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REVIEW

Application of dendritic cell vaccine immunotherapy in gynecologic malignancies

G. V. Zhukova✉, E. M. Frantsiyants, I. V. Kaplieva, T. I. Moiseenko, A. P. Menshenina, A. I. Shikhlyarova, V. A. Bandovkina, E. I. Surikova, E. V. Shalashnaya, Yu. A. Petrova, P. S. Kachesova

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ galya_57@mail.ru

ABSTRACT

The development of antitumor strategies aimed at restoring systemic and local immune regulation is considered one of the most promising directions. Technologies based on dendritic cell vaccines (DCVs), characterized by minimal toxicity and alignment with fundamental immunological mechanisms of antitumor resistance, are of particular interest.

Purpose of the study. Is to evaluate the effectiveness of immunotherapeutic approaches for gynecologic malignancies using DCVs and to outline promising directions for further development.

Materials and methods. A literature search was conducted in the bibliographic registers MEDLINE, ClinicalTrial.gov., eLIBRARY and CyberLeninka, using the search systems PubMed, Google Scholar. The vast majority of the identified sources are indexed in Scopus and Web of Science. The review includes more than 60 publications in Russian and English, over 50 % of which were published within the past five years.

Results. The analysis summarizes data on the clinical outcomes of DCV-based therapy in advanced cervical cancer, endometrial cancer, and ovarian cancer. Reported beneficial effects include temporary disease stabilization, improved overall survival and quality of life in advanced malignancies, enhanced efficacy of subsequent chemotherapy, and occasional cases of partial or complete remission. The review also addresses potential reasons for the limited efficacy of DCVs, as well as possible combinations of this technology with other immunotherapeutic modalities and traditional anticancer treatments. The currently modest therapeutic effectiveness of DCVs in gynecologic cancers may be attributed both to the insufficient maturity of the technology and to inherent mechanisms of tumor immune evasion.

Conclusion. The therapeutic potential of DCVs has not yet been fully realized. Advances in immunotherapy, molecular biology, nanotechnology, and strategies for activating systemic and local antitumor resistance mechanisms provide a foundation for defining future research priorities aimed at improving the efficacy of DCVs as an important component of multimodal treatment for gynecologic malignancies.

Keywords: immunotherapy, dendritic cell vaccines, tumor-specific immune responses, cervical cancer, endometrial cancer, ovarian cancer

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For correspondence: Galina V. Zhukova – Dr. Sc. (Biology), Senior Researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: galya_57@mail.ru
ORCID: https://orcid.org/0000-0001-8832-8219, eLibrary SPIN: 1887-7415, AuthorID: 564827, Scopus Author ID: 7005456284, WoS ResearcherID: Y-4243-2016

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3.1.6. Онкология, лучевая терапия

ОБЗОР

Использование методов иммунотерапии с применением дендритноклеточных вакцин в онкогинекологии

Г. В. Жукова✉, Е. М. Франциянц, И. В. Каплиева, Т. И. Моисеенко, А. П. Меньшенина, А. И. Шихлярова, В. А. Бандовкина, Е. И. Сурикова, Е. В. Шалашная, Ю. А. Петрова, П. С. Качесова

Национальный медицинский исследовательский центр онкологии Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация

✉ galya_57@mail.ru

РЕЗЮМЕ

Разработка методов противоопухолевого лечения, направленных на восстановление системной и локальной иммунной регуляции, рассматривается в качестве наиболее перспективной стратегии в современной онкологии. Большой интерес представляют технологии с использованием дендритноклеточных вакцин (ДКВ), отличающиеся отсутствием токсичности и соответствующие фундаментальным иммунным механизмам противоопухолевой резистентности.

Цель исследования. Изучить эффективность методов иммунотерапии онкогинекологических заболеваний с использованием ДКВ и перспективные направления их развития

Материалы и методы. Проведен поиск литературы в библиографических реестрах MEDLINE, ClinicalTrial.gov., eLIBRARY и КиберЛенинка, с использованием поисковых систем PubMed, Google Scholar. Подавляющее большинство источников включены в базы данных Scopus и WoS. В настоящем обзоре рассмотрено более 60 работ на русском и английском языках, более 50 % которых опубликованы в течение последних пяти лет.

Результаты. Проанализированы сведения о результатах применения ДКВ при терапии распространенных форм рака шейки матки, рака эндометрия и рака яичников. Положительные эффекты ДКВ включают временную стабилизацию заболевания, увеличение продолжительности и качества жизни при распространенном злокачественном процессе, повышение эффективности химиотерапии после ДКВ, отдельные случаи частичной и полной ремиссии. Рассматривают причины недостаточной эффективности ДКВ, варианты сочетания данной технологии с другими методами иммунотерапии и традиционным противоопухолевым лечением. Невысокая эффективность ДКВ в отношении онкогинекологических заболеваний на современном этапе может быть обусловлена недостаточной разработанностью технологии и объективными сложностями преодоления механизмов уклонения опухоли от иммунного надзора.

Заключение. Потенциал ДКВ как метода противоопухолевого лечения в настоящее время не реализован. Анализ современных достижений в области иммунотерапии, молекулярной биологии, нанотехнологий и подходов к активизации системных и локальных механизмов противоопухолевой резистентности позволяет определить направление дальнейших исследований, нацеленных на повышение эффективности ДКВ как важного компонента комплексного лечения онкогинекологических заболеваний.

Ключевые слова: иммунотерапия, дендритноклеточные вакцины, опухолеспецифические иммунные реакции, рак шейки матки, рак эндометрия, рак яичников

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Для корреспонденции: Жукова Галина Витальевна – доктор биологических наук, старший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации, г. Ростов-на-Дону, Российская Федерация
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14 Линия, д. 63
E-mail: galya_57@mail.ru
ORCID: https://orcid.org/0000-0001-8832-8219, eLibrary SPIN: 1887-7415, AuthorID: 564827, Scopus Author ID: 7005456284, WoS ResearcherID: Y-4243-2016

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INTRODUCTION

The ability of malignant cell systems to suppress immune surveillance, together with their unrestricted proliferative activity, distinct metabolism that ensures preferential access to the host's energy and biosynthetic resources, and the loss of contact inhibition, represents one of the most significant pathogenetic characteristics of malignant tumors [1]. Despite the widespread introduction and ongoing refinement of radiation therapy, systemic anticancer treatments, and the expanding panel of plant-derived cytotoxic agents (including taxanes and others) [2], the search for therapeutic approaches aimed at restoring systemic and local immune regulation of cellular life cycles and tissue development is increasingly regarded as one of the most promising strategies in fundamental and clinical oncology. In this context, the development of novel and effective methods of tumor immunotherapy continues to generate considerable interest and high expectations.

Purpose of the study is to evaluate the effectiveness of immunotherapeutic approaches for gynecologic malignancies using dendritic cell vaccines and to outline promising directions for further development.

General background on dendritic cell vaccines

It is well established that various immune system cell types are capable, in one way or another, of directly damaging malignantly transformed cells. Such reactions have been described for natural killer cells [3], B-lymphocytes [4], neutrophils [5], monocytes [6], and tissue basophils [7]. Activation of these cells can be achieved not only through cytokines but also through systemic regulatory influences on the central components of the integrated neuroendocrine-immune system [8], mediated by factors of various origins, including phytoimmunomodulators [2, 9], weak electromagnetic radiation, and biologically active fluids [10]. Approaches aimed at mobilizing these processes are classified as nonspecific immunotherapy and hold significant theoretical and practical value.

At present, multiple directions in tumor immunotherapy are being developed, focusing on direct or indirect stimulation of the effector arm of the immune system, whose activity is suppressed under conditions of malignant growth. Historically, the first variant of tumor immunotherapy involved bacterial vaccines [11], initiated over a century ago with William Coley's vaccine, which was successfully applied to soft-tissue sarcomas. A widely used contemporary immunotherapeutic approach is antibody-dependent cytotoxicity, implemented through monoclonal antibody therapy capable of enhancing antitumor cytotoxic responses via Fc-receptor interactions of not only T-lymphocytes but also other immune system elements [12]. Additional strategies include cytotoxic lymphocytes activated *in vitro* through various methods [13], as well as tumor-infiltrating lymphocytes extracted from a patient's tumor tissue, expanded *ex vivo*, and reinfused into the same patient (TIL therapy) [14].

More recent immunotherapy modalities demonstrating high clinical efficacy in recent years include the use of genetically modified T-cells engineered to express CAR-T or TCR-T receptors, which enhance their ability to selectively destroy tumor cells [15]. CAR-T therapy is primarily applied in hematologic malignancies and targets surface antigens, whereas TCR-T approaches can be effective in selected solid tumors by recognizing intracellular antigens. For several cancers, favorable outcomes have been achieved through the inclusion of immune checkpoint inhibitors (ICIs) in multimodal treatment regimens [16].

However, the priority goal of tumor immunotherapy should be the ability to orchestrate robust tumor-specific immune responses – i. e., the activation of tumor antigen (TA) recognition and presentation, generation of highly active tumor-specific cytotoxic T-cells, and massive destruction of transformed cells through apoptosis, enabling rapid and economical clearance of cellular debris without the toxic sequelae characteristic of necrosis [17]. In this context,

methods employing dendritic cell vaccines (DCVs) attract particular attention, since dendritic cells (DCs) are the most effective antigen-presenting components of the immune system. DCs originate from bone marrow hematopoietic progenitors, form reticular cellular networks widely distributed throughout the organism, and play a key role in immune surveillance [18]. These professional antigen-presenting cells require minimal amounts of antigen to stimulate cytotoxic lymphocyte proliferation and can induce lymphoproliferative responses using antigen quantities approximately 100-fold lower than those required for macrophages or B-lymphocytes. Importantly, DCs can migrate into lymph nodes and initiate the formation of tumor-specific cytotoxic T-cells [19].

Mobilization of DCs occurs under the influence of tumor antigens, which are internalized by phagocytosis; DCs then migrate to the lymph nodes, where the antigens are processed into peptides and presented in complex with major histocompatibility complex (HLA) molecules to T-cells.

In addition to their pathogenetic mechanism of action, personalized DCVs are characterized by low toxicity and relative technical simplicity of production [18, 19]. DCV preparation generally includes: (1) isolation of precursor cells from blood (monocytes) or bone marrow (CD34+ hematopoietic stem cells); (2) stimulation of their maturation and differentiation into activated DCs using cytokine cocktails and autologous tumor antigens *ex vivo*; and (3) reinfusion of mature DCs into the patient. After administration, activated DCs migrate to lymph nodes and present tumor antigens to CD4+ and CD8+ T-cells, initiating an adaptive immune response. A less common approach involves *in vivo* expansion of circulating DCs via hematopoietic growth factors such as Flt3L and granulocyte colony-stimulating factor (G-CSF).

The use of precursor populations rather than endogenous mature DCs is explained by the heterogeneity and immunosuppressive phenotype of endogenous DCs in the tumor microenvironment, as well as the relative ease of obtaining enough monocytes and bone-marrow progenitors [20]. A major challenge is the selection of tumor antigens and maturation cocktails to generate highly immunogenic DCs optimally targeted toward malignant cells. Mature DCs differ significantly from immature forms in their molecular profiles, morphology, and functional activity [21]. To enhance immunogenicity, a variety of adjuvants are used, including bacterial and viral components, gangliosides, recombinant proteins, immunogenic peptides, anti-idiotype monoclonal antibodies, mucins (notably MUC1), genetically or chemically modified tumor cells, tumor lysates, and others [18–20]. Adjuvant selection depends on tumor type and localization. Common elements across DCV protocols include the route and schedule of administration (intradermal or subcutaneous, at least 3–4 injections at 1–2-week intervals) and typical dosing (10^6–10^7 DCs per injection).

Despite the clear objective of achieving complete tumor regression through DC-based activation of antitumor immunity, this goal has not yet been realized. Complete responses have been most frequently observed in melanoma, one of the most aggressive and highly immunogenic tumors [19, 22], usually accounting for no more than 3–7 % of cases in specific cohorts. More favorable long-term outcomes – complete remission in one-third of melanoma patients – were reported with DCV administration after primary tumor resection and removal of macrometastases, with follow-up exceeding six years [23]. Studies of DCV efficacy in cutaneous melanoma have also been conducted by domestic researchers [24, 25]. Complete tumor regression in other malignancies has been documented far less frequently [26].

To date, despite their excellent safety profile and minimal toxicity, current DCV formulations have not demonstrated sufficiently strong or consistent antitumor activity [19, 27]. Limited efficacy is attributed primarily to the low immunogenicity of tumor antigens used for DC stimulation, immunosuppressive influences of the tumor microenvironment, and negative selection of cytotoxic T-cells in the thymus.

To mitigate these obstacles and improve therapeutic outcomes, DCVs are increasingly combined with other immunotherapeutic modalities. Promising combinations include DCVs with ICIs, TIL therapy, and TCR/CAR-T-based cellular therapies [18].

Dendritic cell vaccines in the immunotherapy of gynecologic malignancies

The question of whether tumor immunotherapy can be effectively applied to gynecologic cancers carries considerable scientific and practical significance. Persistently high incidence and mortality rates, which have shown little reduction over more than a decade, together with the limited therapeutic effectiveness for women with malignant tumors of the reproductive system, remain among the most urgent challenges in modern oncology. Although cervical cancer (CC) is the only gynecologic malignancy with a well-established etiologic factor – oncogenic human papillomavirus (HPV) subtypes – and despite the existence of effective screening programs and primary/secondary prevention strategies, the incidence of CC continues to rise both in Russia and worldwide. A trend toward a younger age at diagnosis has been observed, and first-year mortality exceeds one-tenth of newly diagnosed cases [28, 29]. This situation is further complicated by insufficiently optimized protocols for preoperative radiotherapy, which represents one of the main treatment modalities for patients with advanced CC [30].

Endometrial cancer (EC) is the most prevalent gynecologic malignancy in developed countries. In Russia, EC accounted for 8 % of all newly diagnosed cancers among women in 2023, exceeding the incidence of cervical cancer and ovarian cancer (OC) by 1.8-fold or more [28]. The incidence of EC continues to increase due to population aging and obesity-related factors. The greatest therapeutic challenges arise in advanced-stage disease. Significant molecular-genetic and histological heterogeneity in EC results in substantial variations in clinical outcomes and prognosis, prompting the development of an additional molecular classification system as an essential prerequisite for creating algorithms for personalized treatment – an approach that remains insufficiently established to date [31].

Mortality associated with OC is the highest among gynecologic cancers [28, 32]. Platinum resistance – developing in 75–90 % of patients after repeated chemotherapy courses – rapid progression of metastases in the omentum and pelvic organs due to exfoliation of tumor cells into serous fluid, and the predominance of high-grade serous carcinoma, the most aggressive OC subtype, severely limit the chances of achieving even temporary disease control and account for the high lethality in this patient population.

Evidence of the immunogenicity of malignant tumors of the female reproductive system [33, 34] provides an additional rationale for pursuing effective immunotherapeutic approaches for gynecologic cancers, including those based on dendritic cell vaccines (DCVs).

Cervical cancer

At the present stage, dendritic cell vaccines (DCVs) are used only as an adjunct modality in the treatment of malignant tumors localized in the uterus, and their clinical application remains limited. In cervical cancer (CC), considerably more is known about the integration of passive immunotherapy approaches – particularly immune checkpoint inhibition [35] and TIL therapy [36] – into multimodal treatment regimens. These methods may exert a meaningful therapeutic effect in selected disseminated forms of CC.

In Russia, experimental and clinical studies involving DCVs for the treatment of CC were conducted at the National Medical Research Center of Oncology (Rostov-on-Don). A DCV was developed based on monocytes derived from the peripheral blood of CC patients, using GM–CSF, IL-4, and TNF-α for maturation, and loaded with HeLa cell lysate to generate mature activated DCs [37]. This vaccine was subse-

quently evaluated as part of a combined treatment strategy for CC patients with different extents of disease [38].

In five patients with CC stage T4aN1M1 (bladder and distal ureter invasion), bilateral nephrostomies, multiple distant metastases, severe endogenous intoxication, grade III anemia, and cachexia, DCV was administered with palliative intent as the only available treatment option. Disease stabilization for 6–12 months was achieved, with a mean overall survival of 14.8 months. Among eleven patients with progressive CC following standard therapy, DCV combined with palliative polychemotherapy (PCT) resulted in stabilization in approximately half of the cases. Progression-free survival and mean overall survival in this group reached 15.8 and 32 months, respectively. In three patients with CC T2bN1M0 whose tumors remained unresectable after standard chemoradiation, DCV administered alongside second-line PCT induced complete tumor regression. However, the authors noted that in 18 % of cases the DCV-based treatment produced no meaningful effect and failed to halt disease progression [39].

In incurable and progressive CC, DCV use resulted in significant improvements in quality of life compared with chemoradiation alone, largely owing to marked analgesic and anti-inflammatory effects. Pain relief typically occurred after 2–3 DCV administrations. Immunologic and biochemical indicators in DCV-treated patients demonstrated improved systemic homeostasis after at least six DCV cycles, including restoration of previously reduced NK-cell and CD8+ T-cell levels, increased Tm/Th0 ratios ("memory" / "naive" T-cells) among CD4+ and CD8+ subsets, and normalization of albumin functionality, medium molecular weight molecules, and blood redox parameters [39].

Earlier reports by Santin A. D. and colleagues from the University of Arkansas for Medical Sciences similarly described improved therapeutic outcomes and patient status following DCV administration in CC [40, 41]. Their work examined DCVs produced from monocytes stimulated with GM–CSF and loaded with HPV E6 and E7 oncoproteins – antigens frequently expressed in HPV-associated tumors. These oncoproteins were considered suitable targets for therapeutic vaccination against HPV-infected cancer cells. In a study of 18 patients with advanced CC, clinical benefit was observed in four cases: disease stabilization for one year in two patients, and complete tumor regression following PCT administered after vaccination in another two [40].

In a phase II study evaluating DCV in 14 patients with advanced or recurrent CC, stabilization was documented in five patients for up to eight months after four DCV administrations, accompanied by immunologic evidence of activated cytotoxic T-cell responses. The same report described a case of widespread chemoresistant CC with multiple pulmonary macrometastases, where repeated DCV administration produced prolonged stabilization exceeding one year and partial regression of a major lung metastasis. In another setting, DCV combined with low-dose recombinant IL-2 produced temporary disease control in two of four heavily pretreated CC patients with metastatic or recurrent disease, increasing survival from 5 to 13 months after treatment initiation.

In many of these studies, clinical responses correlated with delayed-type hypersensitivity reactions, activation of CD8+ cytotoxic T-cells, and other effector components of the antitumor immune response. The authors concluded that the limited efficacy of DCVs in advanced refractory CC is likely related to immunosuppressive effects of prior chemotherapy and radiotherapy, creating significant barriers to DCV effectiveness. They emphasized the need for trials in earlier stages of CC and earlier treatment windows.

A later trial investigated DCV in patients with CC stage Ib and IIa after radical surgery, using escalating doses of DCV generated through stimulation with recombinant HPV16/18 E7 antigens and keyhole limpet hemocyanin (KLH) as an immunologic marker. After five DCV doses administered at three-week intervals, all participants demonstrated CD4+ T-cell

and B-cell responses. The authors concluded that DCV was safe, immunogenic, and potentially beneficial for CC patients with limited tumor burden or high risk of recurrence [41]. This conclusion was partly supported by subsequent studies conducted at Shanghai University Hospital and Suzhou University Hospital [42]. In patients with squamous cell or adenocarcinoma of the cervix (mostly stage IIa or IIb), postoperative adjuvant treatment consisted of either cisplatin-based chemotherapy alone or chemotherapy combined with DCV. In the DCV group, the vaccine formulation included co-cultured DCs and T-killers rather than isolated antigens. The combined therapy yielded significantly improved immune parameters, a two-fold reduction in cumulative three-year recurrence rate, and an increase in three-year survival from 56.4 % to 80 %.

Isolated reports of successful treatment of disseminated CC with distant metastases following DCV – similar to the case reported by Santin A. D. et al. [40] – have also been documented by other researchers. One study from the Chennai Cancer Institute (India) described a complete clinical response after vaccination with DCs loaded with autologous tumor lysate followed by cisplatin chemotherapy, with no signs of recurrence for more than six years [43]. The reasons for such selective responsiveness to DCV-containing treatment regimens in advanced CC remain unclear.

Recent studies on DCVs for CC have focused on strategies to enhance their therapeutic efficacy, including identification of highly immunogenic CC antigens or methods to improve their presentation [44], development of nanoscale technologies to improve immune effector targeting within tumor tissue, and optimization of the CC tumor microenvironment [45]. At present, these investigations remain predominantly experimental.

Endometrial cancer

The use of dendritic cell vaccines (DCVs) in patients with endometrial cancer (EC) is currently even less common than in cervical cancer. Much more frequently, passive immunotherapy with immune checkpoint inhibitors (ICIs) is considered a promising treatment option for EC [35, 46], owing to the relatively high effectiveness of ICIs in this setting. It has been shown that EC with microsatellite instability (MSI-positive subtype) is highly sensitive to ICIs, with objective response rates to pembrolizumab exceeding 50 %. Even in MSI-negative EC, the use of pembrolizumab is considered appropriate when combined with the multikinase inhibitor lenvatinib.

The focus of active immunotherapy using DCVs on restoring fundamental defense mechanisms of immune surveillance, the high efficacy of tumor antigen (TA)-dependent cytotoxic T-cell responses (where preserved), and the favorable safety profile of DCVs have naturally attracted considerable interest among researchers developing antitumor strategies for EC. This interest has also been driven in part by the limited treatment options for uterine sarcomas and recurrent carcinomas of the uterus, particularly serous endometrial carcinoma [47, 48]. By 2014, fewer than ten studies on DCVs in EC had been published, each including only 1–6 patients [47]. The most systematic work in this area was conducted by Santin A. D. and colleagues at the University of Arkansas for Medical Sciences. In one study, the authors reported outcomes in a 65-year-old patient with progressive, chemoresistant serous endometrial carcinoma and hepatic metastases that increased significantly in size over the three weeks preceding treatment initiation [49]. After three DCV administrations at 3–4-week intervals, immunologic monitoring revealed signs of T-cell cytotoxic responses, while computed tomography demonstrated stabilization of liver metastases. The authors attributed this relatively modest effect to the inability of activated T-cells to adequately penetrate a bulky tumor mass.

Subsequently, the same group published data on the immunogenic effects of autologous DCs stimulated with tumor lysate, showing that DCVs were capable of inducing tumor-specific T-cell responses against autologous uterine cancer in three EC pa-

tients, although clinical efficacy was not evaluated in that study [50].

In work by Coosemans A. and colleagues from the Leuven Cancer Institute (Belgium), which used the Wilms' tumor gene 1 (WT1) product – a known immunogenic antigen in EC – as a TA, emphasis was likewise placed on the feasibility and safety of DCV use in EC rather than on clearly demonstrated clinical benefit [51, 52]. In a 46-year-old patient with terminal-stage serous EC, four weekly DCV injections were well tolerated, accompanied by a 2.5-fold increase in WT1-specific T-cells and a reduction in CA-125 levels. In a comprehensive review published in 2014 [47], the authors concluded that DCV-based immunotherapy in EC remained in its infancy due to insufficient knowledge of local and systemic immune features in this disease. At the same time, recognizing the evident negative impact of immunosuppressive elements within the tumor microenvironment on DCV efficacy, they proposed that the most promising immunotherapeutic strategy for EC might involve combining DCVs with ICIs.

It must be acknowledged that the deficit of knowledge regarding local and systemic immune processes in EC has not yet been overcome. This situation is further complicated by considerable molecular-genetic and histological heterogeneity, which underlies substantial variability in prognosis and hampers the development of personalized treatment algorithms [31, 33]. Analysis of the available literature suggests minimal progress in DCV-based immunotherapy for EC. International treatment guidelines for EC do not currently mention active immunotherapy as a therapeutic option [53]. At the same time, isolated reports have emerged describing combinations of chemotherapy (CT) and DCVs in EC. For example, investigators at the Radboud University Medical Center in Nijmegen (Netherlands) conducted an exploratory study evaluating carboplatin/paclitaxel combined with DCVs loaded with MUC1 and survivin in patients with metastatic EC [54]. Given the severity of disease, the primary positive endpoint was the ability to complete the full treatment schedule without severe complications. This endpoint was achieved in five of seven patients. Antigen-specific immune responses were documented in only two cases.

These findings indicate that DCVs may be a promising component of multimodal therapy in EC and support the need for further development of effective algorithms for their use.

Ovarian cancer

In ovarian cancer (OC), the gynecologic malignancy with the highest mortality and a pronounced tendency toward chemoresistance – the search for new strategies to inhibit tumor growth and induce regression is of particular urgency. As in CC and EC, ICIs are the most widely used immunotherapeutic agents in OC [35, 55]. Tumor sensitivity to PD-1/PD-L1 pathway inhibition is tightly linked to the presence of microsatellite instability; however, MSI-positive advanced OC accounts for less than 10 % of cases, a considerably lower proportion than in CC and EC [35]. This highlights the pressing need to explore additional immunotherapeutic approaches for OC.

A positive correlation between intratumoral densities of mature DCs and CD8+ cytotoxic T-lymphocytes and survival in advanced OC [34, 56] further strengthens interest in DCV-based strategies in this disease. Indeed, more DCV-related studies have been conducted in OC than in CC or EC.

As in most solid tumors, a complete characterization of the OC-associated TA repertoire is not yet available, but several antigens with significant immunogenic potential have been identified. These include cdr2, HER-2/neu, mesothelin, cancer–testis antigens such as NY-ESO-1, melanoma-associated antigens of the MAGE family expressed in OC, the surface protein Sp17, mucins (MUC16 and MUC1), the cancer antigen CA-125, and universal tumor antigens such as survivin [56]. In a randomized open-label phase I/II trial conducted at the Ovarian Cancer Research Center, University of Pennsylvania (USA), DCs loaded

with Her2/neu, hTERT, and PADRE peptides were administered to 11 patients with advanced OC who were in remission following standard therapy. DCVs were delivered either alone or in combination with low-dose intravenous cyclophosphamide; all patients also received pneumococcal vaccination [57]. The DCVs containing immunogenic peptides produced heterogeneous outcomes: two patients experienced relapse during the vaccination course; nine completed all four DCV injections. Among these nine, three developed recurrences at 6, 17, and 26 months, whereas six remained disease-free for at least three years after treatment. Overall three-year survival reached 90 %, which was interpreted as a favorable result. Slight improvements in survival were observed in the cyclophosphamide group compared with controls. However, immunologic analyses revealed only weak peptide-specific immune responses and a substantial immunosuppressive effect of pneumococcal vaccination, underscoring the need to optimize the combinatorial treatment strategy.

In a study by the Dendritic Cell Vaccine Working Group of the Japanese Society of Innovative Cell Therapy (J-SICT), 56 patients with advanced OC, previously treated with standard therapy, received DCs loaded with synthetic peptides [58]. The investigators confirmed DCV safety and immunogenicity but reported only modest clinical benefit. Similarly modest results were obtained in another study using WT1 peptide-loaded DCVs [59], where only one of three patients with chemoresistant recurrent OC experienced disease stabilization and improved quality of life.

More pronounced clinical effects were observed with autologous tumor lysate–based DCVs and combinations of DCVs with other antitumor modalities. Chemical modification of tumor lysates has been explored as a means of increasing TA immunogenicity and, consequently, overall DCV effectiveness. A notable example is a single-center phase I trial in 22 patients with recurrent OC, in which DCVs were generated from DCs stimulated with lysates of autologous tumor cells oxidized by hypochlorous acid (HOCl) [60]. The resulting DCVs were administered intranodally over extended periods, until disease progression or exhaustion of the immune response, in three regimens: DCV alone, DCV plus bevacizumab, or DCV plus bevacizumab and low-dose cyclophosphamide. Half of the patients mounted T-cell responses to autologous tumor antigens (as indicated by increased IFN-γ production); these patients experienced the most pronounced clinical benefits. Two patients achieved partial responses, and 13 experienced disease stabilization, with a median duration of 14 months. Two-year survival was 100 % in patients with detectable immune responses to DCVs, compared with only 25 % in those without such responses. The best outcomes were obtained with the combination of DCVs, bevacizumab, and cyclophosphamide.

These examples illustrate the principal results of DCV-based therapy in OC. Unfortunately, the observed benefits are not clearly superior to those achieved with other immunotherapeutic approaches in advanced OC – including cytokine therapy [56, 61], ICIs [35, 55, 58], TIL therapy, and TCR/CAR-T-based cellular therapies [56]. Nonetheless, the pathogenetic alignment of DCVs with fundamental mechanisms of antitumor resistance, together with isolated reports of robust tumor-specific immune responses and complete remission of advanced OC under DCV-based regimens [62], indicate that the therapeutic potential of DCVs in OC remains largely unrealized.

Critical analyses of accumulated clinical data [63, 64] suggest that objective response rates to DCVs in OC and other tumor types do not exceed 15 %. Phase III trials of DCVs are lacking, and most information on clinical activity derives from phase I/II studies employing short-term endpoints. Moreover, antitumor vaccine trials frequently enroll patients with stage IV disease and prior failure of standard therapy, i. e., the most challenging patient population, which substantially limits assessment of DCV potential. Objective comparisons are also

complicated by marked variation in DCV strategies – including DC subtype, manufacturing processes, antigen source, route of administration, and concomitant treatments – hindering robust cross-trial evaluation. Further difficulties arise from the absence of reliable predictive biomarkers for assessing true therapeutic effectiveness of DCVs. Some authors also point to experimental evidence suggesting functional superiority of DCs derived from bone-marrow progenitors over those generated from peripheral blood monocytes, which are far more commonly used in clinical trials [65].

Recent comprehensive reviews on DCV use in OC have focused on analyzing the existing experimental and clinical data and exploring strategies to enhance DCV efficacy. Particular attention has been devoted to the immunogenicity of TAs used for DC activation, methods to obtain TA sets that best represent the mutanome (i. e., the specific pattern of somatic mutations defining the antigenic landscape of an individual tumor), and selection of rational combinations of DCVs with other immunotherapies, with emphasis on pairing DCVs with ICIs to alleviate the immunosuppressive tumor microenvironment and, where appropriate, integrating CT and targeted therapy [64, 65].

Prospects for the Use of Dendritic Cell Vaccines in the Treatment of Gynecologic Malignancies

The main strategies for improving DCV effectiveness in gynecologic cancers largely parallel those pursued for tumors of other localizations. As repeatedly noted, key issues include the generation of personalized, highly immunogenic TA sets; in-depth comparative evaluation of DCVs based on peripheral blood monocytes versus bone-marrow progenitors; selection of optimal adjuvants to enhance TA and DC properties; methods to overcome the immunosuppressive tumor microenvironment that attenuates tumor-specific cytotoxic T-cell activity; rational design of combination regimens incorporating DCVs with other immunotherapies, targeted agents, and chemoradiotherapy; identification of biomarkers predictive of DCV efficacy; optimization of the immune microenvironment; and criteria for appropriate patient selection and timing of DCV administration within multimodal treatment algorithms to maximize therapeutic benefit [15, 19, 64].

In recent years, several next-generation DCV platforms have been developed, including biomaterial-based DC vaccines that employ implantable biocompatible scaffolds for localized antigen delivery and DC activation; immunogenic cell death–inducing DC vaccines loaded with fragments of tumor cells undergoing immune-mediated death; mRNA-pulsed DC vaccines encoding tumor antigens; DC small extracellular vesicle (sEV)-based vaccines; tumor sEV-based DC vaccines derived from cancer stem cell exosomes; and other DCV formats [18, 20]. In addressing the challenge of combining DCVs with other modalities to counteract tumor heterogeneity, suboptimal activity of *ex vivo*–matured DCs, the immunosuppressive tumor microenvironment, cytokine therapy–related toxicities, and additional obstacles, it is logical to consider the rapidly evolving field of nanotechnology [66]. Nanoparticulate liposomal RNA vaccines encoding highly immunogenic neoantigens and adjuvants may enable precise targeting of effector immune cells, the tumor microenvironment, and distinct tumor subregions characterized by marked molecular-genetic and proliferative heterogeneity. Such approaches also offer the possibility of modulating DCs *in vivo* under near-physiologic conditions, thus supporting the initiation of tumor-specific immune responses through controlled, sustained release of active components.

In our view, another promising avenue involves combining DCVs with strategies that activate non-specific immune mechanisms via neuroendocrine-immune regulatory centers or through interactions between tumor-specific processes and innate lymphoid cell systems [10, 67].

CONCLUSION

Active tumor immunotherapy based on dendritic cell vaccines remains a field whose therapeutic potential has not yet been fully realized. The absence of systemic toxicity and the pathogenetic congruence of this technology with fundamental mechanisms of antitumor resistance support its consideration as a promising and safe approach to cancer treatment. The high prevalence of gynecologic malignancies, their substantial incidence and mortality, rapid asymptomatic progression and metastasis, high rates of recurrence and drug resistance, and the inherent immunogenicity of tumors of the female reproductive system all underscore the need to develop novel treatment modalities incorporating immunotherapeutic strategies.

The currently modest efficacy of DCVs in gynecologic cancers reflects both the limited maturity of the technology and the objective difficulties associated with overcoming tumor immune evasion. Critical analysis of DCV use in cervical, endometrial, and ovarian cancers, together with current advances in immunotherapy, molecular-genetic technologies, nanotechnology, and strategies for activating systemic and local antitumor resistance mechanisms, provides a foundation for future research aimed at enhancing the effectiveness of DCVs as an important component of multimodal treatment for gynecologic malignancies.

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Information about authors:

Galina V. Zhukova ✉ – Dr. Sc. (Biology), Senior Researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-8832-8219, eLibrary SPIN: 1887-7415, AuthorID: 564827, Scopus Author ID: 7005456284, WoS ResearcherID: Y-4243-2016

Elena M. Frantsiyants – Dr. Sci. (Biology), Professor, Deputy General Director for Science, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: http://orcid.org/0000-0003-3618-6890, eLibrary SPIN: 9427-9928, AuthorID: 462868, Scopus Author ID: 55890047700, WoS ResearcherID: Y-1491-2018

Irina V. Kaplieva – Dr. Sci. (Medicine), Associate Professor, Head of the Laboratory of Study of Malignant Tumor Pathogenesis, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: http://orcid.org/0000-0002-3972-2452, eLibrary SPIN: 5047-1541, AuthorID: 734116, Scopus AuthorID: 23994000800, WoS ResearcherID: AAE-3540-2019

Tatiana I. Moiseenko – Dr. Sci. (Medicine), Professor, Chief Researcher, Department of Oncogynecology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-9683-2164, eLibrary SPIN: 6341-0549, AuthorID: 705829, Scopus Author ID: 57194270696

Anna P. Menshenina – Dr. Sci. (Medicine), ociate Professor, Leading Researcher at the Department of Oncogynecology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-7968-5078, eLibrary SPIN: 6845-4794, AuthorID: 715810, Scopus Author ID: 57191983118

Alla I. Shikhlyarova – Dr. Sci. (Biology), Professor, Senior Researcher, Laboratory of Study of Malignant Tumor Pathogenesis, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0003-2943-7655, eLibrary SPIN: 6271-0717, AuthorID: 482103, Scopus AuthorID: 6507723229, WoS ResearcherID: Y-6275-2018

Valerija A. Bandovkina – Dr. Sci. (Biology), Leading Researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-2302-8271, eLibrary SPIN: 8806-2641, AuthorID: 696989, Scopus Author ID: 57194276288

Ekaterina I. Surikova – Cand. Sci. (Biology), Senior Researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-4318-7587, eLibrary SPIN: 2401-4115, AuthorID: 301537, Scopus Author ID: 6507092816

Elena V. Shalashnaya – Cand. Sci. (Biology), Senior Researcher, Laboratory of Study of Malignant Tumor Pathogenesis, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: http://orcid.org/0000-0001-7742-4918, eLibrary SPIN: 2752-0907, AuthorID: 476958, Scopus AuthorID: 55144159900, WoS ResearcherID: AAE-4085-2022

Yulia A. Petrova – Cand. Sci. (Biology), Senior Researcher at Laboratory of Malignant Tumor Pathogenesis Study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0002-2674-9832, eLibrary SPIN: 2168-8737, AuthorID: 558241, Scopus Author ID: 37026863400

Polina S. Kachesova – Cand. Sci. (Biology), research associate, Laboratory of Study of Malignant Tumor Pathogenesis, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
ORCID: https://orcid.org/0000-0001-6928-5014, eLibrary SPIN: 5784-0475, Author ID: 571595, Scopus AuthorID: 55144158500, WoS ResearcherID: AAF-3998-2019

Contribution of the authors:

Zhukova G. V. – literature search and analysis, text writing;
Frantsiyants E. M. – concept development, scientific editing;
Kaplieva I. V. – concept development, scientific editing;
Moiseenko T. I. – participation in the search of dendritic cell vaccines effects in patients with cervical cancer, literature analysis, scientific editing;
Menshenina A. P. – search of dendritic cell vaccines effects in patients with cervical cancer, scientific editing;
Shikhlyarova A. I. – participation in literature search and analysis, scientific editing;
Bandovkina V. A. – participation in literature search and analysis;
Surikova E. I. – participation in literature search and analysis;
Shalashnaya E. V. – participation in literature search and analysis;
Petrova Yu. A. – participation in literature search and analysis;
Kachesova P. S. – participation in literature search and analysis.
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