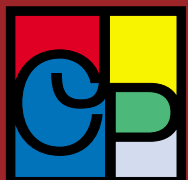


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RADIOIMMUNOTHERAPY OF
NON-HODGKIN'S LYMPHOMA



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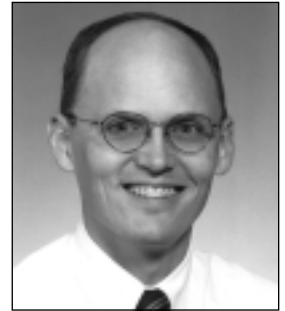
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Monoclonal Antibody Therapy in Non-Hodgkin's Lymphoma: An Overview

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Radiolabeled antibodies represent an incremental step forward in our goal of achieving functional immunotherapy in cancer. By way of perspective, if you look at immunotherapy highlights, the notion of using our immune system to treat cancer dates back now over a century, and in fact as far ago as 1904, when Ehrlich talked about "magic bullets." The dream became closer to reality in 1975 with Kohler and Milstein's work on the production of monoclonal antibodies, followed by clinical trials of the use of murine monoclonal antibodies in lymphoma.

The use of antibodies to treat cancer is based on the original hypothesis that the monoclonal antibodies can act as anti-cancer therapies by attaching to an external surface molecule and either delivering a toxin or inducing complement-mediated lysis or antibody-dependent cellular cytotoxicity. The underlying theme is that with the right tools, ultimately we can manipulate the immune system to fight cancer, much in the way it fights infections.

Much of the early work in this modality of therapy, just like the other modalities, radiotherapy and chemotherapy, has started and become most studied with the lymphomas. In part this is because lymphomas are potentially more sensitive to immunotherapy than other cancers, but ultimately because they are easy to work with in vitro, they have a number of well-defined antigens that are either cell- or tissue-specific and are biologically important, there are effective animal models in which to test them, and, importantly, they are sensitive to a variety of noxious agents.

The results of initial trials in which surface immunoglobulin was targeted using monoclonal murine antibodies were mixed. There were certainly several responders proving proof of concept, and some responses were clinically meaningful. However, the murine antibody was felt to be imperfect due to its immunogenicity, its imperfect activation of immune effector mechanisms, and what was felt to be suboptimal pharmacokinetics.

The decades following those initial trials focussed on ways to take incremental steps from those initial murine antibodies. One direction of improvement has been the humanization of unlabeled antibodies. Other directions studied include the use of immunotoxins, and, of course, the use of radiolabeled attachments to increase the potency of monoclonal antibodies.

Considering the variety of antibodies that are going to come into the clinical arena for testing and for clinical use, it is important to recognize that they are targeted against a variety of antigens, and that there are properties of the antigen that should be considered. Ideally we'd like them to be tumor-specific, or at least tissue-specific, and, for practical reasons, it would make sense if the antigen is preserved and somewhat ubiquitous throughout the species, so that individual antibodies don't have to be made.

Also, there are some disadvantages to targeted antigen that is shed out into the circulation. Ideally, the targeted antigen should be focussed on the cell surface. It is important to recognize that

when the antibody interacts with the antigen, it has the potential to undergo immodulation and the antibody-antigen complex can either be internalized or shed out into the circulation, or it can remain fixed on the surface of the cell.

Finally, it is becoming important to realize the function of the antigen actually being targeted, because a number of antigens have important roles in cell cycle, cell growth, and cell death mechanisms.

In addition to considering the antigen that is targeted, the basic function of the construct of the antibody is important. Remember that these antibodies, as immunoglobulin molecules, have a hypervariable region which is responsible for the binding specificity. It's the other end of the antibody, the FC portion, that is generally accepted to mediate most of the biologic activity through either its complement binding or through binding to FC receptors.

Recall that the original antibodies were pure murine in nature, which caused the basis of a number of concerns. To alleviate these concerns, research has been conducted on the use of humanized antibodies, which are now technically available for production, but have not gone very far in clinical studies. When we talk about humanization of antibodies, we are often referring to a variable degree of chimerism.

To focus on the advances made with the unlabeled antibodies through the process of humanization, keep in mind that humanized antibodies are anticipated to have longer circulating half-life, be less immunogenic, and be more more potent in terms of antibody-dependent cellular cytotoxicity and complement-mediated lysis.

One hypothesis as to how these antibodies work, in simplistic terms, is that the antibody attaches to the antigen and then through its FC portion interacts with NK cells or the cellular effector mechanisms of the immune system. An alternative view is that when the antibody attaches to the antigen, it induces the complement cascade and ultimate cell death through that mechanism.

Mitch Reff demonstrated, at least with C2B8, the parental protein of rituximab, that when comparing the chimeric version of the antibody to the murine version of the antibody in assays that utilized ADCC of complement-mediated lysis of CD20 positive cells, the chimeric protein was much more efficient at inducing either ADCC or complement-mediated lysis of antigen-positive cell lines. And so it was with that general concept that these antibodies moved forward again into the clinic for another foray.

The first antibody to take advantage of that was the Campath-1H, which targets CD52, is expressed on B-cells and T-cells and monocytes, and is ubiquitous throughout the human population.

When the humanized version of Campath was given to patients with a variety of lymphoid malignancies, it was found to be very ef-

fective at depleting circulating tumor cells in the blood and bone marrow. But, for a variety of reasons, lymph nodes that were involved with tumors were relatively resistant to the effects of Campath. There was relatively profound monocyte depletion due to the distribution of CD52 with T-cells and B-cells and monocytes, which led initially to subsequent infections and required new strategies for infection control.

Rituximab was another antibody then to take advantage of the technology to make chimeric or humanized antibodies. Recall that it is chimeric with the variable region being murine and the backbone human IgG1. It targets CD20, which again, is expressed on all B-cells, but not T-cells, or NK cells, and is felt, to some extent, to be involved in regulating the cell cycle.

To summarize a large body of work on rituximab in low-grade non-Hodgkin's lymphoma: it was observed initially, when given to patients with relapsed disease at 375mg/m² weekly X four doses, that from a safety standpoint there was a unique infusion-related syndrome, while otherwise Grade III cytopenias were infrequent. There was B-cell depletion but no apparent resulting infections, and no immunogenicity. Importantly, a number of reports have described a 50% overall response rate, with median response duration of about one year.

It is important to recognize that these results represent proof of concept. They were not designed to show how to treat patients, but literally just to prove the concept that these antibodies have clinical activity. No matter how long these initial studies are followed, they will never give any insight in terms of how we have changed the natural history of those patients' disease.

When we go back and look at some of the subsets in these initial trials, it is important to recognize that the follicular histologies were very susceptible to rituximab, with response rates greater than 50% in a number of reports.

When patients who previously responded were re-treated, overall response rates were about 40%, but median time to progression was actually longer than was seen for the initial response, and that's something that is potentially unique to immunotherapy.

More recently, rituximab has been studied as a first-line therapy for low-grade lymphoma patients. Results suggest that rituximab in this setting has an initial response rate of about 45%, but with increasing cycles can be brought to as high as 71%.

It is important in the field of oncology to consider how to combine rituximab with our other tools for the treatment of low-grade lymphomas. Czuczman reported in the *Journal of Clinical Oncology* on 40 patients with low-grade lymphoma who were largely previously untreated. When he combined CHOP and rituximab, he found an overall response rate of 100%, with the majority of those being complete responses. Twenty-eight of those patients remain in ongoing remission at 40 months.

The promising results of these Phase II studies, while not showing for sure that we have changed the natural history of low-grade lymphomas, have led to the generation of larger cooperative group studies, including those at SWOG and ECOG, both of which involve chemotherapy followed by rituximab. Additionally, Bob Marcus in the United Kingdom is looking at concurrent chemotherapy with CVP and rituximab versus CVP alone, and MD Anderson researchers are exploring a combination of rituximab and the FND regimen.

The field is moving forward now, targeting other molecules, such as CD52, CD22, and HLA-DR. Testing antibodies that target alternative molecules is not based on the hypothesis that ADCC or complement-mediated lysis may be improved, but rather that dif-

ferent molecules may initiate different intracellular signaling cascades that might influence cell growth, cycling, and death.

Epratuzumab is an antibody targeting CD22, which, again, is B-cell specific, is found on the surface and cytoplasmic cellular portions, and is not shed. It binds across a wide range of lymphoma subtypes and has minimal reactivity with normal tissues. Epratuzumab is the humanized version of the murine LL2 antibody. It is CDR-grafted into an IgG1 backbone. Radiolabeled and unconjugated constructs with epratuzumab are under evaluation. Reports on Phase I-II studies of this antibody in more than one hundred subjects show that the therapy is well tolerated, with no grade III-IV infusion reactions and no observed immunogenicity. It was tolerated well in patients previously treated with either rituximab or stem cell transplant.

Hu1D10 is an antibody against HLADR, which is a potentially attractive target because it is known to play a role in B-cell signaling and is not shed. The Hu1D10 antibody, again, is a humanized, CDR-grafted IgG1. It binds again across a relatively wide range of lymphoma subtypes, but is not as ubiquitously expressed across the species, with only about two-thirds of patients with B-cell lymphoma reacting with 1D10. In addition, it is not quite as tissue-specific as other antibodies, in that it also reacts with some benign B-cells and some interstitial cells in a variety of organs. A 20-patient Phase I study of Hu1D10 has been completed, with results suggesting that there may be a unique mechanism of action invoked by targeting HLADR.

Regarding use of the antibodies in aggressive non-Hodgkin's lymphoma, which has not been as extensively studied yet, Bertrand Coiffier has reported on a series of 54 patients with intermediate and high-grade non-Hodgkin's lymphoma that were treated with rituximab as a single agent. This was a very heterogeneous patient population here; some in first relapse, some in primary refractory, some PR, and some actually in the first line of therapy. Eight weekly infusions resulted in an overall response rate of 32%, again providing a proof of concept that there is some clinical activity.

In an upcoming article in the *Journal of Clinical Oncology*, Julie Vose describes a Phase II study in which rituximab plus CHOP was combined to treat newly diagnosed large-cell, or aggressive, lymphomas. Thirty-three patients with untreated aggressive non-Hodgkin's lymphoma all received six cycles of rituximab followed by CHOP, resulting in an overall response rate of 94% at 24 weeks. Serious adverse events in this study were no different than expected for CHOP alone.

ECOG, CALGB, and SWOG are cooperating in a study where elderly patients with newly diagnosed diffuse large-cell lymphoma are randomized to CHOP versus CHOP plus rituximab, and then responders are either randomized to observation or consolidative or maintenance therapy. Additionally, Bertrand Coiffier and the GELA group will soon be presenting their first analysis of a study completed in Europe of CHOP versus rituximab plus CHOP.

To summarize, it appears fairly clear that we may have impacted the natural history of some of these patients with lymphoma through the use of antibodies, particularly with the chimeric CD20 antibody. Further maturation of randomized studies may demonstrate that such therapy can be clinically effective and useful.

Finally, continued development of this field may center on targeting other antigens, continuing to examine various antibody-plus-chemotherapy combinations, and exploring the potential of radioimmunotherapies. *BLR*

Radioimmunotherapy Agents: What They Are and How They Work

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Radioimmunotherapy is very appealing for treatment of lymphoma, in that lymphoma cells remain inherently sensitive to radiotherapy even when resistant to chemotherapy. The advantage to radioimmunotherapy is that the cell does not have to be bound by the antibody to receive the cytotoxic radiation. For example, if a radiolabeled antibody binds to one, but not the other, of two lymphoma cells in close proximity, the unbound cell will still receive the radiation similar to the cell that is bound. The advantage, then, is that radioimmunotherapy tries to overcome some of the problems that we have seen with antibody therapy alone. This differs from the treatments that we have now for lymphoma.

With external beam therapy we are radiating a limited area of the body. With chemotherapy, the treatment is a systemic treatment that goes throughout the body, and the therapy depends on the differences in sensitivity from the normal tissue compared to the tumor. With targeted radioimmunotherapy, however, the antibody is actually the carrier for the toxic substance, and delivers the toxic substance to the site of the tumor.

This report focusses mainly on the CD20 antigen, which is expressed only on B-cells. CD20 is important for cell cycle initiation and cell differentiation, and is ideal for targeting due to the fact that it is anchored into the membrane and doesn't shed or internalize. CD20 is also an excellent tumor target in that it is expressed almost exclusively on lymphoma cells. Plasma cells, which make the immunoglobulin, do not generally express this antigen, so they continue to make immunoglobulin to protect from infection. Similarly, pluripotent stem cells do not express CD20, so they continue to make cell precursors. While these cell populations are lowered both with this therapy and with the anti-CD20 monoclonal antibody therapies, they soon replenish and, in most cases, it does not appear that there is an increased risk of infection for the patient.

There are two radioisotopes that are being used today for radioimmunotherapy. The first is yttrium-90, which decays to zirconium-90, and has a half-life of 64 hours. There is essentially no gamma radiation associated with Y-90, making it impossible to image directly.

Iodine-131, the other radioisotope being used in clinical trials at this time, has been available for many years for treating thyroid cancer. It is now being used to attach to an antibody to provide a way of performing radioimmunotherapy. I-131 has a half-life of eight days – significantly longer than Y-90. It also differs from the Y-90 in that it gives off gamma radiation, which can be imaged with a standard gamma camera.

The issue of radioactive decay is important because it is the mechanism by which the antibody is visualized when it is a gamma ray, and is the means by which the therapeutic potential of the iso-

tope is realized through either an alpha-meter or a beta-meter.

With the alpha decay, the Iodine releases a helium nucleus, which is an alpha particle. This is very high energy, but travels for a very short distance. There are clinical trials being conducted today where alpha emitters are being used for radioimmunotherapy.

Beta-minus decay emits an electron and an antineutrino. This has very low mass, but has a longer path length than does the alpha particle. Beta-plus decay is what PET scanners use today with the positron emitting radioisotopes. It is very similar to a beta-minus, but the electron with the positive charge annihilates, resulting in the production of a gamma photon.

Gamma photons are also produced with gamma emitters, which are used in nuclear medicine today for cardiac studies and oncology studies.

This report discusses, for the most part, beta decay, because that is the type of treatment that is associated with radioimmunotherapy. In beta decay, a neutron inside the nucleus of an atom breaks down and changes to a proton, emits an electron, and then the atomic number goes up by one and the mass number remains unchanged.

It is understood that beta emission from radioisotopes allows us to kill tumor cells, but that it will also kill normal cells. So as the blood circulates through the bone marrow, there's beta decay from the radioisotope, and there is radiation that is being delivered to the bone marrow cells. In the case of normal bone marrow without lymphoma involvement, there appears to be less radiation to the bone marrow, compared to patients who have significant involvement of lymphoma in the bone marrow.

One of the more important points to understand about radioimmunotherapy is the conjugation, which is the chemical linkage of the radioisotope to the antibody. This linkage is what allows the therapy to be delivered to the tumor cell. If there is a weak linkage, the radioisotope separates from the antibody, resulting in the radioisotope no longer being delivered to the tumor cell, but instead being deposited in an organ or being skewed from the body.

In circumstances where an isotope comes off the antibody, and some of the isotope will come off in any sort of conjugation, the yttrium-90 goes to the bone and I-131 goes to the thyroid and stomach, so they have different routes of excretion following release of the isotope from the antibody.

Significant advances in the area of isotope conjugation have been made over the last 20 years in terms of radioimmunotherapy or in terms of targeted therapy. We now have excellent conjugation methods to attach the radioisotope to the antibody.

In the case of Y-90, conjugation is achieved using key molecules which hold the isotope, and which are in turn bound to the antibody.

In the case of I-131 labeling, the I-131 itself is chemically linked to the antibody. There is not a conjugated molecule, but rather a direct linkage -- a chemical bond -- and there are several different methods for accomplishing that. The I-131 conjugation methods, then, generally require some sort of separation of the free isotope from the antibody once the labelling is completed.

If you look at the two radioisotopes that are primarily being used in radioimmunotherapy, you will see that Y-90 does not have a gamma emission, which is good and bad. It cannot be imaged directly, so if the way that this is being used requires an image to be made, you would have to use another isotope. Indium-111, which is very similar to Y-90 and binds similarly with the conjugation, is imaggable, and has been used for this purpose. I-131 does have a gamma emission, and can be imaged with a gamma camera. The disadvantage to the gamma emission is that when you begin to look at protection and release of patients from the hospital, the gamma emission requires that patients receiving higher doses of I-131 have to have restrictions on their living patterns or remain in the hospital after treatment. The lack of a gamma emission from Y-90 is helpful in patients in that they can go directly home.

In terms of releasing individuals after we have a pharmaceutical administration of a gamma emitter, there have been new rules that have been written and are in effect. In many places in the United States, an individual can be released once the radiation dose is calculated to be less than 500 mg or 0.5 grams. What this means is that once a patient receives a therapeutic dose of radioisotope, if there is enough gamma emission to give off more than 100 mg, the patient then has to have written instructions given and cannot be released until the point where they are unlikely to give someone else 500 mg. These rules really apply to I-131 labeled antibodies. The yttrium-90 antibody really has very few restrictions due to the fact that there is no gamma emission being given off from the radioisotope.

Another factor to consider in the beta emissions of Y-90 and I-131 is path length. Y-90 has a longer path length, with about 90% of the energy being deposited within 5 mm, compared to about 1 mm with I-131. The longer path length of Y-90 means that larger

tumors may receive a higher dose of radiation, but also that adjacent normal cells could receive more radiation from the Y-90, compared to I-131.

Studies of radioimmunotherapy for non-Hodgkin's lymphoma using the yttrium-labeled antibody Zevalin have been conducted. In these studies, patients received rituximab pretreatment with a cold antibody, followed by the indium-labelled Zevalin for imaging. The reason the indium-labelled Zevalin is used is because you cannot image the yttrium. On day seven, then, patients who met the criteria for treatment went ahead and received an additional dose of rituximab pretreatment, followed immediately by the yttrium 90-labelled Zevalin.

In radioimmunotherapy with the I-131-labeled antibody Bexxar, patients are started on potassium iodide to try to reduce the amount of iodine that would be received by the patient's thyroid. Patients then receive unlabeled antibody, followed by a trace-labelled I-131 antibody. The patients then have whole body imaging done on three occasions over the next week. The imaging data is then used to calculate the dose of radiolabeled antibody, which tends to be 65-75 cGy, depending on platelet counts. This treatment dose is preceded again by a dose of the unlabelled antibody.

The best way to dose the antibodies is still under investigation. I think the biodistribution of the Y-90 and the I-131 labelled antibodies help dictate which one will need to have the dose calculated based on the excretion date and which one may not.

The I-131 antibodies have significantly more whole-body excretion compared to Y-90. The urinary excretion for Y-90 is about 5-11% over a week, compared to 46-90% at 48 hours for the I-131 antibodies. So there is more of I-131 that is coming off of antibodies, or at least more being secreted from the body, making it more important to do the scans to determine appropriate dosing for patients treated with I-131.

With Y-90, the radioisotope really ends up in either the liver, spleens or a tumor; very little of it comes out of the body. Accordingly, the dosimetry of whole-body clearance does not appear to be required to determine Y-90 radioimmunotherapy dosing. *BLR*

Early Clinical Experience with Yttrium-Labeled Radioimmunotherapy in Patients with Relapsed Low-Grade Non-Hodgkin's Lymphoma

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When we begin to consider the subject of early clinical experiences with yttrium-labeled radioimmunotherapy in patients with lymphomas, it is useful to review certain information about the diseases themselves, and then begin to think about how the radiolabeled monoclonal antibodies may play a role in treatment.

The incidence of lymphoma is increasing. There are about 50,000-60,000 new cases per year, with 240,000 cases at any given time. Lymphomas can, in most classifications, be divided almost equally, with low-grade, intermediate-grade, and high-grade each occurring in about one-third of cases.

This discussion of the role of radioimmunotherapy in the treatment of lymphomas will center on low-grade and intermediate-grade lymphomas, because the initial trials of this therapy have been conducted in patients with those subtypes.

In the case of low-grade lymphomas, most patients present with advanced stages of the disease, and we think of them as incurable by conventional therapy. This status, however, makes them candidates for novel therapy.

With intermediate-grade lymphomas, about 40% of patients are thought to be curable with conventional chemotherapy. Median survival is about 2 to 2.5 years, and those 60% of patients that are not curable by conventional therapy are candidates, again, for novel approaches.

In both low-grade and intermediate-grade lymphomas, we are able to take advantage of the fact that the diseases are predominantly of B-cell origin, and for the most part they express the CD-20 antigen, which lends itself to targeting with antibodies.

Keep in mind that in all of the trials discussed in this report, yttrium is actually linked to the murine antibody, not to the humanized antibody. This is the case because there was concern that since half-life is longer in the humanized antibody, there would be extensive exposure to the radiolabel, and, therefore, more toxicity.

Zevalin is yttrium linked to the murine monoclonal antibody C2B8 by means of a novel chelate -- the so-called MX-DTPA chelate -- which is conjugated to the antibody, forming a strong urea-type bond. This bonding results in very stable retention of yttrium.

This antibody targets the CD-20 antigen, which is hydrophobic, and, most importantly, does not shed, internalize, or modulate. This means that once the antigen is exposed to the antibody, inside or outside the cell it is not lost.

The initial Phase I/II trial of Zevalin, launched about three years ago, was a dose-escalating study of 0.2, 0.3, or 0.4 millicuries per kilogram (mCu/kg) of yttrium-labeled monoclonal antibody. Patients with low-grade, intermediate-grade, or mantle-cell non-Hodgkin's lymphoma were eligible. Patients in all of the trials discussed must have had less than 25% lymphoma involvement of the

marrow, baseline platelet count of greater than 100,000, at least in the initial studies, no prior stem cell transplant, and, in the initial trial, no prior treatment with Rituxan.

On day zero patients first received a dose of Rituxan -- so the humanized antibody first -- followed by an injection of indium-labeled C2B8 for imaging purposes. The rationale for giving the Rituxan first was based on Phase I data from Susan Knox and others, which suggested strongly that the binding of a radioimmunoconjugate to lymphoma was enhanced if there was pre-treatment with cold antibody. The reasons for this aren't clear, but the prevailing opinion is that you can take up binding sites in the periphery and allow more of the radioimmunoconjugate to get to the tumor through this method. There is some thought from others, however, that by giving the Rituxan first a localized tumor response, in which cytokines are released and binding sites for the radiolabeled antibody are freed up, is induced.

On days zero through six, scans and dosimetry calculations were conducted. After the indium injection, the dose to normal organs was determined. Then, on day seven, another dose of cold antibody was administered, followed by the yttrium-labeled C2B8 given in about a 10-15 minute injection.

In all of these trials treatment was administered on an outpatient basis.

Looking at the original group of 57 patients, the median age was 60, most were male, and each had undergone prior therapy. The number of prior therapies ranged from one to eight, with a median of two. Most patients had been diagnosed with lymphoma about four years previously, and there were clearly displayed variations in terms of resistance to chemotherapy in the cohort. About 40% of patients had bone marrow involvement. About 25-27% of patients had extra-nodal involvement. Fifteen percent had splenomegaly, and 37% of patients had bulky disease, defined as greater than a seven centimeter mass.

The overall response rate in all 51 evaluable patients was 67%. If you look, however, at the 34 patients who had low-grade lymphoma, the response rate was 82%. Interestingly, 27% of patients had complete remission.

In the 14 patients with intermediate-grade lymphoma the response rate was lower at about 43%, although this patient subset showed a surprisingly high complete remission rate.

Of interest, there were three patients in this initial trial with mantle cell lymphoma. And while the response rate was zero in these patients, at least two of them had massive splenomegaly, both of whom showed evidence of dramatic reduction in the spleen size, but no response in their indicator lesions following therapy. What this appears to indicate is that we have what has been referred to as a 'sink phenomenon' with the radioimmunotherapy; that the

dose of radiation will go to the bulkiest site of disease. This, then, gives us pause about future studies and how to approach this problem to see if we can do something about the spleen prior to radioimmunotherapy.

In terms of response and time to progression there really was no significant difference between the 0.2 mCu/kg, 0.3 mCu/kg, and 0.4 mCu/kg doses. Also in these studies it was determined that the 0.4 mCu/kg dose was the maximum tolerated dose, although it should be noted that that dose was not surpassed. So while the traditional scheme for determining maximum tolerated dose wasn't used in these trials, 0.4 mCu/kg seemed to be the dose that was well tolerated, with blood counts recovering usually within about two weeks.

The toxicity was primarily hematologic and transient, and there was no major organ dysfunction in these initial studies. The mean serum immunoglobulin levels remained within the normal range and only 4% of patients had a decrease of 50% from baseline. Over a one-year period 6% of patients developed infections which required hospitalizations, and all of these recovered. The human anti-mouse antibody (HAMA) and the human anti-chimeric antibody (HACA) response occurred in about 2% of patients.

If you look at the hematologic toxicity, specifically in the 0.4 mCu/kg cohort, the median platelet nadir was about 50,000, and the median time to recovery was 14 days. The median neutrophil nadir was 1,100, with recovery in about 10 days. And the median hemoglobin nadir was about 9.9 grams/deciliter. In short, these toxicity data indicate a fairly acceptable toxicity in the 0.4 mCu/kg cohort in this Phase I,II trial.

According to indium scans taken at 144 hours, there was fairly impressive uptake of the antibodies at tumor sites. These scans can also be used as a measure of hepatic or other organ uptake, and one of the focuses of this Phase I/II study was to get an assessment of dosimetry to try and correlate dosimetry, if possible, with toxicity. So in the initial group of patients, the dose of yttrium was measured in two ways: it was measured directly and it was also mea-

sured as a predicted value from the indium scans. There was fairly good correlation between the two measures, so in subsequent patients the dosimetry was only done on the indium scans.

There was no correlation of toxicity with absorbed radiation doses. If you look at absolute neutrophil count nadirs and you measure them against the median red marrow dose derived by scans or by blood samples, and against the median total body dose, there was no correlation. In fact, surprisingly, the best correlation with neutrophil toxicity and platelet toxicity was the extent of marrow involvement. So patients with between 20 and 25% involvement had more toxicity than those between with between 15 and 20% involvement, etc.

A follow-up study conducted after the initial Phase I,II trial involved 35 patients with platelet counts between 100,000 and 150,000, who were treated with a lower dose of Zevalin at 0.3 mCu/mg. The design was similar so that Rituxan was first given, indium given, and then Rituxan followed by Zevalin. Bone marrow was involved in about 65% of patients, 27% of patients had splenomegaly, 50% had bulky disease, and again, there was no major organ dysfunction. Toxicity was, again, primarily hematologic and reversible. In these patients with lower platelet counts, the median absolute neutrophil count nadir was 600 instead of 1,100, and median platelet nadir was about 31,000. The overall response rate was about 67%. So, there is similar data in a slightly higher risk cohort of patients.

In summary, these trials have shown overall response rates on the order of 80% for yttrium-labeled monoclonal antibody therapy in the treatment of low- and intermediate-grade non-Hodgkin's lymphoma. The toxicity profiles showed that primary toxicity was hematologic and reversible. The maximum tolerated dose of the radionuclide was 0.4 mCu/kg, and treatment was administered on an outpatient basis.

It is hoped that these trials will pave the way for future studies using radioimmunotherapy in patients with non-Hodgkin's lymphoma. *BLR*

Radioimmunotherapy in Patients with Non-Hodgkin's Lymphoma Refractory to Chemotherapy and Immunotherapy

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In 1998, after the initial Rituxan study was published, showing about a 50% response rate for the antibody, and results of the Phase I,II study of Zevalin were released, showing about an 80% response rate, questions arose as to what yttrium was really adding in Zevalin. This question was addressed in prospective trials by doing two separate trials.

The first trial was a randomized trial in which patients were randomized to receive either the Zevalin (yttrium conjugate) or rituximab. There were 134 patients in the study, which was closed in August 1999.

The second study looked at patients with Rituxan failure and then treated them with the yttrium-label antibody. Our hypothesis was that, indeed, the yttrium was adding something to the response rate. Patients received either the standard regimen of Rituxan (375mg/m² every week for four doses) at that time, or the Zevalin regimen that was used in the preliminary trials.

The primary variable, the objective of the trial, was to look at the overall response rate. The study was blinded and all the scans were reviewed by a separate panel called the 'LEXCOR Panel,' which is a group of radiologists and lymphoma experts who looked at all the scans to further document the response rates, not knowing whether the patient had received Rituxan or Zevalin.

The secondary variable was to look at the duration of response and the time to progression, and also to again confirm where the dosimetry was needed for safety.

The inclusion criteria were very similar to those described for the early trials of Zevalin, i.e., good performance status, a CD20 positive lymphoma, platelet count of over 150,000, an absolute neutrophil count over 1500, and less than 25% marrow involvement. Participants could not have CLL or over 5,000 circulating malignant lymphocytes. Patients could not have a CNS lymphoma or HIV-related lymphoma. They had to have fairly normal liver and kidney function, and they could not have undergone any prior anti-CD20 therapy.

The patient characteristics were well-balanced, so that study participants were equally divided between the Zevalin and the rituximab arms. There was no difference in the age or gender between the two arms.

Looking at patient demographics a little more closely, it can be seen that patients up to age 80 were treated in both groups, with the median age being about 60. Most of them had received two prior chemotherapy regimens, and about half were resistant to their last chemotherapy. About 40% had bone marrow involvement. About half had bulky disease, depending on how you defined it, 50% of them greater than 5 cm.

So, the study participants were a fairly representative group of what clinicians see in their practices. About 60% had been resistant

to any prior chemotherapy.

Remember, the goal of the study was to look at the response rate, and what was found was that the results were very similar to those previously published for Rituxan in the Phase III study, and in the Phase I,II study of Zevalin. Overall, it was shown that Zevalin therapy was associated with an 80% response rate, while rituximab was associated with a response rate of 50%. The complete response rates were 34% for Zevalin, and 20% for rituximab.

Statistically significantly greater clinical efficacy was found for Zevalin, compared to rituximab, in all of the different patient groups. In other words, if you looked at older patients versus younger or males versus females or patients that had bone marrow involvement or not, Zevalin was superior as far as the response rate.

Given that the last patients were added to this study only about one year ago, there are not a lot of data regarding time to progression and duration of response. In an abstract published at the 42nd annual meeting of the American Society of Hematology (December, 2000), it is mentioned that the time to progression at this point is not yet different between the two arms. However, if you look at the time to next anti-cancer therapy, in other words the time when the patient next required treatment, you can see that there does appear to be some difference.

Adverse effects in this trial were just what you would expect for Rituxan or Zevalin. There was really no major organ dysfunction. We have not seen any of that in any of the trials with Zevalin, as far as kidney, liver, heart, lung. The only toxicity has been hematologic. There were very low HAMA and HACA rates.

Hematologic toxicity associated with these agents is significant. Zevalin-treated patients had a platelet nadir of about 41,000 and ANC nadir of 900 neutrophils. They were also a little more anemic than those in the Rituxan arm. Only about 6% of patients had Grade IV toxicity of platelet counts less than 10,000.

Overall, the single-agent response rates in this trial appear to indicate a statistically significantly higher efficacy for Zevalin, compared to Rituxan.

About the same time as the study just discussed, another study was conducted to approach the question of whether yttrium was adding anything to standard therapy. This study took patients who had undergone Rituxan therapy but had failed it. Failure of Rituxan therapy was defined in two ways: a patient responded, but the response lasted less than six months, or a patient was simply refractory to the therapy.

This was a single-arm, multi-center, open-label trial. There were 57 patients involved in the trial, almost all of whom were diagnosed with follicular lymphomas. All these patients received the standard 0.4 mCu/kg dose of Zevalin. The trial closed also about a year ago.

The primary objective of this trial was to determine the overall response rate in this population, while the secondary goal was to compare the overall response rate and duration of response to what the patients had previously received with their last chemotherapy or their last dose of rituximab.

The response evaluation in this study was performed by the investigators at each site by looking at the scans, doing measurements, and coding the responses. The scans were then sent to the central LEXCOR panel for independent evaluation, which may have added a lot of work to the trial, but added a lot of validity in the sense that these investigators did not know what this patient was receiving and where they were in the treatment course.

The patient characteristics in this trial were actually a little different than in the other trials. They were about the same age group and most had follicular lymphomas, but they had undergone more prior therapies. A third of them had bone marrow involvement, and almost three-fourths of the patients had bulky disease, depending on how it is defined (here, greater than 5 cm). About 30% had had prior radiotherapy. And if you look at resistance to their previous chemotherapy, about 82% of the patients had shown some resistance to prior chemotherapy.

So, overall, the disease was more advanced in this group than in previous trials.

Using international workshop criteria that are now in place, an overall response rate of 74% was observed, with most responses being partial remissions. Overall response using IDEC criteria, which use a more strict 28-day confirmation, was 59%.

Median time to progression in this study was about nine months, although a few people have not yet relapsed.

Another question asked in this trial was, "How did the response to Zevalin compare with the prior response to chemotherapy?" What the investigators wanted to show was that the Zevalin response was at least as good as the patients' last chemotherapy. Data indicate about what you might expect: if patients were resistant to their last chemotherapy and then got

Zevalin, they had a lower (47%) response rate; whereas if they had some chemotherapy response and then relapsed prior to this trial, their response rate was better (64%).

Looking at adverse events for this trial, there was an absolute neutrophil count nadir of about 700 k/ul. Nadirs for platelets and hemoglobin were about 33,000 k/ul and 9.9 gm/dl, respectively. It is interesting to note that the nadirs in this study all came out in about 50-60 days, compared to 10-14 days associated with chemotherapy-typical nadirs. This is a characteristic of radioimmunotherapy. It takes about 8-13 days to recover those counts. Usually it is a rather gentle drop, with not a lot of patient toxicity or needing to go in the hospital. Again, the adverse events were primarily hematologic. There was no major organ dysfunction. And the HACA rate in this trial was less than 2%.

There was, however, one case of acute myelogenous leukemia. This is something that we are going to need to watch. There have been other trials of other radiolabeled antibodies that have seen myelodysplastic syndromes occurring, and we must be very careful to monitor this as the years go by to see what the actual rate of these conditions is going to be in this patient population.

In summary this trial showed, again, an excellent overall response rate. The response rate associated with Zevalin was significantly greater than overall response rates to prior Rituxan therapy, and about the same as response rates to most recent chemotherapy.

It should also be pointed out that this treatment is quite easy to give. It is delivered over one week, which is certainly an advantage of this kind of treatment in the relapsed lymphoma patient.

These two trials, I believe, provide the evidence to the effect that adding the radioactive particle, the yttrium in this case, does seem to add efficacy beyond what cold, or non-labeled, antibody provides by itself. Of course, the long-term follow-up data are going to be very important in determining overall survival rates, times to progression, and durations of response. *BLR*

Radioimmunotherapy in Hematologic Malignancies: Future Directions

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There are a number of radiolabelled antibodies currently being investigated for treatment of hematologic malignancies. Each has its advantages and drawbacks. The question that needs to be answered is: Which is the winner?

The first of these radioimmunoconjugates is I-131 tositumomab, an IGG-2A anti-CD20, the brand name of which is Bexxar. Although it has some beta emissions, it is primarily a gamma emitter. Unlike Zevalin, Bexxar is generally given with dosimetry. On day zero an unlabeled pre-dose is infused over the course of an hour, and then a dosimetric dose is used to determine patient-specific PK. On days 0, 2, 3, or 4, 6, or 7, three whole body counts are performed, and on days 7-14 a therapeutic dose of 450 mg of cold tositumomab is given, the millicurie dose of I-131 determined by the dosimetry.

In Bexxar clinical trials, 40% of patients had an elevated LDH, 40% had bulky disease, and the median number of prior chemotherapy regimens was three. These patients generally didn't respond to the last chemotherapy, with only 17% showing a complete response, and 30% a partial response that lasted just five months. After treatment with Bexxar, the 192 patients with low-grade lymphoma showed a response rate of 80%, which lasted a median of 11.7 months; complete response was 36%, lasting a median of five years. Of the transformed lymphomas, half responded, lasting about a year; 30% complete remissions, lasting almost two years. The 18 patients with intermediate grade lymphoma failed to respond.

Kaminski et al presented the findings of a tositumomab trial at ASCO 2000. That trial consisted of 76 previously untreated patients, 29% of whom had high tumor burden. The overall response rate was 97%. Three-quarters of those who started off PCR-positive became PCR-negative. At the time of that presentation, the median response duration had not yet been reached. Toxicities of this therapy included human anti-mouse (HAMA) in two-thirds of patients, and two-thirds of these developed flu-like symptoms which researchers attributed to the antibody. There was moderate reversal of myelosuppression, with nadirs at 4-7 weeks. No supportive care was needed, and the patients recovered totally after around 10-12 weeks.

There are some newer radiolabelled antibodies coming along. There is an ongoing Phase I trial of yttrium-labelled anti-CD22, which is epratuzumab. It includes different kinds of antibodies, and some patients have had prior autologous stem cell transplant, some have not, many patients have had prior rituximab therapy, some with partial remission. It is too early to give much data.

Another is Lym-1. It's another IGG-2A, which targets the beta chain of HLA-DR10. It works by the usual mechanisms. Its dose-

limiting toxicity has been thrombocytopenia with some hypotension. A series of papers have been published, including 25 lymphomas and 5 CLLs who progressed after standard therapy. Tumor regression started quickly and they claim a 10% complete and 47% partial response rate. But the response criteria are not exactly what one would call conventional.

Those are not the only isotopes that can be used to treated lymphomas, and there are a few new ones which are less prevalent. Copper67 has a half life of 62 hours, a very short penetration, which for some situations might be good and for others might be bad. It has beta emissions comparable to I-131, but the gamma emissions are much more favorable, more like Bexxar, for imaging. It is nicely retained in tumors in vitro, and its hematologic toxicity is what is dose limiting.

In an article recently published in the *British Journal of Cancer*, 211-astatine was conjugated with rituximab, an alpha emitter this time. This radioimmunoconjugate was reported to have a very short half-life, short path length, and a very high tumor to normal cell toxicity ratio in vitro. It is expected to enter clinical trials soon.

Two of these radioimmunoconjugates may be on the market in the very near future. Can we increase their activity? When is the optimal time to give them? How best can we combine or sequence them with chemotherapy or with other monoclonal antibodies? Can we reduce the toxicities? And which is 'the winner'?

To increase the activity, one can consider increasing the dose, give repeated administrations, enhance antigen expression, augment effector cell function, and combine with other agents. There has been some important work done in increasing the dose of I-131 anti-B1, which is similar to Bexxar.

The first Phase I/II study of I-131 anti-B1 showed that when the patient was used as their own control, the probability of remaining free from failure was significantly longer than the patient's best prior chemotherapy response, and certainly their last chemotherapy response. In a recent paper that came out in *Blood*, the same radioimmunoconjugate was then combined with high doses of cyclophosphamide in patients with either low-grade or aggressive lymphoma. The results were compared with institutional data using the same chemotherapy without the radioimmunoconjugate. This comparative analysis suggested that with historical controls, a much better progression-free survival rate is attained when the radioimmunoconjugate is added than with the same preparative regimen, particularly for the indolent and aggressive lymphomas. The goal is to eventually replace total-body irradiation with a radioimmunoconjugate.

There are very limited data on repeated dosing with radioimmunoconjugates. Can it be done? In Kaminski's recent paper in *Blood*, seven of the 53 patients got a second dose in order to get a

better response, but it didn't work. Only one patient went from stable disease to partial response. None of the other patients improved the quality of their response. However, there were 16 patients who progressed after getting the antibody and were re-treated. They had nine responses of the 16, including five complete remissions, with a median progression-free survival of 11 and a half months. So, yes, they can be re-administered.

What about hooking them to other forms of antibodies? There are a number of unconjugated antibodies that are candidates. Rituximab is generally given with Zevalin, Campath, epratuzimab HU1D10, and devacizumab. They do exist, and clinical trials in the future will probably combine one or more of these with the concept of targeting multiple antigens and attacking the lymphoma cell through multiple targets.

There are a number of ways to augment effector cell function. One option is to augment CD20 expression. This is an interesting concept that is in clinical trials and is based on the use of IL-12, which has a regulatory effect on T cells. It facilitates specific cytolytic T-cell responses, promotes the development of TH-1 cells, enhances antibody-dependent cellular cytotoxicity, enhances NK activity, and, importantly, induces gamma-interferon and TNF secretion by T-cells and NK-cells.

The concept is to hook the antibody to the lymphoma cell. It attracts, through ADCC, natural killer cells, T-cells, and macrophages. In the presence of IL-12 you get a virtual local explosion of gamma-interferon and TNF that further kills the tumor cells, as more and more T, NK, and macrophages are drawn into this network.

Well, when is the best time to use radioimmunoconjugates? Initial therapy is when they're likely to have their greatest activity, but the downside is that they may cause reduced tolerance to subsequent chemotherapy.

What about a salvage therapy? There has been a high response rate in chemotherapy and monoclonal antibody failures, but a lower response rate than with front-line. As shown both by Zevalin and Bexxar, there is increased myelosuppression and a greater risk of secondary myelodysplasia.

If you look at tositumomab I-131 by the amount of prior therapy, the response rate goes down, the median duration of response goes down from "not-reached" to a year, to seven months; the complete response rate goes down; and the median duration of those complete responses goes down dramatically. In addition, the toxicity goes up. The number of patients requiring platelet transfusion goes from zero up to 16; red cell from zero to 15. The patients requiring growth factor also increases.

It is difficult to increase radiolabeled antibody activity by combining them with chemotherapy because these are myelotoxic compounds. So you have a couple of options: you can sequence them, but which is the best direction, antibody first, chemotherapy after, or the converse? There are data which suggest that the antibody should be given first in vitro. They can possibly be combined using growth factors or with stem cell support.

One concept of sequencing them is in the Southwest Oncology Group trial, currently ongoing, in which CHOP is being compared in advance-stage indolent lymphomas with CHOP and Bexxar. Another sequencing concept is Czuczman's rituximab vs. CHOP, followed by Bexxar.

Is there life after radioimmunoconjugate therapy? Can you do

something once the patient relapses? The answer is: I don't know.

Half of the patients in the tositumomab experiments received some chemotherapy, a quarter got radiation, and there were other treatments as well. However, the company did not follow those patients, so there is no record of response. But the possibility of autologous stem cell transplants can be considered in a very small number of patients. All 10 had successful harvests after I-131 and 8 of the 10 engrafted. So there is this potential.

In order to reduce toxicity, an effective dose can be lowered, particularly in the setting of thrombocytopenia. You have to protect normal target organs, as with I-131 tositumomab, where the thyroid must be protected. Secondary AML and MDS can be minimized, perhaps by selecting those patients ahead of time who have clonal hematopoiesis or prior cytogenetic abnormalities, because those are the patients most likely to develop secondary MDS. You can conceivably reduce HAMA by pre-treatment with an immunosuppressant drug like fludarabine. In an institutional experience, three courses of fludarabine were given, followed later by Bexxar. The 14 evaluable untreated patients in this series showed a very high response rate. There were two complete remissions, 11 partials, and nobody developed HAMA, compared to 65% in the previous study. Remember that HAMA is only important if you plan on using the drug repeatedly.

So, which is the winner?

If you look at the data in these two studies of Y90 ibritumomab and I-131 tositumomab, the overall response rate and the complete remissions are almost identical, and the median response duration is exactly identical.

So, what happens when a patient fails rituximab? If a patient responded to rituximab and then relapsed, they have a 40% chance of responding again with an 11% complete remission and the responses lasting at least as long as the first response.

With either of these radioimmunoconjugates, the likelihood of getting a secondary response is in the range of 60%, and a complete response in the range of around 20%. Quite comparable, but they do tell you that they're quite effective, probably due to the radiolabeling.

Another way to pick the winner is its toxicity, including myelosuppression, organ damage, and secondary malignancies? And which is going to be the least toxic to the surrounding world, with regards to radiation exposure?

What may be the most critical point in deciding the winner is which will be the most convenient to administer and which will turn out to be the most cost-effective? If they both get on the market, this may be a rare example of when price gets driven by competition in this industry, and driven down.

We now have several highly active radioimmunoconjugates. Their use may vary with the clinical indication. There may be a role for both of these, as well as for a number of unconjugated antibodies. There is no room for single-agent comparisons. The most important goal for all investigators is to move the field forward; to find which one of these agents is the one that is best integrated into a multi-modality approach, combining or sequencing it with chemotherapy, combining it with other unconjugated antibodies, with cytokines, or followed with a vaccine.

More information about these trials can be obtained from local cancer center, your local cooperative group, the pharmaceutical sponsors, or the National Cancer Institute. *BLR*

Q&A Session

From the Radioimmunotherapy of Low-Grade Non-Hodgkin's Lymphoma Symposium
American Society for Hematology 42nd Annual Meeting
December 1, 2000, in San Francisco, California

Question: *Dr. Gordon:* Brian, I noticed on one of your slides that the response rate to Rituxan was higher in patients that had had a previous transplant. Do you have any thoughts about why that may be the case, or does that give you some ideas about what to do post-transplant with Rituxan?

Answer: *Dr. Link:* In the so-called large Phase II pivotal study, there were 23 patients who had previously had autologous bone marrow transplant for their relapsed lymphoma. In that subset of patients, 78% achieved overall response. We assumed it was a quirk of observation. However, it has been noted by other series of investigations as well, so it appears to be a consistent observation. But the short answer to your questions is: I have not heard any satisfying explanation, and I'm not even sure I've heard very many satisfying hypotheses as to why it may be.

Answer: *Dr. Cheson:* I'm not sure it's specific for the antibody either. In the experience at our institution in patients with Hodgkin's disease who failed autologous stem cell transplant, they had an amazingly high response to vinblastine, much higher than you would have expected in any other setting, like 50-60%.

Answer: *Dr. Gordon:* I think Tom raised the issue of secondary leukemia in the Zevalin studies, and also in the Bexxar studies. Since the one patient that you described was ours, I think I can give you a little bit more data which are interesting. This is someone who had had a couple of other therapies and developed an 11Q2.3 acute leukemia within a year following Zevalin therapy. Since we had bone marrow prior to the Zevalin, we had the opportunity to look for the 11Q2.3, and it wasn't there. These are data I think we're going to have to pay attention to as we start introducing new therapies into the treatment of lymphoma.

Answer: *Dr. Cheson:* If you look at the Bexxar data that Kaminski just updated a few months ago, many of the patients who developed a secondary MDS/AML did have prior cytogenetic abnormalities. So, I think it's not an all or nothing. I think some will and some won't.

Question: *Audience Member:* Are there any hypotheses about the mechanism of resistance to the radioimmunoconjugates?

Answer: *Dr. Wiseman:* Some of these patients may have had prior radiotherapy, and so that may have induced some resistance, but I think that most of the patients we see in these trials have not. They have been patients with more advanced stage disease that had prior chemotherapy, and I think it's more of a problem of delivery of the radioisotope. I think that if you can get enough of the radioisotope there that you can see a response. But there are times

when, in larger masses, the antibody is not getting into the center of the tumor.

Question: *Audience Member:* Are there any antibody therapies being developed for Hodgkin's disease?

Answer: *Dr. Cheson:* Yes, there are a number of antibodies being developed for Hodgkin's disease. There is a radioimmunoconjugate, the anti-ferritin, which has had sort of a checkered history. There was also a bi-specific monoclonal. Now there's a HEFA, which is an anti-CD30 monoclonal that has been on the shelf at the NCI for a number of years and is now being humanized in anticipation of clinical trials. And rituximab has a significant response rate in those patients with Hodgkin's disease who are CD20+.

Question: *Audience Member:* Conceptually, there is a potential advantage for having a moderate amount of tumor available to have a clustering of the radioisotope effect to maximize your advantage for the crossfire. I was curious if there were any good models that would predict what an optimal size tumor might be to take advantage of the added radioimmunoconjugate. I was also curious to know if you have gone back and looked at the difference in patients who had large tumors vs. the patients who had small tumor burden. Was the difference between the radioimmunoconjugate and the unlabeled antibody more evident in one group over another?

Answer: *Dr. Wiseman:* Theoretically, you're getting a better response if you have a larger tumor, especially with the longer path-length of beta-emitters on the mathematical model. If there's just a single cell binding the antibody, much of the radiation that would be delivered by that antibody would not be received by the cell to which it was bound.

Question: *Audience Member:* So then, how would we reconcile that with our instincts to use immunotherapy as mop-up or adjuvant after maximum de-bulking with chemotherapy?

Answer: *Dr. Cheson:* That was the initial instinct we had – minimal residual disease and then clean it up. I think we're learning more and more that the antibody sensitizes tumor cells to chemotherapy. In a number of studies that aren't published yet, there appear to be higher response rates when the antibody is given first, followed by the chemotherapy. You can infer that, for example, from the Czuczman CHOP-rituximab study. I expect you'll get much higher results with that than you would with CHOP first and antibody later. Therefore, the way to do these may be to have one antibody there first and then to do clean-up with another kind of antibody. But we have to learn which is best in each one of those

indications; maybe better to have rituximab there first and then clean it up with a radioimmunoconjugate. Those are the kind of trials that need to be done.

Answer: *Dr. Gordon:* If you look at radioimmunotherapy as a mop-up, there is some concern about toxicity to normal organs if you don't have a tumor sink there to take up the radioimmunoconjugate. So, I think that needs to be looked at as we design new trials.

Answer: *Dr. Cheson:* The Europeans are embarking on a study of chemotherapy for indolent lymphomas, and whether you get a maximum response randomizing to a radioimmunoconjugate, I guess it would have to be Zevalin over there, vs. no further therapy. So, we may find out how toxic it is, by letting the Europeans find out for us.

Answer: *Dr. Wiseman:* I think you're potentially going to have a different bio-distribution; that you're going to have less taken up by the tumor if there is a smaller amount of tumor present. That's going to allow a longer time in circulation, which may give more radiation to bone marrow. On the other hand, part of the dose to the bone marrow comes from the marrow being involved by lymphoma, and if you had a minimal residual disease you would end up with less radiation. So, I think it's something that requires a careful look, and maybe even a different dosing scheme compared to patients with bulkier disease.

Question: *Audience Member:* There are data with Bexxar on re-treatment. Are we going to see some data using re-treatment with Zevalin?

Answer: *Dr. Witzig:* There are no data yet. We have a trial that is going to give patients two sequential doses about four months apart. We're going to be doing the indium imaging, so I think we'll be able to answer the question of how they image the second time, and what the toxicity is.

Question: *Audience Member:* Do you think it would be an advantage to combine different modalities in a single molecule? For example, to have the human FC to give complement fixation and ADCC along with the radioimmunoconjugate? Are there any plans to use radiolabelled rituximab? You said that the reason you'd shied away from it initially was its long half-life, but is that still something you see as a problem after these Phase I and II studies?

Answer: *Dr. Gordon:* I think it's unlikely that we'll see a change in the molecule. I think that if we were using the Rituxan, the chimeric antibody linked to the yttrium, it would not be as much of a problem as people thought it was going to be several years ago. But I doubt that we're going to go back to that.

Answer: *Dr. Wiseman:* The one difference between the unlabeled antibody and the labeled antibody was that you're really using the labeled antibody to deliver the radiation to the cell. I think the FC portion becomes less important in that situation, unless you're going to have the radiation be delivered and then have the FC portion there to somehow be involved in the ADCC. What is best for the unlabeled antibody would be a long circulation and active immunoglobulin for the antibody molecule. For the radioim-

munotherapy, you prefer a shorter circulation time to avoid the radiation to the marrow and you're looking at the best molecule to penetrate and bring that radiation into the tumor. I think they are two different strategies and, although combining them may be interesting, you might run into the problem that one strategy might be in opposition to the other.

Answer: *Dr. Link:* And it's also important to recognize that the unlabeled chimeric protein is given along with the murine labeled protein. So, in theory, you could take advantage of both biologic effects, if in fact they exist clinically.

Question: *Audience Member:* I have a question about the second malignancies, myelodysplasias, and so on. I wonder, with a low dose of radiation, whether that would be responsible or if the patients had had prior alkylating agents or etoposide.

Answer: *Dr. Gordon:* No, actually that's what is interesting. That patient had only chlorambucil on two separate occasions; no adriamycin, no etoposide, no growth factor, and no transplant.

Question: *Audience Member:* Was the response rate higher with Zevalin or Rituxan after transplant?

Answer: *Dr. Cheson:* Rituxan.

Question: *Audience Member:* There seems to be a growing body of evidence that there's a benefit conveyed by radioimmunotherapy relative to, say, naked antibody. What will it take before radioimmunotherapy is considered an alternative to Rituxan as opposed to a follow-up, assuming that you get better responses and better response durations, particularly in younger patients whose immune systems may be able to tolerate the radioimmunotherapy better?

Answer: *Dr. Cheson:* Well, since you don't get a longer response duration in Tom's study, it's going to take a lot more than response rate. You know, we've been fooled for decades getting higher response rates in follicular lymphomas and then not translating into prolonged survival. I think it's going to be hard not to use rituximab first, because you get a year with virtually no toxicity. You can give it over and over again; you can give chemotherapy after that. I think that for all intents and purposes, I'd probably use it after I used an unconjugated antibody.

Question: *Audience Member:* If I had a patient where I really felt I needed a response now, and Tom's data holds up, it would certainly seem to me logical to consider the more potent antibody, recognizing that we may or may not get more duration from it.

Answer: *Dr. Witzig:* The other thing that is interesting to remember is that the best responses that have been seen with these radiolabelled antibodies are in the context of a transplant. That's why I think we need to know whether people can get a second dose, because if you play the Zevalin card in a younger patient up front and then you can't give it to them later, that's going to also influence how you sequence things. If a person is 80 years old and you're not considering a transplant, you could give the Zevalin now. Those are the questions that need to be answered. But I think that, in the end, the best response rate may be in the context with transplant. *BLR*

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