Dendritic Cells: Emerging Roles in Tumor Immunotherapy

Patricia C. Buchsel, RN, MSN, FAAN, and Elaine S. DeMeyer, RN, MSN, AOCN

The purpose of this article is to examine the use of myeloid dendritic cells (DCs) as immunotherapy in the treatment of cancer. DCs can be stimulated either from circulating blood or bone marrow progenitor cells using cytokines, particularly granulocyte macrophage–colony-stimulating factor (GM-CSF) (e.g., sargramostim, Leukine®). GM-CSF has been shown to promote maturation, mobilization, and antigen presentation of DCs in vivo or ex vivo as a therapeutic cancer vaccine. Once stimulated, DCs can present tumor antigen to naive T cells to initiate an immune response. In addition to myeloid-related DC stimulation, antitumor properties of GM-CSF include direct cytotoxicity, antiangiogenesis properties, and potential upregulation of antibody-dependent cellular cytotoxicity. Oncology nurses need to be knowledgeable regarding new therapies. Using knowledge gained through reading professional journals and self-education, nurses can inform patients of new therapies, which may increase patients’ hope.

At a Glance

✦ Tumor immunotherapy is a treatment that enhances the immune system to destroy cancer cells.
✦ Strategies to improve dendritic cell (DC) function include augmentation with granulocyte macrophage–colony-stimulating factor (GM-CSF) use alone, in DC-based vaccines, as a vaccine adjuvant, or in combination therapy and may play a role in enhancing antibody-dependent cellular cytotoxicity.
✦ Nursing implications include the need to seek an understanding of the evolving uses of GM-CSF as a possible antitumor agent, to encourage patients to enter approved clinical trials, and to manage the care of those seeking emerging treatments.

DeMeyer & Buchsel, 2005). Table 1 lists current National Cancer Institute open trials involving DC therapy.

This article has several purposes. The first is to offer a brief discussion of the relationship between a defective immune system and cancer. An appreciation of the relationship is essential to

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### Table 1. Current Clinical Trials in Vaccine Therapy

<table>
<thead>
<tr>
<th>STUDY OBJECTIVE</th>
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<th>TYPE OF TRIAL</th>
<th>STUDY QUESTION</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Determine the safety and feasibility of administering one or two courses of vaccination with CAP 1–6D and CMV pp65 peptide-pulsed autologous DCs in patients with refractory stage IV CEA-expressing malignancies</td>
<td>Refractory stage IV CEA-expressing malignancies</td>
<td>Phase I</td>
<td>Can vaccines derived from a patient’s own white cells and tumor cells be administered to determine whether the patient’s immune system will destroy the cancer?</td>
<td>NCI 00057915</td>
</tr>
<tr>
<td>Cancer vaccine clinical trials after HCT</td>
<td>Breast cancer</td>
<td>Phase I and II</td>
<td>Can the use of immunotherapy with CEA RNA-pulsed autologous DCs achieve a complete remission after HCT?</td>
<td>NCI 98-1455</td>
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<tr>
<td>Vaccine therapy with GM-CSF compared with placebo and GM-CSF following treatment with rituximab</td>
<td>B-cell non-Hodgkin lymphoma</td>
<td>Phase III</td>
<td>Will combining rituximab and GM-CSF administered with a conjugate vaccine shorten disease progression in patients who have newly diagnosed relapsed or refractory disease?</td>
<td>NCI 00089115</td>
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<tr>
<td>Randomized trial of patient-specific vaccination with conjugated follicular lymphoma-derived idiotype with local GM-CSF in first complete remission</td>
<td>Lymphoma</td>
<td>Phase III</td>
<td>Will an experimental autologous vaccine using GM-CSF be as effective as traditional treatment in achieving long-term survival compared to traditional therapies?</td>
<td>NCI T 00001945</td>
</tr>
<tr>
<td>Study vaccine therapy with MART-1 adenovirus-transduced DCs treating patients with stage IV or recurrent malignant melanoma</td>
<td>Melanoma</td>
<td>Phase I and II</td>
<td>What are the clinical responses of vaccine therapy in treating patients with stage IV or recurrent malignant melanoma in a dose-escalation study?</td>
<td>NCI 00039325</td>
</tr>
<tr>
<td>Study of immune responses to antigen-bearing DCs</td>
<td>Melanoma</td>
<td>Phase I and II</td>
<td>Can several tumor antigens made in the laboratory be combined with DCs to make T cells work against tumor cells in patients with advanced lymphoma?</td>
<td>NCI 00039325</td>
</tr>
<tr>
<td>Vaccine therapy in treating patients with stage IIIB, IIIC, or IV cancer</td>
<td>Melanoma</td>
<td>Phase I and II</td>
<td>What is the immune response in patients with stage IIIB, IIIC, or IV melanoma treated with vaccine comprising multiple synthetic melanoma peptides, montanide ISA-51, and sargramostim (GM-CSF)?</td>
<td>NCI 5906</td>
</tr>
<tr>
<td>Injection of an adjuvant in patients with stage IIIB, IIIC, or IV melanoma with multi-epitope peptide vaccine using GM-CSF DNA as an adjuvant; a pilot trial to assess safety and immunity</td>
<td>Melanoma</td>
<td>Phase I and II</td>
<td>What is the optimal dose of GM-CSF used as an adjuvant to vaccines containing fragments of two proteins (gp100 peptide and tyrosinase peptide)? What is the effectiveness of the vaccine in immunizing patients with stage II–IV melanoma?</td>
<td>NCI 00085189</td>
</tr>
<tr>
<td>A randomized placebo-controlled trial of yeast-derived GM-CSF peptide vaccination versus placebo in patients with no evidence of clinical disease after complete surgical resection of locally advanced or stage IV melanoma</td>
<td>Melanoma</td>
<td>Phase III</td>
<td>What is the survival rate and time to progression of patients with completely resected stage IV melanoma or stage III melanoma who receive a peptide vaccine with GM-CSF adjuvant?</td>
<td>NCI 000005034; Southwest Oncology Group E 4697</td>
</tr>
<tr>
<td>Evaluation of the effects of local GM-CSF in adjuvant administration in the skin and sentinel lymph nodes</td>
<td>Not a treatment trial</td>
<td>–</td>
<td>What is the optimal administration site for GM-CSF injections to facilitate mature DC performance when given as a vaccine adjuvant?</td>
<td>University of Virginia Health Care System HIC No. 8350; MEL No. 38</td>
</tr>
<tr>
<td>A safety and feasibility study of active immunotherapy in patients with metastatic prostate carcinoma using autologous DCs pulsed with antigen encoded in amplified autologous tumor</td>
<td>Metastatic prostate carcinoma</td>
<td>Phase I</td>
<td>Is it possible to administer a vaccine to induce an antitumor effect using patients’ DCs cultured with their tumor tissues?</td>
<td>NCI 00006430</td>
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<td>Vaccine therapy in treating patients with stage IIIB, IIIC, or IV cancer</td>
<td>Melanoma</td>
<td>Phase I and II</td>
<td>What is the immune response in patients with stage IIIB, IIIC, or IV melanoma treated with vaccine-containing multiple synthetic melanoma peptides, montanide ISA-51, and GM-CSF?</td>
<td>NCI NCT00089219</td>
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<td>Evaluation of local GM-CSF in adjuvant therapy and the number of vaccine sites</td>
<td>Melanoma</td>
<td>Phase III</td>
<td>What is the safety and efficacy of vaccine adjuvant (montanide adjuvant alone versus montanide with</td>
<td>University of Pennsylvania Medical Cancer</td>
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CAP—adenylate cyclase–associated protein; CEA—carcinoembryonic antigen; CMV—cytomegalovirus; CTA—carcinoembryonic tumor antigen; DC—dendritic cell; GM-CSF—granulocyte macrophage–colony-stimulating factor; HCT—hematopoietic stem cell transplantation; MART-1—melanoma antigen recognized by T cells; MDA—malon dialdehyde; NCI—National Cancer Institute; pp65—specific T cell; PSA—prostate-specific antigen

Note. Based on information from National Cancer Institute, 2005.
understanding the use of rhCSFs to stimulate the immune system for improved response rates, particularly in patients with a variety of solid tumors. Second, clinical strategies to improve DC function will be discussed. Content will include examination of the rationale and clinical uses of tumor immunotherapy approaches focusing on DCs in vivo with the use of GM-CSF or ex vivo to manufacture a DC-based cancer vaccine. A summary of current evidence-based DC research in melanoma, breast, and prostate cancer is included. Finally, discussion will include the role of various cytokines in combination with targeted therapy (e.g., monoclonal antibodies) in an effort to further enhance immune-mediated cell kill via ADCC. Nursing implications focusing on emerging administration techniques and management of patients receiving the novel therapies will be addressed.

**Immune Defects in Cancer**

The immune system is a dynamic and complex network of physical barriers, cell types, and bloodborne proteins that defends the body against pathogenetic organisms such as cancer and other antigens. Recent literature discusses this complex topic (Janeway, Travers, Walport, & Capra, 2001; Mautner & Huang, 2003; Schmidt & Wood, 2003; Sompayrac, 2003). The cardinal features of the adaptive immune system are specificity and memory. If altered cell signaling disrupts either, dysfunction may occur. For example, endogenous growth factors that regulate specific cell growth may aberrantly adhere to toxic cell membranes and communicate (via signal transduction) a message to the internal cell structures to proliferate. Other cellular environments that produce dysfunction are listed in Figure 1.

Although innate and adaptive immunity play significant roles in the immune response to tumors, cytotoxic T cells (CD8+) are critical to establishing antitumor activity. The roles of T cells are listed in Figure 2. A healthy immune system most often recognizes and destroys tumor cells, but when the immune system fails, disease occurs.

Table 1. Current Clinical Trials in Vaccine Therapy (Continued)

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<td>Evaluation of the safety and immunogenicity of vaccination with multiple synthetic melanoma peptides with GM-CSF in adjuvant therapy in patients with advanced melanoma</td>
<td>Advanced melanoma</td>
<td>Phase I and II</td>
<td>Can a 12-polyvariant epitope vaccine derived from MDA or CTA tumors be combined in a vaccine with GM-CSF as an antigen? If so, what is the immunogenicity, safety, and efficacy of the vaccine?</td>
<td>Center Study No. 03-138s</td>
</tr>
<tr>
<td>Vaccine therapy in treating patients with metastatic cancer</td>
<td>Stage IV</td>
<td>Phase I</td>
<td>What is the safety and feasibility of administering one to two courses of vaccination with antigen peptides (CAP 1–6D) and CMV pp65 peptide mixed with autologous DCs in patients with refractory stage IV CEA-expressing malignancies? What are the antitumor effects?</td>
<td>NCI 00057915</td>
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<td>A safety and feasibility study of active immunotherapy in patients with metastatic prostate carcinoma using autologous DCs pulsed with RNA encoding PSA</td>
<td>Prostate carcinoma</td>
<td>Phase I</td>
<td>How safe and effective is a vaccine made with PSA with RNA-pulsed autologous DCs?</td>
<td>NCI 00446993</td>
</tr>
<tr>
<td>Vaccine therapy with or without GM-CSF in treating patients with metastatic prostate cancer</td>
<td>Prostate cancer</td>
<td>Phase I and II pilot study</td>
<td>Does GM-CSF enhance the efficacy of treatment in vaccines containing combinations of triad of costimulatory molecules or Fowlpox in patients with metastatic prostate cancer?</td>
<td>NCI-03-C-0176</td>
</tr>
<tr>
<td>Vaccine of biotherapy of autologous tumor cells and DCs as active specific immunotherapy</td>
<td>Renal cell stage IV</td>
<td>Phase I and II</td>
<td>Can a patient’s own tumor cells be grown in a laboratory, radiated so they can stop growing, frozen, and given back to the patient as DCs?</td>
<td>Hoag Hospital; reviewed by NCI’s Physician’s Data Query and the U.S. Food and Drug Administration</td>
</tr>
</tbody>
</table>

**Note.** Based on information from National Cancer Institute, 2005.

- Poor antigen expression
- Alterations in T-cell receptors
- Insufficient antigen-presenting cells
- Acquired deficiencies to immune sensitivity (i.e., age)
- Disease antigens that are recognized as self-antigens
- A cytokine environment at the tumor site that cannot support T cells (Muehlbauer & Schwartzentruber, 2003)

![Figure 1. Cellular Environments That Produce Dysfunction](image-url)
Without the presence of a sufficient number of functional DCs to present information or T cells to target tumors, the immune system is compromised and disease can occur (Lonial, 2004; Sompayrac, 2003).

**Role of Colony-Stimulating Factors in Tumor Immunotherapy**

Cancer immunotherapy involving DCs aims to improve DC antigen presentation. GM-CSF is being studied for its immunomodulatory ability alone and in combination with other cytokines as well as being investigated as a surgical adjuvant (including neoadjuvant) and a vaccine adjuvant. With cytokines such as interleukin-2 (IL-2), GM-CSF is being studied for its role in improving DC and T-cell levels to compensate for a dysfunctional immune system (O’Day et al., 2002). Tumor immunotherapy, also known as immune modulation or immunomodulation, refers to treatments that modulate, manipulate, or enhance the body’s immune system to treat cancer. Many forms of tumor immunotherapy involve enhancing DCs. Granulocyte macrophage–vivo or colony-stimulating factor–induced DC tumor immunotherapy involves stimulating DC1s ex vivo to augment antigen presentation and further enhance an immune response.

GM-CSF and G-CSF are known to stimulate the myeloid cell line. However, only GM-CSF has the ability to stimulate DC1s. In their review of the literature, Waller and Ernsto (2003) documented studies that concluded that GM-CSF has an advantage over G-CSF in the stimulation of DC1s. The findings encouraged studies examining the use of GM-CSF alone or in combination therapy for its antitumor effect on solid tumors. The purpose of the studies would be to determine whether stimulation of immune surveillance by activating functional lymphocytes could provide cytotoxic activity to cancer cells. GM-CSF may have antitumor properties such as:

- Enhancing monocytes, which have tumoricidal activity against certain types of cancers (e.g., melanoma)
- Allowing DCs to enhance ADCC (Czuczman, Reising, Rapasky, & Hernandex-Ilizalturri, 2002; Mellstedt et al., 1999; Sondel & Hank, 2001)
- Having the potential ability to act as an antiangiogenesis agent by blocking the angiogenic process of solid tumors (Arceci & Mackall, 2002).

**Clinical Strategies to Improve Dendritic Cell Function**

DC tumor immunotherapy involves stimulating DC1s from circulating blood or bone marrow progenitor cells of the myeloid cell lineage. Three main strategies to improve DC function are (a) augmentation of DC function in vivo with the use of cytokines, (b) maturation of DCs ex vivo to manufacture a DC-based cancer vaccine, and (c) use of cytokines as vaccine adjuvants.

**Cytokine Use Alone to Augment Dendritic Cell Function**

GM-CSF as an antitumor agent is being investigated as a means of stimulating immunity in various stages of the cancer care continuum, including as a neoadjuvant treatment for breast cancer, a surgical adjuvant in melanoma, and salvage therapy for hormone refractory prostate cancer (HRPC). Studies have been performed primarily in patients with solid tumors. The following sections summarize clinical research in this area.

**Melanoma:** Survival rates for patients with stage IV melanoma are measured in months rather than years, and only a small number survive beyond one year (Balch et al., 2001; Miller & Mihm, 2006). Adjuvant therapy with single agent or combination chemotherapy has shown not only minimal benefit but also substantial adverse effects. Newer therapies for melanoma are focusing on the role of immune modulation. Because GM-CSF has various antitumor properties in melanoma, including the ability to stimulate and enhance critical effector cells known as NK cells, monocytes, neutrophils, and DCs in the immune system, studies are under way to determine the role of GM-CSF in the treatment of melanoma (Janeway et al., 2001; Leong et al., 1999).

**Role of colony-stimulating factors in tumor immunology:** Spitler et al. (2000) conducted a historic, controlled open-label trial (N = 48) of GM-CSF used as a surgical adjuvant treatment for patients at high risk for recurrence of melanoma. All patients underwent maximal surgical resection followed by GM-CSF administered at 125 mcg/m² per day for 14 days every 28 days. The cycle continued for one year. The research indicated that the one-year survival rate for patients receiving GM-CSF was nearly double that of the historically matched control group, whereas the two-year survival was nearly four times greater among recipients of GM-CSF. Median survival was 12.2 months for the control group, compared to 17.5 months for the group receiving GM-CSF. Because patients experienced disease recurrences after GM-CSF was discontinued at one year, the study was extended to three years. Interim analysis at 18 months continued to show a survival advantage in the GM-CSF group (Spitler, 2002; Spitler et al.). Phase III studies are needed to confirm the results. A multi-institutional, intergroup randomized, prospective National Cancer Institute clinical trial is accruing 600 patients with locally advanced or metastatic melanoma to assess the effect of GM-CSF therapy alone or with a peptide vaccine therapy to compare the effectiveness of each (National Cancer Institute, 2005). At the time this article was published, the study was continuing to recruit patients.

Although studies using biotherapy to treat patients with melanoma have been promising, recurrence of disease remains a significant obstacle. To address the issue, researchers sought to identify a therapeutic maintenance regimen with a low toxicity profile. Thirty-three patients were entered in a phase II historic control study using IL-2 and GM-CSF to stimulate T cells and DC1s, respectively. Patients were treated with low-dose IL-2 and GM-CSF combined with monthly or bimonthly intermediate- or high-dose IL-2 via IV during a 12-month period. Five patients achieved...
a complete response, and four patients maintained stable disease for at least six months on maintenance biotherapy. The median progression-free survival and overall survival (OS) were 8.1 months and 18.5 months, respectively, compared with historic controls. A favorable toxicity profile also was noted. The data are encouraging, but the results arise from only a single institution in a small study group. Researchers now are studying the same protocol in a multi-institution study before moving into a phase III trial (O’Day et al., 2002).

The location of injection of GM-CSF for treatment of tumors such as melanoma may prove to be as critical as the cytokines selected for immune modulation. The critical area for DC activation appears to be the sentinel node that immediately drains the tumor. In a phase II trial (N = 12), researchers determined that GM-CSF injected intradermally around the excision site of a melanoma tumor increased the number and activation state of DCs in the sentinel node. Researchers hypothesized that peritumoral treatment with GM-CSF may minimize micrometastasis of melanoma by facilitating the activation of tumor-specific cytotoxic T cells by DCs. A larger prospective study is being planned to confirm the theory (Vuylsteke et al., 2004).

Breast cancer: Investigators studied the efficacy of GM-CSF in combination with neoadjuvant chemotherapy in women with locally advanced breast cancer (LABC) (Honkoop et al., 1999). The researchers believed that the use of chemotherapy in combination with GM-CSF prior to removal of the primary tumor and its draining lymph nodes would stimulate a cytotoxic T-cell response against the tumor. In addition, they postulated that tumor-derived antiangiogenic factors would be able to inhibit micrometastasis during the neoadjuvant treatment. In a phase II, open-label, historic control trial of 42 patients with LABC treated with 250 mcg/m² per day of GM-CSF on days 2–12, response rates were almost double compared with patients who received chemotherapy alone. Median follow-up was three years. An interesting finding in patients receiving GM-CSF in neoadjuvant chemotherapy was that GM-CSF strengthened the immune response to the tumor while diminishing neutropenia. On examination of the sentinel node, researchers concluded that even a small increase in DC levels (>8%) improved survival (Pinedo et al., 2003). Currently, a phase III, international, multicenter trial (Sinoza trial) of patients with LABC is under way to test the effects of neoadjuvant treatment with GM-CSF compared to neoadjuvant treatment with G-CSF on disease-free survival and OS. No interim results have been published (Pinedo et al., 2003).

Prostate cancer: The role of GM-CSF alone or in combination therapy has been studied to determine the efficacy of activating immune response for antitumor activity in HRPC. Small et al. (1999) conducted two sequential studies using GM-CSF in patients with advanced HRPC. In the first study cohort (n = 23), GM-CSF was administered at a dose of 250 mcg/m² for the first 14 days in a 28-day cycle. In that group, 43% showed a reduction in prostate-specific antigen (PSA). The second cohort (n = 13) received the 14-day induction dose of GM-CSF followed by a maintenance dose of 250 mcg/m² given three times per week. Maintenance therapy continued until disease progressed. All but one patient experienced a decline in PSA levels, with a median response of 3.5 months (Small et al.).

Rini, Weinberg, Bok, and Small (2003) examined the antitumor effect of GM-CSF in patients with prostate cancer previously treated with surgery or radiation who exhibited nonmetastatic disease as measured by a rising PSA of 0.4–6.0 ng/ml (Rini et al.). Thirty patients were treated with 250 mcg/m² of GM-CSF on days 1–14 of a 28-day cycle. Three patients achieved a 50% reduction in PSA. For the patient in whom the treatment doubling time could be calculated, the median PSA doubling time increased from 8.4–15 months (p = 0.001). The median slope of the PSA-versus-time curve decreased with treatment, with an average treatment duration of 16.5 cycles (range = 5–33). The treatment was well tolerated, and researchers concluded that GM-CSF had an antitumor effect in patients with serologic progression of prostate cancer after definitive local therapy as measured by PSA declines.

In addition to DC1 stimulation, GM-CSF appears to have antiangiogenesis properties for tumors such as prostate cancer. GM-CSF in combination with thalidomide is being investigated for the treatment of HRPC. One hypothesis for combining GM-CSF and thalidomide is that both agents have demonstrated the ability to inhibit angiogenic processes of solid tumors. Researchers have theorized that each acts as an antiangiogenesis agent via different pathways. Blockage of one or more of the pathways may result in starving the tumor, thus leading to cell death. Another rationale for the combination therapy is that researchers have found that GM-CSF activates DCs and thalidomide modulates T cells and NK cell function (Richardson, Hideshima, & Anderson, 2002).

Another study examined efficacy administering GM-CSF 250 mcg/m² and thalidomide 100 mg in a phase I trial (N = 10) (Lilly, Rowsell, Gurrola, & Ruckle, 2004). GM-CSF was administered daily for 14 days and then every other day for three months (Lilly et al.). Thalidomide was taken daily starting on day 15 and continued for three months. Because of significant toxicity, the dose of thalidomide was reduced to 100 mg in combination with GM-CSF 500 mcg in cohort 2, then, in cohort 3, 250 mcg of GM-CSF and 100 mg of thalidomide were administered. Seven evaluable patients achieved an average PSA decrease of 50.4%, and one patient had a 60% decrease in the tumor. Lilly
Dendritic Cell–Based Vaccines

The second strategy to improve DC function is to mature the DCs ex vivo to manufacture a therapeutic cancer vaccine (see Figure 3). DC-based vaccination involves exposing immature DCs to tumor antigen and then administering the sensitized DCs for antigen presentation to T cells (Figueroa & Melief, 2004). Investigation of DC-based cancer vaccines has been spurred by the ability to cultivate, culture, mature, and load tumor-associated antigen onto large numbers of DCs from monocytes or progenitor stem cells (CD34+ cells) for use in a variety of cancers. The first DC-based cancer vaccine was administered to a patient with lymphoma in the mid-1990s (Hsu et al., 1996). Numerous academic and commercial centers are investigating DC-based vaccines to treat a variety of tumors. Among them, GM-CSF also is being explored as a neoadjuvant agent prior to radical prostatectomy.

**Figure 3. Dendritic Cell Vaccination**

Note. Figure courtesy of Creative Cancer Concepts, Inc. Used with permission.

et al. concluded that low tumor burden may be important in the duration of response to the treatment, because PSA responses were much longer if pretreatment PSA was lower than 50 ng/ml, compared to higher than 50 ng/ml (26.4 weeks versus 9.5 weeks, respectively). The researchers concluded that immunomodulation might be useful in delaying the progress of minimal HRPC. Results of the ongoing study have established the safety of the regimen, but efficacy continues to be examined (Garcia et al., 2006). GM-CSF also is being explored as a neoadjuvant agent prior to radical prostatectomy.

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Researchers are continuing to investigate whether DCs generated from monocytes or early progenitor stem cells are more effective for DC-based vaccines. Monocyte-derived DCs are the easiest, fastest, and most cost-effective because a mobilizing agent is not needed to collect monocytes (Morse, 2002). To obtain progenitor stem cells, a patient or donor must receive a mobilizing agent, such as GM-CSF or G-CSF, prior to collection of the stem cells during apheresis. Once the monocyte or progenitor stem cells are collected, they are cultured in a laboratory with various cytokines to stimulate DC growth. When large numbers of immature DCs have been obtained, they are loaded or pulsed with tumor antigen (also called tumor peptides or cancer proteins). Various tumor antigens, both general and specific, have been examined.

DC-based vaccines can be made from general tumor antigens or from antigens specific to individual patients’ tumors. General vaccines involve using an antigen that commonly is found in most cancers or for a specific tumor type, such as PSA or carcinoembryonic antigen. The tumor antigens can be called “off the shelf” because they are purchased for this use. Some tumor antigens are associated with the major histocompatibility complex, which also is known as the human leukocyte antigen (HLA). Because of that limitation, DC-based vaccines cannot be manufactured for all patients but only for those who are a certain HLA type. For example, in the Eastern Cooperative Oncology Group 4697 melanoma trial, patients were randomized to receive vaccine or no vaccine based on HLA status. Only patients who are HLA type 2A can receive the vaccine. Some protocols load several tumor antigens instead of a single antigen onto the DC in an attempt to improve the chances of immune system recognition (King, 2004; Nestle et al., 1998). Specific vaccines, also called patient-specific vaccines, are tailored specifically to an individual patient by using a sample of the patient’s tumor to load onto the DC. To manufacture a patient-specific vaccine, enough tumors must be present to load onto the DC (King).

Autologous or allogeneic cells can be used to create a general or specific DC vaccine. Debate is ongoing regarding whether immature DCs exposed to an antigen should be administered directly into patients or whether DCs need to be matured with more cytokines in a laboratory prior to administration. Only mature DCs have the ability to present tumor antigen to T cells for recognition (DeMeyer & Buchsel, 2005). Because DC-based vaccines mimic the physiologic migration of DCs to regional lymph nodes, researchers now are seeking the most effective injection method to maximize trafficking of DCs to draining lymph nodes. Currently, subcutaneous, IV, intranodal, intradermal, and intratumoral methods of DC vaccine administration are being studied (Hohenstein, King, Fiore, O’Brien, & Blumel, 2005; Morse, 2002).

Once the vaccine is administered, the mature DCs seek out naïve T cells in the spleen and lymph nodes. The DCs then “educate” the T cells to initiate an immune response. Once activated, the T cells secrete cytokines to stimulate more DCs to mature. DCs travel to lymph nodes. Collect progenitor cells (mobilized stem cells or monocytes; autologous or allogeneic). Isolate progenitor cells (may freeze stem cells until needed). Load immature DCs with tumor antigen (may be matured in lab after loading). Culture DCs (approximately 7–10 days). Add cytokines to grow DCs (cytokine cocktail). Some cytokines are used to grow immature DCs, and others are used to mature DCs in a laboratory prior to administration to patients. Calcium also has been used to transform monocytes into DCs (Czerniecki et al., 1997). GM-CSF is the cytokine used in most vaccine recipes because of its ability to stimulate DC1 growth from monocytes or progenitor stem cells.

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DC-based vaccines can be made from general tumor antigens or from antigens specific to individual patients’ tumors. General vaccines involve using an antigen that commonly is found in most cancers or for a specific tumor type, such as PSA or carcinoembryonic antigen. The tumor antigens can be called “off the shelf” because they are purchased for this use. Some tumor antigens are associated with the major histocompatibility complex, which also is known as the human leukocyte antigen (HLA). Because of that limitation, DC-based vaccines cannot be manufactured for all patients but only for those who are a certain HLA type. For example, in the Eastern Cooperative Oncology Group 4697 melanoma trial, patients were randomized to receive vaccine or no vaccine based on HLA status. Only patients who are HLA type 2A can receive the vaccine. Some protocols load several tumor antigens instead of a single antigen onto the DC in an attempt to improve the chances of immune system recognition (King, 2004; Nestle et al., 1998). Specific vaccines, also called patient-specific vaccines, are tailored specifically to an individual patient by using a sample of the patient’s tumor to load onto the DC. To manufacture a patient-specific vaccine, enough tumors must be present to load onto the DC (King).

Autologous or allogeneic cells can be used to create a general or specific DC vaccine. Debate is ongoing regarding whether immature DCs exposed to an antigen should be administered directly into patients or whether DCs need to be matured with more cytokines in a laboratory prior to administration. Only mature DCs have the ability to present tumor antigen to T cells for recognition (DeMeyer & Buchsel, 2005). Because DC-based vaccines mimic the physiologic migration of DCs to regional lymph nodes, researchers now are seeking the most effective injection method to maximize trafficking of DCs to draining lymph nodes. Currently, subcutaneous, IV, intranodal, intradermal, and intratumoral methods of DC vaccine administration are being studied (Hohenstein, King, Fiore, O’Brien, & Blumel, 2005; Morse, 2002).

Once the vaccine is administered, the mature DCs seek out naïve T cells in the spleen and lymph nodes. The DCs then “educate” the T cells to initiate an immune response. Once activated, the T cells secrete cytokines to stimulate more DCs to mature. DCs travel to lymph nodes. Collect progenitor cells (mobilized stem cells or monocytes; autologous or allogeneic). Isolate progenitor cells (may freeze stem cells until needed). Load immature DCs with tumor antigen (may be matured in lab after loading). Culture DCs (approximately 7–10 days). Add cytokines to grow DCs (cytokine cocktail).
cells travel to attack and kill the cancer cells. To obtain optimal stimulation of the immune system, the DC-based vaccines appear to need repeated administration over several weeks to months. For example, a DC vaccine schedule for melanoma could involve injecting the vaccine every two to four weeks for a series of eight injections given over several months (Palucka et al., 2005).

GM-CSF can be used to grow DCs from stem cells or monocytes to manufacture a DC-based vaccine, or it can be incorporated into the vaccine product itself. One example is the Provenge™ vaccine (Dendreon, Seattle, WA) for prostate cancer. Provenge is a vaccine that incorporates a specific antigen (tumor) plus GM-CSF loaded (mixed) into a patient’s (autologous) expanded antigen-presenting cells (DCs) (Small et al., 2006).

Phase I and phase II studies using Provenge in men with HRPC have shown it to be safe and of potential benefit. Results of a phase III, double-blind, randomized trial recently have been released. In the study, 82 patients were randomized to receive Provenge and 45 to receive placebo. The end points were delay in pain and median time to tumor progression. No differences were found in time to tumor progression between the two arms of the study; however, patients with Gleeson scores lower than seven had decreased time to tumor progression compared to controls, which was not observed in patients who had Gleeson scores of eight or higher. Time to tumor progression was nine weeks for the control group and 16 weeks for the vaccine group in those with low Gleeson scores. A similar observation was made regarding time to pain development.

Cytokines as Vaccine Adjuvants

The third strategy to improve DC function involves the use of cytokines such as GM-CSF as a vaccine adjuvant (Chang, Lomazow, Joy Somberg, Stan, & Perales, 2004). In the cancer vaccine setting, the term adjuvant is used in reference to agents that may further enhance the immune system by luring DCs and immune cells to the site of injection (King, Blumel, & O’Brien, 2005). Such agents include GM-CSF, IL-2, and interferon (Kinzler & Brown, 2001). In addition, an adjuvant may act as a decoy in tricking the immune system into mounting an offense against the carrier protein and, consequently, a patient’s tumor (Hohenstein et al., 2005). The unique deception by the carrier protein has been referred to as an immune system Trojan horse (Baggers, Ratzinger, & Young, 2000). As a vaccine adjuvant, the purpose of GM-CSF is to augment or enhance the cancer vaccine used to treat various types of cancer (Atzpodien, Fluck, & Reitz, 2004; Dillman et al., 2005). An example of the third strategy involves injecting GM-CSF subcutaneously around the vaccine injection site to recruit more DCs, particularly Langerhan cells, to optimize antigen presentation.

Granulocyte Macrophage–Colony-Stimulating Factor and Antibody-Dependent Cellular Cytotoxicity

GM-CSF plays a major role in stimulating effector cells to enhance ADCC. ADCC is a process in which antibody-coated cells are destroyed by the immune system (see Figure 4). Effector cells include NK cells, monocytes, macrophages, neutrophils, and DCs. Antibodies assist in tumor destruction by “tagging” the invader, thereby identifying the tumor. Antibodies bind to the Fc regions, leaving their Fc tails available to bind to Fc receptors primarily on the surface of the NK cells and macrophages (see Figure 5). The antibodies form a “bridge” between the tumor and the immune cells. On recognition of the target (tumor), the immune cells bind to the antibody and initiate processes that lead to cellular death. In addition to ADCC, antibodies are involved with other immune system processes, including neutralization, opsonization (enhanced phagocytosis), and complement-dependent cytotoxicity (cell death by complement) (Janeway et al., 2001).

Various cytokines, such as IL-2, interferon, G-CSF, and GM-CSF, are being investigated for their ability to enhance ADCC to improve the efficacy of monoclonal antibodies (Davis et al., 2000; Eisenbeis et al., 2004; Janakiraman et al., 2001; Liu et al., 2003; Niitsu et al., 2004; Osterweil, 2004; Sondel & Hank, 1997, 2001; van der Kolk, de Haas, Grillo-Lopez, Baars, & van Oers, 2002; van der Kolk, Grillo-Lopez, Baars, & van Oers, 2003; Venugopal et al., 2001; Venugopal, Gregory, et al., 2003; Venugopal, Oers, et al., 2003).
Table 2. A Process of Patient-Specific, Autologous, Monocyte-Derived Dendritic Cell Vaccine: Nursing Considerations and Rationale

<table>
<thead>
<tr>
<th>VACCINE OR ADJUVANT THERAPY</th>
<th>NURSING CONSIDERATIONS</th>
<th>RATIONALE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevaccine phase</strong></td>
<td>Give patients and caregivers a general overview of the process of the vaccine.</td>
<td>If patients become eligible for a clinical trial, a detailed teaching program should be developed.</td>
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<td></td>
<td>Offer a tour of the treatment facility to include the apheresis unit and outpatient clinic.</td>
<td>Patients and family members familiar with the clinical environment prior to treatment will have reduced anxiety levels.</td>
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<tr>
<td><strong>Informed consent and screening process</strong></td>
<td>Coordinate and monitor patient history and physical, including complete blood count of CD4+, CD8+, serum creatinine, BUN, LDH, HIV, hepatitis screen, antinuclear antibodies and antihistone antibody, anti-double-stranded DNA, antithyroid antibody, rheumatoid factor, urinalysis pregnancy test, CT scans of chest and abdomen, magnetic resonance imaging of brain, electrocardiogram, and chest x-ray per protocol.</td>
<td>Patients must meet protocol inclusion criteria to include disease staging, existence, and status of comorbid disease that would compromise their treatment.</td>
</tr>
<tr>
<td><strong>Vaccine production</strong></td>
<td></td>
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<tr>
<td>Tissue acquisition and vaccine production</td>
<td>Coordinate surgery schedule for excision of tumor.</td>
<td>Tumor mass is diminished; tumor peptides are collected and processed for vaccine.</td>
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<tr>
<td></td>
<td>Tumor proteins to make the vaccine may be collected from the tumor, a core needle biopsy, fine needle biopsy, bone marrow biopsy, and peripheral blood.</td>
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<td></td>
<td>Assess patients for healing of surgical or biopsy sites.</td>
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<tr>
<td></td>
<td>Coordinate tumor collection to create vaccine.</td>
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<tr>
<td><strong>DC vaccines</strong></td>
<td>Coordinate monocyte apheresis; prepare patients and caregivers for possible adverse effects.</td>
<td>DC vaccine produced ex vivo in combination with GM-CSF, tumor peptides, interleukin-2, and interferon.</td>
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<td></td>
<td>Assess and manage symptoms of hypokalemia, such as chilling, shaking, vertigo, paresthesia, nausea, and fatigue.</td>
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<td></td>
<td>Administer antacids prior to and during apheresis.</td>
<td>Exposure of patients’ blood to anticoagulant during the apheresis process causes a loss of calcium, resulting in hypocalcemia.</td>
</tr>
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<td></td>
<td>Administer 1 g calcium gluconate orally as needed for citrate toxicity.</td>
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<tr>
<td><strong>Vaccine administration</strong></td>
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<tr>
<td>Vaccine with GM-CSF adjuvant</td>
<td>Teach patients and caregivers to self-administer GM-CSF if dictated by protocol.</td>
<td>GM-CSF stimulates patients’ DCs to boost the immune system.</td>
</tr>
<tr>
<td>Vaccine can be administered by different routes (i.e., via IV, subcutaneously, intermodal, interdermal).</td>
<td>May pretreat with antipyretics and antihistamines</td>
<td>Patients have different side effects with different routes of administration; monitor for low blood pressure, fever, or chills with systemic administration; research is needed to determine the optimal site.</td>
</tr>
<tr>
<td>Vaccine may be manufactured with GM-CSF contained within the vaccine.</td>
<td>Assess the vaccination site for redness, swelling, pain, and itching.</td>
<td>May not be eligible for topical treatment</td>
</tr>
<tr>
<td><strong>GM-CSF administered as adjuvant therapy</strong></td>
<td>Mark the vaccine site with a “bull’s-eye” so that GM-CSF is injected near the vaccine site.</td>
<td>The closer the adjuvant is administered to the site of vaccine administration, the more potential for DC recruitment</td>
</tr>
<tr>
<td><strong>Monitor patients for possible toxicities</strong></td>
<td>Flulike syndrome: fever, chill, rash, sweats, general malaise, and injection site irritation; assessment and management to include acetaminophen or nonsteroidal anti-inflammatory agents for flulike symptoms or injection site tenderness</td>
<td>Common symptoms of GM-CSF vaccine injections; not known whether the vaccine or the adjuvant is the causative factor.</td>
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<td></td>
<td>Monitor patients for at least 15 minutes after vaccine administration.</td>
<td>Steroids may interfere with the body’s capacity to develop an immune response.</td>
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<td></td>
<td>Monitor white blood count and humoral cellular responses to the vaccine.</td>
<td>Patients may have an allergic reaction to the vaccine.</td>
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<td></td>
<td>Closely monitor patients for potential autoimmune adverse effects.</td>
<td>Colony-stimulating factors can cause significant increases in white blood counts.</td>
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<tr>
<td></td>
<td></td>
<td>Assess for patients’ immune status against vaccine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Some evidence shows that vaccine therapy and GM-CSF may cause progression of autoimmune disease.</td>
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</table>

BUN—blood urea nitrogen; CT—computed tomography; DC—dendritic cell; GM-CSF—granulocyte macrophage–colony-stimulating factor; LDH—lactate dehydrogenase

*Note. Based on information from Hohenstein et al., 2005; Muehlbauer & Schwartzentruber, 2003.*

(Continued on next page)
Venugopal, Wooldridge, et al., 2003). The cytokines appear to provide a synergistic, beneficial effect on ADCC by increasing the volume of circulating antibodies and upregulating the number of circulating activated effector cells.

Most of the research has been done with rituximab because it was the first monoclonal antibody to be approved, in 1997. Rituximab is indicated for the treatment of patients with relapsed or refractory low-grade or follicular CD20 antigen–positive, B-cell non-Hodgkin lymphoma. Tumor kill by rituximab occurs through a variety of mechanisms of action (Johnson & Glennie, 2003; Villamor, Montserrat, & Colomer, 2003). Rituximab has been shown to induce apoptosis, complement-mediated lysis, and ADCC in vitro (Cartron, Watier, Golay, & Solal-Celigny, 2004). The effectiveness of the immune responses is dependent on adequate complement proteins and effector cells.

GM-CSF appears to improve rituximab activity by enhancing ADCC. Proposed mechanisms include upregulation of various effector cells, enhancement of the activity of effector cells by increasing the “appetite” of the phagocytes to recognize “tagged” opsonized invaders, and potential upregulation of the CD 20 antigen target (Stockmeyer et al., 2001; Venugopal et al., 2000). Researchers have studied various combinations of GM-CSF with rituximab, with or without chemotherapy, including

- GM-CSF plus rituximab (Janakiraman et al., 2001; Liu et al., 2003; McLaughlin & Rodriguez, 2001)
- GM-CSF plus etoposide, methylprednisone, cytarabine, and cisplatin (Venugopal, Gregory, et al., 2003)
- GM-CSF plus rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (Olivieri et al., 2001; Venugopal, Wooldridge, et al., 2003).

Initial studies suggested that the addition of GM-CSF may improve response rates in lymphoma without any additional toxicity. Larger phase III trials will be needed to determine the optimal timing, dosing, and effect of GM-CSF.

Nursing Implications

The nursing implications of administering GM-CSF as a supportive care agent for patients with clinical neutropenia have been reviewed, and side effects of GM-CSF have been noted to be mild (Beveridge et al., 1997; Buchsel, Forgey, Grape, & Hammann, 2002; Dorr, 1995; Glaspy, 2003). GM-CSF administered in a tumor immunology protocol requires that oncology nurses acquire knowledge of complex immunotherapy, cell biology, and tumor immunology. Knowledgeable practitioners are challenged to understand treatment rationales and objectives, administration techniques, and patient evaluation during treatment and follow-up care (see Table 2).

Side effects from DC-based vaccines appear to depend on the route of administration. Currently, optimal techniques are not known for injecting DC-based vaccines as well as administering GM-CSF as an antitumor vaccine adjuvant or alone as an antitumor agent. Approaches traditionally used in the supportive care setting, such as applying ice prior to injection, choosing injection sites such as the arm, leg, or abdomen, or using topical creams, may not be appropriate for antitumor therapy. Ice and topical creams may affect DCs given in vaccine form (B. Chang, personal communication, February 21, 2005); however, a recent publication favored the traditional approach of GM-CSF administration when used alone or as a vaccine adjuvant (Hohenstein et al., 2005). These issues present a rich opportunity for nursing research. Typically, adverse events are minimal when GM-CSF is administered alone, but in combination therapy with biotherapy such as IL-2, more adverse events have been noted and most likely are associated with chemotheraphy or IL-2.

Methods for enhancing the immune system quickly are moving from the bench to the bedside as data from clinical research mature. By definition, phase III clinical trials create a cohort of hopeful, but sometimes disappointed, patients who receive placebo. Patients will require psychological support and guidance to other clinical trials. Communication, coordination, and a multidisciplinary approach are critical components of a seamless antitumor program. Community-based nurses referring patients to research centers to be entered into clinical trials will further educate and evaluate these patients. Research nurses practicing in these areas are in a unique position to implement studies of nursing-sensitive outcomes and evidence-based nursing protocols (Doran, 2003). Nurses will continue to play a critical role in therapy administration, toxicity management, education, and advocacy for patients receiving tumor immunotherapy agents. Although significant strides have been made to improve life expectancy and maximize quality of life for patients with cancer, more effective and less toxic approaches are needed. Correcting or stimulating

### Table 2. A Process of Patient-Specific, Autologous, Monocyte-Derived Dendritic Cell Vaccine: Nursing Considerations and Rationale (Continued)

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</tr>
</thead>
<tbody>
<tr>
<td>Follow-up after vaccine therapy</td>
<td>• Monitor disease outcome.</td>
<td>Usually, patients with an autoimmune history are excluded from vaccine trials.</td>
</tr>
<tr>
<td></td>
<td>• Monitor adverse effects of vaccine and GM-CSF.</td>
<td>Typically, the entire course of treatment includes five to seven immunization series during about six months.</td>
</tr>
<tr>
<td></td>
<td>• Short- and long-term follow-up is needed for safety and efficacy of protocol.</td>
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**Note.** Based on information from Hohenstein et al., 2005; Muehlbauer & Schwartzentruber, 2003.
the body’s own defenses to cure cancer with agents such as GM-CSF may achieve this long-awaited goal.

Summary

Although great strides have been made in advancing therapies for cancer and other diseases, much work is needed to recognize and target cancer cells while sparing healthy cells. Advances in understanding the role of the immune system in disease have allowed researchers to capitalize on knowledge to manipulate and augment the immune system to recognize tumor cells through novel and emerging methods to augment the effector arms of the immune system. GM-CSF has been identified as a widely used hematopoietic growth factor for DC stimulation in vivo and ex vivo. As an antitumor agent, GM-CSF is being studied in a variety of malignancies, in various stages of the cancer care continuum, and in combination with various agents. Of particular interest are trials involving GM-CSF with rituximab in non-Hodgkin lymphoma, thalidomide for prostate cancer, and IL-2 to treat melanoma. Investigators are continuing to explore the expanding abilities of GM-CSF in DC stimulation, enhancing ADCC, and determining its potential role in blocking angiogenesis.

The disciplines of immunotherapy and biotherapy are elucidating the secrets of the immune system to fight cancer. Oncology nurses increasingly are involved in administering emerging biologic therapies such as antitumor agents. Similar to learning anatomy and physiology to understand the effects of cancer therapy, oncology nurses are mandated to learn cellular biology and structure to appreciate new technology. Oncology nurses practicing in clinical trials in the antitumor setting are in an excellent position to educate the nursing community regarding the status of clinical trials, injection techniques, and management of possible emerging acute and long-term complications.

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References


