Critical Reviews in Oncology / Hematology 128 (2018) 30–42

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Therapeutic vaccines and immune checkpoints inhibition options for gynecological cancers

Chiara Di Tucci*, Michele Carlo Schiavi, Pierangelo Faiano, Ottavia D'Oria, Giovanni Prata, Valentina Sciuga, Andrea Giannini, Innocenza Palaia, Ludovico Muzii, Pierluigi Benedetti Panici

Department of Gynecological and Obstetric Sciences, and Urological Sciences, University of Rome "Sapienza", Umberto I Hospital, Rome, Italy

ARTICLE INFO

Keywords:
Gynecological cancers
Immunotherapy
HPV vaccines
Immune checkpoint blockade
Clinical trials

ABSTRACT

Treatments for gynecological cancer include surgery, chemotherapy, and radiation. However, overall survival is not improved, and novel approaches are needed. Immunotherapy has been proven efficacious in various types of cancers and multiple approaches have been recently developed. Since numerous gynecological cancers are associated to human papilloma virus (HPV) infections, therapeutic vaccines, targeting HPV epitopes, have been developed. The advancing understanding of the immune system, regulatory pathways and tumor microenvironment have produced a major interest in immune checkpoint blockade, Indeed, immune checkpoint molecules are important clinical targets in a wide variety of tumors, including gynecological.

In this review, we will describe the immunotherapeutic targets and modalities available and review the most recent immunotherapeutic clinical trials in the context of gynecological cancers. The synergic results obtained from the combination of HPV therapeutic vaccines with radiotherapy, chemotherapy, or immune checkpoint inhibitors, may underlie the potential for a novel therapeutic scenario for these tumors.

1. Introduction

Gynecologic cancer is any cancer that starts in a woman's reproductive organs such as ovary, uterine, vagina and vulva (Coukos et al., 2016). Each gynecologic cancer is unique, with different clinical symptoms, risk factors, prevention strategies and treatments (Alkatout et al., 2015; Colombo and Peiretti, 2010; Yang et al., 2016). Multiple treatment modalities for gynecologic cancers include surgery, chemotherapy, and radiation, depending on the kind of cancer and how far it has spread (Cortez et al., 2017; Ventriglia et al., 2017; van Poelgeest et al., 2016). In the last years, many attempts have been made on therapies to improve overall survival (OS) in gynecological cancer (Colombo and Peiretti, 2010; Di Donato et al., 2016). Some authors investigated new alternative therapies to reduce the high incidence of radiotherapy long-term complications and the poor control of micrometastasis in cervical cancer. In other cases, the association of more than one treatment improved OS and disease free survival. Neoadjuvant chemotherapy followed by radical surgery is considered an effective treatment, for cervical cancer, in term of OS if compared to radiotherapy alone (Colombo and Peiretti, 2010). In addition, adjuvant chemotherapies seem to be effective in term of disease free survival (DFS) after chemoradiation and after NACT + RS (Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008; Angioli et al., 2012). Treatments for ovarian cancer (OC) include surgery and chemotherapy, usually paclitaxel and carboplatin, however a little room of improvement have been succeeded in the last two decades (Luvero et al., 2014). The progression-free survival (PFS) has remained fairly constant at about 18 months, and many tumors present a poor prognosis or are diagnosed as advanced, metastatic and recurrent (Luvero et al., 2014). For this reason, in the last few decades, new strategies have been developed targeting known dysfunctional molecular pathways for immunotherapy (Angioli et al., 2012).

Tumor biology studies on signaling pathways in immune cells and the tumor microenvironment have led to the discoveries of multiple therapeutic modalities, such as immune checkpoint blockade, therapeutic vaccines and adoptive T-cell therapy, which have shown promising results in gynecological cancers (Iwai et al., 2017; Liao, 2016).

In this review, we will describe the immunotherapeutic options

Abbreviations: HPV, human papilloma virus; CC, cervical cancer; EC, endometrial cancer; CIN, cervical intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VaIN, vaginal intraepithelial neoplasia; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; PD-1, programmed cell-death 1; PD-L1, programmed cell-death ligand 1; ACT, adoptive cell transfer; APC, antigen presenting cells; MHC, major histocompatibility complex; DC, dendritic cells

* Corresponding author at: Department of Gynecological and Obstetric Sciences, and Urological Sciences, University of Rome "Sapienza", Umberto I Hospital, Viale del Policlinico 155, 00161 Rome, Italy.

E-mail addresses: chiara.ditucci@uniroma1.it (C. Di Tucci), michelecarlo.schiavi@uniroma1.it (M.C. Schiavi), pierangelo.faiano@uniroma1.it (P. Faiano), ottavia.doria@uniroma1.it (O. D'Oria), giovanni.prata@uniroma1.it (G. Prata), valentina.sciuga@uniroma1.it (V. Sciuga).

https://doi.org/10.1016/j.critrevonc.2018.05.011
Received 2 January 2018; Received in revised form 21 April 2018; Accepted 14 May 2018

currently available, report the results of the clinical trials and on going studies on immunotherapies for gynecological cancers, including in ovarian, endometrial, cervical, premalignant lesions, vulvar and vagina cancers.

2. Cancer immunotherapy

Cancer immune treatments can be considered tools tackling tumors by inducing, boosting or suppressing the immune response. These therapies are have been classified as active and passive therapy, depending on the mechanism through which they stimulate the host's immune system against the tumor (Longoria and Eskander, 2015; Mellman et al., 2011). A direct engagement of the host immune system would represent an active mechanism whereas, activation of the immune system against cancer cells by a drug with an intrinsic antineoplastic activity, would be considered as passive therapy (Galluzzi et al., 2014). Conversely, it has been proposed to classify immune therapies based on their antigen-specificity, since, for some of them, the active/passive classification have not been proved to exhaustivelydescribe their mechanism of action (Galluzzi et al., 2014).

To date, immunotherapies implemented in gynecological tumors have been therapeutic anti-cancer vaccines, immunomodulatory monoclonal antibodies (mAbs), oncolytic viruses and immunostimulatory cytokines, adoptive cell transfer, tumor-targeting mAbs and bispecific T-cell engager (Galluzzi et al., 2014).

2.1. Anti-cancer vaccines

Virus-associated diseases, including cancers, derive from established viral infections, such as hepatitis B virus and human papillomavirus (HPV). Cervical cancer, which is the fourth most common cancer in women, is caused by HPV (Yang et al., 2016). Moreover, there are indications for a role of HPV for 5 other types of cancers: penile, vaginal, vulvar, anal, and oropharynx including the base of the tongue and tonsils (Lee et al., 2016). Therapeutic HPV vaccines have been developed to stimulate cell-mediated immune responses targeting established HPV infected cells. Multiple types of vaccines have been already tested in clinical trials and most of them contain HPV oncoprotein E6 and E7, which are presented to the antigen presenting cells (APCs) and stimulate antigen presentation through major histocompatibility complex (MHC) class I and MHC class II (Yang et al., 2016). This stimulation leads to the generation of CD8+ cytotoxic T cell or CD4+ helper T cell responses, respectively. Therapeutic HPV vaccines (Table 1, Fig. 1A) are classified in four categories: live vector-based, peptide-protein based, nucleic-acid based and whole cell-based vaccine.

2.1.1. Whole cell-based vaccines

There are two types: dendritic cell (DC)-based and tumor-cell based (Table 1, Fig. 1A).

Tumor cell-based vaccine derived from tumor cells, *ex vivo* manipulated in order to express proteins able to stimulate an immune response *in vivo* (Fig. 1A). Specifically, HPV-transformed cells are transfected with immunostimulatory genes, such as interleukin (IL)-2, IL-12, and granulocyte macrophage colony stimulating factor (GM-CSF). These cells induced the differentiation of naïve T cells into effector or helper T cells, and the stimulation of stem cells to produce granulocytes, in mice models bearing HPV-16 induced tumors (Yang et al., 2016).

DC-based HPV vaccines are made by introducing HPV antigens or tumor associated antigens (TAA) (being either DNA, RNA, peptides, proteins, viral gene transfer or even tumor lysates) into the DC cells through different molecular biology strategies (Fig. 1A) and then injected into the patients (Yang et al., 2016). A major advantage is that DC cells naturally possess an efficient antigen-specific immune response against cancer (Santin et al., 2005). Nevertheless, DCs may undergo to T-cell mediated apoptosis, limiting their immunotherapeutic efficacy. Anti-apoptotic genes or a mix of siRNAs targeting immunosuppressive factors have been introduced into these vaccines in order to enhance the immunogenic response and antitumor effect in mice (Santin et al., 2005). A major drawback for DCs vaccines is that they are individualized and not feasible for a large-scale production.

2.1.2. Live vector-based vaccines

These types of vaccines can be differentiated as bacterial or viral vectors (Table 1, Fig. 1A). The advantage of live vector-based vaccines is their ability to replicate, wide spread the antigens throughout the body, and to be highly immunogenic (Yang et al., 2016). However, they might produce risk for immune-compromised patients (Yang et al., 2016).

Among bacterial vectors, *Listeria monocytogenes* has been one of the most promising (Yang et al., 2016). Preclinical data with Listeria E7-based vaccines have shown spontaneous tumor shrinkage, in E6/E7-expressing solid tumors, in mice (Yang et al., 2016). Other types of bacteria vectors contain mutant strains, such *Salmonella, Shigella,* and *E. coli*, having a plasmid with the sequence for the antigen of interest (Yang et al., 2016).

Viral vectors used to deliver HPV E6 and E7 antigens include adenoviruses, adeno- associated viruses, alphavirus and vaccinia virus. The major advantage of viral vectors is their ability to efficaciously infect and express antigens, but they trigger antiviral immune responses and neutralizing antibodies, limiting the effectiveness of subsequent administrations of the vaccine (Yang et al., 2016; Lee et al., 2016). Vaccinia viruses have been considered the most promising. They are double-stranded-DNA virus, with a large genome and highly infectivity. Since they rarely get aberrant integration of the host's DNA, they have been largely used, in preclinical settings, to present antigen through DCs(Gomez-Gutierrez et al., 2007).

Various preclinical studies have been performed with adenoviruses based vaccines. In mice models, vaccination with adenovirus E7/CRT vector successfully eliminated the tumor (Gomez-Gutierrez et al., 2007).

2.1.3. Peptide and protein-based vaccines

These vaccines contain HPV antigens/epitope, which are directly processed by DCs and presented on either MHC class I or II molecules to stimulate CD8+ or CD4+ T-cell immune responses (Yang et al., 2016). Both peptide- and protein-based vaccines are stable, safe (Table 1, Fig. 1A).

Peptide-based vaccines produce a poor immune response because contain short peptides, that do not always include the sequence responsible of the immune response. Moreover, they are not able to trigger an efficient response, due to the MHC specificity for each individual (Vici et al., 2016). To overcome these issues, in preclinical models, peptide-based vaccines have been produced with overlapping long-peptide sequences, effective for antigen specific T cell responses (Vici et al., 2016). In order activate innate and adaptive immunity and prevent a rapid clearance, these vaccines are usually linked to lipids and adjuvants, such as chemokines, cytokines, and Toll-like receptor (TLR) ligands (Yang et al., 2016).

Unlike peptide-based, protein based vaccines express a wider collection of sequences recognized by the human leukocyte antigen (HLA) epitopes. This overcomes the main limitation of peptide-based, which triggers only MHC system (Yang et al., 2016).

2.1.4. Nucleic acid-based vaccines

These types of vaccines are classified as DNA and RNA bases, both safe, stable, easy to produce (Fig. 1A). Although they trigger a long immune response, they do not generate neutralizing antibodies, making multiple vaccinations needed (Table 1) (Yang et al., 2016).

DNA vaccines contain a DNA plasmid encoding modified HPV E6 and E7, which is introduced into the patient through intramuscular injections. The target cells for these vaccines are myocytes, which are