Therapeutic Cancer Vaccines: An Emerging Treatment Option

Susan E. King, MS, RN, OCN®

A vaccine is a foreign substance injected to stimulate the immune system to launch an immune response against the specific target or targets contained in the vaccine. A prophylactic vaccine is intended to prevent disease by protecting an individual from developing the disease. Therapeutic vaccines are designed to treat people affected by a disease with the goal of stimulating or boosting the body’s immune defenses to fight the disease (Davis, 2002). Prophylactic and therapeutic vaccines can produce immune responses that last a lifetime (e.g., polio vaccines), or boosters may be required to maintain immunity (e.g., tetanus booster every 10 years).

Prophylactic cancer vaccines are not yet possible because of the variation among different cancers even within the same type of cancer. However, hepatitis B virus (HBV), Epstein-Barr virus (EBV), and human papillomavirus (HPV) play a role in the development of certain cancers such as hepatocellular carcinoma, lymphoma, and cervical cancer, respectively (Disis, Morse, & Weber, 2002). The closest science has come to a prophylactic vaccine is the hepatitis B vaccine, which prevents infections and reducing the morbidity and mortality associated with HBV infections in the hepatocellular carcinoma has been greatly reduced in Malaysia, Singapore, and Taiwan, where these diseases occurred in high numbers (Chang et al., 1997; Pajeau & Bennett, 1996).

HPV, with more than 100 known strains, has been linked to nearly every case of cervical cancer. Prophylactic vaccines that prevent HPV are being studied (NCI, 2003a). HPV vaccines may reduce the incidence of cervical cancer dramatically (American Cancer Society [ACS], 2003). As an example, the HPV quadrivalent vaccine contains the proteins from four HPV strains: HPV 16 and 18, which are linked to two-thirds of the worldwide cases of cervical cancer, and HPV 6 and 11, the strains most commonly associated with genital warts, which also are linked to cervical cancer (Bass, 2002; NCI, 2003a). Currently, more than 28 vaccines are being studied with the goal of eliminating HPV infections and reducing the morbidity and mortality associated with HPV-related cervical cancers (Likes & Itano, 2003).

In the future, prophylactic cancer vaccines may prevent cancer in populations at risk. However, identifying appropriate populations for these vaccines will be an issue (Poole, Bommiasamy, Bocchetta, & Kast, 2003). Some people with genetic abnormalities never develop cancer, so determining who should be immunized with a prophylactic vaccine is difficult. However, as more is known about why some people develop cancer, researchers may be able to determine who might benefit from a prophylactic cancer vaccine.

Therapeutic Cancer Vaccines

The concept of therapeutic vaccines as a way to treat and possibly cure cancer dates back at least 100 years (Duke University Medical Center Genitourinary Cancer Immunotherapy Program, 2001; Jaffee, 2000). They are a form of active immunotherapy, inducing the host to make an immune response against its own tumor cells (Press, Leonard, Coiffier, Levy, & Timmerman, 2001). These vaccines target tumor-associated antigens (TAAs), which are simply molecules on the surface of the tumor cell (AVI BioPharma, 2003). The overall goal of a therapeutic cancer vaccine is to produce a potent immune response that involves the cellular and humoral arms of the immune system resulting in a T-cell and antibody response (Cell Genesys, 2003). The two arms of the immune system appear to be complementary and work together to induce tumor regression and long-lasting immunity to the disease being treated. This article reviews the history of cancer vaccine development, autologous and allogeneic vaccines, vaccine targets, carrier proteins, adjuvants, and clinical trial data of studies evaluating cancer vaccines. Knowledge of this emerging cancer treatment option will enable oncology nurses to be informed about cancer vaccines and accurately provide information about them to patients.

Key Words: cancer vaccines

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complementary, working together to induce tumor regression and long-lasting immunity to the disease being treated (Vose, 2001). When the immune system is activated by exposure to an antigen, some cells become “memory cells” that can quickly respond and destroy any cells with that antigen when they appear in the future.

Tumor cells can be immunogenic, meaning that they can activate the immune system to destroy these abnormal cells. One reason tumor cells may escape immune surveillance is because they are so much like normal cells that they simply cannot stimulate a strong, effective immune response (Berinstein, 2003; Ruffini, Neepilau, Kwak, & Biragyn, 2002). Also, cancer cells are able to “trick” the immune system and escape destruction by changing their characteristics slightly (Fielding, 2002).

All of this knowledge allows researchers to develop more effective therapeutic cancer vaccines (Yu & Restifo, 2002). As more is known about how the body fights cancer on its own, therapeutic cancer vaccines are being developed to enlist the body’s immune system to fight cancer (Cell Genesys, 2003). Many of the new, targeted cancer treatments, including therapeutic cancer vaccines, attempt to make a tumor appear foreign so the immune system will take action and destroy the cancer cells (Disis et al., 2002; NCI, 2003a).

Since the 1990s, tumor immunologists have identified more than 500 tumor antigens, which also may be referred to as targets, receptors, or molecules (Disis et al., 2002; Yu & Restifo, 2002). Tumors of the breast, colon, ovary, and other sites contain a number of different antigens, many of which the body can mount an immune response against. Some of these antigens actually can be measured in the blood (e.g., carcinoembryonic antigen [CEA] and prostate-specific antigen [PSA]), whereas others can be detected only by using more sensitive tests such as flow cytometry. Many of these TAAs are found on multiple solid tumor types (see Table 1). Examples include CEA, PSA, melanoma antigen genes (MAGE 1, 2, and 3), melanoma antigen recognized by T-cells (MART-1), gp100, HER-2, mucins (MUC1), and prostatic acid phosphatase. To be clinically useful, some therapeutic cancer vaccines need to include multiple proteins so they target the tumor and the regulatory proteins that may be responsible for tumor cell proliferation (Disis et al.).

In addition to the knowledge about the immune system that has been gained in recent years, significant advances in molecular biology and genomics also have aided in the development of therapeutic cancer vaccines. Until recently, the technology to develop vaccines to target specific antigens was not available. Furthermore, the expense of manufacturing these vaccines, especially patient-specific vaccines, was prohibitive. Because of recent advances in technology, therapeutic cancer vaccines have a prominent place as a new strategy for treating cancer (AVI BioPharma, 2003) and potentially will become a standard method of cancer treatment in three to five years (Cryoma Labs, 2003b).

In February 2001, Canadian authorities approved Melacine® (Corixa Corporation, Seattle, WA), a vaccine for the treatment of stage IV melanoma. As of the time of this publication, the U.S. Food and Drug Administration (FDA) had not yet approved any therapeutic cancer vaccines. However, a 2003 search of NCI’s Physician Data Query (PDQ®) found 81 active clinical trials using therapeutic cancer vaccines, more than twice as many trials as were found in a 2002 PDQ search. Table 2 provides a summary of some of the types of vaccines being evaluated to treat a variety of cancers.

### Table 1. Tumor-Associated Antigens and Where They Are Found

<table>
<thead>
<tr>
<th>Type of Antigen</th>
<th>Antigen Name</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer-testis antigens, also known as carcinofetal or oncofetal antigens</td>
<td>Melanoma antigen gene (AGE), genitourinary AGE, breast AGE, renal AGE, lung AGE, sarcoma AGE, head and neck AGE, NY-ESO-1, all X-linked</td>
<td>Usually only seen in the fetus, on the placenta of pregnant women, and on the germ cells of the testis</td>
</tr>
<tr>
<td>Differentiation antigens</td>
<td>Melanoma antigen recognized by T-cells (melan-A), gp100, tyrosinase, TRP-2, prostate-specific antigen, carcinoembryonic antigen, HER-2/neu, epidermal growth factor receptor</td>
<td>Present in many tumor types, including renal cell, head and neck, breast, melanoma, lung, and sarcoma</td>
</tr>
<tr>
<td>Viral-specific antigens</td>
<td>Human papillomavirus 16 E6/E7, Epstein-Barr virus, LMP1, human T-lymphotropic virus</td>
<td>Clearly foreign antigens</td>
</tr>
<tr>
<td>True mutated tumor-specific proteins</td>
<td>Betacatenin, MUM-1 and -3, p53, p15, p16, caspase, human leukocyte antigen-A2, RU2AS</td>
<td>Clearly foreign antigens; not useful in general antitumor therapy because these are patient-specific</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Mucin-1 ganglioside molecules (e.g., GM2, GD2, GD3)</td>
<td>mucin is found on the mucus cells of the gastrointestinal tract.</td>
</tr>
<tr>
<td>Proteins</td>
<td>Heat shock protein (e.g., gp96)</td>
<td>Stress proteins are produced by cells in response to heat, low sugar levels, and other stress signals.</td>
</tr>
</tbody>
</table>

### Autologous Versus Allogeneic Vaccines

Therapeutic cancer vaccines fall into two categories: (a) autologous vaccines, often referred to as patient-specific vaccines, and (b) allogeneic vaccines, also known as “off-the-shelf” vaccines. The personalized, or patient-specific, vaccines are made using a patient’s own tumor cells.

Some production methods require the use of live cells, meaning that fresh tissue from the tumor has to be transported overnight on ice to the manufacturer. Other production methods use DNA or RNA that can be obtained from either fresh or frozen tumor tissue. Patients and healthcare providers must understand that the genetic material needed...
Table 2. Cancers for Which Therapeutic Vaccines Are Being Developed

<table>
<thead>
<tr>
<th>Type</th>
<th>Vaccine Name</th>
<th>Sponsor/Company</th>
<th>Type of Vaccine</th>
<th>Disease Stage, Vaccine Use, or Research Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast, metastatic</td>
<td>Theratope®</td>
<td>BioMira, EMD Pharmaceuticals, Merck KgA</td>
<td>Synthetic siaty-l-Tr vaccine conjugated with keyhole limpet hemocyanin (KLH)</td>
<td>Theratope plus aromatase inhibitor and fulvestrant</td>
</tr>
<tr>
<td>Cervical</td>
<td>Human papillomavirus (HPV) quad-rivalent vaccine</td>
<td>Merck &amp; Company, Inc.</td>
<td>HPV: HPV 16 and 18 (the types that account for more than two-thirds of cases worldwide) and HPV 6 and 11 (the types associated with genital warts)</td>
<td>To assess whether the vaccine prevents HPV infection and precancerous lesions</td>
</tr>
<tr>
<td>Lung cancer, local small cell</td>
<td>BEC2 vaccine</td>
<td>European Organization for Research and Treatment of Cancer (EORTC)</td>
<td>BEC2 (a mouse antibody engineered to resemble the human protein GD3 ganglioside) plus bacillus calmette guerin (BCG)</td>
<td>Local disease</td>
</tr>
<tr>
<td>Melanoma, stage IV</td>
<td>Oncophage® (HSPPC-96)</td>
<td>Antigenics</td>
<td>Heat shock proteins (gp96) and associated peptides from patient’s tumor*</td>
<td>Compares vaccine with interleukin-2, dacarbazine, and temozolomide (DTIC) (conventional chemotherapy regimen)</td>
</tr>
<tr>
<td>Melanoma, stage II</td>
<td>Not named</td>
<td>EORTC</td>
<td>GM2, a common antigen on melanoma cells, conjugated to KLH, given with QS21</td>
<td>Disease-free and overall survival after primary diagnosis of stage II melanoma</td>
</tr>
<tr>
<td>Melanoma of the eye</td>
<td>Not named</td>
<td>EORTC</td>
<td>Vaccine of several melanoma differentiation peptides</td>
<td>High risk for liver metastasis or developing recurrent melanoma of the eye</td>
</tr>
<tr>
<td>Melanoma, metastatic</td>
<td>Not named</td>
<td>National Cancer Institute (NCI)</td>
<td>Peptide vaccine of melanocyte-specific antigens (tyrosinase, gp100 and melanoma antigen recognized by T-cells), given with granulocyte macrophage-colony-stimulating factor (GM-CSF)</td>
<td>Local or advanced metastatic melanoma</td>
</tr>
<tr>
<td>Melanoma, stage IV</td>
<td>Oncophage® (HSPPC-96)</td>
<td>Jonsson CCC</td>
<td>Heat shock protein-peptide complex from surgically removed tissue</td>
<td>Compares vaccine to interleukin-2 and/or chemotherapy (DTIC and temozolomide)</td>
</tr>
<tr>
<td>Melanoma, metastatic</td>
<td>Not named</td>
<td>NCI</td>
<td>Peptide vaccine of gp100:209–217 (210M) with Montanide ISA-51, an oil used to enhance immune response</td>
<td>Compares high-density interleukin-2 with or without vaccine</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Not named</td>
<td>NCI</td>
<td>Patient-derived, idiotype vaccine derived from the myeloma Ig conjugated with KLH, given with GM-CSF</td>
<td>Sibling transplant donor and patient alone are vaccinated to assess antitumor effect</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma (NHL), follicular</td>
<td>Not named</td>
<td>NCI and Bio Vest (manufactures idiotype-KLH)</td>
<td>Idiotype vaccine* conjugated to KLH, given with GM-CSF</td>
<td>Given after prednisone, doxorubicin, cyclophosphamide, and etoposide chemotherapy</td>
</tr>
<tr>
<td>NHL, follicular</td>
<td>MyVax® Personalized Immuno-therapy</td>
<td>Genitope Corporation</td>
<td>Idiotype vaccine* conjugated to KLH, given with GM-CSF</td>
<td>Given after cyclophosphamide, vincristine, and prednisone chemotherapy</td>
</tr>
<tr>
<td>Prostate, metastatic</td>
<td>Not named</td>
<td>Northwest Biotherapeutics</td>
<td>Dendritic cell vaccine (peripheral blood mononuclear cells plus interleukin-4 plus GM-CSF) treated with BCG and stimulated with prostate-specific antigen</td>
<td>Compares disease progression and survival in patients who get peripheral blood mononuclear cells to those who receive the dendritic cell vaccine</td>
</tr>
<tr>
<td>Renal cell, non-metastatic</td>
<td>Oncophage® (HSPPC-96)</td>
<td>Antigenics</td>
<td>Heat shock proteins and associated peptides from patient’s tumor</td>
<td>After surgical resection</td>
</tr>
</tbody>
</table>

* Indicates vaccines that are patient specific or personalized

To make these vaccines cannot be extracted from tissue that has been embedded in paraffin blocks or preserved in formalin. As more patients become interested in therapeutic cancer vaccines, especially personalized vaccines, they will begin to demand that tumor tissue be frozen at the time of biopsy. Because this area of research is growing so rapidly, at least one company, CryoMa Labs, will cryopreserve tumor cells and provide long-term storage for patients who want the option of having a personalized vaccine made in the future (CryoMa Labs, 2003a). Some patients are willing to pay to have this done, but the companies studying therapeutic vaccines often require recently acquired tumor tissue so they have some assurance that they are making a vaccine to a tumor that has not changed characteristics in response to the immune system’s surveillance.

The surface of all cells contains antigens or targets. Some of these antigens are found on normal and tumor cells. One way to treat cancer is to target the TAAs, the antigens that are unique to the cancer cells but not expressed by normal cells (NCI, 2003a). These TAAs can be attached to something
that the body will recognize as foreign, thus stimulating an immune response and causing the tumor cells to die. Once the immune response is started, the patient’s own immune system will seek out and destroy the cancer cells, helping to rid the entire body of cancer (Kinzel & Brown, 2001). This immune response is expected to continue indefinitely, preventing that specific cancer from recurring in the future (Duke, 2003).

Results from early-stage clinical trials with therapeutic cancer vaccines have been encouraging. These studies have shown that vaccines are safe and well tolerated; however, they have not yet shown that they can improve overall survival and freedom from disease. Even if a cure cannot be guaranteed, booster treatments given at regular intervals may maintain patients’ immune response and might be an acceptable option for patients who otherwise would receive chemotherapy or monoclonal antibody therapy.

The allogeneic, or off-the-shelf, vaccines are made from the tumor cells of several people having a specific cancer or tumor cell line. The goal of allogeneic therapeutic cancer vaccines is to induce an immune response to as many TAAs as possible in one vaccine. Because of the variability within tumor types, a patient’s tumor should be tested for the antigens in the vaccine to determine whether it will be effective.

### Antigens, Carrier Proteins, and Adjuvants

Table 2 shows some of the different types of vaccines being used in clinical trials in the United States and Europe (NCI, 2003a). Each type of vaccine has a slightly different way of presenting the TAAs to the immune system to stimulate an immune response. Regardless of how a vaccine is produced, one or more of a disease’s TAAs are used to produce specific immune responses and fight the disease (de Grujil & Curiel, 1999). Vaccines may be manufactured from a whole tumor cell; a protein from a TAA; fragments of proteins also called peptides; lysates, which are the broken membranes of a tumor cell; or a variety of gene therapy approaches which use the protein sequences of the TAAs (Nestle et al., 1998; Vermoken et al., 1999).

Immunizations usually consist of three components administered together to produce the maximum immune effect: (a) the TAAs or vaccine target, (b) a carrier protein, and (c) an adjuvant. In most therapeutic cancer vaccines, the TAAs and the carrier protein are conjugated or chemically linked. The adjuvant either is mixed with the TAAs or administered in a separate injection at the same site as the antigen and carrier protein conjugate; the combined components often are referred to as the vaccine.

### Tumor-Associated Antigens or Vaccine Target

Therapeutic cancer vaccines can target any number of TAAs. Allogeneic vaccines often target the most common antigens seen in a specific disease or cancer in general. The patient-specific or personalized, autologous vaccines are customized so the TAAs in these vaccines are specific to a patient’s tumor cells. The cells that make up each tumor are considered to be genetically identical because they descended from one abnormal cell that escaped surveillance by the immune system (Sklar et al., 1984).

One example is the idiotypic (Id) protein found on the surface of non-Hodgkin lymphoma (NHL) cells. The Id protein can be identified and a vaccine produced from a very small sample of a patient’s tumor. Animal studies show that the Id protein alone does not stimulate a person’s immune system adequately. To produce an immune response strong enough for the immune system to identify and attack the tumor in the future, the Id protein is coupled with a carrier protein and administered with an adjuvant (Genitope Corporation, 2003a; Hsu et al., 1997; Kwak et al., 1992).

### Carrier Proteins

Carrier proteins are highly immunogenic proteins that help the immune system to recognize the attached TAAs as foreign. A carrier protein actually serves as a decoy, attracting the attention of the immune system and initiating an immune response to the TAAs.

In many therapeutic cancer vaccine studies, keyhole limpet hemocyanin (KLH) is used as the carrier protein. KLH is the oxygen-carrying molecule (i.e., hemoglobin equivalent) of the California giant keyhole limpet (Megathura crenulata). In humans, KLH is a foreign protein, causing vigorous local reactions and triggering a strong immune response. When KLH by itself is injected subcutaneously, most patients develop redness, erythema, and induration at the injection site. This reaction occurs because of a localized immune response to the foreign protein. The immune system also is capable of producing antibodies and T-cells against KLH.

When KLH is coupled with a TAA, it triggers the same reaction as when it is injected alone, but it also triggers an immune response to the TAA even though the TAA was not seen previously as foreign. The goal is for patients to mount an antibody (humoral) and a T-cell (cellular) response against the TAAs and the KLH protein in the conjugated vaccine. Studies have shown a strong correlation between clinical responses and the development of humoral and cellular responses (Timmerman, 2003). Although KLH is a non-specific immune modulator similar to interleukin-2 (IL-2) and interferon alpha (IFN-α), researchers do not know whether any cancer fighting benefit is associated with administering the carrier protein alone.

Bacillus calmette guerin (BCG) is an inactivated form of the tuberculosis bacterium that has been used routinely for decades to vaccinate against tuberculosis (Kinzel & Brown, 2001). BCG is added to cancer vaccines with the goal of boosting the immune response to the vaccine antigen. Researchers do not understand why BCG may be effective in producing immune responses, but BCG has been used for years with other vaccines and has been found to be an effective nonspecific immune modulator (NCI, 2003a).

### Adjuvants

Adjuvants are agents that also are known to boost the immune system by luring dendritic and other immune system cells to the site of injection (Jaffee, 2000). The adjuvants used most often with therapeutic cancer vaccines are immune modulators already approved for use. They include granulocyte macrophage–colony-stimulating factor (GM-CSF), IL-2, IFN-α, and the investigational agents DETOX (Ribi Immunochem Research Inc., Hamilton, MT), Freund’s complete adjuvant (CFA), QS-21, and Montanide ISA-51.

GM-CSF is a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoietic progenitor cells. GM-CSF activates macrophages, results in an increase in the functional capacity of monocytes, and serves as the principal mediator for the proliferation, maturation, migration, and antigen-presenting properties of dendritic cells (Timmerman, 2003). GM-CSF is used as an adjuvant because it helps to recruit dendritic cells locally to the site of injection. Dendritic cells help with the processing and presentation of the TAA to B-cells and T-cells that are responsible for generating an immune response. The analogy that dendritic cells are like butlers because they are responsible for “serving up” antigens to the immune system presents a particularly vivid image.

IL-2 is a protein, made in small quantities by the body’s immune system, known to cause proliferation of T-cells and boost the cancer-killing abilities of natural killer cells. Although IL-2 has been shown to activate
The immune system, it is a nonspecific immune modulator, and many researchers believe that IL-2 alone or even in combination with the TAA will not be enough to prevent disease recurrence. Studies currently are under way to determine whether IL-2 will improve the effectiveness of therapeutic cancer vaccines. Although IL-2 was approved as a cancer treatment in 1986, currently it is being studied as an adjuvant with therapeutic cancer vaccines.

Of the interferon family, IFN-α is the most extensively studied and often is used as part of combination therapies. Evidence suggests that adding IFN-α to chemotherapy improves response rates and prolongs survival, so researchers speculate that it also could improve the effectiveness of cancer vaccines (Rubin, 2001).

DETOX is a detoxified endotoxin that acts as a nonspecific immune modulator. It has been used extensively with Melacine in the melanoma vaccine trials and currently is being used in other trials (Kinzler & Brown, 2001). CFA, which first was used by Salk with the polio vaccine in the 1950s, and Freund’s incomplete adjuvant (IFA) also are being studied as potential adjuvants in cancer vaccine trials (Kinzler & Brown). CFA consists of heat-killed mycobacterial cells suspended in mineral oil. IFA is the mineral oil without the mycobacterial cells, so researchers believe that it is less effective than CFA at enhancing cell-mediated immune responses (Kinzler & Brown).

Two newer adjuvants being studied are QS21, a plant extract, and Montanide ISA-51, an oil-based liquid. They are being used in clinical trials with several peptide vaccines (Kinzler & Brown, 2001). Both are being studied to see whether they are better at producing immune responses than the approved cytokines and biologics currently being used.

**Clinical Trial Experience**

Given the large number of early-stage (phase I and II) studies being conducted with therapeutic cancer vaccines, discussing the therapeutic cancer vaccines in phase III clinical trials seems useful. Although several of these investigational cancer vaccines have been used in phase III trials, none of them has received FDA approval. Therefore, looking at several of the largest trials using therapeutic cancer vaccines may be helpful.

Melacine is a simple lysate (made using broken cells) of two melanoma cell lines and the proprietary adjuvant, Enhanzyn™ (Corixa Corporation, Seattle, WA). The two cell lines are chosen because they express many TAAs and because of their ability to generate T-cell responses in vitro. Melacine has been tested and shown to have a finite response rate (less than 10%) when compared to the Dartmouth chemotherapy regimen (carmustine, dacarbazine, and cisplatin along with tamoxifen) in a phase III randomized trial. The Melacine response and survival rates actually were comparable with the chemotherapy regimen but with significantly less toxicity (Hsueh et al., 2002). These trial results led to the Canadian approval of Melacine for use in stage IV melanoma. However, the FDA has not approved the vaccine for use in the United States.

Canvaxin™ (CancerVax Corporation, Carlsbad, CA) is a vaccine composed of three allogeneic tumor cell lines that express at least 38 tumor- or melanoma-associated antigens (CancerVax Corporation, 2003b). Many of these antigens are commonly expressed in tumors: MART-1 in 90%, gp100 in 65%, and MAGE in slightly more than 50% of melanoma tumors. Canvaxin has been administered to more than 2,600 patients with melanoma in phase II trials (CancerVax Corporation, 2003a). Results of phase II studies in patients with stage III and IV melanoma showed a statistically significant increase in median overall survival rates in patients who received the vaccine compared to historical controls. The company has resumed enrolling two phase III, randomized, double-blind, placebo-controlled clinical trials for patients with stage III and IV melanoma after a period during which the company’s studies were on clinical hold to allow standardization of the vaccine manufacturing process. Because many of the same TAAs also are seen in colon tumors, CancerVax Corporation is planning to open a pivotal phase II and III study using Canvaxin to treat advanced colon cancer (CancerVax Corporation, 2003c).

Dendreon Corporation (Seattle, WA) recently completed a phase III clinical trial of the therapeutic prostate cancer vaccine Provenge®. The vaccine generally is well tolerated. The most common side effects were mild infusion-related fevers and chills that resolved in one to two days (Dendreon Corporation, 2003). Previously reported data from the Provenge trial showed a statistically significant benefit in men with Gleason scores of seven or less (Dendreon Corporation). Data from November 2003 show a median survival time of 26.3 months for patients treated with Provenge compared to 19.3 months for those receiving placebo (Dendreon Corporation). The company currently is conducting a second phase III trial to confirm the findings and to seek FDA approval of the vaccine.

Cancer vaccines may have the biggest impact on NHL treatment. Since the late 1980s, Id vaccines have been developed, and the speed of the development is encouraging to patients with indolent NHL who have no known cure for their disease (Bendandi, 2001). Timmerman (2002) wrote that follicular NHL may be the disease most responsive to immune stimulation as evidenced by its ability to undergo spontaneous regression, its ability to respond to nonspecific immune modulators such as BCG and IL-2, as well as the high number of responses to passive immunotherapy such as the B-cell specific (anti-CD20) monoclonal antibody rituximab (Rituxan®, Biogen Idec, San Diego, CA). Id vaccines have been shown to clear residual tumor cells from the blood and produce long-term, disease-free survival in patients with lymphoma (Bendandi, 2000; BioVest, 2003).

Genitope Corporation (Redwood City, CA) and NCI each are conducting large phase III studies of Id vaccines with the carrier protein KLH and the adjuvant GM-CSF in patients with previously untreated follicular NHL. The production methods for the vaccines are different, but they are similar in their treatment schema (Genitope Corporation, 2003b; NCI, 2003b). The Id vaccine used in the NCI trial is produced using the original production technique called “rescue fusion,” which fuses the tumor cells with a myeloma cell, producing a hybridoma that then secretes the Id protein. Genitope Corporation’s MyVax™ Personalized Immunotherapy is manufactured using a molecular rescue method. The molecular rescue method uses Genitope’s patented Hi-GET® technology and allows for predictable, efficient production of recombinant Id vaccine.

Patients in both studies are required to receive standard chemotherapy before the vaccine is administered. Patients in the Genitope trial receive eight cycles of cyclophosphamide, vincristine, and prednisone, whereas the patients in the NCI trial receive eight cycles of prednisone, doxorubicin, cyclophosphamide, and etoposide. Patients must respond to this initial chemotherapy before receiving the vaccine. Genitope Corporation requires that patients achieve at least a partial response to chemotherapy, whereas the NCI study requires that a complete response be achieved. These study designs support the theory that vaccines may be most effective in the setting of minimal residual disease. Both of these trials are randomized and double blind, so some patients will receive their personalized vaccine (Id-KLH) and some will receive the control agent (KLH) alone. All patients receive GM-CSF with their immunizations.

Theratope® (Biomira, Edmonton, Canada) is a sialyl-Tn (STn) vaccine given with the adjuvant DETOX. STn is a carbohydrate
associated with membrane-bound mucin found on several types of cancer cells. Patients with adenocarcinoma and high levels of STn have poorer outcomes than those with normal levels, so STn was thought to be a good vaccine candidate. In February 2002, Biomira began a phase II study to evaluate the vaccine when administered with chemotherapy in patients with colorectal cancers. Theratope given with the adjuvant DETOX also was used to vaccinate 40 high-risk women with breast and ovarian cancer after stem cell transplant. A nonrandomized comparison between the vaccinated and nonvaccinated groups showed prolonged overall survival and recurrence-free survival in the vaccinated group (Holmberg et al., 2000). Based on these results, a phase III randomized clinical trial was conducted using Theratope to treat women with metastatic breast cancer. This study was closed to enrollment in March 2001 with 1,030 women enrolled. The trial, conducted at more than 120 sites in 15 countries, is the largest therapeutic cancer vaccine trial in women with metastatic breast cancer (Biomira, 2003). On June 16, 2003, the results of the study were released and did not show a statistically significant difference in time to progression or overall survival between the patients who received the vaccine and those who did not (Biomira). The women who were receiving hormonal therapy after chemotherapy appeared to have an improvement in survival, and additional analysis of this subset of study participants is currently under way (Biomira).

Oncophage® (Antigenics Inc., New York, NY), a personalized heat shock protein vaccine for renal cell and metastatic melanoma, is in late-stage clinical trials. Results from a phase III trial of the vaccine in kidney cancer are expected later this year. In September 2003, the FDA placed the company’s two phase III trials on partial clinical hold while it attempted to develop product characterization information for the vaccine (Antigenics Inc., 2003a, 2003b). The safety of the vaccine was not in question, so patients being immunized continued to receive their vaccine, and the hold was lifted in November 2003 (Antigenics Inc., 2003b). However, this is not the first time the FDA has put a therapeutic vaccine trial on partial clinical hold to resolve questions about the characteristics of the vaccine.

**Case Study 1**

A 44-year-old female with a history of stage IIIIB, estrogen-receptor negative, progesterone-receptor negative, HER-2/neu negative breast cancer is interested in participating in a clinical trial of a therapeutic vaccine for breast cancer. The patient had undergone a lumpectomy and axillary lymph node dissection followed by chemotherapy with cyclophosphamide, adriamycin, and fluorouracil and Taxotere® (docetaxol, Aventis, Bridgewater, NJ) as well as local, fractionated radiation to the breast and axilla. She has been disease free for two years but is aware that she is at high risk for disease recurrence and is interested in participating in a cancer vaccine clinical trial.

**Question:** Where might you direct this patient to look for information on clinical trials of therapeutic cancer vaccines?

**Answer:** PDQ is an excellent resource for patients and healthcare providers. This database, accessed from www.cancer.gov, includes all phases of clinical trials and can be searched by disease type or treatment type.

**Question:** How can you help this patient to determine whether a clinical trial of a therapeutic cancer vaccine might be appropriate for her?

**Answer:** If this patient does not have active disease, she will have difficulty participating in an autologous (personalized) vaccine trial unless she has tissue from her diagnostic biopsy or lumpectomy frozen for use in such a study. She might be eligible for a phase I or pilot study of an allogeneic vaccine for women who are at high risk for recurrence.

**Case Study 2**

A 45-year-old male with a new diagnosis of indolent, follicular NHL presents to discuss treatment options with his hematologist. He does not want to have chemotherapy because his research has shown that chemotherapy does not improve overall survival when administered at diagnosis. However, he is aware of a phase III clinical trial of a therapeutic cancer vaccine in NHL and is interested in participating.

**Question:** What can you tell the patient about the clinical experiences with therapeutic cancer vaccines in NHL?

**Answer:** Id vaccines have been studied in NHL for more than a decade. These vaccines appear to be safe and generally are well tolerated, but no therapeutic cancer vaccine is approved by the FDA for use in the United States. Numerous studies are being conducted with therapeutic cancer vaccines in NHL and many other liquid and solid tumors.

**Question:** What would you tell the patient about receiving chemotherapy?

**Answer:** The patient’s tumor burden may need to be reduced with chemotherapy so that the immune system will be able to rid the body of residual disease. Vaccines may work best in the setting of minimal residual disease and with slower growing tumors or indolent hematologic malignancies.

**Summary**

Although some prophylactic cancer vaccines are in development, the bulk of the work with cancer vaccines is in the area of therapeutic cancer vaccines (“Developing cancer vaccines,” 2003). As advances are made in immunology, genetics, and a host of other scientific areas, people who are at high risk for developing cancer may be identified and can receive prophylactic vaccines (Timmerman & Levy, 2000). Until that time, only therapeutic cancer vaccines will be tested in patients with cancer.

With the exception of the hepatitis B vaccine, all therapeutic cancer vaccines are investigational. These investigational agents have yet to show prolonged survival in randomized trials in patients with cancer. However, much work in this area still must be completed and the extensive research, and experience gained in lymphoma may be applied to other tumors with well-defined TAs (Stevenson et al., 1995). Therapeutic cancer vaccines could be approved for clinical use within three to five years (Cryoma Labs, 2003b). Cost-effective production of therapeutic cancer vaccines, especially personalized vaccines, for thousands of patients represents a challenge for companies in the future (Timmerman, 2003).

Researchers also must consider whether current trials using therapeutic cancer vaccines are occurring in optimal settings (Weiner & Kim, 2002). Investigational therapies are often used in advanced cancer, but researchers have sufficient knowledge about the functioning of the immune system to speculate that vaccines may not be most effective in this setting. Giving vaccines at the time of initial diagnosis, when patients’ immune systems have not been bombarded with chemotherapy and the cancer has not become treatment-resistant, may be more effective than waiting until patients have failed several other therapies (Bendandi, 2000). Demonstrating that cancer vaccines are effective will be difficult if they are used in clinical trials that enroll patients with bulky, relapsed disease. These patients are less likely to respond to cancer vaccines than patients who are in remission or have minimal disease either at diagnosis or after treatment to reduce the amount of the tumor (Press et al., 2001). Determining the timing of therapeutic cancer vaccines and the optimal immunization schedule will be essential to their success.
Frost and Sullivan (2001) predicted that vaccines for melanoma and colorectal cancer would be available to patients in 2002, but this has not yet become a reality. However, with more than 150 other vaccines in development, this innovative new cancer treatment will be seen in the near future. Healthcare providers should be prepared to discuss this emerging new therapy with patients. What is known is that therapeutic cancer vaccines are generally safe and well tolerated. They usually produce fewer side effects when compared to chemotherapy, monoclonal antibodies, and other biologic agents. The most frequently reported side effects are (a) local injection site reactions, including redness, pain, swelling, and itching, and (b) flu-like symptoms, including fever, chills, and fatigue as well as muscle and joint aches (CancerVax Corporation, 2003b).

At this time, researchers have not determined whether therapeutic cancer vaccines will be used as monotherapy (by themselves), adjuvant therapy (after surgery, radiation, or chemotherapy has been used to reduce tumor burden), or maintenance therapy to ensure that immune responses remain robust so recurrent disease can be prevented (New Medicine, Inc., 1997). Cancer vaccines are an emerging treatment strategy in the ongoing battle against cancer. See Figure 1 for a list of commonly asked questions regarding cancer vaccines.

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References


1. Are any cancer vaccines approved for use in the United States? The U.S. Food and Drug Administration’s (FDA’s) Web site states that the hepatitis B vaccine is an approved cancer vaccine. Because hepatitis B is known to increase the risk of primary liver cancer in a subset of the population, the FDA considers this vaccine to be a prophylactic cancer vaccine (National Cancer Institute, 2003a).
2. What are the side effects if a patient accidentally receives a patient-specific cancer vaccine that was produced for another patient? The most frequently occurring side effect is local injection site reaction, which still would be expected because the reaction occurs as a result of the injection of a foreign protein. Therapeutic effect would not be expected because the vaccine was made for another patient.
3. What medications are contraindicated for patients receiving therapeutic cancer vaccines? Steroids are absolutely contraindicated because they inhibit the immune system from responding to the vaccine. Fludarabine may be contraindicated because it eliminates the T-cells that are essential for humoral immune responses. Concurrent rituximab therapy also may be contraindicated because it reduces the circulating B-cells that may be important for achieving an immune response.
4. A patient wants to have tumor tissue frozen for use in making a patient-specific vaccine should it become commercially available. The patient also is inquiring about tissue banking. What are the differences? Can tissue from the tissue bank later be used for making a vaccine for the patient? Tissue banking often is used to procure multiple specimens from people with the same diagnosis. It is a way to determine the genetic and molecular similarities and differences among specimens when the pathologic diagnosis is the same. The antigens found in each tumor type are being cataloged by establishing specialized tissue banks in the United States and Canada. Tissue samples from patients with cancer are being cataloged so that retrospective research can be conducted if and when new genetic characteristics or markers are identified. At this time, only limited opportunities are available for tissue banking. The possibility exists that this could be a future source of tissue for vaccine production. This may depend on whether the tissue bank simply stores the frozen tumor tissue or if it makes cell suspensions from the tissue. Many companies will use only tissue that has not been manipulated for manufacturing vaccines, and they often require that the tissue be acquired recently (e.g., within 90 days prior to submission).
5. How are monoclonal antibodies different from therapeutic vaccines? Monoclonal antibodies attach to a single target on the cell surface. This target also may be present on normal cells as in the case of CD20-positive B-cells. Cancer vaccines target the tumor cells, and normal cells are not affected. Monoclonal antibodies provide passive or short-term immunity, whereas vaccines induce active immunity that can result in long-term and possibly lifelong disease control.

Figure 1. Commonly Asked Questions About Cancer Vaccines
Therapeutic Cancer Vaccines: An Emerging Treatment Option

Therapeutic cancer vaccines produce T-cell and antibody responses. They are thought to trick the immune system into attacking the carrier protein and the patient’s tumor. Antigens, or targets, are on the surface of all cells, and one way to treat cancer is to target the antigens that are unique to cancer cells but not found on the surface of normal cells. Therapeutic cancer vaccines can target any number of these tumor-associated antigens (TAAs).

Carrier proteins are highly immunogenic proteins that help the immune system to recognize the attached TAAs as foreign. Adjuvants are agents that boost the immune system by luring dendritic cells to the injection site. They are thought to trick the immune system into attacking the carrier protein and the patient’s tumor.