Advanced clinical trials of dendritic cell vaccines in ovarian cancer

Quan Guo ,[1] Qing Yang,[1] Jun Li,[1] Guipeng Liu,[1] Igor Nikoulin,[2] Steve Jia[3]

[1]Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang, China
[2]Research and Development, IriSys, LLC, San Diego, California, USA
[3]RD Center, Pacificbio Inc, Irvine, California, USA

Correspondence to
Dr Quan Guo, Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang 110004, China; guoq@sj-hospital.org

Accepted 23 June 2020
Published Online First 27 July 2020

ABSTRACT

Epithelial ovarian cancer (EOC) is the most common and leading cause of death for gynecologic cancer in the western world. Current standard treatments with limited selection of chemotherapies cannot meet patients' urgent needs. Immunotherapies have recently demonstrated clinical benefits in a variety of solid tumors and may offer a promising frontier for treating EOC. Dendritic cells (DCs) are key coordinators of the innate and adaptive immune system in induction of antitumor immunity. DC-based vaccinations showed clinical benefits and encouraging safety profiles in a few phase II clinical trials for patients with EOC and currently are in a phase III double-blind, randomized, placebo-controlled clinical trial. In this review, we have searched Pubmed and Clinicaltrials. gov databases for past and current phase II or phase III clinical trials with focus on EOC and DC vaccines. Outcomes and implications of the completed and ongoing trials are discussed.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most frequent and deadly gynecological cancers with 22 530 estimated new cases and 13 980 deaths in 2019 in the USA.[1] Current standard treatments include surgery and chemotherapy and result in up to 70% of relapse rate and a median progression-free survival (PFS) of 12–18 months.[2–4] Based on improved clinical outcomes, US Food and Drug Administration (FDA) has approved four drugs: one antiangiogenesis inhibitor (bevacizumab) and three poly-ADP-ribose polymerase inhibitors (PARPi) (niraparib, olaparib and rucaparib).[5] However, prognosis for patients with advanced EOC is still poor and survival rates have improved only modestly.[6]

Clearly, there is a critical need for new treatment options, and immunotherapy is one attractive alternative. Immunotherapy approach aims to prevent local immune suppression and activate human immune system capable of killing tumor cells. Multiple immunotherapeutic modalities are currently developed and tested in clinical trials. Therapeutic antibodies, immune checkpoint blockade, chimeric antigen receptor-modified T (CAR-T) cells and cancer vaccines have showed preclinical success and entered clinical studies.[7] Most of these therapies are still in early-phase testing for EOC, but the initial data in ovarian cancer and successful use in other types of cancers suggest that some of these approaches may ultimately prove useful.[8]

A few monoclonal antibodies against tumor antigens have been explored in EOC, but randomized phase II studies failed to demonstrate significant clinical benefits.[9 10] Check point blockade agents, antiprogrammed death 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors, nivolumab, pembrolizumab, avelumab and atezolizumab, have been approved FDA since 2014 for many types of cancers.[11] Data from advanced clinical trials using check point inhibitors showed encouraging results and ongoing phase III clinical trials are evaluating the roles of these inhibitors in combination with chemotherapy in EOC.[12] CAR-T therapy involving infusion of ex vivo activated and expanded tumor-specific T cells has been explored in several hematologic malignancies and currently constitutes early research in ovarian cancer.[8] Although prophylactic vaccines for prevention of infectious diseases have led to major achievements and therapeutic cancer vaccines have shown promising immunological responses, clinical effectiveness of the cancer vaccines is yet to be confirmed for EOC.[13 14]

Dendritic cells (DCs) are the most potent antigen-presenting cell population for priming and activating naïve T cells to target tumors. Tumor antigens such as whole tumor cell lysate or tumor-associated peptides/proteins (P/PA) are pulsed onto DCs ex vivo and subsequently administrated to patients as DC vaccines.[15 16] DC vaccination looked promising after Sipuleucel-T approval in 2010, a DC-based immunotherapy for the treatment of advanced prostate cancer.[17] One phase III trial is currently evaluating the efficacy adjuvant vaccination using RNA-loaded autologous DC vaccine to treat patients with uveal melanoma (NCT01983748) and the other phase III trial is currently evaluating active immunization in adjuvant therapy of patients with stage 3 melanoma with natural DCs pulsed with tumor peptides (NCT02993315).

Thus, DC vaccination might offer unique opportunity for targeting of EOC with minimal side effects and possible improvement in clinical efficacy.

To cite: Guo Q, Yang Q, Li J, *et al*. *J Investig Med* 2020;**68**:1223–1227.

In this review, we describe past and current publications aiming for the phase II and phase III EOC clinical trials using DC vaccines. Pubmed and Clinicaltrials.gov databases are searched and lessons from completed trials and implications from the current trials are discussed.

METHODS

The database of Pubmed was searched with key words grouped in the following two categories: (1) "ovarian cancer", "dendritic cell", trial and (2) "ovarian cancer", trial, vaccine, from May 2012 to February 2020. The database of Clinicaltrials.gov was searched with key words: "ovarian cancer", "phase III", "phase II", "dendritic cell". Only publications and information related to completed and ongoing phase III and phase II trials are included. Publications and information related to withdrawn, suspended, terminated, unknown status, standard chemotherapy trials, and trials without DC vaccines are excluded.

RESULTS

We found 12 qualified phase III/II studies related to DC vaccines in EOC including five completed studies with published results and seven on-going studies. Details of the clinical trials are reviewed.

Tumor cells and tumor-derived P/PA are two major sources of antigens to stimulate the DCs. Preparation of DC-based vaccine involves presentation of the tumor antigens to the DCs. DC vaccines can be subdivided into two categories according to loaded antigens: tumor cell lysate and tumor-derived P/PA.

DC VACCINE WITH WHOLE TUMOR CELL ANTIGEN

One phase III and six phase II ongoing trials indicate that this group of DC vaccines hold potential for more promising clinical outcomes in patients with EOC.

In a pilot clinical trial, oxidized autologous whole-tumor cell lysate was pulsed into DCs obtained from patients as personalized vaccines. The vaccines were injected intranodally in platinum-treated, immunotherapy-naïve patients with recurrent ovarian cancer. The vaccines were administered alone (cohort 1, n=5), in combination with bevacizumab (cohort 2, n=10), or bevacizumab plus low-dose intravenous cyclophosphamide (cohort 3, n=10) until disease progression or vaccine exhaustion. No serious adverse events were observed while significantly prolonged patient survival and T cell responses to tumor antigens were seen. Overall from the 25 patients treated, 2 patients showed partial response and 13 patients experienced stable disease, which persisted for a median of 14 months from enrolment. The 2-year overall survival (OS) rates of the responded patients was 100% and the best results were obtained with the triple combination of DC vaccine plus bevacizumab and cyclophosphamide.[18–20]

More encouraging clinical results were presented in a Plenary Session of the 50th Annual Meeting of Society of Gynecologic Oncology on Women's Cancer.[21] In a randomized, open label, placebo-controlled, multicenter phase II clinical trial SOV02, 64 patients with recurrent EOC received autologous DC vaccine pulsed with tumor cell lysate (DCVAC/OvCa) in combination with platinum-based chemotherapy. Treatment with DCVAC/OvCa was very well tolerated and did not lead to any treatment discontinuation. Median OS was significantly longer of DCVAC/OvCa versus placebo: 35.5 months vs 22.3 months (HR=0.38 p=0.0032) and median PFS was: 11.3 months vs 9.5 months (table 1). Patients received DCVAC/OvCa, decreased the risk of death by 62%. The combination of chemotherapy plus the DC vaccine corresponded to 73% survival at 2 years, compared with 41% survival when chemotherapy was used alone. A multicenter, double-blind, randomized, placebo-controlled, phase III clinical trial, VITALIA, will be initiated (NCT 03905902). In VITALIA trial, 678 patients with EOC will receive DCVAC/OvCa or placebo with platinum-based chemotherapy, with or without use of bevacizumab during the induction stage. In the maintenance stage, patients will continue treatment with the DC vaccine in combination with bevacizumab and PARPi or best supportive care only (table 1).[21] The trial is estimated to have results in 2027.

Six ongoing phase II DC vaccine trials are still in early stages. One trial is double-blind, randomized, placebo-controlled study with a DC vaccine AVOVA-1 (NCT02033616), while remaining five trials are non-placebo-controlled (NPC) studies (table 1). AVOVA-1 is an autologous DCs loaded with autologous tumor cells lysate that will be injected to EOC patients with granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjuvant while autologous monocytes (MC) with GM-CSF as an adjuvant will serve as placebo. The primary endpoint of the trial is OS and PFS will be a secondary endpoint. Trial designs of the five open-label NPC phase II studies are similar in terms of enrolled patients (18–36) and primary/secondary endpoints: immunologic responses and toxicities of adverse events. However, combination therapies for these five DC vaccine trials are different : (1) carboplatin and gemcitabine or carboplatin and paclitaxel followed by DC vaccine (DCVAC/OvCa) (NCT03657966); (2) DC vaccine plus GM-CSF or DC vaccine plus GM-CSF and imiquimod (NCT00799110; (3) DC vaccine plus natural killer cell-like cytotoxic T-lymphocytes (NCT03735589); (4) DC vaccine plus cisplatin and celecoxib or DC vaccine plus cisplatin and interferon alpha-2b (NCT02432378) and (5) DC vaccine only (NCT00703105). Results from the six trials are expected from 2020 to 2023.

DC VACCINE WITH TUMOR-DERIVED P/PA ANTIGEN

Although some clinical benefits and immunologic responses were seen in phase II trials conducted for DC vaccines with P/PA, no ongoing phase II or phase III trials of this group of DC vaccines are found by our search. Thus, the data obtained from completed studies may not be encouraging enough to carry more clinical trials in near future.

Mucin 1 (MUC1) antigen, highly expressed by EOC cells, is a promising target for DC vaccine CVac. A single arm open label phase II trial showed that CVac was well tolerated with some clinical activity (table 2).[22] In an open label randomized placebo-controlled phase IIb trial, CVac was studied as a maintenance therapy for 56 patients with EOC in first (CR1) or second clinical remission (CR2), while standard of care (SOC) served as placebo control. Therapy was safe with 12.5% for grade 3–4 treatment-emergent adverse events (TEAEs). Although median PFS of all patients was

Table 1 Phase II/III clinical trials for patients with EOC by DC vaccines pulsed with whole tumor cell antigens

Study phase and design	Patient number	DC vaccine treatment	Control arm	Primary endpoints	Secondary endpoints	Trial ID/Ref.
Multicenter, double-blind, randomized, placebo-controlled, phase III	678		Stage I: Placebo+carboplatin and gemcitabine or carboplatin and paclitaxel Stage II: Placebo+bevacizumab or PARPi	OS	PFS, ORR, DOR, TEAEs	NCT03905902/[21]
SOV02 : randomized, open-label, parallel-group, multicenter phase II	64	DC pulsed with tumor cell lysate (DCVAC/OvCa)	Carboplatin and gemcitabine	Median OS: 35.5 vs 22.3 months (HR=0.38 p=0.0032)	Median PFS: 11.3 vs 9.5 months	21
Single-arm, open-label, multicenter, phase II	30	DC pulsed with tumor cell lysate (DCVAC/OvCa)	No	PFS	OS, ORR, DOR, AEs,	NCT03657966
Single-arm, open-label, phase II	36	DC pulsed with tumor cell lysate or WT1 and MUC1 peptide	No	ORR	TAEs	NCT00703105
Open label, randomized, parallel assignment, phase II	23	DC pulsed with tumor cell lysate	No	Cellular immunity	TAEs, ORR	NCT00799110
Multicenter, double-blind, randomized, placebo-controlled, phase II	99	DC pulsed with tumor cell lysate (AVOVA-1)	MC+GM-CSF	OS	PFS	NCT02033616
Single-arm, open-label, phase I/IIa	18	Alpha-DC1 vaccine	No	AEs>grade 3, Immunologic responses,	ORR, OS, PFS	NCT03735589
Open label, randomized, parallel assignment, phase II	25	DC vaccine	No	AEs>grade 3, Immunologic response		NCT02432378

AEs, Incidence of adverse events; DC, dendritic cell; DOR, duration of response; EOC, epithelial ovarian cancer; GM-CSF, granulocyte-macrophage colony-stimulating factor; MC, monocytes cell; MUC1, Mucin 1; ORR, objective response rate; OS, Overall survival; PARP, Poly ADP-ribose Polymerase; PFS, progression-free survival; Ref, Reference; TAEs, toxicities of adverse events; TEAEs, treatment emergent adverse events; WT1, Wilms' tumor protein 1.

not significantly longer in the treated group compared with SOC group (13 months vs 9 months, (HR)=0.73, p=0.36,), analysis by remission status showed CR2 patients had longer median PFS in the CVac-treated group than SOC (>13 months vs 5 months; HR=0.32, p=0.04,) and longer median OS(>42 months vs 26 months; HR=0.17, CI 0.02 to 1.4, p=0.07). This result indicated that CVac monotherapy may have improved PFS and OS only for CR2 patients with EOC (table 2).[23]

In a prospective single-arm open-label phase II trial, 56 patients with recurrent EOC were treated by DC vaccines targeted to Wilms' tumor protein 1 (WT1) and MUC1 synthesized peptides. No serious TEAEs were observed, and 71% enrolled patients developed immunologic responses.

Table 2 Phase II clinical trials for patients with EOC with DC vaccines pulsed tumor P/PA antigens

Study phase and design	Patient number	DC vaccine method	Control arm	Primary endpoints	Secondary endpoints	Trial ID/Ref.
Open label, randomized, parallel assignment, phase IIb	56	DC pulsed with MUC1 (CVac)	Placebo	Median PFS: 13 vs 9 months (HR)=0.73, p=0.36) CR1 subgroup: median PFS 13 vs 18 months (HR=1.18; CI 0.52 to 2.71, p=0.69). CR2 subgroup: median PFS: >13 vs 5 months (HR=0.32, p=0.04)	CR2 subgroup: median OS: >42 vs 26 months (HR=0.17; CI 0.02 to 1.4, p=0.07). TEAEs>grade 3: 12.5%	NCT01068509/23
Single-arm, open-label, phase II	28	DC pulsed with MUC1 (CVac)	No	CA125 response or stabilization: 15%	AEs>grade 3: 0	22
Open label, parallel assignment, phase II	21	Arm a: P53 peptides, intravenous Arm b: DC pulsed P53 peptides, SC	No	Immunologic response: Arm a vs Arm b=69% vs 83%	Median PFS: 4.2 vs 8.7 months; Median OS: 40.8 vs 29.6 months: AEs>grade 3: 0, 0 for both	25
Single-arm, open-label, phase II	56	DC pulsed with MUC1, WT-1 peptides, intravenous	No	Immunologic response: 71%. Median OS : 30.4 months	AEs>grade 3: 0	24

AEs, incidence of adverse events; CR1, first clinical remission; CR2, second clinical remission; DC, dendritic cell; EOC, epithelial ovarian cancer; MUC1, Mucin 1; OS, overall survival; PFS, progression-free survival; P/PA, peptide/protein; Ref, Reference; SC, subcutaneous; TEAEs, treatment emergent adverse events; WT1, Wilms' tumor protein 1.

The median OS from recurrent EOC diagnosis was 30.4 months (table 2).[24]

In an open label two-arm phase II trial, a DC vaccine pulsed with p53 peptide plus interleukin-2 (IL-2) was compared with a p53 vaccine using p53 peptide as an antigen admixed with montanide and GM-CSF to inject patients directly. Both vaccination approaches showed comparable clinical benefits with minimal toxicity. Immunologic responses were similar: p53 vaccine versus DC vaccine=69% vs 83%; median PFS (4.2 months vs 8.7 months) and median OS (40.8 months vs 29.6 months) were not different (table 2).[25] This result indicated that DC vaccine pulsed by p53 peptide may not give any clinical advantages over direct injection of p53 peptide as antigen to the patients with EOC.

DISCUSSION

Although immunotherapy has a strong rationale, there is no US FDA approved immunotherapy for patients with EOC yet. Among all categories of immunotherapy, the immune checkpoint blockade inhibitors might be the most probable candidates for FDA approval. JAVELIN Ovarian 200 (NCT02580058), the first randomized phase III trial to evaluate avelumab (PD-L1 inhibitor) monotherapy, as well as its combination with chemotherapy is near completed,[26] and four ongoing phase III trials of atezolizumab (PD-L1 inhibitor) with bevacizumab plus chemotherapy are estimated to be completed in the near future. New approvals may be anticipated if favorable results from these trials can be generated.[12] Combination therapy of phase III trial of pembrolizumab (NCT03740165) and nivolumab (NCT03522246) are in early stages with expected completion in more than 5 years.

The clinical studies of CAR-T cell therapy in EOC are limited. Only two phase I trials of CAR-T treatments targeting folate receptor-α, reported certain levels of immunologic responses.[27] No phase III trials and only four ongoing phase I/ II trials are listed in the Clinicaltrials database.

Early phase I and/or phase II clinical trials of antibody-based therapies other than DC cancer vaccines demonstrated less clinical effect in EOC trials. Neither reported phase III trial results nor ongoing phase III trials for these groups of treatments were found by our search since more profound clinical outcomes may be required before larger advanced clinical trials can be initiated.

As cancer vaccine, DC vaccine may hold the most potential to reach market for patients with EOC. Implications from the DC vaccine clinical trials described in this review are: (1) DC vaccines based on the whole tumor cell antigens loaded into DCs generate stronger immunologic reactions compared with tumor-derived P/PA antigens and thus can lead to better clinical outcomes in the clinical trials; (2) the combination of DC vaccines with other approved therapies (PD-1/PD-L1, PARPi and chemotherapy) may show better therapeutic efficacy without more toxicity; (3) addition of cytokines like GM-CSF, INF and IL-2 as adjuvants to the DC vaccines might improve the antitumor response, but needs further confirmation in future clinical trials; and (4) careful selection of subgroups of patients with EOC may be a critical factor to achieve the best results in future clinical trials. Phase II trial of the DC vaccine CVac showed that only patients in CR2 but not in CR1 stage could benefit from this therapy.[23] For clinical trials using combination therapy of DC vaccine with PD-1/PD-L1 or PARPi, subgroups of patients with different levels of PD-1/PD-L1 or gene mutation status may be enrolled into different arms according to particular combinations of inhibitors to fully take the advantage of approved target-therapy power.[28]

The phase III trial VITALIA seems to be the best designed DC vaccine trial with tumor cell lysate antigen and combination treatments with approved drugs including bevacizumab, PARPi, and chemo agents. This trial is an upscaled and advanced trial based on the encouraging results from the phase II trial SOV02. If the clinical benefits of SOV02 are confirmed in VITALIA trial, the first DC vaccine approval for EOC might be anticipated.

Contributors QG and SJ developed the review concept and structure. All authors reviewed the literature, wrote and edited the manuscript and approved the final version.

Funding This work was supported by a grant from the National Natural Science Foundation of China (No. 81872125).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Quan Guo http://orcid.org/0000-0002-9906-6899

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