

# Radioimmunotherapy: a novel treatment of non-Hodgkin lymphoma

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## SUMMARY

<sup>90</sup>Y-ibritumomab tiuxetan (Zevalin) and <sup>131</sup>I-tositumomab (Bexxar) are current choices for radioimmunotherapy (RIT) of patients with follicular rituximab-relapsed or refractory CD20+ follicular B-cell NHL. Bexxar is available in the United States and Canada, while Zevalin was approved for use only in Europe. The Zevalin regimen consists of rituximab ("cold", chimeric antibody) and <sup>90</sup>Y-ibritumomab tiuxetan ("hot" antibody). In Bexxar regimen, a tositumomab (murine antibody) is used as both, the unlabelled and labelled antibody. In both cases, the therapeutic infusion of "hot" or radiolabelled component is preceded one week earlier by an infusion of a "cold" or unlabelled antibody. In the US, the whole-body scanning using <sup>111</sup>In-ibritumomab following the initial rituximab infusion is required for determination of biodistribution before the therapeutic dose of Zevalin. Bexxar regimen includes three whole body scans during the week after an imaging dose of <sup>131</sup>I-tositumomab, which are necessary for calculation of the therapeutic dose of <sup>131</sup>I-tositumomab. For each regimen, patients with a platelet count  $\geq 150 \times 10^9/L$  receive a full therapeutic dose, whereas patients with platelet counts  $>100 \times 10^9/L < 150 \times 10^9/L$  receive a modified dose of radiolabelled antibody. Therapeutic dose of Zevalin is 11-15 MBq/kg (up to maximum of 1200 MBq), while the dose of Bexxar is 1.85-5.55 GBq (maximal tolerated absorbed dose for the whole body is 75cGy). If compared to alternative treatments, the radioimmunotherapy with Bexxar and Zevalin achieves longer time to progression and longer duration of response with overall response rate between 80% to almost 100%. Repeated treatment with Zevalin or Bexxar is possible. The additional subsequent conventional therapy is compatible. Radioimmunotherapy is radiation safe and well tolerated treatment with primarily transient haematological adverse events. Pregnancy and lactation are contraindications for radioimmunotherapy. Beta radiation of <sup>90</sup>Y allows treatment on outpatient basis.

**KEY WORDS:** Radioimmunotherapy; Lymphoma, Non-Hodgkin; Lymphoma, B-Cell; Antibodies, Monoclonal; Iodine Radioisotopes; Yttrium Radioisotopes

## NON-HODGKIN LYMPHOMA

Malignant lymphomas derived from a lymphoid tissue. Histopathologically, lymphomas are classified to non-Hodgkin's lymphoma (NHL) and Hodgkin's disease. Based on their lineage, NHLs are classified as either B-cell lymphomas or T-cell lymphomas. The majority of lymphomas are derived from B cells and hence are known as B-cell lymphomas (1). Clinical classification of NHLs includes indolent (low-grade) lymphoma that account for almost 50% of NHLs, and aggressive (high-grade) lymphoma. While aggressive NHLs are potentially curable with conventional therapies, indolent lymphomas usually become refractory to treatment. Non-Hodgkin lymphomas are a heterogeneous group of 25 subtypes of malignancies of the lymphatic system (2-4).

Aetiology of NHL is multifactorial and includes: 1) infectious agents (Epstein-Barr virus, human T-cell leukemia-lymphoma virus type 1, human herpes virus type S, Helicobacter pylori); 2) immunodeficiency syndrome: congenital (Wiskott-Aldrich syndrome, Ataxia-telangiectasia), acquired (AIDS, Hodgkin's disease) and autoimmune disorders (Rheumatoid arthritis, Systemic lupus erythematosus, hashimoto's disease); 3) environmental exposure (pesticides such as: organophosphates, phenoxyherbicides, organic solvents such as: benzene, styrene, trichlorethylene, formaldehyde, permanent hair dyes and drugs such as immunosuppressive agents, phenytoin); and 4) genetic factors (chromosomal translocation, oncogene activation such as *bcl-2* and *c-myc*). The incidence of NHL has increased during the last decades affected by the AIDS, epidemic, an ageing population and the increasing number of organ transplantations. The

incidence of NHL is approximately 10/100.000 female patients per year and 14/100.000 male patients per year (5,6). In the European union in 1997 there was a total of 51,470 cases of NHL and 25,339 deaths from the disease (7).

## TREATMENT OF NHL

Follicular NHL is the most common indolent NHL with a slow course of the disease. Usually these patients are asymptomatic; the disease may be discovered by chance or after evaluation of palpable lymphadenopathy. A therapeutic paradigm for the treatment of indolent lymphomas has been dominated by two factors: a generally slow rate of disease progression (median survival duration of 5-10 years), and a failure of any therapeutic approach to influence the natural history of the disease (8). Some clinicians suggest no treatment until symptoms appear, in order to limit chemotherapy-induced toxicity and resistance and to preserve the quality of life (9,10). This approach is supported by the results of clinical studies which indicate that overall survival is not compromised by the "watch-and-wait" approach, rather than administering aggressive treatment. The presence of increasing lymphadenopathy, hepatosplenomegaly, disease-related symptoms or progressively compromised bone marrow, indicates the time to start treatment. At present, there is no universally accepted consensus regarding adequate treatment. Traditional chemotherapies have ranged from single-agents (chlorambucil or cyclophosphamide), to combinations such as CVP (cyclophosphamide, vincristine, prednisone) and more intensive programmes, such as CHOP (cyclophosphamide, vincristine, doxorubicin,

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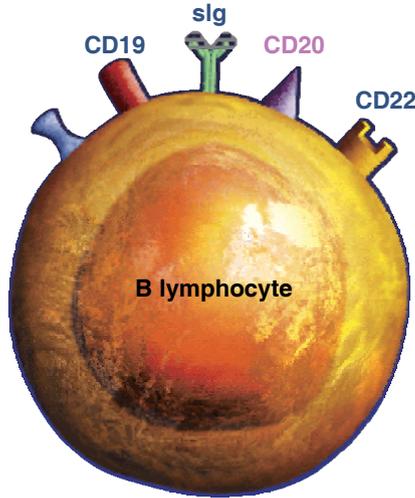


Figure 1. B-cell antigens  
(Adapted from Press O, et al. *Cancer J Sci Am.* 1998;4(Suppl 2):S19–26.)

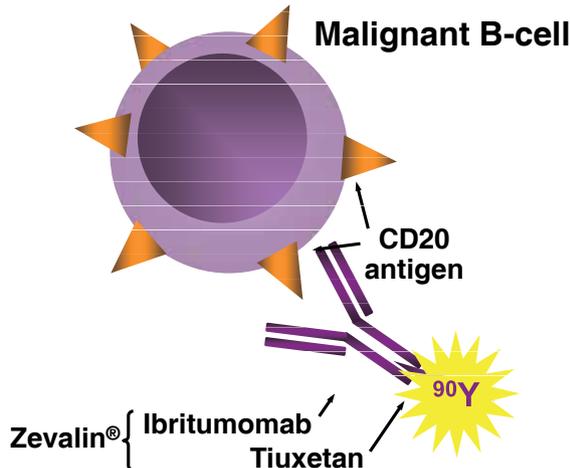


Figure 2. Zevalin, consists of anti-CD20 murine Mab conjugated to the radioisotope 90-yttrium ( $^{90}\text{Y}$ ), targets CD20 antigen of malignant B-cells  
(Adapted from Zevalin® a physician's slide resource (on DVD). Shering AG; 2005.)

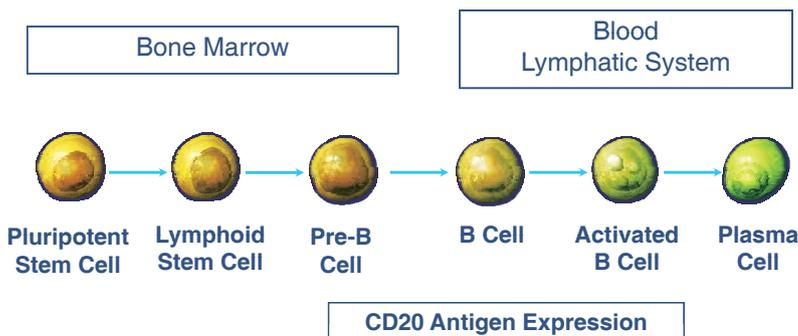


Figure 3. B-Cell Life Cycle of CD20 Expression  
(Adapted from Press O, et al. *Semin Oncol.* 1999;265(Suppl 14):58–65.)

prednisone). However, compared with each other, none of these treatments achieved prolonged survival (11).

Although most patients will respond to the traditional chemotherapeutic regimens, the duration of remission is variable, and 50% of the patients with low-grade lymphoma will relapse within 10 years. Relapsed patients are retreated, but with each subsequent relapse, the duration of remission becomes shorter (1).

Treatment with monoclonal antibodies (Mab) was the first successful targeted therapy for cancer. Unlike chemotherapy, antibodies are directed against tumor-specific cell-surface antigens, resulting in targeted killing of malignant cells. This treatment has low toxicity, relatively sparing the normal tissues and may be used as an alternative or combined with conventional chemotherapy. Most of the successful antibodies have targeted the CD20 antigen. Rituximab, initially known as IDEC C2B8, is an unconjugated, chimeric Mab to CD20 (Rituxan, Genentech Inc, South San Francisco, CA, and Biogen Idec Inc, Cambridge, MA). It was the first Mab approved in 1997, by the US Food and Drug Administration (FDA) for use in the treatment of cancer. In Europe, rituximab was approved by the European Medicines Evaluation Agency (EMA) in 1998 for the treatment of patients with relapsed or refractory low-grade or follicular CD20+ B-cell NHL. Rituximab has had an enormous beneficial effect on the clinical course of patients with low-grade lymphomas such as: relief of symptoms, prolonging the symptom-free period, and reduction of side effects associated with chemotherapy (12). However, only 50% of patients respond to rituximab, while others show disease progression, or relapse after a brief response. Surgery and external beam radiation are not useful in the management of NHL patients who are refractory to the standard therapeutic modalities (13).

### RADIOIMMUNOTHERAPY

Since NHL patients often have repeated relapses with fewer and shorter remissions in response to therapy, targeted radionuclide therapy is needed especially for those with relapsing, refractory, or transformed disease. Radioimmunotherapy combines the targeting ability of an anti-CD20 monoclonal antibody and the radiation emitted from radionuclides ( $^{90}\text{Y}$  or  $^{131}\text{I}$ ). After several clinical trials between 1996 and 1999,  $^{90}\text{Y}$ -ibritumomab tiuxetan (Zevalin, Biogen Idec Inc) was approved for marketing in the USA in February 2002, and in Europe in January 2004. The radioimmunoconjugate  $^{131}\text{I}$ -tositumomab (Bexxar, Corixa Corporation, Seattle, WA) was approved by the FDA in 2003 (12). Surface proteins (epitopes) provide specific sites for generation of monoclonal antibodies. CD20 antigen is one of the many epitopes expressed on the surface of normal mature B-cells and on more than 90% of malignant B-cells (Figure 1) (1,14). The CD20 antigen is an ideal target antigen for therapy against B-cell NHL because it does not circulate as free protein that could block anti-CD20 antibody targeting, does not shed from the cell surface upon binding to anti-CD20, and is minimally internalized after antibody binding (Figure 2) (1,15,16). Targeting of CD20 antigen with radioimmunotherapy hits only B-cells, but not stem or plasma cells. Therefore, cell-line continuity is maintained after the radioimmunotherapy as CD20 antigen is not expressed on pluripotent hematopoietic stem cells and progenitor B-cells (Figure 3) (1,17,18).

## ELIGIBILITY CRITERIA

Patients who are considered for radioimmunotherapy with Bexxar or Zevalin should have histopathologic confirmation of NHL lymphoma with the expression of the CD20 epitope. At present, this kind of therapy is limited to patients with follicular low-grade lymphoma who have relapsed after treatment with rituximab or who are refractory (failed to respond) to rituximab. Patients should also have a recent bone marrow biopsy (within last 6-8 weeks) showing less than 25% of bone marrow involvement. Severe bone marrow toxicity is an adverse effect that occurs in patients who have 25% or more bone marrow involvement. A platelet count greater than  $100 \times 10^9/L$  is recommended for radioimmunotherapy. Patients with a platelet count greater than  $150 \times 10^9/L$  receive a full dose, while those with platelet count between  $100 \times 10^9/L$  and  $150 \times 10^9/L$  receive a modified amount of the therapeutic radiolabelled antibody. Pregnancy and breast-feeding are contraindications to treatment with radiolabelled antibodies (1).

## NUCLEAR MEDICINE IN TREATMENT OF NHL

Radioimmunotherapy involves the administration of radiolabelled monoclonal antibodies that deliver radionuclides specifically to the surface of tumor cells with a minimal radiation to normal tissues. Therapy with radiolabelled antibodies has several advantages over external radiation therapy. Conventional radiotherapy delivers relatively high radiation dose intermittently for short periods, while radioimmunotherapy delivers lower radiation continuously to the tumor cells preventing cells from progressing past the G2 phase of the cell cycle. Higher dose rates of radiation are more toxic, but on the other hand, continuous delivery of radiation may enhance cytotoxicity by preventing DNA repair. Radiation can be delivered to neighboring tumor cells that are antigen negative or to which antibody has not bound through a "cross-fire" effect. This effect is particularly useful in the treatment of tumors with heterogeneous antigen expression, as well as bulky or poorly vascularized tumors where some cells are inaccessible to monoclonal antibodies (19).

There are two options available for radioimmunotherapy of follicular low-grade NHL lymphoma, Bexxar and Zevalin. Bexxar is composed of  $^{131}I$ -labelled tositumomab and both, the labelled and unlabelled antibody, which is murine CD20 monoclonal antibody, tositumomab (Anti-B1 IgG2a).  $^{90}Y$ -labelled ibritumomab tiuxetan (Zevalin) consists of ibritumomab, that is stable bound to tiuxetan (MX-DTPA, a second-generation chelator), which attaches the high-energy pure  $\beta$  emitter  $^{90}Y$  for the therapy, or the  $\gamma$  emitter  $^{111}In$  for imaging. In the Zevalin regimen, the unlabelled antibody is rituximab (chimeric antibody) while the labelled antibody is ibritumomab (murine antibody) (1, 20).

## Radioisotopes

Currently, there are two radionuclides available for radioimmunotherapy:  $^{90}Y$  and  $^{131}I$ . The properties of each radionuclide are shown in Table 1. The  $^{90}Y$  is a high-energy pure beta emitter, allowing treatment on outpatient basis. Since gamma radiation emitted by  $^{131}I$  may be hazardous to medical personnel and family members, patients might be hospitalized during the treatment of Bexxar. Since  $^{90}Y$  has a shorter half-life than  $^{131}I$ , which is comparable with that of the antibody, the duration of exposure of healthy tissue by free isotopes is limited. In soft tissues, 90% of the emitted energy by  $^{90}Y$  is absorbed within 5 mm of the radiation source (corresponding to a diameter of 100-200 cells), allowing delivery of radiation to the tumor and surrounding cells. This makes treatment of bulky tumors successful (21).

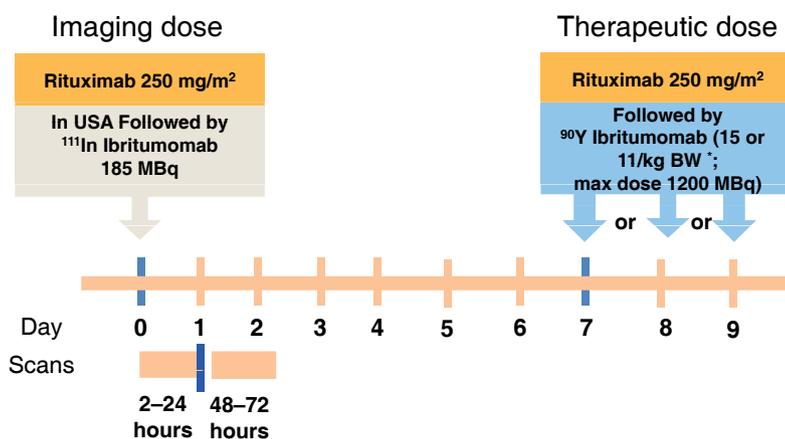
Table 1. Properties of radionuclides  $^{90}Y$  and  $^{131}I$

	Physical half-life (days)	Decay type	Particle energy (MeV)	Primary gamma energy (MeV)	Mean particle path length (mm)
$^{90}Y$	2.7	$\beta$	2.3	None	5.3
$^{131}I$	8	$\beta, \gamma$	0.6	0.364	0.8

## Protocol and dose determination

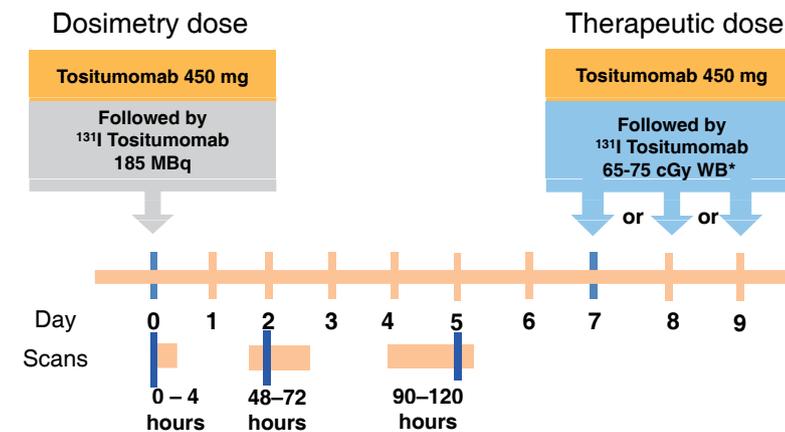
The therapeutic treatment with radiolabelled antibodies may be characterized as a "cold" phase and a "hot" phase separated by approximately one week. The treatment schedule for both products is summarized in Figure 4, and Figure 5.

In both instances, there is an initial infusion of "cold", unlabelled anti-CD20 monoclonal antibody and injection of a tracer or imaging dose of



\*15 MBq/kg in patients with a platelet count  $\geq 150 \times 10^9$  cells/L or 11 MBq/kg with a platelet count  $100 \times 10^9$ – $149 \times 10^9$  cells/L

Figure 4. The therapeutic regimen of  $^{90}Y$ -ibritumomab tiuxetan (Zevalin)



\*75 cGy whole body radiation absorbed dose in patients with a platelet count  $\geq 150 \times 10^9$  cells/L or 65 cGy with a platelet count  $100 \times 10^9$ – $149 \times 10^9$  cells/L

Figure 5. The therapeutic regimen of  $^{131}I$ -tositumomab (Bexxar)

radiolabelled antibody. Before infusion, it is recommended for the patient to receive an oral antipyretic and anti-histamine such as acetaminophen and diphenhydramine. The patient (the vital signs) should be monitored throughout the infusion of both, the unlabelled and labelled antibody. A physician, oncologist or resident, or nurse should be present during the application of unlabelled antibody, while a certified nuclear medicine physician should be present during the infusion of radiolabelled antibody. After completion of the infusions, the patient is monitored for approximately 1 hour. However, the only usual side effect is somnolence (caused by antihistamine). A few days following the regimen, patients could have fatigue and a flu-like syndrome, which disappear within several days. During 6 weeks after the treatment, patients should check complete blood count and platelet count each week. Between 4 and 6 weeks, during the hematologic nadir, patients could experience fatigue again and should be monitored for infections, bruising, and risk of bleeding. The referring oncologist should decide if supportive measures are needed (1).

In the case of Bexxar, the imaging agent is the same,  $^{131}\text{I}$ -tositumomab, but at lower dose, and the “cold” antibody is the unlabelled tositumomab. The gamma emissions of the  $^{131}\text{I}$  can expose an x-ray sufficiently for imaging to determine body distribution and tissue uptake.  $^{111}\text{In}$  (a gamma emitting radio-metal with chemistry similar to  $^{90}\text{Y}$ ) ibritumomab is used for the initial biodistribution studies before application of Zevalin, while patient specific dosimetry is no longer necessary to determine the therapeutic dose. In this case, the “cold”, unlabelled antibody is rituximab, the mouse human-chimeric antibody. The initial dose of “cold” antibody is given to clear circulating CD20+ B lymphocytes that are present in circulation, thus optimizing the biodistribution and enabling targeting of the radiolabelled isotope to the tumor cells. One week later, the therapeutic dose is administered but again is preceded by a cold unlabelled anti-CD20 monoclonal antibody. This is aimed to binding some of the cells on the periphery of tumor masses, which influences radiolabelled antibody to bypass these CD20+ cells to penetrate more deeply into these masses of CD20+ cells in other parts of the tumor. Otherwise, virtually all of the radionuclide might be located on the periphery of the roughly spherical tumor masses of lymphoma. Administration of the “cold” antibody improves biodistribution of the antibodies, thus resulting in increased uptake into tumor lesions (1).

### The Zevalin regimen

The Zevalin administration regimen consists of two intravenously administered doses of rituximab, followed by a single dose of Zevalin. On day one, the first pre-dose of 250 mg/m<sup>2</sup> of rituximab is administered during approximately 3 hours.

In the United States, the whole body imaging is obligatory before the application of Zevalin. At the time of the initial rituximab infusion, the whole body scanning is performed in anterior and posterior views, 24 hours and 72 hours after an intravenous administration of 185 MBq  $^{111}\text{In}$ -ibritumomab. Such whole body imaging is performed in order to confirm normal biodistribution (i.e. absence of significant activity in the kidneys, lungs or other organs) and rule out the abnormal pharmacokinetics (influenced by circulating HAMA or antibody's damage). Expected biodistribution occurs in about 90%. Altered biodistribution is rare, with the incidence of less than 1%, since the FDA approval of the compound in 2003 (20). Recently, however, an

unexpected high frequency of aberrant antibody distribution was reported in the studied patients (22). Altered biodistribution is a contraindication for continuation with the therapeutic dose. If expected biodistribution is seen, patients can receive the following therapeutic dose of Zevalin. On the contrary, in Europe, biodistribution studies are not obligatory before infusion of the therapeutic dose of Zevalin (17).

After the period of 7 to 9 days, usually on day eight, the second infusion of the same dose of rituximab is given to the patient immediately followed by the 10-minute infusion of therapeutic dose of  $^{90}\text{Y}$ -ibritumomab. The optimal dose of Zevalin is based on the patient's platelet count and body weight. The recommended dose for patients with  $\geq 150 \times 10^9$  platelets/L and absolute neutrophil count  $> 1.5 \times 10^9$ /L is 15 MBq  $^{90}\text{Y}$ -radiolabelled Zevalin/kg body weight, up to a maximum of 1200 MBq. The recommended dose for patients with mild thrombocytopenia ( $100 \times 10^9$ /L –  $< 150 \times 10^9$  platelets/L) is 11 MBq  $^{90}\text{Y}$ -radiolabelled Zevalin/kg body weight. Patients with platelet counts of less than  $100 \times 10^9$ /L should not be treated with Zevalin (20).

### The Bexxar regimen

Patients receiving Bexxar therapeutic regimen should be premedicated with SSKI (Lugol's solution or saturated solution of potassium iodide) starting at least 1 day before administration of  $^{131}\text{I}$  tositumomab and continuing for 2 weeks after completion of the therapy. This is aimed to block or, at least, significantly reduce thyroidal iodine uptake.

For  $^{131}\text{I}$ -tositumomab therapy, the whole body scanning is required for establishing dosimetry and clearance of  $^{131}\text{I}$ , from which the individual therapeutic doses of  $^{131}\text{I}$  in Gy of total-body radiation are to be calculated. This calculation is necessary to avoid excessive toxicity and to optimize the therapeutic dose.

The whole-body radiation-absorbed dose is determined from relatively simple measurements made following the administration of a 185 MBq dose of  $^{131}\text{I}$ -tositumomab preceded by an infusion of 450 mg of unlabelled tositumomab. The whole-body counts are determined from the total counts on the anterior and posterior whole-body scans performed an hour after the initial infusion and similar scans obtained 2 days later. The third set of scans is obtained 2-3 days after the second set. Seven to nine days after the initial “dosimetric” dose sequence, the infusion of unlabelled tositumomab in the same dose is repeated followed by the  $^{131}\text{I}$ -tositumomab therapeutic dose of 1.85-5.55 GBq that was determined by dosimetry to deliver 65 or 75 cGy based on the 3 whole-body counts performed after the initial radiolabelled dose. The maximal tolerated dose is usually 75 cGy whole-body radiation-absorbed dose for patients with platelet counts greater than  $150 \times 10^9$ /L. Patients with platelet counts between  $100 \times 10^9$ /L and  $150 \times 10^9$ /L are best managed with 65 cGy whole-body radiation-absorbed dose (23, 24).

There has not been a direct randomized comparison of the clinical efficacy of these two agents. It is not possible to suggest a clear advantage of one agent over another, based on the meta-analysis of the published materials to date. However, there are several issues that might determine the regimen selection. At present, both Zevalin and Bexxar are approved for use in the United States, while in Europe only Zevalin is available. The iodine allergy also could preclude the use of Bexxar. The greater energy of the  $\beta$  particle

associated with  $^{90}\text{Y}$  is superior for the treatment of bulky tumors (greater than 5 cm), whereas the lower energy of  $^{131}\text{I}$  is preferable for treating patients with microscopic tumor foci and marrow involvement (1).

## CLINICAL EFFICACY

Numerous clinical trials have been done to analyze the efficacy of radioimmunotherapy of patients with follicular low-grade Non-Hodgkin's lymphoma. This review will summarize data from several studies and demonstrate positive results and clinical efficacy of Zevalin and Bexxar treatment.

### Zevalin

A phase III randomized study studied the patients with relapsed or refractory low-grade, follicular, or transformed CD20+ transformed NHL. One group of patients was treated with Zevalin, as a novel radioimmunotherapy, while the other group of patients received only rituximab, as an immunotherapy. Patients treated with Zevalin had significantly higher responses than those who received only rituximab (treatment includes administration of 375 mg/m<sup>2</sup> of rituximab per week during 4 weeks): ORR of 80% versus ORR of 56%, respectively ( $p=0.002$ ), and CR of 30% versus CR of 16%, respectively ( $p=0.04$ ). An additional 4% achieved an unconfirmed CR in each group. Patients treated with Zevalin showed trends towards longer time to progression, longer duration of response and longer time to next lymphoma treatment, versus rituximab therapy, particularly in patients with follicular NHL: Kaplan-Meier estimated median duration of response was 14.2 months in the Zevalin group, while 12.1 months were detected in the rituximab group ( $p=0.6$ ), and time to progression was 11.2 versus 10.1 months ( $p=0.173$ ) in all patients. Durable responses of 6 months and longer were 64% versus 47% ( $p=0.03$ ) (25).

Retrospective study done by Wieseman et al, determined the overall response rates ranging from 74% to 82% in patients treated with Zevalin. They reported that  $^{90}\text{Y}$  ibritumomab tiuxetan produces durable long-term responses in patients with relapsed/refractory B-cell NHL. Failure to respond to prior therapy does not preclude achieving a long-term response with  $^{90}\text{Y}$  ibritumomab tiuxetan (26).

Beside impressive clinical results in patients treated with Zevalin, there was a concern that severe bone marrow radiation impairment may occur, rendering the patient ineligible for further therapy. However, Ansell analysed several clinical trials and did not substantiated this concern (27).

### Bexxar

In the study of Fisher et al, 90% of patients treated with Bexxar were staged III or IV, while 46% had bone marrow involvement. Sixty one percent had bulky tumors (diameter greater than 5cm). The ORR was 56%, and the median duration of response was 12.9 months with a range from 10.9 to 17.3 months. A complete remission (CR) was seen in 30% of patients. In the CR group, the median duration of response was almost 5 years (58.4 months), with a minimum duration of 28.3 months. Many patients remained in remission beyond the 5 years that had elapsed at the time of the study (28). Leonard et al. have studied patients who received an abbreviated course of the chemotherapeutic agent, Fludarabine for 3 cycles. This treatment was followed after 6-8 weeks by the Bexxar regimen. The overall response rate (ORR) was 98% with 30 of 35 patients obtaining a CR. The minimal

progression-free survival (PFS) was 27 months and the median PFS had exceeded 48 months of follow-up (29).

In another trial, Bexxar was used as the first, initial therapeutic in 76 patients staged III or IV follicular lymphoma. The ORR was 95%, and CR was reached in 75% of patients (30).

## ADVERSE EVENTS

The most common adverse events associated with the radioimmunotherapy are primarily hematological. In general, hematologic events are mild and transient. Regular monitoring of hematological toxicity is required since nadir occurs around 4 to 6 weeks after the start of treatment with median time to recovery of 1 to 3 weeks (1).

Anaphylactic and other hypersensitivity reactions have been reported in less than 1% of patients following intravenous administration of proteins to patients. Therefore, patients who have previously received mouse-derived proteins should be tested for human anti-mouse antibody (HAMA) before administering Bexxar or Zevalin. Patients who have developed HAMA may have allergic or hypersensitivity reactions when treated with radioimmunotherapy. After radioimmunotherapy, patients should generally be tested for HAMA before any further treatment with mouse-derived proteins.

Non-hematological adverse events are primarily grade 1 or 2 and are not associated with common adverse events, which occur after chemotherapy (e.g. hair loss, severe mucositis, persistent nausea, vomiting). The infusion of the "cold" antibody may be associated with infusion reactions (warm feeling, lightheadedness, chills, hives, dyspnea, and decreased blood pressure). Mild reactions are more common with rituximab than tositumomab. Symptoms usually disappear by slowing the rate of infusion (31).

Although iodine allergy affects a small subset of patients, this should preclude the use of Bexxar in those patients (1).

Effects on fertility and reproductive function are still unknown. However, men and women are advised to use contraception for one year following the treatment with radioimmunotherapy (31).

## RADIATION DOSE AND SAFETY

As already stated, therapeutic activity of Bexxar is determined by dosimetry to deliver 65 to 75 cGy whole-body radiation-absorbed dose, while maximum tolerated dose for Zevalin is 1200 MBq. Since  $^{131}\text{I}$  is both a  $\beta$  and a  $\gamma$  emitter, Bexxar treatment results in greater exposure of medical personnel and a patient's family. Therefore, during the infusion of a therapeutic dose, portable shielding is required to be in place between the patient and the medical personnel. Tables 2 and 3 give a detailed guidance on the duration and proximity to others that would minimize exposure, which patients should obey after their discharge from the hospital. This guidance should be based on a patient-specific dose administered and the biologic turnover rate that had been obtained for the dosimetry measurements. As a pure  $\beta$  emitter, Zevalin must be administered by physicians and other professionals qualified in the safe use and handling of radiopharmaceuticals. Despite bremsstrahlung radiation, which is produced and is detectable, the exposure is not hazardous to medical personnel or family members. Patients are advised to avoid contamination of others with body fluids (saliva, blood, urine, seminal fluid, and stool) (32).

**Table 2. Outpatient release instruction after the Bexxar therapeutic regimen (example of patient who received  $^{131}\text{I}$  activity of 3.2 GBq, measured dose rate of 10 mrem/h at 1 eter)**

Instruction	Duration (days)
Sleep in a separate bed (at least 6 feet from anyone else)	8
Do not take a long trip (4 hours or more) sitting near others (e.g. car, train, airplane, bus)	On a day of release from hospital
3. stay at least 6 feet from children and pregnant women	9
4. Minimize time spent near others and delay return to work	5
5. Continue taking thyroid-protective agent	14

**Table 3. Instructions that have to be followed for the next 14 days**

1. Keep at least 6 feet from others whenever possible
2. When taking shorter trips, sit as far as possible from others
3. Do not let others use your bathroom, if possible
4. Menstruating women should use tampons that can be flushed down the toilet
5. Sit while urinating and flush the toilet three times with the lid down
6. Wash hands often, including after each toilet use, and shower daily
7. Drink plenty of liquids
8. Use separate towels, washcloths, and toothbrush from rest of the household members
9. Use separate dishes and utensils for 1 week and wash separately
10. Hold clothing and linen (sheets and towels) for 1 week before laundering and launder separately from rest of the household's laundry
11. Avoid using disposable items that cannot be flushed down the toilet
12. Inform your physician or other healthcare provider of your treatment
13. Do not breast feed

Instructions regarding the distance and duration of contact are not necessary. As it was already mentioned previously, general performance of dosimetry is not recommended by European Medicine Evaluation Agency (EMA), as individual patient dosimetry results were not predictive for Zevalin toxicity. Clinical studies have shown that there is no correlation between the dosimetry and haematological toxicity. Outpatient administration is possible and depends on regional or local regulations. Minimal exposure to personnel from treated patients of 0.00295 mSv/h was detected at 1m distance immediately after the dosing. The median radiation exposure at 1 m from the patient immediately following infusion was 0.00295 mSv/hour (normal range is 0.0024-0.0039). It was concluded that, even without patient isolation or shielding, radiation exposure to family members during the 7 days following Zevalin was very low and in the background range (33).

## CONCLUSION

Currently, Zevalin and Bexxar are two options available for radioimmunotherapy of the low-grade follicular rituximab refractory or relapsed NHL. Use of each agent requires a "test dose" and multiple imaging sets to confirm biodistribution for Zevalin and to determine the therapeutic dose of Bexxar. The choice of one agent over the other is based upon a number of factors that may vary from patient to patient and facility to facility. Nuclear medicine physicians should be prepared to provide support for the administration of both approved radioimmunotherapy agents. In general, clinical responses are better, and of greater duration, than with alternative available therapies. Overall response rates between 80% and 100% have been detected

in numerous studies. The principle toxicity is hematologic; patients may require supportive measures including growth factors or transfusions, but serious consequences are rare. The procedure is generally well tolerated by patients. Radiation exposure of family members and health care personnel is low, which permits treatment on outpatient basis. In the event of relapse, patients are tolerant to additional subsequent therapy.

## Conflict of interest

We declare no conflicts of interest.

## REFERENCES

- 1 Goldsmith SJ. Radioimmunotherapy of lymphoma: Bexxar and Zevalin. *Semin Nucl Med.* 2010;40:122-35.
- 2 Armitage JO. Treatment of non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328:1023-30.
- 3 Bastion Y, Sebban C, Berger F, Felman P, Salles G, Dumontet C, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. *J Clin Oncol.* 1997;15:1587-94.
- 4 Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J. Lymphoma classification--from controversy to consensus: the R.E.A.L. and WHO Classification of lymphoid neoplasms. *Ann Oncol.* 2000;11 Suppl 1:3-10.
- 5 Hagenbeek A, Kluin PM. Non-Hodgkin's lymphomas. In: Degos L, Linch DC, Löwenberg B, editors. *Textbook of Malignant Haematology.* Chapter 31. London, Martin Dunitz; 1999. p. 635-84.
- 6 Wood AM. Rituximab: An innovative therapy for non-Hodgkin's lymphoma. *Am J Health-Syst Pharm.* 2001;58:215-32.
- 7 Ferlay J, Bray F, Sankila R, Parkin DM. EUCAN: Cancer incidence, mortality and prevalence in the European Union 1997, version 4.0. IARC CancerBase No. 4. Lyon: IARC Press; 1999. Limited version available from: <http://www-dep.iarc.fr/eucan/eucan.htm>.
- 8 Fisher RI. Current therapeutic paradigm for the treatment of non-Hodgkin's lymphoma. *Semin Oncol.* 2000;27:2-8.
- 9 Wood AM. Rituximab: An innovative therapy for non-Hodgkin's lymphoma. *Am J Health-Syst Pharm.* 2001;58:215-32.
- 10 Horning S. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. *Semin Oncol.* 1993;20 Suppl 5:75-88.
- 11 Mavromatis BH, Cheson BD. New strategies for the treatment of indolent non-Hodgkin's lymphomas. *Oncology Spectrums.* 2001;2:706-16.
- 12 Forero A, LoBuglio AF. History of antibody therapy for Non-Hodgkin's lymphoma. *Semin Oncol.* 2003;30 Suppl 17:1-5.
- 13 McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol.* 1998;16:2825-33.
- 14 Press OW. Prospects for the management of non-Hodgkin's lymphomas with monoclonal antibodies and immunoconjugates. *Cancer J Sci Am.* 1998;4 Suppl 2:S19-26.
- 15 White CA, Weaver R, Royston I. Anti-CD20 monoclonal antibody therapy for non-Hodgkin's lymphoma. *Minerva Biotechnol.* 1998;10:108-17.
- 16 Zevalin<sup>®</sup> A physician's slide resource (on DVD). Shering AG; 2005.
- 17 Anderson KC, Bates MP, Slaughenhaupt BL, Pinkus GS, Schlossman SF, Nadler LM. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. *Blood.* 1984;63:1424-33.
- 18 Press OW. Radiolabelled antibody therapy of B-cell lymphomas. *Semin Oncol.* 1999;26 Suppl 14:58-65.
- 19 Press OW. Physics for practitioners: the use of radiolabelled monoclonal antibodies in B-cell non-Hodgkin's lymphoma. *Semin Hematol* 2000;37(Suppl 7):2-8.
- 20 Spies SM. Imaging and dosing in radioimmunotherapy with Yttrium 90 ibritumomab tiuxetan (Zevalin). *Semin Nucl Med.* 2004;34 (Suppl):10-3.
- 21 Zhu X. Radiation safety considerations with Yttrium 90 ibritumomab tiuxetan (Zevalin). *Semin Nucl Med.* 2004;34(Suppl):20-3.
- 22 Arico D, Grana CM, Vanazzi A, Ferrari M, Mallia A, Sansovini M, et al. The role of dosimetry in the high activity 90Y-ibritumomab tiuxetan regimens: Two cases of abnormal biodistribution. *Cancer Biother Radiopharm.* 2009;24:271-5.
- 23 Wahl RL. Tositumomab and  $^{131}\text{I}$  therapy in non-Hodgkin's lymphoma. *J Nucl Med.* 2002;46:128S-140S.

- 24 Britton K. Radioimmunotherapy of non-Hodgkin's lymphoma. *J Nucl Med.* 2004;45:924-5.
- 25 Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R, et al. Randomized controlled trial of Yttrium-90-ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy with relapsed or refractory low-grade, follicular, or transformed B-cell Non-Hodgkin's lymphoma. *J Clin Oncol.* 2002;20:2453-63.
- 26 Wiseman GA, Witzig TE. Yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin) induces long-term durable responses in patients with relapsed or refractory B-Cell non-Hodgkin's lymphoma. *Cancer Biother Radiopharm.* 2005;20:185-8.
- 27 Fisher RI, Kaminski MS, Wahl RL, Knox SJ, Zelenetz AD, Vose JM, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. *J Clin Oncol.* 2005;23:7565-73.
- 28 Leonard JP, Coleman M, Kostakoglu L, Chadburn A, Cesarman E, Furman RR, et al. Abbreviated chemotherapy with fludarabine followed by tositumomab and iodine I-131 tositumomab for untreated follicular lymphoma. *J Clin Oncol* 2005;23:5696-5704.
- 29 Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, Zasadny K, et al. <sup>131</sup>I-tositumomab therapy as initial treatment for follicular lymphoma. *N Engl J Med.* 2005;352:441-9.
- 30 Borghaei H, Schilder RJ. Safety and efficacy of radioimmunotherapy with Yttrium 90 ibritumomab tiuxetan (Zevalin). *Sem Nucl Med.* 2004;34(Suppl):4-9.
- 31 Rutar FJ, Augustine SC, Colcher D, Siegel JA, Jacobson DA, Tempero MA, et al. Outpatient treatment with 131I-anti-B1 antibody: Radiation exposure to family members. *J Nucl Med.* 2001;42:907-15.
- 32 Wiseman G, Leigh B, Witzig T, Gansen D, White C. Radiation exposure is very low to the family members of patients treated with yttrium-90 Zevalin® anti-CD20 monoclonal antibody therapy for lymphoma. *Eur J Nucl Med.* 2001;28:1198.
- 33 Ansell SM, Schilder RJ, Pieslor PC, et al. Antilymphoma treatments given subsequent to yttrium 90 ibritumomab tiuxetan are feasible in patients with progressive non-Hodgkin's lymphoma: A review of the literature. *Clin Lymphoma.* 2004;5:202-4.