Radioimmunotherapy With Tositumomab and Iodine-131 Tositumomab for Low-Grade Non-Hodgkin Lymphoma: Nursing Implications

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Purpose/Objectives: To review radioimmunotherapy approaches for low-grade non-Hodgkin lymphoma (NHL) with a focus on tositumomab and iodine-131 tositumomab (Bexxar®, Corixa Corporation, Seattle, WA, and GlaxoSmithKline, Philadelphia, PA). Nursing implications for Bexxar therapy are reviewed, including radiation safety, patient education, and the management of therapy-related toxicities.

Data Sources: Journal articles, published research data, and clinical experience.

Data Synthesis: The Bexxar treatment regimen (using an anti-CD20 antibody) consists of a dosimetric administration followed 7–14 days later by a patient-specific therapeutic administration. Infusion-related adverse events and myelosuppression are manageable. Patient and caregiver education regarding the benefits of radioimmunotherapy, treatment protocols, and radiation safety precautions is necessary.

Conclusions: Bexxar therapy represents an important new treatment option for patients with low-grade NHL and can be administered on an outpatient basis.

Implications for Nursing: Nurses play a vital role in the success of a Bexxar therapy program by providing patient and caregiver education, patient monitoring, and coordinating treatment schedules.

Key Points . . .

- Radiolabeled monoclonal antibodies have become an important addition to the treatment of low-grade non-Hodgkin lymphoma (NHL).
- Nursing has a critical role in the education, coordination, and management of patients receiving tositumomab and iodine-131 tositumomab.
- Patients can be treated safely with tositumomab and iodine-131 tositumomab with minimal disruption to their lives and minimal side effects.
- Currently, no cure exists for low-grade NHL; however, radioimmunotherapy presents a new class of drug with a proven response and minimal side effects.

Non-Hodgkin lymphoma (NHL) encompasses a diverse group of lymphoid neoplasms that vary greatly in clinical behavior, morphologic appearance, cellular origin, responsiveness to treatment, and curability (Rosenthal & Eyre, 1995). The most common hematologic cancer, NHL is also the sixth leading cause of cancer death and the second fastest-growing cancer in the United States. The American Cancer Society (ACS) estimated that 54,370 new cases will be diagnosed in the United States in 2004, resulting in 19,410 deaths. Since the early 1970s, the incidence for NHL has nearly doubled, rising at a rate of 4% per year or 50% during the past 15 years, which is one of the largest increases for any cancer group (ACS, 2004).

Low-grade lymphomas represent 20%–30% of NHL cases, with a median survival of 7.5–9 years (Rosenthal & Eyre, 1995). Low-grade lymphomas include follicular center cell lymphoma, B-cell chronic lymphocytic leukemia or small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, mantle cell lymphoma, and marginal zone lymphoma (Harris et al., 1994). Approximately 90% of patients present with stage III or IV disease with generalized lymphadenopathy and bone marrow involvement (Rosenthal & Eyre). Despite widespread tumor involvement, low-grade lymphoma often is clinically indolent and patients frequently are asymptomatic for years.

Current Treatment Options

NHL treatment varies widely by histology, stage of disease, age, and physiologic status of the patient. Treatment approaches range from supportive to curative. Current options include watch and wait, chemotherapy, radiotherapy, hematopoietic stem cell transplant, and biologic therapy such as monoclonal antibodies (MAbs). The optimal treatment approach for NHL

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is controversial. An initial remission with chemotherapy often is achieved; however, low-grade NHL inevitably recurs. Reinduction and maintenance of remission are more difficult with each recurrence as the disease becomes more resistant to chemotherapy (Kaminski et al., 1996). Bone marrow or peripheral stem cell transplants, with or without external beam total body radiation, have resulted in a cure for some patients. However, patients who are of advanced age, have comorbid conditions, or have primary resistance to chemotherapy are not candidates for stem cell transplant (Appelbaum et al., 1987). Therefore, alternative therapies are needed.

Monoclonal Antibodies

In addition to standard forms of cancer treatment using surgery, radiation, and chemotherapy, MAbs have gained acceptance for the treatment of NHL. MAbs are able to specifically target tumor cells and induce cell destruction by eliciting immune effector mechanisms or by causing the tumor cells to undergo programmed cell death. Rituximab (Rituxan®, Genentech, Inc., South San Francisco, CA, and Biogen Idec, Inc., Cambridge, MA) is an unconjugated anti-CD20 MAb that currently is available for the treatment of NHL. In patients with relapsed, low-grade follicular NHL, rituximab has demonstrated an overall response rate of 48% (McLaughlin et al., 1998). Single-agent rituximab therapy is limited, however, because most responses are partial and many patients relapse.

To increase the cytotoxicity of MAbs, investigators have conjugated them with toxins, chemotherapeutic agents, or radionuclides. Conjugated MAbs deliver a cytotoxic substance directly to the tumor cells with less toxicity to the normal tissues compared with traditional chemotherapy. One of the most promising new approaches is radioimmunotherapy (RIT), and researchers have determined that radiolabeled MAbs have an important and growing role in the treatment of cancer (Wahl et al., 1998). Radionuclide-labeled MAbs that recognize tumor-associated antigens are administered systemically to selectively target radioactivity to tumor cells. Hematologic malignancies are suitable for RIT because the cells in the blood, spleen, lymph nodes, and bone marrow are more accessible than solid tumor cells (Meredith & LoBuglio, 1997). In addition, lymphomas are exquisitely radiosensitive (Kwak, Grossbard, & Urba, 1995) because they have a poor capacity for repairing radiation damage. Therefore, only a small amount of radiation is needed for an antitumor effect (Meredith & LoBuglio). Specific proteins on the surface of lymphoma cells that differentiate B-cell lymphocytes from other cells in the body serve as the target for the MAbs and ensure targeted therapy (Kaminski et al., 1996).

RIT differs from external beam radiation therapy in several ways. First, RIT delivers radiation at a low, continuous dose rate that initially increases as radiolabeled antibodies accumulate in a tumor and then decreases because of physical decay and biologic clearance. Exposure to continuous, low dose-rate radiation can lead to increased cytotoxicity (Press, 2000). Second, RIT delivers radiation only to the tumor and adjacent cells, generally sparing normal cells. Moreover, an advantage of RIT over unconjugated antibody therapy is that, in a cross-fire effect, the radiation particles can kill adjacent tumor cells regardless of whether they express the target antigen or have the MAb attached (Press; Wilder, DeNardo, & DeNardo, 1996). By preferentially targeting radioactivity to tumor sites, healthy tissues are spared and toxicities are reduced (Kaminski et al., 1996). An advantage of RIT over traditional chemotherapy is that radioisotopes are not subject to multidrug resistance (Wilder et al.). Finally, in addition to the radiation-induced cytotoxicity, MAbs can induce cytotoxicity similar to that of unconjugated antibodies.

One form of RIT was approved by the U.S. Food and Drug Administration for the treatment of relapsed low-grade NHL on February 19, 2002: yttrium 90 (^{90}Y) ibritumomab tiuxetan (Zevalin®, Biogen Idec, Inc.). Ibritumomab, a murine immunoglobulin G MAb, is the predecessor MAb of the engineered mouse or human chimeric antibody, rituximab. Ibritumomab is radiolabeled with ^{90}Y by the linker tiuxetan. ^{90}Y is a pure beta emitter with a mean path length of 5 mm. To assess possible alterations in biodistribution, imaging is performed with ibritumomab that has been radiolabeled with indium 111 (^{111}In), a gamma emitter (Witzig et al., 2002). Zevalin is administered in two sessions, one week apart. An imaging dose of ^{111}In ibritumomab tiuxetan is given after an initial dose of unlabeled rituximab on day 1. On day 8, the therapy dose of ^{90}Y ibritumomab tiuxetan is given, again following unlabeled rituximab (Hendrix, de Leon, & Dillman, 2002). A phase I and II trial of Zevalin had an overall response rate of 64%–67%, with a complete response rate of 26%–28% (Grillo-Lopez, Chinn, & Morena, 1995; Witzig et al., 1999). A phase III randomized study comparing Zevalin with Rituxan in 143 patients with relapsed or refractory low-grade follicular or transformed NHL resulted in an 80% overall response rate (30% complete response and 45% partial response) in the Zevalin group versus 56% for Rituxan (16% complete response and 36% partial response). Despite a statistically significant improvement in response rates, no difference was found in the duration of the response seen with Zevalin compared to Rituxan. The most common hematologic toxicities are reversible myelosuppression with 32% grade 4 (< 500) absolute neutrophils, 25% grade 3 (< 1,000) absolute neutrophils, and 55% grade 3 thrombocytopenia (< 50,000 platelets) (Witzig et al., 2002). Nonhematologic toxicities are related to Rituxan and occur in 10% or more of the patients. They include asthenia (35%), nausea (25%), chills (21%), fever (13%), throat irritation (9%), headache (9%), and rash (7%). Human antimouse antibodies developed in 1.4% and human antichimeric antibodies developed in 0.5% of 211 patients in the four Zevalin trials (Hendrix et al.).

Multiple clinical trials of other RIT agents for the treatment of low-grade lymphoma have been conducted. One such agent is a combination RIT composed of the base MAb, tositumomab, and the radiolabeled MAb, iodine 131 (^{131}I) tositumomab (Bexxar®, Corixa Corporation, Seattle, WA, and GlaxoSmithKline, Philadelphia, PA). Bexxar is composed of an unconjugated murine MAb, tositumomab (specific for CD20), and ^{131}I conjugated tositumomab. The CD20 protein is expressed by more than 95% of normal B cells in the peripheral blood, lymphoid tissue, and bone marrow, and by 90% of malignant B-cell lymphomas. The CD-20 protein is not expressed by early-progenitor B cells, mature plasma cells, T cells, or any other normal hematopoietic or nonhematopoietic tissue (Stashenko, Nadler, Hardy, & Schlossman, 1980). Thus, Bexxar therapy does not cause long-term B-cell depletion, and natural immunity is maintained by mature plasma cells.

The CD-20 protein is an ideal target because it is a stable cell-surface antigen, thus allowing prolonged antibody binding and residence time on the cell surface, extending exposure of the tumor to radiation (Kaminski, Estes, Tuck, et al., 2000). Other antigens on the surface of B cells, such as CD-19 and CD-22, do not display the favorable characteristics of the CD-20 antigen nor are they as abundant on the surface of B cells.

Bexxar Therapy for Non-Hodgkin Lymphoma

Clinical Trials

Bexxar has been studied extensively for the treatment of low-grade NHL since the early 1990s, with more than 1,000 patients entered on clinical trials to date. A phase I and II study at the University of Michigan established the maximum tolerated dose of Bexxar at 75 cGy total body dose in patients with normal platelet counts (Kaminski et al., 1993). This study also demonstrated the improved tumor targeting of the radiolabeled antibody when it is preceded by an unlabeled (unconjugated) antibody. The majority of the patients treated had stage III or IV disease, and 71% had low-grade or transformed low-grade NHL. In addition, many patients were pretreated heavily with chemotherapy (median of three prior therapies). Response to Bexxar therapy was seen in 71% of the 59 patients treated, and 34% achieved a complete response. In long-term follow-up of the complete responders, seven patients remained disease free for as long as six years.

A follow-up multicenter, phase II trial in 47 patients with low-grade (79%) or transformed low-grade (21%) NHL confirmed the efficacy of Bexxar. These patients were pretreated heavily with chemotherapy (median of four prior therapies) and had extensive disease involvement. The overall response rate was 57%, with a complete response rate of 32% (Vose et al., 2000).

A multicenter pivotal trial was conducted in 60 patients with refractory low-grade and transformed low-grade NHL (Kaminski et al., 2001). These patients had to have received at least two protocol-determined, qualifying chemotherapy regimens and either failed to respond to their last chemotherapy or achieved a response of less than six months duration. Only 28% of patients in this trial responded to their last chemotherapy regimen, and only 3% achieved a complete response. The median duration of response to the last chemotherapy regimen was 3.4 months. Because no regimens have been established to treat multiple-relapse patients, the study was designed for patients to serve as their own control. These patients received a median of four prior regimens (range = 2–13), 56% had bone marrow involvement, 44% had elevated lactate dehydrogenase, 38% had bulky disease, and 38% had transformed low-grade NHL.

Following therapy with Bexxar, 67% of patients had an objective response, including 17% complete responses. The primary endpoint of the trial was a comparison of the duration of response to the last chemotherapy regimen with the duration of response to Bexxar. Of the patients with a difference in duration of response greater than 30 days, 26% had a longer duration with their last chemotherapy and 74% had a longer duration of response following treatment with Bexxar. Because patients with low-grade NHL usually have lower response rates and duration of response with successive therapies, the extended duration of response achieved with Bexxar was quite impressive (Kaminski et al., 2001).

Bexxar also has been studied in patients who have failed rituximab (Horning et al., 2000). Of the 40 participants, Bexxar produced a 68% overall response rate, including complete responses in 33% of patients. Because of the favorable responses seen in relapsed and refractory patients, Bexxar has been studied, with excellent preliminary results, as a single agent (Kaminski, Estes, Tuck, et al., 2000) and in combination with other chemotherapy agents (Leonard et al., 2001) in previously untreated patients.

Radiation Safety

Bexxar RIT is an unsealed radioactive source administered via IV and is subject to the same safety precautions that apply to swallowed or injected radioactivity. Once Bexxar is infused, the patient's body fluids are radioactive for a period of time related to the half-life of the isotope used and the rate of elimination of the ^{131}I tositumomab (McDonald & Takahashi, 1999). Prior to the administration of this therapy, the nurse and patient should be knowledgeable of and practice the radiation protection standards and regulations as determined by the U.S. Nuclear Regulatory Commission, their state agency, and institutional guidelines. Reviewing in-depth radiation protection is not within this article's scope. Readers should refer to the *Manual for Radiation Oncology Nursing Practice and Education* (Bruner, Bucholtz, Iwamoto, & Strohl, 1998), as well as to the radiation safety officer in their institution for more information.

^{131}I emits beta particles and gamma photons. The beta emissions exhibit an antitumor effect, and the gamma emissions allow for patient-specific dosing (dosimetry) (Wahl et al., 1998). The path length of beta particles extends over several cell diameters, allowing the radiolabeled antibody, bound to a tumor cell, to destroy antigen-positive (CD-20) cells and antigen-negative neighboring cells with relatively little exposure to surrounding healthy tissues. Gamma emissions travel six to seven feet, can be detected externally (via gamma cameras or probes), and can be used to calculate the appropriate radiation dose for each patient.

Beta particles, once administered by IV, are not an external hazard because the patient's body will provide adequate shielding. However, beta radiation will be excreted in the

Table 1. Nursing Radiation Safety Precautions

Photon Protection	Precautions
Gamma	Outpatients should be treated in an area approved by the radiation safety officer; inpatients should be in a private room located at the end of the hall with a private bathroom. Lead shields are placed around the patient during the infusion of the iodine 131 tositumomab. The patient's chart and door/area should be labeled with a radiation precaution sign.
Beta	Gloves are required when providing direct patient care. The toilet should be flushed three times after patient use. Isolation bags are necessary for linens and trash. All articles and surfaces the patient may touch should be covered in plastic. A plastic sheet is placed between the mattress and the bottom sheet on the patient's bed or chair. Dietary tray and products on the tray should be disposable.

patient's body fluids, which requires special handling. Because gamma rays have a higher penetrating ability, the principles of time, distance, and shielding are used to reduce the potential external hazards of radiation exposure of hospital personnel while patients are in the hospital or outpatient setting (Dunne-Daly, 1999). The amount of time spent near the patient must be minimized, and the distance between the patient and caregiver should be maximized to reduce radiation exposure. In addition, hospital personnel monitoring, typically with a film badge, is required by law, regardless of whether the patient is treated as an in- or outpatient. Table 1 lists some of the specific precautions that must be followed when treating patients with ^{131}I.

The U.S. Nuclear Regulatory Commission determines and recommends the guidelines for safe use of diagnostic and therapeutic applications of radioactive materials, and each state has its own regulatory board that interprets and enforces the commission's guidelines. The Nuclear Regulatory Commission (1997) amended its regulations concerning the release of patients who have been administered radioactive material. These new criteria permit the release of patients if the total effective dose is not likely to exceed 500 mrem. This change in the guidelines allows for the safe release of patients immediately after the therapeutic Bexxar dose provided they meet certain criteria based on administered dose and activity level at one meter. Patients who are released immediately must be given instructions to prevent overexposure to household members. This change in guidelines results in less hospitalization, which significantly reduces healthcare costs, and has personal and psychological benefits for patients and their families, while decreasing the total amount of exposure to healthcare personnel. Because exposure to household members is a one-time event, close monitoring, such as wearing a radiation film badge, is not necessary. A direct dosimetry study also demonstrated that caregivers and family members of patients treated with Bexxar were exposed to 17–409 mrem, which is well within the limits defined by the Nuclear Regulatory Commission (Rutar et al., 2001).

Nursing Implications

Patient and Family Member Education

Patient and caregiver education is a critical component for patients undergoing RIT with Bexxar. Patient education can minimize anxiety, complications, and radiation exposure of caregivers, family, and healthcare workers. Nurses must ensure that patients and caregivers understand accountability related to receiving RIT. Patient education must emphasize compliance with radiation safety measures as well as prevention, recognition, and management of side effects. An explanation of how RIT differs from traditional chemotherapy and radiation therapy also is necessary. Topics for patient and caregiver education are detailed in Table 2, and radiation safety precautions that must be reviewed with patients are described in Table 3 (Siegel, Kroll, Regan, Kaminski, & Wahl, 2002).

A calendar of the treatment schedule should be provided. Patients should be informed that they will receive two injections of antibody on each treatment day. Nurses should describe the purpose of the gamma scan and probe count that measures the amount of radioactivity in the patient's body, tracks the antibody to lymphoma sites, and helps to determine body clearance time. Patients should be reassured that the infusion on the first day of treatment contains only a very small amount of radiation and they do not need to isolate themselves from their family.

Table 2. Topics for Patient and Family Member Education

Topic	Key Points
Radioimmunotherapy	Monoclonal antibody targeting, rationale for radioimmunotherapy, benefits of iodine 131, and need for gamma scans and probe counts
Treatment protocols	Pretherapy tests and procedures; treatment and follow-up schedule
Radiation safety	Explanation of time, distance, and shielding precautions to reduce radiation exposure to others; radiation safety protocols to be followed on patient release (see Table 3)

Pretherapy Assessment

The majority of patients who receive RIT with Bexxar can be treated on an outpatient basis. Prior to initiation of therapy, assessment of the patient's and family's ability to comply with the radiation precautions is necessary. Patients must be able to care for themselves when they are radioactive to minimize the radiation exposure to others. Patients

Table 3. Radiation Safety Precautions Following Bexxar® Therapy

Instruction	Average Duration of Instruction[a]
• Maintain a distance of six feet from others whenever possible.	4 days
• Avoid close contact with infants and pregnant women.	8 days
• Avoid sharing a common bed.	8 days
• For short trips during the period of restricted travel, sit as far away from others as possible.	4 days
• General radiation safety precautions	7 days
– Have sole use of a bathroom if possible.	
– Sit while urinating, and flush the toilet three times with the lid down.	
– Wash hands frequently, including after each toilet use; shower daily.	
– Drink plenty of fluids.	
– Keep dishes and utensils separate and wash separately.	
– Use separate towels, washcloths, and toothbrush from the rest of household.	
– Avoid using disposable items that cannot be flushed down the toilet.	
– Hold clothing and linens (sheets and towels) before laundering, and launder separately from other household laundry.	
– Share radiation safety instructions with healthcare professionals, family members, and all caregivers.	

[a] The number of days the instruction must be in place will vary for each patient and is dependent on patient-specific calculations performed prior to patient release from the hospital.

Note. Based on information from Siegel et al., 2002.

Table 4. Collaborative Treatment Team Responsibilities

Department or Staff Member	Responsibilities
Nuclear medicine	Schedule treatment regimen. Explain radioimmunotherapy and Bexxar®; provide treatment regimen. Administration guidelines Room set-up Radiation safety
Oncologist	Prescribe thyroid-blocking medication.
Oncology nurse	Define treatment team roles and responsibilities. Review patient selection criteria. Review schedule of evaluations. Confirm initiation of thyroid-blocking medication on day 1. Review treatment side effects and toxicities. Outline follow-up schedule. Educate patient and family.
Outpatient or inpatient nurse	Define treatment team roles and responsibilities. Radioimmunotherapy and Bexxar overview: Explain treatment regimen. Review patient selection criteria. Outline follow-up schedule. Radiation safety and patient isolation

who are bedridden or incontinent, have drains or wounds, or are unable to follow the radiation precautions may not be candidates for outpatient therapy. Home arrangements should be reviewed with the patient and family to identify problems in complying with the radiation precautions. Questions to consider include the following: Are separate sleeping arrangements feasible such that a six-foot perimeter is maintained around the patient? Is a separate bathroom available? Are small children or pets in the home who may not be able to comply with the isolation? Is a dishwasher available in the home? Using a dishwasher to wash a patient's dishes will decrease radiation exposure to caregivers. If a dishwasher is not available and the patient is unable to wash his or her own dishes, the caregiver should wear household rubber gloves when washing the dishes. Transportation from the treatment facility also should be evaluated. Patients should spend no more than four hours (per 24 hours) traveling by car or mass transportation for the first four days after treatment to prevent overexposure to others (Siegel et al., 2002).

Administration

A collaborative treatment team approach is critical for successful therapy. Team members include the patient, a medical oncologist, a nuclear medicine physician, a radiation oncologist, a radiopharmacist, a nuclear medicine technologist, nurses, a coordinator (often a nurse coordinator), and a radiation safety officer. The roles of the treatment team members are detailed in Table 4.

Twenty-four hours prior to the initiation of Bexxar therapy, all patients receive a saturated solution of potassium iodide, Lugol's solution, or potassium iodide tablets to inhibit uptake of free iodine by the thyroid. This medication must be continued for at least two weeks after treatment is completed (for a total of three weeks). Absorption of radioactive iodine into the thyroid damages thyroid tissue and could result in hypothyroidism if the thyroid is not blocked prior to and during therapy. To date, the incidence of hypothyroidism after Bexxar therapy as evidenced by elevated thyroid-stimulating hormone is 9.1% at two years and 17.4% at four years (Corixa Corporation, 2003).

After preparation of radiolabeled tositumomab in the nuclear pharmacy, Bexxar is administered in two sessions, 7–14 days apart (see Table 5). Thirty minutes prior to each session, patients are premedicated with acetaminophen 650 mg and diphenhydramine 50 mg. The IV set-up should include an in-line, 0.22-micron filter. Vital signs should be taken every 15 minutes during the infusions. If any of the adverse events listed in Table 6 occur, the rate of the infusion should be decreased as indicated.

During the first session (day 1), unlabeled tositumomab is infused followed by ^{131}I tositumomab. The first infusion of 450 mg of unlabeled tositumomab, diluted in 50 cc of normal saline, is infused over one hour or longer, depending on the occurrence of infusion-related side effects. Following the infusion, an additional 50 cc of normal saline should be administered over 10 minutes. Unlabeled tositumomab is delivered first to optimize biodistribution and tumor targeting. By preblocking normal CD-20 sites, such as B cells in the peripheral blood, bone marrow, and spleen, the unlabeled antibody provides better distribution of the ^{131}I tositumomab.

Table 5. Sample Treatment Schedule

	Treatment Day																	
Treatment	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16[a]**	**28**
Saturated solution of potassium iodide	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dosimetric dose		x																
Gamma scans or counts[b]		x	x	x	x	x		x	x									
Therapeutic dose								x										
Radiation precautions[c]								x	x	x	x	x	x	x	x			
Complete blood count	x																	x
Thyroid-stimulating hormone	x																	

[a] Patient continues to receive saturated solution of potassium iodide to day 28.

[b] A gamma scan or count needs to be performed once from days 2–5 and once from days 7–8.

[c] Radiation precautions must be in effect for seven days beginning on the day of the therapeutic administration.

Table 6. Infusion Rate Adjustment for Adverse Events

Infusion Rate Adjustment	Fever	Rigors	Mucosal Congestion or Edema	Drop in Systolic Blood Pressure (%)
Decrease by 50%	38.5°–38.9°C	Mild to moderate	Mild to moderate	30–49
Stop infusion[a]	≥ 39°C	Severe	Severe	50

[a] Temporarily discontinue

After receiving the unlabeled tositumomab and just prior to receiving the radiolabeled (dosimetric) dose of tositumomab, the patient should empty his or her bladder of urine. The large antibody protein and IV fluids will cause an increase in urine production, and after the dosimetric dose is infused, the patient will not be permitted to empty his or her bladder until after the gamma scan.

The dosimetric infusion consists of 35 mg of tositumomab labeled with 5 mCi ^{131}I diluted in 30 ml of normal saline and infused over 20 minutes. At the end of the dosimetric dose, another 30 cc of normal saline is infused over 10 minutes. The amount of radiation that the patient receives with this dose does not require radiation safety precautions.

Dosimetry studies determine the whole body clearance rate of the radiolabeled antibody. This information is important to determine a whole body radiation dose for treatment planning and assessment of results. The pharmacokinetics of the radiolabeled antibody is influenced by tumor bulk, antibody clearance, and individual metabolic differences (Wilder et al., 1996). Therefore, the therapeutic radiation dose is individualized. A whole body gamma camera scan is obtained within several hours of receiving the dosimetric dose on day 0. Gamma scans are repeated on day 2, 3, or 4 and on day 6 or 7. Because the elimination of the antibody and radioactivity is variable, patients must receive individualized amounts of radioactivity in millicurie to achieve the same total body dose. A patient who quickly eliminates ^{131}I tositumomab will require delivery of a higher millicurie dose than a patient who eliminates the ^{131}I tositumomab slowly to receive the same total body dose of 75 cGy. Therefore, doses can vary from 38–239 mCi depending on patient characteristics. Dosimetry studies for patient-specific dosing are important to minimize under- or overdosing (Kaminski, Estes, Zasadny, et al., 2000).

The therapeutic dose is given 7–14 days after the dosimetric dose. Patients are premedicated with acetaminophen and diphenhydramine 30 minutes prior to receiving the MAb. The therapeutic dose is 75 cGy for patients with a platelet count of more than 150,000 and 65 cGy for patients with a platelet count of 100,001–150,000. Dose corrections also are made for obese patients based on their ideal body weight. Patients again receive 450 mg of unlabeled Bexxar over one hour followed by flushing with normal saline over 10 minutes. The therapeutic dose of ^{131}I labeled tositumomab then is administered over 20 minutes, followed by a flush of normal saline over 10 minutes as with the dosimetric dose.

Toxicities and Management

Bexxar therapy generally is well tolerated. Side effects can be divided into nonhematologic and hematologic toxicities. Table 7 summarizes the side effects and general nursing management for patients undergoing Bexxar therapy.

Nonhematologic acute effects: Bexxar is a murine (mouse) MAb and, like any foreign protein, may induce an allergic reaction. Foreign proteins from different species are potent immunogens (Tizard, 1992). Infusion-related toxicities include fever, chills, rigors, asthenia, erythematous rash, urticaria, pruritus, mucous membrane congestion, and cough. Nausea, which may be caused by a saturated solution of potassium iodide or other thyroid-protective medication, and vomiting rarely occur. Hypotension and anaphylaxis occur in less than 1% of patients (Corixa Corporation, 2003). Infusion rate adjustments are recommended if the patient develops fever, rigors, mucosal congestion or edema, or hypotension. Most nonhematologic side effects are grade I or II in severity, are transient and reversible, and rarely require supportive care. The occurrence of fever and chills may be related to the presence of circulating lymphoma cells in the bloodstream. The incidence of urticaria and pruritus is highest in patients who have lymphomatous involvement of their skin. Patients who display side effects during the dosimetric infusion generally will not experience infusion-related side effects during the therapeutic infusion.

Nonhematologic delayed effects: Delayed toxicities can occur within the first 24–48 hours or may not occur until 7–14 days later. One of the delayed toxicities is a compilation of side effects that can include fever, chills, rigors, nausea, headache, asthenia, pain, urticaria, pruritus, rash, emesis, arthralgias, and myalgias. This delayed reaction may be a result of human antimouse antibody formation, where immune complexes are deposited in the tissues. Additional side effects

Table 7. Supportive Care for the Most Common Toxicities

Toxicity	Suggested Supportive Care
Nonhematologic	
• Asthenia	Suggest energy conservation, rest, setting priorities, and delegating tasks.
• Fever	Administer acetaminophen and diphenhydramine; monitor vital signs. Admit patient if fever persists.
• Nausea or vomiting	Administer antiemetics, assess dehydration and electrolyte levels, and monitor nutritional status.
• Chills	Wrap patient in warm blankets, and increase ambient air temperature.
• Pruritus	Maintain hydration, maintain humidity at 30%–40%, and administer antihistamines, corticosteroids, or analgesics as appropriate.
• Anorexia	Educate and administer nutritional supplements and appetite stimulants.
• Hypotension	Monitor vital signs; check for orthostatic tolerance every four hours; monitor for tachycardia, dizziness, and shortness of breath; and administer fluids.
Hematologic	
• Neutropenia	Granulocyte colony-stimulating factors
• Thrombocytopenia	Platelet transfusion
• Anemia	Red blood cell transfusion and erythropoietin

are fatigue, anorexia, nasal congestion, tumor site pain, reactive lymph nodes, and conjunctivitis.

Hematologic delayed effects: Suppression of the bone marrow is seen 5–7 weeks after treatment, with recovery in approximately 8–10 weeks. This is later than generally observed after chemotherapy, where bone marrow suppression is seen 10–14 days after treatment. Bone marrow suppression typically is more complicated and prolonged in patients who previously have been treated with multiple courses of chemotherapy or radiation, have undergone a stem cell transplant, or have low baseline blood counts. The platelet count frequently decreases first, followed by a decrease in the white blood cell count. Hemoglobin is affected minimally. Platelets are the first to recover, followed by the white blood cells. Supportive care with blood products or colony-stimulating factors is required in 25%–30% of patients receiving Bexxar (Kaminski et al., 2001; Vose et al., 2000).

Conclusion

This is an exciting time in the treatment of NHL, providing hope for patients with few treatment options. Nurses will play a critical role incorporating RIT into practice. RIT has been shown to be effective, well tolerated, easily administered, and safe for patients, families, and staff. With minimal impact on lifestyle, patient and family quality of life is enhanced when compared to traditional chemotherapy or radiation therapy. Length of treatment time is two weeks versus four to six months with chemotherapy and two to five weeks with radiation therapy, whereas side effects are experienced once versus four to eight times with chemotherapy. Thus, many patients are able to maintain an active life with an interruption of only one to two weeks as a result of treatment, radiation precautions, and side effects.

As RIT is incorporated into treatment regimens for patients with NHL, nurses must become knowledgeable about RIT and comfortable with all aspects of this exciting therapy. Nurses will be responsible for patient, caregiver, and peer education; will participate in the safe administration of RIT (understanding specific state regulations for radiation precautions); will maintain radiation precautions; and will manage patients' side effects.

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