Immunotherapy for ovarian cancer: recent advances and perspectives

Emese Zsiros[a], *Janos Tanyi*[a], *Klara Balint*[a], *and Lana E. Kandalaft*[a,b]

Purpose of review
Epithelial ovarian cancer is the most frequent cause of gynecologic cancer-related mortality in women, and prognosis for patients with recurrent or metastatic disease is extremely poor. Therefore, there is an enormous unmet need for the development of novel therapies in this indication. Although surgery and chemotherapy can improve survival rates, it is necessary to integrate alternative strategies, such as immunotherapy to improve the outcomes for patients with advanced ovarian cancer.

Recent findings
We will discuss the rationale of immunotherapy and some of the mechanisms of immunogenicity in ovarian cancer. We will highlight current results with cancer vaccines, adoptive T-cell therapy and immunomodulatory agents and will summarize the immune effects of selected chemotherapeutic agents, radiotherapy and recent results with combinatorial approaches in this disease setting. We will also discuss recent and potential future therapeutic interventions that might circumvent tumor-mediated immunosuppression.

Summary
Dramatic increase in the number of immunotherapy clinical trials was seen in the past decade with promising results in enhancing antitumor immune response and cancer vaccine efficacy. The future challenge for immunotherapy against ovarian cancer is to use a combinatorial approach to test rational, potentially synergistic immunotherapy combinations that can induce efficient antitumor immunity and prolong patients' survival.

Keywords
immunomodulation, immunotherapy, ovarian cancer

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most common cause of gynecological cancer-associated death among women, with approximately 239 000 new cases to be diagnosed in the world in 2014 [1]. Cytoreductive surgery and platinum-based chemotherapy has remained the mainstay of ovarian cancer treatment and as the disease is discovered at an advanced stage, the prognosis is poor with a 5-year survival rate of 38%. There is a vital need for alternative treatments to increase the response rate and survival [2]. Recent scientific evidence demonstrated that EOC is an immunogenic tumor that can be recognized by the host immune system [3]. Spontaneous antitumor immune response of tumor-reactive T-cells and antibodies can be detected in peripheral blood, tumors and ascites of EOC patients with advanced disease [4,5]. These tumor-reactive T-cells are oligoclonal, recognize autologous tumor-associated antigens (TAAs) *in vitro* and exhibit tumor-specific cytolytic activity *ex vivo* [6]. The frequency of serological responses to these antigens varies according to tumor type, stage or grade [7]. Our knowledge of TAAs expressed by EOC is still limited; some of the best-studied antigens in ovarian cancer patients are New York-esophageal-1 (NY-ESO-1), p53, human epidermal growth factor receptor 2 (Her2)/neu, survivin, folate receptor-α, sperm surface protein Sp17, WT1, MUC1, melanoma associated antigen-3 (MAGE3) and human telomerase reverse transcriptase (hTERT)

[a]Ovarian Cancer Research Center, Smilow Translational Research Center, Perelman School of Medicine of University of Pennsylvania Philadelphia, Pennsylvania, USA and [b]Department of Oncology, Ludwig Cancer Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Correspondence to Lana E. Kandalaft, PharmD, PhD, MTR, Department of Oncology, Ludwig Cancer Center, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. Tel: +41 (0)21 314 78 23; e-mail: lknd@mail.med.upenn.edu, lana.kandalaft@chuv.ch

Curr Opin Oncol 2014, 26:492–500
DOI:10.1097/CCO.0000000000000111

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KEY POINTS

- Ovarian cancer has been validated as a target for immunotherapy.
- Current clinical trials of cancer vaccine, adoptive T-cell transfer or immunomodulatory agents demonstrated that antitumor immunity can be augmented and can improve overall survival.
- New combinatorial approaches comprising of immunotherapy, chemotherapy and radiotherapy need to be tested to enhance therapeutic efficacy.

[8]. Most of these mutations detected in EOC are somatic, they are rarely shared among different tumors and exhibit an extreme degree of heterogeneity with an average of 60 private, nonsynonymous mutations per tumor in ovarian cancer [9], representing a major challenge for the development of a 'one-glove-fits-all' type of immunotherapy targeting all these mutations.

Despite the expression of TAAs by ovarian cancer, spontaneous antitumor immune response has only been demonstrated in approximately 55% of patients with ovarian cancer in the form of intraepithelial tumor-infiltrating lymphocytes (TILs) [10]. Coukos *et al.* reported that patients whose tumors had TILs experienced longer progression-free and overall survival [3,11–13]. On the contrary, immune evasion mechanisms in this patient population correlated with poor survival, such as $CD4^+CD25^+FoxP3^+$ T regulatory (Treg) cells [14,15], programmed death ligand 1 (PD-L1 or B7-H1), a ligand for the immunosuppressive T-cell receptor programmed death 1 [16] and endothelin B receptor, which suppresses T-cell-endothelial adhesive interactions and T-cell homing to tumor [17,18]. Finally, a recent study demonstrated a strong correlation between low-immune gene signature expression and the development of high-risk tumors [19].

The association of TILs with prolonged survival, as well as the association of immune escape mechanisms with poor survival, suggests that ovarian cancer patients could respond to the same immunotherapy approaches, such as interleukin-2, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) or programmed death-1 antibodies or adoptive transfer of ex-vivo expanded TIL, similarly to patients with other immunogenic tumors, such as melanoma [20]. In this review, we will discuss the mechanisms of immunogenicity in ovarian cancer, will highlight current results with cancer vaccines, adoptive T-cell therapy and immunomodulatory agents and will summarize the immune effects of selected chemotherapeutic agents, radiotherapy and recent results with combinatorial approaches. We will also discuss recent and potential future therapeutic interventions that might circumvent tumor-mediated immunosuppression.

RATIONALE FOR IMMUNOMODULATORY AGENTS, OPPORTUNITIES AND CLINICAL RESULTS TO DATE

Harnessing the immune system to treat cancer is the major goal of immunotherapy. Although the identification of several tumor-specific antigens in ovarian cancer has provided the foundation for designing successful immunotherapies, it still has to overcome the immune escape of the tumor or cancer immunoediting. The mechanisms for immunomodulation (therapeutic intervention aimed at modifying the body's immune response) in ovarian cancer include activation of professional antigen-presenting cells (APCs) by engaging costimulatory receptors (such as CD40), activation of effector T lymphocytes by immunostimulatory monoclonal antibodies (mAb) and finally depletion of Treg or immunosuppressive machineries (Fig. 1).

DENDRITIC CELL ACTIVATION

The initiation of an adaptive immune response requires the recognition of the antigen presented on a primary major histocompatibility complex (MHC) II on the surface of APCs by the T-cell antigen receptor, TCR (primary signal). Subsequently, secondary signals' costimulation with CD40 ligand (CD40L) expressed by activated T-cells engaging CD40 expressed by B cells and APCs are necessary for the secretion of cytokines (interleukin-1, interleukin-6, interleukin-8,interleukin-12, tumor necrosis factor-α and macrophage inflammatory protein-1α) to further enhance, modify and skew the responding $CD4^+$to $CD8^+$effector cells [21▪▪].

CD40-CD40L interactions facilitate dendritic cells to increase expression of CD80 and CD86 and thereby activate T-cells. CD40 antibody showed remarkable therapeutic activity in B-cell lymphomas with 80–100% of mice cured. CD40L antibody treatment was also found to inhibit tumor cell growth in an ovarian carcinoma cell line and freshly obtained ovarian carcinoma cells [22]. Several clinical CD40 antibodies, such as dacetuzumab and lucatumumab, have demonstrated long-term complete remissions in patients with advanced squamous cell cancer [23▪] and clinical benefit in patients with melanoma [24].

The effect of CD40 antibodies has been tested in combination with other cancer immunotherapies, in particular interleukin-2 [25]. A fully human mAb

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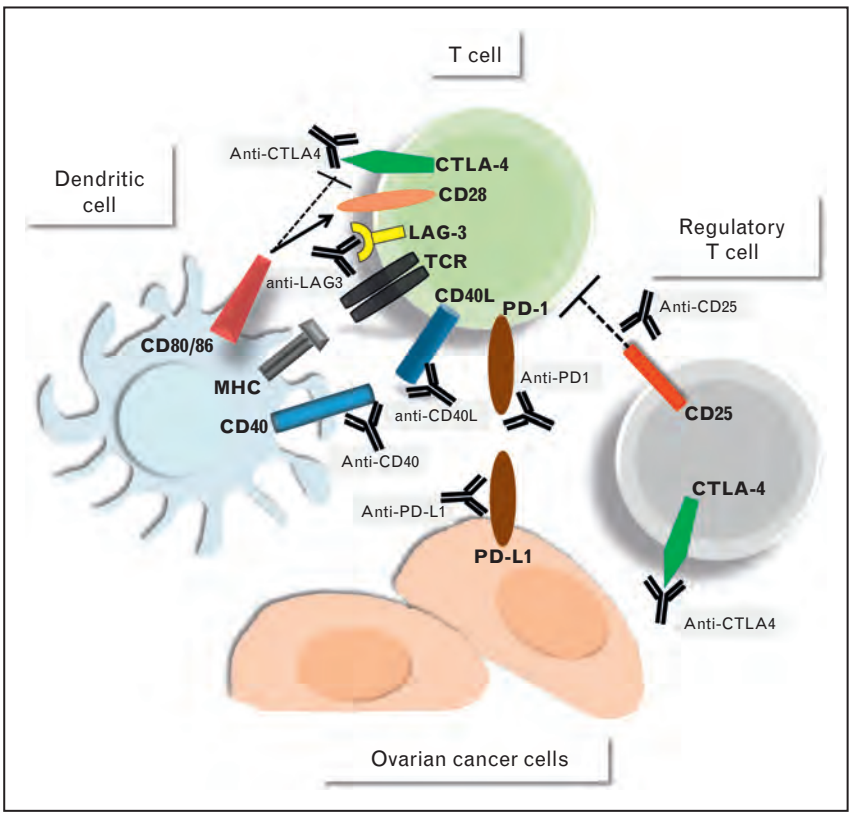

FIGURE 1. Opportunities of immune modulation in ovarian cancer. CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-L1, programmed death ligand 1; PD1, programmed death 1.

(CP-870,893)-recognizing CD40 has also been used in pancreatic cancer in combination with gemcitabine and induced major clinical remission [22]. Agonistic CD40 antibody was used in combination with toll-like receptor-3 (TLR3) agonist and demonstrated the transformation of dendritic cells from an immunosuppressive to an immunostimulatory cell type in a mouse model [26]; however, none of these therapies have been tested in ovarian carcinoma. These combinations merit further testing in patients with ovarian cancer.

Other dendritic cell activation mechanisms involve controlled pore glass (CpG) oligonucleotides. The immune system recognizes these oligonucleotides through TLR9 receptors that activate B-lymphocytes and dendritic cells. Intratumoral injection of CpG after radiation therapy promotes systemic lymphoma eradication in mice [27], with interesting results in humans [28]. This type of treatment is practical, well tolerated, and repeatable and warrants further investigation in ovarian cancer.

EFFECTOR T-CELL ACTIVATION

T-cell activation requires a primary signal through TCR and cognate antigen complex with MHC and a secondary signal, such as costimulatory CD28 and inducible T-cell costimulator (ICOS). This activation is regulated by inhibitory receptors, such as CTLA-4 and programmed death-1. New therapies aimed at overcoming these mechanisms of peripheral tolerance by blocking the inhibitory checkpoints CTLA-4-CD80/86, programmed death-1, PD-L1, T-cell immunoglobulin-mucin-3-galectin-9 (TIM-3-GAL9) and lymphocyte-activation gene 3 (LAG3)-MHC-II with mAb to sustain the activation and proliferation of tumor-specific T-cells and to prevent energy or exhaustion resulting in an effective tumor-specific immune response [29▪▪]. Additional check-point inhibitors include transforming growth factor beta (TGFβ) and interleukin-10 [30].

The majority of CTLA-4 blockade (ipilimumab) clinical data come from studies in patients with melanoma [31,32]. In ovarian cancer, Hodi *et al.* [33] reported that one patient vaccinated with granulocyte-macrophage colony-stimulating factor modified irradiated autologous tumor cells and treated with ipilimumab demonstrated an objective response with durable remission for 4 years while receiving multiple infusions of CTLA-4 antibody. Tumor regression correlated with the $CD8^+$/Treg ratio, suggesting that Treg depletion may provide a highly effective form of treatment when given in combination with the tumor vaccine and CTLA-4

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antibody [33]. Future studies will help answer the role of anti–CTLA-4 therapy in ovarian cancer. A new phase II clinical trial is being conducted to evaluate ipilimumab as monotherapy in ovarian cancer patients in the United States of America (NCT01611558).

Programmed death-1 is an immunoglobulin superfamily surface molecule that upon binding to PD-L1 and PD-L2 promotes apoptosis in self-reacting T-cells through a mechanism that is distinct from CTLA-4 [34]. Elimination of the programmed death-1 pathway can result in the breakdown of immune tolerance against tumors. In preclinical studies, antibodies blocking PD-L1 or programmed death-1 profoundly enhanced the efficacy of immunotherapy in tumors with constitutive expression of PD-L1, including ovarian cancer. A phase I study using programmed death-1 blocking antibody (CT-011) demonstrated a 33% clinical benefit, including one patient with complete remission [35].

Dual blockade of programmed death-1 and CTLA-4 resulted in reversal of $CD8^+$TIL dysfunction and led to tumor rejection in two-thirds of an ovarian cancer mouse model [36,37]. The potential of this combination has recently been highlighted in a phase I-II trial of ipilimumab and nivolumab (programmed death-1 antibody) in melanoma patients [38▪], however yet to be explored in patients with ovarian cancer. Currently, a phase I trial is being conducted to investigate the safety and tolerability of anti-PD-L1 antibody as monotherapy in patients with metastatic or advanced solid tumors, including ovarian cancer patients (NCT01772004) [39].

Dual programmed death-1 and LAG-3 blockade has a synergistic effect on tumor clearance, and thus could be used as one of the future combinatorial immunotherapeutic approaches [40]. Dual blockade of these two molecules during T-cell priming efficiently augmented proliferation and cytokine production by NY-ESO-1-specific $CD8^+$ T-cells in ovarian cancer patients [41]. A phase I trial is currently investigating the combination of anti-LAG-3 (BMS-986016) and programmed death-1 antibodies (BMS-936558) in melanoma and advanced solid tumors; however, its effect on ovarian cancer patients has not been tested.

T REGULATORY CELL DEPLETION

Tregs are potent immunosuppressive cells that promote progression of cancer through their ability to limit antitumor immunity and enhance angiogenesis. Several Treg-depleting strategies have been frequently used in clinical settings, such as metronomic low-dose oral (50 mg twice daily) or intravenous cyclophosphamide [42]. Cyclophosphamide has been successfully combined with different types of cancer vaccines [43,44]. In a phase II trial, p53-synthetic long peptide vaccine was combined with low-dose cyclophosphamide and found to induce higher p53-specific responses compared with p53-synthetic long peptide monotherapy and produced a clinical response in 20% of patients [45].

Other approaches for Treg depletion include targeting the interleukin-2 receptor alpha chain, also known as CD25. Preclinical models showed that anti-CD25 monoclonal antibody treatment before vaccination led to complete tumor rejection and establishment of long-lasting tumor immunity with long-lasting $CD4^+CD25^+$Treg cells reduction [46]. Daclizumab, the Food and Drug Administration-approved, cell depleting, humanized immunoglobulin G1 (IgG1)-kappa mAb that binds specifically to CD25, has been well tolerated in patients, and demonstrated durable Treg suppression when in combination with hTERT peptide vaccine in breast cancer patients [47]. It is currently being evaluated in clinical trials for a variety of cancers, including ovarian [48].

ROLE OF NONIMMUNOTHERAPEUTICS IN IMMUNOMODULATION

Immunomodulatory effects on cytokine and cell-mediated responses can be induced also by non-immunotherapeutics, such as standard chemotherapy and radiotherapy.

STANDARD CHEMOTHERAPY

Chemotherapy is generally thought to act through selective killing of tumor cells or by irreversibly arresting their growth. Accumulating evidence indicates that several chemotherapeutics are more efficacious in immunocompetent versus immunodeficient hosts [49] and in fact have important 'off-target' immunologic effects to play.

Interestingly, treatment with Taxol (paclitaxel), an antimicrotubule agent, in advanced ovarian cancer was shown to upregulate the cytotoxic T-cell function that has been attributed to Taxol-induced tumor apoptosis and the accessibility of tumor antigens. Platinum-based therapies have also been shown to enhance the immunostimulatory potential of dendritic cells and decrease the immunosuppressive capacity of tumor cells through a STAT6-mediated pathway [50]. Moreover, an enhancement of the overall antitumor effect was observed in mice treated with an ovalbumin vaccine combined with cytotoxic doses of carboplatin and paclitaxel when compared with ovalbumin vaccine alone [51▪▪]. More recently, a clinical trial in advanced cervical

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carcinoma demonstrated that depletion of myeloid suppressor cells by a carboplatin/paclitaxel chemotherapy standard regimen enhances the immune response to human papillomavirus vaccine, with sustained human papillomavirus 16-specific T-cell responses throughout several cycles of chemotherapy [52].

PEGylated liposomal doxorubicin (PLD) has also been shown to synergize with pleiomorphic immunomodulatory drugs, such as interleukin-18 [53], as well as vaccines and adoptive T-cell therapy. Facciabene *et al.* [54] have successfully combined PLD with a TLR-8 agonist (VTX-2337) in a humanized mouse model and have translated this to a phase I trial in advanced, platinum-resistant ovarian cancer patients (NCT01294293, $n = 13$) in which the combination proved superior to historic data obtained with PLD monotherapy. This is at present tested through a randomized placebo-controlled, phase II trial comparing Doxil versus Doxil + VTX-2337 [Gynecological Oncology Group (GOG)-3003, NCT01666444]. Other agents include 5-fluorouracil, which rendered human colon carcinoma cells more sensitive to lysis by tumor-specific cytotoxic T-cells [55]. Bevacizumab, which is a humanized monoclonal antibody that neutralizes human vascular endothelial growth factor , also has a role in immunomodulation as it restores dendritic cell function and enhances antitumor immune responses and the efficacy of tumor vaccines.

Understanding the immunological events occurring in both animal models and patients undergoing chemotherapy should guide decisions about the development of appropriate combinations and scheduling for the integration of chemotherapy with immunotherapy, which can certainly improve therapeutic management of this disease.

RADIOTHERAPY

Radiotherapy is perceived as an immunosuppressive modality; however, recent data from multiple cancer models have provided plentiful evidence that some of the effects of ionizing radiation are recognized as powerful adjuvant to systemic antitumor immunity. Radiotherapy is able to induce an immune-mediated abscopal effect whereby the radiation causes indirect antitumor effects in non-treated areas, destroying tumors outside the radiation field. The abscopal effect is mediated by the increased cell surface expression of MHC class I molecules, cytokine release of interferon-β and tumor necrosis factor α and increased priming of antigen-specific dendritic cells and by stimulation of systemic innate (natural killer cell-mediated) and adaptive (dendritic cell and cytotoxic T lymphocyte -mediated) immunity against the tumor [56].

In preclinical models, promising results have been obtained by combining radiotherapy with targeted interventions, such as anti-CTLA-4, dendritic cell vaccines and adoptive T-cell therapy. First, the combination of subcutaneous granulocyte-macrophage colony-stimulating factor with local radiotherapy was tested in patients with metastatic solid tumors [57], and as a result, an abscopal response was detected in 30% of the patients. Fractionated radiotherapy given as neoadjuvant was combined with dendritic cell vaccine in sarcoma patients and showed remarkable progression-free survival results [58]. Similar results were seen in glioblastoma patients with a combination approach of dendritic cell vaccine, radiotherapy and chemotherapy [59]. The combination of radiotherapy with ipilimumab has also been tested in a phase I/II trial in patients with metastatic prostate cancer [60]. Randomized phase III trials are underway to further test the possible benefits of this combination. The optimal radiation regimens (doses and fractionations) to be used for immunomodulation remain to be defined [61]. In ovarian cancer, only radioactively labelled antibody therapies, such as the radionuclide therapy with (90)Y- or (177)Lu-CC49 [62], have been tested so far. The combination of radiation therapy and one or more immune-based modalities should be a promising synergistic approach to providing long-term survival with minimal toxicity.

RATIONALE FOR CELLULAR-BASED THERAPIES

Cell-based therapy is founded on the facts that cells can perform complex biological functions and therapeutic tasks, can have exquisite sensitivity and specificity and can be engineered to increase efficacy [63▪]. (Different approaches are depicted in Fig. 2.)

VACCINES

Consistent with experience in other immunogenic tumors [64], vaccines have shown limited efficacy as monotherapy in patients with advanced recurrent disease but the results are notable and provide basis for further optimization. In a retrospective review of patients treated in the adjuvant setting after secondary complete response, Sabbatini *et al.* [65] demonstrated that patients vaccinated with monovalent or heptavalent vaccines against carbohydrate epitopes experienced significantly longer time to progression and higher progression-free survival rates relative to controls treated with alternative consolidation therapies. Various phase I studies in which advanced ovarian cancer patients were vaccinated with different vaccines including antiidiotype ACA-125 (antiidiotypic cancer antigen-125), an

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analog of cancer antigen-125 (CA-125) [66], carcinoembryonic antigen-mucin-1-triad of costimulatory molecules (CEA-MUC-1-TRICOM) poxviral-based vaccine [67], HER2 vaccine [68] and p53 peptide antigen vaccine [45,69] have resulted in improved survival and the induction of antigen-specific T-cell and humoral immunity. Odunsi *et al.* [70] used recombinant poxviruses (vaccinia and fowlpox)-expressing tumor-associated antigens (NY-ESO-1) as cancer vaccines to induce tumor-specific immune response in 22 EOC patients with advanced disease with a median progression-free survival of 21 months (95% confidence interval, 16–29 months), and median overall survival of 48 months. However, a phase III placebo-controlled maintenance therapy trial of abagovomab (anti-CA-125) 2 mg versus placebo failed to prolong progression-free survival or overall survival [71▪▪]. An alternative approach to vaccines directed toward specific antigens is whole tumor antigen vaccines created using tumor cells, autologous tumor lysate or tumor-derived RNA (Fig. 2) [72–74]. We and others have also shown objective responses in recurrent advanced ovarian cancer patients when vaccinated with dendritic cell-based whole tumor vaccination [75], or viral oncolysate vaccine generated from ovarian cancer cell lines infected with influenza-A virus [76,77] or with autologous tumor cells infected with Newcastle disease virus [78].

A major limitation of cancer vaccines stems from the inability to elicit a rapid and overwhelming T-cell response, which is required to reject established tumors. This problem is magnified in ovarian cancer by the paucity of well characterized rejection antigens and by the significant molecular heterogeneity of the disease [79]. Even when a defined target is available, and vaccination successfully induces an immune response, the long-term benefit can be limited by tumor evolution. In a recent study, one patient experienced complete objective response to NY-ESO-1 peptide vaccine, but later recurred with a NY-ESO-1-negative tumor, proving that single-target immunization can result in immune escape tumor variants following initial response [80]. Recent advances in the clinical application of immunotherapy suggest that immunotherapy with 'personalized' private antigens (that arise from mutations) could also be expected to induce rapid and strong secondary immune responses (reviewed in [81,82]). The current view is that both approaches, targeting public or targeting private antigens, can be beneficial. However, to increase the clinical benefits one should choose a patient population with small volume or no disease with good performance status and should vaccinate in combination with other immunomodulatory agents to maximize the efficacy of the vaccine.

ADOPTIVE T-CELL THERAPY

To be effective, cancer immunotherapy is dependent on the presence of sufficient numbers of anti-tumor lymphocytes with appropriate homing and effector functions that enable them to seek out and destroy cancer cells *in vivo*. The adoptive transfer of ex-vivo expanded, tumor-reactive T-cells holds the

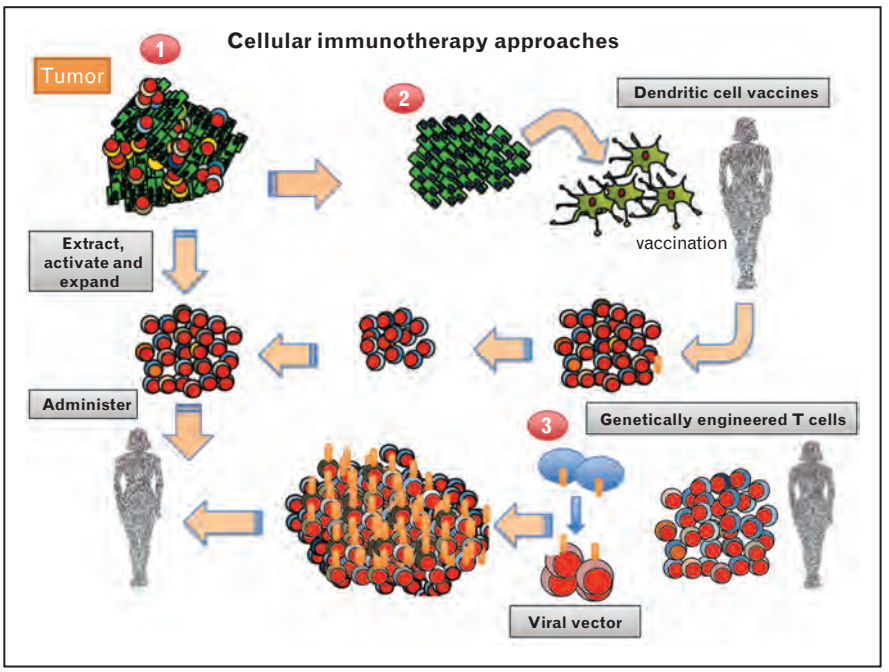

FIGURE 2. Immunotherapeutic approaches for cellular therapies. 1, tumor infiltrating T-cells; 2, dendritic cell vaccines; 3, genetically engineered T-cells.

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potential of achieving this for the treatment of established tumors [82].

In an early pilot T-cell transfer trial in which autologous tumor-infiltrating lymphocytes were administered after surgical resection and cisplatin chemotherapy, the disease-free survival and overall survival was found to be prolonged in ovarian cancer patients (Fig. 2) [83]. In another study, administration of TILs (alone or in combination with chemotherapy) was shown to induce objective cancer regressions [84]. Although TILs represent the candidate tumor-reactive cell population for adoptive immunotherapy, alternative approaches have been employed to generate large numbers of tumor-reactive $CD8^+$ and $CD4^+$ T-cells against ovarian cancer. Killing of ovarian cancer cells can be achieved by retargeting of T lymphocytes using F (Ab')2 fragments of a bispecific monoclonal antibody (OC/TR), directed to the CD3 molecule on T lymphocytes and to the folate receptor on ovarian carcinoma cells [85]. Intraperitoneal infusions of activated autologous OC/TR-retargeted peripheral blood T-cells with recombinant interleukin-2 induced objective tumor regression in three out of 19 patients [86], with detectable OC/TR-directed lymphocytes in the peritoneal cavity of treated patients after infusion.

We have recently reported a phase I study of a combinatorial approach encompassing dendritic cell-based autologous whole tumor vaccination and antiangiogenesis therapy, followed by the adoptive transfer of autologous vaccine-primed CD3/CD28-costimulated lymphocytes [75]. Three patients with residual measurable disease who have been previously vaccinated with a whole tumor lysate vaccine received outpatient lymphodepletion and adoptive T-cell transfer, which was well tolerated and resulted in a durable reduction of circulating regulatory T-cells and in increased $CD8^+$ lymphocyte counts. The vaccine-induced restoration of antitumor immunity was achieved in two individuals, who also demonstrated clinical benefits, including one complete response.

Adoptive T-cell therapy can become more effective and powerful by genetically engineering patients' lymphocytes, endowing them with more tumor specificity (Fig. 2). Genes used to modify T-cells include those encoding TCRs and chimeric antigen receptors (CARs). TCR-based engineering represents a compelling strategy for ovarian cancer therapy as TCRs that recognize human leukocyte antigen-A2 restricted epitopes from known ovarian cancer antigens, such as NY-ESO-1, p53 and others [87].

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 antibody, linked to intracellular signaling modules that mediate T-cell activation [88]. Some of the generated CARs, which have been investigated *in vitro* and *in vivo* and are relevant to ovarian cancer, are folate receptor-alpha, MUC-16, HER-2 [89,90] and mesothelin [91]. One study of adoptive transfer of CARs in ovarian cancer demonstrated safety but showed no clinical response because of low expression of the transgenic CAR and poor persistence of the transferred T-cells [85]. Improved success of CARs in the clinic requires a panel of bioengineered T-cells with different specificities, custom-made for each individual, which is technically and economically challenging.

CONCLUSION

In the past decades, we have seen a dramatic increase in the number of immunotherapy clinical trials to enhance antitumor immune response and cancer vaccine efficacy. Sufficient evidence indicates that ovarian cancers are indeed immunogenic tumors and excellent candidates for immunotherapy. Both passive and active immunotherapeutic modalities have shown potential clinical benefit in at least a subset of these patients. Future challenge for immunotherapy against ovarian cancer is to use a combinatorial approach to test rational immunomodulatory combinations that can induce efficient antitumor immunity that may achieve prolonged patient survival. The other major challenge for cellular immunotherapeutics is the development of manufacturing technologies that are less costly and do not require a very complex infrastructure so therapy can be accessible by the masses.

Acknowledgements

This study was supported by National Institution of Health R01 grant FD003520–02, the Ovarian Cancer Immunotherapy Initiative and the Marcus Foundation.

Conflicts of interest

The authors declare no conflict of interest.

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