Radioimmunotherapy—A New Approach in the Management of Non-Hodgkin Lymphoma

a report by
Timothy M Illidge

Professor, Targeted Therapy and Oncology, Christie Hospital, Manchester

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Timothy M Illidge is Professor of Targeted Therapy and Oncology and Cancer Research UK (CRUK) Senior Clinical Research Fellow at the CRUK Paterson Institute and Christie Hospital in Manchester, UK. He serves on the radiotherapy and lymphoma groups of the National Cancer Research Institute and is chairman of the research committee of the Royal College of Radiologists. He currently leads the pre–clinical and clinical radioimmunotherapy programme at the Christie Hospital at Manchester University, where he has a special interest in the management of lymphoma. Dr Illidge completed research fellowships at the Cancer Research Council (UK) where he was Senior Lecturer and Honorary Consultant in Oncology at Southampton University Hospitals NHS Trust, and at Stanford University, California, where he was a member of the clinical radioimmunotherapy programme. After completing an undergraduate degree at London University, he received his medical degree from Guy's Hospital Medical School (London) and his PhD from the University of Southampton (UK).

Despite the sensitivity of most lymphomas to initial therapy with chemotherapy or radiotherapy, the majority of patients with advanced non-Hodgkin's lymphoma (NHL) eventually relapse and die of their disease.[1] Furthermore, patients with advanced low-grade lymphomas remain incurable and their survival has not altered since the early 1960s.[2] The introduction of monoclonal antibody (mAb)-based therapy initially with rituximab in the late 1990s and, more recently, with the conjugation of radioisotopes to mAb as part of radioimmunotherapy (RIT) has provided fresh hope for NHL patients that their prognosis can be improved. Rituximab has now become integrated in the treatment of most NHL and while the response rates of rituximab as a single agent remain modest, with complete response rates in single figures,[3] combining rituximab with combination chemotherapy (CHOP) has shown a survival advantage when used in the treatment of aggressive lymphomas, and dramatic improvements in progression-free survival.[4-6]

To date, antibodies directed toward the CD20 antigen have dominated the field of mAb therapy and RIT of lymphoma. CD20 is highly expressed on mature B-cells and present on 95% of B-cell lymphomas,[7,8] It is neither internalised nor shed from the cell surface and appears on binding to mAbs to initiate signaling and trigger apoptosis through a caspase-dependent pathway.[8]

^{131}I labelled tositumomab (Bexxar™) and ^{90}Y labelled ibritumomab tiuxetan (Zevalin®) are highly promising therapies with significantly increased overall and complete response rates over rituximab. Both drugs appear able to offer long durable remissions for some patients. As Zevalin is the first and only one of this class of radioimmunconjugates to have been granted EU approval (May 2004), this brief article will be limited to describing Zevalin.

The introduction of Zevalin has some parallels with the initial introduction of rituximab into clinical practice in the late 1990s. There is no doubting that this is an active drug but considerable uncertainty remains as to when and how to best integrate Zevalin into clinical practice even within the licensed indication of relapsed follicular lymphoma. Furthermore, there are many new opportunities to explore integrating Zevalin into the treatment of other NHL.

Over the last year, encouraging data has emerged that suggests that Zevalin may play a useful role as consolidation after brief chemotherapy for untreated follicular lymphoma. It can form a component in the treatment of diffuse large B-cell lymphoma (DLBCL) and may be integrated into the conditioning regimen for autologous stem cell transplant instead of total body irradiation (TBI).

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What is Zevalin RIT?

Zevalin is composed of the monoclonal antibody ibritumomab, covalently bound to tiuxetan, a high-affinity chelator for the radioisotope ^{90}Y Ibritumomab is a murine IgG1 kappa monoclonal antibody that specifically targets the CD20 antigen.[9] The tiuxetan chelator creates a high-affinity, stable urea-type bond between the antibody and the radioisotope, to prevent the radioisotope dissociating and circulating around the body.[10]

The Zevalin treatment consists of a pre-treatment of the rituximab. The regimen is delivered over seven to nine days on an out-patient basis. A typical course of treatment involves a one-day iv infusion of rituximab 250mg/m^2; a second iv infusion of rituximab on day seven, eight or nine; immediately followed by a iv 'slow push' 10-minute infusion of ^{90}Y-labelled Zevalin. By labelling mAbs with beta-emitting radioisotopes, radiation can be targeted to the tumor increasing the potential for clinical response. Lymphomas are highly radiosensitive tumors and localised irradiation is the only treatment that potentially offers curative treatment for those patients with early-stage low-grade lymphomas.[10] RIT has the potential advantage over other mAb-directed therapy in that it may kill tumor cells not directly targeted by the mAb via the 'crossfire effect'. This can provide cell kill to adjacent, antigen-negative tumor cells.[10,11]

The unlabelled antibodies may bring about anti-tumor effects not only by recruiting the host immune system but also through inducing cell cycle arrest or apoptosis. Pre-clinical work indicates that intrinsic cytotoxicity of mAb in RIT may be as important as its ability to effectively deliver targeted radiotherapy.[12,13] This suggests that there may be a synergistic interaction between the mAb effector mechanisms and the radiation.

^{90}Yttrium (now licensed for use with Zevalin under the brand name Yttracis®) offers a number of advantages over the most commonly used radioisotope in oncology practice ^{131}Iodine. ^{90}Y is a pure beta emitter delivering higher energy radiation (2.3MeV v 0.6MeV) at a longer path length (5.3mm versus 0.8mm). This enhances the crossfire effect and may be advantageous in treating larger, less well-vascularised tumour nodules.[8] The physical half-life is 64 hours, which matches the biological half-life of murine monoclonal antibody of Zevalin, and the absence of penetrating gamma emissions enables delivery as an out-patient.

Zevalin is dosed according to the patient's body weight and baseline platelet counts. For patients with platelet counts ≥150,000/mm^3, 5MBq/kg body weight is given, up to a maximum allowable dose of 1200MBq. For patients with platelet counts of 100,000–149,000/mm^3, Zevalin is dosed at 11MBq/kg, up to a maximum allowable dose of 1200 MBq.

Figure 1: Dosing Schedule for Zevalin[13]

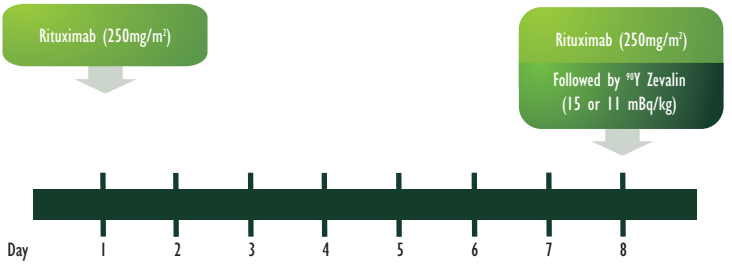

Table 1: Results of Initial Studies of Zevalin

	Phase I/II	Phase II	Phase III
	n=51	n=30	n=73
Overall Response %	73	83	80
Median DR (months)	11.7	11.5	13.9
CR, Cru %	29*	47	34
Median DR (months)	28*	23	23
On–going CR, Cru %	19	14	32
Median DR (months)	62.1	41.2	42.2
Range	60+ to 66+	40+ to 42+	33+ to 48+

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Gordon et al., Blood *(2004);103(12): pp. 4,429–4,431.*

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ZEVALIN,® as part of the ZEVALIN therapeutic regimen, is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma (NHL), including patients with Rituximab-refractory follicular NHL.

Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates. The effects of the ZEVALIN therapeutic regimen on survival are not known.

WARNINGS

Fatal Infusion Reactions: Deaths have occurred within 24 hours of Rituximab infusion, an essential component of the ZEVALIN therapeutic regimen. These fatalities were associated with an infusion reaction symptom complex that included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first Rituximab infusion (see WARNINGS and ADVERSE REACTIONS). Patients who develop severe infusion reactions should have Rituximab, In-111 ZEVALIN, and Y-90 ZEVALIN infusions discontinued and receive medical treatment.

Prolonged and Severe Cytopenias: Y-90 ZEVALIN administration results in severe and prolonged cytopenias in most patients. The ZEVALIN therapeutic regimen should not be administered to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve (see WARNINGS and ADVERSE REACTIONS).

Severe Cutaneous and Mucocutaneous Reactions: Severe cutaneous and mucocutaneous reactions, some with fatal outcome, have been reported in association with the ZEVALIN therapeutic regimen. Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further component of the ZEVALIN therapeutic regimen and should seek prompt medical evaluation (see WARNINGS and ADVERSE REACTIONS).

Dosing

- The prescribed, measured, and administered dose of Y-90 ZEVALIN should not exceed the absolute maximum allowable dose of 32.0 mCi (1184 MBq).
- Y-90 ZEVALIN should not be administered to patients with altered biodistribution as determined by imaging with In-111 ZEVALIN.

In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

Please see full prescribing information for ZEVALIN and Rituximab including their respective Boxed WARNINGS, available at www.ZEVALIN.com

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Brief Summary of Prescribing Information

WARNINGS

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In-111 ZEVALIN and Y-90 ZEVALIN are radiopharmaceuticals and should be used only by physicians and other professionals qualified by training and experienced in the safe use and handling of radionuclides.

INDICATIONS AND USAGE: ZEVALIN, as part of the ZEVALIN therapeutic regimen is indicated for the treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma, including patients with Rituximab refractory follicular non-Hodgkin's lymphoma. Determination of the effectiveness of the ZEVALIN therapeutic regimen in a relapsed or refractory patient population is based on overall response rates. The effects of the ZEVALIN therapeutic regimen on survival are not known.

CONTRAINDICATIONS: The ZEVALIN therapeutic regimen is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product, including Rituximab, yttrium chloride, and indium chloride.

WARNINGS (See BOXED WARNING):Altered Biodistribution: Y-90 ZEVALIN should not be administered to patients with altered biodistribution of In-111 ZEVALIN. In a post-marketing registry designed to collect biodistribution images and other information in reported cases of altered biodistribution, there were 12 (1.3%) patients reported to have altered biodistribution among 953 patients registered.

Severe Infusion Reactions (See PRECAUTIONS, Hypersensitivity): The ZEVALIN therapeutic regimen may cause severe, and potentially fatal, infusion reactions. These severe reactions typically occur during the first Rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reaction may include hypotension, angioedema, hypoxia, or bronchospasm, and may require interruption of Rituximab, In-111 ZEVALIN, or Y-90 ZEVALIN administration. The most severe manifestations and sequelae may include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. **Because the ZEVALIN therapeutic regimen includes the use of Rituximab, see also prescribing information for RITUXAN (Rituximab).**

Cytopenias (See ADVERSE REACTIONS, Hematologic Events): The most common severe adverse events reported with the ZEVALIN therapeutic regimen were thrombocytopenia (61% of patients with platelet counts <50,000 cells/mm^3) and neutropenia (57% of patients with absolute neutrophil count (ANC) <1,000 cells/mm^3) in patients with ≥150,000 platelets/mm^3 prior to treatment. Both incidences of severe thrombocytopenia and neutropenia increased to 78% and 74% for patients with mild thrombocytopenia at baseline (platelet count of 100,000 to 149,000 cells/mm^3). For all patients, the median time to nadir was 7-9 weeks and the median duration of cytopenias was 22-35 days. In <5% of cases, patients experienced severe cytopenia that extended beyond the prospectively defined protocol treatment period of 12 weeks following administration of the ZEVALIN therapeutic regimen. Some of these patients eventually recovered from cytopenia, while others experienced progressive disease, received further anti-cancer therapy, or died of their lymphoma without having recovered from cytopenia. The cytopenias may have influenced subsequent treatment decisions.

Hemorrhage, including fatal cerebral hemorrhage, and severe infections have occurred in a minority of patients in clinical studies. Careful monitoring for and management of cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the ZEVALIN therapeutic regimen are necessary. Caution should be exercised in treating patients with drugs that interfere with platelet function or coagulation following the ZEVALIN therapeutic regimen and patients receiving such agents should be closely monitored.

The ZEVALIN therapeutic regimen should not be administered to patients with ≥25% lymphoma marrow involvement and/or impaired bone marrow reserve, e.g., prior myeloablative therapies; platelet count <100,000 cells/mm^3; neutrophil count <1,500 cells/mm^3; hypocellular bone marrow (≤15% cellularity or marked reduction in bone marrow precursors); or to patients with a history of failed stem cell collection.

Severe Cutaneous and Mucocutaneous Reactions (See BOXED WARNINGS and ADVERSE REACTIONS): There have been postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis in patients who received the ZEVALIN therapeutic regimen. Some of these events were fatal. The onset of the reactions was variable; in some cases, acute, (days) and in others, delayed (3-4 months). Patients experiencing a severe cutaneous or mucocutaneous reaction should not receive any further components of the ZEVALIN therapeutic regimen and should seek prompt medical evaluation.

Secondary Malignancies: Out of 349 patients treated with the ZEVALIN therapeutic regimen, three cases of acute myelogenous leukemia and two cases of myelodysplastic syndrome have been reported following the ZEVALIN therapeutic regimen (see ADVERSE REACTIONS).

Pregnancy Category D: Y-90 ZEVALIN can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Creutzfeldt-Jakob Disease (CJD): This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

PRECAUTIONS: The ZEVALIN therapeutic regimen is intended as a single course treatment. The safety and toxicity profile from multiple courses of the ZEVALIN therapeutic regimen or of other forms of therapeutic irradiation preceding, following, or in combination with the ZEVALIN therapeutic regimen have not been established.

Radionuclide Precautions: The contents of the ZEVALIN kit are not radioactive. However, during and after radiolabeling ZEVALIN with In-111 or Y-90, care should be taken to minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

Hypersensitivity: Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of an allergic reaction during administration of ZEVALIN. Patients who have received murine proteins should be screened for human anti-mouse antibodies (HAMA). Patients with evidence of HAMA have not been studied and may be at increased risk of allergic or serious hypersensitivity reactions during ZEVALIN therapeutic regimen administrations.

Immunization: The safety of immunization with live viral vaccines following the ZEVALIN therapeutic regimen has not been studied. Also, the ability of patients who received the ZEVALIN therapeutic regimen to generate a primary or anamnestic humoral response to any vaccine has not been studied.

Laboratory Monitoring: Complete blood counts (CBC) and platelet counts should be obtained weekly following the ZEVALIN therapeutic regimen and should continue until levels recover. CBC and platelet counts should be monitored more frequently in patients who develop severe cytopenia, or as clinically indicated.

Drug Interactions: No formal drug interaction studies have been performed with ZEVALIN. Due to the frequent occurrence of severe and prolonged thrombocytopenia, the potential benefits of medications which interfere with platelet function and/or anticoagulation should be weighed against the potential increased risks of bleeding and hemorrhage. Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. In addition, the transfusion practices for such patients may need to be modified given the increased risk of bleeding.

Patients in clinical studies were prohibited from receiving growth factor treatment for 2 weeks prior to the ZEVALIN therapeutic regimen as well as for 2 weeks following completion of the regimen.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of the ZEVALIN therapeutic regimen, or to determine its effects on fertility in males or females. However, radiation is a potential carcinogen and mutagen. The ZEVALIN therapeutic regimen results in a significant radiation dose to the testes. The radiation dose to the ovaries has not been established. There have been no studies to evaluate whether the ZEVALIN therapeutic regimen causes hypogonadism, premature menopause, azoospermia and/or mutagenic alterations to germ cells. There is a potential risk that the ZEVALIN therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the ZEVALIN therapeutic regimen.

Pregnancy Category D: See WARNINGS.

Nursing Mothers: It is not known whether ZEVALIN is excreted in human milk. Because human IgG is excreted in human milk and the potential for ZEVALIN exposure in the infant is unknown, women should be advised to discontinue nursing and formula feeding should be substituted for breast feedings.

Geriatric Use: Of 349 patients treated with the ZEVALIN therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pediatric Use: The safety and effectiveness of the ZEVALIN therapeutic regimen in children have not been established.

ADVERSE REACTIONS: Safety data, except where indicated, are based upon 349 patients treated in 5 clinical studies with the ZEVALIN therapeutic regimen. Because the ZEVALIN therapeutic regimen includes the use of Rituximab, also see prescribing information for RITUXAN (Rituximab).

The most serious adverse reactions caused by the ZEVALIN therapeutic regimen include prolonged and severe cytopenias, infections (predominantly bacterial in origin), hemorrhage while thrombocytopenic (resulting in deaths), and allergic reactions (bronchospasm and angioedema). In addition, patients who have received the ZEVALIN therapeutic regimen have developed myeloid malignancies and dysplasias. Fatal infusion reactions have occurred following the infusion of Rituximab.

In postmarketing reports, cutaneous and mucocutaneous reactions have been associated with the ZEVALIN therapeutic regimen. Please refer to the BOXED WARNINGS and WARNINGS sections for detailed descriptions of these reactions.

The most common toxicities reported were neutropenia, thrombocytopenia, anemia, gastrointestinal symptoms (nausea, vomiting, abdominal pain, and diarrhea), increased cough, dyspnea, dizziness, arthralgia, anorexia, anxiety, and ecchymosis. Hematologic toxicity was often severe and prolonged, whereas most non-hematologic toxicity was mild in severity. Table 7 lists adverse events that occurred in ≥5% of patients. A more detailed description of the incidence and duration of hematologic toxicities, according to baseline platelet count (as an indicator of bone marrow reserve) is provided in Table 8, Hematologic Toxicity.

Table 7. Incidence of Adverse Events in ≥5 % of Patients Receiving the ZEVALIN Therapeutic Regimen† (N = 349)

	All Grades %	Grade 3/4 %
Any Adverse Event	**99**	**89**
Body as a Whole	**80**	**12**
Asthenia	43	3
Infection	29	5
Chills	24	<1
Fever	17	1
Abdominal Pain	16	3
Pain	13	1
Headache	12	1
Throat Irritation	10	0
Back Pain	8	1
Flushing	6	0
Cardiovascular System	**17**	**3**
Hypotension	6	1
Digestive System	**48**	**3**
Nausea	31	1
Vomiting	12	0
Diarrhea	9	<1
Anorexia	8	0
Abdominal Enlargement	5	0
Constipation	5	0
Hemic and Lymphatic System	**98**	**86**
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	<1
Metabolic and Nutritional Disorders	**23**	**3**
Peripheral Edema	8	1
Angioedema	5	<1
Musculoskeletal System	**18**	**1**
Arthralgia	7	1
Myalgia	7	<1
Nervous System	**27**	**2**
Dizziness	10	<1
Insomnia	5	0
Respiratory System	**36**	**3**
Dyspnea	14	2
Increased Cough	10	0
Rhinitis	6	0
Bronchospasm	5	0
Skin and Appendages	**28**	**1**
Pruritus	9	<1
Rash	8	<1
Special Senses	**7**	**<1**
Urogenital System	**6**	**<1**

† Adverse events were followed for a period of 12 weeks following the first Rituximab infusion of the ZEVALIN therapeutic regimen. Note: All adverse events are included, regardless of relationship.

The following adverse events (except for those noted in Table 7) occurred in between 1 and 4% of patients during the treatment period: urticaria (4%), anxiety (4%), dyspepsia (4%), sweats (4%), petechia (3%), epistaxis (3%), allergic reaction (2%), and melena (2%).

Severe or life-threatening adverse events occurring in 1-5% of patients (except for those noted in Table 7) consisted of pancytopenia (2%), allergic reaction (1%), gastrointestinal hemorrhage (1%), melena (1%), tumor pain (1%), and apnea (1%). The following severe or life-threatening events occurred in <1% of patients: angioedema, tachycardia, urticaria, arthritis, lung edema, pulmonary embolus, encephalopathy, hematemesis, subdural hematoma, and vaginal hemorrhage.

Hematologic Events: Hematologic toxicity was the most frequently observed adverse event in clinical trials. Table 8 presents the incidence and duration of severe hematologic toxicity for patients with normal baseline platelet count (≥150,000 cells/mm^3) treated with the ZEVALIN therapeutic regimen and patients with mild thrombocytopenia (platelet count 100,000 to 149,000 cells/mm^3) at baseline who were treated with a modified ZEVALIN therapeutic regimen that included a lower Y-90 ZEVALIN dose at 0.3 mCi/kg (11.1 MBq/kg).

Table 8. Severe Hematologic Toxicity

	ZEVALIN therapeutic regimen using 0.4 mCi/kg Y-90 dose (14.8 MBq/kg)	Modified ZEVALIN therapeutic regimen using 0.3 mCi/kg Y-90 dose (11.1 MBq/kg)
ANC		
Median nadir (cells/mm^3)	800	600
Per Patient Incidence ANC <1000 cells/mm^3	57%	74%
Per Patient Incidence ANC <500 cells/mm^3	30%	35%
Median Duration (Days)* ANC <1000 cells/mm^3	22	29
Platelets		
Median nadir (cells/mm^3)	41,000	24,000
Per Patient Incidence Platelets <50,000 cells/mm^3	61%	78%
Per Patient Incidence Platelets <10,000 cells/mm^3	10%	14%
Median Duration (Days)# Platelets <50,000 cells/mm^3	24	35

* Median duration of neutropenia for patients with ANC <1000 cells/mm^3 (Date from last laboratory value showing ANC ≥1000 cells/mm^3 to date of first laboratory value following nadir showing ANC ≥1000 cells/mm^3, censored at initiation of next treatment or death)

Median duration of thrombocytopenia for patients with platelets <50,000 cells/mm^3 (Date from last laboratory value showing platelet count ≥50,000 cells/mm^3 to date of first laboratory value following nadir showing platelet count ≥50,000 cells/mm^3, censored at initiation of next treatment or death)

Median time to ANC nadir was 62 days, to platelet nadir was 53 days, and to hemoglobin nadir was 68 days. Information on growth factor use and platelet transfusions is based on 211 patients for whom data were collected. Filgrastim was given to 13% of patients and erythropoietin to 8%. Platelet transfusions were given to 22% of patients and red blood cell transfusions to 20%.

Infectious Events: During the first 3 months after initiating the ZEVALIN therapeutic regimen, 29% of patients developed infections. Three percent of patients developed serious infections comprising urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection. Life threatening infections were reported for 2% of patients that included sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis. During follow-up from 3 months to 4 years after the start of treatment with ZEVALIN, 6% of patients developed infections. Two percent of patients had serious infections comprising urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis. One percent of patients had life threatening infections that included bacterial pneumonia, respiratory disease, and sepsis.

Secondary Malignancies: A total of 2% of patients developed secondary malignancies following the ZEVALIN therapeutic regimen. One patient developed a Grade 1 meningioma, three developed acute myelogenous leukemia, and two developed a myelodysplastic syndrome. The onset of a second cancer was 8-34 months following the ZEVALIN therapeutic regimen and 4 to 14 years following the patients' diagnosis of NHL.

Immunogenicity: Of 211 patients who received the ZEVALIN therapeutic regimen in clinical trials and who were followed for 90 days, there were eight (3.8%) patients with evidence of human anti-mouse antibody (HAMA) (n=5) or human anti-chimeric antibody (HACA) (n=4) at any time during the course of the study. Two patients had low titers of HAMA prior to initiation of the ZEVALIN therapeutic regimen; one remained positive without an increase in titer while the other had a negative titer post-treatment. Three patients had evidence of HACA responses prior to initiation of the ZEVALIN therapeutic regimen; one had a marked increase in HACA titer while the other two had negative titers post-treatment. Of the three patients who had negative HAMA or HACA titers prior to the ZEVALIN therapeutic regimen, two developed HAMA in absence of HACA titers, and one had both HAMA and HACA positive titers post-treatment. Evidence of immunogenicity may be masked in patients who are lymphopenic. There has not been adequate evaluation of HAMA and HACA at delayed timepoints, concurrent with the recovery from lymphopenia at 6-12 months, to establish whether masking of the immunogenicity at early timepoints occurs. The data reflect the percentage of patients whose test results were considered positive for antibodies to Ibritumomab or Rituximab using kinetic enzyme immunoassays to Ibritumomab and Rituximab. The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling and concomitant medications. Comparisons of the incidence of HAMA/HACA to the ZEVALIN therapeutic regimen with the incidence of antibodies to other products may be misleading.

OVERDOSAGE: Doses as high as 0.52 mCi/kg (19.2 MBq/kg) of Y-90 ZEVALIN were administered in ZEVALIN therapeutic regimen clinical trials and severe hematological toxicities were observed. No fatalities or second organ injury resulting from overdosage administrations were documented. However, single doses up to 50 mCi (1850 MBq) of Y-90 ZEVALIN, and multiple doses of 20 mCi (740 MBq) followed by 40 mCi (1480 MBq) of Y-90 ZEVALIN were studied in a limited number of subjects. In these trials, some patients required autologous stem cell support to manage hematological toxicity.

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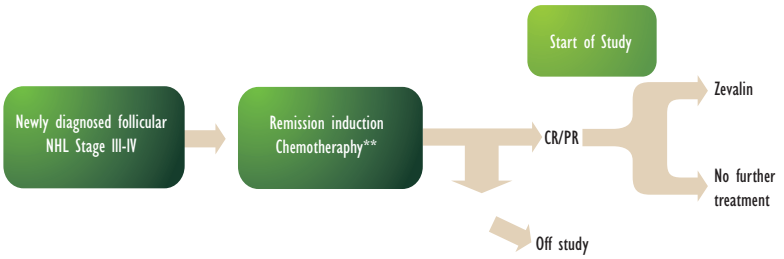
Clinical Experience with Zevalin RIT

Zevalin RIT has been used for over 10 years and has emerged as a safe, effective and well tolerated therapy for relapsed 'low-grade' NHL.[10] The majority of patients treated in the registration approval studies had relapsed follicular lymphoma. These published studies consistently show high rates of overall and complete response rates in relapsed follicular lymphoma.

Even in previously heavily pre-treated patients who had received a median of four different chemotherapy regimens and who either did not respond to prior rituximab therapy or had disease progression within six months of therapy, the overall response rate of 74%, with 15% complete responses were seen.[10] A randomised controlled trial of Zevalin versus rituximab in relapsed or refractory low-grade or transformed follicular B-cell NHL was performed with the primary aim of demonstrating superior response rates of Zevalin over rituximab.[9] Seventy-three patients received two doses of rituximab 250mg/m^2 a week apart as pre-dosing followed by a single dose of Zevalin 0.4mCi/kg (15Mbq/kg). Seventy patients in the control arm received rituximab 375mg/m^2 weekly for four weeks. The overall response rate was 80% for the Zevalin group versus 56% for the rituximab alone group (p=0.002). Complete responses were 30% and 16% in the Zevalin and rituximab groups respectively. Both regimens were well tolerated but, as expected, there was more myelosuppression in the RIT group.

These highly promising results demonstrated that Zevalin led to superior overall and complete response rates to those seen with rituximab, and for patients with follicular lymphoma this translated into a significant improvement in the time to treatment failure. An interesting and potentially important finding to emerge from this study was the high level of activity of Zevalin in patients who had become refractory to chemotherapy, which was significantly greater than that seen with rituximab. This data suggests the Zevalin offers hope for meaningful clinical responses even in patients who have become refractory to chemotherapy.

Figure 2: Stages to Zevalin Treatment



Perhaps the most impressive finding to emerge from these initial studies was that around 70% of the patients who achieve a CR remain in remission for years – some patients treated in the early studies are now in remission for more than five years after Zevalin treatment, with a median follow up of almost four years (see *Table 1*).[11,14]

An analysis of prognostic factors has confirmed that this remarkable durability of response is unlikely to be accounted for by patient selection as most of these durable remissions have been achieved in heavily chemotherapy pre-treated and chemo-refractory patients with validated poor prognostic factors, such as extensive prior therapy (one to nine regimens), bulky disease, high lactate dehydrogenase (LDH) and extranodal disease. Only disease bulk correlated with the overall response rate (<5cm) (89 patients objective response rate (ORR) 90% (p<0.001).[12,15]

Examining the toxicity seen for patients treated in the Zevalin trials (n=261) indicates that 28% will experience grade 4 neutropenia and 8% will experience grade 4 thrombocytopenia.[14] The non-hematological toxicity is extremely modest and even the hematological toxicity can be minimised if appropriate precautions are taken. Patients who have been heavily treated with chemotherapy, such as those with a reduced platelet count (<150 x 109/L), need to be given a reduced dose of radioactivity. With this in mind, Zevalin 0.3mCi/kg (11.1 MBq/kg) proved to be both safe and efficacious.[13,14,16-18]

14. *Gordon L I, et., "Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study",* Blood *(2004);103(12): pp. 4,429–4,431.*
15. *Czuczman, M S, et al., "Multivariate analysis of prognostic factors correlated with response to 90Y ibritumomab tiuxetan (Zevalin) radioimmunotherapy for non-Hodgkin's lymphoma",* Proc Am Soc Clin Oncol *(2002);21: Abstract 1,062.*
16. *Witzig T E, et al., "Treatment with ibritumomab tiuxetan radioimmunotherap in patietns with rituximab-refractory follicular non-Hodgkin's lymphoma",* J Clin Oncol *(2002);20(15): pp. 3,262–3,269.*
17. *Wiseman G A, et al., "ibritumomab tiuxetan radioimmunotherapy for patietns with relapsed or refractory non-Hodgkin lymphoma and mild thrombocytopenia – a phase II multicenter trial",* Blood *(2002);99(12): pp. 4,336–4,342.*
18. *Witzig T E, et al., "Safety of yttrium-90 ibritumomab tiuxeta radioimmunotherapy for relapsed low-grade, follicular, or transfromed non-Hodgkin's lymphoma",* J Clin Oncol *(2003);21(7): pp. 1,263–1,270.*

Although the results for single agent RIT are encouraging, the future is likely to involve integrating RIT into chemotherapy treatment protocols, and the current challenge for clinical investigators is to determine the optimal approach of integrating Zevalin RIT into chemotherapy schedules. Early data using Zevalin given to consolidate clinical responses following both shortened or full course chemotherapy look extremely promising.

Shipley and colleagues presented impressive data demonstrating the ability of Zevalin to convert partial response after brief chemotherapy to complete responses. In this study patients were treated with four weekly infusions of rituximab followed by three cycles of R-CHOP followed eight weeks later by Zevalin. Of the 22 patients who had completed the protocol there was a 40% CR rate before Zevalin, which was converted to a 86% CR rate after Zevalin.[19]

a randomisation for ^{90}Y ibritumomab tiuxetan (Zevalin) after full course R-CHOP chemotherapy is under way.

The dose-limiting toxicity from RIT is myelosuppression with delayed thrombocytopaenia and neutropaenia occurring at around four to six weeks after therapy. The extent and duration of the myelosuppression appears to depend on bone marrow reserve (amount of previous chemotherapy, age of patient), degree of bone marrow infiltration, pharmacokinetics of the mAb and the stability of the radioimmunoconjugate.

Higher myeloablative doses may, however, be delivered safely with support from an autologous stem cell transplant. Zevalin RIT is currently being extensively investigated as a component of high dose therapy and

The future for RIT is ... likely to involve integration into chemotherapy schedules... this type of approach offers great promise for the future treatment of lymphoma.

The large European intergroup study in previously untreated follicular lymphoma, which randomised patients to Zevalin after initial chemotherapy, has now completed accrual with over 400 patients recruited, and will provide invaluable data as to whether Zevalin may has a role as consolidation after primary chemotherapy.

Clinical responses have also been observed for Zevalin in transformed follicular and relapsed *de novo* diffuse large B-cell lymphoma (DLBC). Small numbers of patients were treated as part of the initial phase I/II study and response rates of 58% with a 33% CR rate were found. A recent European phase II trial with over 100 patients older than 60 with relapsed DLBC has confirmed this impressive response rate in large numbers of patients with relapsed DLBC unsuitable for transplantation.[20] Given this high single agent activity, clinical trials are now under way to integrate Zevalin into the front line treatment of DLBC and a large intergroup study with Zevalin have been added to high dose chemotherapy with the 'standard' conditioning regimen of BCNU, Etoposide, Ara-C and Melphalan (BEAM). The early results confirm the feasibility of this approach and these important studies are on-going.

Conclusion

In summary, Zevalin RIT offers an excellent treatment alternative in relapsed follicular lymphoma and provides an attractive alternative in second relapse after R-Chemo schedules for many patients. Promising results are emerging in the treatment of aggressive lymphoma and RIT is now being integrated into treatment schedules for DLBC including high dose therapy and ASCT. The future for RIT is therefore likely to involve integration into chemotherapy schedules, and the recent clinical results suggests that this type of approach offers great promise for the future treatment of lymphoma. ■

19. *Shipley D L, et al., "Phase II trial of rituximab and short duration chemotherapy followed by 90Y-ibritumomab tiuxetan as first-line treatment for patients with follicular lymphoma: A Minnie Pearl Cancer Research Network phase II trial",* J Clin Oncol *(2004);22, No 14S: Abstract 6,519.*

20. *Morschhauser, F, et al., "Yttrium-90 ibritumomab tiuxetan (Zevalin) for patients with relapsed/refractory diffuse large B-cell lymphoma not appropriate for autologous stem cell transplantation: Results of an open-label phase II trial",* Blood *(2004);104(11): Abstract 130.*