**THERAPY, Review Article**

# Radioimmunotherapy with Yettrium90 - Ibritumomab Tiuxetan (Zevalin): A Novel Therapeutic Approach in Patients with non Hodgkin's Lymphoma

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**Non Hodgkin's Lymphoma (NHL):**

NHL represents group of closely related B- and T-cell malignancies of the lymphatic system .Most NHL are of B cell origin and express surface antigenCD20. The incidence of NHL has increased substantially in the past 20 years, now it ranks fifth in cancer incidence and mortality. The increasing incidence is poorly understood [(1)]**.** NHL's are divided clinically into aggressive or high grade lymphoma and indolent or low grade lymphoma. High grade lymphomas grow rapidly, have in general rapidly developing symptoms, but are potentially curable, they represent 65% of NHL's. Diffuse large B cell lymphoma (31% of all NHL subtypes) is the commonest aggressive type. While low grade lymphomas grow slower, have in general slower developing symptoms, most patients relapse after treatment , they represent 35% of NHL's, follicular lymphoma (22% of all NHL subtypes)is the commonest indolent type **2,3** (Fig1).

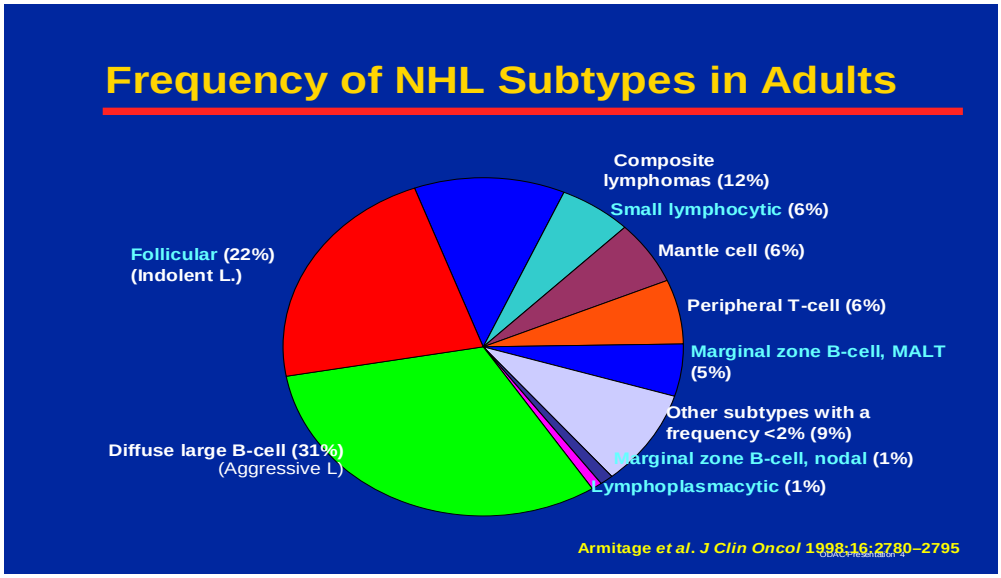


**Fig (1):** Frequency of NHL subtypes in adults (quoted from Armitage & Weisenburger, 1998 [3])

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Conventional chemotherapy regimens cure fewer than 50% of patients with aggressive NHL and fewer than 5% with indolent lymphoma. However, the majority of patients remain responsive to remarkably low doses of external beam radiotherapy. The disease course of indolent lymphomas is typically characterized by multiple relapses and progressively shorter response durations with subsequent therapies using different chemotherapeutic regimens (Fig2). Conventional chemotherapy is not curative in indolent lymphomas, with a median survival of 8-10 years [4, 5].

To improve outcome different therapeutic approaches have been tested as part of first line therapy, including immunotherapy with interferon and/or Rituximab and consolidation with myeloablative therapy followed by autologous stem cell transplantation (ASCT). These approaches induce variable complete response (CR)/unconfirmed CR (Cru) rates ranging from 20% to 75%. Additional treatment strategies are needed to further improve CR rates, thereby potentially improving response duration and outcome [6,7].

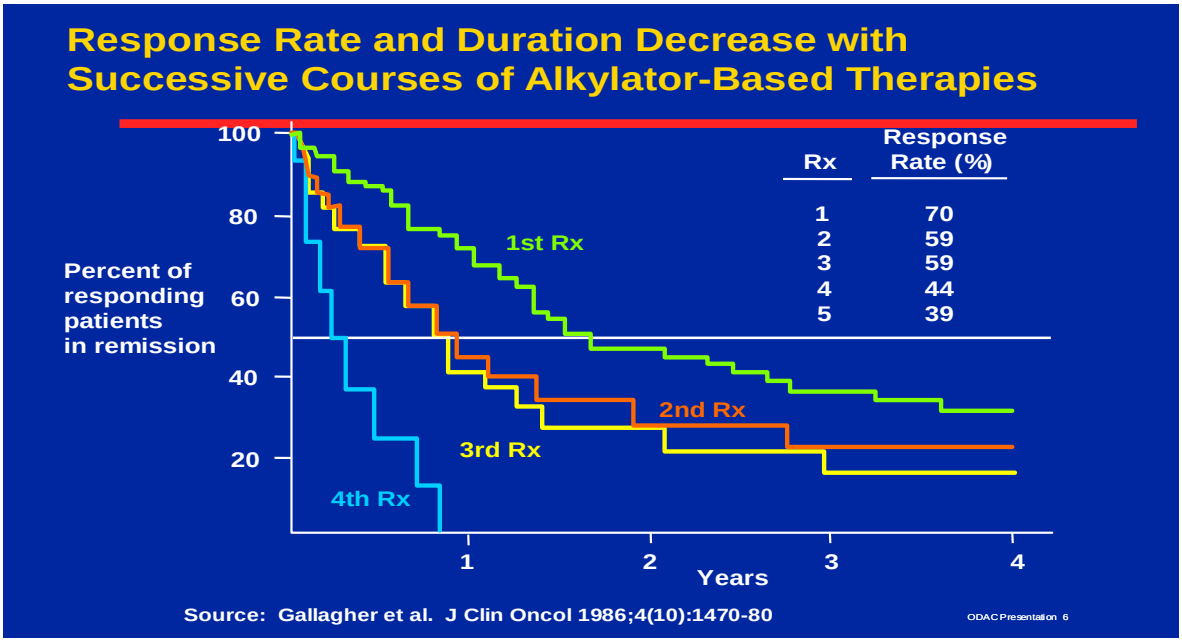



**Fig (2):** Response rate and duration of response decreases with successive chemotherapy in low grade lymphomas (quoted from Gallagher et al, 1986 [6]).

**Mechanism of action of Anti CD20**:

David Maloney in 1997**(8)** presented an overview of the mechanisms of action of immunotherapy, in particular the anti CD20 antibody, Rituximab. The characteristics of the target antigen contribute to the efficacy of antibody – directed therapy. Several factors are important. Ideally the antigen should be tumor specific and present on the cells of the malignant clone and should not be expressed on critical host cells. In addition, the antigen should be present in high density, should not be shed or secreted, modulated or mutate. Actually, CD20 is a 33-37 kDa, non-glycosylated phosphoprotein expressed on the surface of almost all normal and malignant B cells but not stem or plasma cells (Fig3) [9,10] .It acts as a calcium channel involved in B cell cycle initiation ,activation and progression . CD20 is not tumor specific but it is B cell specific; it does not modulate, does not shed

or secreted and importantly it does not appear to undergo mutation. Unfortunately, CD20 is not critical to the tumor cell and can be detected with no ill effect. It has been reported that CD20 expression correlates to some extent with tumor histology and response rate to Rituximab appears to differ with histologic subtype. However, CD20 is considered a good target antigen, suitable for both naked and radiolabeled antibodies [11, 12]

The exact mechanism of the antitumor effect of antiCD20 monoclonal antibodies remain unknown , but it is generally accepted that host immune effector mechanisms are involved including complement mediated cytotoxicity (CDC),antibody dependent cellular cytotoxicity (ADCC), and induction of apoptosis by CD20 cross linking. Also direct effects, induction of secondary immune reactions and synergy with chemotherapy can be involved in mechanism of action .It is likely that antiCD20 antibodies act through a combination of CDC,ADCC and direct effects. [12].

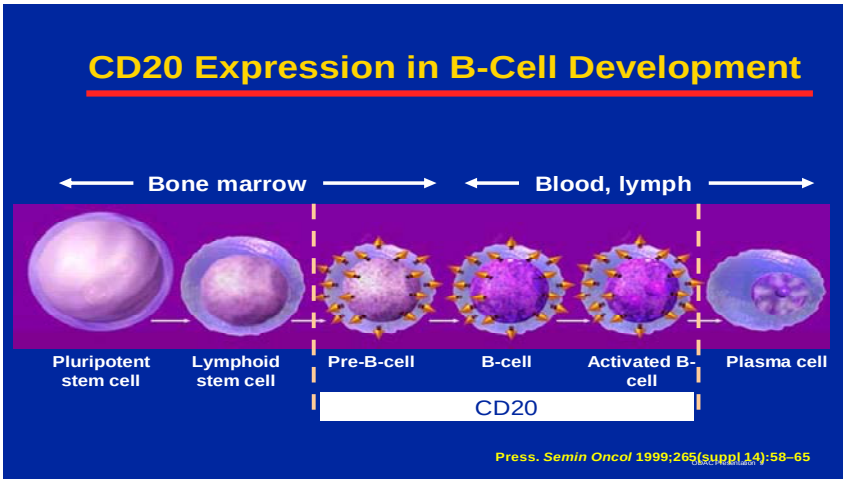



**Fig 3**: CD20 is expressed on the surface of most normal Bcells but not stem cells or plasma cells. (quoted from Press,1999 [13])

**Radioimmunotherapy (RIT):**

The use of radiolabeled antibodies as a potential cancer treatment was first explored in the 1950's. In the mid-1970's, technological advancements allowed for the design and production of monoclonal antibodies directed against specific cellular antigens, including monoclonal antibodies directed against specific tumor-associated antigens. The feasibility of combining a monoclonal antibody with a radioisotope in order to deliver a therapeutic dose of radiation to a tumor cell has been studied since the early 1980's.

NHL are inherently sensitive to irradiation and earlier stages of the disease with localized involvement are treated with radiotherapy with a curative intent. Majority of patients remain responsive to remarkably low dose of external beam radiotherapy, despite low response to conventional chemotherapy. Yet, in patients with advanced stages of the disease external beam irradiation can not be used to treat all involved sites simultaneously for fear of effects of radiation on normal tissue and significant bone marrow suppression .These

facts raise the concept of the use RIT which represents a more targeted strategy using radiotherapy involving the use of radiolabeled monoclonal antibody for targeting systemic radiation to tumor cells, sparing normal tissues with relatively less myelosuppressive effects[5]. RIT is distinct from conventional radiotherapy as it entails continuous exposure of tumor cells to low dose irradiation with intensity decreasing overtime. The effectiveness of RIT is related to cell death occurring after G2/M arrest, which appears to occur primarily through apoptosis, rather than through necrotic cell death that is characteristic of the effects of external beam irradiation and chemotherapy [13, 14].

Radiolabeled monoclonal antibodies have several advantages over unconjugated or naked monoclonal antibodies, for example, a functional immune system is not required to kill tumor cells, which is important because many patients with NHL have defective or suppressed immune system. The B emission of I-131 and Y-90 are effective over around 100-500 typical cell diameter (mean path length in soft tissue of 1mm for I131 and 5mm for Y90), resulting in a cross fire or bystandard effect on nearby tumor cells. The cross fire effect enables the eradication of cells that are not necessarily targeted by the antibody, but are affected by irradiation i.e. neighboring tumor cells that do not express the target antigen or are inaccessible to the antibody, which may be particularly beneficial for the treatment of bulky tumors and tumors that are poorly vascularized [15]. The advantages of RIT are:

- RIT delivers continuous low-dose radiation to tumour cells.
- Targeted radiation of RIT destroys neighbouring tumour cells by a 'cross-fire' effect.
- Effective in bulky or poorly vascularized tumours.
- Multiple disease sites are targeted simultaneously.
- Limited exposure of healthy tissues to radiation.

Several issues must be considered in designing a successful radiolabeled antibody. The choice of radionuclide will make a difference to the safety and efficacy of treatment [16]. The nature of the chelating agent is also important. If radionuclide is allowed to escape from an immunoconjugate; uptake by the skeleton will result in bone marrow toxicity. Minimum escape should increase the tolerable dose. The linker that holds the antibody and chelator together may also be relevant. In order to reduce radiation dose to the liver, a degradable peptide linker might be used, enabling cleavage close to radioactive metal, which should result in a small radioactive moiety that will be rapidly excreted by the kidneys and not retained. So, for successful RIT we should have specific surface antigen with the use of selective antibody to this antigen. Also, we should choose the proper isotope that has to be strongly attached to the selective antibody. The availability of these factors ensures successful RIT with zevalin [16,17].

There are two approaches in administering RIT, a single large dose or multiple small doses (fractionation). If the treatment protocol requires administration of a single therapeutic dose, the amount of radionuclide given may be the maximum tolerable dose (MTD), for the dose limiting critical tissue, usually the bone marrow. Fractionation is a strategy for overcoming non uniform radiation doses that occur because of heterogenous drug distribution resulting in underdose of some regions. The rationale behind fractionation is based on evidence

that radiation dose to the tumor and the dose tolerated to normal tissues can be increased when a fractionated dose is given compared with administration of a single dose. Fractionation resulted in significantly less bone marrow suppression in comparison to same amount of radioactivity given in a single dose, so fractionation can be used to decrease toxicity and increase MTD [18, 19]. The application of radiosensitizers can be employed with RIT as it has unique characters in that there is a time difference between irradiation of normal tissue (occurs early prior to target localization) and irradiation of the tumor, so if the timing of delivery of radiosensitizer is correct, it would be possible to achieve an enhancing effect of the radiosensitizer in the tumor and not in normal tissue. With external beam irradiation this is not possible as both normal and tumor cells are exposed to irradiation simultaneously [15].

**Yettrium 90 - Ibritumomab Tiuxetan (Zevalin):**

Zevalin comprises ibritumomab, a murine IgG1 anti-CD20 antibody, linked by a chelator, tiuxetan, to the radioisotopeY-90.Tiuxetan is covalently linked to ibritumomab through the Fc portion of the antibody, providing a high affinity chelation site for either Y-90, or for imaging purposes Indium-111.So Zevalin is considered an ideal radioimmunotherapeutic agent, with highly specific antibody to which is attached strongly the proper isotope(Y-90), through a strong chelator,Tiuxetan (Fig4). Dosimetry and imaging studies using In111 –labeled Zevalin revealed generally low uptake of radioactivity by organs throughout the body (in particular the bone marrow), with rapid uptake by the tumor. Dosimetry and imaging are useful to demonstrate specific tumor targeting and radiation absorbed doses for tumor and normal tissues which can be calculated to determine dose limiting tissues for RIT. Dosimetry does not correlate with toxicity and no longer necessary in the standard use of Zevalin [19,20]. Clinical variables, such as baseline platelet count, percentage bone marrow involvement and patient weight have proved to be more predictive of toxicity than dosimetry [15].

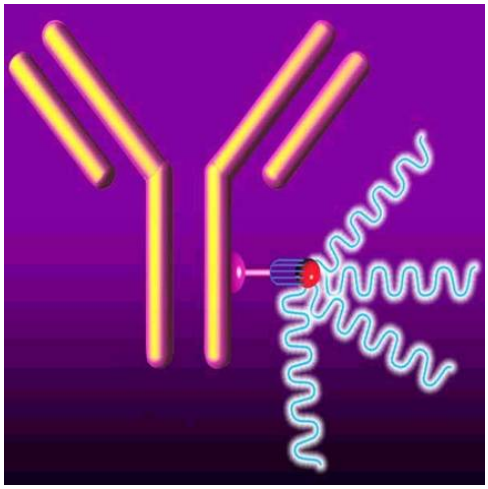


**Fig. (4):** Zevalin: antibody(Ibritumomab) linked strongly to Y90 through chelator (tiuxetan). (quoted from Chinn et al,1999[21])

**Clinical efficacy of Zevalin:**

In the last decade of the previous century, a lot of studies had been started to assess the role of zevalin in patients with NHL. These include phase I, II and III studies done on around 500 patients. These studies were done on patients with relapsed or refractory low-grade follicular NHL, CD20+ transformed B-cell NHL and patients with rituximab-refractory follicular NHL. Zevalin regimen entails giving Rituximab 250mg /m 2 infusion in day 1, in day 8 the same dose of Rituximab is given followed by Zevalin infusion in a dose of 0.4mCi/Kg if platelets count is more than 150,000/cc (maximum allowable dose is 32mCi) or 0.3mCi/Kg if the platelets count ranges from 100,000 to 150,000/cc. Cold antibody is an important component of the treatment regimen, it is used to bind to peripheral antigen sites. It will bind and deplete B cells in the peripheral blood and bone marrow, and around 80% of B cells in the lymph nodes. When preceded by cold antibody, the radiolabeled antibody will localize to the lymph nodes and bind to B cells not bound by the cold antibody **(15).** So, the role of unlabeled antibody is to optimize radiolabeled antibody concentration in tumor sites presumably by partially saturating easily accessible B cells in the blood and the spleen and permitting sufficient radiolabeled antibody to by pass these sites and penetrate less accessible compartments (17).

Results showed that zevalin is effective and well tolerated in patients with relapsed or refractory follicular or transformed NHL .In a phase III study zevalin was compared with single agent rituximab. The overall response rate (ORR) was significantly greater in the zevalin arm, the ORR with zevalin was 80% with complete response in 30% of patients. These figures were 56% and 15% respectively for rituximab, with a statistically significant difference in favor of zevalin(p value:0.002).Time to disease progression (TTP), duration of response and time to next treatment were longer in the zevalin arm in responders and in those who achieved complete remission, yet the difference was not statistically significant (22,23).

Patients who are refractory to rituximab have also been successfully treated with Zevalin, In a study done on 54 patients with low grade NHL who had failed to respond to rituximab or had relapsed within 6 month of receiving rituximab therapy. The ORR rate to Zevalin was found to be 74%, out of them 15% showed CR and 59% showed partial response (PR). The ORR to the most recent prior treatment with rituximab was 31%, the difference was statistically significant ($p< 0.001$). The median duration of response with zevalin therapy was 11.5 months compared with 3 months for the previous treatment with rituximab ($p<0.001$) (24,25).

In patients with mild thrombocytopenia (platelets count: 100,000-150,000/cc), in whom we are obliged to reduce the dose of Zevalin (0.3mCi/Kg), the ORR to zevalin was reported to be 83%, (CR rate of 37%; 10% Cru and 36% PR). The TTP for all patients was 9.4 months, while for responders it was 12.6 months. These date confirmed that zevalin remains effective at this low dose level (0.3 mC/kg) (26).

All these data with an overall response rate around 80% and CR rate reaching up to 47% paved the way to FDA approval for the application of RIT with zevalin in patients with NHL in February 2002.

In USA, the FDA has required imaging for safety purposes to determine biodistribution, so immediately after the cold antibody

infusion in day 1, injection of In-111 labeled zevalin was added to the protocol. Biodistribution was assessed by a visual examination of whole body planar imaging at 2-24 hours, 48-72 hours and if necessary at 90-120 hours after injection. The first image can be expected to display detectable uptake in blood pool areas, with less activity on subsequent images. There is likely to be high uptake in normal liver and spleen, but low uptake in kidneys, urinary bladder and bowel. Altered biodistribution can be detected by imaging as prominent bone marrow uptake in early scan, diffuse uptake in lungs ,renal uptake or intense areas of bowel uptake .However, there is evidence that if the appropriate inclusion/exclusion criteria for patients to receive zevalin are adhered to ,imaging does not improve safety, these exclusion criteria include patients with impaired bone marrow reserve as determined by platelets less than 100,000/mm or neutropenia less than 1500/mm, bone marrow with more than 25% lymphoma, hypocellular bone marrow (cellularity less than 15%), marked reduction in bone marrow precursors ,failure of stem cell collection , radiotherapy to more than 25% of bone marrow as well as prior high dose myeloablative therapies including previous RIT [19,20].

Yet, it was addressed that sequential doses of zevalin could be administerd to patients with low grade NHL, without the use of prophylactic growth factors. Eligible patients had relapsed following previous treatment, with platelets more than 150000/mm, absolute neutrophil count more than 1500/mm and adequate stem cell harvest. A second zevalin dose of 0.2mCi/Kg body weight can be given 3-6 month post the initial dose of zevalin. It was concluded that these doses of zevalin can be administered safely and did not require the use of stem cells or prophylactic growth factors [27].

Many post FDA approval studies had been done to maximize efficacy and minimize adverse events of RIT applying zevalin early in the course of the disease whether prior to or immediately after chemotherapy. Also, it was studied prior to ASCT or in association with other monoclonal antibodies .The goal of these studies is developing a multimodality approach that combines RIT with other biologic agents and possibly chemotherapy as front line treatment to improve outcome in patients with NHL.

Wiseman and Witzig in 2005**(28)** confirmed the long term response in patients with relapsed/refractory NHL to zevalin despite failure to response to prior therapy. They stated that the latter does not preclude achieving a long term response with zevalin[28]. These data were also confirmed by Jacobs et al 2005 [29] who reported that zevalin treatment may provide a clinical benefit in carefully selected extensively treated patients with low grade NHL.

Joyce et al, 2005 [30] stated that Yttrium 90 is feasible and safe in NHL patients with a history of ASCT. Nademanee et al, 2005[31] employed high dose Zevalin in combination with high dose etoposide and cyclophosphamide followed by autologous stem cell transplantation in patients with poor risk or relapsed NHL. They reported that this regimen is well tolerated with overall 2 year survival of 92% and relapse free survival of 78%.They demonstrated the feasibility of administering high dose zevalin with high dose etoposide and cyclophosphamide followed by ASCT[31]. Several single arm studies have also demonstrated that upfront RIT administered either alone or with chemotherapy to previously untreated indolent non Hodgkin's

lymphoma patients results in an overall response rates of 90-100%, complete response rates of 60-95% and durable remission [32].

Some trials employed Zevalin in the treatment of Patients with Relapsed/ Refractory diffuse Large B-cell Lymphoma (DLBCL) and in Relapsed /Refractory mantle Cell Lymphoma (MCL). Initial results showed that Zevalin has useful activity in treatment of DLBCL and MCL with no unexpected toxicities, they reported that further studies are needed to assess the exact role of zevalin in these types of high grade lymphomas [33, 34]. Also, it was reported that the addition of Zevalin to a standard condition regimen for patients undergoing ASCT improves overall survival and progression-free survival among older patients with diffuse large B-cell lymphoma, These favorable outcomes suggest that prospective study in a randomized trial is warranted for proper evaluation of role of zevalin on survival in this particular group of patients [35].

It was reported by Jacobs et al,2008 [36] that adding zevalin RIT to a short course first-line treatment followed by rituximab weekly for four weeks almost doubled the rate of complete response in patients with follicular lymphoma, from 46% with a standard treatment regimen to 89%. These data add to the growing body of evidence that using RIT as part of front-line treatment may increase complete response rates. It is actually now believed that zevalin may play an important role in the treatment of lymphoma in the front-line setting and it was reported that data continues to underscore the impact that RIT can have in treatment of NHL [36].

The results of the First -line Indolent Trial (FIT study)by Morschhauser et al,2008 [7] was the first study presenting impressive evidence that zevalin consolidation dramatically improved the median progression free survival(PFS) in all patient population regardless of prognostic score or chemotherapy induction regimen. They reported that RIT with zevalin resulted in high conversion rate from PR to CR/Cru, found in 77% of patients regardless of type of first line treatment regimen administered. They also reported high overall complete remission rate of 87% and significant prolongation of median PFS. They finally concluded that consolidation with zevalin has proven to be highly effective in patients with advanced stage follicular NHL in first remission [7].

Another study published by Devizzi et al [37] studying the efficacy of high dose Y-90 Zevalin after five sequential cycles of chemotherapy as an outpatient preparative regimen for autologous hematopoietic cell transplantation .They stated that after a median observation time of 30 months ,the overall response rate was 87% and event free survival rate (EFS)was 69%.They finally concluded that high dose Y-90 Zevalin is an innovative myeloablative regimen with no significant short term toxicity and wide applicability [37].

Together these last two studies published in November 2008 seemed to confirm and extend prior data demonstrating the tremendous potential role of RIT for the treatment of B cell NHL at diagnosis and after relapse at both conventional and myeloablative doses [17].

**Adverse events:**

No acute adverse events have been described with $^{90}$Y-ibritumomab tiuxetan treatment, but steroids and antihistamines should be available for use in the event of an allergic reaction [38]

Adverse Events (AEs) are primarily haematological and are predictable and manageable, they are consequent to temporary myelosuppression, that is, primarily, granulocytopenia and thrombocytopenia. Haematological nadirs are usually reached 4–8 weeks after administration of $^{90}$Y-ibritumomab tiuxetan**.** The majority of patients with grade 3 or 4 haematological toxicities do not require transfusion or growth factor support. Grade 4 neutropenia was reported in 30% of patients and grade 4 thrombocytopenia in 10% of patients[39].Despite the relatively high incidence of grade 3 and 4 neutropenia, the percentage of patients requiring hospitalization for infection in several studies were only around 7% [7]. Other studies reported that platelet transfusion was needed in 18%-22% of patients and red blood cell transfusion in 12%[22], these figures are comparable or even less than those reported for different chemotherapeutic regimens employed for treatment of patients with relapsed NHL. An important issue is that zevalin is not associated with common AEs commonly encountered with chemotherapy (e.g. hair loss, severe mucositis, persistent nausea, vomiting) **[7].**

Most Frequent Non-haematological AEs are primarily Grade 1–2as asthenia, chills, fever, flushing, pruritis, headache, throat irritation, dizziness, abdominal pain, ecchymosis, coughing and rash (Fig5)[39]

A potential toxicity of real concern with radioimmunotherapy is secondary malignancies, in particular myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), in a recent survey of 746 patients treated with standard dose of zevalin the cumulative incidence of these malignancies at 2 years was 1.9% [40].In the study done by Devizzi et al,2008 on 30 patients with NHL treated with zevalin prior to ASCT **(37)** no single case of MDS or AML has been reported during a follow up period of 30 month after high dose RIT**.**

**Practical precautions with zevalin**

Hypersensitivity reactions are rare (~1%) but possible .Patients who have previously received mouse-derived proteins should be tested for HAMA before administering Zevalin [41].

-Regular monitoring of haematological toxicity is required, nadir occurs around 4-8 weeks after start of treatment with median time to recovery of 1–3 weeks. Weekly complete blood counts should be performed from 2 weeks after $^{90}$Y-ibritumomab tiuxetan administration until recovery from cytopenia. Particular attention should be given to the development of thrombocytopenia. If the platelets count falls to 30 x $10^9$/l, the count should be checked at least three times per week until signs of recovery occur. If the platelets count continues to fall below 30 x $10^9$/l, platelet transfusion should be given according to local guidelines. Anaemia is generally relatively mild; however, if required, red blood cell transfusions and/or recombinant erythropoietin may be administered, according to local guidelines. Antibiotic prophylaxis is not routinely required for patients with granulocytopenia, and support with haematopoietic growth factors should be left at the discretion of the treating physician, and in accordance with local guidelines [38]**.**

**-**Effects on fertility and reproductive function are unknown, men and women should use contraception for 1 year [41]**.**

**Safety profile**

During zevalin clinical development, individual tumor radiation absorbed dose estimates as high as 778 cGy/mCi have been reported. Although solid organ toxicity has

not been directly attributed to radiation from adjacent tumors, careful consideration should be applied before proceeding with treatment in patients with very high tumor uptake next to critical organs or structures[42].

As regards the patient himself the highest radiation absorbed dose goes to the spleen then to the liver. All radiation absorbed doses are well below the accepted tissue dose limits (fig6)[20,43].

As Y-90 is a pure beta emitter, there is minimal exposure to personnel from treated patients (0.00295 mSv/h at1 m immediately after dosing) so isolation room is not required and outpatient administration is possible (depending on region/local regulations):

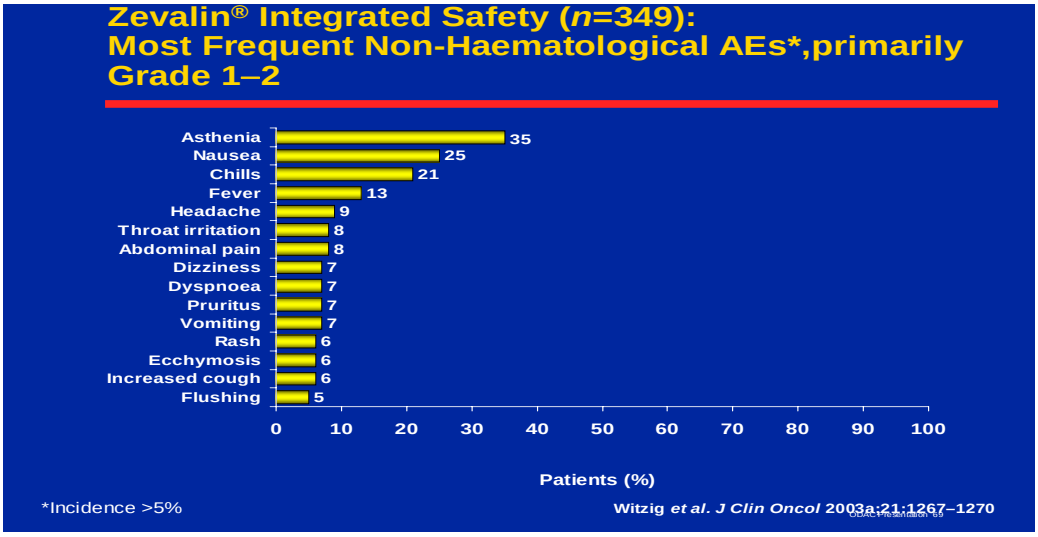



**Fig (5):** Most frequent non hematological toxicities (quoted from Witzig et al,2003[39])

- Exposure to patient's family members (first week ~0.035 mSv) is in the range of European background radiation (0.04–0.15 mSv/week)
- Cumulative maximum urinary excretion over 1 week = 85 MBq (2.3 mCi).
- No relevant gastrointestinal excretion has been found.
- Small amounts of blood (e.g. menstruation, cuts, haemorrhoids) contain critical levels of radioactivity.

For safety of the patient and contacts the patient is released after zevalin therapy with the following precautions [44,45],for 1 week after treatment patient should clean up spilled urine and dispose body-fluid–contaminated material, so that others will not inadvertently handle it (i.e. flush down the toilet or place in a plastic bag in household waste) .Also, hands should be washed thoroughly after using the toilet. For 1 year after treatment, the patient should use reliable contraception methods [44].

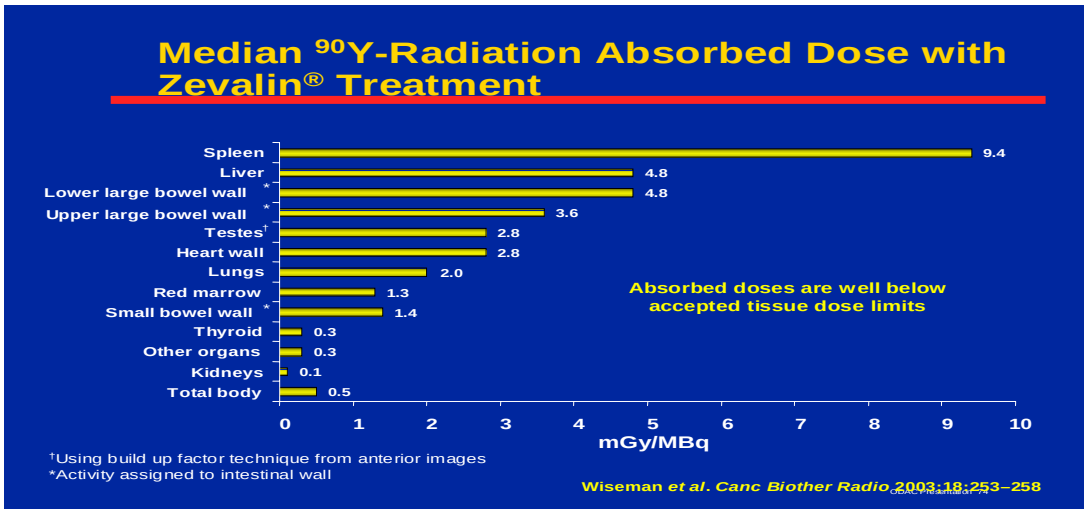



**Fig (6):** Median radiation absorbed dose with zevalin (quoted from Wiseman et al, 2003[43])

**Patient follow-up after $^{90}$Y-ibritumomab tiuxetan treatment**

In view of the supportive care that may be required, it is strongly recommended that a haemato-oncologist is responsible for the follow-up of patients given $^{90}$Y-ibritumomab tiuxetan. However, the nuclear medicine physician must be kept informed of the patient's progress, and documentation of long-term follow-up should be available. Follow-up examinations should include weekly complete blood counts (including platelets), which should start from week 2 following $^{90}$Y-ibritumomab tiuxetan administration and continue until recovery occurs from thrombocytopenia and/or granulocytopenia. If indicated, physical examinations should also be conducted. Response to treatment should be assessed at 3 months after administration of $^{90}$Y-ibritumomab tiuxetan, using international guidelines of response criteria. Clinicians should be aware that the quality of response may improve beyond 3 months[38, 46].

**Evaluation of response**

Standardized criteria for response assessment in patients with lymphoma rely mostly on measurement of tumor size by CT scan. Yet, the positive predictive value of CT may be as low as 40%, as anatomical imaging is not optimal for discriminating active disease from post therapeutic fibrosis. Metabolic imaging using PET can take the upper hand in this particular issue. CR or PR are diagnosed by either modalities (Fig7& Fig8). The concept of CR uncertain (Cru) reflects the unknown significance of persistent radiologic abnormalities in patients who otherwise seem to be in CR. The value of functional or metabolic imaging has been raised in these particular patients with assessment of response using PET/CT (Fig 9), which was reported by many authors to be the most useful imaging modality for assessment of response in these group of patients .It was reported that a decrease of 89% in the FDG-PET uptake index allows outcome prediction with high specificity. Data demonstrate that FDG-PET can discriminate accurately between active lymphomatous infiltrates and non active fibrotic tissue, it is also an important prognostic tool with a high negative predictive value [47].

The use of combined FDG PET/CT may enable superior assessment of response to 90Y–ibritumomab tiuxetan treatment than the use of CT alone, at which one may

underestimate 90Y–ibritumomab tiuxetan response by considering inactive residual CT masses to be residual disease [48].

Jacene et al, 2009 [49] concluded that in non-Hodgkin's lymphoma, $^{18}$F-FDG uptake in tumors typically drops significantly after RIT. A continued decline in tumor SUV max between 12 and 24 weeks without additional therapy can occur, suggesting a need for delayed-response assessment. In patients who progress after RIT, new sites of disease commonly develop, rather than recurrence or progression at previous disease sites. They also reported that large declines in $^{18}$F-FDG uptake tend to be seen in those with the longest progression-free survival [49].

**Fig 7:** Complete response

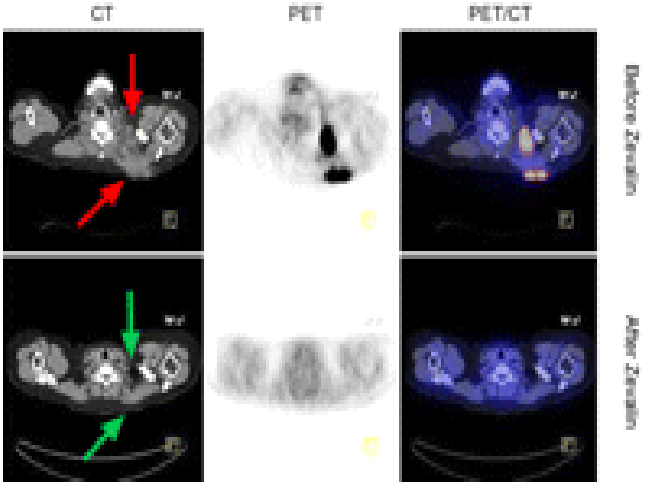



**Fig 8 :** Partial response

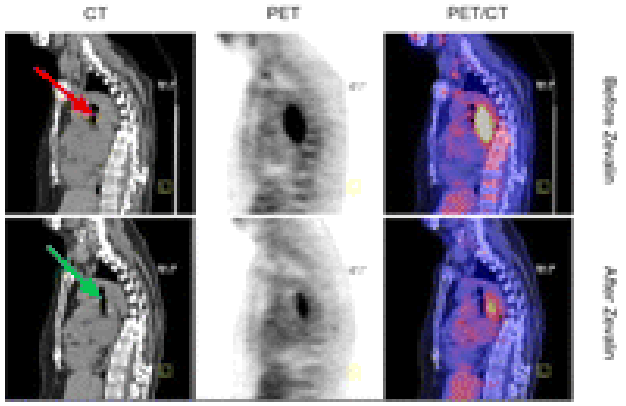
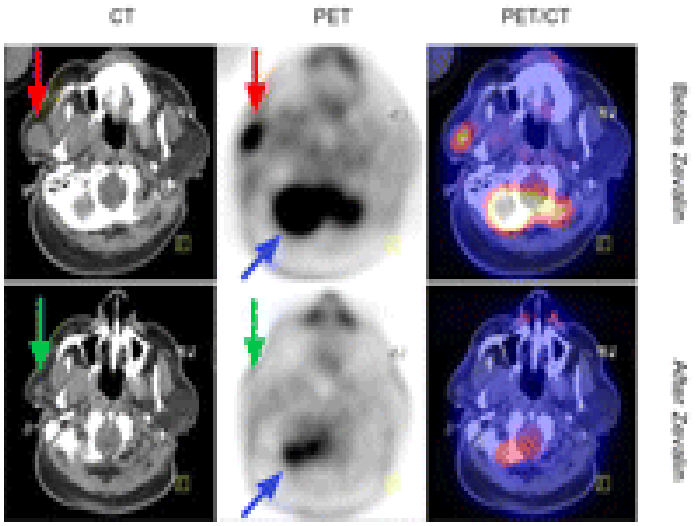


**Fig 9:** Partial response by CT scan of the mass in right parotid region, with complete response by PET,with significant reduction of SUV from 6.3 to 1.2.




**(Fig7, 8&9):** Upper raw: pre-zevalin PET/CT-Lower raw: Post-zevalin PET/CT (quoted from Jacene et al, 2009 [49])

**The underuse mystery**

With the current data as regards effect of zevalin with high response rate, ease of administration, long PFS, manageable adverse events and good tolerability ,it was expected that the drug is going to take off rapidly despite low initial sales , like another slow starter, rituximab, approved 5 years earlier. To the degree that with introduction of zevalin users fear that other lymphoma drugs will disappear. But what happened was completely the reverse, over 4 years, sales of Zevalin, improved little and are now declining. A second lymphoma radiopharmaceutical, Bexxar (131I-labeled tositumomab), approved in June 2003, was less lucky than zevalin and has sold even less [(50)].

There is a lot of debate about the reason of the underuse mystery. It seems to be related at least partially to logistic and financial issues involved in transfer of care from the oncologist to nuclear medicine physician. Also, there is doctor's discomfort in giving radioactive material due to exaggerated fears of delayed effects such as marrow damage and secondary malignancies .The cost of RIT is not the reason, either; it's no more expensive than chemotherapy plus rituximab[(17)].

The main knock against RIT is that it hasn't yet shown a survival advantage for patients, which is the ultimate standard for cancer therapy. None of the studies showed a statistically significant survival advantage. But of course it hasn't been demonstrated for many of the other agents that have been widely used. Large randomized clinical trials that should settle the survival question for RIT are under way and if RIT proved to have a survival advantage, it will take the upper hand in management of patients with relapsed or refractory low grade NHL [(50, 51)].

Finally, it is concluded that the effect of RIT in treatment of NHL is tremendous, at diagnosis and after relapse at both conventional and myeloablative doses. RIT

is given on out patient basis with few precautions to the patient and his family. AE's are mainly haematological. If overall survival advantage in favor of RIT is proved, RIT should take the upper hand in management of patients with B cell lymphomas. With all these encouraging results several questions remain unanswered regarding RIT. It is not known at what phase of the disease the application of RIT is optimal, however, if patients were treated earlier in the course of their disease, tumors would probably be smaller and the bone marrow may not have been severely compromised by other agents. Furthermore, treatment of other indolent and aggressive lymphomas should be addressed and combined modality treatment examined, prospective phase III randomized trials are required to tackle these issues.

The future success of RIT lies in the communication between oncologist and nuclear medicine physician, actually communication is the key to the progress of RIT. A team approach of the oncologist, oncology nursing staff, radiopharmacist, radiation safety officer, nuclear medicine and radiation oncology personnel is mandatory to achieve this success, they need to work together not only for the benefit of the patients but for the benefit of research.

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