

## Evidence Based Guideline

# Radioimmunotherapy in the Treatment of Non-Hodgkin Lymphoma

**File Name:** radioimmunotherapy\_in\_the\_treatment\_of\_non\_hodgkin\_lymphoma  
**Origination:** 9/2009  
**Last CAP Review:** 3/2012  
**Next CAP Review:** 3/2013  
**Last Review:** 3/2012

### Description of Procedure or Service

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Radioimmunotherapy involves the administration of an antibody linked to a radioisotope, targeted to a specific cell type. Ibritumomab (Zevalin®) and tositumomab (Bexxar®) are radioimmunoconjugates that target cell surface CD20 found on normal B lymphocytes and more than 90% of B-cell non-Hodgkin lymphomas (NHL).

#### Background

CD20-based radioimmunotherapy for non-Hodgkin lymphoma (NHL) is similar to the anti-CD20 monoclonal antibody rituximab, which is widely used against B-cell malignancies, however, 90Y-ibritumomab tiuxetan uses a monoclonal anti-CD20 antibody to deliver beta-emitting yttrium-90 and 131I-tositumomab is an iodine-131-loaded antibody.

Radioimmunotherapy offers several advantages over external-beam irradiation in the treatment of NHL, a relatively radiosensitive disease. Radioimmunotherapy is given intravenously and, therefore, normal tissues overlying the tumor are spared significant radiation exposure. Radioimmunotherapy provides systemic radiation treatment to known as well as unsuspected tumor cells and a "bystander effect" may be observed, since the radiation emitted from the isotopes is deposited over several cell diameters with poorly perfused or non-antigen-expressing cells within a tumor mass suffering the cytotoxic radiation effect.

Low-grade or indolent lymphomas usually present with advanced stage disease, and are not considered curable with current treatments, including chemotherapy. The disease course is usually prolonged, with a median survival of 7–10 years, and is characterized by initial response to chemotherapy, multiple relapses and increasing resistance to treatment. In addition, approximately 60% of patients may transform to a more aggressive type of lymphoma. Although rituximab is widely used in the treatment of B-cell NHL, not all patients respond, and a certain number of patients eventually develop resistance to the drug, necessitating additional treatments after rituximab.

A review article summarizes the various approaches to using radioimmunotherapy in NHL, including in newly diagnosed disease as well as in patients with recurrent B-cell lymphoma, in combination with chemotherapy or other monoclonal antibodies, with hematopoietic stem-cell transplant, as well as the use of pretargeting strategies to minimize toxicity and the simultaneous targeting of multiple B-cell antigens.

#### Regulatory Status

Ibritumomab tiuxetan (Zevalin®) was granted accelerated approval by the U.S. Food and Drug Administration (FDA) in February 2002 for the treatment of patients with relapsed or refractory low-grade, follicular or transformed B-cell non-Hodgkin lymphoma, including patients with rituximab

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refractory follicular non-Hodgkin lymphoma. In September 2009, the FDA approved ibritumomab (Zevalin®) for consolidation therapy in previously untreated follicular lymphoma in patients who achieve a partial or complete response to first-line chemotherapy.

Tositumomab (Bexxar®) was granted approval by the FDA in June 2003 for the treatment of patients with CD20-positive, follicular, non-Hodgkin lymphoma, with or without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy.

**\*\*\*Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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A single course of tositumomab (Bexxar®) used for the treatment of antigen CD20-positive, follicular, non-Hodgkin lymphoma, with or without transformation, whose disease is refractory to rituximab and has relapsed following chemotherapy may be appropriate.\*

A single course of ibritumomab tiuxetan (Zevalin®) used for the treatment of patients with relapsed or refractory CD-20-positive low-grade, follicular, or transformed B-cell non-Hodgkin lymphoma, including patients with rituximab refractory follicular non-Hodgkin lymphoma, may be appropriate.\*

The use of tositumomab (Bexxar®) or ibritumomab tiuxetan (Zevalin®) for the initial treatment of follicular lymphoma may be appropriate in patients who are unable to tolerate standard chemotherapy, e.g., elderly or frail patients.

The use of tositumomab (Bexxar®) or ibritumomab tiuxetan (Zevalin®)\* for consolidation after chemotherapy in non-Hodgkin lymphoma patients who achieve a partial or complete response may be appropriate.

\* indicates an FDA-labeled indication.

Multiple studies have shown that the use of radioimmunotherapy in treating relapsed or refractory non-Hodgkin lymphoma can induce remissions in 50–80% of patients, with 15–50% achieving complete remission.

For patients with previously untreated non-Hodgkin lymphoma, achievement of a complete remission with consolidation after induction chemotherapy has been associated with longer progression-free and overall survival rates and is a prerequisite for cure in diffuse large cell lymphoma. Radioimmunotherapy as consolidation following induction therapy in previously untreated patients with advanced follicular lymphoma has demonstrated high overall response rates, complete remission rates, and prolonged progression-free survival in one Phase III and several Phase II trials.

## Medical Evidence regarding Radioimmunotherapy in the Treatment of Non-Hodgkin Lymphoma indicates it is not recommended in the following situations

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1. For conditions other than those listed above.
2. The use of tositumomab (Bexxar®) or ibritumomab tiuxetan (Zevalin®) for consolidation after

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chemotherapy or as part of a preparatory regimen prior to hematopoietic stem-cell transplantation is not recommended.

Due to the hematologic effects associated with the use of these agents (i.e., cytopenias), it is recommended that they not be used in patients with more than 25% bone marrow involvement by lymphoma and/or in patients with impaired bone marrow reserve (i.e., a platelet count less than 100,000/mm<sup>3</sup> or a neutrophil count less than 1,500/mm<sup>3</sup>).

The data on the use of radioimmunotherapy as part of the conditioning regimen prior to hematopoietic stem-cell transplant are promising but evolving. Preliminary data suggest there may be a role for radioimmunotherapy, particularly in patients who may not be able to tolerate potentially curative high-dose chemotherapy and/or total body irradiation because of the risk of excessive treatment-related morbidity and mortality. Several Phase III trials are underway examining the role of radioimmunotherapy in both autologous and reduced-intensity allogeneic hematopoietic stem-cell transplants.

## Benefits Application

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This evidence based guideline relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this guideline.

## Billing/Coding/Physician Documentation Information

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This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 79403, A9543, A9545*

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.50, 4/24/09

Senior Medical Director - 8/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.50, 8/12/2010

Specialty Matched Consultant Advisory Panel – 3/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.50, 8/11/2011

Specialty Matched Consultant Advisory Panel – 3/2012

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## Policy Implementation/Update Information

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9/14/09 New evidence based guideline adopted from the BCBS Association. Reviewed by Senior Medical Director 8/13/09. (btw)

6/22/10 Policy Guideline Number(s) removed (amw)

4/26/11 Specialty Matched Consultant Advisory Panel review March 30, 2011. The following statements were added to the “Evidence Based Guideline” section: “The use of tositumomab (Bexxar®) or ibritumomab tiuxetan (Zevalin®) for the initial treatment of follicular lymphoma may be appropriate in patients who are unable to tolerate standard chemotherapy, e.g., elderly or frail patients.” “The use of tositumomab (Bexxar®) or ibritumomab tiuxetan (Zevalin®)\* for consolidation after chemotherapy in non-Hodgkin lymphoma patients who achieve a partial or complete response may be appropriate.” “Multiple studies have shown that the use of radioimmunotherapy in treating relapsed or refractory non-Hodgkin lymphoma can induce remissions in 50–80% of patients, with 15–50% achieving complete remission.” “For patients with previously untreated non-Hodgkin lymphoma, achievement of a complete remission with consolidation after induction chemotherapy has been associated with longer progression-free and overall survival rates and is a prerequisite for cure in diffuse large cell lymphoma. Radioimmunotherapy as consolidation following induction therapy in previously untreated patients with advanced follicular lymphoma has demonstrated high overall response rates, complete remission rates, and prolonged progression-free survival in one Phase III and several Phase II trials.” The following was removed from the “When Not Recommended” section; “The use of tositumomab (Bexxar®) or ibritumomab tiuxetan (Zevalin®) for the initial treatment of NHL is not recommended.” Added the following information the section; “The data on the use of radioimmunotherapy as part of the conditioning regimen prior to hematopoietic stem-cell transplant are promising but evolving. Preliminary data suggest there may be a role for radioimmunotherapy, particularly in patients who may not be able to tolerate potentially curative high-dose chemotherapy and/or total body irradiation because of the risk of excessive treatment-related morbidity and mortality. Several Phase III trials are underway examining the role of radioimmunotherapy in both autologous and reduced-intensity allogeneic hematopoietic stem-cell transplants.” References added. (btw)

10/11/11 Reference added. (btw)

4/17/12 Specialty Matched Consultant Advisory Panel review 3/21/2012. No change to guideline. (btw)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.