Vaccines for Ovarian Carcinoma

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Tumor vaccines can induce specific immune responses against ovarian cancer.

Background: Metastasis to the abdominal cavity is the primary cause of morbidity and mortality in patients with ovarian cancer. Beyond surgery and chemotherapy combinations, strategies that target tumor cells in vivo are being investigated, such as the use of recombinant cytokines to up-regulate or modulate the cell-mediated or humoral immune response.

Methods: The authors report on their experience with tumor vaccines, including first-generation vaccines, peptide vaccines, and polynucleotide vaccines, in the treatment of ovarian cancer

Results: Cytokines may stimulate proliferation or activation of effector cells that mediate either major histocompatibility restricted cytotoxicity (adaptive immunity) or natural (innate) immunity. Cytokines are often pleiotropic, and their effects may depend on concentration, scheduling, and responsiveness of the cell populations to which they are directed. They also have been used to enhance the efficacy of tumor vaccines that have reached a higher level of sophistication. Recently designed tumor vaccines are capable of stimulating antitumor immune responses that recognize tumor cell epitopes or that have the potential to act synergistically with cytokines such as interleukin-2 and interleukin-12.

Conclusions: Enthusiasm for antitumor vaccine strategies is supported by accumulating clinical reports of responses following treatments using a variety of vaccines. Additional research is needed to determine optimum vaccine approaches for the treatment or prevention of ovarian cancer.

Introduction

In the United States, epithelial ovarian carcinoma accounts for 90% of ovarian malignancies and is the second most common gynecologic cancer. More than 25,000 new cases were reported in 1998, and the disease causes an estimated 14,500 deaths annually. The majority of patients are diagnosed when the disease is advanced, and risk factors remain largely unknown. A family history of ovarian cancer and mutations in the BRCA1 or BRCA2 genes are important predisposing factors for familial disease, which accounts for approximately 10% of cases. Because the diagnosis is made at an advanced stage and because ovarian tumors are only moderately sensitive to chemotherapy, cure rates have remained essentially unchanged for many years. Mortality is usually caused by intestinal obstruction resulting from extensive peritoneal and serosal involvement. Treatment involves cytoreductive surgery, including a bilateral salpingo-oophorectomy and in most cases a total hysterectomy, followed by platinum-based chemotherapy with or without paclitaxel. Treatment for recurring or persistent disease after first-line chemotherapy may include reinduction therapy with first-line chemotherapy agents such as carboplatin or the taxanes, high-dose chemotherapy, or second-line agents such as hycamptamine. Further treatment for recurrent or persistent disease is essentially palliative. Therapies under investigation include a variety of novel immunotherapy and gene transfer approaches, among other modalities.

Background

Recent advances in tumor immunology are focusing attention on antigen epitopes, mechanisms for recognition of these epitopes, and specific mechanisms involved in the activation of T cells against tumor cells. In addition, the role of immune suppressor factors and the interactions with other factors, such as those that may promote angiogenesis and peritumoral fibrosis in the tumor microenvironment, are receiving more consideration.

The first generation of therapeutic vaccines against ovarian cancer involved the use of irradiated autologous or allogeneic tumor cells or extracts of tumor cells. Researchers at the University of Texas M.D. Anderson Cancer Center employed lysates of allogeneic tumor cells obtained from tumor cell lines that had been infected with an attenuated form of the influenza virus. This approach could be considered a prototype for the gene transfer therapies of today. Viral infection of tumors in vivo was shown to render animals tumor-free through the induction of viral oncolysis, and animals were also found to be immune to rechallenge with identical tumors. In a different approach, bacillus Calmette-Guérin (BCG) was co-administered with tumor cells with encouraging results.

Peptides derived from tumor-associated or tumor-specific (mutated) antigens are presented in the grooves of major histocompatibility complex (MHC) class I or class II molecules, where they activate either CD8+ T cells with cytotoxic T lymphocyte (CTL) activity or CD4+ T lymphocytes that secrete cytokines capable of inhibiting the growth of tumor cells. Dendritic cells may be the most important of the antigen-presenting cells (APCs) since they are able to present antigen-derived peptides and provide the necessary stimuli through co-stimulation (eg, B7 molecules) and through the actions of certain accessory factors (eg, intercellular adhesion molecules [CD54]). It is possible that tumor antigens derived from allogeneic tumor cell vaccines can be reprocessed and presented by APCs such as dendritic cells or certain macrophages. Research conducted at our center has demonstrated the presence of APCs in the peritoneal cavities and in the blood of ovarian cancer patients. However, the surface antigen characteristics of these cells suggest that further maturation may be required for optimum antigen-presenting function. Current research efforts are examining methods in which dendritic cells can be manipulated so that they are phenotypically and functionally matured.

Tumor-cell peptide epitopes are generally recognized by T lymphocytes in the context of MHC class I or class II molecules, although other mechanisms for T-cell receptor activation do not require presentation in the context of the MHC (eg, MUC1 antigen).

Peptide-MHC-mediated activation of T cells is subverted when MHC expression is down-regulated or absent. Co-stimulatory molecules such as B7 and other accessory molecules such as intercellular adhesion molecules (ICAM) need to be co-presented with tumor antigen peptide-loaded MHC molecules in order to simulate an effective antitumor cell response by the T cells. It is thought that the use of recombinant cytokines such as recombinant interleukin-2 (rIL-2), which itself stimulates cytotoxic lymphocytes belonging to the T cell or natural killer (NK) cell lineages, might replace the need for co-stimulation. However, co-stimulatory antigens have other important functions, including protection of activated lymphocytes from apoptosis. Moreover, rIL-2 may have pleiotropic functions that could also interfere with T cell activation. The NK...
immune system is phylogenetically more primitive and may have a more important role in the control of hematologic malignancies than in the control of solid malignancies in vivo. Moreover, NK cells are present in much smaller numbers than T cells in association with ovarian cancer.

Cultures of mixtures of ovarian tumor cells and T lymphocytes have been shown to generate either CD8+ TCR-alpha-beta+ or CD4+ TCR-alpha-beta+ T-cell lines in vitro. The CD8+ TCR-alpha-beta+ T-cell lines exhibited preferential cytotoxicity against autologous ovarian tumor cells in the presence of low concentrations of rIL-2,8 or produced interferon-gamma (IFN-gamma), granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor-alpha (TNF-alpha) in an antigen-dependent or antigen-independent fashion. Although adoptive therapy using these T-cell lines has been employed by us and by others, further research is needed to improve the success rate for the expansion of these T-cell lines. The lines are, however, useful for identifying antigen epitopes or peptides that could be employed as tumor vaccines.

Cytokines are believed to attract lymphocytes to the site of malignancy by stimulating the local production of chemokines. Cytokines such as IFN-gamma, IL-2, TNF, and GM-CSF contribute to the proliferation and differentiation of mononuclear lymphocytes, including monocytes, macrophages, B cells, and dendritic cells, that are involved with antitumor immunity. Recombinant IL-2 enhances the cytotoxic activity of T cells and non-T cells, but it also can stimulate other cells, including cells of the monocyte/macrophage lineage. Like many other cytokines, rIL-2 is pleiotropic and thus can stimulate other cells or the production of other cytokines whose effects differ from that of rIL-2 and may even suppress T-cell activation. Recombinant IL-12, which was previously called NK cell-stimulating factor, is the largest cytokine described to date. It comprises two subunits of 35 and 40 kDa that stimulate cytotoxic activity of NK cells and T lymphocytes, respectively. Recombinant IL-12 binds to its beta-2 receptor on activated T cells, which results in the secretion of IFN-gamma, a function of T-effector cells. In contrast, T-suppressor cells secrete either B-cell stimulatory cytokines (eg, IL-4, -5, and -6) or suppressor cytokines such as IL-10. Several interferon-inducible proteins have been detected following the activation of T-effector cells by rIL-12. One of these is interferon-inducible protein-10, a C-X-C chemokine. This chemokine has important biologic effects, including an antitumor response mediated through the down-regulation of angiogenesis-inhibiting molecules such as basic fibroblast growth factor. The response of T cells to rIL-12 is increased if T-effector cells have been previously activated. A recent report from our group on the intraperitoneal injection of rIL-12 in patients with ovarian carcinoma is showing clinical activity without significant drug-related toxicity.

Cytokines can induce a strong adaptive immune response but can also produce inhibitory effects. Intraperitoneal rIL-2 administration has resulted in increased concentrations of IL-10 in the peritoneal cavities of patients with ovarian cancer. Recent studies in our laboratory suggest that CD14+ DR+ monocytes are largely responsible for the production of IL-10 in ovarian cancer patients, whereas both monocytes and tumor cells can contribute to the production of transforming growth factor-beta (TGF-beta) isotypes, which in their activated state are also potent immune-suppressor molecules.

**Tumor Vaccines**

Tumor vaccines may be employed therapeutically or for prophylaxis after primary therapy. Vaccines that enhance or generate humoral responses produce antibodies that can be detected over a relatively long period. To be effective, these antibodies need to be capable of targeting cell surface antigens in live cell assays. Maintaining specific cellular immune responses to antigen epitopes (adaptive immunity) may require more frequent immunizations, although memory cells can sustain the ability to respond to rechallenge with the immunizing epitope. Again, the epitope has to be recognized by specifically sensitized CTL on the tumor cells that express these antigens in their natural state.

Several vaccine approaches have been employed, including virus-augmented vaccines, peptides derived from tumor-associated antigens, intact irradiated tumor cells transduced with co-stimulatory or other antigens, and carbohydrate or glycolipid vaccines. Recently, DNA vaccine approaches have been introduced.

**First-Generation Vaccines**

In 1796, Edward Jenner used live cowpox virus to inoculate against the human variola virus, which causes smallpox. The related vaccinia virus has been used to protect against smallpox, and because of their potent immunization properties, recombinant forms of vaccinia have been produced that protect against other viruses. Other early vaccines were made from inactivated whole bacterial or attenuated viruses. Viral pathogens were attenuated by growing them under conditions that caused them to mutate, which also prevented them from inducing a pathologic response in the human host. The mutated viruses caused the immunized subject to produce an immune response that controlled proliferation of the pathogens. A virus can also be attenuated by recombinant DNA techniques. Although the gene encoding virulence is removed, a virus can still be recognized for its antigenicity and can produce immune protective effects by initiating a response against surface membrane epitopes.

Vaccination using either attenuated forms of virus or heat-killed viruses may lead to long-lasting immune responses against virus pathogens. Early clinical trials of tumor vaccines against ovarian cancer included the use of nonviable extracts obtained from ultraviolet-irradiated allogeneic tumor cells. X-ray irradiation prevents tumor cells used in the preparation of vaccines from growing and may enhance their immunogenicity by increasing the expression of MHC antigens. We have employed intraperitoneal therapy with ovarian viral oncolysates made from an attenuated Puerto Rican strain of influenza virus. The virus infected allogeneic tumor cell lines, and nonviable extracts of infected cells were used as tumor vaccines. Virus infection of the tumor cells resulted in the expression of viral antigens in proximity to tumor-associated antigens. The viral antigens appeared to function as haptens. Ovarian cancer patients in whom first infected cells were used as tumor vaccines. Virus infection of the tumor cells resulted in the expression of viral antigens in proximity to tumor-associated antigens, intact irradiated tumor cells transduced with co-stimulatory or other antigens, and carbohydrate or glycolipid vaccines. Recently, DNA vaccine approaches have been introduced.

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Fig 1. - Regression of malignant pleural effusion after ovarian viral oncolysate. Panel 1: before cyst fluid removal; panel 2: after fluid removal; panels 3 and 4: after infection with viral oncolysate. From Freedman RS.
Peptide Vaccines

Peptide subunits that match to certain human leukocyte antigen (HLA) haplotypes (eg, HLA-A2) have been derived from tumor-associated antigens. Much less is known about the tumor-associated antigens that elicit MHC-restricted CTLs in ovarian cancer than about the antigens associated with melanoma. Peptide vaccines have the potential to induce immune responses in vivo that are specific for epitopes on the tumor cells and therefore could have therapeutic potential. Peptides that elicit MHC class I-restricted responses are usually octamer in size and have been produced with high purity and in large quantities. Several tumor-associated peptides have been identified in ovarian cancer patients. The HER-2/neu proto-oncogene is overexpressed in approximately 30% of patients with ovarian cancer, and such tumors are associated with a worse prognosis than HER-2/neu-negative tumors. The GP2 peptide that is derived from the HER-2/neu protein is HLA-A2.1-restricted and is recognized by T-cell lines developed from patients with ovarian cancer. However, recent studies suggest that immunizing patients who have breast, ovarian, or colon cancers that overexpress HER-2/neu results in CTL that recognize the peptide alone but not necessarily in the context of tumor cells that naturally express HER-2/neu protein.

Peptide vaccines require some form of adjuvant to enhance the immune response. The optimum peptide-based vaccine may need to consist of multiple peptides (polyvalent) to account for both intratumoral heterogeneity and haplotype differences. Antigens that are restricted to HLA-A2+ cells will likely be ineffective in more than 50% of patients of any ethnic group, and in fact, the frequency of the A2+ haplotype in ovarian cancer patients is unknown. The number of known MHC motif-associated antigens that elicit MHC-restricted and is recognized by T cells that secrete tumor-inhibitor cytokines.

We have also studied the effects of a sialylated Tn (sTn) antigen vaccine in a recent clinical trial. Carbohydrate-derived antigens not expressed on normal cells include O-linked mucin glycans Tn, T, and sTn. The clinical trial used a vaccine that incorporated a synthetic analog of sTn [NANAalpa (2-6) GalNAC conjugated with keyhole limpet hemocyanin (KLH)] and mixed with Detox-B SE adjuvant (Biomira Inc, Edmonton, Alberta, Canada) for injection into patients. The vaccine was well tolerated and produced an immunologic response in vivo. Although no objective responses were observed at either of two doses examined, a number of patients had stable disease for prolonged periods.

To be effective, vaccines for patients with ovarian cancer will need to comprise a broad range of epitopes to compensate for tumor heterogeneity. In the case of carbohydrate or glycoprotein antigens, it is essential to be able to demonstrate antibody binding to cell-surface antigens in live cell assays using the serum of immunized patients. Carbohydrate-derived vaccines also require co-administration of adjuvants, and the safety of these adjuvants will need to be examined when different routes of administration are used.

Polynucleotide Vaccines

Genetic immunization is a relatively new process that uses polynucleotides as vaccines made up of DNA to promote the stimulation of an immune response. DNA incorporated in a bacterial plasmid and containing a strong eukaryotic promoter to ensure transcription of a target gene is inoculated into the cells of interest, and the expression of plasmid-encoded protein allows the host to generate an adequate immune response. Protective immune responses have resulted from using DNA-encoded viral, bacterial, parasitic, and tumor antigens. Some advantages of these vaccines include their ease of construction and ability to produce a long-lasting immune response. These responses have induced lifelong protective immunity in mice.

Plasmid-encoded antigen is processed similarly to antigen synthesized from virus and results in activation of CTL and stimulation of Th helper cells and B cells. This type of vaccine is more stable and less expensive than most recombinant protein vaccines. It can be directly injected into cells by syringe or coated on microgold particles for injection by a gene gun. It also can be inserted into the genome of viruses that are used as vectors for insertion. These methods have been shown to be both effective and safe in neonatal mice and could have potential value in patients with ovarian cancer.

Vectors that encode for genes, cytokines, or co-stimulatory molecules can be employed to induce antitumor immune responses in vivo. Studies in our laboratory are examining the effects of using autologous ovarian tumor cells that have been transduced with the gene that encodes for the naturally occurring B7.1 (CD80) co-stimulatory molecule (Fig 2). The low expression of the CD80 molecule on peritoneal exudate cells may interfere with activation of an effective immune response in vivo. A canarypox vector that incorporates the gene for hB7.1 (ALVAC-hB7.1) (Paster Merieux Connaught, Strasbourg, France) has been constructed and safely administered to healthy subjects. We are producing autologous tumor cell vaccines that include tumor cells obtained from patients during surgery for ovarian cancer or from malignant ascites. The tumor cells are infected with ALVAC-hB7.1 after treatment of the cells in vitro with recombinant IFN-gamma (rIFN-gamma). This results in the production of an autologous tumor cell vaccine that exhibits increased expression of HLA class I and class II, CD54 (ICAM), and the CD80 (B7.1) co-stimulatory molecule. To inhibit their growth, the tumor cells are irradiated before readministration to patients. This tumor vaccine requires a vector that can efficiently infect cells and transduce the gene of interest. It is not clear if a transgene would be useful for ovarian cancer.
hypothesized that tumor cells that are modified in this manner might perform the functions of APCs. Vaccines of this type could be efficient at activating T cells against tumor-associated antigens that are expressed by the patient's own tumor and in the context of the patient's own HLA haplotype. A typical result showing expression of CD80 (B7.1), HLA class I, and HLA class II on autologous ovarian tumor cells after infection of the cells with ALVAC-hB7.1 is shown in Fig 1. A possible limitation to the use of autologous vaccines is the amount of tumor, 50 g or more, that is required for the production of multiple doses. However, such large amounts of tumor and, in certain patients, large number of ascites containing tumor cells are available from patients who are undergoing initial or salvage surgery for ovarian cancer. These vaccines can be prepared and stored at ultra-low temperatures until administered, usually following reduction of the tumor burden with chemotherapy or secondary cytoreductive surgery.

Fig 2. - Antigen expression in tumor cells infected with ALVAC-hB7.1. Freshly obtained tumor cells treated with recombinant interferon-gamma and then infected with the ALVAC-hB7.1 canarypox vector that expresses the gene for human 7.1. Results obtained by fluorescence-activated cell sorting show high expression of B7.1 (CD80) and increased expression of HLA class I and class II antigens in contrast to almost no expression of B7.1 in the non-infected cells.

Routes of Entry

How a vaccine is administered needs consideration. Different routes of vaccine administration may stimulate the populations of mononuclear leukocytes differently.22 Vaccines have been administered by the following routes: oral, intranasal, intravenous, intradermal, intramuscular, and intraperitoneal. In the case of ovarian cancer, the routes used are intradermal, intramuscular, and intraperitoneal. There could be a particular advantage to the use of the intraperitoneal approach, which might stimulate immune cells at the site of the tumor, bypassing the capillary barrier.21

Intradermal or Intracutaneous Injection

Vaccines injected into the skin encounter professional APCs called Langerhans cells (dendritic cells). Antigens incorporated into vaccines are transported to the draining lymph nodes, where T-cell activation occurs. This route of administration produces systemic immune responses to an antigen. Dosing and optimal frequency of administration need to be determined for each vaccine approach because responses may be either enhanced or decreased with repeated vaccinations. It is unknown whether peripheral sites of vaccination would generate CTL responses of a sufficient degree to target tumor cells that are growing on surfaces in the peritoneal cavity. It is possible that both intracutaneous and intraperitoneal routes might be needed.

Intramuscular Injection

Vaccines injected intramuscularly are taken up by APCs (primarily dendritic cells) or the muscle cells. Muscle cells are thought to be the primary cells of infection, but they express low levels of MHC class I molecules and no MHC class II molecules. Vaccines that encode for tumor antigens and that are expressed by muscle cells would therefore have to be taken up by APCs and re-presented (cross-priming) in the context of MHC molecules for T-cell activation.31 Vaccines that encode genes for cytokines and tumor antigens can also be taken up by APCs for activation of lymphocytes. A potential problem with this route of vaccination, which has also been seen after intradermal or intracutaneous vaccination, is that only a small number of lymphocytes able to produce an effective adaptive immune response are activated. This might be a less important issue for patients who are immunized with vaccines that are designed to generate antibodies in contrast to activated CTLs. Responses may involve innate immunity, and a memory-dependent strong effector CD8+ CTL response may not develop following this approach.

Intraperitoneal Injection

Approximately 80% of patients with late-stage ovarian cancer have metastases involving the peritoneum or serosa of abdominal organs. The peritoneal cavities of ovarian cancer patients contain large numbers of monocytes, macrophages, and T cells and small numbers of NK cells (CD3−, CD56+) and dendritic cells. We have successfully administered vaccines to this site, and significant responses were observed in patients who received intraperitoneal virus augmented vaccines.6,22 Patients who have metastases to the peritoneal cavity and a low tumor burden after chemotherapy are suitable candidates for intraperitoneal immunotherapy. Intraperitoneal injections of cytokines or vaccines put activating molecules into direct contact with local immunoreactive cells in the peritoneal cavity and bypass any capillary barrier. Our current autologous vaccine protocol utilizes an intraperitoneal approach for delivery of B7.1 (CD80)-transduced tumor cells that have been infected with ALVAC-hB7.1. Irradiated tumor cells that express B7.1 are administered intraperitoneally in a sequence with intraperitoneal rIFN-gamma, which is used to enhance the expression of MHC on the tumor cells in vivo. We have previously shown that intraperitoneal rIFN-gamma enhances the density of MHC class I and class II antigens on metastatic ovarian cancer cells in peritoneal exudates. Future studies may incorporate other cytokines, such as rIL-12, and strategies that interfere with suppressor cytokines such as TGF-beta and IL-10.

Conclusions

A tumor vaccine approach is needed for the induction of specific immune responses against ovarian cancer. It is believed that such vaccines will have low overall toxicity, although it will be important to monitor patients for autoimmune responses against normal tissues. Sensitive RT-PCR assays that measure changes in cytokine transcripts may complement other methods that can detect immunologic responses at the cellular level.32 The most recent tumor vaccine strategies have shown variable results in clinical trials. Further improvements may be expected with the development of effective, highly specific polyvalent vaccines that have the ability to control factors in the tumor microenvironment that could interfere with the activation of T cells. Until these vaccines are developed, the use of genetically modified autologous tumor vaccines is a reasonable alternative. Certain cytokines such as rIL-12, rIFN-gamma, or rIL-2 may synergize with vaccines, so it is necessary to develop optimum working doses and schedules that combine tumor vaccines with these cytokines. Our group is currently also studying a novel growth factor that stimulates the proliferation and maturation of
dendritic cells called Flt3 ligand (Immunex, Seattle, Wash) in patients with ovarian cancer. The use of tumor vaccines and cytokines is being actively investigated in several laboratories, including our own.

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