THE UNIVERSITY OF NEW MEXICO
HEALTH SCIENCES CENTER
COLLEGE OF PHARMACY
ALBUQUERQUE, NEW MEXICO

Correspondence Continuing Education Courses For Nuclear Pharmacists and Nuclear Medicine Professionals

VOLUME IX, NUMBER 5

The Treatment of Low-Grade B-Cell Non-Hodgkin's Lymphomas with Radiopharmaceuticals

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STATEMENT OF OBJECTIVES

Upon completion of this continuing education module, the reader should be able to:

1. Describe the natural history of non-Hodgkin's lymphoma (NHL).
2. List the signs and symptoms of NHL.
3. Discuss the clinical classification systems used in NHL.
4. List the current treatment options for patients with NHL.
5. Explain the rationale for molecular targeting in the therapy of NHL.
6. Describe the patient treatment schema for Bexxar® and Zevalin™ therapies.
7. Calculate the therapeutic dose of ^{131}I-tositumomab based upon patient-specific parameters.
8. Compare the results of the pivotal clinical trials for Bexxar® and Zevalin™
9. Describe the appropriate acquisition, storage and preparation of Bexxar® and Zevalin™.
10. Discuss measurement considerations for pure beta emitters such as ^{90}Y and the importance of geometric dependency in ionization chambers.
11. Describe the radiation safety procedures necessary to minimize personnel exposure when working with Bexxar® and Zevalin™.
12. List the NRC-recognized dose-based limits used for the "early release" of patients treated with therapeutic radiopharmaceuticals.
13. Explain the pharmacoeconomic and outcomes analysis of Rituxan™.
14. Discuss the expanded role for radiopharmacists in caring for patients receiving radioimmonotherapy for NHL.

COURSE OUTLINE

THE TREATMENT OF LOW-GRADE B-CELL NON-HODGKIN'S LYMPHOMAS WITH RADIOPHARMACEUTICALS

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BASIC FACTS OF NON-HODGKIN'S LYMPHOMA

Non-Hodgkin's lymphomas are the fifth leading cause of cancer morbidity and mortality. Since the early 1970s, the incidence of non-Hodgkin's lymphoma has nearly doubled, although during the 1990s the rate of increase appeared to slow.[1] The estimated numbers of new cases of non-Hodgkin's lymphoma by state are given in Table 1. The deaths for males and females from non-Hodgkin's lymphoma in the year 2001 were estimated at 13,800 and 12,500, respectively. This represents approximately 5% of all cancer deaths for both men and women. Estimated deaths by state are given in Table 2. Survival rates for non-Hodgkin's lymphoma vary widely based upon the histopathology and the stage of disease. The one-year survival rate for non-Hodgkin's lymphoma is 70 percent; the five-year rate is 51 percent. Relative 10-year survival rates after diagnosis for non-Hodgkin's disease decline to 41 percent; the 15-year survival rate is 35 percent.[2] Most patients with NHL will achieve remissions after chemotherapy. But, generally, patients diagnosed with intermediate- or high-grade NHL can achieve a cure. Patients in the low-grade category are rarely cured having a median survival rate of 6-10 years from initial diagnosis. These types of low-grade B-Cell lymphomas are indolent and refractory to therapy and are the focus of this review.

Etiology of Non-Hodgkin's Lymphoma

The etiology of NHL is unknown but an increased incidence is seen with certain infectious agents; in immunodeficiency syndromes that are congenital, acquired, or autoimmune in nature; with environmental exposures; and there are also genetic predisposing factors (see Table 3).

Risk factors for NHL are largely unknown but in part involve reduced immune function and exposure to certain agents. Human immunodeficiency virus and human T-Cell leukemia lymphoma virus are associated with an increased risk of NHL. Persons with organ transplants have a more than 100 times higher risk due to altered immune function. Other possible risk factors include occupational exposures to herbicides and perhaps other chemicals.

Table 1. Estimated New Non-Hodgkin's Lymphoma by State in 2001*

Alabama	800	Kansas	500	Oklahoma	700
Alaska	100	Kentucky	900	Oregon	800
Arizona	1000	Louisiana	900	Pennsylvania	3000
Arkansas	600	Maine	300	Rhode Island	300
California	5300	Maryland	900	South Carolina	700
Colorado	700	Massachusetts	1400	South Dakota	200
Connecticut	800	Michigan	2200	Tennessee	1200
Delaware	200	Minnesota	1200	Texas	3600
District of Columbia	100	Mississippi	500	Utah	300
Florida	4200	Missouri	1200	Vermont	100
Georgia	1100	Montana	200	Virginia	1200
Hawaii	300	Nebraska	300	Washington	1100
Idaho	200	Nevada	400	West Virginia	500
Illinois	2500	New Hampshire	300	Wisconsin	1300
Indiana	1300	New Jersey	2000	Wyoming	100
Iowa	700	New Mexico	300	**United States**	**56,200**
		New York	3700		
		North Carolina	1400		
		North Dakota	100		
		Ohio	2700		

**** From Cancer Facts and Figures 2001. American Cancer Society[1]***

Table 2. Estimated Deaths from Non-Hodgkin's Lymphoma by State in 2001*

Alabama	400	Kansas	200	Oklahoma	300
Alaska	<50	Kentucky	400	Oregon	400
Arizona	500	Louisiana	400	Pennsylvania	1400
Arkansas	300	Maine	200	Rhode Island	100
California	2500	Maryland	400	South Carolina	300
Colorado	300	Massachusetts	700	South Dakota	100
Connecticut	400	Michigan	1000	Tennessee	600
Delaware	100	Minnesota	500	Texas	1700
District of Columbia	<50	Mississippi	200	Utah	200
Florida	2000	Missouri	600	Vermont	100
Georgia	500	Montana	100	Virginia	600
Hawaii	100	Nebraska	200	Washington	500
Idaho	100	Nevada	200	West Virginia	200
Illinois	1200	New Hampshire	100	Wisconsin	600
Indiana	600	New Jersey	900	Wyoming	<50
Iowa	300	New Mexico	100	**United States**	**26,300**
		New York	1700		
		North Carolina	700		
		North Dakota	100		
		Ohio	1300		

* ***From Cancer Facts and Figures 2001. American Cancer Society[1]***

Table 3. Etiology of Non-Hodgkin's Lymphoma

Predisposing Factors	Agent/Condition	Lymphoma
Infectious Agents	EBV	Burkitt's
	HTLV-1	ATL/L
	Helicobacter pylori	MALT
Immunodeficiency Syndrome - Congenital	Ataxia	Suspected
	Telangiectasia	Suspected
Immunodeficiency Syndrome - Acquired	AIDS	CNS B-Cell Lymphoma
	Acquired Hypogammaglobulinemia	Suspected
	Graft-versus-host disease	Suspected
Immunodeficiency Syndrome - Autoimmune	Hashimoto's Thyroiditis	MALT
	Sjögren's Syndrome	MALT
	Systemic Lupus Erythematosis	Suspected
	Rheumatoid Arthritis	Suspected
Environmental Exposure	High Dose Radiation	Leukemia and lymphoma
	Chemicals	
	-Dyes & Solvents	Suspected
	-Phenoxyherbacides	Suspected
	-Organophosphates	Suspected
Genetic	Wiskott-Aldrich syndrome	Suspected
	Klinefelter's Syndrome	Suspected
	Chediak-Higashi syndrome	Suspected

EBV=Epstein Barr Virus; HTLV-1=Human T-cell Leukemia/lymphoma virus; ATL/L =Adult T-cell leukemia/lymphoma; and MALT=Marginal zone B-cell of mucosa-associated lymphoid tissue.

Signs and Symptoms

Signs and symptoms of lymphoma include enlarged lymph nodes, itching, fever, night sweats, anemia, weight loss, and malaise. The lymphadenopathy is usually painless and occurs in the cervical or supraclavicular regions. Hepatomegaly and splenomegaly may occur in patients with generalized lymph system involvement. Patients with abdominal involvement may present with palpable masses, nausea, vomiting, pain, and gastrointestinal bleeding. Abdominal involvement is more common in NHL than in Hodgkin's disease. Disease that involves the bone marrow can produce symptoms of neutropenia, anemia, and thrombocytopenia. Again, bone marrow involvement is more common in NHL than in Hodgkin's disease. Constitutional symptoms (B symptoms) including itching, fever, night sweats, and weight loss are less common in NHL than in Hodgkin's disease. Fever can come and go for periods of several days or weeks.

Classifications of Non-Hodgkin's Lymphoma

Confusion sometimes comes about in classifying NHL due to the lack of consensus on lymphoma classification and terminology. The International Working Group Formulation (WF) system of classifying NHL was used in the United States summary and description of a working formulation for clinical usage. The non-Hodgkin's and the Kiel classification system have been used in Europe.[2]

There are three major categories in the WF system, each with three subtypes:

- Low-grade lymphomas
- Intermediate-grade lymphomas
- High-grade

Classification of NHL has evolved with the increase in the knowledge of the biology of the immune system. The Revised European-American Classification of Lymphoid Neoplasms (REAL) was adopted as a new approach to lymphoma classification in 1994.[3] This is the forerunner to the new World Health Organization classification of lymphomas. The REAL classification system uses all available information including: histology, genetic features and clinical features. These are coupled with clinical prognostic factors that include disease stage, patient age and performance status. Clinicians are dependent upon the correct diagnosis of NHL as one of the most important parts of the patient therapy. The

Table 4. Classification and Frequency of Non Hodgkin's Lymphomas

REAL Classification	Frequency	WF Classification
Large B-Cell	31%	Low-, Intermediate-, and High-grade
Follicular	22%	Low- and Intermediate-grade
Small lymphocytic	6%	Low-grade
Mantle cell	6%	Intermediate- and high–grade
Peripheral T-Cell	6%	Intermediate- and high–grade
Marginal zone B-Cell of mucosa-associated lymphoid tissue (MALT)	5%	Low-grade
Primary mediastinal large B-Cell	2%	No specific classification
Anaplastic large T-/null-cell	2%	No specific classification
Lymphoblastic (T/B)	2%	High-grade
Burkitt-like	2%	No specific classification
Marginal zone B-Cell (nodal type)	1%	No specific classification
Lymphoplasmacytic	1%	No specific classification
Burkitt's	<1%	No specific classification

REAL classification system is the currently preferred but medical literature and product package inserts use both systems to categorize NHL. The most frequent lymphoma types that are recognized in the new classification system are compared to the WF classification system and presented in Table 4.

Indolent Lymphomas

Thirty percent of NHLs are classified as "indolent", reflecting their natural history. The largest group of "indolent" NHLs is follicular lymphomas. The natural history of lymphoma is characterized by periods of waxing and waning. Often patients experience episodes of remission, or a stabilization of their disease, followed by relapse or recurrence. Diffuse large B-Cell and follicular lymphomas compose the most frequently occurring groups. Therapies for NHL are based upon the proper pathologic classification of the disease and they range from observation of the patient through routine medical check ups to more aggressive multi-drug regimens, with and without radiation. Response rates generally decrease with retreatment. Often patients will relapse, experience recurrence of their disease, or become refractory to therapy, sometimes transforming to a more aggressive, high-grade histology.

THERAPEUTIC OPTIONS

Treatment options for indolent lymphomas are controversial since relapse with low-grade NHL is inevitable. Treatment of NHL is palliative by nature and should not be initiated unless clearly warranted. While patients do respond to second and third-line therapies for NHL, the quality of their response becomes poorer and the duration greatly reduced. A tremendous array of standard therapeutic regimens has been used in patients with indolent NHL (see Table 5). These range from a "watchful waiting" approach to single agent regimes using alkylating agents, radiation therapy, combination alkylating agent–based chemotherapy with or without an anthracycline, purine analog-based chemotherapy, or bone marrow transplant and combination chemotherapy. These therapies have no survival advantage over one another. None of these therapies have produced durable cures and the prognosis for these patients has remained unchanged for more than 20 years. The approaches to therapies depend upon the oncologist and their experience with the NHL. Several other regimens including the use of cytokines, monoclonal antibody therapy, high dose chemotherapies with stem cell rescue are under investigation.

Molecular Targeting

Molecular targeting using monoclonal antibodies (MAb) is a new therapeutic approach to the treatment of NHL. Unlabeled, or nonradiolabeled MAbs can target specific antigens on tumors causing cell death while sparing normal tissue with fewer side effects than standard chemotherapy. These MAbs can also be used to deliver drugs, toxins, or radionuclides to the tumor site.

Antigen Targets in B-Cell Lymphomas

Many antigens have been used as targets

Table 5. Treatment Options for NHL

- Watchful waiting, supportive care
- Single-agent chemotherapy
- Involved-field radiation
- Combination chemotherapy
  - Anthracycline-containing
  - Purine analog-containing
- Autologous or allogenic bone marrow transplantation
- Antibody therapy
  - Immunotherapy
    - Rituximab (Rituxan®)
  - Radioimmunotherapy
    - ^{131}I-tositumomab (Bexxar®)
    - ^{90}Y-Ibritumomab tiuxetan(Zevalin™)

Table 6. Examples af Antigens Expressed in Lymphomas

NHL Subtype	Target Antigen
Follicular	CD20
Small-cell	CD20
Low-grade B-Cell	CD52
Cutaneous T-Cell	CD52
T-lymphocytic leukemia	CD52
Chronic lymphocytic leukemia	CD52
Low-grade B-Cell	Idiotype

for antibodies in the treatment of various lymphomas with MAbs (see Table 6). The designation CD refers to cluster of differentiation. These are cell surface molecules on blood cells that are identifiable by MAbs. CD markers are given designation numbers. B-Cell lymphomas express CD19, CD20, CD22, CD37, HLA-DR and Idiotype Ig antigens. The CD5 antigen is a potential target in T-Cell tumors, chronic lymphocytic leukemia and mantle cell lymphoma. The CD25 antigen has been targeted in adult T-Cell lymphomas. The CD 52 antigen, found on all leukocytes, has been used as a target for treatment of B- and T-Cell tumors.

CD20

The CD20 antigen, an unglycosolated phosphoprotein, has a molecular structure similar to that of a transmembrane ion channel. It may be involved in B-Cell activation. Experimental studies have shown that the CD20 antigen has many characteristics that make it a suitable substrate for therapy of certain lymphomas. It is expressed on the surface of 95% of B-Cell malignancies. It does not circulate in the blood stream allowing for better tumor targeting. It does not modulate (internalize) leaving the antigen-antibody complex on the cell, surface which can cause an added cytotoxic effect.

MAb Nomenclature

A review of the USAN methods for naming monoclonal antibodies (MAbs) Table 5 may be used to recognize protein source characteristics and clinical applications of these biotechnology drugs simply by observing how they are named. The suffix –mab is used for monoclonal antibodies and for antibody fragments. The letter preceding the –mab identifies the source of the product (e.g., a – r**a**t , e – hamst**e**r, **i** – pr**i**mate, **o** – m**o**use, **u** – h**u**man, **xi** – chimeric - a combination of human and animal fragments). The general disease state subclass must be incorporated into the name using a code syllable. Subclasses include: -vir- – viral, -bac- – bacterial, -lim- – immune (immunomodulator), -cir- – cardiovascular; and tumors of the areas of involvement: -col- – colon, -mel- –melanoma, -mar- mammary, -tum- or -tu- – miscellaneous tumor. This designation precedes the source, mab combination. A unique name is created by the addition of a distinct, compatible, syllable as the starting prefix. The drug manufacturer selects this prefix. If another chemical or a radionuclide is added to the MAb a second word or word order is generally added. In the case of the radiolabeled products, the word order includes the name of the radionuclide, element symbol, isotope number, then the name of the monoclonal antibody as in: ^{131}I-tositumomab. (See Table 7.)

Table 7. Nomenclature of Monoclonal Antibodies

Ibritumomab		Rituximab		Tositumomab	
Ibri-	unique	Ri-	unique	Tosi-	Unique
-tum-	Miscellaneous tumors	-tu-	Miscellaneous tumors	-tum-	Miscellaneous Tumors
-o-	Mouse	-xi-	Chimeric	-o-	Mouse
-mab	Monoclonal Antibody	-mab	Monoclonal Antibody	-mab	Monoclonal Antibody

Nonradiolabeled Antibody Therapy

The use of antibodies in the therapy of NHL is not approved for "first-line" therapy although physicians use their judgment and have applied "off-label" uses of these drugs in patient care. Rituximab is currently approved in the treatment of relapsed or refractory low-grade or follicular, CD20+, B-Cell non-Hodgkin's lymphoma (NHL).[6] It is a chimeric human-mouse MAb having a human Fc portion to mediate complement and antibody related cell cytotoxicity as well as reducing the potential for the formation of Human Antimurine Antibody (HAMA).

There is also the potential for the formation of Human Antichimeric Antibodies (HACA).

Mechanisms of Action

There are several mechanisms that may be responsible for apoptosis when using nonradiolabeled MAbs.[7,8] They include complement fixation, antibody-dependent cell cytoxicity (ADCC), and negative signaling.[9] Cell lysis is the result of complement fixation. In this process the antibody binds to the antigen site on the tumor cell and complement binds to the Fc portion of the antibody resulting in the complement cascade. In the ADCC, an effector cell (granulocyte, natural killer (NK) cell, or T-Cell) binds to the tumor cell via the MAb-antigen complex on the cell surface. Again, tumor cell lysis occurs being brought about by these interactions. Finally, negative signaling pathways cause apoptosis when the MAb-antigen complex on the cell membrane activates intracellular signaling pathways in the tumor cells.

Rituxan Dosage and Administration

The usual dose of rituxamab is 375 mg/m^2 by intravenous infusion once weekly for 4 or 8 doses. Rituxamab must be infused slowly. It cannot be administered as an intravenous bolus or push. The first infusion should be administered at an initial rate of 50 mg/hr. If hypersensitivity or infusion reactions do not occur, the infusion rate can be increased by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or stopped. The infusion may continue at one-half the previous rate when the patient ‘s symptoms improve.

If the patient tolerated the first infusion well, subsequent infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. The infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (e.g., intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells (> $25{,}000/mm^3$) with or without evidence of high tumor burden.

Common adverse events are associate with an infusion-related symptom complex, including fever, chills/rigors, asthenia, nausea, and headache. Grades 3 and 4 cytopenias reported in clinical trials were infrequent, and included lymphopenia, neutropenia, leukopenia, anemia, and thrombocytopenia.[6]

Radiolabeled Antibody Therapies

A disadvantage of using nonradiolabeled MAbs in NHL therapy is the potential for limited access to tumor cells because of antigen-negative tumor cells and poor vascular access to tumor cells. This disadvantage can be overcome by using radionuclides to form radioimmunoconjugates. Lymphomas are highly radiosensitive. The tumoricidal activity of the radionuclides labeled to the antibodies have direct effects and by-stander or crossfire effects since the beta-particle emissions can travel several cell diameters. Therefore, antigen-negative tumor cells and tumor cells with poor vascular access in the vicinity of the emitted radiation may be killed. Iodine I-131 (^{131}I) and Yttrium Y-90 (^{90}Y) are the most common radionuclides used in therapy of NHL at this juncture. The characteristics of these two are listed in Table 8. Two regimens that include a combination immunotherapy-radioimmunotherapy have been submitted to the FDA for approval. Zevalin™ (ibritumomab tiuxetan) has received FDA approval for the treatment of low-grade B-Cell NHL for patients who have not responded to standard chemotherapy treatments or to the use of Rituxan®

Table 8. Comparison fo Monoclonal Antibodies for Low-Grade B-Cell Lymphoma

Drug	Rituximab (Rituxan)	Tositumomab ^{131}I-Tositumomab (Bexxar®)	Rituximab ^{111}In/^{90}Y-Ibritumomab tiuxetan (Zevalin™)
Target antigen	CD20	CD20 tiuxetan	CD20
Antibody construct	Chimeric	Murine	Murine
Mechanism of action	ADCC, CDC, apoptosis	ADCC, CDC, apoptosis, radiation	ADCC, CDC, apoptosis, radiation
Administration schedule	375 mg/m^2 i.v. weekly X 4	Dosimetry = 5 mCi Day 0 Therapy = 75 cGy Day 7-14	Imaging = ^{111}In 5mCi Therapy = ^{90}Y up to 32mCi
Radioactivity/Radiation dose	None	^{131}I 65-75cGy TBD (91± 29 mCi)	^{90}Y max 32 mCi (0.3 - 0.4mCi/kg)
Toxicity	Infusion related HACA-reactions	Infusion related, myelosupression, HAMA-reactions	Infusion related, myelosupression, HAMA/HACA-reactions
Overall Response rate (CR)	48% (6%)	65% (17%) 97% (63%)	67% (26%)
Other CD20+ve neoplasms with documented activity	Large-cell, Mantle-cell, Waldenstrom's	Transformed Low-grade	Large-cell

ADCC = antibody dependent cellular cytotoxicity; CDC = compliment dependent cytotoxicity

Table 9. Radionuclides Used in Radioimmunotherapy

^{131}Iodine

- 8 day half-life
  - Allows Centralized Labeling
- Readily Available/Low Cost
- Widely Used Clinically
- Ease of Labeling
- Beta and Gamma Emissions
  - Gamma Imaging
  - Easily Quantitated in Dose Calibrator*
- Moderate ß Energy Emission
  - 191 KeV average

  1 mm Range for ß Particle
  - 50 Cell Diameters
- Best for Small Tumors and Micrometastases
- Still Efficacious for Heterogeneous Distribution in Tumors

^{90}Yttrium

- 64 hour half-life
  - Necessitates Local Labeling
- Limited Availability
- Requires Chelate Conjugation
- Pure Beta Emission
  - Bremsstrahlung Imaging
  - Difficult to Quantitate in Dose Calibrator*
- High b Energy Emission
  - 935 KeV average
- 5 mm Range for ß Particle
  - 250 Cell Diameters
- Best for Larger Tumors
- Maybe More Efficacious for Heterogeneous Distribution in Tumors

**Ionization chamber*

(Rituximab), alone.[10] Bexxar® (tositumomab, iodine ^{131}I-tositumomab) remains under review for the treatment of low-grade B-Cell NHL.

Radioimmunotherapy – Zevalin™

Radioimmunotherapy with Zevalin™ (ibritumomab tiuxetan) consists of the murine MAb ibritumomab (IDEC-2B8) complexed to ^{90}Y via the linker chelator tiuxetan (isothiocyanatobenzyl MX-DTPA). A comparison of the properties of ^{90}Y and ^{131}I is found in Table 9. Because the radioactive decay of ^{90}Y is via pure β- emission, gamma scintigraphy is not possible. This has limited the ability to perform patient-specific dosimetry. A radiolabeled tracer dose for gamma camera-based biodistribution studies is prepared using ^{111}In radiometal, ibritumomab, and the tiuxetan chelator. The ratios of the percent-injected dose per gram of tissue for ^{90}Y-ibritumomab/^{111}In-ibritumomab are comparable in the blood, liver, and kidney. However, there is a marked increase in the bone where the ratio of ^{90}Y-ibritumomab/^{111}In-ibritumomab percent-injected dose per gram of tissue is 1.47, 1.65, 1.88 at 1, 24, and 72 hours, respectively.[11] A schematic of the pharmacokinetic model for Zevalin™ is found in Figure 1.

Biodistribution Procedure

In this therapy, patients receive a combination of Rituxan, ^{111}In-ibritumomab, and ibritumomab ^{90}Y. The treatment schedule for the Zevalin™ therapy is given in Figure 2. A single infusion of Rituxan (250 mg/m^2) is administered initially. Patients are premedicated one-half hour before antibody infusion with diphenhydramine 50 mg and acetaminophen 650 mg to avoid infusion related reactions. The Rituxan solution is prepared for infusion by diluting it to a final concentration of 1 mg to 4 mg in normal saline or 5% dextrose in water. This is administered at an initial rate of 50 mg/hr. If infusion related-events do not occur, the infusion rate can be increased every thirty minutes to a maximum of 400 mg/hr.[6] Five millicuries (mCi) of ^{111}In-ibritumomab is infused directly into the patient through the administration set infusion port after stopping the flow of the primary IV. The radiopharmaceutical is administered slowly over a 10-minute period through a 0.22-micron filter. This is flushed with 10 mL of normal saline over a 10-minute period. Imaging to determine biodistribution follows at designated intervals.

Figure 1. Compartmental Model for ^{90}Y-Mab and Metabolites

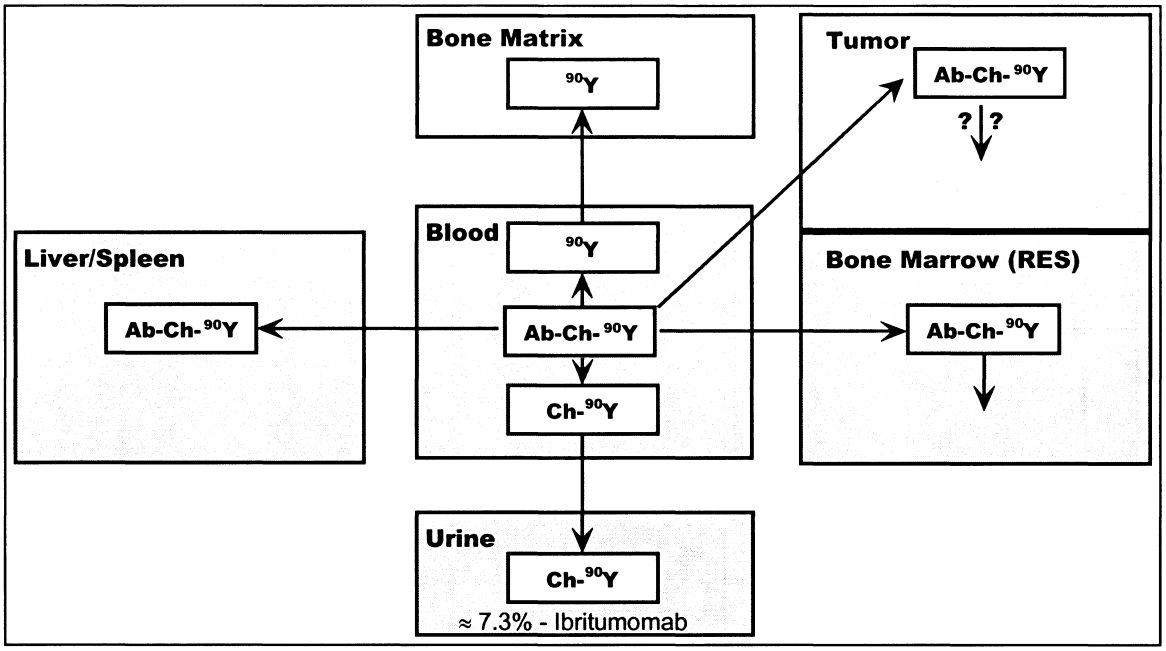
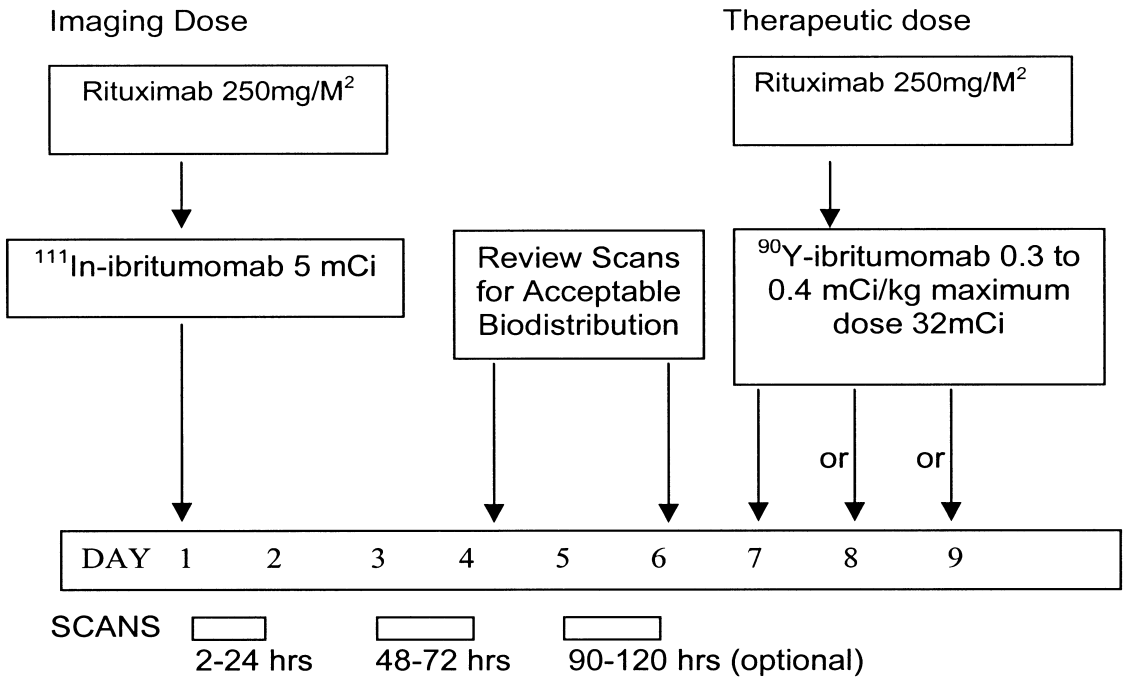


Figure 2. Zevalin™ Treatment Schedule.



Therapeutic Administration

One week later the patient receives a second infusion of Rituxan™ (250 mg/m^2). ^{90}Y-ibritumomab (2 mg antibody labeled with 0.3 or 0.4 mCi/kg of ^{90}Y depending on the patient's baseline platelet count) is administered using the same process as with the ^{111}In-ibritumomab. The recommended maximum dose of ^{90}Y-ibritumomab is 32 mCi. Products should be shielded properly and handled in a fashion to avoid foaming. This is important because the foaming may lead to denaturing of the protein products altering their biodistribution. The therapeutic dose should be administered within four hours of the Rituximab dose.

Results of Clinical Trails with Zevalin™

Phase I/II trials using a single dose of 20-50 mCi IDEC-Y2B8 found a maximum tolerated dose of 0.4 μCi/kg in most patients and 0.3 μCi/kg in patients with mild thrombocytopenia. The overall response rate is 67% (26% CR, 41% PR) for all histologies at all doses, and 82% in patients with low-grade, indolent lymphomas.[7] Mild hematologic toxicities included platelet counts less than 10,000/μL in 10% of patients, and an absolute neutrophil count (ANC) less than 500/μL in 28% of patients. HAMA positive responses were observed in 3.8% of the patients treated and followed for 90 days.

The interim results of a randomized Phase III trial comparing rituximab and "Zevalin™ therapy" have been reported.[12] The results of a predefined interim analysis performed on the first 90 patients to evaluate the accuracy of response rates demonstrated an overall response rate of 80% for patients receiving "Zevalin™ therapy" compared to 44% for rituximab-treated patients (P <0.001).

Radioimmunotherapy - Bexxar®

Bexxar® therapy is the most extensively studied RIT treatment of relapsed or refractory B-Cell NHL.[13-24] It is currently under review by the FDA. Tositumomab is an immunoglobulin G2a murine antibody. Bexxar® therapy combines tositumomab, a murine anti CD20 MAb, and ^{131}I-labeled tositumomab. The treatment is unique in that the therapeutic administered activity is determined based upon the patient-specific

pharmacokinetics, whole-body residence time of the ^{131}I-tositumomab, and pre-therapy platelet count. The treatment therefore includes a dosimetric dose administered 7 to 14 days prior to the therapeutic radioimmunoconjugate.

Dosimetric Dose Procedure

The initial phase of the treatment includes 450 mg of nonradiolabeled tositumomab administered in 50 mL of normal saline over a 60-minute period followed by a 10 mL saline flush over 10 minutes. This dose partially blocks CD20 sites present in the circulation, the bone marrow, and the spleen improving the distribution of the ^{131}I-tositumomab to the tumor site. A schematic for the pharmacokinetic model for Bexxar® is found in Figure 3. It also has a therapeutic effect as described above. All patients are premedicated one-half hour before antibody infusion with diphenhydramine 50 mg and acetaminophen 650 mg to avoid allergic reactions. Saturated solution of potassium iodide (SSKI) is also administered starting one day prior to the dosimetric dose and continued throughout the treatment phase and for at least 14 days post radioimmunotherapy infusion to inhibit thyroid uptake of free Iodine I-131. The dosimetric dose of Iodine ^{131}I-tositumomab consists of 5 mCi of Iodine I-131 incorporated on 35 mg of tositumomab in 30 mL of normal saline. It is administered over a 20-minute period followed by a 30 mL saline flush over 10 minutes. Immediately after the administration the patient receives a total body gamma camera scan. Two additional gamma camera scans are obtained over the next seven days. This information is used to determine the residence time and subsequently to calculate the number of millicuries needed to deliver a 75-cGy total body radiation dose (TBD). The TBD must be adjusted to 65 cGy in patients with thrombocytopenia. The therapeutic dosing scheme is the same as the dosimetric process with the exception that the amount of ^{131}I-tositumomab is much greater. Figure 4 illustrates the dosing scheme for Bexxar® therapy.

Calculation of the Therapeutic Dose of Bexxar®

Therapy with Bexxar® is individualized using its total elimination rate from the patient. The rate of its clearance is variable from patient to patient. The total body dose (TBD) of 75 cGy has

Figure 3. Compartmental Model for ^{131}I-Mab and Metabolites

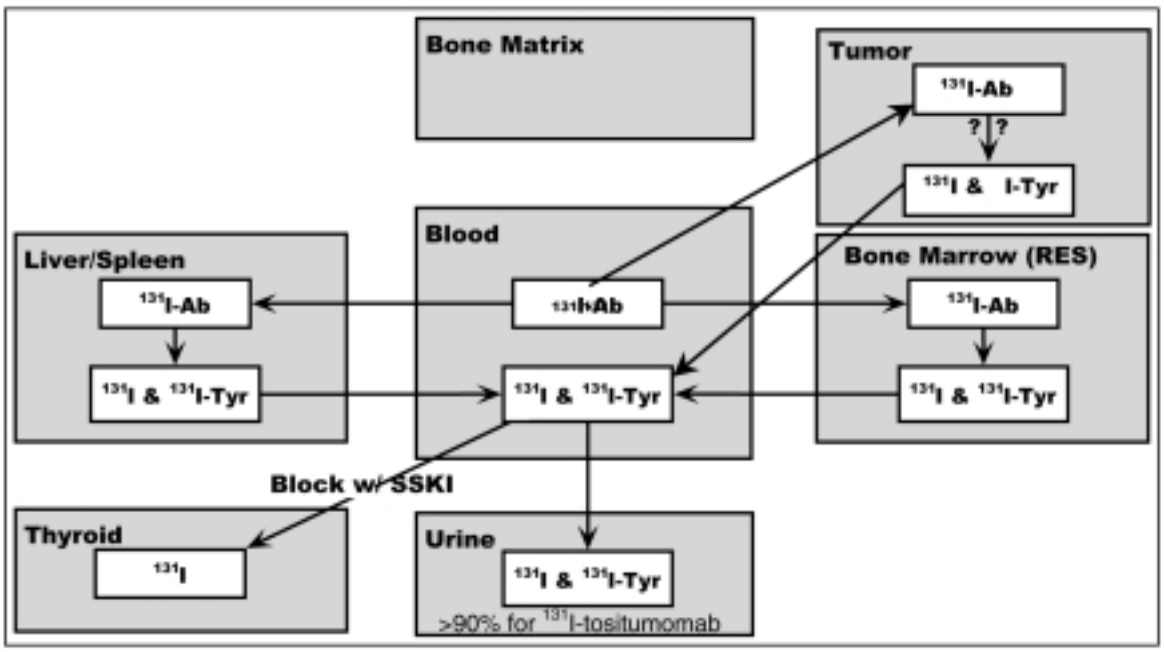
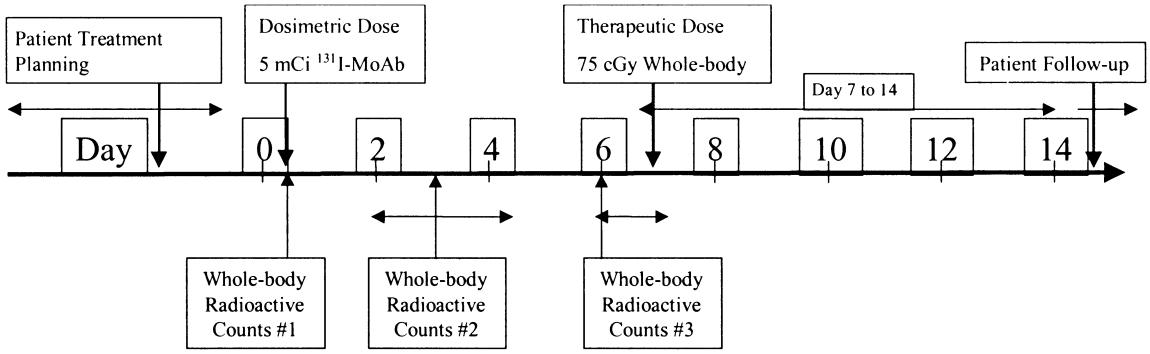


Figure 4. Bexxar® Treatment Scheme



been determined to be the most effective therapeutic dose with acceptable hematologic effects. A retrospective analysis of 262 patients' data indicated that using a fixed dosing schedule (1.21 mCi/kg) would have resulted in 19% of the patients being under dosed by greater than 10%, and 38% being overdosed by greater than 10%. Only 43% of the patients reviewed would have received appropriate therapy. Therefore, the therapeutic dose of ^{131}I-tositumomab is patient-specific and based on the patient's weight and retention of the agent.[25, 26] The elimination kinetics of ^{131}I-tositumomab are sequentially measured in patients over seven days using whole-body scans obtained from an appropriately collimated and calibrated gamma camera. Generally, whole body counts are obtained at three time points in the nuclear medicine department. A linear regression allows one to determine the time at which 37% of the injected dose remains in the patient. This is termed the "Residence Time" and abbreviated using the Greek letter τ. A summary of the patient dose calculation method is found in Table 10.

By calculating the percentage of injected activity remaining at each of the three time points, and subsequently plotting these data on semi-logarithmic graph paper, the patient-specific residence time is determined. That value is applied, along with the value termed activity-hours (a value arrived at by using the patient's maximum effective mass and the activity hours needed to deliver a 75-cGy TBD), in the following equation:

$$\text{Therapeutic Dose (mCi)} = \frac{\text{Activity hr (mCi x hr)}}{\text{Residence time (hr)}} \times \frac{\text{Desired TBD (cGy)}}{\text{75 cGy}}$$

The total body dose is reduced to 65 cGy in patients having baseline platelet counts between 100,000 and 150,000 cells/μL. For excessively obese patients, (patients weighing more than 137% o f

Table 10. Calculation of Therapy Dose

1. Determine patient's maximum effective mass in kg
   Male = 65.76 + 1.452 (height in cm – 152)
   Female = 62.34 +1.247 (height in cm –152)
2. Determine activity hours to deliver 75 cGy (or desired dose)
   Use reference table of derived values
   For patients 140-160 kg: Activity hours = 14,287 + (88.74)(weight in kg – 140)
3. Determine patient's residence time (Rt)
   Percent injected radioactivity remaining at 3 time points following dosimetric dose
4. Divide activity hours (#2) by residence time (#3)
5. Adjust dose to 65 cGy TBD for patients with PLTs =100K-150K
6. Multiply #4 by (the desired TBD divided by 75 cGy TBD)

their lean body mass), the calculations to determine the ^{131}I-tositumomab activity to be administered use 137% of the patient's lean body mass rather than their actual body weight.

Therapeutic Dose

The second phase of treatment is similar to the dosimetric administration. The patient is premedicated as before and the administration of the nonradiolabeled tositumomab and the radiolabeled tositumomab is administered at the same rate. The amount of the ^{131}I-tositumomab is increased to the calculated activity. In this case, the patient must be monitored to ensure that they meet release criteria.

Results of Clinical Trials with Bexxar®

In a review of data from multicenter trials of Bexxar® therapy of 179 patients with follicular NHL, 27 responses were observed in 81% (145 of 179) of patients, of these 39% had a complete response. The median duration of response and complete response was 11 months and 57 months, respectively. The principle toxicity observed was hematologic, reductions in ANC and platelet counts, with recovery occurring in 8-9 weeks. Transient, mild to moderate nonhematologic adverse experiences, were also observed, the most frequent being fatigue which occurred in 39% of the patients (see Table 11 for summary of non-hematologic adverse experiences). Infusion related adverse reactions were usually associated with the tositumomab administration and included fever, chills, hypotension, and rigors. These reactions are most easily resolved with a rate adjustment of antibody infusion (Table 12). In this review, adjustments were required in only 7% and 2% of the dosimetric and therapeutic dose infusions, respectively. HAMA positive responses were observed in 11% of the patients who were previously treated with chemotherapy.

RADIOPHARMACY PRACTICE ISSUES

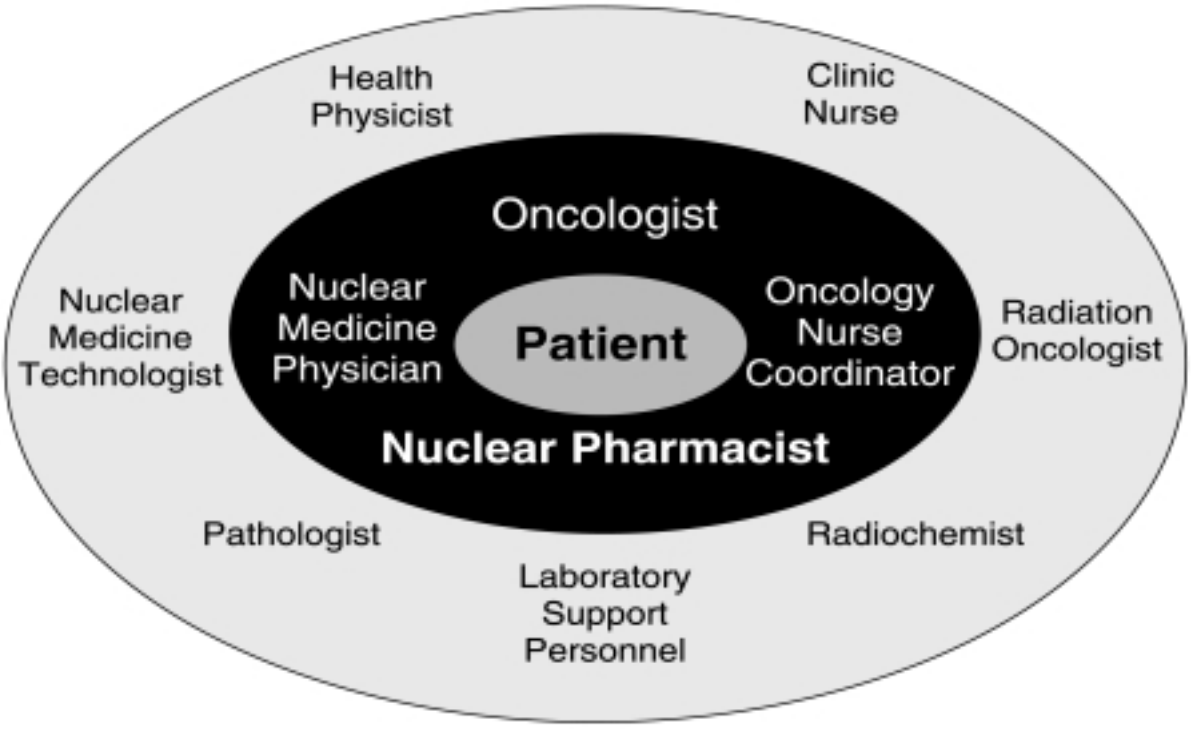
Several issues involving routine radiopharmacy practice must be addressed when working with newer radioimmunotherapy products. Bexxar® Therapy and Zevalin™ Therapy both require therapeutic plans of two to three weeks. Because of this, the coordination of the therapy requires good communication between the supplier, the referring physician, the nuclear

Table 11. Reported Incidence (%) of Nonhematologic Adverse Events

Adverse Event	Rituximab (N=356)				^{131}I-tositumomab (N=308)				IDEC-Y2B8 (N=211)			
	All Grades		Grade 3-4		All Grades		Grade 3-4		All Grades		Grade 3-4	
	N	%	N	%	N	%	N	%	N	%	N	%
Any Event	352	99	203	57	NA	NA	NA	NA	181	86	26	12
Asthenia	93	26	4	1	144	47	6	2	83	39	5	2
Fever	189	53	4	1	135	44	6	2	40	19	2	1
Nausea	82	23	4	1	140	45	8	3	65	31	NA	NA
Headache	68	19	4	1	79	26	4	1	29	14	NA	NA
Chills	117	33	11	3	71	23	7	2	52	25	1	<1
Myalgia	36	10	4	1	64	21	5	2	11	5	1	<1
Arthralgia	36	10	4	1	65	21	6	6	15	7	1	<1
Infection	110	31	14	4	61	20	1	<1	78	37	11	1
Anorexia	NA	NA	NA	NA	73	24	0	0	16	8	NA	NA
Rash	53	15	4	1	73	24	2	<1	17	8	1	<1
Pruritus	50	14	4	1	54	18	0	0	21	10	1	<1
Vomiting	36	10	4	1	52	17	5	2	23	11	NA	NA
Pain	43	12	4	1	73	24	2	<1	14	7	1	<1

Rituximab Package insert © 2001; Bexxar® Investigator's brochure18 January 2001;
Zevalin™ Investigator's brochure Nov. 2000 5th ed.
Vose J. ASH Poster: I-131 tositumomab for patients with follicular lymphoma overall experience by histology.

Figure 5. Radioimmunoconjugate Team



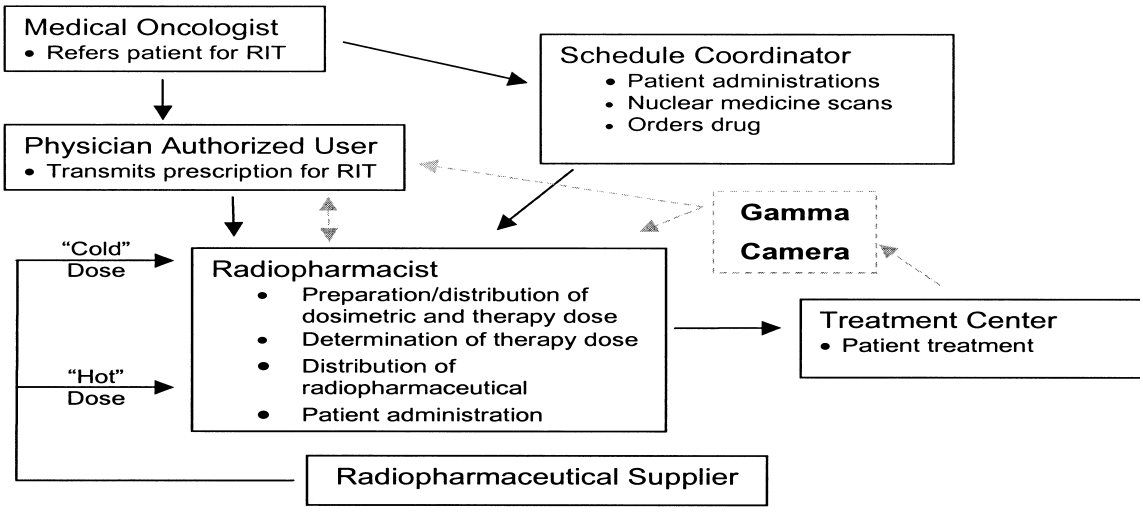
medicine department, and the radiopharmacy (Figure 5). A schematic model for medication ordering, distribution, and administration of radioimmunotherapy to patients is also found in Figure 6. An opportunity for pharmacists to expand the pharmaceutical care they provide is created by the unique nature of these drugs. Table 13 presents some of these unique opportunities, and they are discussed more fully later in this lesson.

Supply and Storage of Bexxar®®

Although the product is still in Phase III testing, it is anticipated that in Bexxar® Therapy the nonradiolabeled and the radiolabeled drugs (supplied as one therapy unit) will be available for shipment every Monday or Tuesday. A treatment timeline for Bexxar® therapy is shown in Figure 4. An order will be placed to the supplier by Wednesday the week prior to a patient's dosimetric dose. ^{131}I-tositumomab is prepared at a centralized manufacturing facility and is shipped frozen, on dry ice, to radiopharmacies or the end user. The product arrives on Tuesday, with an activity reference time of noon ET, expiring Friday at midnight. This allows for administrations on Tuesday through Friday within 72 hours of the calibration time. It must be stored in its frozen condition (at -20°C) until the day of use. Thawing time is approximately 1.0 – 1.5 hours. The volumes of the dosimetric and the therapeutic doses are 20-24 mL. Once thawed the product is stable for eight hours when refrigerated.

The nonradiolabeled tositumomab comes as a component part of the shipment and must be refrigerated (2°C-8°C) prior to use. Three vials of nonradiolabeled MAb are supplied with both the dosimetric and the therapeutic MAbs. One is a 3-mL vial containing 2.5 mL of the MAb. This is referred to as the "top-off" vial. It is used to bring the total amount of MAb in the dosimetric and therapeutic doses to 35 mg. The other two are 20-mL vials each containing 225 mg of nonradiolabeled MAb in 16 mL to be used for the 450 mg dose of tositumomab. These two vials may be forwarded to the nuclear medicine department or their pharmacy department for onsite preparation or

Figure 6. Medicine Ordering, Distribution, and Administration to Patients.



it may be prepared and dispensed for the patient from the radiopharmacy depending upon state pharmacy regulations and site preference.

Dosimetric and therapeutic doses are to be administered 7 to 14 days apart. Based on the results of the first and second whole body counts an estimated therapeutic dose should be calculated. Because the therapeutic dose is specific for an individual patient, two vials of the therapeutic product may be required for a treatment if the patient's radiopharmaceutical clearance and body size so dictate. Again, orders for the therapeutic dose must be placed to the supplier prior to Wednesday.

Bexxar® doses are prepared at room temperature in a laminar flow environment, using aseptic technique and appropriate shielding. Dosmetric and therapeutic doses are compounded by adding the required activity and volume of ^{131}I-tositumomab to a sterile, pyrogen-free, 50-mL vial. The concentration of tositumomab is brought to 35 mg using the contents of the "top off" vial and the final volume to brought to 30 mL with sterile normal saline.

Supply, Storage, and Preparation of Zevalin™

Zevalin™ therapy requires the preparation of the ^{111}In-ibritumomab and ^{90}Y-ibritumomab using radiopharmaceutical kits. Both are prepared using the same components of the kit with some minor radiolabeling adjustments. At

Table 13. The Role of the Radiopharmacist Working in Collaboration with Nuclear Medicine Physician

- Coordinate and schedule treatment
- Order cold and hot pharmaceuticals
- Prescribe SSKI
- Administer radiolabeled dosimetric dose infusion
- Monitor patient infusion
- Determine patient-specific pharmacokinetics
- Calculate patient-specific therapeutic dose
- Monitor patient infusion
- Administer therapeutic dose
- Determine releasability of patient
- Instruct patient on radiation safety precautions

this time, ^{90}Y Yttrium chloride is commercially available only on Tuesday and Wednesday of each week. According to that availability, therapies using Zevalin™ must be scheduled on these days. The radiolabeling kit requires storage at 2-8^{o} C. Each of the two kits contains four vials, one each of ibritumomab tiuxetan in low-metal normal saline (3.2 mg in 2 mL 0.9% sodium chloride solution), 50 mM low-metal sodium acetate (13.6 mg in 2 mL Sterile Water for Injection), 7.5 % Human Serum Albumin in phosphate buffered saline and 1mM DTPA (HSA 750 mg, Sodium Chloride 76 mg, Sodium Phosphate dibasic heptahydrate 21 mg, DTPA 4 mg, Potassium Phosphate monobasic 2 mg, Potassium Chloride 2 mg, in sterile water for injection 10 mL), and an empty, sterile, pyrogen-free, reaction vial.

Zevalin™ Kit Preparation

The Zevalin™ kit preparation is performed at room temperature in a laminar air-flow environment, using aseptic technique. Preparations with both radionuclides are similar. The basic compounding sequence is as follows:

- Add the sodium acetate buffer to the vial containing the radiometal (^{111}In or ^{90}Y)
- Remove the buffered radiometal solution and transfer to the reaction vial containing the ibritumomab tiuxetan. (Approximately 6 mCi of ^{111}In and 40 mCi of ^{90}Y are added for the reactions.)
- Incubate 30 minutes for ^{111}In or 5 minutes for ^{90}Y
- Add the phosphate buffered albumin and DTPA in order to buffer the solution and chelate any free radiometals.

More detailed compounding instructions are found in the manufacturers' package insert. Incubation times are critical for ^{90}Y due to a potential for radio-degradation of the product. Acrylic shielding of the ^{90}Y is required to reduce radiation exposure. Lead shielding is required for the ^{111}In product.

Quality Control Procedures for Zevalin™

A standard ITLC-SG strip developed in 0.9% sodium chloride (normal saline) used to assess the incorporation of the radionuclides chelated to the MAb. Any free radiometals chelated to DTPA will migrate to the solvent front. The incorporation of the radionuclides must be greater than 95% before it can be released for clinical use. After incorporation the radionuclides, ^{90}Y-ibritumomab is stable for up to eight hours if refrigerated and ^{111}In-ibritumomab may be used up to twelve hours after preparation if refrigerated.

Measurement of ^{90}Yttrium

^{90}Yttrium is a pure beta emitter and measurements in ionization chambers (dose calibrators) are highly dependant upon geometry. Currently, there is controversy concerning the measurement of ^{90}Y using dose calibrators that have not been calibrated for accuracy to a National Institutes of Standards and Technology (NIST) traceable source. Dose calibrator settings for ^{90}Y must be established for each dose calibrator in the radiopharmacy and for each geometry to be assayed. Since ^{90}Y will be measured in many different geometries, vials of various size and make up, and syringes with and without needles attached, dose calibrator settings must be established for each of these. An important point to remember in the development of the settings is that established settings may differ based upon the manufacturer of the vials and syringes. Therefore, if the source of syringes changes in the pharmacy, calibrator settings will need to be established for the newly supplied items. It is anticipated that the method for determining dose calibrator settings for ^{90}Y will be supplied by the Zevalin™ Therapy suppliers.

Radiation Safety and Regulatory Issues

Handling Zevalin™ or Bexxar® requires special consideration of radiation safety and regulatory issues. Because of the relatively high mCi quantities (40 mCi in the case of ^{90}Y and >100 mCi for ^{131}I) of these drugs required for therapy, and the fact that they are parenterals rather than oral dosage forms, special handling considerations must be employed.

Precautions with Bexxar®

Most radiopharmacists are very familiar with the required radiation safety precautions and bioassay programs associated with handling large amounts of ^{131}I radioiodine. However, handling large quantities ^{131}I parenterals may not be commonplace in many radiopharmacy practice settings. ^{131}I Bexxar® is manufactured at a central location and arrives in its final form as a frozen shipment and must be thawed prior to dispensing. Because this form of ^{131}I radioiodine is intended for intravenous injection, aseptic technique must be employed. This requires the use of a laminar flow hood rather than a simple glove box or fume hood. Pharmacies may have to modify their equipment and/or facilities to include laminar flow hoods appropriate for handling large amounts of ^{131}I Bexxar®. Facilities might require additional equipment or remodeling of the laboratory. A very small amount of volatile Iodine 131 can be present in the shipping vial. The use of a disposable charcoal filter unit affixed to sterile airway to vent the shipping vial can reduce the potential for exposure to volatile Iodine when preparing Bexxar® doses. Appropriate high-Z material shielding must be used when handling syringes and vials containing this therapeutic radiopharmaceutical.

Precautions with Zevalin™

^{90}Yttrium and is a pure beta emitter with a maximum energy of 2.8 MeV, therefore, hand exposures when manipulating this product can be significant. Consequently, direct hand-contact with syringes and vials containing ^{90}Y must be strictly avoided. Precautions must also be used to avoid the production of Bremsstrahlung radiation. Shielding using low-Z materials such as acrylic, rather than lead, is required. Radiation sources such as vials and syringes should be shielded using > 0.5 inches of acrylic shielding. One manufacturer, Perkin-Elmer Life Sciences, recommends an additional layer of lead (0.3 mm) surround the low-Z material. Personnel handling ^{90}Y should do so working behind a 0.5-inch acrylic shield. (These are available through several suppliers.) ^{90}Yttrium (Zevalin™) is radiolabeled on site at the nuclear pharmacy by combining ^{90}Y-YCl_3 with the appropriate radiopharmaceutical kit. This requires manipulation of a therapeutic amount of this pure beta emitter. Radiopharmacists should become familiar with the chemistry of yttrium and work with extra caution in handling this radiochemical. These manipulations should be performed on a surface covered with disposable absorbent material and monitored periodically to avoid the potential spread of ^{90}Y contamination. A bioassay program for ^{90}Y maybe required for those compounding this radiopharmaceutical.

The compounding/dispensing activities required for both Zevalin™ and Bexxar® are similar in that, in each case, the final patient dose must be prepared. Handling procedures should be reviewed and approved by health physicists and/or radiation safety personnel prior to working with ^{131}I-tositumomab or ^{90}Y-ibritumomab tiuxetan parenterals.

Licensing

Holders of Radioactive Materials (RAM) Licenses may have to modify or amend their licenses to allow possession (and use) of ^{90}Y. Care should be taken to request possession limits in quantities sufficient to meet expected demand. Once established, 5-10 patient therapies per week may not be unusual in some practice settings. Therefore, a possession limit of 200-500 mCi of ^{90}Y as ^{90}Y-Cl_3 in 0.1 N HCl liquid is not unreasonable. Consideration should also be given to the quantity and physical form of ^{131}I radiodine permitted on the facility's RAM license to ensure that the appropriate capability exists to dispense ^{131}I Bexxar®.

Patient Release

The Nuclear Regulatory Commission (NRC) amended patient release criteria in 1997. (See Appendix A.) This amendment expanded the activity-based limit to include activity and dose-based criteria. The activity-based limit of 30 mCi was intended to apply only to patients being treated with Iodine-131 as sodium iodide, but it was applied to other therapeutic radiopharmaceuticals in the absence of more

specific regulatory guidance. The dose-based limit allows patient release to be determined using 1 of 3 ways: default tables of administered activity, default tables of patient dose rates, or use of patient-specific dose calculations. Advantages of the new dose-based limits include that it works for any radionuclide, it can include internal doses, it is easy to measure, and very few patients may require hospitalization. Reduced hospitalizations should lower health care costs and reduce radiation exposure to health care professionals who otherwise care for these patients in-house. It may also increase access to these therapies because of their availability to outpatients. Patients may benefit on an emotional basis because of reduced hospitalization time, less estrangement from family members, and a potential for reduction in lost productivity. These options also allow for a more scientific approach to account for patient release. Currently outpatient treatment and patient release can be used in 20 NRC regulated states and 18 "agreement" regulated states. Variance for license-specific outpatient therapy and release can be obtained in 4 "agreement" states. Eight states have not adopted the regulatory change and this treatment currently must be performed on an inpatient basis. Rutar and colleagues monitored caregivers of 22 patients who had received varying therapeutic amounts of ^{131}I-tositumomab using a variety of dosimeters.[28] Patients and caregivers were instructed on methods of maintaining radiation exposures as low as reasonably achievable (ALARA). All radiation doses received by the caregivers were below the regulatory limit of 500 mrem.

The risk of radiation exposure to others from patients receiving Zevalin™ therapy should be minimal since most of the activity is retained and ^{90}Y is a pure beta emitter. Patients and caregivers must still be instructed regarding radiation exposure in the case of Zevalin™ therapy. The external radiation exposure dose-rate to caregivers from patients receiving beta-emitting radiopharmaceutical is very low. Wiseman's group, in a study of 13 family members of patients treated with Zevalin™, placed personal dosimeters on these individuals and found a median deep dose equivalent over 7 days of 3.5 mrem (range 1.4-7.9 mrem).[29] There is a renal elimination component of ^{90}Y in this therapy (7.3% +/- 3.2%), therefore, the chance of touch contamination exists and a discussion of the methods used to keep exposure ALARA is warranted. Wagner and associates recommend that up to three days after treatment with ^{90}Y Ibritumomab Tiuxetan that any spilled urine or any body fluids should be cleaned up and disposal of any body fluid containing materials should be by flushing them down the toilet or by placing them in a plastic bag in the household trash.[30] Hands should be washed thoroughly after using the toilet. They also recommend the use of condoms for sexual relations up to one week after therapy.

PHARMACOECONOMIC AND OUTCOMES ANALYSIS FOR RITUXIMAB

As the optimal therapy for patients with relapsed indolent NHL is unclear, the role of the various therapies is likely to be determined based upon the relative efficacy, toxicity, and cost. A recently published analysis conducted a literature review and a retrospective analysis of patients receiving combination chemotherapy for relapsed indolent NHL to determine the response rates and the duration of response when treated with CHOP or fludaribine.[31] The response rates and median duration of response for these regimens were found to be similar, and similar to those reported in Phase II investigations of rituximab. Therefore, efficacy appearing equal between the cohorts, a cost minimization study was conducted. The treatment costs per patient of drug-related events such as nausea/vomiting, neutropenia, fever/infection, thrombocytopenia, anemia, and other events requiring treatment were £5,049 ($7,407) for CHOP, £2,953 ($4,332) for fludarabine, and £109 ($160) for rituximab. When the costs of a full course of each treatment were compared, the average cost per patient for CHOP, fludarabine, and rituximab were £7210 ($10,577), £10,022 ($14,702), and £6,080 ($8,919), respectively. In this analysis,

rituximab demonstrated a similar efficacy rate to CHOP and fludarabine, while presenting significantly fewer drug-related adverse events and lower costs per patient, largely due to the greatly reduced side effects resulting from immunotherapy using rituximab when compared to chemotherapy.

While one maybe tempted to infer that the same would be true for either ^{131}I-tositumomab or IDEC-Y2B8 since data from earlier trials of these RIT agents have demonstrated superior efficacy to rituximab alone, it is not possible to reach such a conclusion. One could posit that a similar analysis of RIT agents compared to rituximab, CHOP, and fludarabine could yield even more compelling results due to the many advantages of RIT over chemotherapy: one-time therapy, lack of noxious side effect profiles associated with chemotherapy agents, administration via peripheral rather than central IV, and outpatient rather than in-patient therapy. There maybe an additional advantage in the use of RIT compared to more conventional multi-cycle chemotherapy regimens, but this information is not yet available for either product and thus their pharmacoeconomic impact remains to be determined.

EXPANDED ROLE FOR THE RADIOPHARMACIST

The complexities of radioimmunotherapies require a multidisciplinary, coordinated approach to individual patient treatment and management and offer the potential for expanding the role of radiopharmacist to include provision of specialized pharmaceutical care. Several activities involved with the management of these therapies can be a part of the responsibility of the nuclear pharmacist. These include planning and scheduling treatments, administration of diagnostic and therapeutic radiopharmaceuticals, individualized patient dose calculations, patient monitoring, and patient counseling, coordination of the treatment with the receipt, compounding, quality control testing, and dispensing of the radiopharmaceutical. The pharmacist may ensure that concomitant medications are administered prior to or during the therapies. For instance, in both therapies diphenhydramine and acetaminophen are administered to reduce the potential for adverse reactions caused by the foreign protein. In Bexxar® therapy SSKI is used during and two weeks after the therapy as a radioprotectant. In some institutions nuclear pharmacists have assisted in the administration of the dosimetric and therapeutic radiopharmaceuticals under the supervision of nuclear medicine physicians or radiation oncologists. In the case of Bexxar®, radiopharmacists may determine individualized patient doses based on total body counts in collaboration with nuclear medicine physician and/or radiation oncologists. As a part of the multidisciplinary team the radiopharmacist can assume many responsibilities.[32]

CONCLUSION

The development of radioimmunotherapy is steadily advancing. Zevalin™ is the first FDA approved NHL therapy to combine a MAb with a radionuclide. These new therapeutic radiopharmaceuticals will certainly have an impact on the practice of radiopharmacy. The radiolabeled MAbs have proven to be effective in the treatment of low-grade B-Cell NHL when used alone or in combination with other regimens. Patient therapies with these agents will require coordination, teamwork and the application of radiation physics, safety, chemistry, and biological principles that differ from diagnostic radiopharmaceutical preparations. Opportunities to develop new roles for radiopharmacists now exist and will expand as these therapies become established and their use becomes more widespread.

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APPENDIX A

10 CFR Sec. 35.75 Release of individuals containing radiopharmaceuticals or permanent implants.
(a) The licensee may authorize the release from its control of any individual who has been administered radiopharmaceuticals or permanent implants containing radioactive material if the total effective dose equivalent to any other individual from exposure to the released individual is not likely to exceed 5 millisieverts (0.5 rem).\1

\1\Regulatory Guide 8.39, "Release of Patients Administered Radioactive Materials," describes methods for calculating doses to other individuals and contains tables of activities not likely to cause doses exceeding 5 millisieverts (0.5 rem).

(b) The licensee shall provide the released individual with instructions, including written instructions, on actions recommended to maintain doses to other individuals as low as is reasonably achievable if the total effective dose equivalent to any other individual is likely to exceed 1 millisievert (0.1 rem). If the dose to a breast-feeding infant or child could exceed 1 millisievert (0.1 rem) assuming there were no interruption of breast-feeding, the instructions shall also include:
(1) Guidance on the interruption or discontinuation of breast-feeding and
(2) Information on the consequences of failure to follow the guidance.
(c) The licensee shall maintain a record of the basis for authorizing the release of an individual, for 3 years after the date of release, if the total effective dose equivalent is calculated by:
(1) Using the retained activity rather than the activity administered,
(2) Using an occupancy factor less than 0.25 at 1 meter,
(3) Using the biological or effective half-life, or
(4) Considering the shielding by tissue.
(d) The licensee shall maintain a record, for 3 years after the date of release, that instructions were provided to a breast-feeding woman if the radiation dose to the infant or child from continued breast-feeding could result in a total effective dose equivalent exceeding 5 millisieverts (0.5 rem)

QUESTIONS

1. NHL is the _____ leading cause of cancer morbidity and mortality.

    a. Tenth
    b. Second
    c. Fifth
    d. Number One

2. Since the early 1970's, the incidence of NHL has _____ .

    a. Nearly Doubled
    b. Decreased
    c. Remained Unchanged
    d. Increased five-fold

3. The one and five year survival rate for NHL is ____ % and ____ %, respectively.

    a. 80 and 70
    b. 70 and 50
    c. 45 and 35
    d. 60 and 45

4. Patients with low-grade NHL are rarely cured, having a median survival rate of 6-10 years from initial diagnosis.

    a. True
    b. False

5. The etiology of NHL is unknown, but an increased incidence is associated with

    a. Infectious Agents
    b. Immunodeficiency's
    c. Environmental exposure
    d. All of the above

6. The risk of NHL in patients following organ transplant is _____ due to altered immune function.

    a. Unchanged
    b. More than 100 times higher
    c. Increased nearly 10 times
    d. Decrease

7. Signs and symptoms of lymphoma include painless lymphadenopathy, pruritis, fever, night sweats, anemia, weight loss and malaise.

    a. True
    b. False

8. Abdominal involvement may present with palpable, nausea, vomiting, pain, and GI bleeding, and is more common in NHL in Hodgkin's disease.

    a. True
    b. False

9. Constitutional symptoms including itching, fever, night sweats and weight loss, that are less common in NHL than in Hodgkin's disease, are also known as _____.

    a. T Symptoms
    b. Bunny Syndrome
    c. B Symptoms
    d. Proger Syndrome

Match the following REAL Classification of NHL to the appropriate Working Formula Classification.

10. Large B-Cell

    a. Low-Grade, Intermediate and High-Grade
    b. Intermediate and High-Grade
    c. High-Grade
    d. Low-Grade

11. Follicular
    a. Low-Grade, Intermediate and High-Grade
    b. Intermediate and High-Grade
    c. High-Grade
    d. Low-Grade

12. Small Lymphocytic
    a. Low-Grade, Intermediate and High-Grade
    b. Intermediate and High-Grade
    c. High-Grade
    d. Low-Grade

13. Mantle Cell

    a. Low-Grade, Intermediate and High-Grade
    b. Intermediate and High-Grade
    c. High-Grade
    d. Low-Grade

14. The largest group of indolent NHL's are lymphomas.

    a. Follicular
    b. Large B-Cell
    c. Mantle Cell
    d. Peripheral T-Cell

15. Monoclonal antibodies can target specific antigens on tumors causing cell death by which of the following mechanisms?

    a. Antibody-dependent cell cytotoxicity (ADCC)
    b. Complement fixation causing cell lysis
    c. Negative signaling causing apoptosis
    d. Any or all of the above

16. Cluster Differentiation (CD) Marker 20 is express on normal and malignant B-Cells.

    a. True
    b. False

17. Which of the following statements regarding radioimmunotherapy of NHL using ^{131}I tositumomab (Bexxar®) is/are true?

    a. The administered activity is determined using patient-specific pharmacokinetics.
    b. Treatment includes 450 mg of non radiolabeled tositumomab, which improves tumor targeting of Bexxar®.
    c. All patients are pretreated with saturated solution of potassium iodide (SSKI), a thyroid protectant, one day prior to and for 14 days following therapy.
    d. All of the above.

18. Patient-specific pharmacokinetics are determined in order to calculate the administered activity necessary to deliver 75 cGy total body dose (TBD). A fixed dosing schedule (mCi/kg) has been shown to result in _____.

    a. 19% of the patients being underdosed by greater than 10%.
    b. 38% of patients being overdosed by greater than 10%.
    c. Only 43% of patients receiving the correct dose of 75 cGy +/- 10%.
    d. All of the above

19. Following the administration of a 5mCi dosimetric dose of ^{131}I-tositumomab, determining the percent injected activity remaining at each of three time points _____.

    a. Allows patient-specific residence times to be calculated.
    b. Reduces infusion-related side effects.
    c. Is determined by whole-body gamma camera imaging.
    d. A and C only

20. For excessively obese patients (weighing in excess of 137% of their lean body mass), the dose is adjusted by using _____.

    a. the patient's lean body mass rather than their weight.
    b. 137% of the patient's lean body mass rather than their weight.
    c. 73% of the patient's weight rather than their weight.
    d. the patient's actual body weight.

21. Patient's treated with ^{90}Y-ibritumomab tiuxetan (IDEC-Y2B8 or Zevalin™) will _____

    a. Receive a single infusion of rituximab (250 *mg*/m^2) prior to the IDEC-Y2B8 administration.
    b. Receive a co-administration of ^{111}In ibritumomab tiuxetan to allow gamma imaging.
    c. Experience lower incidence of HAMA\ reactions.
    d. A and C only

22. The intravenous administration of monoclonal antibodies (or proteins of any kind) should be done through a 0.22 um filter to avoid the infusion of protein aggregates that may increase the incidence of infusion-related side effects.

    a. True
    b. False

23. Which of the following statements regarding ^{90}Y measurements is/are correct?

    a. ^{90}Yttrium is a pure beta emitter and measurements in ionization chambers are highly geometry dependant.
    b. Potentiometer (POT) settings must be empirically derived for each dose calibrator used to measure patient doses.
    c. The type material and source of vessel, volume measured, and position in the ionization chamber will effect the accuracy of measurements of ^{90}Y.
    d. All of the above.

24. Patients receiving radioimmunotherapy of NHL using Bexxar® or Zevalin™ may be immediately released if the exposure to others is not likely to exceed 0.5 mSv (0.5 rem). Which of the following methods may be used to determine if patients maybe released?

    a. Default tables of administered activity
    b. Default tables of patient dose rates
    c. Use of patient-specific dose calculations
    d. Any of the above

25. A pharmacoecomomic and outcomes analysis of therapies for NHL compared rituximab, CHOP, and fludaribine. Because patient response rates and median duration of response were similar, which of the following pharmacoeconomic studies is appropriate:

    a. Cost-minimization analysis
    b. Cost-effectiveness
    c. Cost-benefit
    d. Cost-utility