Denileukin Diftitox
as Novel Targeted Therapy
in Non-Hodgkin’s Lymphoma

Pamela L. Walker, RN, OCN®, and Nam H. Dang, MD, PhD

Non-Hodgkin’s lymphoma (NHL) is a complex group of hematologic malignancies. The majority are B-cell lineage, with 10%–20% arising from T-cell lineage. Detailed knowledge of the subtypes and staging of NHL is essential to plan treatment and provide effective management of treatment-related side effects. Although numerous regimens have demonstrated efficacy in the treatment of NHL, some subtypes of lymphomas generally are not curable. The recent development of targeted therapies such as denileukin diftitox (Ontak®, Ligand Pharmaceuticals, Inc., San Diego, CA) has resulted in potentially significant advances in the treatment of NHL. Oncology nurses must gain a better understanding of the unique mechanism of action of this agent and its side effects to successfully manage patients being treated with this novel therapy.

Key Words: lymphoma, non-Hodgkin; fatigue; pruritus; vascular leak syndrome

H odgkin’s disease and non-Hodgkin’s lymphoma (NHL) are two distinct diseases that together account for 5% of all cancers in the United States. In 2003, an estimated 53,000 new cases of NHL were diagnosed. Although intensive research has shed light on some aspects of NHL, a detailed understanding of the disease biology still is relatively limited. Unfortunately, the incidence rate of NHL has doubled since the 1970s (American Cancer Society, 2003).

NHL rarely occurs before the age of 10; however, its incidence rises after age 25, with the sharpest increase occurring after age 55. The survival rate of NHL is related to age and consistently is lower for individuals older than 65 (Ries et al., 2000). The rising incidence of NHL creates a need for oncology nurses to gain a better understanding of the complexity and treatment management of this diverse group of malignancies.

Classification, Staging, and Prognostic Factors

NHL encompasses a complex group of hematologic malignancies that have common and diverse features. Classification and staging of NHL subtypes are critical in determining disease prognosis and treatment. Key classification schemes currently used include a combination of the Working Formulation, Revised European American Classification Lymphoma, and World Health Organization classification system (Harris et al., 1994, 2000a, 2000b). The Ann Arbor staging system is the most widely used staging system (Rosenberg, 1977). Staging studies use different imaging techniques, including computed tomography (CT) scans, plain films, magnetic resonance imaging, and radionuclide imaging positron emission tomography and gallium scan, as well as bone marrow biopsy and aspiration. Hematologic laboratory studies such as complete blood count with differential and liver function tests, including lactic dehydrogenase (LDH) and β2-microglobulin, are helpful with staging and prognostic factors. The International Prognostic Index (IPI) is used to classify patients by age (younger than 60 versus older than 60), performance status (0 or 1 versus 2–4), LDH (normal versus elevated), number of extra nodal sites (0 or 1 versus 2–4), and stage (I or II versus III or IV). The IPI score not only serves as a prognostic factor but also assists with treatment planning (Fisher, 2003).

Low-Grade B-Cell Non-Hodgkin’s Lymphoma

Several subtypes of NHL belong to the low-grade or indolent B-cell NHL classification; the most common is follicular lymphoma (FL), which comprises 25%–40% of all adult lymphomas (Seng & Peterson, 1997). Disease often presents with asymptomatic, chronically waxing and waning lymphadenopathy detected by patients or healthcare providers.
Vague symptoms such as fatigue, abdominal fullness, and fever also may be present. Thirty percent of newly diagnosed patients with FL will have B-cell symptoms (e.g., night sweats, fever, weight loss). Almost 80% of newly diagnosed patients with FL have advanced disease (stage III or IV), with 50% having bone marrow involvement (Seng & Peterson).

Although numerous treatment options are effective in controlling the disease, FL rarely is curable. Options vary from the “watch and wait” approach to more aggressive treatment with chemotherapy at the time of diagnosis. Based on experience at Stanford University (Horning & Rosenberg, 1984), the “watch and wait” approach suggests that observation at the time of diagnosis does not compromise the benefit of subsequent treatment or the overall survival outcome. On the other hand, proponents of the more aggressive approach believe that with scientific advances such as the development of new drug therapies and better supportive care, initial treatment at the time of diagnosis may lead to better overall survival. Because FL is a slow-growing disease, studies with longer patient follow-up are needed to determine whether “watch and wait” or upfront treatment is ultimately the superior approach. Common chemotherapy regimens used for the treatment of FL most often include alkylating agents, such as cyclophosphamide, in combination with other cytotoxic drugs (Hoppe, Kushin, Kaplan, Rosenberg, & Brown, 1981). Unfortunately, alkylating agents are associated with long-term risk of myelodysplasia and secondary leukemias (Hoppe et al.). Purine analogs are gaining importance in the treatment for FL. Examples of purine analogs are fludarabine, cladribine, and pentostatin, with fludarabine being the most widely used in FL (Cheson, 1999). The recent development of rituximab, the monoclonal antibody against CD20, has opened a new chapter in the treatment of FL. Rituximab, given in combination with chemotherapy regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), offers great potential in treating FL (Czuczman et al., 1999).

**Aggressive B-Cell Non-Hodgkin’s Lymphoma**

Diffuse large cell lymphoma (DLCL) is the second most common B-cell NHL, although understanding of the biology of this NHL is still in its infancy. Unlike FL, DLCL is an aggressive, fatal disease with survival being less than two years from the time of diagnosis if left untreated (McKelvey & Moon, 1977). The first-line treatment strategy for DLCL is combination chemotherapy. CHOP is the first-generation combination chemotherapy regimen, developed in the late 1970s (Elias, Portlock, & Rosenberg, 1978), and has remained the standard treatment for more than 20 years (Khaled et al., 1999). The role of rituximab, the anti-CD20 monoclonal antibody, in combination with chemotherapy such as CHOP, is showing great promise in patients with DLCL and potentially is curable (Coiffier et al., 2002). The benefit of CHOP in patients with more advanced disease is limited and may require more intense therapy such as high-dose chemotherapy with stem cell rescue.

Mantle cell lymphoma (MCL) is another aggressive lymphoma subtype, with patients often presenting with advanced disease and high burden of extranodal involvement (Bosch et al., 1998). The extranodal sites most frequently involved with MCL are the spleen, bone marrow, peripheral blood, and gastrointestinal tract (Cohen, Kurtin, Donovan, & Hanson, 1998). Having the worst properties of both the indolent and aggressive NHL, MCL generally is considered incurable. Given its aggressive nature, many clinicians believe that aggressive treatment regimens represent the major method to improve the clinical outcome for patients with MCL. A 1998 clinical trial investigated the effect of the alternating combination chemotherapy regimen Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) and MTX-Ara C (methotrexate and high-dose cytarabine), followed by stem cell transplantation. The response rate to this regimen is 94%, with 38% having a complete remission (Khoury et al., 1998). However, disease-free survival after Hyper-CVAD and MTX-Ara C alone in this study was difficult to assess because the majority of patients proceeded to bone marrow transplantation. Another study was conducted to evaluate the efficacy of the combination of Hyper-CVAD and MTX-Ara C alone in previously untreated patients with MCL who are older than 65, demonstrating a complete remission rate of 68% with a median failure-free survival of 15 months (Romaguera et al., 2000). This treatment regimen requires further evaluation to determine its long-term survival benefit. Other treatment strategies are available for patients with MCL, including those involving radiation and biologic agents such as rituximab. The role of high-dose therapy and stem cell transplantation still is under active investigation.

**Low-Grade T-Cell Non-Hodgkin’s Lymphoma**

Although 80%–90% of NHLs are of B-cell lineage, the remaining 10%–20% comprise T-cell lineage. Cutaneous T-cell lymphoma (CTCL) is a lymphoproliferative disorder characterized by clonal accumulation of malignant T lymphocytes on the skin (Siegel et al., 2000). The most common CTCL is mycosis fungoides (MF), which derives its name from the mushroom-shaped tumors produced on the skin. Although the median age at diagnosis is 55–60, the incidence of MF increases with age as reported by the National Cancer Institute Surveillance, Epidemiology, and End Results program (Ries et al., 2000). Skin lesions occur as patches, plaques, or tumors, and all three stages may be present simultaneously. The lesions are most commonly found on the face and in the major skin folds. Pathology of the lesions is characterized by atypical T lymphocytes that express CD4 and infrequently CD8. Meanwhile, expression of the CD25 component of the interleukin-2 (IL-2) receptor complex is seen in approximately half of the patients with MF. MF is staged by the degree of skin involvement and the presence of lymphadenopathy. CT scans and bone marrow assessments are used to evaluate disease involvement, which frequently is found in the liver and bone marrow. Patients with stage IA and IB (skin patches or plaques without lymph node involvement) have an excellent prognosis, whereas patients with stage IV (with visceral disease) unfortunately have a poor prognosis regardless of skin stage. Patients with stage II or III disease have a prognosis similar to patients with follicular B-cell lymphoma (Sausville et al., 1988).

MF treatment is related to disease stage, with stage I and II A disease often treated with topical chemotherapy agents using mechloretamine (nitrogen mustard) and carbustine. Ninety-seven percent of 172 patients with stage I disease and 64% of
patients with stage II MF experienced three-year survival (Zackheim, 1994). Phototherapy known as psoralen plus ultraviolet A (PUVA), which uses ultraviolet A with a psoralen-based photosensitizing agent, is the most common phototherapy used for early-stage MF. This treatment consists of 8-methoxypsoralen as an oral agent activated by ultraviolet light exposure. This treatment for MF has been well established for more than 20 years, with a response rate of 59% (Briffa, Warin, Harrington, & Bleehen, 1980), which improved to 80% with the addition of interferon (IFN) (Kuzel et al., 1990). The side effects related to PUVA therapy include nausea, erythema, pruritus, and chronic dry skin (Briffa et al.). Radiation therapy also is effective treatment in the early and advanced stages of MF. Several successful trials have used radiation therapy in combination with other therapies, such as PUVA and systemic and topical chemotherapy with total-skin electron beam therapy (Reddy et al., 1992). Chemotherapy also plays a role in MF treatment, often as a single agent of pulse steroids, alkylating agents, or methotrexate (Rosen & Foss, 1995). Up to 30% of patients receiving single-agent chemotherapy achieve a short duration response. Purine analogs such as pentostatin (deoxcoformycin) and fludarabine have been used in clinical trials and have produced a good response rate; however, the duration of response was short (Foss et al., 1992). The combination chemotherapy regimen of etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone had a high response rate but short response duration (Akpek, Koh, Bogen, O’Hara, & Foss, 1999). IFN has played a role in the treatment of MF in clinical trials with complete remissions as high as 40%. For example, Foss et al. reported the results of a phase II study using IFN and pentostatin in patients with MF, noting a response rate of 42%. Additional research is needed with IFN in combination with other chemotherapy drugs.

Several novel therapies are being used to treat MF and CTCL. One therapy demonstrating effectiveness is the fusion toxin denileukin diftitox (Ontak®, Ligand Pharmaceuticals, Inc., San Diego, CA). In a phase III trial with Ontak, for heavily pretreated (more than five prior treatments) patients with persistent or recurrent stage IB to IV A CTCL, 20% of patients receiving the drug achieved a partial remission and 10% had a complete remission (Olsen et al., 2001). Retinoids have been used since the 1980s to treat MF, with response rates being 40%–68% overall and durable remissions of 58% of patients at five-year follow-up (Aviles, Guzman, Garcia, & Diaz-Maqeo, 1996). Clinical trials using bexarotene gel (Targetretin®, Ligand Pharmaceuticals, Inc.) in patients with early-stage CTCL are showing clinical response in a significant number of patients. Other novel therapies under investigation in early clinical trials include high-dose IL-2, alemtuzumab (anti-CD52 monoclonal antibody), and other targeted therapies (Lundin et al., 1998). Because CTCL is an indolent disease, the goal of treatment should be to prevent progression and establish a complete remission with a long duration, similar to the case with indolent B-cell NHL.

### Aggressive T-Cell Lymphoma

Accounting for the majority of T-cell NHL, peripheral T-cell lymphoma (PTCL) arises from the post-thymic lymphoid T-cell at different stages of cell differentiation (Sato & Dang, 2003; Suchi et al., 1987). The higher incidence of PTCL in Japan and other Eastern countries, as compared to Western countries, is thought to be partly related to the human T-cell lymphotropic virus type 1 (Nakamura et al., 1993). Presenting with an enlarged node or an extranodal mass, patients with T-cell NHL often have B-cell symptoms and advanced-stage disease at initial diagnosis, including disease involving the bone marrow and skin. PTCL is associated strongly with hemophagocytic syndrome, which includes fever, hepatosplenomegaly, abnormal liver function tests, thrombocytopenia, and erythrophagocytosis on bone marrow biopsy (Chan, Pi, Chan, Todd, & Ho, 1989; Falini et al., 1990). Once a diagnosis of PTCL is established, treatment most likely will be combination chemotherapy. A six-drug clinical trial was developed to evaluate the combination of cyclophosphamide, doxorubicin, procarbazine, bleomycin, vincristine, and prednisone (Armitage et al., 1989) involving patients with stage I and III PTCL having a 73% overall survival and 66% event-free survival at three years. However, no patients with stage IV PTCL had a complete remission or survived longer than two years. Other alternate regimens include CHOP, Hyper-CVAD, and bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone—a regimen that excludes procarbazine. Patients who relapse after a combination chemotherapy regimen have an extremely bleak prognosis, with one approach for salvage therapy being autologous bone marrow transplantation (Vose et al., 1990). Effective new therapy urgently is needed for the treatment of PTCL.

### Novel Therapy: Denileukin Diftitox

In the search for novel treatment modalities, molecular targeted therapy holds great promise in treating B- and T-cell disease. Ontak is a genetically engineered fusion protein that directs the lethal action of the diphtheria toxin to cells bearing the IL-2 receptor complex on their surfaces (Waters et al., 1990). IL-2 binds specifically to the surface receptors; the toxin fragment then is internalized, leading to disruption of protein synthesis and eventual cell death. In contrast to conventional chemotherapy, with its nonspecific toxic effect on tumor as well as normal neighboring cells, the targeted-therapy approach of Ontak specifically kills tumors expressing the high-affinity IL-2 receptors while sparing non-expressing neighboring cells. Therefore, the appeal of this approach lies in its ability to maximize tumor targeting while minimizing potential side effects.

Ontak was approved by the U.S. Food and Drug Administration in February 1999 for the treatment of CTCL that expresses the CD25 component of the IL-2 receptor complex. This approval was based on a phase III trial of Ontak in patients with CD25-positive CTCL (Olsen et al., 2001). When the drug was approved for use in CTCL, tumor CD25 expression initially was thought to be necessary for drug activity. However, the expression of CD25 has been found to vary within the same patient when multiple biopsies were performed (Foss, 2000). In addition, the level of CD25 on the cell surface needed to be detected by currently available technology is higher than the level of CD25 needed for effective killing by the potent denileukin diftitox fusion protein. Furthermore, the IL-2 receptor complex is composed of three different protein chains, including CD25 (p55), CD122 (p75), and CD132 (p64). When all three chains are expressed on the cell surface, the IL-2 receptor binds with high affinity to its ligand as the high-affinity receptor. On the other hand, the binding affinity to IL-2 decreases when the IL-2 receptor complex does not express its full complement (Foss). The previously indicated reasons would imply that CD25 tumor expression may not strongly correlate with tumor response to Ontak. Indeed, patients with low or undetectable CD25 expression can respond to drug treatment. For example, patients who originally responded toOntak with CD25-positive CTCL subsequently developed CD25-negative CTCL on relapse. When retreated with Ontak, several patients again experienced response to treatment (Olsen et al.).
A phase II clinical trial was initiated at the University of Texas M.D. Anderson Cancer Center in Houston to evaluate the effect of Ontak in relapsed or refractory B- and T-cell NHL (except CTCL), regardless of tumor CD25 status. An interim analysis recently was conducted with 33 patients (Dang et al., 2003). The median number of previous treatment modalities was four, with several patients having previously undergone autologous stem cell transplantation. Bone marrow suppression commonly was seen at study enrollment for this heavily pretreated patient population as reflected by mean absolute neutrophil count of 2.6/mm³, hemoglobin of 11.3 g/dl, and platelets of 152,000/mm³ at study entry. Ontak was administered at an initial dose level of 18 mcg/kg per day over 60 minutes once daily for five days every three weeks for a maximum of eight cycles, with a dose reduction to 9 mcg/kg per day once daily for five days for grade 2 or 3 toxicities. Patients were medicated with corticosteroids prior to each Ontak infusion to reduce and prevent hypersensitivity reactions. Ontak had activity in patients with B- and T-cell NHL, with 45% of patients achieving stable disease, partial remission, or complete remission (21% achieving either partial remission or complete remission). Treatment was well tolerated, with the majority of toxicities being grade 1 or 2 and transient. Common toxicities included hypoalbuminemia, elevation of transaminases, fatigue, fever, and skin reactions such as rash and pruritus.

Side-Effect Management

In contrast to conventional chemotherapy agents with their toxicities, Ontak’s unique mechanism of action as targeted therapy minimizes potential side effects. Although specific toxicities occur with Ontak, the therapy is well tolerated with careful assessment and monitoring of patients. The most common Ontak-related side effects observed in patients with NHL were hypoalbuminemia and elevated transaminases; however, results from weekly laboratory studies demonstrated that these abnormalities tended to be limited and transient. Treatment was delayed until albumin reached a level of 3 g/dl or greater and transaminases returned to grade 1 level (≤ 2.5 high normal value). When treatment resumed, the dose was reduced to 9 mcg/kg per day.

Patients reporting fatigue as a side effect should be encouraged to pace daily activities and allow for rest periods. The greatest degree of fatigue has been reported to occur within the first week of treatment and improved during the remainder of the cycle. Meanwhile, fever was reported by affected patients to occur approximately 48–72 hours after Ontak treatment. Although fever in treated patients was thought to be related to Ontak therapy, patients with a temperature greater than 101°F typically were screened for occult infection (complete blood count with differential, blood and urine cultures, and chest x-rays were performed).

Approximately one-third of patients reported skin reactions. To help maintain skin integrity, patients need to be instructed to stay well hydrated with a generous daily fluid intake of one to three liters. They also should be encouraged to take tepid showers or baths and to use moisturizing lotions liberally. In the case of moderate to severe pruritus, patients were instructed to use over-the-counter antihistamines topically and orally.

A potentially serious side effect of Ontak therapy seen in earlier trials is vascular leak syndrome (VLS). VLS can be identified with the occurrence of two or more of the following side effects: edema, hypoalbuminemia (< 2.8 g/dl), or hypotension. The highest incidence of VLS occurred with the first cycle of Ontak and was unlikely to recur with subsequent cycles. To prevent this development, patients were medicated with corticosteroids prior to each Ontak infusion. They also were instructed to notify their physicians or nurses about any signs and symptoms of edema, weight gain of more than five pounds, pedal edema, dyspnea, or any overall awareness of new restriction of jewelry or clothing following their Ontak treatment. Generally, patients who reported edema subsequently were treated for approximately three to seven days with a mild diuretic with resolution of the edema. As nursing personnel became familiar with the management of the unique side effects of Ontak, most of the Ontak-related toxicities diminished in severity and were better detected and managed with each subsequent cycle of treatment, according to the authors’ experience. In addition, the authors’ detailed knowledge of the side effects of Ontak allowed for improved communication between the medical team and patients throughout treatment, thus enhancing patient education and leading to greater patient compliance.

A key factor in patient compliance with treatment is the level of patient awareness and understanding of the side effects related to Ontak therapy, as instructed by oncology nurses. To ensure informed consent and quality patient education prior to administration of Ontak, nurses meet with patients and their families to verbally review the side effects related to treatment. Patients then are given printed teaching material outlining the side effects along with the contact telephone number for the research nurse. Patients are instructed to contact their local oncologists or report to the emergency center with any emergent problem or with any sign or symptom of infection. After they receive Ontak infusion and throughout their treatment, patients are contacted weekly via telephone by the nurse to monitor and assess possible side effects related to therapy. In addition, close collaboration between the institutional research team administering the clinical trial and the local medical personnel is of the utmost importance in ensuring quality patient management and enhancing compliance to Ontak treatment, thus optimizing patient care and the chance of experiencing success with drug therapy.

Conclusion

NHLs represent a complex classification of hematologic malignancies that are increasing in frequency. Detailed classification and staging are needed to ensure optimal disease treatment and management. Once treatment is initiated, prudent management of side effects will successfully guide patients through therapy. Although some NHL subtypes are responsive to current treatment modalities, others need further advancements in treatment strategies to improve overall survival. When possible, patients should be offered research protocols with the hope that advances in therapies will lead to improved overall survival in NHL. A novel therapy that appears to display clinical benefit in NHL is the fusion protein denileukin difitox (Ontak). The authors’ experience with earlier trials, as well as with the ongoing phase II trial involving patients with NHL, indicates that Ontak is well tolerated and that the majority of the side effects are transient and diminish in severity with each treatment cycle. To ensure patient safety and optimize treatment benefit, nursing personnel must have a firm understanding of Ontak’s unique mechanism of action and the nursing management of its side effects.

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Author Contact: Pamela L. Walker, RN, OCN®, can be reached at plwalker@mdanderson.org.
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Rapid Recap
Denileukin Diftitox as Novel Targeted Therapy in Non-Hodgkin’s Lymphoma

- Although non-Hodgkin’s lymphoma (NHL) is an uncommon cancer, its incidence has doubled since the 1970s.
- Follicular lymphoma, which comprises 25%–40% of adult B-cell NHLs, is a low-grade or indolent disease.
- Diffuse large cell lymphoma and mantle cell lymphoma are aggressive diseases that require systemic treatment.
- Cutaneous T-cell lymphoma (CTCL) is a lymphoproliferative disorder characterized by the accumulation of malignant T lymphocytes on the skin. Mycosis fungoides is a type of CTCL.
- Denileukin diftitox (Ontak®, Ligand Pharmaceuticals, Inc., San Diego, CA) is a targeted therapy that holds promise in treating B- and T-cell NHL. Common side effects include transient hypoalbuminemia and elevated serum transaminases, fatigue, fever, and skin reactions (rash and pruritus).