EANM procedure guideline of radio-immunotherapy for B-cell lymphoma with ^{90}Y-radiolabeled ibritumomab tiuxetan (Zevalin®)

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Abstract. EMEA has approved ^{90}Y-radiolabelled ibritumomab tiuxetan, Zevalin®, in Europe for the treatment of adult patients with rituximab-relapsed or -refractory CD20+ follicular B-cell non-Hodgkin´s lymphoma (NHL) in January 2004. The number of European nuclear medicine departments using Zevalin® is continuously increasing, since the therapy is often considered successful.
The Therapy-, the Oncology- and the Dosimetry Committees have worked together in order to define some EANM Guidelines on the use of Zevalin®, paying particular attention to the problems related to Nuclear Medicine. The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients who may be candidates for radio-immunotherapy. These guidelines also stress a close collaboration with the physician(s) treating the patient for the underlying disease.

Key Words: guidelines, nuclear medicine, ^{90}Y- ibritumomab tiuxetan, non-Hodgkin's lymphoma, radioimmunotherapy

I. Purpose

The purpose of this guideline is to assist the nuclear medicine physician in treating and managing patients who may be candidates for radio-immunotherapy because of relapsed or refractory CD20+ follicular B-cell non-Hodgkin´s lymphoma (NHL).

II. Background Information and Definitions

A. Definitions

1. Radio-immunotherapy (RIT) for relapsed or refractory CD20-positive B-cell NHL means intravenous administration of ^{90}yttrium [^{90}Y]-labelled ibritumomab tiuxetan (Zevalin®).
2. ^{90}Y(III)chloride is produced through decay of the radioactive precursor nuclide ^{90}strontium [^{90}Sr]. The decay of ^{90}Y is accompanied by the release of beta radiation with a maximum energy of 2.281 MeV (99.98%) into stable ^{90}zirconium [^{90}Zr], with a half life of 64 h (2.7 d). Ibritumomab tiuxetan is a conjugated murine anti-CD20 antibody genetically engineered from Chinese hamster ovary (CHO) line using the MX-DTPA chelating agent.
3. The ibritumomab tiuxetan antibody targets the CD20 antigen, which is expressed on the surface of normal (except for pre-B cells and secretory B cells) and malignant B lymphocytes.

B. Background

^{90}Y is a virtually pure β^--emitter, with a high β^--energy and an effective pathlength of 5.3 mm, meaning that 90% of its energy is absorbed within a sphere with 5.3-mm radius. This pathlength corresponds to 100-200 cell diameters, giving ^{90}Y a broad crossfire effect when it is conjugated to monoclonal antibody such as ibritumomab.

Ibritumomab tiuxetan consists of ibritumomab, the parent murine monoclonal antibody from which the widely used chimeric monoclonal antibody rituximab (Mabthera®) was derived, and tiuxetan which is the chelate for the radionuclide. Development of human antimouse or human antichimeric antibodies (HAMA or HACHA, respectively) is reported to be in the range of 1%-2% of patients treated with Zevalin®. The low incidence of HAMA might partly be due to the immunocompromised status of lymphoma patients due to the disease itself as well as to previous therapies. The fact that rituximab is used for pre-targeting also reduces the incidence of HAMA.

Pharmacokinetic studies have shown that almost the entire radioactivity of Zevalin® is retained within the body after injection. The mean effective half life for Zevalin® in blood is 27 h (range 14-44 h), provided that pre-treatment with rituximab is performed and that there are no detectable HAMA. Urinary excretion is the primary clearance mechanism, and it accounts for the elimination of only 7.3% +/- 3.2% of the administered activity over 7 day.

Pre-targeting with unlabelled chimeric Mab (= preload) as part of a treatment with Zevalin® leads to a more favourable biodistribution of the subsequently injected radiolabelled antibody by clearing peripheral B-cells from the circulation. Not only does the unlabelled Mab prevent the radiolabelled antibody to bind non-tumour sites (normal B-cells, spleen), but it is also said to facilitate deeper penetration into the tumour, translating into a more homogenous distribution. Furthermore, rituximab itself induces several mechanisms of tumour cell killing such as antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC), but also direct induction of apoptosis and possibly cell cycling blockade. In radio-immunotherapy the biological effects of the monoclonal antibody and of radiation are thought to be synergistic.

III. Indications

EMEA has approved ^{90}Y-radiolabelled ibritumomab tiuxetan, Zevalin®, in Europe for the treatment of adult patients with rituximab-relapsed or -refractory CD20+ follicular B-cell NHL in January 2004.

Contra indications:

Exclusion criteria for treatment with ^{90}Y-ibritumomab tiuxetan are indicated in the summary of product characteristics (**table 1**).

Table 1. Exclusion criteria for treatment

- pregnancy and continuing breast feeding
- known hypersensitivity to ^{90}Y-ibritumomab tiuxetan, yttrium chloride, other murine proteins, or any of their components
- children and adolescents under 18 years of age
- marked bone marrow suppression (< 1.5 x 10^9/L leukocytes; < 100 x 10^9/L thrombocytes)
- greater than 25% of bone marrow infiltration by lymphoma cells, as judged by bone marrow biopsy.
- previous external beam radiation involving >25% of the active bone marrow
- prior bone marrow or stem cell transplantation
- detectable HAMA, depending on titer

The peripheral blood cell count should not be lower than the limits stated above. However, lower blood counts do not constitute an absolute contraindication, but they do increase the risk of severe and prolonged bone marrow suppression and subsequently infection and/or bleeding. The indication in such a case should be determined after weighing the benefits and disadvantages of all available alternatives in term of local and systemic interventions.

IV. Procedure

A. Facility and personnel

1. Therapy with ^{90}Y-ibritumomab tiuxetan should only be performed in facilities capable of meeting the standards for treatment with unsealed radioactive sources and licensed according to the national regulations.
2. The personnel engaged in the procedures must have the required qualification and the appropriate government authorisation for the use and manipulation of radionuclides.
3. A representative of the nuclear medicine service is responsible synchronizing and organizing the coordination of all pre-treatment and treatment steps along

with the referring haematology-oncology service, the services preparing the radiopharmaceutical agent and other participants.

4. Proof of training in radiochemical labelling procedures, including quality control, is required.
5. This radiopharmaceutical agent may be received, used and administered only by authorized persons in designated settings. Its receipt, storage, use, transfer and disposal are subject to national regulations.

B. Patient Preparation and Data required

1. Patient information: age, sex, height, weight, diagnosis.
2. Indication for the therapy.
3. Information on the previous therapies (including data on previously completed radiotherapy and/or autologous/allogenic stem cell transplantation). Previous chemotherapy – especially if recent – or external beam radiation therapy involving active bone marrow can worsen radionuclide-induced leukocytopenia and/or thrombocytopenia.
4. A representative (>2 cm long cylinder) bone marrow biopsy from the iliac crest must not show a > 25% tumour infiltration (number of lymphoma cells as a percentage of nucleated cells). The biopsy must have been performed no earlier than:
    i. the last time at which disease progression was detected;
    ii. or in any case a maximum of 3 months before the scheduled therapy date.

   In addition, the density of cells under normal haematopoiesis must be judged adequate to ensure satisfactory haematopoietic recovery after myelosuppressive therapy.
5. Pregnancy must be excluded prior to radionuclide therapy, while breast feeding must be stopped.
6. Current medications, especially those that can affect coagulation or blood cell counts must be recorded.
7. Blood profile, prothrombin time (INR), and serum creatinine and bilirubin tests within 1 week prior to therapy. There is no adequate experience with the use of Zevalin® in patients with increased creatinine or bilirubin levels. Usually it is advised that therapy should not be performed if these values are above 2.5 times the upper normal limit of the local laboratory.
8. Estimation of life expectancy (life expectancy > 3 months, Karnofsky index > 70%). A patient with a life expectancy of less than 3-4 weeks is unlikely to benefit from treatment. Similarly, patients showing rapidly progressing disease are not candidates for RIT because of delayed efficacy of the treatment.
9. Probably due to methodological problems, the dosimetry performed during the registration trials showed a poor absorbed dose-response relationship, meaning that the pre-therapeutic dosimetry did neither predict therapeutic efficacy nor toxicity of the treatment. Thus, there is no evidence that currently available dose calculations can predict either therapeutic efficacy nor toxicity of the treatment.

   For this reason, EMEA has accepted that no such dosimetry studies are required in the EU. The injected activity is determined according to body weight and platelet counts.

Pre-therapeutic imaging with ^{111}In-ibritumomab tiuxetan is mandatory in Switzerland and the US. The imaging is performed not for dosimetric purposes but to confirm the expected biodistribution, as an additional safety measure before administering the Zevalin® therapy.
Dosimetry should be performed, however, when Zevalin® is used as an investigational treatment at activities or indications different from the one defined in the registration trials in patients with indolent B-cell lymphomas.
Presently, there are several clinical trials underway with a special focus on pre-therapeutic dosimetry using ^{111}In and applying more sophisticated dosimetry protocols as compared to the registration trials.

C. Patient Information and Instruction

The treatment must be performed in close collaboration with the physician(s) treating the patient for the underlying disease.

Prior to planning the treatment, the nuclear medicine physician, directly responsible for the treatment and subsequent follow-up, must personally verify the safety-related suitability criteria of the patient and discuss all technical and clinical aspects of the radio-immunotherapy with the patient.

The patients should be provided with written guidelines on the radiation therapy, anticipated adverse events and contact telephone numbers. The precautions that should be followed during the first week are listed in **table 2.**

Table 2. Items to be included in patient education and counselling
(Modified from Hagenbeek and Lewington, Ann Oncol 2005)

Radioimmunotherapy
-Generic guidelines describing administration and information relevant to radioimmunotherapy regimens
-Specific information describing the ^{90}Y-ibritumomab tiuxetan treatment, including possible adverse events and safety precautions required during actual treatment
-Risk of radiation exposure to others
-As there is minimal risk of radiation exposure to people in contact with the patient, social interaction with friends, family and pets is without risk

-During treatment, the patients need not change their routine activities, and no special precautions are required, such as separate toilet or separate cutlery, and dishes to the rest of the family

Following treatment for 1 week:

-Patients should use condoms if they engage in sexual activity

-When urinating, males should urinate sitting down; any spilt urine should be cleaned and cleaning cloths should be disposed of in waste disposal or by flushing them down the toilet

-All patients should wash their hands after urination

Contraceptive advice

-As with other anticancer treatments, contraception to avoid pregnancy is recommended for 1 year following treatment

-Possible long-term effects

-Male patients may experience a temporary loss of fertility and may have a low risk of permanent sterility

-Although there are no studies validating this risk, Zevalin® treatment results in a radiation dose to the testes. Thus, if prior therapies have not damaged sperm quality, male patients may be advised to consider semen cryopreservation

-It is unlikely that fertility is affected in female patients

-Prior treatment with chemotherapy may contribute to the low incidence of secondary malignancies (1.4%) observed after Zevalin® treatment, which is in the range reported following alkylator-based chemotherapy alone [1% to 8%]. No secondary malignancies have been reported to date with first–line use of radioimmunotherapy

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After informing the patient both verbally and in writing, the patient must give consent to the treatment, either verbally or in writing, depending on national legislation. Legal provisions must be observed, including obtaining written informed consent where appropriate.

D. Administration

It is not necessary for the patient to be fasting before therapy. Care must be taken to ensure adequate hydration.

Prior to therapy with ^{90}Y-ibritumomab tiuxetan, two infusions with rituximab are administered. These rituximab infusions must be performed under the responsibility of an experienced haematologist-oncologist who is familiar with rituximab:

Day 1: Infusion of 250mg/m² rituximab. The volume of normal saline solution, which contains the rituximab stock solution, and the infusion must comply with the recommendations contained in the package insert of the preparation. In Switserland and the U.S. this infusion is followed by IV infusion of ^{111}In-ibritumomab tiuxetan (180 MBq) over 10 minutes. At least one anterior and posterior whole body scan has to be recorded within 24 hours and 7-9 days after injection.

Day 7 or 8 or 9: Infusion of 250 mg/m² rituximab, followed by administration of ^{90}Y-ibritumomab tiuxetan as slow IV infusion over 10 minutes. Zevalin® should not be administered as an intravenous bolus.

For patients with platelets $\geq$ 150 x 10^9/L, the recommended administered activity of ^{90}Y-ibritumomab tiuxetan is 15 MBq (0.4 mCi) per body weight (kg) up to a maximum limit of 1200 MBq (32 mCi). Patients with platelet counts of 100-149 x 10^9/L should receive 11 MBq/kg (0.3mCi/ kg).

There are insufficient data on the effects of re-treatment of patients with Zevalin® . The MTD for haematological toxicity at repeated treatment may be lower.

If the average radiochemical purity is less than 95%, the preparation must not be administered. After labelling, Zevalin® must be stored at 2-8 ˚C, protected from light and administered within 8 hours. The Zevalin® infusion should be performed within 4 hours after the second rituximab infusion, but it can be postponed up to 48 hours without another pre-load of rituximab.

The infusion of the radiopharmaceutical agent must take place via a venous catheter or an indwelling infusion device to ensure safe intravenous administration and prevent paravascular infiltration. The simplest method to check for proper venous access, even during the administration, is to run a free rapid infusion of normal saline during the injection into the same venous access. If a slowdown in drop speed occurs, check the position of the venous access. Zevalin® should either be administered directly through a three way valve line or using a remote infusion system shielded with Perspex®. A line filter is required. After infusion of Zevalin® flush the line with at least 10 ml of sodium chloride (0.9%) solution, to ensure administration of the full dose of radiopharmaceutical agent. The residual activity in the needle and/or the infusion kit and catheter can be measured to calculate the precise activity administered.

In the event of extravasation, the infusion must be immediately halted. Extravasation can lead to radionecrosis. There is no specific therapy for paravenous infiltration. If extravasation should occur, local hyperthermia, elevation of the extremity, and gentle massage might somewhat favour lymphatic drainage and thereby reduce the local radiation dose. The event must be recorded in the procedure report.

Anaphylactic and other hypersensitivity reactions have been reported in less than 1% of patients following the intravenous administration of proteins to patients. Blood pressure and pulse should be monitored just as with any administration of monoclonal antibodies. An emergency kit including glucocorticoids and antihistamines should be kept on hand.

Depending on national/regional regulations, hospitalization may not be required for Zevalin® administration. The patient is discharged after completion of the infusion and an adequate period of observation for side effects (20-30 minutes). The nursing staff attending hospitalized patients and relatives dealing with patient excretions should wear rubber gloves to prevent skin contamination from contact with patient excretion. Social contacts with relatives or other patients, as well as pets, do not carry any risk.

E. Precautions, follow-up and side-effects

The nuclear medicine specialist must participate in the ongoing and follow-up care of the patient as a part of the patient management team.

It should be noted that a reduction of 30-70% in leukocyte and platelet counts from their baseline levels is possible, sometimes very rapidly. The nadir usually occurs about 7-9 weeks after therapy (median: day 60), i.e. later than after chemotherapy. Weekly blood tests from the second post-therapy week on are recommended until baseline levels have been reached. If levels drop faster than expected, shorter-term controls should be instituted. If the platelets fall below 30 x 10^9/L, levels should be checked at least three times per week. Platelet transfusions and growth factors should be administered if indicated. The patient should also be informed of the increased risk of infection and bleeding.

Response to treatment should be assessed three months after therapy of Zevalin® using the international guidelines on response criteria. It should be emphasized that quality of response may still be improved beyond three months.

Side Effects:
For side effects (WHO grades 1-2) observed during therapy see **table 3**.

Table 3. Zevalin® therapy: non-haematological adverse events
(Modified from Witzig et al, J Clin Oncol 2003)

Side-effect	**(%)**
asthenia	35
nausea	25
chills	21
fever	13
headache	9
throat irritation	9
abdominal pain	8
dizziness	8
vomiting	7
dyspnea	7
pruritus	7
rash	7
cough	6
ecchymosis	6
flushing	5

Treatment period is the time from the first rituximab infusion to 12 weeks after the ^{90}Y-ibritumomab tiuxetan injection.
Neutropenia, leukopenia, thrombocytopenia not included.

F. Radiopharmaceutical

Approved name: ^{90}Y- ibritumomab tiuxetan or Zevalin®

Table 4. Zevalin®: physical characteristics

Nuclide	Radiopharmaceutical	Half -life	max. ß energy	mean ß energy	Radius of a unit density sphere inside of which 90% of the energy is emitted	Photon yield (E>20 keV)
Y-90	Ibritumomab tiuxetan	2.67 days	2.281 MeV	0.933 MeV	5.3 mm	$<10^{-7}$

Labelling:

Ibritumomab tiuxetan is supplied as a kit containing the non-radioactive components required for generating a single dose of ^{90}Y-labelled ibritumomab tiuxetan. The kit must be stored at 2°-8° C and should not be frozen. Likewise, the preparation of ^{90}Y-ibritumomab tiuxetan is performed at room temperature. After radiolabelling it may be stored at 2°-8° C (in a refrigerator) and protected from light for a maximum of 8 hours.
A bottle with piercable seal contains 3.2 mg (1.6 mg/ml) ibritumomab tiuxetan. The kit also contains: 2 ml sodium acetate solution in a bottle with piercable seal; 10 ml formulated buffer solution in a bottle with piercable seal; and an empty 10 ml reaction vial. The final formulation after radiolabelling contains 2.08 mg ibritumomab tiuxetan in a total volume of 10 ml.

The radioactive component, ^{90}Y, must be obtained separately upon order from the manufacturer. Use only carrier-free ^{90}Y of pharmaceutical grade quality for antibody labelling. Metal contamination has a detrimental effect on the labelling efficiency.

Labelling and preparation of Zevalin® should be performed where appropriate facilities for shielding, calibration and quality control are in place. Training on labelling and calibration is a prerequisite. Labelling must be performed only by qualified personnel with appropriate authorisation for the use and manipulation of radionuclides.

Providing the procedure is strictly adhered to, labelling is straightforward and failures are rare. It is crucial that radiopharmaceutical-grade ^{90}Y is used for antibody labelling, and aseptic technique must be maintained at all stages of preparation. Detailed guidelines on labelling and preparation can be found in the summary of product characteristics.

Before Zevalin® is injected, the administered activity in the 10 mL syringe must be measured using a calibrator.

Use protective shields for needles and containers. Observe local regulations for procedures involving unsealed radioactive sources. Use at least 1 cm-thick perspex or lead-loaded perspex shields during labelling. Use forceps and tongs as gripping tools. Plastic gloves, disposable waterproof gowns, and plexiglass eye protection should be used.

Dosimetry:

Table 5. Organ radiation absorbed dose factors (mGy/MBq) for ^{90}Y, based upon pre-therapeutic ^{111}In imaging
(*Modified from Wiseman et al, Crit Rev Oncol Hematol 2001*)

Organ	Number of Patients	Median	Range
Spleen	166	7.35	0,37-29,70
Liver	179	4.32	0,85-17,55
Lungs	179	2.05	0,59-4,86
Red Marrow (blood derived)	179	0.59	0,09-1,84
Red Marrow (sacrum derived)	179	0.97[1]	
Kidneys[2]	179	0.22	0,00-0,95
Bone surfaces[3]	179	0.53	0,09-1,31
Urinary bladder wall	179	0.89	0,38-2,32
Other organs[45]	179	0.41	0,06-0,62
Total body	179	0.54	0,27-0,78

1. Rescaled according to the ratio of the absorbed doses given by Wiseman (J Nucl Med 2003)
2. The doses to the kidneys were calculated without any correction of the individual patient kidney mass.
3. Dose to the bone surfaces includes contributions from both red marrow and whole-body remainder
4. Includes adrenals, brain, breasts, gall bladder wall, heart wall, lower intestine wall, muscles, pancreas, skin, small intestine, stomach, thymus, thyroid, upper large intestine wall, ovaries and uterus (female patients) or testes (male patients).
5. In some publications the dose to the testes has been reported to be higher. Caution is advised for young male patients.

These organ radiation absorbed doses were assessed using the data of registration trials. They should not be used prospectively to predict the toxicity in an individual patient. Particularly the red marrow absorbed doses are strongly dependent on the quantification method. Should additional data become available these dose estimates will be updated accordingly.
Should a pre-treatment absorbed dose estimate be needed, than the highest absorbed dose values should be used as a conservative estimate.

Quality control:

Labelling efficiency:

- A quality control procedure is mandatory before administration of Zevalin®. Thin layer chromatography is recommended for this purpose. A gamma counter is adequate for measurements.
- A labelling efficiency of 95% or more is required.
- Common sources of error in quality control are: drop size, dead-time error during measurement of the thin layer chromatography strips.

Activity measurement:

- Dose calibrators must have been calibrated using a source of ^{90}Y of known activity and volume before preparing the first patient dose of Zevalin®.
- The same measurement equipment used for the baseline measurement must also be used for subsequent activity measurements; otherwise, recalibration will be necessary.
- Activity measurement must be performed under the appropriate geometric- and volume- and material-specific (plastic needles, glass vials) conditions.

V. Issues requiring further clarification

- The use of Zevalin® in a broader indication area
- Re-treatment
- Myeloablative strategies
- The role of patient dosimetry.

VI. Concise bibliography

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VII. Disclaimer

The European Association of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high quality nuclear medicine procedures. These generic recommendations cannot be rigidly applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.

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