

⁹⁰Yttrium ibritumomab tiuxetan in the treatment of non-Hodgkin's lymphoma: current status and future prospects

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Abstract: After nearly three decades with little change in the treatment for B-cell non-Hodgkin's lymphoma, the addition of immunotherapy has had a profound effect on the treatment of this group of diseases. A more subtle addition to the armamentarium has been the radiolabeled monoclonal antibodies, ⁹⁰yttrium ibritumomab tiuxetan and ¹³¹iodine tositumomab. Unfortunately these drugs have been underutilized. This is, in part, because of the need for coordination between specialties, concern about long-term effects, possible limitations on the tolerance of subsequent therapies and, in part, because of reimbursement factors. In this review, the studies in relapsed and refractory disease are discussed and the very promising results reported from phase II studies using radioimmunotherapy as first-line. Potential mechanisms of resistance to monoclonal antibodies are postulated based on alterations in cell signaling pathways that have been observed in lymphoma cell lines resistant to rituximab. It is anticipated that as mechanisms of resistance are better understood for both unlabeled and labeled monoclonal antibodies, biomarkers will not only predict their efficacy but also lead to the development of therapies to overcome resistance.

Keywords: immunotherapy, radioimmunotherapy, ibritumomab, zevalin, non-Hodgkin lymphoma

Introduction

The non-Hodgkin's lymphomas (NHL) are a diverse group of lymphoid neoplasms that collectively rank fifth in cancer incidence and mortality in the US (Parker et al 1996; Müller et al 2005). The incidence and prevalence of NHL has risen 150% over the past few decades (Aisenberg 1995; Edwards et al 2005) The incidence increases with age, as most patients are older than age 60 at diagnosis, and males overall are affected about 1.5 times more often than females. In 2007, it is estimated that there will be 63,000 new cases and over 18,000 deaths in the US from NHL (National Cancer Institute 2007).

NHL are categorized according to the World Health Organization (WHO) classification. The WHO system was developed to help standardize the diagnosis of lymphomas based on histologic, molecular, genetic, and immunologic criteria. The majority of adult lymphomas are B cell in origin; the most common subtypes are follicular lymphoma and diffuse large B-cell lymphoma which account for 25% and 35% of cases, respectively. Other less common subtypes of B-cell lymphoma include mantle cell lymphoma, small lymphocytic lymphoma, and marginal zone lymphoma (Harris et al 2000; World Health Organization 2001).

Approximately, 95% of B-cell lymphomas have a CD20 surface antigen. CD20 (membrane-spanning 4-domain, group A, member 1) is a nonglycosylated protein of 33 to 35 kDa expressed on the cell surface of human B lymphocytes. The gene

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for CD20 (MS4A1) is switched on at the pre-B-cell stage of B-cell development, expressed throughout B-cell maturation, and lost during final maturation to plasma cells (Cartron et al 2004). The configuration of CD20, which is anchored in the cell membrane, protects antigen shedding. CD20 is expressed on the B-cell at a high density in excess of 100,000 copies per cell but does appear to vary by histologic subtype. The exact function of CD20 has not been fully elucidated. There is no ligand to CD20 that has been identified; and mice that are CD20-deficient do not demonstrate abnormal B-cell function. However, studies suggest that CD20 serves as a kinase in Ca^{2+} influx across plasma membranes and in doing so may have a role in regulating cell cycle progression (Golay et al 1985). Anti-CD20 monoclonal antibodies have an effect on regulation of the cell cycle and induce a wide variety of signaling events which lead to the induction of apoptosis, as well as through a number of other potential mechanisms.

Rituximab is a chimeric murine/human monoclonal antibody produced by recombinant technology from the parent murine monoclonal antibody, ibritumomab. It binds specifically to the CD20 antigen with an apparent avidity 5–11 nM *in vitro* which is about one log greater than its parent murine antibody (IDEC Pharmaceuticals 2001). It was engineered by fusing the light- and heavy-chain variable domains of 2B8 murine monoclonal anti-CD20 antibody and human kappa light-chain and gamma 1 heavy-chain constant regions (Reff et al 1994). In 1997 it became the first monoclonal antibody for hematologic malignancies approved by the US Food and Drug Administration (FDA).

The anti-CD20 monoclonal antibody, rituximab, appears to have several mechanisms of action and their relative influence on these mechanisms may account for differences in sensitivity across histologic subtypes of B-cell lymphomas. *In vitro* studies indicate that rituximab induces complement-dependent cytotoxicity (CDC) in B-cell lymphoma lines. This CDC lysis correlates in part with the level of CD20 expression but may also be dependent on the interaction with complement regulatory proteins (Golay et al 2000, 2001; Treon et al 2001). The increase in complement activation products which often occurs with the first infusion of rituximab has been described as “cytokine-release syndrome” (Winkler et al 1999) with associated fever, rigors, headache, and rarely cardiovascular collapse.

Antibody-dependent cytotoxicity (ADCC) is another mechanism that results in tumor cell lysis. Binding of the antibody to the target antigen allows for the recruitment of effector cells such as NK cells and macrophages, which

express Fc receptors. These cells are then directed toward the target cells inducing either phagocytosis or release of their cytotoxic granules to promote cell killing. There are several classes of Fc receptors. The presence of the $Fc\gamma RIIIa$ genotype correlates with clinical and molecular responses in untreated follicular lymphoma confirming that ADCC is an important mechanism of action of rituximab (Cartron et al 2002; Weng and Levy 2002, 2003). One of the effects of the immunomodulatory derivatives is to enhance N-K cell activity. It is of interest that preliminary data suggests potent synergy of the combination of thalidomide, a potential stimulator of N-K cell activity, and rituximab in relapsed mantle cell lymphoma. This possible synergy merits further investigation particularly as more potent immunomodulatory analogs become available (Kaufmann et al 2004).

Several studies have indicated that the maximal clinical response to rituximab may take several months suggesting additional mechanisms of action. One such hypothesis is that peptides from lysed lymphoma cells are presented to dendritic cells with the generation of specific cytolytic T lymphocytes (Kalergis and Ravetch 2002; Rafiq et al 2002; Selenko et al 2002). While there are experimental data in murine models supporting this passive immunotherapy model, human data are lacking.

Mechanism of resistance to monoclonal antibody therapy are under investigation. The clinical observations are that previously untreated patients with low-grade and follicular lymphoma have a much higher overall response rate and complete response rate than patients with prior treatment, and that, patients will eventually become resistant or refractory to rituximab therapy. There are many possible explanations for this resistance. *In vitro* manipulation of the extracellular epitope of the CD20 loop alters the binding to anti-CD20 monoclonal antibodies, and thus, suggests that critical mutations in CD20 may be one mechanism of resistance (Binder et al 2006). In another model using rituximab sensitive and resistant cell clones, surface CD20 expression has been demonstrated to be diminished in resistant line (Czuczman et al 2004). Studies of the phenotypic cell signaling profiles of rituximab sensitive and resistant cell clones demonstrate that rituximab failed to chemosensitize rituximab-resistant clones which exhibited constitutively hyperactivation of NF- κ B and ERK1/2 pathways, which leads to overexpression of resistance factors such as Bcl-2, Bcl-xL, and Mcl-1 (Jazirehi et al 2004, 2005, 2007). An understanding of altered cell signaling and resistance may have implications for combining agents which will reverse resistance.

At the same time that preclinical and clinical evaluation was taking place with unlabeled anti-CD20 monoclonal antibody, radiolabeling technologies made it possible to chelate radioactive isotopes to monoclonal antibodies, which retain their specificity and could provide targeted delivery of localized radiation (Chinn et al 1999). Anti-CD20 radio-immunoconjugates, which link the isotopes ⁹⁰yttrium (⁹⁰Y) and ¹³¹iodine (¹³¹I) to murine monoclonal antibodies, were subsequently approved by the US FDA for the treatment of relapsed, and refractory low-grade lymphoma in 2002 and 2003, respectively. Radioimmunoconjugates are an attractive therapeutic option for lymphomas presumably because of the inherent sensitivity of malignant lymphoma cells to ionizing radiation coupled with the mechanism of action associated with anti-CD20 binding. The popular thinking is that high energy isotopes will deliver targeted radiation. In the case of ⁹⁰Y-ibritumomab tiuxetan, the radiolabel is a pure beta emitter with a short path length. This means that 90% of the dose is delivered within a range of 5 mm in tissue. This equates to a few hundred cell diameters and provides the thesis for a radiation crossfire effect in which cell kill can occur not only to cells with bound antibody but also cells at some distance which may not bind antibody and, hence, may be particularly beneficial in bulky or poorly vascularized tumors (Jacobs et al 2005; Skvortsova et al 2005). In a small pilot clinical study, intratumoral distribution of monoclonal antibody and quantitative assessment of radioactivity was examined in patients' nodal tissues sampled after therapy with ⁹⁰Y-ibritumomab tiuxetan by autoradiography and measuring decay events. There was a general correlation between radioactivity in the tissue, isotopic localization to the cell surface membrane and response to therapy. A failure to bind to malignant lymphocytes would appear to be one explanation for lack to response to radioimmunotherapy (RIT) (Jacobs et al 2005) (Figure 1).

Several in vitro studies suggest that there are more complex mechanisms accounting for the additive or synergistic

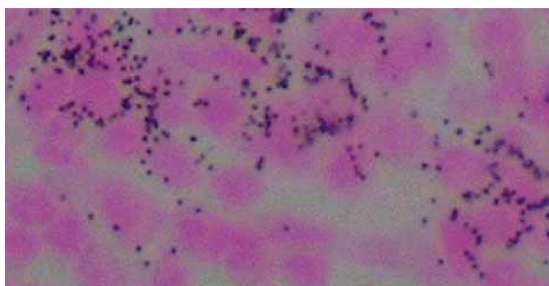


Figure 1 Autoradiographic localization of ⁹⁰Y-ibritumomab tiuxetan from lymph node on a patient sampled 4 days after treatment.

effects of radiation and monoclonal antibody therapy. When combining rituximab and external beam radiation there was a synergistic increase in expression of proteins involved in apoptosis and cell-cycle regulation (Skvortsova et al 2005). In these in vitro studies, enhanced antiproliferative and apoptotic effects of rituximab and radiation were achieved through inhibition of c-myc and Bcl-xL expression. In another model evaluating the interaction between radiation and a monoclonal antibody, ionizing radiation was observed to trigger epidermal growth factor (EGF) import into the nucleus and as a consequence increase in DNA-repair kinase activity. By pretreatment with anti-EGFR antibody DNA repair was inhibited and resulted in increased radiosensitivity of the treated cells (Milas et al 2000; Dittman et al 2005). In another murine lymphoma model, I-¹³¹ labeled anti-MHC class II monoclonal antibody, while an excellent vector to deliver radiotherapy to a target, did not result in long-term clearance of tumor. However, by combining the radiation delivery antibody with an unlabeled anti-idiotypic (Du et al 2007) long-term tumor eradication was observed. Clinical data supporting an additive effect of radiation and monoclonal antibody come from a study in patients with relapsed/refractory B-cell lymphoma patients in which unlabeled tositumomab was compared with ¹³¹I-tositumomab. The overall response favored the radiolabeled monoclonal antibody 55% versus 19%. In addition 13 of 19 patients crossed over from the unlabeled antibody to the labeled antibody responded (Davis et al 2004). Additional study is needed to elucidate more fully the effects of ionizing irradiation and monoclonal antibody to realize the potential of this therapy.

⁹⁰Y-ibritumomab tiuxetan (Zevalin[®]) and ¹³¹I-tositumomab (Bexxar[®]) are FDA-approved for therapy for relapsed or refractory low-grade lymphoma with or without transformation. Ibritumomab, the murine IgG₁ anti-CD20 antibody that is the parent of the chimeric antibody rituximab, is covalently linked to the MX-DTPA linker-chelator tiuxetan, which provides a high-affinity chelation site for ⁹⁰Y or for scanning purposes to ¹¹¹indium (¹¹¹In). As mentioned above, ⁹⁰Y is a pure beta emitter with a half-life of 64 hours and a maximum energy of 2.3 MeV and a mean path length in soft tissue of 5.3 mm. With ⁹⁰Y-ibritumomab tiuxetan, the radiation absorbed dose is primarily delivered to the region of binding with minimal free yttrium in the serum or cleared in the urine, thus allowing the prescribed dose to be based on a fixed amount of radioactivity per body weight. The dose of ⁹⁰Y-ibritumomab tiuxetan is calculated by body weight in kilograms and is 0.4 mCi/kg for patients with a platelet count $\geq 150,000 \times 10^9/\text{mL}$ or 0.3 mCi/kg for a platelet count

between 100,000 and $149,000 \times 10^9/\text{mL}$. The maximum dose administered is 32 mCi. The ^{90}Y -ibritumomab regimen can be conveniently administered over one week as an outpatient. On day 1, rituximab at $250 \text{ mg}/\text{m}^2$ is infused and within 4 hours of completion, a tracer dose of ^{111}In ibritumomab, 5 mCi, is administered over 10 minutes. Gamma scanning is performed once at 24–72 hours to confirm the expected biodistribution. On day 8, rituximab is repeated at $250 \text{ mg}/\text{m}^2$ and the therapeutic dose of ^{90}Y -ibritumomab tiuxetan is administered (Dillman 2002). Following treatment with ^{90}Y -ibritumomab tiuxetan, patients do not require isolation and only minimal radiation precautions are required such as avoiding contact with bodily fluids for the first week after treatment (Witzig et al 1999, 2003a; Dillman 2002; Wiseman et al 2002; White 2004; Johnston et al 2006).

Tositumomab, a murine IgG_{2a} monoclonal antibody specific for CD20, is labeled with ^{131}I . ^{131}I is a beta and gamma emitter with a half-life of 8 days, maximum particle energy of 0.5 MeV and a path length of 0.8 mm. Because of individual patient variability in clearance of ^{131}I -tositumomab, a dosimetric dose consisting of 10 mg of antibody labeled with approximately 5 mCi ^{131}I is administered over 30 minutes. Using a NaI scintillation probe and gamma camera, serial total body radioactivity counts are obtained and total-body clearance kinetics are measured over three time points in order to calculate the millicuries to produce a total body therapeutic dose of 75 cGy for patients with a platelet count $\geq 150,000 \times 10^9/\text{mL}$ and 65 cGy for patients with a platelet count of 100,000 to $149,000 \times 10^9/\text{mL}$. As the ^{131}I -conjugated antibody is metabolized, free ^{131}I metabolites are released into the bloodstream and rapidly excreted in the urine. Patients receive potassium iodide 120 mg daily, as thyroid blockage, administered from 24 hours prior to the dosimetric dose and continued for 14 days after the therapeutic administration. Institutional policies vary with regard to in-patient or out-patient administration of ^{131}I -tositumomab (Vose et al 2000; Kaminski et al 2000, 2001).

The major toxicity with both radiolabeled antibodies is reversible myelosuppression. The hematologic toxicity tends to occur at 5–7 weeks after treatment and may take 2–4 weeks for recovery. With ^{90}Y -ibritumomab tiuxetan, Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 30%, 10% and 4% of patients, respectively (Witzig et al 2003a). Growth factors, blood and platelet transfusion support are required in about 20% of patients (Dillman 2002). Hematologic toxicity increased with the degree of bone marrow involvement, number of prior regimens, and prior therapy with fludarabine. Two studies report treatment of

patients with ^{90}Y -ibritumomab tiuxetan and one report of ^{131}I -tositumomab with prior high-dose therapy with manageable hematologic toxicity (Kaminski et al 2000; Vose et al 2003; Jacobs et al 2005). In a review of 349 patients treated with ^{90}Y -ibritumomab tiuxetan for safety, the grade 3 or 4 non-hematologic toxicities occurred in 11% of patients; asthenia was most common and occurred in only 6 patients. Hospitalizations with infection during the treatment period occurred in 23 patients (7%) with 6 patient having neutropenic fever (Witzig et al 2003a). Hematologic toxicities are similar with ^{131}I -tositumomab. Human anti-mouse antibodies (HAMA) may be detected in the serum in approximately 2% of heavily pretreated patients with the ^{90}Y -ibritumomab tiuxetan and 10% of heavily pretreated patients with the ^{131}I -tositumomab (Kaminski et al 2001). However, HAMA were detected in 48 of 76 (63%) previously untreated patients with follicular lymphoma following infusion with ^{131}I -tositumomab (Kaminski et al 2005). The potential advantages of a HAMA or human anti-globulin antibody (HAGA) have not been generally appreciated and are not well studied after ibritumomab or tositumomab. However, following administration of RIT, the development of polyclonal HAGA directed against epitopes on the administered antibody may generate anti-idiotypic antibody that can mimic the tumor antigen and facilitate host recognition of the tumor. This may have a clinical benefit (DeNardo et al 2003; Azinovic et al 2006). Certain murine antibody-based assays such as prostate-specific antigen may be unreliable in HAMA positive patients. A major long-term concern with both radiolabeled antibodies has been the potential for myelodysplasia and acute leukemia. Thus far, it appears to be about 3%, which is the frequency of these toxicities in lymphoma patients receiving extensive chemotherapy (Czuczman et al 2004; Bennett et al 2005). In the study of 76 previously untreated patients who received ^{131}I -tositumomab, there have been no cases of MDS (Kaminski et al 2005). Another delayed toxicity of ^{131}I -tositumomab is hypothyroidism, which may occur in a small number of patients despite pretreatment with potassium iodide (Kaminski et al 2000).

Patients relapsing after radioimmunotherapy can be treated feasibly with subsequent therapy. In 58 patient treated after ^{90}Y -ibritumomab failure at a single institution, the median number of additional regimens was two (range one to seven). The therapies ranged from single agent chemotherapy to combination regimens to bone marrow transplant. The tolerability of salvage treatment seemed to be similar to the same salvage therapy in patients who did not receive ibritumomab (Ansell et al 2002). Relapsed patients can safely receive radiation. In

a recent report 20 of 26 sites in 19 patients responded to radiation after ⁹⁰Y-ibritumomab tiuxetan. There were no unexpected toxicities (Justice et al 2006).

Treatment of relapsed or refractory patients with follicular lymphoma with ⁹⁰Y-ibritumomab tiuxetan

There are multiple studies which demonstrate the efficacy of both ibritumomab tiuxetan and tositumomab in relapsed and rituximab-refractory follicular lymphoma (Kaminski et al 2001; Witzig et al 2002a, b). This review will focus mainly on the studies with ⁹⁰Y-ibritumomab tiuxetan. The entry criteria in the pivotal studies with ⁹⁰Y-ibritumomab tiuxetan required adequate bone marrow reserve as determined by peripheral counts showing absolute neutrophils of at least $1500 \times 10^9/\text{mL}$ and a platelet count of $>100,000 \times 10^9/\text{mL}$. Bone marrow criteria included a cellularity of at least 15% of the marrow space and less than 25% of the marrow space occupied by lymphoma. Patients with prior high-dose therapy with bone marrow rescue were excluded. Under these circumstances, it was established that for patients with a platelet count of $100,000 \times 10^9/\text{mL}$ to $149,000 \times 10^9/\text{mL}$, a dose of 0.3 mCi/kg was well tolerated and that for patients with a platelet count $>150,000 \times 10^9/\text{mL}$, a dose of 0.4 mCi/kg was well tolerated. The maximum dose for either group was 32 mCi/kg. The randomized, multicenter phase III study that compared ⁹⁰Y-ibritumomab tiuxetan to rituximab included 143 patients. Eligible patients had prior chemotherapy but were rituximab naïve. There were 113 patients with follicular lymphoma, 17 patients with non-follicular low-grade lymphoma and 13 patients with transformed lymphoma. Patient characteristics were well balanced with Stage III/IV disease in 90% and mean and median prior treatments of 2 in each arm. The overall response rate (ORR), complete response rate and complete response rate unconfirmed (CR and CRu) were 80% and 34% for ⁹⁰Y-ibritumomab tiuxetan and 56% and 20% for rituximab. Age did not predict response rate nor toxicity but patients with bulky disease fared less well. The estimated median duration of response for

the follicular lymphoma patients was 18.5 months versus 12.1 months favoring the ⁹⁰Y-ibritumomab arm (Witzig et al 2002b). In a single arm study patients with rituximab refractory follicular lymphoma were treated with ⁹⁰Y-ibritumomab tiuxetan. Rituximab refractory is defined as failure to respond to rituximab or relapse within 6 months of the last course of therapy. Fifty-four patients with a median number of 4 prior regimens had an overall and complete response rate of 74% and 15% respectively. The median duration of response was estimated to be 6.4 months (Witzig et al 2002a). In an analysis of 1177 patients treated with ¹³¹I-tositumomab, overall response, complete response and duration of response decreased as the number of prior therapies increased (Gregory et al 2005). In Table 1, the response rate and duration of response in patients with follicular lymphoma are compared based on the prior therapy. The decrease in complete response and duration of response is striking most likely reflecting effect of prior therapy and not inherent differences in the efficacy of the radioimmunotherapies.

First-line treatment of follicular lymphoma with RIT alone or in sequence

There is one study which has used radioimmunotherapy as first-line single agent therapy in follicular lymphoma. Seventy-six patients with follicular lymphoma, stage III and IV, and grade 1 or 2 histology received tositumomab. The overall response and complete response rates were 95% and 75% respectively. The ability to achieve a complete response was decreased in patients with a bulky mass of at least 5 cm and if bone marrow involvement was present. At the time of publication, the median follow-up was 5.1 years, the actuarial 5-year progression-free survival was 59% and the median progression-free survival was 6.1 years. The annualized rate of relapse was 25% during the first year and decreased to 13% in the second year, 12% in the third year, and 4.4% per year after 3 years (Kaminski et al 2003a). Non-hematologic toxicities were mild, mostly infusion-related and with low incidence of headache, arthralgias, and myalgias.

Table 1 Effect of prior treatment on response to radioimmunotherapy (RIT) in follicular lymphoma (FL)

No. of patients	RIT	Prior chemotherapy	Prior rituximab	Complete response %	Any response %	Duration in months
76 (Kaminski et al 2005)	¹³¹ I	No	No	75	95	73
73 (Witzig et al 2002b)	⁹⁰ Y	Yes	No	30	86	14.2
57 (Witzig et al 2002a)	⁹⁰ Y	Yes	Yes	14	70	6.4

In long-term follow-up 13% of patients required thyroid replacement. There were no cases of myelodysplastic syndrome or acute leukemia observed after a median follow-up of 5.1 years. Antimouse antibodies (HAMA) were detected in 63% of patients. The antibodies were detected a median of 3.3 weeks after the dosimetric dose of ^{131}I -tositumomab and remained detectable for a median of 5.5 months. The development of high levels of HAMA within the first two weeks of the therapeutic dose was associated with fever, myalgias, arthralgia, or rash lasting 3–4 days without apparent sequelae. Thus, in selected patients, a single dose of ^{131}I -tositumomab appears both safe and effective.

There are 6 studies that have employed chemotherapy followed by RIT as part of first-line therapy (Link et al 2004; Shipley et al 2004; Leonard et al 2005; Press et al 2006; Zinzani et al 2006; Jankowitz et al 2007). As shown in Table 2, each of these studies reports a high complete response rate ranging from 67% to 90%. But, in addition, each of these studies suggests that the complete response rate nearly doubled after RIT. In evaluating these and future studies, it is essential to compare characteristics such as Follicular Lymphoma International Prognostic Index (FLIPI) score (Solal-Céligny et al 2004), bulk of disease, histologic grade, and criteria for determination of complete response. In one study, 59 of 60 patients had a baseline positive PET scan. Restaging imaging included either a fused PET-CT or a PET and CT and followed the recently revised guidelines for staging NHL (Cheson et al 2007; Juweid et al 2007). There is 10% discordance between using CT criteria for complete response or CRu and a negative PET scan. Also in this study, the majority of patients had marrow involvement, two-thirds had intermediate or high FLIPI score, and half the patients had masses greater than 5 cm and histologic grade 2 or 3. Combining PET and CT scans for evaluation of response, the complete response rate doubled following RIT (Jankowitz et al 2007). Some of these studies included measurement of BCL-2 rearrangement in blood or bone marrow. In these

subset analyses, conversion of BCL-2 from positive to negative in blood and/or bone marrow correlated with prolonged remission. Several clinical trials suggest that patients achieving a molecular response have a significantly longer failure-free survival than those who did not (Czuczman et al 2001; Lehy et al 2006). The implication is that the depth of complete response is greater in patients with a complete response who have converted from PRC positive BCL-2 in blood or bone marrow to PRC negative. While it is often cited that the t(14; 18) translocation of the BCL-2 proto-oncogene is expressed in blood or bone marrow in 80% of patients with follicular lymphoma, the detection rate in recent phase II studies has been substantially lower, 40%–70% (Kaminski et al 2005; Press et al 2006; Jankowitz et al 2007). In future studies, it may be informative to correlate PET scan negativity with minimal residual disease as determined by BCL-2 assay. However, as yet there is not a standardized, uniformly accepted polymerase chain reaction (PCR) assay to measure BCL-2 rearrangement. As a look into the future, it seems likely to us that determination of cell signaling pathways will be predictive of response to monoclonal antibody therapy and be useful in delineating the mechanisms of synergy between targeted radiation and the effects of anti-CD20 therapy. For now, we await the results of the Intergroup S0016 which is a phase III randomized study comparing CHOP-R with CHOP followed by ^{131}I -tositumomab in previously untreated patients with follicular lymphoma. The primary endpoint is progression-free survival and secondary outcomes are overall response rates and toxicities.

Marginal zone B cell lymphoma

This subtype of NHL accounts for about 8% of lymphomas and include nodal and extranodal marginal zone lymphoma, gastric mucosa-associated lymphoid tissue and splenic zone lymphoma. The immunophenotype of marginal lymphomas is distinct from other small lymphocytic lymphomas: the antigen profile for the marginal zone lymphomas include CD19, CD20, CD22 positive and CD5, CD10, CD23, and CD11C negative. In a phase II study including 34 patients with gastric and non-gastric marginal zone lymphoma of which 23 had no prior therapy, rituximab produced an overall and complete response rate of 73% and 44%, respectively. The median duration of response was 10.5 months. Studies with radioimmunotherapy are limited with these patients included in phase II studies of low-grade NHL. The randomized study of ^{90}Y -ibritumomab versus rituximab included 9 patients on the ibritumomab arm with nonfollicular low grade lymphoma. Two of these patients had

Table 2 First-line therapy in follicular lymphoma (FL) with sequential chemotherapy followed by radioimmunotherapy (RIT)

Author	Chemotherapy	RIT	No. of patients	CR
Leonard et al 2005	F × 3	I-131	35	86%
Zinzani et al 2006	FM × 6	Y-90	19	73%
Press et al 2006	CHOP × 6	I-131	90	69%
Shipley et al 2004	CHOP-R × 3	Y-90	22	86%
Link et al 2004	CVP × 6	I-131	30	80%
Jankowitz et al 2007	CHOP-R × 3 R × 4	Y-90	60	90%

marginal zone lymphomas and both achieved a complete response (Witzig et al 2002b). A study using ¹³¹I-rituximab included 6 patients with marginal lymphoma who relapsed after prior therapy, all responded and 5 achieved a complete response (Lehy et al 2006).

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is a distinct entity with characteristic histological appearance, phenotypic profile and chromosomal translocation, t(11; 14). The antigen profile includes CD20, CD19 and CD5 positive, and is BCL-2 and cyclin D1 positive but usually CD10 and BCL-6 negative. Like follicular lymphoma, mantle cell lymphoma is sensitive to radiation with local tumor being very responsive. About a third of patient with relapsed mantle cell lymphoma will respond to radioimmunotherapy. In a study of 15 patients with heavily pretreated MCL (median number of 3 prior regimens and a range of 1 to 6), who were treated with ⁹⁰Y-ibritumomab tiuxetan, there were 5 objective responses and a median response duration of 5.7 months (Oki et al 2004). A phase II trial from the European MCL Network treated relapsed mantle cell lymphoma patients with cytoreductive therapy followed by ibritumomab. A complete response occurred in 2 of 16 patients after chemotherapy with 7 of 14 partial responders achieving a complete response after RIT (Oki et al 2004). An ECOG phase II trial that recently completed accrual in previously untreated MCL patients treated with CHOP-R × 4 cycles followed by ⁹⁰Y-ibritumomab tiuxetan reported a complete response rate after CHOP-R of 14% with an increase to 45% after ⁹⁰Y-ibritumomab tiuxetan (Smith et al 2006). High-dose myeloablative radioimmunotherapy has been used alone and in combination with high-dose chemotherapy in relapsed mantle cell lymphoma. Seven patients with relapsed mantle cell lymphoma, all of who had received CHOP or CHOP-like regimens as first-line therapy, and also relapsed after high-dose chemotherapy with autologous stem cell transplantation were treated with a myeloablative dose of ¹³¹I C2B8 (rituximab) (Behr et al 2002). Six patients achieved a complete response and with a median follow-up of 25 months, 5 patients are still in complete response at time of publication. Sixteen patients with relapsed mantle cell lymphoma with a median of three prior regimens received ¹³¹I-tositumomab at a median dose of 510 mCi and 8–13 days later received high-dose etoposide/cyclophosphamide with autologous stem cells. Twelve patients had no progression of lymphoma 6–57 months after treatment with overall survival and progression-free survival at 3 years estimated

to be 93% and 61%, respectively (Press et al 2000). Another approach in relapsed mantle cell lymphoma is to sequence bortezomib with RIT to determine if drug resistance can be overcome. Additional clinical trials employing RIT will be necessary to determine the role of RIT in mantle cell lymphoma and to define optimal treatment strategies.

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group of aggressive lymphomas which accounts for about 30% of all NHL (Armitage and Weisenburger 1998). Gene expression array data have demonstrated that DLBCL is a heterogeneous group of diseases based on the tumor genotype (Alizadeh et al 2000). At least 3 distinct genetic types were identified. The most common type, occurring in 40% of the cases, was associated with rearrangements of *BCL-6* in the absence of other known genetic lesions. The second type involved the activation of *BCL-2* (Gascoyne et al 1997). Cases with neither *BCL-2* or *BCL-6* rearrangements comprise the third genetic group of DLBCL. These genetic subgroups have prognostic relevance since the presence of *BCL-2* confers a poor prognosis, while the presence of *BCL-6* denotes a favorable prognosis (Ye et al 1993). DLBCL can arise de novo, or may transform from a low-grade lymphoma such as small B cell lymphoma or follicular lymphoma.

In the initial studies with ⁹⁰Y-ibritumomab tiuxetan, eligible patients included transformed and intermediate grade diffuse large B-cell lymphoma. At least a partial response was observed in 11 of 23 patients (Witzig et al 2002a). A series of patients at least 60 years old with relapsed or refractory DLBCL where treated with ⁹⁰Y-ibritumomab tiuxetan and analyzed according to prior therapy. The overall response rate and median survival of approximately 50% and 22 months, respectively, and were similar in induction failures and relapse from complete remission if they did not have prior rituximab; however, the group of patients relapsing after chemotherapy and rituximab had a overall response rate and median survival of approximately 20% and 4.6 months (Morschhauser et al 2007). This is of interest because it indicates that resistance to antibody is itself sufficient to largely abrogate the effects of radiation. Several studies with slightly different designs are evaluating chemotherapy-rituximab followed by ⁹⁰Y-ibritumomab compared with chemotherapy-rituximab alone as first-line therapy.

Small lymphocytic lymphoma

Small lymphocytic lymphoma (SLL) is the nodal counterpart of chronic lymphocytic lymphoma. SLL cells have a lower

density of CD20 than other B cell malignancies. In clinical trials, SLL has a lower response rate to rituximab than follicular lymphoma. The poor response rate to rituximab is particularly striking in patients who have failed prior therapy. Combining three series, 6 of 49 patients with prior therapy responded to single agent rituximab (McLaughlin et al 1998; Davis et al 1999; Piro et al 1999). This is contrasted to responses with single-agent therapy in 15 of 22 patients with no prior therapy (Hainsworth et al 2003). A small number of patients with SLL were included in the early trials with ^{90}Y -ibritumomab. In one study 3 of 6 patients achieved a partial response (Witzig et al 2002b), and in the study of patients with mild thrombocytopenia, SLL patients treated with ^{90}Y -ibritumomab, the response rate in small lymphocytic lymphoma and transformed B-cell lymphoma was noted to be significantly lower than in follicular lymphoma (Wiseman et al 2002). In our personal experience, the response rate in SLL is poor and all the responses have been partial.

Radioimmunotherapy and high-dose chemotherapy with stem cells

There are several phase I/II and phase II studies combining either ^{90}Y -ibritumomab tiuxetan or ^{131}I -tositumomab either alone or with high-dose chemotherapy and stem cell rescue (Press et al 2000; Gopal et al 2003; Winter et al 2004; Nademanee et al 2005; Vose et al 2005). With ^{131}I -tositumomab, the target dose of radiation to the critical normal organs such as lung, liver and kidneys was 2000–2700 cGy. Using the standard dose of ^{131}I to achieve a total body dose of 75 cGy, depending upon dosimetry, the actual ^{131}I dose varies from 1184 to 8510 MBq. By comparison, with the high dose regimen the actual ^{131}I dose varies from 10064 to 31080 MBq. The regimens employing ^{90}Y -ibritumomab tiuxetan deliver a target dose of 1000 cGy to highest normal organ with a median administered dose of 71.6 mCi (range 36.6–105 mCi). The maximum conventional dose of ^{90}Y -ibritumomab tiuxetan is 32 mCi. These studies have shown that it is feasible to give high dose of RIT and further that there is no additional toxicity of combining high-dose RIT with high-dose chemotherapy with stem cell rescue. To date in phase I/II and phase II studies, overall response rates have been substantial in diffuse large B-cell, follicular lymphoma and mantle cell lymphoma. However, in the absence of larger, comparative studies it remains difficult to sort out the role of each component such as high-dose chemotherapy alone or with high- vs low-dose radioimmunotherapy.

Unusual adverse events

Anaphylactic reaction

The package inserts for RIT warn of allergic reactions such as angioedema, acute respiratory distress, hypoxia, bronchospasm, and even anaphylactic shock with first exposure to the monoclonal antibody component of the drug. There are a few series of cases in which responders to RIT have been re-treated. One report describes 32 patients who because of initial response to ^{131}I -tositumomab, were re-treated with ^{131}I -tositumomab tiuxetan. The overall and complete response rates to re-treatment were 52% and 25%, respectively. The median duration of complete response was 35 months. One patient experienced an anaphylactoid-type reaction associated with unlabeled tositumomab infusion during the therapeutic dose. In another phase I study in which 15 patients received a sequential second dose of ^{90}Y -ibritumomab tiuxetan, there were no unexpected side effects reported (Witzig et al 2003b). The overall response rate was 83%. We reported a case of an anaphylactic reaction in a 45-year-old man with an 8-year history of heavily treated follicular lymphoma who was receiving a second treatment with ^{90}Y -ibritumomab tiuxetan. On day 1 of the re-treatment the ibritumomab tiuxetan regimen, the patient received rituximab followed by ^{111}In -ibritumomab tiuxetan without any difficulty. His biodistribution scan was unremarkable. One week later, he returned for the therapeutic dose. Again, rituximab was administered without any reaction but after less than 1.0 ml of ^{90}Y -ibritumomab tiuxetan, the patient complained of chest pain. He was observed to have shallow respirations, hypotension and incontinence. He responded to resuscitative measures. A HAMA was measured and was strongly positive.

The anaphylactic reaction of our patient represents an immunologic response from a clonal population of “memory” B-cells. Presumably, his primary immune response occurred with his first exposure to the dosimetric dose of ^{111}In -ibritumomab tiuxetan. With his initial therapeutic dose 1 week later, he had no reaction. There is generally a lag of 5–7 days before antibody levels start to rise in the primary immune response (Goldsby et al 2000). In a secondary immune response, the lag time before antibody levels start to rise is much shorter (1–2 days) and the levels are much higher (100 to 1000-fold higher) (Goldsby et al 2000). Thus, when patients are re-treated with murine and chimeric antibodies, their secondary immune response will result in more rapid antibody formation. Our patient’s re-treatment dosimetric dose likely incited a secondary immune response with amplification of a HAMA-producing population of memory

B-cells which prompted his robust immunologic response to his therapeutic dose 6 days later.

The median time that HAMA antibodies remained detectable in the serum of previously untreated patients using ¹³¹I-tositumomab was 5.5 months (range 1.1–25.1) (Kaminski et al 2005). Our patient was nearly 2 years out from his initial treatment with radioimmunotherapy, and he may or not have had detectable HAMA in his serum prior to his dosimetric dose, but he clearly had maintained his amnestic response. While this is an unusual reaction even in patients with HAMA, this case illustrates that even heavily pretreated patients may have a robust immune response, and it would be prudent to check HAMA levels in all patients prior to re-treatment with radioimmunotherapy.⁵⁰

Radiation fibrosis

A 75-year-old man with relapsed follicular non-Hodgkin lymphoma confined to a solitary lung mass was treated with ⁹⁰Y-ibritumomab tiuxetan. Imaging with PET/CT showed a complete response 3 months after RIT. Thirteen months after RIT, his PET/CT scan showed an FDG-avid infiltrate in the area of the prior lung mass. Bronchoscopy failed to review evidence of recurrent lymphoma and all

cultures were negative. The patient was followed over the next 2 years with serial PET-CT scans (Figure 2). His latest scan 2 years after treatment showed persistent scarring in the area of previous disease with a marked decrease in SUV consistent with radiation fibrosis. Radiation-induced lung injury after therapy with ⁹⁰Y-theraspheres was previously reported in the setting of intraarterial microspheres used to treat inoperable hepatic tumors. This occurs when there is a large shunt in the liver and the spheres become trapped in the small vessels of the lung. This is the first case in which radiation-induced radiographic changes are reported after RIT for lymphoma. In this case the area of fibrosis was limited to the site of prior lymphoma. Radiation-induced lung injury occurs after a latent period and is separated into 2 categories, which are acute and chronic phases (McDonald et al 1995; Lasky and Merrill 2005). Acute radiation pneumonitis occurs 1–3 months after exposure. Chronic radiation-induced lung injury consists of fibrosis which may be seen 6 months after exposure and can progress over years.

This patient represents an unusual case in that there was a solitary lung mass which appeared similar to a solid tumor without evidence of disseminated disease. For this reason, we suspect that he may have received a concentrated dose of radiation, at a low-dose rate. The ¹¹¹In-ibritumomab tiuxetan

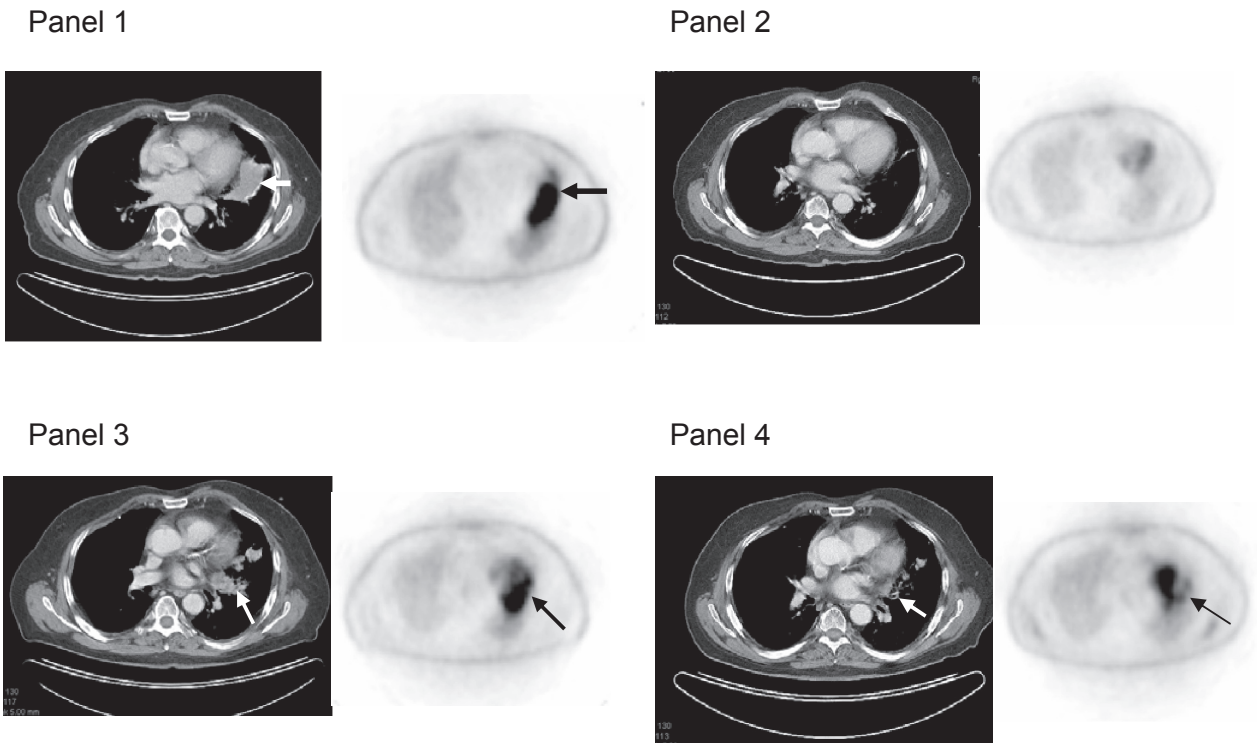


Figure 2 Panel 1 shows large left lung mass on CT scan with corresponding FDG-avidity, biopsy proven follicular lymphoma. Panel 2, 3 months later shows resolution of mass on CT scan and FDG-negative scan. Panel 3, 12 months after ⁹⁰Y-ibritumomab tiuxetan shows infiltrative mass on CT scan and FDG-avid area apart from the heart. Bronchoscopy was negative for recurrent lymphoma and cultures were negative. Panel 4, 24 months after treatment there is residual scarring with decreased FDG-avidity.

with subsequent scanning with a gamma camera showed uptake in this mass and was used to estimate the radiation delivered to the region of interest (ROI) which we estimated to be a minimum of 980 rads. It is difficult to compare the physiologic effect of a dose of external beam radiation at 200 rads per fraction with that of continuous low-dose radiation which is delivered by RIT.

Prior case reports have indicated that PET imaging may reveal FDG uptake in radiation pneumonitis (Lin et al 2000; Alavi et al 2002). PET positivity may be expected given the inflammatory nature of the disorder, including infiltration of leukocytes and pneumocyte proliferation (Alavi et al 2002). It was critically important in this case not to assume that the PET-positive infiltrate was the result of recurrent lymphoma. Nearly 2 years elapsed before there was a significant fall in the FDG-avidity in the left lung.

Serum sickness

A previously healthy 47-year-old woman was treated for follicular lymphoma, grade III, with CHOP-R followed by ^{90}Y -ibritumomab tiuxetan and rituximab. She developed a serum sickness-like illness 2 weeks after initiating ^{111}In -ibritumomab and while she was receiving post-RIT rituximab with fever, myalgias, arthralgias, and pleural and pericardial effusions. Despite anti-inflammatory therapies her symptoms persisted for 10 months before ultimate resolution. Her symptoms responded to high dose steroids but with each attempt at tapering, inflammatory markers increased and symptoms recurred. The addition of methotrexate and colchicine was ineffective. With the combination of indomethacin and prednisone, doses were gradually tapered and discontinued. In Figure 3 is shown a CT chest scan with pleural and pericardial effusions and the accompanying graph (Figure 4) is the time course of inflammatory markers.



Figure 3 CT scan with moderate pleural effusion and small pericardial effusion in patient with serum-sickness like syndrome. Both effusions rapidly cleared with steroid administration.

The occurrence of serum sickness after therapy with rituximab has been previously reported in 19 patients. In general, symptoms consisted of fever, myalgias, and arthralgias which responded promptly to corticosteroids. Serum sickness has been reported after rituximab in 2 patients with follicular lymphoma (Seror et al 2007), although other reported cases occurred in patients previously diagnosed with autoimmune disorders. This type of reaction has not been reported after RIT. In this patient, we are unable to determine which is the more likely causative agent rituximab or ibritumomab. Theoretically, the antibody ^{90}Y -ibritumomab may be more likely since it is a pure murine molecule, as opposed to rituximab, the majority of which is humanized. Serum testing was not definitive, as both HAMA and HACA were negative.

As monoclonal antibody use continues for various malignant and non-malignant diseases, and as ^{90}Y -ibritumomab tiuxetan is used earlier in the course of disease in patients with lymphoma when patients are less immunocompromised, clinicians should be aware of this potential complication.

Summary

The development of anti-CD20 monoclonal antibody therapy has had a major impact on the treatment of B-cell NHL. It has been demonstrated in randomized clinical trials in patients with diffuse large B-cell lymphoma that the addition of rituximab to CHOP has improved the overall response rate and improved survival. What role of radioimmunotherapy will have on this subtype of lymphoma and in what setting remains to be defined. Current studies in previously untreated patients with stage I and II disease as well as in advanced disease may provide additional insight. Whether RIT will find a place in the treatment algorithm of mantle cell lymphoma similarly awaits additional trials and maturation of data from the ECOG study and others. In a summary of SWOG trials in follicular lymphoma comparing studies from 1974 to 1983 and 1988 to 1994 and from 1998 to 2000, it is apparent that the introduction of monoclonal antibody therapy has had a beneficial effect on progression-free survival and overall survival, however, it is as yet not possible to define differences between labeled and unlabeled antibody. Notwithstanding, it is clear that RIT can produce significant responses in patients with relapsed follicular lymphoma including those patients refractory to rituximab. The place of RIT as a first-line single agent or sequentially with chemotherapy needs to be determined by well-designed clinical trials. The results of the large

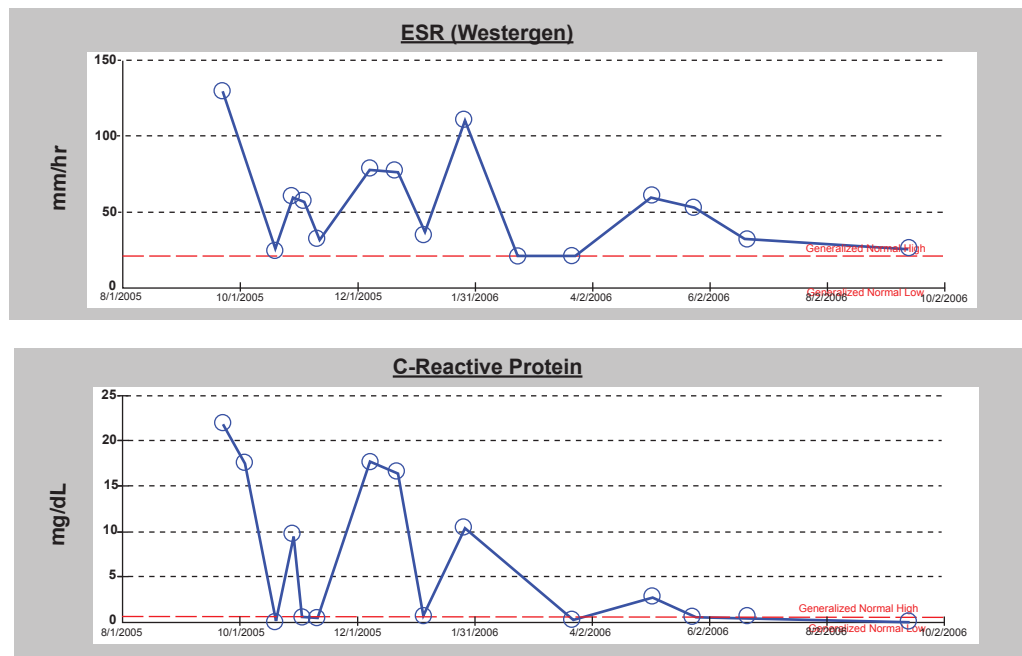


Figure 4 Graphs of sed rate and c-reactive protein in patient with serum-sickness like syndrome following immunotherapy with ibritumomab and rituximab. The rise in inflammatory markers corresponded with attempts at tapering of the dose of steroid.

randomized Intergroup study may not be available for several years. It is also likely that by further elucidating the interaction of labeled and unlabeled monoclonal antibody and defining the mechanism of action of these agents on cell signaling a scientific rationale for designing optimal use of these agents will become a reality. We would envision that there will be patterns of expression of cell signaling proteins that will be predictive of response or resistance to antibody therapy and, may also, provide insight into combination of agents which will enhance response or overcome resistance. For lymphomas, apoptosis seems to be a critical pathway for cell death and it is likely that radioimmunotherapy will be demonstrated to have a role in apoptotic cell death through cell signaling mechanisms.

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