Patient-Specific Vaccine Therapy for Non-Hodgkin Lymphoma

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Non-Hodgkin lymphoma (NHL) is a hematologic cancer in which cells of the lymphatic system called lymphocytes (also known as B cells and T cells) become malignant. NHL is the sixth most common cancer among men and women. Approximately 54,000 new cases of NHL were expected to be diagnosed in the United States in 2004 (Jemal et al., 2004).

NHL has many different subtypes. Follicular NHL, the second most common subtype after diffuse large B-cell lymphoma (see Figure 1), has been the main focus of vaccine clinical trials (The Non-Hodgkin’s Lymphoma Classification Project, 1997). Follicular NHL arises from B cells and usually presents with painless enlargement of lymph nodes. These lymphomas are considered low-grade or indolent in nature as compared to other more aggressive histologies. Because the disease is slow growing, many patients live with follicular NHL for several months to years before initial treatment. Occasionally, spontaneous regression followed by regrowth of tumors is seen. Therefore, a watch-and-wait approach often is recommended until the disease becomes more aggressive or causes symptoms that require treatment. Although follicular NHL usually responds to initial therapy, no cure exists, and treatment is considered palliative. The disease is characterized by multiple relapses and remissions, with a median overall survival of 10 years. Several effective therapies for follicular NHL exist (e.g., chemotherapy, antibody therapy, radiation therapy); however, no improvement in overall survival has been demonstrated with these therapies alone or in combination (Horning, 1993; Rohatiner & Lister, 1998).

Follicular non-Hodgkin lymphoma (NHL) is an indolent, or slow-growing, malignant disease of the lymphoid tissue, which usually responds to initial therapy. However, the disease is characterized by multiple relapses and remissions, eventually causing death. Several effective therapies are available, but improvement of overall survival in patients with follicular NHL has not been demonstrated. Stimulation of the immune system to recognize malignant lymphoma cells as foreign has been demonstrated as a viable treatment option for patients with follicular NHL. Patient-specific vaccine therapy is a new form of active immunotherapy being studied for NHL. Clinical trials have shown a benefit for patients receiving this type of therapy. This article will provide a foundation for nurses caring for patients receiving patient-specific vaccine therapy.

Non-Hodgkin Lymphoma and the Immune System

NHL arises from normal B cells and T cells. The B cells and T cells are lymphocytes, which are the primary cells necessary to elicit strong immune system responses (Kunkel, 2004). Eliciting an immune response against NHL has been attempted with the intent to stimulate the immune system to recognize antigens on the malignant cells as foreign.

The immune system is a complex one, designed to protect individuals from foreign substances such as pathogens and tumors. Blood lymphocytes (B cells and T cells) and dendritic cells play important roles in immunity. Two types of immunity exist: humoral and cellular. When B cells are stimulated by a foreign antigen, a humoral response occurs. B cells mature into plasma cells and memory B cells. Plasma cells are active with the initial immune response. Memory B cells become active with subsequent responses that occur with future exposures to the same foreign antigen (Bauer, 2000). The B cells then produce antibodies, which bind with the antigen, inactivating the foreign substance. When T cells are stimulated, a cellular response occurs. Cellular responses occur against the body’s own cells that have become infected or malignant. The T cells bind to antigens on the cells, causing cell death.

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As part of an immune response, B and T cells can differentiate into memory cells, which provide permanent immunity against a specific antigen. T cells can recognize an antigen after it is processed and presented by dendritic cells, macrophages, and B cells (Bauer, 2000). Dendritic cells are the most potent antigen-presenting cells (APCs) in the immune system. Only dendritic cells can initiate an immune response in a host not previously exposed to specific antigens. Dendritic cells can stimulate T cells and natural killer cells to destroy tumor cells (Ribas, Butterfield, Glaspy, & Economou, 2003).

Passive and active forms of immunotherapeutic treatments have been used in the treatment of NHL. Rituximab is an example of passive immunotherapy in which the monoclonal antibody is produced outside of the body rather than by the patient’s immune system (American Cancer Society, 2003). The antibody is injected or infused into the body to target a specific antigen. Vaccine therapy is an example of active immunotherapy. Vaccines work by stimulating the body’s immune system to attack the tumor through B cell antibody production (humoral response), activation of T cells (cellular response), and other immune activation. Active immunotherapy is effective longer than passive immunotherapy because the patient’s immune system is more likely to produce memory cells against the antigen (Vose, 2002).

The vaccines currently under investigation for lymphoma are personalized, meaning that they are made from a patient’s own tumor and can only modulate the immune system of the person for whom they are made. Each normal B cell expresses a unique immunoglobulin on the surface, called the idiotype. When a B cell undergoes malignant transformation, the idiotype that is specific to the malignant cell can serve as a tumor-specific target (Miller, Lowder, Meeker, Brown, & Levy, 1987) (see Figure 2). This target is useful in patient-specific immunotherapy in which the idiotype protein is used to manufacture a patient-specific vaccine. The vaccine will target the lymphoma cell, and normal cells will not be affected (King, 2004). Follicular B-cell lymphoma is an ideal malignancy for patient-specific vaccine therapy because each tumor has the necessary idiotype cell surface marker and the disease is slow growing, which allows time for production of the vaccine.

### Components of Patient-Specific Vaccines

Patient-specific vaccines are made up of several components administered together to get the maximum immune effect. These components may include an idiotype protein, a carrier protein, and an adjuvant.

The term idiotype refers to the unique determinants (identifiers) present in the variable regions of the surface immunoglobulin on the lymphoma cell. The immunoglobulin (Y-shaped antibody) of each B cell is unique and contains two variable regions that act as receptors to foreign antigens. When a B cell undergoes malignant transformation, the variable regions of the immunoglobulin undergo a genetic rearrangement (Davis, Maloney, Czerwinski, Liles, & Levy, 1998). The unique determinants on the immunoglobulin include two identical heavy chains and two identical light chains that are expressed by the malignant B-cell lymphoma but not by normal B cells (Hsu et al., 1997) (see Figure 3). Idiotype vaccines require that the light chain and the heavy chain be identified to effectively produce a vaccine. Each lymphoma cell expresses the same unique target or idiotype (Davis et al.; Kunkel, 2004).

The malignant B cell maintains self-antigens that were expressed on the normal, nonmalignant B cell. Therefore, these antigens may not be able to express a strong immune response against what it considers to be itself because of immunologic tolerance (Kunkel, 2004). Because of this, administering the tumor idiotype protein alone as a vaccine may not be enough to stimulate production of antibodies against the tumor. A correlation appears to exist between the development of an immune response and long-term disease remission. To maximize the immune response, the idiotype protein typically is conjugated with a carrier protein and administered with an adjuvant (Kinzler & Brown, 2001; Kunkel).

Carrier proteins are highly immunogenic and chemically linked to the idiotype protein. This helps the immune system to recognize the idiotype protein as foreign. The most recent work with vaccine therapy uses keyhole limpet hemocyanin (KLH) as the
is produced while the patient is receiving the standard chemotherapy regimen. The patient’s immune system is given several weeks to recover after chemotherapy and before beginning vaccinations. The vaccinations then are given in a series of injections over a period of weeks or months (see Figure 4). Clinical trials continue to evaluate the most effective treatment schedules.

**Treatment Schedule**

The treatment schedules for lymphoma vaccine therapy are varied. The most common schedule tested in clinical trials for newly diagnosed patients consists of several immunizations following chemotherapy. Once tumor tissue has been obtained for vaccine production, patients typically receive a standard chemotherapy regimen until remission. A low tumor burden at time of immunization may be ideal for vaccine therapy (Kinzler & Brown, 2001). The vaccine carrier protein. The KLH protein is taken from the California giant sea snail called *Megathura crenulata*. In humans, KLH is seen as a foreign protein that triggers a vigorous immune response, including injection site reactions, in most patients. When the idiotype protein and KLH are combined (Id-KLH) for injection, an immune response can be mounted (Neelapu, Basker, & Kwak, 2001).

Adjuvants are agents that are known to boost the immune system. An adjuvant also may act as a decoy, tricking the immune system into attacking the carrier protein, the attached idiotype protein, and, subsequently, the patient’s tumor (National Cancer Institute, 2003). Examples of adjuvants used currently with patient-specific vaccines include granulocyte macrophage–colony-stimulating factor (GM-CSF), interleukin-2, and interferon (Kinzler & Brown, 2001). A common immunologic adjuvant used with Id-KLH is GM-CSF; a hematopoietic growth factor. GM-CSF is believed to recruit dendritic cells by encouraging antigen presentation directly to the Id-KLH injection site, helping to generate an immune response (King, 2004; Ribas et al., 2003).

**Vaccine Trials for Follicular Lymphoma**

The first clinical trial using idiotype vaccine therapy for follicular NHL was initiated at Stanford University in 1988 (Hsu et al., 1997). An important observation in the trial was that patients who developed a positive humoral response had a more favorable disease response and prolonged disease-free survival as compared to those who did not mount an immune response. The patients were observed for overall survival from the time of diagnosis and compared with a group of 260 historical control patients from the Stanford University School of Medicine database who had the same diagnosis and chemotherapy treatment (Levy, 1999) (see Figure 5).

In a similar trial using Id-KLH plus GM-CSF for follicular NHL, Bendandi et al. (1999) reported that they were able to induce molecular remissions in patients who were bcl-2 (B-cell lymphoma-2) positive prior to receiving a patient-specific vaccine. Eight of eleven patients converted from bcl-2 positive to bcl-2 negative by molecular testing after receiving vaccinations. The presence of the bcl-2 protein, also known as chromosomal translocation t(14;18), suggests that residual lymphoma is present even though a patient may be in clinical remission based on standard diagnostic tests. This protein prevents programmed cell death by apoptosis and has been correlated with a shortened clinical remission (Meijerink, 1997; Weisenburger et al., 2000). Patients with persistent circulating tumor cells that are bcl-2 positive by polymerase chain reaction technique are considered at risk for relapse (Bendandi et al.). An increased immune response and ability to achieve molecular remission with conversions to bcl-2 negativity strengthened the role of Id-KLH (Kunkel, 2004).

Timmerman et al. (2001) also reported a phase II trial for newly diagnosed follicular lymphoma. Molecular biology techniques were used to produce the idiotype protein. Positive humoral and cellular responses were observed in this trial. Molecular responses and tumor regressions also were reported. Based on the results of the study, a phase III clinical trial was initiated by Genitope Corporation, based in Redwood City, CA.

**Vaccine Production Strategies**

Recent advances in molecular biology and cell culture technology have led to improvements in production methods for vaccines (Timmerman, 2003). Production of a vaccine may take weeks to months, depending...
on the complexity of the manufacturing process used. The type of tissue or tumor cells needed also depends on the manufacturing method used. Some manufacturing methods require the use of fresh tissue because the tumor cells must remain alive. Other methods may allow for the use of frozen tissue (King, 2004).

Timmerman (2003) provided an overview of the current methods used to manufacture idiotype vaccines for lymphoma. One of the methods is a manufacturing process developed by Genitope Corporation using a combination of molecular biology and gene amplification techniques. The process is used to produce MyVax Personalized Immunotherapy (Genitope Corporation, 2004; King, 2004) (see Figure 6). The National Cancer Institute uses a rescue-fusion method that fuses the tumor cell with a myeloma cell. This produces a hybridoma, which secretes the idiotype protein (King). Favrille Corporation in San Diego, CA, produces the idiotype protein for FavrId™ using sf19 insect cells (Timmerman). Large Scale Biology in Vacaville, CA, also produces an idiotype vaccine using the tobacco plant (Large Scale Biology, 2005).

Other advances in vaccine production have led to the development of vaccines using dendritic cells, tumor DNA, heat shock proteins, and viral vectors. Timmerman et al. (2002) reported that patients with follicular NHL who were given dendritic cell vaccine were able to mount a positive immune response against the idiotype. The patients also showed tumor regression and a prolonged time to progression after vaccination. The dendritic cells are collected from the peripheral blood by leukapheresis and then exposed to a cytokine, causing the cells to differentiate (Jaffee, 2000). In the Timmerman et al. (2002) study, the dendritic cells were mixed or “pulsed” with the patient’s tumor antigen to create a vaccine, which was administered by IV infusion. Each infusion was followed two weeks later with subcutaneous injections of tumor antigen and immune stimulant without dendritic cells (Timmerman et al., 2002).

A DNA vaccine is made by isolating DNA, which is the genetic information of the tumor antigen from the tumor. The DNA then is combined or fused with proteins, bacteria, viruses, or other adjuvants so that the DNA can be processed by APCs. Once injected into the patient, the altered DNA is anticipated to be seen as foreign and, therefore, stimulate an immune response (Kunkel, 2004; National Cancer Institute, 2003, 2004b).

Heat shock vaccines consist of heat shock proteins (HSPs) and associated peptide complexes found in tumor cells. HSPs are isolated when a tumor cell is subjected to environmental changes, thereby releasing immune stimulators inside the cell. When administered to a patient, HSPs function as a danger signal to the immune system and generate a response against the disease (Antigenics, 2003).

A virus also may be enlisted to help deliver a tumor antigen to the immune system (National Cancer Institute, 2003). Viral vaccines prompt a patient’s immune system to react to the injected virus that has been modified to carry the immune-stimulating genes from a tumor without causing disease (Davis, 2002). This technique introduces the tumor antigen gene into viruses, which then attract APCs and maximize the immune response (Muehlbauer & Schwartzentzuber, 2003).

### Nursing Considerations

Although vaccine therapy generally is well tolerated, nurses caring for patients receiving it should understand the treatment rationale and plan. They also must provide patients with adequate education regarding this therapy.

Depending on the vaccine treatment schedule, patients may be required to self-inject the adjuvant for a number of days after Id-KLH administration. Therefore, self-injection techniques and return demonstrations are recommended with the first and possibly subsequent injections. Because the adjuvant assists with recruitment of dendritic cells, it should be injected near the site where the patient-specific vaccine is administered. For this reason, the injection site must be marked clearly (see Figure 7).

During vaccine therapy, nurses should stress the possible treatment-related toxicities. The most common are flu-like symptoms (fevers, chills, sweats, and generalized body aches and pains) and localized skin irritations (redness, swelling, induration, tenderness, and itching) (Kinzler & Brown, 2001; Muehlbauer & Schwartzentzuber, 2003). Patients should be aware that a localized skin irritation can become rather large (see Figure 8). These are expected toxicities that may be associated with the vaccine and/or adjuvant.

Symptom management for these patients may include over-the-counter medications such as acetaminophen or nonsteroidal anti-inflammatory drugs for the flu-like symptoms or injection site tenderness. Applying ice as needed for comfort to the affected sites.

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**Figure 5. Overall Survival in Patients With a Positive Immune Response (Responders) Versus No Immune Response (Nonresponders) Compared to Historical Controls**


**Figure 6. Production of Recombinant Idiotype and Keyhole Limpet Hemocyanin Using Gene Amplification Technology**

*Note. Image courtesy of Genitope Corporation. Reprinted with permission.*

**Figure 7. Vaccine Administration**

The vaccine is given by subcutaneous injection. Adjuvant also is given subcutaneously at the same site of vaccine to help recruit the immune system. A bull’s-eye can be drawn on the patient’s skin to mark the site clearly for subsequent self-injections of the adjuvant.
usually is an effective local treatment of injection site reactions (Genitope Corporation, 2003). Pruritus can be treated with over-the-counter medications such as nonsteroidal antiinflammatory cream. Some researchers believe that steroids may interfere with the body’s capacity to develop an immune response; therefore, their use has been discouraged (King, 2004).

Routine hematology and chemistry profiles should be monitored on a regular basis. Although no dramatic changes in laboratory values are expected, patients receiving the adjuvant, GM-CSF, may experience an elevated white blood cell count. Periodic measurements of immune response (e.g., humoral, cellular) may be assessed to determine whether a patient has mounted a response against the disease. Clinical trials continue to evaluate the significance of immune response testing.

A concern exists of developing or exacerbating autoimmune diseases with vaccine therapy. This has been demonstrated in patients with chronic arthritis who received adult rubella and hepatitis B vaccinations. Although the patients were not immunized with a dendritic adjuvant, the risk of patient-specific lymphoma vaccines causing an autoimmune response exists (Geier & Geier, 2002), Wraith, Goldman, and Lam (2003) provided a review of possible association and related risks of vaccination and autoimmune disease. Clinical evidence also exists that stimulation of the dendritic cell lines while receiving vaccine therapy may cause progression of autoimmune disease. Therefore, patients with a history of autoimmune disease should be observed for potential autoimmune adverse effects or excluded from this type of therapy (Bondanza et al., 2003).

**References**


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**Future Directions**

The future of vaccine therapy is very exciting, but efficacy has yet to be established. Currently, two phase III randomized, double-blind trials of Id-KLH vaccines in untreated follicular NHL are under way in the United States. The two trials are sponsored by the National Cancer Institute and Genitope Corporation. Patients on each trial receive chemotherapy after tissue acquisition for vaccine production. Patients in remission following induction chemotherapy are randomized to receive double-blind (Id-KLH plus GM-CSF versus KLH alone plus GM-CSF) vaccinations according to the treatment schedule (Timmerman, 2003). Results of these pivotal trials will be very important in determining the overall effectiveness of vaccine therapy and may change treatment outcomes for patients with follicular NHL. In 2004, a third phase III trial of an Id-KLH vaccine following rituximab opened for treatment of naive patients or patients with relapsed or refractory follicular NHL (National Cancer Institute, 2004a).

Clinical trials will help healthcare professionals learn more about which types of lymphoma will have the greatest benefit from patient-specific vaccine therapy. Timing of vaccination also is an important consideration. Must patients be treated with chemotherapy before vaccination, and what type of treatment is best? Is vaccination at time of initial diagnosis best, or should vaccinations follow peripheral stem cell transplantation? Booster injections also may play an important role in maintaining remissions after initial responses to patient-specific vaccine therapy. Many of these questions are being studied in clinical trials. Time will tell how this new and exciting therapy will benefit patients with follicular NHL.

**Figure 8. Injection Site Reaction**
Rapid Recap

**Patient-Specific Vaccine Therapy for Non-Hodgkin Lymphoma**

- Patient-specific vaccine therapy is a unique and personalized approach to the treatment of non-Hodgkin lymphoma.
- Patient-specific vaccine therapy typically consists of the administration of an idiotype protein, a carrier protein, and an adjuvant.
- Clinical trials that support the use of patient-specific vaccine therapy have been conducted.
- Patient-specific vaccine therapy has limited side effects and generally is well tolerated by patients.


