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IODINE-131-RITUXIMAB RADIOIMMUNOTHERAPY FOR NON-HODGKIN'S LYMPHOMA

HEALTH TECHNOLOGY ASSESSMENT SECTION
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

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DISCLOSURE

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EXECUTIVE SUMMARY

Background

Cancer is one of the most common non-communicable diseases in Malaysia and contributed to 13.56% of all deaths in the Ministry of Health Hospital in 2015. The five leading cancers among population of Malaysia in 2007 to 2011 were breast (17.7%), colorectal (13.2%), lung (10.2%), lymphoma (5.2%) and nasopharynx (4.9%).

Non-Hodgkin's lymphoma (NHL) is the main type of lymphoma which comprises a heterogonous group of B-cell or T-cell malignancies with a wide range of aggressiveness. Non-Hodgkin's lymphoma may be indolent (slow growing) or aggressive (fast growing). The most common types of NHL in adults are diffuse large B-cell lymphoma (DLBCL), which is usually aggressive, and follicular lymphoma (FL), which is usually indolent.

Rituximab, an anti-CD20 monoclonal antibody has favourably improved the outcomes of patients with NHL, particularly those with DLBCL and FL. Radioimmunotherapy (RIT) with Iodine-131-rituximab (I-131-rituximab) has been shown as a more effective treatment compared to treatment with rituximab alone. There are two commercially RIT agents approved by United State Food and Drug Administration (US FDA); ibritumomab tiuxetan (Zevalin®) which delivers yttrium-90 (Y-90) and tositumomab (Bexxar®), which delivers iodine-131 (I-131). Iodine-131-tositumomab has been withdrawn from the market in 2014 due to dramatic decline in its used. Both Y-90 and I-131 are beta emitters, but I-131 is much more accessible and cheaper in Malaysia and has longer life compared to Y-90. Ibritumomab and tositumomab are both murine anti-CD20 monoclonal antibody, but it is not available in Malaysia. Rituximab is more accessible in Malaysia and there are established methods available for self-labelling of I-131-rituximab with lower cost compared to the commercial Zevalin® and Bexxar®.

Hence, this technology review was requested by Nuclear Medicine Specialist, Ministry of Health Malaysia to review the safety and efficacy of I-131-rituximab RIT in patients with NHL.

Objective/aim

To assess the safety, effectiveness, cost-effectiveness of I-131-rituximab RIT in patients with NHL.

Results and conclusions

A total of 323 titles were identified through the Ovid interface and PubMed. There were fourteen articles included in this review; two cohort studies and twelve clinical trials.

- **Effectiveness**
  There was limited fair level of retrievable evidence to suggest that I-131-rituximab RIT was effective as a first line treatment for NHL. Evidence demonstrated that I-131-rituximab RIT was effective for newly diagnosed, advanced stage, symptomatic follicular NHL. The overall response rate (ORR) at three months was 99% with 88% achieving Deauville category 1 to 3.

  There was fair level of retrievable evidence that showed I-131-rituximab RIT was effective for treatment of relapsed or refractory NHL. However, the response rate and median survival rate varies greatly. The ORR range from 29% to 97%, complete response (CR) range from 12.5% to 77%, and partial response (PR) range from 17% to 29%. The median overall survivor range from 11.3 months to 87 months while the median progression free survival (PFS) range from 13 months to 71 months. It seems to be more effective for indolent NHL compared to aggressive NHL.

  Evidence also suggest that I-131-rituximab RIT was effective when used as repeated treatment for patients with relapsed or refractory NHL including those with aggressive NHL. It was also effective when used as combination treatment for NHL with longer PFS.

  However, there was no study retrieved comparing the effectiveness of I-131-rituximab with other established RIT like Y-90-ibritumomab and I-131-tositumomab.

- **Safety**
  There was fair level of retrievable evidence to suggest that treatment using I-131-rituximab NHL was safe and tolerable. However, most common toxicity reported was grade III or IV haematological toxicities and hypothyroidism. Combination of I-131-rituximab RIT and high dose chemotherapy increased the toxicity. There was one treatment related mortality (5%) which occurred in patient treated with I-131-rituximab RIT plus high dose chemotherapy. A study reported that radiation exposure to carers and family members of outpatients undergoing I-131-rituximab RIT were compliance with international guidelines.

- **Cost effectiveness**
  There was no retrievable evidence on the cost-effectiveness of I-131-rituximab RIT for NHL. The estimated cost of a self-labelled I-131-rituximab RIT per patient was RM 23997.72.

Methods

Electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present, EMBASE – 1996 to November 2016, EBM Reviews - Cochrane Central

Register of Controlled Trials - November 2016, EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to November 2016, EBM Reviews - Health Technology Assessment – 4th Quarter 2016, EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2015. Searches were also run in PubMed. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 30th November 2016.

IODINE-131-RITUXIMAB RADIOIMMUNOTHERAPY FOR NON-HODGKIN'S LYMPHOMA

1. BACKGROUND

Cancer is one of the most common non-communicable diseases in Malaysia and contributed to 13.56% of all deaths in the Ministry of Health Hospitals in 2015.[1] The five leading cancers among population of Malaysia in 2007 to 2011 were breast (17.7%), colorectal (13.2%), lung (10.2%), lymphoma (5.2%) and nasopharynx (4.9%).[2]

Lymphoma has been identified as the fourth most common cancer among males and general population. Non-Hodgkin's lymphoma (NHL) is the main type of lymphoma which comprises a heterogonous group of B-cell or T-cell malignancies with a wide range of aggressiveness. Non-Hodgkin's lymphoma may be indolent (slow growing) or aggressive (fast growing). The most common types of NHL in adults are diffuse large B-cell lymphoma (DLBCL), which is usually aggressive, and follicular lymphoma (FL), which is usually indolent. There were 5,374 cases of lymphoma diagnosed in 2007 to 2011 and registered at National Cancer Registry (NCR), comprising of 3,171 males and 2,203 females. The Age Standardised Rates (ASR) for males was 5.5 per 100,000 population and 3.8 per 100,000 populations for females.[2,3]

Radioimmunotherapy (RIT) is a combination of radiation therapy and immunotherapy used to treat non-Hodgkin B-cell lymphoma and other types of cancer. Radioimmunotherapy uses engineered monoclonal antibodies paired with radioactive materials called radiotracers. When injected into the patient's bloodstream, they bind to cancer cells and deliver a high dose of radiation directly to the tumour.[4] Study done by Ahmed et al. (2010) has shown that RIT is a safe and effective treatment for patients with relapsed or refractory indolent NHL.

Rituximab, an anti-CD20 monoclonal antibody has favourably improved the outcomes of patients with NHL, particularly those with DLBCL and FL. The addition of rituximab on chemotherapy significantly improve the overall response rate (ORR) and survival when given at diagnosis and relapse.[5] Rituximab is ideal for RIT because it is easily iodinated and CD20 antigen is found on more than 95% of B-cell NHL.[6]

There are two commercially RIT agents approved by United State Food and Drug Administration (US FDA); ibritumomab tiuxetan (Zevalin®) which delivers yttrium-90 (Y-90) and tositumomab (Bexxar®), which delivers iodine-131 (I-131). Iodine-131-tositumomab has been withdrawn from the market in 2014 due to dramatic decline in its use.[6] Both Y-90 and I-131 are beta emitters, but I-131 is much more accessible and cheaper in Malaysia and has longer life compared to Y-90. Ibritumomab and tositumomab are both murine anti-CD20

monoclonal antibody, but it is not available in Malaysia. Rituximab is more accessible in Malaysia and there are established methods available for self-labelling of I-131-rituximab with lower cost compared to the commercial Zevalin® and Bexxar®.[7]

Hence, this technology review was requested by Nuclear Medicine Specialist, Ministry of Health Malaysia to review the safety and efficacy of I-131-rituximab RIT in patients with NHL.

2. OBJECTIVE / AIM

To assess the safety, effectiveness, cost-effectiveness of I-131-rituximab RIT in patients with NHL.

3. TECHNICAL FEATURES

3.1. Radiochemistry of I-131-rituximab

Rituximab is a genetically engineered monoclonal immunoglobulin G1-subclass monoclonal antibody that targets a protein called CD20, which is found on the surface of white blood cells called B-lymphocytes (B-cells). CD20 can be found on normal B-cells or malignant B-cells that occur in many types of NHL. Rituximab will bind to CD20 and triggers the body's immune system to attack the cell and destroy them. It was approved for treatment of relapsed or refractory low grade or follicular CD20 positive B cell NHL. [8,9]

Iodine-131 was chosen as the therapeutic nuclide because of its gamma emission that can be used for external gamma-camera imaging and dosimetry. Its beta emission has a lower energy and a shorter range compared with other beta emitters, such as Y-90 and therefore, may be more appropriate in the setting of minimal residual disease.[8]

3.2. Radiolabeling of I-131-rituximab

There are two established methods in radiolabeling of rituximab; Chloramine T method and Iodogen method.

3.2.1. Chloramine T method

Chloramine T (N-chloro-4-methylbenzenesulfonamide sodium salt) is a mild oxidizing agent which causes oxidation of radioiodine and enables covalent binding of the halogen to the monoclonal antibody. The radiohalogen is oxidized to reactive species, which attacks the most electronegative site on the antibody. The oxidation is stopped after a brief period of time by addition of reducing agent.[7]

3.2.2. Iodogen method

A water-insoluble oxidizing agent Iodogen (1,3,4,6-tetrachloro-3α,6α-diphenyl glycoluril) which can limit protein damage due to oxidation during radiolabeling, is dissolved in an organic solvent and is coated in the walls of glass reaction tube. Radiolabeling is then initiated by the addition of

protein and carrier-free sodium iodide-131 (Na I-131) in aqueous solution. After a set time, the process is stopped by removal of the reaction mixture.[10]

3.3. Dosimetry

Reliable dosimetry may minimise toxicity and improve treatment efficacy. It has been found experimentally that a mean prescribed dose (MPD) of 0.75 Gray (Gy) to whole body, when applied to I-131-anti-CD20 RIT of NHL, causes only modest and self-limited myelotoxicity.[11]

The protocol for determining the therapy activity of I-131-rituximab delivering the MPD of 0.75 Gy to whole body was developed at the University of Michigan. A tracer activity of 200 megabecquerel (MBq) I-131-rituximab was administered intravenously following a full immunotherapeutic loading dose of 375 mg/m^2 unlabeled rituximab. Whole body imaging and background scans were acquired on a dual-head camera, in the same geometry at one hour, three and five days respectively. The residence time was calculated by plotting the geometric mean counts at the three time points. An automated EXCEL work sheet facilitated calculation of residence time in hours. The amount of therapeutic I-131-rituximab activity to be administered within the limit of 0.75 Gy prescribed dose to whole body was then computed and administered to the patient after an additional 375 mg/m^2 loading dose of unlabeled rituximab.[9]

4. METHODS

4.1. Searching

Electronic databases were searched through the Ovid interface:

- Ovid MEDLINE® In-process and other Non-indexed citations and Ovid MEDLINE® 1946 to present
- EMBASE – 1996 to November 2016
- EBM Reviews - Cochrane Central Register of Controlled Trials – November 2016
- EBM Reviews - Cochrane Database of Systematic Reviews - 2005 to November 2016
- EBM Reviews - Health Technology Assessment – 4th Quarter 2016
- EBM Reviews – NHS Economic Evaluation Database 1st Quarter 2015

Searches were also run in PubMed. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 30 November 2016.

Appendix 1 shows the detailed search strategies.

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full text articles for final article selection.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patients with Non-Hodgkin's lymphoma
Interventions	Iodine-131-rituximab radioimmunotherapy
Comparators	Yttrium-90-ibritumomab/Iodine-131-tositumomab/no comparator
Outcomes	Overall response rate, complete response, progression-free survival, overall survival, adverse events, complications, economic implication (cost-effectiveness, cost-utility, cost-analysis), organization.
Study design	Health Technology Assessment (HTA) reports, Systematic review (SR) and Meta-analyses, Randomized Controlled Trials (RCT), Non-randomized controlled trials (NRCT), cohort studies, cross-sectional studies, case control studies, case series.

Exclusion criteria

Study design	Studies conducted in animals, narrative reviews, case reports
	Non English full text articles

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and graded according to US/Canadian preventive services task force (Appendix 2). Data were extracted and summarised in evidence table as in Appendix 3.

5. RESULTS AND DISCUSSION

A total of 323 titles were identified through the Ovid interface and PubMed. There were fourteen articles included in this review; two cohort studies and twelve clinical trials. However, there was no retrievable evidence from the scientific databases on cost-effectiveness of this technology. The studies retrieved and included in this review were conducted in Western Australia, Germany, South Korea and Malaysia.

5.1. EFFICACY / EFFECTIVENESS

5.1.1. *First line treatment for NHL*

McQuillan et al. conducted a multicentre, phase II clinical trial to determine the safety, efficacy and durability of response of I-131-rituximab in the first line treatment of newly diagnosed patients with advanced, symptomatic follicular NHL. Between April 2006 and September 2013, 68 patients (aged 31 to 89 years) from five institutions in Western Australia were enrolled in INITIAL study (Indolent Non-Hodgkin Immunoradio-therapy Initiated Approach in Lymphoma). Fifty-one patients (75%) had stage III or IV disease and 50 patients (74%) had intermediate or high risk baseline Follicular Lymphoma International Prognostic Index (FLIPI) score. Bulky disease was present in six patients (9%) and bone marrow involvement was identified in 18 (25%) patients. All patients received four cycles of 375mg/m^2 rituximab at weekly intervals prior to treatment. Radioimmunotherapy with I-131-rituximab on an outpatient basis was given according to the standard personalised dosimetry protocol predicated on a whole body radiation absorption dose of 0.75 Gy. All patients were followed up to seven years. Patients who achieved standard response received maintenance therapy for one year. Baseline and three-month ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging which was analyzed according to Lymphoma Deauville five-point scale was used to evaluate response and predict prognosis. The overall response rate (ORR) for three months was 99%, with 88% achieving Deauville category 1 to 3. Fifty six patients (82%) achieved a complete response (CR), 11 patients (16%) achieved a partial response (PR), and one patient (1%) had progressive disease (PD). These satisfactory responders did not reach median time-to-next-treatment, versus a median of 29 months for a category 4 to 5 response ($p<0.0001$). This study suggested that I-131-rituximab RIT in newly diagnosed, advanced stage, symptomatic follicular NHL is an effective, practical and affordable alternative to existing conventional chemotherapies, with lower toxicity and durable remissions.[12, level II-2]

5.1.2. *Treatment for relapsed or refractory NHL*

Turner et al. conducted a phase II clinical trial to develop and evaluate a safe, reliable, efficacious, and relatively inexpensive practical approach to widen the availability of RIT for patients with relapsed or refractory low grade NHL. Forty-two patients who had been heavily pre-treated with chemotherapy and therapeutic regimen were enrolled in this study. Eighty percent of patients had relapsed low grade NHL; small lymphocytic lymphoma and follicular lymphoma grade 1 and 2, and 20% of patients had relapsed intermediate grade lymphoma; follicular lymphoma grade 3 and mantle cell lymphoma. All patients received therapeutic loading doses of unlabeled rituximab (375 mg/m^2) immediately prior to administration of tracer (200 MBq I-131) or therapy (1.7 to 4.3 GBq I-131) activities of I-131-rituximab to provide additive immunotherapy and enhance tumor uptake of the

radiolabeled antibody. Radiolabeling of rituximab was done by using modification of standard Chloramine T method with a semi automated remote controlled shielded kit system in a hospital radiopharmacy. The ORR was 71% in 35 patients with a median follow up of 14 months (range 4 to 28 months). Nineteen patients (54%) achieved CR, with median duration of 20 months. Partial response was observed in six patients (17%) with median duration of eight months. The overall survival (OS) at 25 months were 66% and the progression- free survival (PFS) were 29% at median duration of 14 months. The authors suggested that rituximab can be safely, reliably, effectively, and inexpensively radiolabeled with therapeutic activities of iodine-131 for treatment of NHL.[9, level II-2]

Leahy et al. (2006) conducted a multicentre, phase II clinical trial between May 2000 and December 2004 at Fremantle Hospital, Western Australia. Ninety-one patients aged between 30 and 84 years old with relapsed (n=76) or refractory (n=15) follicular, mucosa-associated lymphoid tissue (MALT)/marginal zone, or small lymphocytic NHL were entered into this study. In-house radioiodination of ritixumab was done by using chloramines T method. After a standard loading dose of rituximab 375 mg/m^2, individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. The administered therapeutic activities ranged from 1.36 to 5.34 GBq. The referring physicians had discretion to prescribe a standard four-dose once weekly regimen of 375 mg/m^2 rituximab in conjunction with RIT. Thus 59 patients received two additional dose rituximab during the two weeks after tracer and therapeutic administration. The remaining patients received two-dose rituximab on the days of the tracer and therapeutic doses of 131-I-rituximab. The ORR was observed in 69 patients (76%), with 53% attaining a CR or CR unconfirmed (CRu). Median duration of response for patients achieving CR or CRu was 20 versus seven months for those with a PR (p=0.121). The median PFS was 13 months, with 14% remaining relapse free beyond four years. Median follow-up was 23 months, with a four year actuarial survival rate of 57% ± 10%. There is no significant different between patients receiving two or four doses of unlabelled rituximab. The authors concluded that I-131-rituximab RIT for patients with relapsed or refractory indolent NHL is safe and effective.[13, level II-2]

Leahy et al. (2011) reported a ten year, single centre clinical trial with I-131-rituximab for relapsed or refractory indolent NHL. All 142 patients selected had relapsed lymphoma and comprised follicular (107 patients), mantle (eight patients), mucosa-associated lymphoid tissue (six patients), and small lymphocytic lymphoma (21 patients). The first 66 patients were taken from the previous study[14] to provide information regarding long-term follow up of I-131-rituximab. Another 76 patients were enrolled later and were treated as outpatients with the same clinical protocol. All patients received the standard

four-dose once-weekly regimen of 375 mg/m^2 rituximab, with the tracer dose of I-131-rituximab given on week one and the therapy dose on week two. Two further doses of unlabelled rituximab were administered on weeks three and four. The ORR was observed in 97 patients (68%) with CR in 50% of patients. The median OS was 87 months (range 1 to 131). The median PFS for all responding patients and those with stable disease was 39 months (range 3 to 108), and for patients in CR/CRu, median PFS was 63 months. Prior rituximab therapy made no statistical different to ORR, but was associated with a significant reduced CR/CRu (p=0.001) rate. The authors suggested that RIT with I-131-rituximab in routine clinical outpatient practice provides cost effective, safe treatment of relapsed or refractory indolent NHL, with half of patients achieving durable, complete remission with potential for repeat RIT on relapse.[14, level II-2]

Kang et al. (2011) conducted a phase II clinical trial to evaluate the safety and efficacy of RIT I-131-rituximab for treating Korean patients with relapsed or refractory B-cell NHL. Between May 2004 and October 2006, 24 patients aged 34 to 73 years old received a single treatment of I-131-rituximab. All patients selected had diffuse large B-cell lymphoma (DLBCL) (11 patients) and low grade B-cell NHL (LGL) (13 patients). All patients received unlabeled ritixumab (70mg) immediately prior to the administration of a therapeutic dose of I-131-rituximab. A dose of 200 mCi of radioiodide was chosen as a fixed dose. Iodination of the antibody was done using Iodo-Beads. The ORR was observed in seven patients (29%), 46% patients with LGL have three CR and three PR, and 9% of patients with DLBCL have one PR. There was a statistically significant different of response between patients with LGL and the patients with DLBCL (46% versus 9%, p=0.049). The median response duration was 2.9 months (range 1.1 to 64.9 months). After a median follow-up of 55.1 months (range 31.5 to 69.3 months), the median PFS for all patients was 2.2 months (95% CI 1.1, 3.3 months). The median OS was 11.3 months (95% CI 0.8, 21.8 months) with a 3-year survival rate of 21%. There was a statistically significant different between the LGL and DLBCL for the median PFS (4.5 months versus 1.3 months, p=0.0007). The authors concluded that RIT with I-131-rituximab seems to be effective and tolerable for patients with refractory LGL, although this treatment had modest activity in patients with refractory DLBCL.[15, level II-3]

Bienert et al. conducted an uncontrolled clinical trial to evaluate the safety, toxicity and therapeutic response of RIT using I-131-rituximab in previously heavily treated patients with B-cell NHL. Between March 2001 and December 2003, nine patients aged 31 to 74 years were treated with RIT. All patients had progressive or recurrent disease and multiple prior chemotherapies or radiotherapies. Four patients have DLBCL and five patients have LGL. Eight of nine patients progressed upon immunotherapy with rituximab, two of four patients with mantle cell lymphomas (MCL) received RIT for consolidation after salvage therapy. Rituximab was labelled

with I-131 using the Iodogen method. The administered activity (2200±600 MBq) was based on a dosimetrically calculated 45 cGy total body radiation dose. All patients received an intravenous infusion of 2.5mg/kg of rituximab seven to 14 days prior to RIT. Three out of nine (33%) patients responded, one patient (11%) with DLBCL achieved CR ongoing at 14 months and two patients (22%) with FL and MCL achieved PR progressing at 12 and 13 months after treatment. One partial responder was re-treated with RIT and achieved an additional progression-free interval of seven months. Of two patients who received RIT as an additional treatment after salvage chemotherapy, one continues to be disease free at nine months and one relapsed at five months' follow-up. The authors suggested that RIT with I-131-rituximab in previously heavily treated B-cell NHL patients was safe and well tolerated. Radioimmunotherapy was less efficient in patients with bulky disease and elevated serum lactate dehydrogenase (LDH).[16, level II-2]

Kruger et al. (2014) conducted a non-randomised, uncontrolled clinical trial to evaluate the response and toxicity after long term follow-up of I-131-rituximab RIT in patients with follicular lymphoma under the routine clinical care of a single haematologist over a period of 12 years. Between 2001 and 2013, 31 patients aged between 30 to 74 years were enrolled into this study. All patients received 131-I-rituximab RIT according to a standard, personalized dosimetry protocol predicated upon a prescribed whole body radiation absorbed dose of 0.75Gy. Four doses of maintenance rituximab were subsequently administered over 12 months. Response rate was 97% with 24 patients (77%) experiencing CR confirmed on 18F-FDG-PET-CT and 4 patients (13%) experienced PR. The PFS was 71 months (range 6 to 152) and median OS has not been reached after a median follow up of 65 months. The authors stated that durable control of FL by I-131-rituximab RIT is achievable without significant toxicity in non-selected patients, including those pre-treated with chemotherapy.[17,level II-2]

Kuan et al. conducted an uncontrolled clinical trial and report a pioneer experience in Malaysia on self-labelling I-131-rituximab. Seven patients aged between 26 and 62 years with relapsed or refractory CD20+ indolent or aggressive NHL were selected. Four patients had DLBCL, two patients had FL and one patient had Primary Mediastinal (thymic) Large B-cell Lymphoma (PMBL). Prior to dosimetry studies and therapy, desired activity of I-131-rituximab was administered intravenously following a loading dose of 375 mg/m^2 unlabelled rituximab. In house radiolabeling was done using Chloramine T method. Five patients (71%) achieved CR and two patients (29%) achieved PR three to four months after treatment. Two patients (29%) with refractory disease achieved CR/PR after the treatment. One patient achieved CR after second relapse. Of the remaining four patients who developed PR after first line treatment, three achieved a CR and one achieved a PR.[7, level II-3]

5.1.3. *Repeat treatment for relapsed or refractory NHL*

Bishton et al. conducted a retrospective cohort study to examine the short- and long-term effects of a second treatment with I-131-rituximab in patients with indolent B-cell NHL following a relapse. Two institutional databases from January 2000 to July 2007 for retreatment of I-131-rituximab were analyzed. Response duration following first and second treatment and haematological toxicity were compared. Sixteen patients who had received a second course of I-131-rituximab were identified. Fifteen of the patients had FL and one patient had MCL. Fourteen of 16 (87.5%) patients responded with nine (64%) had CR, with a median duration of 10.5 months in responders. Following the first treatment, 11 (69%) of these patients had achieved a CR, while the median time to progression (TTP) was 14 months (p=0.96 compared with duration of second response, 10.5 months). Six of 13 reresponders had the same or a longer response and six more remain in CR. The median event-free survival was not significantly different for the two treatments. The actuarial PFS rate at 12 months was 36% for repeat treatment patients. The study suggested that retreatment with I-131-rituximab is an efficacious and safe option for patients who have responded previously to I-131-rituximab, with the duration of second or subsequent responses often exceeding the first response.[18, level II-2]

Following his study in 2011, Kang et al. conducted another phase II clinical trial to investigate whether repeated treatment with I-131-rituximab could improve the response. Between July 2005 and February 2012, 31 patients received repeated treatment of I-131-rituximab using the same RIT protocol in the previous study. All patients selected had MCL (12 patients), DLBCL (seven patients), marginal zone B cell lymphoma (six patients), FL (four patients), Burkitt's lymphoma (one patient), and small lymphocytic lymphoma (one patient). The ORR was observed in 21 (68%) of patients which showed a two-fold increase compared to single treatment in the previous study. The median response duration was 8.6 months which shown a three-fold increased compared to single treatment. After a median follow-up of 21.8 months (range 1.6-79.7 months), the median PFS for all patients was 9.8 months (95% CI 7.9, 11.7 months). The median OS was 48.2 months (95% CI 41.7, 54.7 months) with a five year survival rate of 42%. Compared to a single treatment, repeated RIT with I-131-rituximab increased the response rate and duration for patients with relapsed or refractory B cell NHL, including those with aggressive histology.[19, level II-2]

Another clinical trial conducted by Leahy et al. (2011) reported a relapse in 16 patients after RIT and they received a second course of I-131-rituximab. The ORR was 94% (15), CR/CRu was achieved in 69% (11) of patients, PR in 25% (16) and one patient had stable disease after the initial RIT. Ten of these 16 repeat treatment patients subsequently achieved a second response with ORR in 63% of patients.[15, level II-3]

5.1.4. *Combination treatment for NHL*

Kruger et al. conducted a phase II clinical trial to investigate the response and toxicity of I-131-rituximab with carmustine, etoposide, cytarabine, and mephalan (BEAM) conditioning regimen in autologous stem cell transplantation (ASCT) for NHL. Sixteen patients aged between 34 and 71 years were entered into this study. Seven of the patients had DLBCL, six patients had MCL, three patients had aggressive FL, and one patient had MALT. Radioimmunotherapy with I-131-rituximab on an outpatient basis was given on day -15 before ASCT. The BEAM conditioning regimen was commenced on day -6. Evaluable engraftment data were available for 15 patients who had 16 ASCTs. Engraftment was achieved in all patients, 15 (94%) ASCTs achieved a CR, and one ASCTs achieved a PR. At a median follow up of 44 months (range 4 to 108 months) post-ASCT, 12 patients were alive, nine remain in remission, four patients have relapsed and needing subsequent treatment and four patients died. Progression-free survival for patients with DLBCL was longer compared to patients with other histological type [median PFS not reached (range 6 to 77 months) versus 4 months (range 3 to 5 months)]. Progression- free survival for patients with DLBCL was longer compared to patients with aggressive or transformed follicular lymphoma (median PFS not reached versus 4 months, p=0.0039). This study suggests that the addition of I-131-rituximab RIT to BEAM conditioning, before ASCT, for relapsed or primary refractory B-cell NHL improves disease eradication, compared with BEAM conditioning alone, without significant additional toxicity.[20, level II-3]

A phase I/II clinical trial was conducted by Wagner et al. to evaluate a tandem therapy approach comprising myeloablative RIT with I-131-rituximab followed by high dose chemotherapy with ASCT in heavily pre-treated patients with relapsed or refractory B-cell NHL. Twenty three patients aged between 31 to 67 years were enrolled into this study. All patients selected had indolent lymphoma (65%), aggressive lymphoma (13%) and MCL (22%). Biodistribution and dosimetric studies were performed to determine I-131 activity required to induce a total body dose of 21 to 27 Gy to critical organs. All patients received therapeutic infusion of radiolabelled rituximab (40mg rituximab). Six of 23 patients RIT were combined with high dose chemotherapy EAM. Eight of 23 patients received a sequential high-dose chemotherapy (BEAM protocol) followed by second ASCT. The ORR was 87% with 64% of patients achieving CR (14/22) and 23% (5/22) achieving a PR. Complete response rate was higher in tandem therapy group compared to RIT alone (33% versus 75%). The median PFS and OS were 47.5 and 101.5 months respectively, with a median follow-up of 9.5 years (range 6.2 to 12.2 years). There was no significant difference between RIT and RIT in combination with high dose chemotherapy with or without a second ASCT in improving PFS and OS. The long term outcome with regard to OS was 43% of patients (10/23) being alive and 39% (9/23) still in CR after a median follow-up of 9.5 years. The authors concluded that myeloablative RIT with I-

131-rituximab followed by ASCT is feasible, well tolerated and effective in high risk B-cell NHL.[21, level II-3]

Shin et al. conducted a phase II clinical trial to investigate the efficacy and safety of I-131-rituximab as consolidation therapy after standard combination chemotherapy or R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone) in patients with DLBCL. Sixteen patients aged between 50 and 73 years who had advanced or bulky staged DLBCL and achieved CR or PR after six to eight cycles of R-CHOP were enrolled. All patients received a single dose of I-131-rituximab after the completion of six or eight cycles of R-CHOP. Six (38%) patients achieved CR after three cycles of R-CHOP, and another nine (56%) patients further achieved CR after the completion of six or eight cycles of R-CHOP. Two-year relapse free survival was 88%, and 5-year relapse free survival was 81%. The authors concluded that I-131-rituximab showed promising efficacy as consolidation treatment for patients with DLBCL.[22, level II-3]

5.2. SAFETY

Calais and Turner conducted a prospective cohort study to establish the safety of outpatient I-131-Rituximab RIT by measuring the radiation exposure of hospital staff, carers, and members of the public and by estimating the environmental impact of radioactive urinary excretion. Two hundred consecutive outpatients undergoing I-131-rituximab RIT of NHL with personalized prescribed dosimetry were studied. After administration of I-131-rituximab therapy (therapeutic activities between 1 and 4.5 GBq), patients were required to remain at home for one week. Carers and cohabitants of patients were issued with thermoluminescent dosimeter (TLC) badges to measure the exposure rate. Carer was requested to provide one badge for visitors to share, thus giving a ‘cumulative visitor’ reading. For the first 100 patients, the entire urine output for seven days after therapy and was collected for return and disposal. After one week, the patients were visited by physicist at home, the exposure rate of one meter was measured, and the TLC badges were collected. Mean radiation exposure of adult carers was 0.49 mSv (range, 0.01 to 3.67 mSv). To other co residing family members, mean exposure was 0.23 mSv (range, <0.01 to 1.20 mSv), and for visitors sharing badges, the mean exposure was 0.17 mSv (range, <0.01 to 0.73 mSv). Urinary activity excreted over the week after I-131-rituximab therapy was typically less than 25% of the administered activity. Mild transient myelosuppression was observed in all patients, and in 10% there was grade IV toxicity with respect to platelet and neutrophils count. The authors concluded that I-131-Rituximab RIT for NHL maybe safely administered on an outpatient basis. The median radiation exposure of carers, cohabitants of the patients and visitors was well within the limits recommended by international guidelines. Local regulatory agency-designated patient release rate limit of less than 25 μSv/h at one meter was attained within one week of therapeutic I-131-Rituximab administration.[23, level II-2]

5.2.1. *First line treatment for NHL*

McQuillan et al. conducted a multicentre, phase II clinical trial to determine the safety of I-131-rituximab RIT in the first line treatment of newly diagnosed patients with advanced, symptomatic follicular NHL. A total of 68 patients with follicular lymphoma were followed up to seven years after outpatient I-131-rituximab RIT in conjunction with rituximab, followed by maintenance therapy for one year. One patient died because of NHL during the period of follow up, giving the disease-specific survival rate 99%. They found grade IV hematological toxicity in six patients (9%), five (7%) with thrombocytopenia and five with neutropenia. The nadir in mean platelet count occurred four weeks following therapy, while the nadir in mean neutophil counts occurred six to seven weeks following therapy. One patient required platelet transfusion and one patient required packed red blood cells (RBC). Hypothyroidism was observed in nine patients (13%).[12, level II-2]

5.2.2. *Treatment for relapsed or refractory NHL*

Turner et al. reported a grade III neutopenia in six patients (14%) and grade III thrombocytopenia in four patients (10%) in a phase II clinical trial of 42 patients with relapsed or refractory NHL treated with I-131-rituximab RIT. Grade IV hematological toxicity was observed in two patients (5%) and neither required hemopoeitic support. Hypothyroidism was observed in three patients (7%) and one patient required thyroid hormone replacement therapy.[9, level II-2]

Leahy et al. reported that in 91 patients with relapsed or refractory follicular NHL treated with I-131-rituximab RIT, a grade IV thrombocytopenia was observed in 4% of patients and grade IV neutopenia in 16% of patients, with nadir at six to seven weeks after treatment. Three patients required platelet transfusions, one patient required packed RBCs, and one patient received granulocyte colony stimulating factor. Five patients (5.5%) developed a myelodysplastic syndrome (MDS) after a median follow up of 23 months. One patient experienced disease progression to acute myeloid leukemia (AML). Treatment-related hypothyroidism was observed in 9% of patients.[13, level II-3]

Leahy et al. conducted another clinical trial in 142 patients with relapsed NHL. The study reported a grade IV neutropenia in 14 (10%) of patients, grade IV thrombocytopenia in nine (6%) of patient, with nadir at five to seven weeks after treatment. Three patients required platelet transfusion, one patient developed grade IV anemia and required packed RBCs and one patient received granulocyte colony stimulating factor. Six patients (4%) developed a MDS, one patient experienced disease progression to AML, and 20 patients (14%) had an elevated thyroid stimulating hormone (TSH).[14, level II-3]

Kang et al. conducted a phase II clinical trial in 24 patients with relapsed or refractory NHL. The study reported a grade III or IV neutropenia in 21% of patients and grade III or IV thrombocytopenia in 33% of patients. Six patients required platelet transfusion, two patients required packed RBCs and three patients received granulocyte-colony stimulating factor. Treatment related mortality was observed in one patient who had been previously treated with high dose chemotherapy plus total body irradiation (TBI) with ASCT. The median times to nadirs were 31 days for platelets and 32 days for neutrophils. One patient experienced interstitial pneumonitis during the second month after treatment with I-131-rituximab.[15, level II-3]

An uncontrolled clinical trial conducted by Bienert et al. reported a reversible grade III or IV haematological toxicity in seven (78%) of nine patients. Median nadirs were 35 days for platelets, 44 days for leucocytes and 57 days for erythrocytes. Sixteen percent of the patients with more than two prior chemotherapies had grade IV thrombocytopenia, compared to 7% with two or fewer prior chemotherapies. Four patients had epistaxis, pneumonia, neutropenic fever or anaemic dyspnoea. Four non-responders with bulky disease died 4.8±2.0 months after therapy. Three patients had an elevated LDH level prior to RIT and none of the patients responded.[16, level II-3]

Kruger et al. reported grade III or IV neutropenia in four (13%) of 31 patients. Grade III or IV thrombocytopenia occurred in one (3%) patient. Subclinical hypothyroidism occurred in four (13%) patients and myelodysplasia occurred in only one patient. [17, level II-3]

Kuan et al. reported that three (43%) of seven patients developed grade IV haemotological toxicity, one (14%) patient developed acute hepatitis and one (14%) patient developed mild rituximab related infusion reaction. [7, level III]

5.2.3. *Repeat treatment for relapsed or refractory NHL*

A prospective cohort study by Bishton et al. involving sixteen patients receiving second therapy of I-131-rituximab reported that 28.6% patients experienced grade III or IV neutropenia, while 26.7% patients experienced grade III or IV thrombocytopenia. Two patients (13%) required packed RBC transfusion. The median time to both neutrophils and platelet nadirs was six weeks. Four patients (25%) developed hypothyroidism with three (19%) requiring thyroxine. One patient developed AML, with no other cases of MDS.[18, level II-2]

Kang et al. (2013) reported a grade III or IV neutropenia in 72% of patients, and grade III or IV thrombocytopenia in 66% of patients. Fifteen (52%) patients required platelet transfusion, seven (24%) required pack RBCs, and 14 (48%) received granulocyte colony stimulating factor. The median times to nadirs were 33 days for platelets and 44 days for neurophils.[19, level II-3]

A single centre clinical trial conducted by Leahy et al. (2011) reported a grade III or IV neutropenia in two (12%) of 16 patients and thrombocytopenia in three patients (19%) after receiving second course of I-131-rituximab following a relapse.[14, level III]

5.2.4. *Combination treatment for NHL*

A phase II clinical trial by Kruger et al. reported grade III or IV toxicity which comprised of mucositis occurring in four (25%) of 16 patients receiving I-131-rituximab with BEAM conditioning ASCT. Hypothyroidism occurred in three patients (19%) and all were treated with thyroxine.[20, level II-3]

Wagner et al. reported a treatment related death in one patient after receiving I-131-rituximab RIT in combination with high dose chemotherapy EAM. All 23 patients in the clinical trial experienced a grade III or IV haematology toxicity. One (4%) patient developed AML after treatment of myeloablative RIT alone. Two (9%) patients developed secondary MDS, one after myeloablative RIT alone, and the second patient after RIT plus BEAM. The higher grade III or IV toxicity were correlated with the combination of RIT plus high dose chemotherapy approach (p=0.005) and the incidence of mucositis (p=0.002). [21, level II-3]

A phase II clinical trial by Shin et al. reported a toxicity events of all grades occurred in 11 (69%) of 16 patients and a grade III or IV event occurred in four patients (25%), which were all hematologic toxicities. Two patients experienced neutropenia and thrombocytopenia of grade III or more, and the other two experienced only thrombocytopenia. [22, level II-3]

5.3. COST / COST-EFFECTIVENESS

There was no retrievable evidence on cost-effectiveness of I-131-rituximab for treatment of NHL. However, McQuillan et al. reported that the estimated marginal cost of I-131-rituximab was AUD 1500 (RM 5034) per patient, while the cost of four unlabeled rituximab infusion received during induction therapy was AUD 13500 (RM 45305) and the cost of the associated three-monthly unlabeled rituximab infusion received during a 12-month period of maintenance therapy was AUD 13500 per patient.[12]

In a study conducted in Malaysia, Kuan et al. reported that the cost of self-labelled I-131-rituximab was a quarter the cost of commercially available Y-90-ibritumomab tiuxetan (Zevalin®). The estimated cost of a patient receiving two doses of I-131-rituximab for dosimetry study and therapy dose was RM 23997.72. The cost of rituximab maintenance for two years was three to five times higher compared to the self labelled 131-I-rituximab, depending whether rituximab maintenance was given every two or three monthly. [7]

5.4. LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search but only English full text articles were included in this review. Most of the studies retrieved and included in this review were non-randomised clinical trials with no control group. Some of the included studies also have small sample size.

6. CONCLUSION

6.1. EFFECTIVENESS

There was limited fair level of retrievable evidence to suggest that I-131-rituximab RIT was effective as a first line treatment for NHL. Evidence demonstrated that I-131-rituximab RIT was effective for newly diagnosed, advanced stage, symptomatic follicular NHL. The ORR for three months was 99% with 88% achieving Deauville category 1 to 3.

There was fair level of retrievable evidence that showed I-131-rituximab RIT was effective for treatment of relapsed or refractory NHL. However, the response rate and median survival rate varies greatly. The ORR range from 29% to 97%, CR range from 12.5% to 77%, and PR range from 17% to 29%. The median OS range from 11.3 months to 87 months while the median PFS range from 13 months to 71 months. It seems to be more effective for indolent NHL compared to aggressive NHL.

Evidence also suggest that I-131-rituximab RIT was effective when used as repeated treatment for patients with relapsed or refractory NHL including those with aggressive NHL. It was also effective when used as combination treatment for NHL with longer PFS.

However, there was no study retrieved comparing the effectiveness of I-131-rituximab with other established RIT like Y-90-ibritumomab and I-131-tositumomab.

6.2. SAFETY

There was fair level of retrievable evidence to suggest that treatment using I-131-rituximab NHL was safe and tolerable. However, most common toxicity reported was grade III or IV haematological toxicities and hypothyroidism. Combination of I-131-rituximab RIT and high dose chemotherapy increased the toxicity. There was one treatment related mortality (5%) which occurred in a patient treated with I-131-rituximab RIT plus high dose chemotherapy. A study reported that radiation exposure to carers and family members of outpatients undergoing I-131-rituximab RIT were compliance with international guidelines.

6.3. COST / COST-EFFECTIVENESS

There was no retrievable evidence on the cost-effectiveness of I-131-rituximab RIT for NHL. The estimated cost of a self-labelled I-131-rituximab RIT per patient was RM 23997.72.

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8. APPENDIX

8.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

1 LYMPHOMA, NON-HODGKIN/ (36939)
2 diffuse lymphoma*.tw. (415)
3 (lymphoma* adj1 (high-grade or intermediate-grade or low-grade)).tw. (2184)
4 (lymphoma adj1 non hodgkin*).tw. (30630)
5 (lymphoma* adj1 mixed lymphocytic-histiocytic).tw. (8)
6 mixed lymphoma*.tw. (69)
7 (mixed cell lymphoma* adj1 diffuse).tw. (29)
8 LYMPHOMA, B-CELL/ (15228)
9 (lymphoma* adj1 b cell).tw. (26708)
10 LYMPHOMA, FOLLICULAR/ (5929)
11 (follicular large cell adj lymphoma*).tw. (53)
12 (follicular lymphoma adj1 (grade 1 or grade 2 or grade 3)).tw. (94)
13 follicular lymphoma*.tw. (6554)
14 (follicular mixed cell adj lymphoma*).tw. (8)
15 ((histiocytic or large lymphoid) adj1 (lymphoma* or nodular)).tw. (1333)
16 ((lymphoma* or follicular) adj1 large cell).tw. (5869)
17 ((lymphoma or follicular) adj1 (mixed cell or mixed lymphocytic-histiocytic)).tw. (81)
18 LYMPHOMA, LARGE-CELL, IMMUNOBLASTIC/ (352)
19 ((lymphoma* or immunoblastic) adj1 (large cell or diffuse)).tw. (6746)
20 LYMPHOMA, MANTLE-CELL/ (2926)
21 ((lymphoma* or centrocytic) adj1 small cell).tw. (195)
22 (lymphoma* adj1 (mantle cell or mantle)).tw. (159)
23 iodine 131 rituximab.tw. (7)
24 ((I-131 or 131-I) adj1 rituximab).tw. (27)
25 ((I131 or 131I) adj1 rituximab).tw. (18)
26 yttrium 90 ibritumomab.tw. (141)
27 ((Y-90 or 90-Y) adj1 ibritumomab).tw. (231)
28 iodine 131 tositumomab.tw. (55)
29 ((I-131 or 131-I) adj1 tositumomab).tw. (157)
30 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (91543)
31 23 or 24 or 25 or 26 or 27 or 28 or 29 (479)
32 30 and 31 (429)
33 limit 32 to (english language and humans) (375)

OTHER DATABASES	
EBM Reviews - Cochrane Central Register of Controlled Trials	Same MeSH, keywords, limits used as per MEDLINE search
EBM Reviews - Cochrane database of systematic reviews	
EBM Reviews - Health Technology Assessment	
EBM Reviews – NHS Economic Evaluation Database	

PubMeD

(((NON-HODGKIN* LYMPHOMA[MeSH Terms]) OR (((((((((NON HODGKIN LYMPHOMA[MeSH Terms]) OR diffuse lymphoma*[Title/Abstract]) OR lymphoma non hodgkin[Title/Abstract]) OR mixed lymphoma*[Title/Abstract]) OR B CELL LYMPHOMA[MeSH Terms]) OR b cell[Title/Abstract]) OR FOLLICULAR LYMPHOMA[MeSH Terms]) OR follicular lymphoma*[Title/Abstract]) OR MANTLE CELL LYMPHOMA[MeSH Terms]))) AND ((((131I-rituximab[Title/Abstract]) OR I131-rituximab[Title/Abstract])) OR ((((((iodine-131 rituximab[Title/Abstract]) OR I-131 rituximab[Title/Abstract]) OR 131-iodine rituximab[Title/Abstract]) OR 131-I rituximab[Title/Abstract]) OR I131 rituximab[Title/Abstract]) OR 131I rituximab[Title/Abstract]))

8.2. Appendix 2

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Evidence Table : Efficacy/Effectiveness
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. McQuillan AD, Macdonald WB, Turner JH. Phase II study of first-line ^{131}I-rituximab radioimmunotherapy in follicular non-Hodgkin lymphoma and prognostic ^{18}F-fluorodeoxyglucose positron emission tomography. Leuk Lymphoma. 2015;56(5):1271-1277 WESTERN AUSTRALIA	Multicentre, phase II clinical trial Objective: To determine the safety, efficacy and durability of response of I-131-rituximab in the first line treatment of a newly diagnosed patients with advanced, symptomatic follicular NHL. Method: Between April 2006 and September 2013, 68 patients from five institutions in Western Australia were enrolled in INITIAL study (Indolent Non-Hodgkin Immunoradio-therapy Initiated Approach in Lymphoma). All patients received 4 cycles of 375mg/m^2 rituximab at weekly intervals. RIT with I-131-rituximab on an outpatient basis was given according to the	II-2	n=68 Aged 31-89 years Patients were previously untreated, advanced, symptomatic grade 1 or 2 CD20-possitive follicular lymphoma. 51 patients (75%) had stage III or IV disease, and 50 patients (74%) had intermediate or high risk baseline FLIPI score. Bulky disease was present in 6 patients (9%). Bone marrow involvement was identified in 18 (25%)	I-131-Rituximab RIT	-	7 years (median follow up= 4 years)	• The ORR for 3 months was 99%, with 88% achieving Deauville category 1 – 3 • 56 patients (82%) achieved a CR, 11 patients (16%) achieved a PR, and 1 patient (1%) had PD. • These satisfactory responders did not reach median time-to-next-treatment, versus a median of 29 months for a category 4–5 response (p<0.0001). • Disease-specific survival rate was 99% Authors conclusion: I-131-rituximab RIT in newly diagnosed, advanced stage, symptomatic follicular NHL is an effective, practical and affordable alternative to existing conventional chemotherapies, with lower toxicity and durable remissions.	

Evidence Table : Efficacy/Effectiveness
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	standard personalized dosimetry protocol predicated on a whole body radiation absorption dose of 0.75Gy. Patients who achieved standard response received maintenance therapy for 1 year. Baseline and 3-month ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging, analyzed according to Lymphoma Deauville five-point scale, was used to evaluate response and predict prognosis.		patients.					

Evidence Table : Efficacy/Effectiveness
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Turner JH, Martindale AA, Boucek J et al. ^{131}I-Anti CD20 radioimmunotherapy of relapsed or refractory non-Hodgkins lymphoma: a phase II clinical trial of a nonmyeloablative dose regimen of chimeric rituximab radiolabeled in a hospital. Cancer Biother Radiopharm. 2003;18(4):513-524. WESTERN AUSTRALIA	Phase II clinical trial Objective: To develop and evaluate a safe, reliable, efficacious, and relatively inexpensive practical approach to widen the availability of RIT for patients with relapsed or refractory low grade NHL. Method: All patients received therapeutic loading doses of unlabeled rituximab (375 mg/m 2) immediately prior to administration of tracer (200 MBq I-131) or therapy (1.7– 4.3 GBq I-131) activities of I-131-rituximab to provide additive immunotherapy and enhance tumor uptake of the radiolabeled antibody. Radiolabeling of rituximab was done by using modification of standard Chloramine-T method with a semiautomated remote controlled shielded kit	II-2	n=42 aged ≤ and > 60 years Patients with relapsed or refractory NHL. 80% of patients had relapsed low grade NHL; small lymphocytic lymphoma and follicular lymphoma grade 1 and 2. 20% of patients had relapsed intermediate grade lymphoma; follicular lymphoma grade 3 and mantle cell lymphoma. Patients had been heavily pretreated with a median of two prior chemotherapy regimens (range	I-131-Rituximab RIT	-	Median follow-up of 14 months (range 4–28 months).	• The ORR was 71% in 35 patients with a median follow-up of 14 months (range 4–28 months). • 19 patients (54%) achieved CR, with median duration 20 months. PR was observed in 6 patients (17%) with median duration of 8 months. • The OS at 25 month were 66% • The PFS were 29% at median duration of 14 months. Authors conclusion: The widely available chimeric anti-CD20 monoclonal antibody rituximab, generally approved for immunotherapy of B cell NHL, has been safely, reliably, effectively, and inexpensively radiolabeled with therapeutic activities of iodine-131.	

Evidence Table : Efficacy/Effectiveness
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	system in a hospital radiopharmacy.		1–4) and three prior therapeutic regimens (range 1–7) including rituximab, interferon, and radiotherapy.					

Evidence Table : Efficacy/Effectiveness
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Leahy MF, Seymour JF, Hicks RJ et al. Multicenter phase II clinical study of iodine-131-rituximab radioimmunotherapy in relapsed or refractory indolent non-Hodgkin's lymphoma. J Clin Oncol. 2006;24(27):4418-4425. WESTERN AUSTRALIA	Multicentre, phase II clinical trial Objective: To evaluate safety and efficacy of I-131-rituximab chimeric anti-CD20 antibody RIT in patients with relapsed or refractory indolent non-Hodgkin's lymphoma (NHL). Method: Between May 2000 and December 2004, 91 patients with relapsed or refractory follicular, mucosa-associated lymphoid tissue (MALT)/marginal zone or small lymphocytic NHL were entered onto the study at Fremantle Hospital (Fremantle, Western Australia) and the Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia). Patients with follicular lymphoma were evaluated further according to the Follicular Lymphoma	II-2	n=91 Aged 30-84 (median age=62) Patients with relapsed (n=76) or refractory (n=15) follicular, mucosa-associated lymphoid tissue (MALT)/marginal zone or small lymphocytic NHL. All patients had histologically confirmed disease, be ≥18 years old, have a WHO performance status of less than 3, and a life expectancy of more than 3 months. Patients who had received previous rituximab were eligible if more than 6 months	I-131-Rituximab RIT		Median follow up = 23 months (range 1-48 month)	• The ORR was observed in 69 patients (76%), with 53% attaining a CR or Cru. • Median duration of response for patients achieving CR/Cru was 20 vs 7 months for those with a partial response (P=0.121). • The median PFS was 13 months, with 14% remaining relapse free beyond 4 years. • Median follow-up was 23 months, with a 4-year actuarial survival rate of 57% ± 10%. • There is no significant different between patients receiving two or four doses of unlabelled rituximab. • Six patients were re-treated, 4 had achieved second response (3 CRs and 1 PR) with median response duration of 11 months. Authors conclusion: I-131-Rituximab RIT of patients with relapsed or refractory indolent NHL is safe and effective. This nonmyeloablative approach may be performed on an outpatient basis and preserves RIT re-treatment options for relapse.	

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	International Prognostic Index (FLIPI) 12 and were stratified into low-, intermediate-, and high-risk groups. In-house radioiodination of ritixumab was done by using chloramine-T method. After a standard loading dose of rituximab 375 mg/m^2, individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. The administered therapeutic activities ranged from 1.36 to 5.34 GBq. The referring physicians had discretion to prescribe a standard four-dose regimen of 375 mg/m2 rituximab in conjunction with RIT. Thus 59 patients received two additional dose rituximab during the 2 weeks after tracer and therapeutic administration. The		had elapsed from treatment.					

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	remaining patients received two-dose rituximab on the days of the tracer and therapeutic doses of 131-I-rituximab. Disease status was evaluated by physical examination; serial computed tomography (CT) scans of chest, abdomen, and pelvis; and bone marrow biopsies (if bone marrow was involved at baseline) at 3, 6,and 12 months after RIT, and then as clinically indicated. Response evaluation was in accord with the International Workshop of Standardized Response Criteria for NHL.Hematologic assessment with full blood counts was carried out weekly from treatment until count recovery, then every 3 months for 2 years. Hepatic and renal function was assessed weekly for 6 weeks, then every 3 months. Thyroid function was monitored at 3-month intervals.							

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4. Leahy MF and Turner JH. Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood. 2011 6;117(1):45-52. WESTERN AUSTRALIA	Single-centre clinical trial Objective: To evaluate a 10-year, single-centre clinical experience with I-131-rituximab for the therapy of relapsed or refractory indolent NHL. Method: A pilot study of 10 patients had demonstrated efficacy and safety of I-131-rituximab RIT, and 132 consecutive patients were subsequently treated. The first 66 patients were taken from the previous study to provide information regarding long-term follow up of I-131-rituximab. Another 76 patients were enrolled later and were treated with the same protocol. In-house radioiodination of ritixumab was done by using chloramine-T method. After a standard loading dose of rituximab 375 mg/m2,	II-2	n=142 median age=61 years (range 30-86) Patients with relapsed lymphoma and comprised follicular (107 patients), mantle (8 patients), mucosa-associated lymphoid tissue (MALT; 6 patients), and small lymphocytic lymphoma (21 patients). All patients had histologically confirmed disease within 1 year before treatment, have been aged more than 18 years, have had a World Health	I-131-Rituximab RIT	-	Median follow up = 32 months (range 3-108 month)	• An ORR was observed in 97 patients (68%) with CR in 50% at 12 week assessment. • The median OS was 87 month (range 1-131). • The median PFS for all responding patients and those with stable disease was 39 months (range 3-108), and for patients in CR/Cru, median PFS was 63 months. • Prior rituximab therapy made no statistical different to ORR, but was associated with a significant reduced CR/Cru (P=0.001) rate. • 16 patients had relapsed after RIT and received second course of I-131-rituximab. The ORR was 94% (15/16), CR/Cru was achieved in 69% (11/16), PR in 25%(4/16) and one patient have stable disease after the initial RIT. Ten patients achieved second response (ORR 63%, 7 CR and 3 PR). Authors conclusion: Radioimmunotherapy with I-131-rituximab in routine clinical outpatient practice provides cost effective, safe treatment of relapsed/ refractory	

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	individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. Patients received the standard 4-dose once-weekly regimen of 375 mg/m2 rituximab, with the tracer dose of I-131-rituximab given on week 1 and the therapy dose on week 2. Two further doses of nonradiolabeled "cold" rituximab were administered on weeks 3 and 4.		Organization performance status of less than 3, and a life expectancy of more than 3 months. Patients admitted to the phase 2 study were required to have relapsed after prior chemotherapy.				indolent NHL, with half of patients achieving durable, complete remission with potential for repeat radioimmunotherapy on relapse.	

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Kang HJ, Lee SS, Kim KM et al. Radioimmunotherapy with ^{131}I-rituximab for patients with relapsed/refractory B-cell non-Hodgkin's lymphoma (NHL). Asia Pac J Clin Oncol. 2011;7(2):136-145 SOUTH KOREA	Phase II clinical trial Objective: To evaluate the safety and efficacy of RIT with radioiodinated human/murine chimeric anti-CD20 monoclonal antibody rituximab (I-131-rituximab) for treating Korean patients with relapsed or refractory B-cell NHL Method: Between May 2004 and October 2006, 24 patients received a single treatment of I-131-rituximab. All patients received unlabeled ritixumab (70mg) immediately prior to the administration of a therapeutic dose of I-131-rituximab. A dose of 200 mCi of radioiodide was chosen as a fixed dose. Iodination of the antibody was done using Iodo-Beads. Whole-body scans were done using gamma camera and blood samples were collected	II-3	n=24 median age= 63 years (range 34-73 years) patients with relapsed or refractory NHL and at least one measurable lesion (longest diameter being ≥1cm), 19-75 years old with an Eastern Cooperative Oncology Group performance status 0-2, and adequate liver, renal, platelet and bone marrow functions. DLBCL = 11 Mantle Cell lymphoma = 6 Marginal zone B-cell lymphoma = 5 Follicular lymphoma = 2	I-131-Rituximab RIT		Median follow up = 55.1 months (range 31.5–69.3 months)	• The ORR was 29% ; • 46% with low grade B-cell NHL (LGL): ○ CR: 12.5% (3/24) ○ PR: 12.5% (3/24) • 9% (one PR) for patients with diffuse large B-cell lymphoma (DLBCL) • There was a statistically significant different of response between patients with LGL and the patients with DLBCL (46% vs 9%, P=0.049) • The median response duration was 2.9 months (range 1.1 to 64.9 months) • After a median follow-up of 55.1 months (range 31.5-69.3 months), the median PFS for all patients was 2.2 months (95% CI 1.1-3.3 months) • The median OS was 11.3 months (95% CI 0.8-21.8 months) with a 3-year survival rate of 21% • There was a statistically significant different between the LGL and DLBCL for the median PFS (4.5 months vs 1.3 months, P=0.0007) Authors conclusion: RIT with I-131-rituximab seems to be	

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	to measure the radioactivity with a gamma counter. The response of the treatment was evaluated 1 month later by ^{18}F-FDG-PET-CT.						effective and tolerable for patients with refractory LGL, although this treatment had modest activity in patients with refractory DLBCL.	

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Bienert M, Reisinger I, Srock S et al. Radioimmunotherapy using ^{131}I-rituximab in patients with advanced stage B-cell non-Hodgkin's lymphoma: initial experience. Eur J Nucl Med Mol Imaging. 2005;32(10):1225-1233. GERMANY	Uncontrolled clinical trial Objective: To evaluate the safety, toxicity and therapeutic response of non-myeloablative RIT using I-131-rituximab in previously heavily treated patients with B-cell non-Hodgkin's lymphoma (B-NHL). Method: Between March 2001 and December 2003, nine patients were treated with RIT. All patients had progressive or recurrent disease and multiple prior chemotherapies or radiotherapies (range 2-7). Eight of nine patients progressed upon immunotherapy with rituximab, two of four patients with mantle cell lymphomas received RIT for consolidation after salvage therapy. Rituximab was labelled with ^{131}I using the Iodogen method. The administered activity	II-2	n=9 4 female and 5 male; median age 59 years, range 31-74 years with relapsed, refractory or transformed B-NHL. Mantle cell lymphoma=4 Follicular lymphoma=1 DLBCL=4	I-131-Rituximab RIT	-	2–39 months (Mean=12 months)	• Three out of nine patients responded, one patient achieved complete response ongoing at 14 months and two partial responses progressing at 12 and 13 months after treatment. One partial responder was re-treated with RIT and achieved an additional progression-free interval of 7months. Authors conclusion: Radioimmunotherapy with I-131-rituximab in previously heavily treated B-NHL patients was safe and well tolerated, and four out of ten therapies induced responses. Radioimmunotherapy was less efficient in patients with bulky disease and elevated LDH. Severe haematological toxicity in seven patients did not cause significant clinical problems. Radioimmunotherapy seems to be an additional therapeutic option in carefully selected therapy-refractory BNHL patients.	

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	(2200±600 MBq) was based on a dosimetrically calculated 45 cGy total body radiation dose. All patients received an intravenous infusion of 2.5mg/kg of rituximab 7 to 14 days prior to RIT. Scintigraphy was performed with a double-head gamma camera (Hawkeye–SPECT/CT, General Electric Healthcare, Connecticut, USA) equipped with a high-energy collimator. Total blood counts were obtained at least once a week. Patients were re-staged 6–8 weeks after RIT by using imaging procedures. Thereafter, physical examination and laboratory testing was performed every 3 months or when patients developed symptoms of recurrence.							

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7. Kruger PC, Joske DJL, Turner JH. Iodine-131 Rituximab Radioimmunotherapy: Durable Control of Follicular Lymphoma. J Nucl Med Radiat Ther. 2014; 5:4. WESTERN AUSTRALIA	Non-randomised, Uncontrolled Clinical Trial Objective: To evaluate the response and toxicity after long term follow-up of I-131-rituximab RIT in patients with follicular lymphoma under the routine clinical care of a single haematologist over a period of 12 years. Method: Radioimmunotherapy with I-131-rituximab was administered to patients according to the standard personalized dosimetry protocol predicated upon a whole body radiation absorbed dose of 0.75Gy. Four doses of maintenance rituximab were administered at three month interval following I-131-rituximab RIT. Response to treatment was assessed with 18F-fluorodeoxyglucose positron emission tomography scan	II-2	n=31 Median age of 54 years (range 30-74) All patients had histologically confirmed follicular lymphoma (FL), an Eastern Co-operative Oncology Group performance status of less than 3, life expectancy of more than 3 months and had received no rituximab within the 6 months prior to 131-I-rituximab RIT were selected.	I-131-Rituximab RIT	-	12 years	• Response rate was 97% with 24/31(77%) experiencing a complete remission (CR) confirmed on ^{18}F-FDG-PET-CT. • Median PFS is 71 months (range 6-152) • The median OS has not been reached after a median follow up of 65 month. Authors conclusion: In real life clinical practice, epitomized by a single hematologist's clinical experience, durable control of FL by ^{131}I-rituximab RIT is achievable without significant toxicity in non-selected patients, including those pretreated with chemotherapy. Subsequent therapeutic options are not compromised upon relapse and outpatient ^{131}I-rituximab RIT is practical, affordable, and preserves quality of life.	

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	combined with computerized tomography scan (^{18}F-FDG-PET-CT) at 3-6 months.							

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
8. Kuan JW, Law CS, Wong XQ et al. A pioneer experience in Malaysia on In-house Radio-labelling of ^{131}I-rituximab in the treatment of Non-Hodgkin's Lymphoma and a case report of high dose ^{131}I-rituximab-BEAM conditioning autologous transplant. Appl Radiat Isot. 2016;116:13-21 MALAYSIA	Uncontrolled clinical trial Objective: To report a pioneer experience in Malaysia on self-labelling I-131-rituximab, substituting autologous haematopoietic stem cell transplantation (HSCT) and a patient, the first reported case receiving high dose I-131-rituximab (6000 MBq/163 mCi) combined with BEAM (carmustine, etoposide, cytarabine and mephalan) conditioning for autologous HSCT. Method: Between August and October 2014, seven patients with histologically proven regractory/relapsed CD20+ indolent or aggressive NHL were selected. Prior to dosimetry studies and therapy, desired activity of I-131-rituximab	II-3	n=7 median age= 60 (range 26-62 years) Patients had either exhausted available options of curative treatment or were chemo-sensitive but unable to receive autologous HSCT as the recommended treatment due to unfitness, failed peripheral blood stem cell (PBSC) mobilization or financial constraint. DLBCL: 4 FL: 2 PMBL: 1	I-131-Rituximab RIT		Median follow up = 20.7 months (8-21.8 months)	• Five patients (71%) achieved CR and two patients (29%) achieved PR three to four months after treatment. • Two patients with refractory disease achieved CR/PR after the treatment. One patient achieved CR after second relapse. Of the remaining four patients who developed PR after first line treatment, three achieved a CR and one PR. Authors conclusion: For resource limited environment and with limited access to expensive modalities like targeted treatments and autologous HSCT or patients who are not fit or fail to mobilise for HSCT, the use of self-labelled 131I-rituximab may be a viable consolidation tool for patients with relapsed refractory lymphoma.	

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	was administered intravenously following a loading dose of 375 mg/m^2 unlabelled rituximab. In-house radioiodination of ritixumab was done by using chloramine-T method. One patient with Primary Mediastinal (thymic) Large B-cell Lymphoma (PMBL) received high dose I-131-rituximab (6000 MBq or 163 mCi) combined with BEAM conditioning for autologous HSCT.							

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Bishton MJ, Leahy MF, Hicks RJ et al. Repeat treatment with iodine-131-rituximab is safe and effective in patients with relapsed indolent B-cell non-Hodgkin's lymphoma who had previously responded to iodine-131-rituximab. Ann Oncol. 2008;19(9):1629-1633. AUSTRALIA	Retrospective cohort study Objective: To examine the short- and long-term effects of a second treatment with I-131-rituximab in patients with indolent B-cell NHL following a relapse. Method: Two institutional databases from January 2000 to July 2007 for retreatment of I-131-rituximab were analyzed. Response duration following first and second treatment and haematological toxicity were compared. In-house radioiodination of ritixumab was done by using chloramine-T method. After a standard loading dose of rituximab 375 mg/m2, individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a	II-2	n=16 All patients had had a previous response >3 months to I-131-rituximab All patients required an adequate bone marrow reserve, as demonstrated by neutrophils >1.5-109/l and platelets >100-109/l FL: 15 MCL: 1	Second course of I-131-Rituximab RIT	First course of I-131-Rituximab RIT		• Fourteen of 16 (87.5%) patients responded with nine complete responses (CR), with a median duration of 10.5 months in responders. Six of 13 reresponders had the same or a longer response and six more remain in complete response. • The median event-free survival was not significantly different for the two treatments. There was no significant difference in the severity of myelosuppression. • The actuarial progression-free survival rate at 12 months was 36%. Authors conclusion: The study show retreatment with I-131-rituximab is an efficacious and safe option for patients who have responded previously to I-131-rituximab, with the duration of second or subsequent responses often exceeding the first response.	

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	therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. The severity of cytopenia, development of myelodysplasia (MDS), acute myeloid leukemia (AML) and hypothyroidism was noted.							

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10. Kang HJ, Lee SS, Byun BH et al. Repeated radioimmunotherapy with ^{131}I-rituximab for patients with low-grade and aggressive relapsed or refractory B cell non-Hodgkin lymphoma. Cancer Chemother Pharmacol. 2013;71(4):945-953 SOUTH KOREA	Phase II clinical trial Objective: To investigate whether repeated administration of I-131-Rituximab at regular intervals could increase the RIT response compared to a single administration of radiolabeled mAB. Method: Between July 2005 and February 2012, 31 patients received repeated treatment of I-131-rituximab. All patients received unlabeled ritixumab (70mg) immediately prior to the administration of a therapeutic dose (200 mCi of radioidodide labelled with 30mg of rituximab diluted in 150ml of normal saline that was infused over 1 hour). Iodination of the antibody was done using Iodo-Beads. The response of the treatment was evaluated 1 month later by ^{18}F-FDG-PET-CT. If a patient	II-3	n=31 median age= 63 years (range 26-75 years) patients with relapsed or refractory NHL and at least one measurable lesion (longest diameter being ≥1cm), 19-75 years old with an Eastern Cooperative Oncology Group performance status 0-2, and adequate liver, renal, platelet and bone marrow functions. MCL: 12 DLBCL: 7 Marginal zone B-cell lymphoma: 6 Follicular lymphoma: 4 FL: 1 Small	I-131-Rituximab RIT		Median follow up=21.8 months	• The ORR was observed in 21 (68%) patients (95% CI 52-84). • The median response duration is 8.6 months. • After a median follow-up of 21.8 months (range 1.6-79.7 months), the median PFS for all patients was 9.8 months (95% CI 7.9-11.7 months) • The median OS was 48.2 months (95% CI 41.7-54.7 months) with a 5-year survival rate of 42% Authors conclusion: Compared to a single treatment, repeated RIT with I-131-rituximab increased the response rate and duration for patients with relapsed or refractory B cell NHL, including those with aggressive histology.	

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	did not progress, subsequent readministration of I-131-Rituximab was performed at 4-week intervals.		lymphocytic lymphoma: 1					

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
11. Kruger PC, Cooney JP, Turner JH. Iodine-131-rituximab radioimmunotherapy with BEAM conditioning and autologous stem cell transplant salvage therapy for relapsed/refractory aggressive non-Hodgkin lymphoma. Cancer Biother. Radiopharm. 2012;27(9):552-560 AUSTRALIA	Phase II clinical trial Objective: To investigate the response and toxicity of I-131-rituximab/carmustine, etoposide, cytarabine, and mephalan (BEAM) conditioning regimen in autologous stem cell transplantation (ASCT) for NHL. Method: Between January 2003 and January 2012, sixteen patients were treated in Fremantle Hospital. RIT with I-131-rituximab on an outpatient basis was given according to the standard personalized dosimetry protocol predicated on a whole body radiation absorption dose of 0.75Gy. The BEAM conditioning regimen was commenced on day -6. Evaluable engraftment data are available for 15 patients who had 16 ASCTs.	II-3	n=16 median age=61 years (34-71 years) Patients with relapsed, refractory, aggressive B-cell NHL DLBCL = 7 Transformed/aggressive FL = 3 MCL = 6 Mucosal associated lymphoid tissue (MALT) = 1	I-131-Rituximab RIT	-	Median follow up = 44 months (range 4-108 months)	• Engraftment was achieved in all patients, 15 (94%) ASCTs achieved a CR, and 1 ASCTs achieved a PR. • At a median follow up of 44 months (range 4–108 months) post-ASCT, 12 patients are alive, 9 remain in remission, 4 patients have relapsed and needing subsequent treatment and 4 patients died. • PFS was analyzed according to prognostic factors: ○ PFS for patients with DLBCL was longer compared to patients with other histological type [median PFS not reached (range 6-77 months) vs 4 months (range 3-5 months)] ○ PFS for patients with DLBCL was longer compared to patients with aggressive/transformed follicular lymphoma (median PFS not reached vs 4 months, p=0.0039) • The median time to absolute neutrophil count >0.5·109/L was 12 days (range 9–25 days). The median time to unsupported platelet count of >20·109/L was 17.5 days (range 10–65 days).	

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							Authors conclusion: This study suggests that the addition of I-131-rituximab RIT to BEAM conditioning, before ASCT, for relapsed or primary refractory B-cell NHL improves disease eradication, compared with BEAM conditioning alone, without significant additional toxicity.	

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12. Wagner JY, Schwarz K, Schreiber S et al. Myeloablative anti-CD20 radioimmunotherapy +/- high-dose chemotherapy followed by autologous stem cell support for relapsed/refractory B-cell lymphoma results in excellent long-term survival. Oncotarget. 2013;4(6):899-910. GERMANY	Phase I/II clinical trial Objective: To evaluate the patient specific activity of I-131-rituximab in a myeloablative setting as a salvage therapy prior to conventional high dose chemotherapy with ASCT. Method: Between January 2000 and October 2004, 23 patients were enrolled to evaluate RIT with I-131-rituximab in a myeloablative setting. Biodistribution and dosimetric studies were performed to determine I-131 activity required to induce a total body dose of 21-27Gy to critical organs. All patients received therapeutic infusion of radiolabelled rituximab (40mg rituximab). 6/23 patients RIT was combined with high dose chemotherapy EAM. 8/23 patients received a sequential high-dose chemotherapy (BEAM protocol) followed by second ASCT.	II-3	n=23 median age=58 (range 31-67 years) Patients with confirmed relapsed or refractory NHL without CR to salvage chemotherapy Indolent lymhphoma= 65% Aggressive lymphoma= 13% Mantle cell lymphoma (MCL)=22% Stage III/IV disease=91%	• I-131-Rituximab RIT only • I-131-Rituximab RIT plus high dose chemotherapy EAM • I-131-Rituximab RIT high-dose chemotherapy (BEAM protocol) followed by second ASCT.	-	-	• The ORR was 87% with 64% of patients achieving CR (14/22) and 23% (5/22) achieving a PR. • CR rate was higher in tandem therapy group compared to RIT alone (33% vs 75%). • The median PFS and OS were 47.5 and 101.5 months, with a median follow-up of 9.5 years (range 6.2-12.2 years) • There is no significant different between RIT and RIT in combination with high dose chemotherapy with or without a second ASCT in improving PFS and OS. • The long term outcome with regard to OS was 43% of patients (10/23) being alive and 39% (9/23) still in CR after a median follow-up of 9.5 years. Authors conclusion: Myeloablative RIT with I-131-rituximab followed by ASCT is feasible, well-tolerated and effective in high risk CD20+ NHL. Combination of RIT and high dose chemotherapy increased toxicity significantly.	

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Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
13. Shin DY, Byun BH, Kim KM et al. Radioimmunotherapy with ^{131}I-rituximab as consolidation therapy for patients with diffuse large B-cell lymphoma. Cancer Chemother Pharmacol. 2016;78(4):825-831 SOUTH KOREA	Phase II clinical trial Objective: To investigate the efficacy and safety of I-131-rituximab as consolidation therapy after standard combination chemotherapy or R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone) in patients with diffuse large B-cell lymphoma (DLBCL). Method: Between December 2005 and June 2011, 16 patients were enrolled and treated with a single dose of I-131-rituximab as consolidation therapy after the completion of six or eight cycles of R-CHOP. The I-131-rituximab treatment was administered within 4 to 8 weeks from the last administration of R-CHOP. All patients received unlabeled ritixumab	II-3	n=16 median age = 55 years (range 50-73) Patients who had been diagnosed with advanced stage (Ann Arbor III or IV) or bulky stage II DLBCL and achieved complete or partial response after six to eight cycles of R-CHOP.	I-131-Rituximab RIT	-	Median follow-up duration = 73 months	• Six patients achieved CR after three cycles of R-CHOP, and another 9 patients further achieved CR after the completion of six or eight cycles of R-CHOP. • Two-year relapse free survival was 88%, and 5-year relapse free survival was 81%. • The median PFS and OS have not yet been reached. Authors conclusion: I-131-rituximab showed promising efficacy as consolidation treatment for patients with DLBCL.	

Evidence Table : Efficacy/Effectiveness
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	(70mg) immediately prior to the administration of a therapeutic dose (200 mCi of radioidodide labelled with 30mg of rituximab) injected intravenously within 4 hours from the administration of unlabelled rituximab). Iodination of the antibody was done using Iodo-Beads.							

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Calais PJ, Turner JH. Outpatient ^{131}I-rituximab radioimmunotherapy for non-Hodgkin lymphoma: a study in safety. Clin Nucl Med. 2012;37(8):732-737. WESTERN AUSTRALIA	Prospective cohort study Objective: To establish the safety of outpatient I-131-Rituximab RIT by measuring the radiation exposure of hospital staff, carers, and members of the public and by estimating the environmental impact of radioactive urinary excretion. Method: Two hundred consecutive outpatients undergoing I-131-rituximab RIT of NHL with personalized prescribed dosimetry were studied. After administration of I-131-rituximab therapy, patients are required to remain at home for one week. Carers and cohabitants of patients were issued with thermoluminescent dosimeter (TLC) badges to measure the exposure rate. Carer was requested to provide one	II-2	n=200 Median age= 62 years old, range 30-89 years. Patients treated for NHL with therapeutic activities between 1 and 4.5 GBq (mean, 2.3 GBq; or between 27 and 121 mCi; mean, 62mCi) predicated on a prescribed whole-body radiation-absorbed dose of 0.75 Gy	I-131-rituximab RIT		7 days	• Mean radiation exposure of adult carers was 0.49 mSv (range, 0.01 to 3.67 mSv). To other coresiding family members, mean exposure was 0.23 mSv (range, <0.01 to 1.20 mSv), and for visitors sharing badges, the mean exposure was 0.17 mSv (range, <0.01 to 0.73 mSv). • Urinary activity excreted over the week after I-131-rituximab therapy was typically less than 25% of the administered activity. • Mild transient myelosuppression was observed in all patients, and in 10% there was grade IV toxicity with respect to platelet and neutrophils count. Authors conclusion: I-131-Rituximab RIT for NHL maybe safely administered on an outpatient basis. The median radiation exposure of carers, cohabitants of the patients and visitors is well within the limits recommended by international guidelines. Local regulatory agency-designated patient release rate limit of less than 25 μSv/h at 1m was attained within 1 week of therapeutic I-131-Rituximab administration.	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	badge for visitors to share, thus giving a 'cumulative visitor' reading. For the first 100 patients, the entire urine output for 7 days after therapy and was collected for return and disposal. After 1 week, the patients were visited by physicist at home, the exposure rate of 1m was measured, and the TLC badges were collected.							

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. McQuillan AD, Macdonald WB, Turner JH. Phase II study of first-line ^{131}I-rituximab radioimmunotherapy in follicular non-Hodgkin lymphoma and prognostic ^{18}F-fluorodeoxyglucose positron emission tomography. Leuk Lymphoma. 2015;56(5):1271-1277 WESTERN AUSTRALIA	Multicentre, phase II clinical trial Objective: To determine the safety, efficacy and durability of response of I-131-rituximab in the first line treatment of a newly diagnosed patients with advanced, symptomatic follicular NHL. Method: Between April 2006 and September 2013, 68 patients from five institutions in Western Australia were enrolled in INITIAL study (Indolent Non-Hodgkin Immunoradio-therapy Initiated Approach in Lymphoma). All patients received 4 cycles of 375mg/m^2 rituximab at weekly intervals. RIT with I-131-rituximab on an outpatient basis was given according to the standard personalized dosimetry protocol predicated on a whole body radiation absorption	II-2	n=68 Aged 31-89 years Patients were previously untreated, advanced, symptomatic grade 1 or 2 CD20-possitive follicular lymphoma. 51 patients (75%) had stage III or IV disease, and 50 patients (74%) had intermediate or high risk baseline FLIPI score.	I-131-Rituximab RIT	-	7 years (median follow up= 4 years)	• One patient died because of NHL due to rapidly progressive disease 10 months following enrollment. • Grade 4 hematological toxicity was seen in 6 patients (9%), 5 (7%) with thrombocytopenia and 5 with neutropenia. The nadir in mean platelet count occurred four weeks following therapy, while the nadir in mean neutophil counts occurred six to seven weeks following therapy. One patient required platelet transfusion and one patient required pack red blood cells (RBC). • Hypothyroidism was observed in nine patients (13%).	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	dose of 0.75Gy. Patients who achieved standard response received maintenance therapy for 1 year. Baseline and 3-month ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging, analyzed according to Lymphoma Deauville five-point scale, was used to evaluate response and predict prognosis.							

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
3. Turner JH, Martindale AA, Boucek J et al. ^{131}I-Anti CD20 radioimmunotherapy of relapsed or refractory non-Hodgkins lymphoma: a phase II clinical trial of a nonmyeloablative dose regimen of chimeric rituximab radiolabeled in a hospital. Cancer Biother Radiopharm. 2003;18(4):513-524. WESTERN AUSTRALIA	Phase II clinical trial Objective: To develop and evaluate a safe, reliable, efficacious, and relatively inexpensive practical approach to widen the availability of RIT for patients with relapsed or refractory low grade NHL. Method: All patients received therapeutic loading doses of unlabeled rituximab (375 mg/m 2) immediately prior to administration of tracer (200 MBq I-131) or therapy (1.7– 4.3 GBq I-131) activities of I-131-rituximab to provide additive immunotherapy and enhance tumor uptake of the radiolabeled antibody. Radiolabeling of rituximab was done by using modification of standard Chloramine-T method with a semiautomated remote controlled shielded kit	II-2	n=42 aged ≤ and > 60 years Patients with relapsed or refractory NHL. 80% of patients had relapsed low grade NHL; small lymphocytic lymphoma and follicular lymphoma grade 1 and 2. 20% of patients had relapsed intermediate grade lymphoma; follicular lymphoma grade 3 and mantle cell lymphoma. Patients had been heavily pretreated with a median of two prior chemotherapy regimens (range	I-131-Rituximab RIT	-	Median follow-up of 14 months (range 4–28 months).	• Grade III neutropenia was observed in 6 patients (14%), and grade III thrombocytopenia was observed in 4 patients (10%). Grade IV hematological toxicity was observed in 2 patients (5%). Hypothyroidism was observed in 3 patients (7%) and 1 patient required thyroid hormone replacement therapy.	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	system in a hospital radiopharmacy.		1–4) and three prior therapeutic regimens (range 1–7) including rituximab, interferon, and radiotherapy.					

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Leahy MF, Seymour JF, Hicks RJ et al. Multicenter phase II clinical study of iodine-131-rituximab radioimmunotherapy in relapsed or refractory indolent non-Hodgkin's lymphoma. J Clin Oncol. 2006;24(27):4418-4425. WESTERN AUSTRALIA	Multicentre, phase II clinical trial Objective: To evaluate safety and efficacy of I-131-rituximab chimeric anti-CD20 antibody RIT in patients with relapsed or refractory indolent non-Hodgkin's lymphoma (NHL). Method: Between May 2000 and December 2004, 91 patients with relapsed or refractory follicular, mucosa-associated lymphoid tissue (MALT)/marginal zone or small lymphocytic NHL were entered onto the study at Fremantle Hospital (Fremantle, Western Australia) and the Peter MacCallum Cancer Centre (Melbourne, Victoria, Australia). Patients with follicular lymphoma were evaluated further according to the Follicular Lymphoma International	II-2	n=91 Aged 30-84 (median age=62) Patients with relapsed (n=76) or refractory (n=15) follicular, mucosa-associated lymphoid tissue (MALT)/marginal zone or small lymphocytic NHL. All patients had histologically confirmed disease, be ≥18 years old, have a WHO performance status of less than 3, and a life expectancy of more than 3 months. Patients who had received previous rituximab were eligible if more than 6 months	I-131-Rituximab RIT		Median follow up = 23 months (range 1-48 month)	• Grade IV thrombocytopenia occurred in 4% and neutropenia occurred in 16% of patients, with nadir at 6 to 7 week after treatment. • Five patients (5.5%) developed a myelodysplastic syndrome (MDS) after a median follow up of 23 months. One patient experienced disease progression to acute myeloid leukemia (AML) • Hypothyroidism was observed in 9% of patients • Hematological toxicity was not increased with re-treatment.	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Prognostic Index (FLIPI) 12 and were stratified into low-, intermediate-, and high-risk groups. In-house radioiodination of ritixumab was done by using chloramine-T method. After a standard loading dose of rituximab 375 mg/m^2, individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. The administered therapeutic activities ranged from 1.36 to 5.34 GBq. The referring physicians had discretion to prescribe a standard four-dose regimen of 375 mg/m2 rituximab in conjunction with RIT. Thus 59 patients received two additional dose rituximab during the 2 weeks after tracer and therapeutic administration. The remaining patients		had elapsed from treatment.					

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	received two-dose rituximab on the days of the tracer and therapeutic doses of 131-I-rituximab. Disease status was evaluated by physical examination; serial computed tomography (CT) scans of chest, abdomen, and pelvis; and bone marrow biopsies (if bone marrow was involved at baseline) at 3, 6,and 12 months after RIT, and then as clinically indicated. Response evaluation was in accord with the International Workshop of Standardized Response Criteria for NHL. Hematologic assessment with full blood counts was carried out weekly from treatment until count recovery, then every 3 months for 2 years. Hepatic and renal function was assessed weekly for 6 weeks, then every 3 months. Thyroid function was monitored at 3-month intervals.							

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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
5. Leahy MF and Turner JH. Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood. 2011 6;117(1):45-52. WESTERN AUSTRALIA	Single-centre clinical trial Objective: To evaluate a 10-year, single-centre clinical experience with I-131-rituximab for the therapy of relapsed or refractory indolent NHL. Method: A pilot study of 10 patients had demonstrated efficacy and safety of I-131-rituximab RIT, and 132 consecutive patients were subsequently treated. The first 66 patients were taken from the previous study to provide information regarding long-term follow up of I-131-rituximab. Another 76 patients were enrolled later and were treated with the same protocol. In-house radioiodination of ritixumab was done by using chloramine-T method. After a standard loading dose of rituximab 375 mg/m2,	II-2	n=142 median age=61 years (range 30-86) Patients with relapsed lymphoma and comprised follicular (107 patients), mantle (8 patients), mucosa-associated lymphoid tissue (MALT; 6 patients), and small lymphocytic lymphoma (21 patients). All patients had histologically confirmed disease within 1 year before treatment, have been aged more than 18 years, have had a World Health Organization	I-131-Rituximab RIT	-	Median follow up = 32 months (range 3-108 month)	• Grade IV neutropenia occurred in 14 (10%) patients. Grade IV thrombocytopenia occurred in 9(6%) patient, with nadir at 5 to 7 weeks after treatment. Six patients (4%) developed a myelodysplastic syndrome (MDS), 1 patient experienced disease progression to acute myeloid leukemia (AML), and 20 patients (14%) had an elevated TSH. • After the first treatment, grade 3/4 neutropenia occurred in 6 patients (37%) and thrombocytopenia in 3 (19%), compared with 2 (12%; P=0.22) and 5 (31%; P=0.658) patients, respectively, after the repeat treatment.	

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. Patients received the standard 4-dose once-weekly regimen of 375 mg/m2 rituximab, with the tracer dose of I-131-rituximab given on week 1 and the therapy dose on week 2. Two further doses of nonradiolabeled "cold" rituximab were administered on weeks 3 and 4.		performance status of less than 3, and a life expectancy of more than 3 months. Patients admitted to the phase 2 study were required to have relapsed after prior chemotherapy.					

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
6. Kang HJ, Lee SS, Kim KM et al. Radioimmunotherapy with ^{131}I-rituximab for patients with relapsed/refractory B-cell non-Hodgkin's lymphoma (NHL). Asia Pac J Clin Oncol. 2011;7(2):136-145 SOUTH KOREA	Phase II clinical trial Objective: To evaluate the safety and efficacy of RIT with radioiodinated human/murine chimeric anti-CD20 monoclonal antibody rituximab (I-131-rituximab) for treating Korean patients with relapsed or refractory B-cell NHL Method: Between May 2004 and October 2006, 24 patients received a single treatment of I-131-rituximab. All patients received unlabeled ritixumab (70mg) immediately prior to the administration of a therapeutic dose of I-131-rituximab. A dose of 200 mCi of radioiodide was chose as a fixed dose. Iodination of the antibody was done using Iodo-Beads. Whole-body scans were done using gamma camera and blood samples were collected	II-3	n=24 median age= 63 years (range 34-73 years) patients with relapsed or refractory NHL and at least one measurable lesion (longest diameter being ≥1cm), 19-75 years old with an Eastern Cooperative Oncology Group performance status 0-2, and adequate liver, renal, platelet and bone marrow functions. DLBCL = 11 Mantle Cell lymphoma = 6 Marginal zone B-cell lymphoma = 5 Follicular lymphoma = 2	I-131-Rituximab RIT		Median follow up = 55.1 months (range 31.5–69.3 months)	• Grade III or IV neutropenia occurred in 21% of patients, and grade III or IV thrombocytopenia occurred in 33% of patients. • Treatment related mortality was observed in one patient who had who had been previously treated with high dose chemotherapy plus total body irradiation (TBI) with ASCT. • Median nadirs were 31 days for platelets and 32 days for neurophils. • One patient experienced interstitial pneumonitis during the second month after treatment with I-131-rituximab.	

Evidence Table : Safety
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	to measure the radioactivity with a gamma counter. The response of the treatment was evaluated 1 month later by ^{18}F-FDG-PET-CT.							

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
7. Bienert M, Reisinger I, Srock S et al. Radioimmunotherapy using ^{131}I-rituximab in patients with advanced stage B-cell non-Hodgkin's lymphoma: initial experience. Eur J Nucl Med Mol Imaging. 2005;32(10):1225-1233. GERMANY	Uncontrolled clinical trial Objective: To evaluate the safety, toxicity and therapeutic response of non-myeloablative RIT using I-131-rituximab in previously heavily treated patients with B-cell non-Hodgkin's lymphoma (B-NHL). Method: Between March 2001 and December 2003, nine patients were treated with RIT. All patients had progressive or recurrent disease and multiple prior chemotherapies or radiotherapies (range 2-7). Eight of nine patients progressed upon immunotherapy with rituximab, two of four patients with mantle cell lymphomas received RIT for consolidation after salvage therapy. Rituximab was labelled with ^{131}I using the Iodogen method. The administered activity	II-2	n=9 4 female and 5 male; median age 59 years, range 31-74 years with relapsed, refractory or transformed B-NHL. Mantle cell lymphoma=4 Follicular lymphoma=1 DLBCL=4	I-131-Rituximab RIT	-	2–39 months (Mean=12 months)	• Four non-responders with bulky disease died 4.8±2.0 months after therapy. Three patients had an elevated serum lactate dehydrogenase (LDH) level prior to RIT and none of the patients responded. Of two patients who received RIT as an additional treatment after salvage chemotherapy, one continues to be disease-free at 9 months and one relapsed at 5 months' follow-up. • Reversible grade III or IV haematological toxicity occurred in 7 (78%) of 9 patients. Median nadirs were 35 days for platelets, 44 days for leucocytes and 57 days for erythrocytes. Four patients had epistaxis, pneumonia, neutropenic fever or anaemic dyspnoea. • 16% of the patients with with more than two prior chemotherapies had grade IV thrombocytopenia, compared to 7% with two or fewer priorchemotherapies.	

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	(2200±600 MBq) was based on a dosimetrically calculated 45 cGy total body radiation dose. All patients received an intravenous infusion of 2.5mg/kg of rituximab 7 to 14 days prior to RIT. Scintigraphy was performed with a double-head gamma camera (Hawkeye–SPECT/CT, General Electric Healthcare, Connecticut, USA) equipped with a high-energy collimator. Total blood counts were obtained at least once a week. Patients were re-staged 6–8 weeks after RIT by using imaging procedures. Thereafter, physical examination and laboratory testing was performed every 3 months or when patients developed symptoms of recurrence.							

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
8. Kruger PC, Joske DJL, Turner JH. Iodine-131 Rituximab Radioimmunotherapy: Durable Control of Follicular Lymphoma. J Nucl Med Radiat Ther. 2014; 5:4. WESTERN AUSTRALIA	Non-randomised, Uncontrolled Clinical Trial Objective: To evaluate the response and toxicity after long term follow-up of I-131-rituximab RIT in patients with follicular lymphoma under the routine clinical care of a single haematologist over a period of 12 years. Method: Radioimmunotherapy with I-131-rituximab was administered to patients according to the standard personalized dosimetry protocol predicated upon a whole body radiation absorbed dose of 0.75Gy. Four doses of maintenance rituximab were administered at three month interval following I-131-rituximab RIT. Response to treatment was assessed with 18F-fluorodeoxyglucose positron emission tomography scan	II-2	n=31 Median age of 54 years (range 30-74) All patients had histologically confirmed follicular lymphoma (FL), an Eastern Co-operative Oncology Group performance status of less than 3, life expectancy of more than 3 months and had received no rituximab within the 6 months prior to 131-I-rituximab RIT were selected.	I-131-Rituximab RIT	-	12 years	• Grade III-IV neutropenia occurred in 4/31(13%) patients. Grade III-IV thrombocytopenia occurred in 1/31(3%) patient. Subclinical hypothyroidism occurred in 4/31(13%) patients and was treated. Myelodysplasia occurred in only one patient.	

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	combined with computerized tomography scan (^{18}F-FDG-PET-CT) at 3-6 months.							

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Kuan JW, Law CS, Wong XQ et al. A pioneer experience in Malaysia on In-house Radio-labelling of ^{131}I-rituximab in the treatment of Non-Hodgkin's Lymphoma and a case report of high dose ^{131}I-rituximab-BEAM conditioning autologous transplant. Appl Radiat Isot. 2016;116:13-21 MALAYSIA	Uncontrolled clinical trial Objective: To report a pioneer experience in Malaysia on self-labelling I-131-rituximab, substituting autologous haematopoietic stem cell transplantation (HSCT) and a patient, the first reported case receiving high dose I-131-rituximab (6000 MBq/163 mCi) combined with BEAM (carmustine, etoposide, cytarabine and mephalan) conditioning for autologous HSCT. Method: Between August and October 2014, seven patients with histologically proven regractory/relapsed CD20+ indolent or aggressive NHL were selected. Prior to dosimetry studies and therapy, desired activity of I-131-rituximab was administered	II-3	n=7 median age= 60 (range 26-62 years) Patients had either exhausted available options of curative treatment or were chemo-sensitive but unable to receive autologous HSCT as the recommended treatment due to unfitness, failed peripheral blood stem cell (PBSC) mobilization or financial constraint. DLBCL: 4 FL: 2 PMBL: 1	I-131-Rituximab RIT		Median follow up = 20.7 months (8-21.8 months)	• Three patients developed grade IV haemotological toxicity, one patient developed acute hepatitis and one patient developed mild rituximab related infusion reaction.	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	intravenously following a loading dose of 375 mg/m^2 unlabelled rituximab. In-house radioiodination of ritixumab was done by using chloramine-T method. One patient with Primary Mediastinal (thymic) Large B-cell Lymphoma (PMBL) received high dose I-131-rituximab (6000 MBq or 163 mCi) combined with BEAM conditioning for autologous HSCT.							

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
10. Bishton MJ, Leahy MF, Hicks RJ et al. Repeat treatment with iodine-131-rituximab is safe and effective in patients with relapsed indolent B-cell non-Hodgkin's lymphoma who had previously responded to iodine-131-rituximab. Ann Oncol. 2008;19(9):1629-1633. AUSTRALIA	Retrospective cohort study Objective: To examine the short- and long-term effects of a second treatment with I-131-rituximab in patients with indolent B-cell NHL following a relapse. Method: Two institutional databases from January 2000 to July 2007 for retreatment of I-131-rituximab were analyzed. Response duration following first and second treatment and haematological toxicity were compared. In-house radioiodination of ritixumab was done by using chloramine-T method. After a standard loading dose of rituximab 375 mg/m2, individualized dosimetry was performed by whole-body gamma imaging of a tracer activity of I-131-rituximab followed by administration of a	II-2	n=16 All patients had had a previous response >3 months to I-131-rituximab All patients required an adequate bone marrow reserve, as demonstrated by neutrophils >1.5-109/l and platelets >100-109/l FL: 15 MCL: 1	Second course of I-131-Rituximab RIT	First course of I-131-Rituximab RIT		• 28.6% patients experienced grade III or IV neutropenia, while 26.7% patients experienced grade III or IV thrombocytopenia. Two (13%) patients required packed RBC transfusion. The median time to both neutrophils and platelet nadirs was six weeks. • Four (25%) patients developed hypothyroidism with three (19%) requiring thyroxine. One patient developed AML, with no other cases of MDS.	

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	therapeutic activity of I-131-rituximab to deliver an estimated whole-body radiation absorbed dose of 0.75 Gy. The severity of cytopenia, development of myelodysplasia (MDS), acute myeloid leukemia (AML) and hypothyroidism was noted.							

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
11. Kang HJ, Lee SS, Byun BH et al. Repeated radioimmunotherapy with ^{131}I-rituximab for patients with low-grade and aggressive relapsed or refractory B cell non-Hodgkin lymphoma. Cancer Chemother Pharmacol. 2013;71(4):945-953 SOUTH KOREA	Phase II clinical trial Objective: To investigate whether repeated administration of I-131-Rituximab at regular intervals could increase the RIT response compared to a single administration of radiolabeled mAB. Method: Between July 2005 and February 2012, 31 patients received repeated treatment of I-131-rituximab. All patients received unlabeled ritixumab (70mg) immediately prior to the administration of a therapeutic dose (200 mCi of radioidodide labelled with 30mg of rituximab diluted in 150ml of normal saline that was infused over 1 hour). Iodination of the antibody was done using Iodo-Beads. The response of the treatment was evaluated 1 month later by ^{18}F-FDG-PET-CT. If a patient	II-3	n=31 median age= 63 years (range 26-75 years) patients with relapsed or refractory NHL and at least one measurable lesion (longest diameter being ≥1cm), 19-75 years old with an Eastern Cooperative Oncology Group performance status 0-2, and adequate liver, renal, platelet and bone marrow functions. MCL: 12 DLBCL: 7 Marginal zone B-cell lymphoma: 6 Follicular lymphoma: 4 FL: 1 Small	I-131-Rituximab RIT		Median follow up=21.8 months	• Grade III or IV neutropenia occurred in 72% of patients, and grade III or IV thrombocytopenia occurred in 66% of patients. • Median nadirs were 33 days for platelets and 44 days for neurophils.	

Evidence Table : Safety
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Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	did not progress, subsequent readministration of I-131-Rituximab was performed at 4-week intervals.		lymphocytic lymphoma: 1					

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy safe for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
12. Kruger PC, Cooney JP, Turner JH. Iodine-131-rituximab radioimmunotherapy with BEAM conditioning and autologous stem cell transplant salvage therapy for relapsed/refractory aggressive non-Hodgkin lymphoma. Cancer Biother. Radiopharm. 2012;27(9):552-560 AUSTRALIA	Phase II clinical trial Objective: To investigate the response and toxicity of I-131-rituximab/carmustine, etoposide, cytarabine, and mephalan (BEAM) conditioning regimen in autologous stem cell transplantation (ASCT) for NHL. Method: Between January 2003 and January 2012, sixteen patients were treated in Fremantle Hospital. RIT with I-131-rituximab on an outpatient basis was given according to the standard personalized dosimetry protocol predicated on a whole body radiation absorption dose of 0.75Gy. The BEAM conditioning regimen was commenced on day -6. Evaluable engraftment data are available for 15 patients who had 16 ASCTs.	II-3	n=16 median age=61 years (34-71 years) Patients with relapsed, refractory, aggressive B-cell NHL DLBCL = 7 Transformed/aggressive FL = 3 MCL = 6 Mucosal associated lymphoid tissue (MALT) = 1	I-131-Rituximab RIT	-	Median follow up = 44 months (range 4-108 months)	• The median time to absolute neutrophil count >0.5·109/L was 12 days (range 9–25 days). The median time to unsupported platelet count of >20·109/L was 17.5 days (range 10–65 days). • Grade 3 or 4 toxicity comprised mucositis occured in 4 patients. • Hypothyroidism occurred in 3 patients (19%)	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
13. Wagner JY, Schwarz K, Schreiber S et al. Myeloablative anti-CD20 radioimmunotherapy +/- high-dose chemotherapy followed by autologous stem cell support for relapsed/refractory B-cell lymphoma results in excellent long-term survival. Oncotarget. 2013;4(6):899-910. GERMANY	Phase I/II clinical trial Objective: To evaluate the patient specific activity of I-131-rituximab in a myeloablative setting as a salvage therapy prior to conventional high dose chemotherapy with ASCT. Method: Between January 2000 and October 2004, 23 patients were enrolled to evaluate RIT with I-131-rituximab in a myeloablative setting. Biodistribution and dosimetric studies were performed to determine I-131 activity required to induce a total body dose of 21-27Gy to critical organs. All patients received therapeutic infusion of radiolabelled rituximab (40mg rituximab). 6/23 patients RIT was combined with high dose chemotherapy EAM. 8/23 patients received a sequential high-dose chemotherapy (BEAM protocol) followed by second ASCT.	II-3	n=23 median age=58 (range 31-67 years) Patients with confirmed relapsed or refractory NHL without CR to salvage chemotherapy Indolent lymhphoma= 65% Aggressive lymphoma= 13% Mantle cell lymphoma (MCL)=22% Stage III/IV disease=91%	• I-131-Rituximab RIT only • I-131-Rituximab RIT plus high dose chemotherapy EAM • I-131-Rituximab RIT high-dose chemotherapy (BEAM protocol) followed by second ASCT.	-	-	• One (5%) patient died after RIT plus EAM. One (5%) patient developed AML after treatment of myeloablative RIT alone. Two (9%) patients developed secondary MDS, one after myeloablative RIT alone, and the second patient after RIT/BEAM. • The higher grade III or IV toxicity were correlated with the combination of RIT plus high dose chemotherapy approach (p=0.005) and the incidence of mucositis (p=0.002).	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
14. Shin DY, Byun BH, Kim KM et al. Radioimmunotherapy with ^{131}I-rituximab as consolidation therapy for patients with diffuse large B-cell lymphoma. Cancer Chemother Pharmacol. 2016;78(4):825-831 SOUTH KOREA	Phase II clinical trial Objective: To investigate the efficacy and safety of I-131-rituximab as consolidation therapy after standard combination chemotherapy or R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisolone) in patients with diffuse large B-cell lymphoma (DLBCL). Method: Between December 2005 and June 2011, 16 patients were enrolled and treated with a single dose of I-131-rituximab as consolidation therapy after the completion of six or eight cycles of R-CHOP. The I-131-rituximab treatment was administered within 4 to 8 weeks from the last administration of R-CHOP. All patients received unlabeled ritixumab	II-3	n=16 median age = 55 years (range 50-73) Patients who had been diagnosed with advanced stage (Ann Arbor III or IV) or bulky stage II DLBCL and achieved complete or partial response after six to eight cycles of R-CHOP.	I-131-Rituximab RIT	-	Median follow-up duration = 73 months	• Toxicity events of all grades occurred in 11 patients (69%) and a grade III or IV event occurred in four patients (25%), which were all hematologic toxicities. Two patients experienced neutopenia and thrombocytopenia of grade III or more, and the other two experienced only thrombocytopenia.	

Evidence Table : Safety
Question : Is I-131-Rituximab radioimmunotherapy effective for non-Hodgkin's lymphoma?

Bibliographic citation	Study Type / Methodology	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	(70mg) immediately prior to the administration of a therapeutic dose (200 mCi of radioidodide labelled with 30mg of rituximab) injected intravenously within 4 hours from the administration of unlabelled rituximab). Iodination of the antibody was done using Iodo-Beads.							