitory receptors [47, 48] can control the intensity, duration and quality of T-cell activation and hence directly control the immune response. These antibodies have recently demonstrated remarkable clinical successes [49]. CTLA-4 is an inhibitory co-receptor, which counters signaling through members of the B7 molecules on the surface of antigen-presenting cells, resulting in termination of T-cell activation, cell cycle arrest and T-cell energy. Blocking CTLA-4 has the potential to directly activate $CD4^+$ and $CD8^+$ effector T cells, leading to tumor clearance. Ipilimumab and tremelimumab are two MAbs specific for CTLA-4, which have been effectively taken to the clinic. Ipilimumab is approved for the treatment of metastatic melanoma, with an improvement in overall survival from 6.4 to 10 months. Hodi et al. [50] reported on 11 OC patients previously vaccinated with GM-CSF modified, irradiated autologous tumor cells who were treated with ipilumimab. One patient demonstrated a durable objective response with multiple remissions over 4 years while receiving multiple infusions of CTLA-4 antibody. Currently, a phase II clinical trial of ipilimumab in relapsed platinum-sensitive OC with measurable disease is ongoing (NCT01611558).

PD-1 is an Ig superfamily surface molecule that upon binding to PD-L1 and PD-L2 ligands promotes suppression in self-reacting T cells through a mechanism that is distinct from CTLA-4 [51]. Elimination of the PD-1 pathway can result in the breakdown of immune tolerance against tumors. Preclinical studies revealed that antibodies blocking PD-L1 or PD-1 potently mobilize immunity in tumors with expression of PD-L1 [52]. Reflecting this, the PD-1 antagonists pembrolizumab and nivolumab are approved for metastatic melanoma, and nivolumab is approved for non-small-cell lung cancer. Recently, results from a phase I trial of nivolumab, in patients with platinum-resistant OC, revealed that the best overall response was 15%, including two

patients with durable complete responses, while the overall disease control rate was 45%. The median progression-free survival time was 3.5 months, and the median overall survival time was 20.0 months [53]. Another phase Ib study was conducted testing pembrolizumab in 26 heavily treated PD-L1+ OC patients [54]. One patient achieved complete response and two patients experienced partial response and six patients had stable disease. Another study used the PD-L1 antagonist avelumab in a phase 1b study of 75 patients with platinum-resistant or chemotherapy-refractory OC regardless of PD-L1 expression [55]. Of the 75 patients enrolled, 67 were evaluable for response, with an ORR of 10.7%, and a DCR of 54.7%, with no CRs, 8 PRs and 33 patients with SD. A phase I study of another PD-L1 antagonist, BMS-936559, revealed one objective response in 17 OC patients [56]. The dual blockade of PD-1 and CTLA-4 has significantly increased objective responses in melanoma and are currently being tested in multiple tumors, including ovarian (NCT01772004) [57].

cytokines

T-cell-activating interleukins. IL-2 is a factor inducing T-cell growth and activation. Subcutaneous IL-2 has been combined at low doses with retinoic acid in the adjuvant setting in an OC trial achieving a 5-year survival rate of 38% [58]. Intraperitoneal IL-2 has also been used as monotherapy in patients with platinum-resistant OC [59], resulting in a ~17% complete pathologic response rate. IL-18 is also an immunostimulatory agent, which has been used in a phase I study, combined with pegylated liposomal doxorubicin (PLD) in patients with recurrent OC. Ten of 16 subjects (63%) completed the study and 5 (31%) progressed on treatment, while 6% had a partial response, and 38% had stable disease [60]. IL-18 could also be combined with vaccines and adoptive T-cell therapy.

interferons. Interferons, originally identified as anti-viral proteins, were also found to block malignant T-cell proliferation. Intraperitoneal interferon-α demonstrated modest efficacy in patients with OC [61, 62] even when combined with cisplatin [63]. Interferon-α at low immune-modulating doses improved the immune and clinical efficacy of denileukin diftitox, an engineered protein combining IL-2 and Diphtheria toxin, which is used to deplete regulatory T cells, in two of three OC patients with manageable toxicities [64]. Gene therapy with adenoviruses engineered to express interferon-β delivered intrapleurally was also used in two OC patients, achieving a complete response in one patient with malignant pleural effusion and distant metastases [65]. Finally, intraperitoneal administration of interferon-γ in OC patients plus front-line chemotherapy improved survival [66].

chemotherapy and RT. Interestingly, standard chemotherapeutics used in OC have demonstrated immunomodulatory properties. For instance, treatment with paclitaxel in advanced OC was shown to up-regulate cytotoxic T-cell function, which was attributed to paclitaxel-induced tumor apoptosis and the release of tumor antigens. Platinum-based therapies have also shown to enhance the immunostimulatory potential of DCs and decrease the immunosuppressive capacity of tumor cells through a STAT6-mediated pathway [67].

PLD has also been shown to synergize with pleomorphic immunomodulatory drugs like IL-18 [68], as well as vaccines and adoptive T-cell therapy. PLD was successfully combined with a Toll-like receptor 8 (TLR8) agonist (Motolimod/VTX-2337) in a humanized mouse model [69] demonstrating potent synergy, prompting translation into a phase I trial in advanced, platinum-resistant OC patients (NCT01294293, $n = 13$) where the combination proved safe, well tolerated and superior to historic data obtained with PLD monotherapy. This is presently tested through a randomized placebo-controlled phase II trial comparing PLD versus PLD + VTX-2337 (GOG-3003, NCT01666444). Other agents include 5-fluorouracil, which can increase tumor cell sensitivity to tumor-specific cytotoxic T cells [70].

radiotherapy. Recent objective clinical responses have been achieved by combining RT and immunotherapy in metastatic cancer patients. RT is able to induce an immune-mediated abscopal effect, whereby RT can cause tumor regression outside of the radiation field. The abscopal effect is mediated by the increased release of immunostimulatory cytokines such as IFN-β and TNFα and increased priming of antigen-specific DCs and by stimulation of systemic adaptive (DC and CTL-dependent) immunity against the tumor [71].

The combination of subcutaneous GM-CSF with local RT was tested in patients with metastatic solid tumors [72] and as a result, an abscopal response was detected in 30% of the patients. Fractionated RT given as neoadjuvant was combined with intratumoral injection of DCs in sarcoma patients, and showed remarkable progression-free survival results [73]. Similar results were seen in glioblastoma patients with a combination approach of DC vaccine, radio- and chemotherapy [74]. The combination of RT with ipilimumab has also been tested in a phase I/II trial in patients with metastatic prostate cancer [75]. Randomized phase III trials are underway to further test the possible benefits of this combination.

conclusions

Immunotherapy is emerging as a highly promising approach to OC therapy. Vaccines, immune checkpoint blockade, cytokines and adoptive T-cell therapy have been associated with clinical activity in a subset of these patients. Current challenges include the testing of rational immunomodulatory combinations with promising activity.

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disclosure

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