Diagnostic imaging prior to ^{90}Y-ibritumomab tiuxetan (Zevalin®) treatment in follicular non-Hodgkin's lymphoma

Abstract

Add-on treatment of follicular non-Hodgkin's lymphoma (NHL) with yttrium-90 labelled (^{90}Y) ibritumomab tiuxetan (Zevalin®) has become an efficacious asset in standard treatment concepts of this disease. First-line treatment with Zevalin® is currently under way. Whereas in the U.S. and Switzerland a prediagnostic imaging with ^{111}In-ibritumomab tiuxetan is mandatory, in Europe there is no such prerequisite. It is shown in this article why a prediagnostic imaging or dosimetry is not necessary as an additional mandatory safety measure to confirm the expected biodistribution.

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Introduction

The treatment of non-Hodgkin's lymphoma (NHL) has changed since the implementation of immunotherapeutic and especially radiolabelled immunotherapeutic concepts into standard treatment regimens.

Most widely studied and recently approved radiolabelled immunotherapies in NHL are yttrium-90 (^{90}Y) labelled ibritumomab tiuxetan (Zevalin®, Bayer Schering Pharma AG, Berlin, Germany) and iodine-131 labelled (^{131}I) tositumomab (Bexxar™, Corixa, Seattle, WA, and Glaxo Smith Kline, Philadelphia, PA, U.S.A.). Both radiolabelled immunotherapy concepts demonstrate a high level of activity in patients whose CD20+ follicular/low-grade or transformed NHL has failed to respond to chemotherapy and rituximab or who relapsed after initial remission phase. In addition, encouraging results of first-line treatment with Zevalin® (Bayer-Schering 304820 FIT-study: Zevalin® for indolent NHL) were presented at the 49th Annual Meeting of December 2007 of the American Society of Hematology *(ASH)*. Zevalin® has reached market authorization for the U.S. in March 2002 and for Europe in January 2004, while Bexxar™ has been approved only in the U.S. Other but not approved, radiolabelled immunotherapies studied in B-cell NHL by various investigators, comprise: LL2 anti-CD22 conjugated to either ^{131}I or ^{90}Y, Lym-1 HLA-DR conjugated to ^{90}Y or copper-67 (^{67}Cu), rituximab anti-CD20, conjugated to astatin-211 (^{211}At) or rhenium-186 (^{186}Re) and B4 anti-CD19, conjugated to ^{90}Y [1-9].

In the following, the essential question of whether diagnostic imaging with indium-111-In-Zevalin® whole body scintigraphy and single-photon emission tomography (SPET) prior to ^{90}Y-Zevalin® therapy in follicular NHL is necessary, will be addressed. Of course, a routine radiological diagnostic evaluation (as e.g. a CT) will always be necessary and is not part of this question.

Zevalin® studies

The Zevalin® therapeutic regimen (Fig. 1) is completed in 7 days, with two hospital visits. On day 1 patients receive an intravenous (i.v.) infusion of cold anti-CD20 monoclonal antibody (rituximab 250 mg/m^2). On days 7, 8 or 9 they receive a second i.v. infusion of cold anti-CD20 followed by i.v. infusion of ^{90}Y labelled Zevalin®. Dosage of Zevalin® is conveniently based on body weight and platelet count [10, 11] with the following parameters: Fifteen MBq/kg in patients with a platelet count ≥150,000 cells/mm^3 and 11 MBq/kg with a platelet count 100,000-149,000 cells/mm^3. Maximum dose is 1,200 MBq. The Zevalin® therapeutic regimen is not based on dosimetry or imaging. Determination of whole-body clearance by imaging is not required, as it could be shown that there is little interpatient variability and the urinary excretion is low and stable (7% of radioactivity in the first week) [10].

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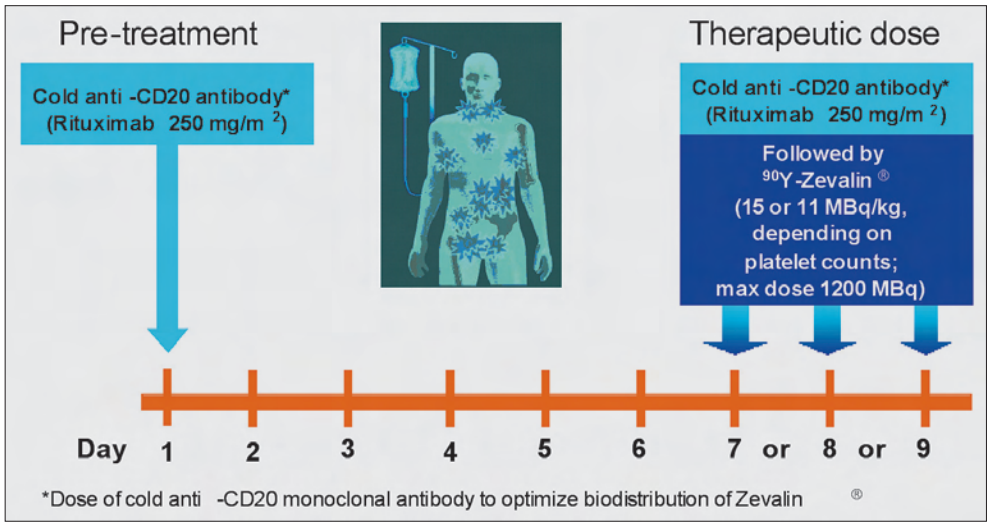

Figure 1. The Zevalin® therapeutic regimen. According to the Summary of Product Characteristics (SmPC), European Medicines Evaluation Agency (EMEA), 2007.

In addition, dosimetry by imaging is not required, as dosimetry in clinical trials has shown no correlation between toxicity and the absorbed dose and all values remained well below the thresholds of 4 Gy for the bone marrow and 20 Gy for other organs [10, 11].

In Europe, Zevalin® gained approval in January 2004 for "the treatment of adult patients with rituximab relapsed or refractory CD20+ follicular B-cell NHL [12]. In Europe, except Switzerland, no dosimetry or pretherapeutic imaging before treatment with ^{111}In Zevalin® is required [13], since in dosimetry studies estimating the radiation absorbed dose from ^{90}Y-Zevalin® treatment to normal organs and bone marrow, it could be shown that there is no hazardous radiation to normal organs and bone marrow [14]. In addition, there was a low variability in pharmacokinetics including elimination with a consistent tumor targeting and a consistent radiation exposure of normal tissue. Finally, the radiation absorbed dose to bone marrow was not predictive of myelotoxicity or efficacy.

Estimated radiation absorbed dose

In Table 1, the estimated radiation absorbed dose to tissues, organs and NHL with standard Zevalin® treatment in a population of 72 patients, is presented [15]. The following conclusions can be drawn from this graph: a) Zevalin® targets the NHL with minimal radiation exposure to healthy tissues and organs. The projected radiation absorbed doses were below the protocol-defined upper limits of 3 Gy to the red marrow and 20 Gy to normal organs. b) Upper ranges for total radiation absorbed (Gy) were: spleen: 19.02, liver: 18.56, lungs: 4.57, bladder wall: 2.70, red marrow: 2.21, kidneys: 0.76 and lymphoma: 242.74.

Table 1. *Estimated radiation absorbed dose to tissues, organs and NHL with standard Zevalin® treatment. Data according to Wiseman et al., 2001 [15].*

Region	Dose (Gy)
Spleen	8.48
Liver	5.32
Lungs	2.15
Bladder wall	0.95
Red marrow	0.71
Kidneys	0.15
Lymphoma	14.84

In a recent dosimetry study from Bischoff-Delaloye et al. (2007) on 69 patients with advanced-stage follicular NHL in the international phase 3 first-line indolent trial (FIT) [16], findings were consistent with the earlier data from Wiseman et al. (2003) [11, 15]. This study confirmed that radiation exposure with Zevalin® treatment is within safe limits to normal organs and that hematologic toxicity does not correlate with red marrow radiation dose estimates [16].

U.S. approved indication for Zevalin®

In the U.S., Zevalin® gained approval already in March 2002 for "the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL, including patients with rituximab refractory follicular NHL [17].

The FDA recommended a mandatory assessment of the biodistribution of Zevalin® with ^{111}In-Zevalin® imaging for safety reasons prior to treatment; a dosimetry was not mandated, however. Until August 2005, the image protocol was as follows: First image 2 to 24 hours after injection, the 2nd image 48 to 72 hours after injection and an optional late image 90 to 120 hours after injection of ^{111}In-Zevalin® [18, 19]. Currently, only one scan at 48 to 72 hours is required in the U.S. [20].

^{111}In-Zevalin® expected biodistribution and imaging

The ^{111}In-Zevalin® expected biodistribution (Table 2) consists of easily detectable uptake in the blood pool that decreases on subsequent scans, moderate to high uptake in uninvolved liver and spleen, and moderately low to very low uptake in uninvolved kidneys, bladder, and bowel. Tumor uptake may be variable, and nonvisualization or poor visualization of tumor uptake is not a reason for not proceeding to the ^{90}Y-Zevalin® therapeutic dose [18, 21].

Table 2. *The expected biodistribution of ^{111}In-Zevalin. Modified according to Spies et al. 2004 [18].*

	Scan 2-24 h (optional)	Scan 48-72 h (mandatory)	Scan 90-120 h (optional)
Tumor	Variable	Variable	Variable
Blood pool	Decreases	Decreases	Present
Kidneys, bladder, bowel	Moderately low to very low	Moderately low to very low	Moderately low to very low
Liver and spleen	Moderately high to high	Moderately high to high	Moderately high to high

Activity should decrease with time (includes large vessels). Tumor visualization not required to assess biodistribution. Note: Normal = uninvolved by tumor.

Table 3. *Altered biodistribution of ^{111}In-Zevalin. Modified according to Spies et al. 2004 [18].*

	Scan 2-24 h (optional)	Scan 48-72 h (mandatory)	Scan 90-120 h (optional)
Blood pool	Not visualized	Not visualized	Not visualized
Kidneys	>Liver in posterior view	>Liver in posterior view	>Liver in posterior view
Bowel	>Liver	>Liver	>Liver
Lungs	Diffuse uptake >Liver	Diffuse uptake >Liver	>Cardiac blood pool

^{111}In-Zevalin® imaging

From the clinical studies undertaken, a diagnostic benefit of ^{111}In-Zevalin® imaging is not evident and also bears the potential to exclude by error, patients from an eventually rescuing treatment.

In addition, in none of the studies from Wiseman et al (2002) and Witzig et al (1999, 2002), unexpected biodistribution or significant organ dysfunction (except hemato-toxicity) was observed [19, 22-24].

Indium-111-Zevalin® imaging remained a mandatory prerequisite of the licensed application in the U.S. and Switzerland, and a postmarketing imaging registry was established to identify cases with potentially altered biodistribution. Data were provided on 953 intent-to-treat patients [20]. Thirty eight cases were identified in this data set who did not initiate Zevalin® treatment. In 22 out of these cases, this decision was made on medical reasons and in 16 it was due to abnormal imaging. In 12 of the latter 16 cases, altered biodistribution was confirmed by central review. In 6 of these, radiolabelling was not performed exactly according to the recommended procedure and after correction of the radiolabelling technique, no altered biodistribution had been observed any more. In the remainder 6 patients (0.6%), altered biodistribution was confirmed by the report of: a) Four cases with prominent bone marrow; b) One case of enhanced renal uptake with insufficient clinical information to explain the aberrant distribution pattern; and c) One case with active pneumonia. Based on this low incidence of altered biodistribution (0.6%), the authors conclude that pretherapeutical imaging may be reduced to a single required scan 2-24 hours post ^{111}In-Zevalin® injection which would have detected all of the observed atypical imaging patterns.

In a critical review of this imaging registry report, only 5 of the 6 aforementioned cases with altered biodistribution were defined as true cases [25]. From these 5 cases, only 2 were correctly selected for radiolabelled immunotherapy according to the official registration guidelines in Europe. This resulting percentage of true altered biodistribution (0.2%) seems to be so small that it can be neglected for a treatment routinely applied in daily practice. Consequently, the reviewers conclude that the very low rate of observed altered distribution does not substantiate the need for a single pretherapeutical ^{111}In-Zevalin® imaging for conventionally dosed ^{90}Y-labelled Zevalin®.

^{111}In-Zevalin® altered biodistribution

Altered biodistribution is rare and if it does occur should be evaluated thoroughly (Table 3). Altered biodistribution will meet these criteria [18, 21]: a) Blood pool not visualized on the first images, indicating rapid clearance of the radiopharmaceutical by the reticuloendothelial system to the liver, spleen, and/or bone marrow. b) Diffuse uptake in normal lung more intense than that in the cardiac blood pool on the first images or more intense than in the liver on the second or third images. c) Kidneys, with greater intensity than the liver on the posterior view of the second or third images. d) Fixed area of uptake throughout the normal bowel, comparable to that in the liver on the second or third images.

In conclusion although in the U.S. setting, the nuclear medicine physician will have to closely work together with the hematologist/oncologist to determine whether to proceed with the therapeutic dose of ^{90}Y-Zevalin® in rare cases of altered biodistribution, in clinical routine Zevalin®, altered biodistribution occurred only rarely. In addition, lack of tumor uptake is not a contraindication to treatment with ^{90}Y-Zevalin®. The above indicate that there is no need for pretreatment ^{111}In-Zevalin® imaging or dosimetry.

"In motley pictures little clarity,
much error and a spark of verity."

Goethe, Faust

Bibliography

1. Juweid ME, Stadtmauer E, Hajjar G et al. Pharmacokinetics, dosimetry, and initial therapeutic results with ^{131}I- and ^{111}In-/^{90}Y-labeled humanized LL2 anti-CD22 monoclonal antibody in patients with relapsed, refractory non-Hodgkin's lymphoma. *Clin Cancer Res* 1999; 5 (10 Suppl): 3292s-3303s.
2. Linden O, Tennvall J, Cavallin-Stahl E et al. Radioimmunotherapy using ^{131}I-labeled anti-CD22 monoclonal antibody (LL2) in patients with previously treated B-cell lymphomas. *Clin Cancer Res* 1999; 5 (10 Suppl): 3287s-3291s.
3. O'Donnell RT, Shen S, Denardo SJ et al. A phase I study of ^{90}Y-2IT-BAD-LYM-1 in patients with non-Hodgkin's lymphoma. *Anticancer Res* 2000; 20: 3647-3655.

4. O'Donnell RT, DeNardo GL, Kukis DL et al. ^{67}Copper-2-iminothiolane-6-[p-(bromoacetamido) benzyl-TETA-Lym-1 for radioimmunotherapy of non-Hodgkin's lymphoma. *Clin Cancer Res* 1999; 5 (10 Suppl): 3330s-3336s.
5. O'Donnell RT, DeNardo GL, Kukis DL et al. A clinical trial of radioimmunotherapy with ^{67}Cu-2IT-BAT-Lym-1 for non-Hodgkin's lymphoma. *J Nucl Med* 1999; 40: 2014-2020.
6. Aurlien E, Larsen RH, Kvalheim G, Bruland OS. Demonstration of highly specific toxicity of the α-emitting radioimmunoconjugate ^{211}At-rituximab against non-Hodgkin's lymphoma cells. *Br J Cancer* 2000; 83: 1375-1379.
7. Ma D, McDevitt MR, Barendswaard E et al. Radioimmunotherapy for model B cell malignancies using ^{90}Y-labeled anti-CD19 and anti-CD20 monoclonal antibodies. *Leukemia* 2002; 16: 60-66.
8. DeNardo GL, DeNardo SJ, Goldstein DS et al. Maximum-tolerated dose, toxicity, and efficacy of ^{131}I-Lym-1 antibody for fractionated radioimmunotherapy of non-Hodgkin's lymphoma. *J Clin Oncol* 1998; 16: 3246-3256.
9. Knop S, Jakob A, Kanz L et al. ^{186}Rhenium-labeled anti-CD20 antibody radioimmunotherapy followed by autologous peripheral blood stem cell transplantation in patients with relapsed or refractory non-Hodgkin lymphoma (letter). *Blood* 2004; 103: 1175.
10. Wagner HN Jr, Wiseman GA, Marcus CS et al. Administration guidelines for radioimmunotherapy of non-Hodgkin's lymphoma with ^{90}Y-labeled anti-CD20 monoclonal antibody. *J Nucl Med* 2002; 43: 267-272.
11. Wiseman GA, Kornmehl E, Leigh B et al. Radiation dosimetry results and safety correlations from ^{90}Y-ibritumomab tiuxetan radioimmunotherapy for relapsed or refractory non-Hodgkin's lymphoma: combined data from 4 clinical trials. *J Nucl Med* 2003; 44: 465-474.
12. Hagenbeek A, Lewington V. Report of a European consensus workshop to develop recommendations for the optimal use of (90)Y-ibritumomab tiuxetan (Zevalin) in lymphoma. *Ann Oncol* 2005; 16: 786-792.
13. Tennvall J, Fischer M, Bischof Delalye A et al. EANM procedure guideline for radio-immunotherapy for B-cell lymphoma with ^{90}Y-radiolabelled ibritumomab tiuxetan (Zevalin). *Eur J Nucl Med Mol Imaging* 2007; 34: 616-622.
14. Wiseman GA, White CA, Stabin M et al. Phase I/II ^{90}Y-Zevalin (yttrium-90 ibritumomab tiuxetan, IDEC-Y2B8) radioimmunotherapy dosimetry results in relapsed or refractory non-Hodgkin's lymphoma. *Eur J Nucl Med* 2000; 27: 766-777.
15. Wiseman GA, White CA, Sparks RB et al. Biodistribution and dosimetry results from a phase III prospectively randomized controlled trial of Zevalin" radioimmunotherapy for low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *Crit Rev Oncol Hematol* 2001; 39: 181-194.
16. Bischof Delalye A, Antonescu C, Hagenbeck A. Dosimetric analysis of ^{90}Y-ibritumomab tiuxetan (Zevalin$^{\beta}$) given as consolidation of first remission in patients with advanced-stage follicular lymphoma in the international phase 3 first-line indolent trial (FIT) (Abstr). *Blood* 2007; in press.
17. Karagiannis TC. Radioimmunotherapy: Principles, current trends and future directions. *Hell J Nucl Med* 2004; 7: 39-43.
18. Spies SM. Imaging and dosing in radioimmunotherapy with yttrium 90 ibritumomab tiuxetan (Zevalin). *Semin Nucl Med* 2004; 34 (suppl. 1): 10-13.
19. Witzig TE, White CA, Wiseman GA et al. Phase I/II trial of IDEC-Y2B8 radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin's lymphoma. *J Clin Oncol.* 1999; 17: 3793-3803.
20. Conti PE, White C, Pieslor P et al. The role of imaging with ^{111}In-ibritumomab tiuxetan in the ibritumomab tiuxetan (Zevalin) regimen: Results from a Zevalin imaging registry. *J Nucl Med* 2005; 46: 1812-1818.
21. Zevalin (ibritumomab tiuxetan) prescribing information. Cambridge MA, Biogen Idec Inc, 2002.
22. Wiseman GA, Gordon LI, Multani PS et al. Ibritumomab tiuxetan radioimmunotherapy for patients with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia: a phase II multicenter trial. *Blood* 2002; 99: 4336-4342.
23. Witzig TE, Gordon LI, Cabanillas F et al. Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. *J Clin Oncol* 2002; 20: 2453-2463.
24. Witzig TE, Flinn IW, Gordon LI et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; 20: 3262-3269.
25. Bischof Delaloye A, Dreyling M. Critical evaluation of Zevalin" (ibritumomab tiuxetan) imaging registry report (27 March 2002 – 31 March 2003). *Bayer Schering Pharma AG, Berlin, Germany, on file*; 1-8.

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