

Review Article

Radioimmunotherapy for Non-Hodgkin Lymphoma : Historical Perspective and Current Status

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Radioimmunotherapy (RIT) treatment for lymphoma is a novel targeted therapeutic approach. Several years of development of radioimmunotherapeutic compounds came to fruition in February of 2002 when ^{90}Y -ibritumomab tiuxetan (ZevalinTM, Y2B8) was approved in the USA and later in Europe, for the treatment of relapsed or refractory, low grade or transformed B-cell lymphoma. ^{90}Y -ibritumomab tiuxetan utilizes a monoclonal anti-CD20 antibody to deliver β -emitting yttrium-90 to the malignant B-cells. Clinical trials have demonstrated its efficacy, which is largely independent of the intrinsic activity of the anti-CD20 antibody. A similar anti-CD20 radiotherapeutic compound, ^{131}I -tositumomab, was subsequently approved in the USA. The advantages of increased efficacy compared to the naked antibody are gained at the expense of myelotoxicity which is dose limiting but reversible. Studies exploring expanded applications of radioimmunotherapy have been recently completed or are under way. It is hoped that RIT will be an ideal agent for consolidation after chemotherapy for both indolent and aggressive non-Hodgkin lymphoma as well as a useful addition to preparatory high dose regimens prior to transplant. RIT has been shown to be an effective and clinically relevant complementary therapeutic approach for patients with lymphoma. [*J Clin Exp Hematopathol* 47(2) : 43-60, 2007]

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INTRODUCTION

The introduction of targeted therapeutic approaches has revolutionized the field of cancer treatment in the last decade. In particular, the use of monoclonal antibodies has been met with considerable success for the treatment of lymphoma. Although engagement and direct interaction with surface proteins appear to be of therapeutic value, antibodies also constitute excellent targeting systems, marking selected cells for the interaction with innate immune effector mechanisms, or by conjugation with moieties of therapeutic value which are thus locally delivered. Radioimmunotherapy (RIT) has been proven to be effective enough, so that the USA Food and Drug Administration approved the first ever radioimmunoconjugate (RIC) for the treatment of a malignancy in February of 2002, when ^{90}Y -ibritumomab tiuxetan (^{90}Y -IT : ZevalinTM) was licensed for the treatment of indolent or transformed, relapsed or refractory B-cell lymphoma. Subsequently, ^{131}I -tositumomab (^{131}I -T : Bexxar) was also approved for indolent

or transformed B-cell non-Hodgkin lymphoma (NHL) relapsed or refractory after rituximab. Thus, CD20-based RIT for NHL follows the path first paved by the successful application of rituximab, an anti-CD20 monoclonal antibody widely used against B-cell malignancies. RIT had previously been tried rather unsuccessfully in a variety of tumour types. Its success in lymphoma is explained by the relative radiosensitivity of the disease, and possibly by the therapeutic value of the direct engagement of CD20 by an antibody.

RIT offers several advantages compared to external beam irradiation. Normal tissues overlying the tumour mass are prevented from significant radiation exposure. Since the RIC is given intravenously, it provides systemic radiation treatment to known as well as unsuspected tumour cells. It should be noted that neither rituximab nor the RIC available or under development are truly tumour specific as they bind to markers present in the normal lymphocyte counterparts. However, mounting experience from trials and clinical practice suggests that prolonged normal B-cell depletion is not associated with significant sequelae, so that narrow targeted approaches based on antibodies recognizing a class-specific target are feasible and reasonably safe. Another advantage of RIT is the relevant bystander effect. Since the radiation emitted from the isotopes carried by the RIC may be deposited in an area covering several cell diameters, poorly perfused or non-antigen expressing cells within the tumour mass also

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suffer the cytotoxic radiation effect. The launching of RIT is presumed to be the first step of the development of a therapeutic modality that complements current treatments of NHL and will hopefully evolve into a robust and well defined strategy for the management of this disease.

SELECTION OF TARGETS FOR RIT

Historical development

The optimal target for RIT has to fulfill several criteria. It has to be expressed in abundance on the surface of the targeted cells, it has to be reasonably selective, and it should not be shed in the circulation. In contrast to immunotoxins, internalization of target after engagement with the antibody is not necessary. Historically, a considerable amount of work has been dedicated to the investigation of Lym-1, an IgG2 murine antibody generated after immunization of mice with Burkitt's lymphoma cells.¹⁻⁶ Lym-1 recognizes an HLA-DR polymorphic variant present preferentially on malignant B-cells. Several trials have documented significant clinical activity in patients with B-cell malignancies. In early Lym-1 studies employing I-131, responses exceeding 50% were noted in patients with a variety of histologies including aggressive NHL, with a defined maximum tolerated radioactivity dose of 100 mCi/m.^{2,7} Encouraging results from trials using fractionated RIT, or conjugation with other isotopes such as copper-67 (⁶⁷Cu) and yttrium-90 (⁹⁰Y) have also been reported; dosimetry analysis favoured the copper-labeled antibody, with the majority of the patients responding.^{8,9} The consistent activity reported by these products has not yet been confirmed in large scale multicenter studies. However, the extensive dosimetry and biodistribution data obtained during the analysis of Lym-1-based RIT were extremely valuable in the advancement of the field of RIT in NHL.^{10,13} For instance, it was shown that the kinetics of indium-labeled antibody were similar and could predict the yttrium-labeled antibody distribution, which supported the clinical development of ⁹⁰Y-ibritumomab-tiuxetan (Zevalin).¹⁴ Furthermore, theoretical and practical considerations for fractionated RIT were addressed in these very important studies at the University of California in Davis.¹⁵⁻¹⁸

Other studies explored targeting CD37 using an iodine-131 loaded antibody;¹⁹ although responses were seen in small number of patients, the target was not specific for B-cells and considerable toxicity was noted. CD22 was targeted by the monoclonal antibody LL2 conjugated to ⁹⁰Y, which is also available in a humanized form (hLL2).²⁰ Anti-CD19, anti-CD40 or anti-idiotypic antibody based RIC has been tested in mice with variable results.^{21,22} A RIC for Hodgkin lymphoma with specificity for CD30 was reported to have sufficient activity in refractory patients to merit further exploration.²³

However, the most successful and clinically advanced

application of RIT involved anti-CD20 antibody-based approaches using initially ¹³¹I and subsequently ⁹⁰Y.²⁴⁻²⁶ Two agents have been extensively tested in a variety of clinical settings. ¹³¹Y-IT (Y2B8, ZevalinTM) is based on the murine anti-CD20 antibody parent of rituximab sharing the same variable region. It is currently commercially available both in the USA and Europe. ¹³¹I-T (BexxarTM) uses the B1 anti-CD20 antibody first developed by Nadler *et al.*²⁷ and is currently available in the USA. These products will be discussed in details below.

ELEMENTS OF RIC

The targeting antibody is usually an IgG of murine origin. There is no clear advantage in using humanized antibodies for RIT other than the theoretical concern regarding the development of anti-murine antibodies (HAMA). The antibody has to be conjugated with the metal isotope using a chelator linker, usually a derivative of diethylenetriaminepentaacetic acid (DTPA) such as MxDTPA or a macrocyclic chelate 1, 4, 7, 10-tetraazacyclododecane-N, N, N, N-tetraacetic acid (DOTA). In the case of iodine, conjugation is achieved by direct covalent bonding (iodination of tyrosine residues). Obviously, conjugation techniques provide a stable attachment of the isotope, with a conjugation rate exceeding 98%. Internalization of the antibody (such as those targeting CD19 or CD22) is not necessary; in fact this could be a disadvantage if iodinated antibodies are used due to the faster antibody metabolism and release of the isotope. Favorable features of the isotope include the emission of radiation energy which is deposited locally, a conveniently short half-life of a few days in order to reduce radiation hazard, biological as well as radiation safety, and lack of affinity with, or accumulation to specific tissues to the greatest possible extent. For the purpose of RIT, isotopes emitting γ rays (photons) are not helpful because most of such a penetrating radiation escapes to the environment. For that reason, only particle-emitting isotopes have been tested in RIT. Alpha-emitters such as bismuth isotopes ²¹²Bi or ²¹³Bi and astatium (²¹¹At) have been tried but appear to be cumbersome for successful clinical use.²⁸ For example, bismuth isotopes have an impractically short half-life of 1 hour. The highly potent radiation of α particles (helium nuclei) is deposited within 50-100 μ m and although it is possible that a few only atoms are enough to kill the targeted cell, there may be a profound non-specific adverse effect against the adjacent normal cells. Furthermore this extremely short path length reduces the crossfire effect, which may be a disadvantage when nodal masses are treated. Hence, β emitters (emission of electrons) are the most convenient and most commonly used isotopes.²⁹

Since there has already been experience with the therapeutic application of ¹³¹I in the treatment of thyroid cancer, this isotope was one of the first tested for RIT. It emits both β

and γ rays. The latter property can be useful for imaging or dosimetry calculation. Its β component is of relatively low energy, hence of a relatively short path length of 0.8 mm. Iodine is released in tissues at a variable rate through dehalogenation or as a result of the immunoglobulin break down in the form of iodinated tyrosine residues which are renally cleared. The avid uptake of ^{131}I by the thyroid gland mandates the use of saturated potassium iodine solution (SSKI, Lugol) to prevent thyroid irradiation. The biological half-life of ^{131}I RIC varies widely and unpredictably among patients and only partially depends on renal clearance. These issues mandate the use of dosimetry in clinical practice.

As a pure β emitter, ^{90}Y seems to offer some theoretical and practical advantages. The lack of γ component simplifies radioprotection during handling and administration of the RIC. It has a shorter $T^{1/2}$ of 64 hours compared to 8 days of ^{131}I , which results in more rapid decay and even better radiation hazard profile after its administration. It provides a high-energy β particle of 2.3 MeV compared to 0.81 MeV of ^{131}I , therefore a longer path length. This is an advantage when bulky disease is treated. Yttrium tends to accumulate in the liver, and it is excreted through the biliary tract. Because of lack of direct γ component, a surrogate isotope is used for imaging or dosimetry. For that purpose, substitution with ^{111}In has been successfully used to predict the pharmacokinetics of ^{90}Y -labelled antibodies.^{15,26,30} Both ^{90}Y and ^{131}I

have been components of anti-CD20 RICs (Table 1).

During the development phase of a RIC compound, dosimetry is required to determine distribution of the radioactivity, radiation exposure of vital or unaffected organs including the bone marrow, the biological half life which is generally slightly shorter from the half life of the isotope, mode of excretion and the ratio of radiation delivery to the tumour mass compared to the unaffected parts of the body. It has become known since early studies, that the distribution of the RIC is greatly improved by a preceding infusion of the plain unconjugated antibody, which is believed to coat the circulating antigens on B-cells and to suppress the low affinity sites, possibly non-specific Fc receptors. This enables the RIC, which is given at stoichiometrically much smaller doses, to evade the circulating B-cells and diffuse to the tissues seeking the tumour masses. It has also been documented that splenomegaly does not significantly affect the kinetics of the antibodies, whereas heavy bone marrow involvement by lymphoma, increases myelotoxicity.^{14,30} The significant intrapersonal variability of the excretion of ^{131}I has led to dosing according to prediction of total body radiation exposure over time (total body dose, TBD), whereas the more predictable elimination of ^{90}Y enables dosing per weight. In clinical applications, pre-treatment imaging for ^{90}Y -IT is performed in the USA but not required in Europe, while and dosimetry for ^{131}I -T is necessary, as described below.

Table 1. Comparison of properties and administration between ^{90}Y -IT and ^{131}I -T

	^{90}Y -IT	^{131}I -T
Isotope used	^{90}Y	^{131}I
Conjugation	chelation (tiuxetan)	direct iodination
Type of radiation	β	β and γ
Beta energy	0.6 mEV	2.9 mEV
Path length	0.8 mm	5.3 mm
Isotope half life	64 hours	8 days
Urinary excretion	minimal	variable
Monoclonal antibody	murine (ibritumomab)	murine (tositumomab)
Pre-infusion antibody	chimeric (rituximab)	murine (tositumomab)
Pre-infusion dose	250 mg of rituximab	450 mg of tositumomab
Tracer imaging	5 mCi of ^{111}In -In	5 mCi of ^{131}I -T
Purpose of tracer	1-2 scans to visually assess distribution*	3 scans to determine clearance and determine therapeutic dose
Therapeutic dose	0.4 mCi/kg (maximum of 32 mCi)	Dose to deliver 75 cGy to total body dose
Reduced dose**	0.3 mCi/kg	65 cGy

* : in selected countries, ** : platelet counts < 100,000/ μl

**⁹⁰Y IBRITUMOMAB TIUXETAN
(⁹⁰Y-IT : ZEVALIN™)**

This is the first RIC approved for the treatment relapsed or refractory low grade or transformed B-cell NHL (⁹⁰Y-Ibritumomab tiuxetan in the USA). The indication in Europe involves patients with follicular lymphoma who have relapsed or are refractory after prior rituximab-containing treatment. Ibritumomab (IDEC-2B8) is the murine anti-CD20 antibody developed by IDEC (San Diego, CA ; marketed by Schering AG in Europe) whose chimeric version, rituximab (Rituxan, Mabthera) is also available and widely used. Tiuxetan connotes the linker used (MxDTPA) to conjugate ⁹⁰Y to the antibody.

During the registrational clinical trials, a meticulous and thorough dosimetry procedure was performed largely using data derived from ¹¹¹In-ibritumomab tiuxetan (¹¹¹In-IT) kinetics.^{31,32} The purpose of dosimetry was to eliminate the possibility of excessive radiation exposure of vital organs. Thus, pharmacokinetics and the biologic half-life based on repetitive blood sampling and total body counts were determined and an exponential or bi-exponential best-fit curve was constructed for each patient. Multiple gamma camera scans were performed during the first week after ¹¹¹In-IT administration. Areas of interest (tumour masses, vital organs) were selected by a cursor and followed longitudinally over time to calculate the residence time (total exposure to radiation), which could be converted to ⁹⁰Y exposure using a known conversion constant between the two isotopes. Thus the expected radiation exposure could be determined in advance, assuming that the pharmacokinetic properties of ¹¹¹In-IT are similar to those of ⁹⁰Y-IT. The validity of this assumption was confirmed in selected patients who underwent pharmacokinetics analysis after ⁹⁰Y-IT administration.³² Patients would be ineligible to proceed with the therapeutic dose of ⁹⁰Y-IT if any of the vital organs or unaffected areas would receive a dose exceeding 2,000 cGy, a limit that was never reached. In addition to the blood derived pharmacokinetics, the radiation exposure of the sacral bone was also calculated as another measure of bone marrow exposure. It became apparent that neither determination of half-life, nor calculation of radiation exposure of the bone marrow using the blood or the sacral bone method correlated with toxicity. Therefore detailed dosimetry was deemed unnecessary for determining the safety of the ⁹⁰Y-IT administration. Based on these, the USA Food and Drug Administration eliminated the requirement for dosimetry for routine clinical use.

Patients considered eligible should satisfy several screening criteria as follows (Table 2) : They should have less than 25% involvement of the bone marrow by disease determined by adequate core biopsy (not aspirate only), absence of myelodysplasia, a baseline neutrophil count > 1,500/ μ l and a platelet count > 100,000/ μ l. These restrictions emerged from

Table 2. Contraindications to conventional dose radioimmunotherapy

Bone marrow involvement by lymphoma > 25%
Neutrophils < 1,500/ μ l
Platelets < 100,000/ μ l
Myelodysplastic or very hypocellular marrow
Prior high dose chemotherapy*
Circulating B-cells > 5,000/ μ l*

* : study questions

the phase I-II trials and protect from potentially serious myelosuppression. Patients with central nervous system disease, circulating lymphoma, or relapsing after high dose chemotherapy were excluded from the clinical trials although it is unlikely that these characteristics constitute absolute contraindications.

The current administration recommendations for ⁹⁰Y-IT (Zevalin) are as follows : Patients first receive an infusion of 250 mg/m² of rituximab. In places outside Europe excluding Switzerland, this is followed by the administration of 5 mCi of ¹¹¹In-IT for the purpose of imaging. Subsequently, a gamma camera scans are performed within 24-48 hours (previously 2 scans). The purpose of the scan is to ascertain optimal biodistribution of the radioactive antibody (performed visually) and thus protect from the theoretical risk of sequestration in vital organs. Such an occurrence was never observed among 349 patients involved in the registrational clinical trials. For that reason, imaging has been eliminated in most Europe. One week after the first administration, patients receive a similar dose of rituximab followed by the therapeutic dose of ⁹⁰Y-IT, given at 0.4 mCi/kg, not to exceed 32 mCi.

For patients with platelet counts ranging between 100,000- 150,000/ μ l, the dose is reduced to 0.3 mCi/kg. The radioactive antibodies have to be ordered by the radiopharmacy in an individualized manner, only after the dose and the date of treatment of a particular patient are determined. Obviously, there is a very brief shelf life of the RIC, not exceeding 1-2 days. They are given as a slow injection over 10 minutes. The amount of antibody injected is less than 5 mg, significantly less than the pre-infused rituximab. Protecting the syringe with a plastic shield suffices to provide radioprotection. Patients are readily discharged with instructions how to properly manage spillage of bodily fluids for the first week after the treatment.³³ Contact isolation is not necessary. The treatment is given once, with expected onset of gradual cytopenia 3-4 weeks after the treatment, nadir on week 6-7 and full haematologic recovery by the third month.

Developmental Clinical Trials

The phase I/II study of ⁹⁰Y-IT included a dose esca-

tion of the dose of rituximab pre-infusion required to optimise the distribution of the radioactive antibody, as well as a dose escalation of the radioactivity of ^{90}Y -IT starting at a dose of 0.2 mCi/kg.³⁴ The minimum optimal dose of rituximab was defined as 250 mg/m², as higher doses did not further improve biodistribution of ^{111}In -IT. Maximum tolerated dose of ^{90}Y -IT was determined to be 0.04 mCi/kg for patients with platelet count over 150,000/ μl , and 0.03 mCi/kg for patients with mild thrombocytopenia. Patients with more than 25% involvement of the bone marrow by disease, radiation to > 25% of the marrow area, and prior high dose chemotherapy were excluded. An 82% response rate was noted among 32 patients with relapsed or refractory, rituximab-naive follicular or low grade NHL; encouraging activity was observed among 14 patients with aggressive NHL with 4 complete regressions (CRs) and 2 partial regressions. None of the 3 patients with mantle cell NHL responded. The median time to progression exceeded one year. The major toxicity was reversible myelosuppression with median absolute neutrophil count (ANC) 1,100/ μl and median thrombocytopenia 49,500/ μl . It became apparent that the extent of bone marrow involvement by lymphoma and the pre-treatment platelet counts correlated with the myelosuppression risk. The remainder of the toxicity was mostly associated with the infusion of rituximab, with the possible exception of mild fatigue and mild nausea.^{34,35}

After these encouraging results, a large randomized study was initiated comparing ^{90}Y -IT to rituximab, involving 143 rituximab naive patients with relapsed or refractory low grade or transformed lymphoma, and similar eligibility criteria as above.³⁶ Approximately half of the patients were resistant to the last chemotherapy regimen, 12% had non-follicular histology and 9% had transformed lymphoma. Bulky disease exceeding 5 cm was present in 45% of the patients. The average number of prior treatments was 2 (range 1-6). Disease characteristics were well balanced between the two groups. Rituximab was given for 4 weekly infusions. The overall response rate and the complete response rate favoured ^{90}Y -IT and were noted in 80% and 30% of the patients versus 56% and 16% achieved with rituximab respectively ($p=0.002$ for overall response). Responses were also noted in 5 out of 9 patients with transformed NHL and in 6 out of nine patients with non-follicular histology. The median ANC nadir was 900/ μl and platelets 41,000/ μl . The incidence of human anti-murine (HAMA) or anti-chimeric antibody (HACA) was 2%. Non-haematologic toxicity was not different in the two groups. The time to progression and the duration of response were not shown to be different, however the median time to next therapy, based on clinical judgment for need for subsequent treatment, was not reached at the time of analysis for the RIC arm and was 15.2 months for the unconjugated antibody arm. Quality of life analysis favoured the RIC arm, reflecting the higher remission rate

achieved in the RIC arm.

A separate study addressed the question of the activity in patients whose disease is resistant to rituximab.³⁷ The study included 54 patients, mostly with follicular lymphoma, with many adverse features and with a median of 4 prior treatments. Bulky disease was present on 74%, whereas 67% had documented resistance to last chemotherapy. Of the 54 patients, 17 had a brief response to rituximab lasting for less than 6 months and the remainder had no response to it. The overall response to ^{90}Y -IT was 74% with a median time to progression for responders of 8.7 months (range 1.7-25.9 months). The duration of response compares favorably with that of the last chemotherapy regimen. For the whole group time to progression (TTP) was 6.8 months. In the subset of patients who had a brief response to rituximab the response rate was 88% and the median duration of response 11.5 months. This study, taken in conjunction with the randomized trial, clearly confirms the significant therapeutic value attributed to the radioactive component, which is distinct from the intrinsic therapeutic benefit of the antibody.

The question of whether mildly thrombocytopenic patients (with platelet count 100,000-150,000/ μl) who receive the reduced dose of ^{90}Y -IT (0.3 mCi/kg) still derive a benefit was addressed in a multicenter phase II trial.³⁸ Responses seem to be similar to those reported in other studies with an overall response rate (ORR) of 83% and CR of 37%, with a TTP for the whole group of 9.4 months. Toxicity was also similar to that observed in other studies, although the median nadir ANC was somewhat lower at 600/ μl .

When all studies are analyzed in aggregate, ^{90}Y -IT seems to be effective in all categories of treated patients. In a multivariate analysis of 203 patients³⁹ the only factor that predicted for better response was tumor bulk. Patients with nodal masses more than 5 cm had a 68% response rate and shorter duration of response, whereas those with smaller tumors had a 90% response rate ($p < 0.001$). Despite the statistical difference, the response rate in patients with bulky disease remains satisfactory. Age, prior radiation, extranodal disease and international prognostic index (IPI) score failed to correlate with outcome. Responses seem to be somewhat less frequent in small lymphocytic lymphoma or transformed lymphoma. Retrospective meta-analysis of the same trials suggest of a considerably better outcome for patients treated upon first relapse of their lymphoma.⁴⁰ For such patients with follicular lymphoma receiving Zevalin as second line treatment, the complete and overall response rate were 51% and 89% respectively, with overall TTP of 15.4 months. The CR rate and TTP are statistically better compared to the group of patients with more prior treatments, although the overall response rate is not. Patients who achieved a CR had a 2-year TTP regardless of the number of prior treatments, defining an optimal subpopulation, with a considerable fraction of those remaining in remission after a follow up of 5

years. Such data suggest that it may be preferable to move up Zevalin treatment in the sequence of therapy for lymphoma, in order to take advantage of the high likelihood of achieving a CR, which confers a longer TTP.

Toxicity

^{90}Y -IT is generally well tolerated and is not associated with most of chemotherapy-related non-haematologic toxicity. Concerns regarding hepatic toxicity due to the accumulation of the isotope have not been confirmed in patients treated in the clinical trials or after marketing, with safety data available from more than 1,000 patients. Myelosuppression is clearly the main and dose limiting toxicity.⁴¹ The median ANC count recorded in the clinical trials was $800/\mu\text{l}$; the median haemoglobin 10.3 g/dl and the median platelet count $37,500/\mu\text{l}$. In contrast to chemotherapy, cytopenia nadirs occur about 7 weeks after the treatment. The duration of the nadir is approximately 2 weeks. Cytopenia is always reversible for patients who receive the treatment within the specified parameters. Patients were occasionally supported with transfusions or growth factors. It has been clearly demonstrated that the likelihood of cytopenia correlates with higher bone marrow involvement with disease (see Table 3).

Thus the incidence of grade IV neutropenia is 53% in patients with 20-25% bone marrow involvement, and only 23% for patients with no obvious disease infiltration. The number of prior treatments also seems to increase the likelihood of grade IV toxicity in a univariate analysis. If preventive growth factor support is desired for patients considered at risk, it is important not to be given during the first week post-treatment, not only because it will be ineffective due to the delayed nadir, but also because it is not advisable to drive progenitor cells into proliferation during the period of activity of the ^{90}Y . Myelodysplasia and acute myelogenous leukemia has been reported to date in 10 out of 770 patients who have received ^{90}Y -IT, 4-34 months since treatment and 1.5 to 14 years since diagnosis. These patients have obviously also been exposed to chemotherapy. Various chromosomal abnormalities including 5q-syndrome have been observed. The

Table 3. ^{90}Y -IT : Correlation between extent of bone marrow involvement and grade IV cytopenia (N = 349)

	Incidence of grade IV toxicity (% bone marrow involvement at baseline)			
	0%	< 5%	5-20%	> 20%
Neutropenia	23%	36%	37%	53%
Anemia	3%	9%	2%	13%
Thrombocytopenia	7%	0%	13%	25%

Grade IV toxicity is defined as neutrophils < $500/\mu\text{l}$, platelets < $10,000/\mu\text{l}$, and Hb < 6.5 g/dl.

incidence of acute myelogenous leukemia/myelodysplastic syndrome is within the expected range, with an annualised rate of 0.21% and 0.62% since initial diagnosis and since RIT respectively.⁴² These data do not support an increased risk compared to historical controls, but longer follow up is necessary.

Despite the incidence of grade IV neutropenia in approximately one third of the patients, the incidence of infections is low. In an analysis of 349 patients enrolled in all registration studies, the incidence of hospitalization for infections was 6.6%, including only 6 cases (2%) of febrile neutropenia.^{43,44} Opportunistic infections such as thrush and herpes zoster were uncommonly seen in 3.4% and 3.7% of the patients respectively. The low incidence of infections can be attributed to the preservation of the integrity of the gastrointestinal mucosa, and the preservation of NK and T-cell counts.^{36,44} As expected, B-cell depletion lasts for approximately 6 months and is associated with a small and transient reduction of IgM, whereas IgG levels are maintained. The remainder of the toxicity is mostly of grade I-II and includes asthenia, nausea, abdominal pain and naturally the rituximab infusion-related toxicity. The incidence of HAMA/HACA is 2% and remains of unclear significance for future treatment with similar or other antibodies.

One of the main earlier concerns related to the ability of these patients to receive subsequent treatment. It appears that the initial theoretical concerns regarding possible irreparable damage to the bone marrow by RIT were not confirmed. In a retrospective analysis of 58 patients with progressive disease after ^{90}Y -IT who were treated with a variety of chemotherapy regimens, the observed toxicity was not dissimilar to matched control group.⁴⁵ Responses were noted in the majority of the patients. Rituximab may also be active for subsequent relapses.⁴⁶ Furthermore, small number of patients have received external beam irradiation or undergone high dose chemotherapy without undue toxicity. Anecdotal evidence suggests that stem cell mobilization has been possible after Y-IT.

One of the important observations is the tolerability of the treatment for elderly patients. In an analysis of toxicity and efficacy in different age groups, it was shown that grade III-IV myelotoxicity was similar in all age groups.⁴⁷ For instance, grade III-IV neutropenia and thrombocytopenia was 68% for the 40 patients over the age of 70 included in the registration studies, as opposed to 66% and 70% respectively for the patients under the age of 60. In the elderly group the ORR and the CR rate were 80% and 38%, in line with the results of younger patients.

Radiation Kinetics and Safety

In the clinical trials, dosimetry studies were performed using ^{111}In -IT. After injection of 5 mCi of ^{111}In -IT, organ ^{111}In activity was measured by region analysis at imaging time

(five scans during days 0-6 post infusion), using the geometric mean and converting to ^{90}Y using the ^{90}Y converting factor. The residence time (total radiation exposure) was calculated from the area under the curve for each organ. Estimated absorbed radiation doses of ^{90}Y -IT in normal organs and bone marrow were calculated using the MIRDOSE3 program. In all patients the calculated radiation dose was within the set limit of 2,000 cGy or 300 cGy for the bone marrow and in fact the exposure was much lower than these limits.³⁰ The median $T^{1/2}$ of ^{90}Y in the blood was 28 hours (range 14-36 hours).^{32,35} The median radiation exposure as calculated in 56 patients enrolled in the phase I/II studies was 13.7 cGy/mCi to liver, 9.8 cGy/mCi in the lungs and 1.5 cGy/mCi to the kidneys.^{31,35} Hence the median liver exposure is in the range of 500 cGy and much less for other organs. The median bone marrow exposure was calculated to be less than 100 cGy. However, it is not entirely clear that the method used for calculating the marrow exposure adequately addressed the factor of bone marrow involvement by disease. In occasional patients, the spleen exposure exceeded the cut off of 2,000 cGy likely due to direct involvement by lymphoma. Such patients received ^{90}Y -IT uneventfully. Predicted median tumour exposure was 1,484-1,712 cGy (range 61-24,274 cGy).³⁰ The kinetics of the antibody and the organ exposure did not seem to correlate with pre-treatment characteristics such as the number of circulating B-cells, rituximab levels or the presence of splenomegaly. Radiation hazard is minimal with ^{90}Y -IT. There is only limited amount of secondary γ rays produced during deceleration of the electrons. Plexiglas or plastic shielding is used during handling of the drug. Radiation is not emitted by patients, but it is contained in bodily fluids. Patients are instructed to avoid exposing others to bodily fluid for the first few days up to a week after treatment. No contact isolation is necessary. Spillage of any fluids should be carefully cleaned and disposed of. Measurements of radiation exposure to nuclear medicine technicians and caregivers have resulted in confirming insignificant exposure due to Zevalin administration.⁴⁸

Activity of ^{90}Y -IT in Other Histologies- Off Label Uses

The activity of ^{90}Y -IT in aggressive B-cell lymphoma has been documented in the phase I/II study.³⁴ In that trial, 12 patients with diffuse B-cell lymphoma were treated (9 diffuse large, 3 diffuse mixed). All patients had prior CHOP followed by a salvage regimen with a median of 2 prior treatments. Responses were seen in 58% of the patients including 4 (33%) with complete response. The median time to next anticancer treatment for the whole group was 9.9 months; the median time to progression for the complete responders has not been reached at 35.5 months follow up (2.5 – 40 + months).⁴⁹

The activity of single agent ^{90}Y -IT in relapsed or refrac-

tory diffuse large B-cell NHL was confirmed in a multicenter prospective phase II European study.⁵⁰ An overall 44% response rate with 27% CR rate were observed. The results favored rituxan naive patients. Long remissions for over 32 years were observed in a subset of patients. In relapsed mantle cell lymphomas the activity of ^{90}Y -IT has been reported in the range of 30-40% but the responses are short-lasting.⁵¹ The above studies rather serve as proof of activity and pave the way for combination with chemotherapy studies as discussed below.

Patients with non-follicular indolent B-cell lymphoma have been included in the registrational clinical trials or the expanded access trial documenting activity of ^{90}Y -IT in entities such as small lymphocytic lymphoma, marginal zone lymphoma or Waldenström's macroglobulinaemia.^{52,53} However, the optimal incorporation of ^{90}Y -IT into the therapeutic strategy of NHL has not been clearly defined.

The question of retreatment is an interesting one. Phase I studies using ^{90}Y -IT for two consecutive treatments, one standard administration, followed by second upon recovery of counts 3-4 months later, with unclear however clinical benefit.⁵⁴ A collection of anecdotes as well as personal experience suggest that retreatment with RIT upon subsequent relapse is possible without excessive toxicity and with expectations for responses.

Combination use with chemotherapy will be discussed below.

^{131}I -TOSITUMOMAB

Iodine-131 tositumomab (^{131}I -T: BexxarTM) consists of the murine IgG2a anti-CD20 antibody anti-B1 (tositumomab) that has undergone iodination of tyrosine residues with radioactive ^{131}I . B1 was the initial term used to describe the CD20 antigen, in conjunction with the development of the first corresponding murine monoclonal antibody. Clinical trials with ^{131}I -T have preceded those with ^{90}Y -IT, hence longer follow up of treated patients and more reliable long-term toxicity observations are available.

Although the therapeutic principle of the two antibodies is similar, there are certain qualitative differences. There have been generally similar treatment criteria that exclude patients with more than 25% bone marrow involvement, neutropenia or thrombocytopenia. Similar to ^{90}Y -IT, ^{131}I -T administration is preceded by an infusion of unlabeled antibody (450 mg administered over 1 hour). The patients receive first a dosimetric dose of ^{131}I -T containing 5 mCi of radioactivity (35 mg). In contrast to ^{90}Y -IT where imaging is required to ensure the safety of the administration, the purpose of dosimetry is to determine the therapeutic dose of ^{131}I -T. Three whole body γ -camera scans are performed on days 0, either day 2, 3 or 4, and on day 6 or 7. These help construct the elimination curve for each individual patient based on total

body counts. The area under the curve corresponds to the cumulative whole body radiation exposure, which of course depends on the elimination rate and the initial dose delivered. This dosimetry method is necessary because of the highly variable elimination of ^{131}I -T among individuals. The therapeutic dose is then calculated based on the biological half-life thus determined and set to deliver the target total body radiation dose (TBD). In patients with platelet count over $150,000/\mu\text{l}$ this is set at 75 cGy, but it is 65 cGy if platelets are in the $100,000$ - $150,000/\mu\text{l}$ range. Therefore, extremely rapid eliminators may receive doses exceeding 200 mCi, whereas very slowly excreting patients may only need less than 50 mCi. The typical dose is approximately 100 mCi. In order to prevent uptake by the thyroid, saturated solution of potassium iodide (SSKI ; Lugol) is given as two drops orally thrice daily beginning one day prior to the dosimetric dose and continuing for at least 14 days following the therapeutic dose. Lead protection is required during manipulation and administration of the drug. In most states, regulations allow outpatient treatment.

Clinical Trials

In early studies ^{131}I -T was given in a variety of methods, including repetitive doses for imaging and variable amounts of tositumomab antibody.^{24,55} Eventually a dose escalation trial established as maximum tolerated dose (MTD) the 75 cGy total body dose and 475 mg as the optimal pre-dose of tositumomab (using corrected optical extinction coefficient).⁵⁵ In a report updating the early single institution experience of the University of Michigan, Kaminski and co-workers reported a 71% response rate including 34% CR among 59 patients (low grade 28, transformed 14, aggressive 17) with relapsed or refractory B-cell NHL.⁵⁶ In patients with low grade or transformed NHL the response rate was 83% compared to 43% in patients with aggressive NHL. The median progression-free survival for responders was 12 months and 20.3 months for complete responders. Lower total body dose of radiation, bulky disease and elevation of lactate dehydrogenase (LDH) predicted for somewhat inferior chance for response. Retreatment was given upon progression in 16 responders, resulting in 9 responses. Four patients have developed myelodysplasia 1.2 to 7.5 years after treatment. Since all of them were heavily pretreated with a median of 4 chemotherapy regimens, the contribution of ^{131}I -T to this is unknown. Ten patients developed HAMA but some of those had received multiple dosimetric doses or retreatment.

At a subsequent confirmatory multicenter trial conducted at 6 centers in USA and UK, a response rate of 57% was observed among 47 patients with relapsed or refractory or transformed B-cell NHL, with 4 median prior treatments.⁵⁷ Half patients had bone marrow involvement up to 25%. The median duration of response was 9.9 months. The CR rate

was 32% with a median duration of 19.9 months. Bulky disease, transformed histology or LDH elevation did not appear to be adverse response predictors in this study. The mean activity of the delivered therapeutic dose was 88 mCi (range 45 to 177 mCi) and the mean biologic $T^{1/2}$ of ^{131}I -T was 65.8 hours (SD : 12.9 hours). Normal organs received a modest radiation dose with the kidneys, spleen, liver, bladder and lung receiving mean doses of 499, 383, 225, 183 cGy respectively. Tumours received an average dose of 795 cGy, approximately ten times higher than the total body dose. The principal toxicity is haematologic, with five patients reaching a nadir platelet count of less than $100,000/\mu\text{l}$ and two patients ANC of less than $100/\mu\text{l}$. The haematologic nadir occurred at 6-7 weeks and was for ANC, haemoglobin and platelets $800/\mu\text{l}$, 10.2 g/dl and $43,000/\mu\text{l}$ respectively. HAMA was noted in only one patient.

Similar results were obtained from a multicenter pivotal trial conducted for registration purposes. Sixty patients with low grade (60%) or transformed lymphoma (38%) failing a median of 4 therapies were included. Patients with transformed NHL had at least one aggressive regimen.⁵⁸ Patients were rituximab-naïve and had failed their last treatment or had relapsed within 6 months. Bulky disease (nodal mass 5 cm or more) was present in 65% and the bone marrow was involved in 56%. Responses were noted in 65%. Responses were higher for low-grade lymphoma (partial response : 81%, CR : 20%). Response rates also depended on tumour burden, prior radiotherapy and the number of prior therapies. The median neutrophil count nadir was $800/\mu\text{l}$ and the median platelet count was $50,000/\mu\text{l}$. The median duration of response was 6.5 months and in most patients this was a longer period compared to their response to the last qualifying chemotherapy regimen. In the small subset of patients with CR, the median duration has not been reached after a median follow up of 47 months. A smaller trial involving 40 patients refractory to demonstrated the activity of ^{131}I -T in this population, with a documented overall response of 68%, and a time to progression for all patients of 12 months (95% CI : 5.7-not reached).⁵⁹

A study including previously untreated patients with low grade follicular NHL indicated a higher activity in early disease.⁶⁰ Among 76 patients with follicular small cleaved or mixed cell lymphoma, a response rate of 95% was seen, including 56% CR. After a median follow up of 43 months, the actuarial five year progression-free survival was 62%. The neutrophil nadir was $1,300/\mu\text{l}$, and the median platelet nadir $83,000/\mu\text{l}$, with incidence of grade III/IV neutropenia or thrombocytopenia of 34% and 17% respectively, reflecting more robust marrow tolerance in this untreated cohort. Since such patients are also less immunocompromized, 63% were found to develop HAMA, frequently associated with a flu-like syndrome. Apparently, development of HAMA antibodies does not appear to affect adversely subsequent treatments

with rituximab.⁶¹ These excellent results should be viewed with caution since it is known that better responses are usually obtained earlier in the treatment sequence of patients with follicular NHL, particularly if low-risk patients are included. The prudence of applying a new therapy with not precisely defined long-term toxicity in patients with long life expectancy should be confirmed by longer follow up of this cohort.

The result of a multicenter expanded access ¹³¹I-T program have been reported in abstract form and suggest an overall response rate of 59% with 26% CR among 394 evaluable patients, with a median time to progression of 7 months for all patients. This study established the feasibility of ¹³¹I-T administration outside academic centers.

Work by Press and others have demonstrated the feasibility of incorporating "high dose" ¹³¹I-T as part of the myeloablative treatment prior to high dose chemotherapy followed by autologous stem cell transplantation for B-cell lymphoma including mantle cell lymphoma.^{62,63} The ¹³¹I-T dose is determined based on the estimated radiation exposure to normal organs, which resulted in the administration of a median of 510 mCi. The early results appear encouraging when compared to historical controls.

It can be concluded that ¹³¹I-T has satisfactory activity against patients with B-cell lymphoma, attributable to targeted irradiation of the tumor and independent of the intrinsic activity of the antibody. The magnitude of clinical benefit and myelotoxicity seem to be analogous to the results achieved with ⁹⁰Y-IT suggesting of a "class effect" whereby the isotope used is less important for the antitumor activity, although it dictates the type of radiosafety procedures required.

Toxicity

¹³¹I-T is generally well tolerated.^{56,58} Infusion reactions are generally mild, infrequently requiring infusion rate decrease. The most common immediate non-haematologic events are mild malaise and nausea, probably related to the radioactive component. Arthralgia, anorexia, myalgia, or rash occur in less than 20% of the patients, occasionally associated with HAMA development. Thyroid dysfunction as measured by post-treatment thyroid stimulating hormone (TSH) elevation occurs in less than 10% of the patients. The predominant toxicity is reversible pancytopenia. Grade IV neutropenia and thrombocytopenia occurred in 20% of the patients in early studies. Similarly to ⁹⁰Y-IT, nadirs typically occur around the sixth week post treatment⁵⁸ and last approximately 2 weeks. In the expanded access study, summarizing experience from 425 patients grade IV neutropenia was seen in 14% of the patients while the median ANC was 1,300/ μ l, possibly reflecting a somewhat different population of patients. Transfusion of blood products or growth factor support is occasionally needed. The incidence of HAMA seems to depend on the amount of prior treatments. Thus, in most studies

treating relapsed patients, it is found to be less than 10%, a rate higher than that observed with ⁹⁰Y-IT; when ¹³¹I-T is used as first line treatment, the reported incidence was 65% probably attributable to a more intact immune system in such patients. The clinical relevance of the development of HAMA (or HACA) is unclear. Development of acute myelogenous leukemia or myelodysplastic syndrome has been reported in up to 6.3% of the patients with calculated annualised incidence of 3.8%/year.⁶⁴ There is anecdotal experience of stem cell collection after ¹³¹I-T. Tumors receive a medium of 1,010 cGy (standard deviation 696 cGy) whereas normal organs receive less than 200 cGy in general.⁶⁴ Spleen exposure can be higher often due to involvement. In contrast to ⁹⁰Y-IT, the radiation exposure of the kidneys is higher but the liver irradiation is less, reflecting the different mode of excretion of the respective isotopes used. Release instructions include avoidance of close contacts for 1-2 weeks, no bed sharing for 1-2 weeks, and avoidance of crowded public places for at least 1 week.⁶⁵ Contact with pregnant women or children is to be avoided. Based on radiation activity measurements at 1 m immediately after administration of ¹³¹I-T it can be calculated that family members or care providers will receive less than 500 mrem of radioactivity. Individualized instruction take into account the total residence time of the radioactivity and the emission at 1 m, 1 hour after dosing.⁶⁶ In a study of actual exposure of family members of 22 patients who received ¹³¹I-T (25.4-128 mCi), the observed measurements ranged from 27-451 mrem, with a mean of 168 mrem.⁶⁷

RIT COMBINATION WITH CHEMOTHERAPY

Given the myelotoxicity of RIT, it can not be easily combined with chemotherapy. During the period of 2-3 months following administration of standard doses RIT, myelotoxic chemotherapy can not be safely administered, as it may interfere with the recovery of marrow function. However, it is reasonable to assume a synergistic action of chemotherapy and RIT-based tumor radiation, so that it might be of interest to combine RIT with concurrent chemotherapy. For instance, RIT could be administered with the last cycle of a prescribed chemotherapy schedule in order to avoid cycle delay, but such a trial has not been conducted to date. Combination with chemotherapy may be easier tested in the context of stem cell rescue. In the latter case, dose escalation is possible, which has obvious therapeutic advantage. Myelosuppression ceases to be the dose limiting toxicity, raising again the question of a maximum tolerated dose of such application. Pertinent to combinations with chemotherapy is the fact that the radiation is delivered by the RIC over a period of several days, depending on the half life of the isotope used, so that in essence concurrent radiation with chemotherapy is treatment is delivered even if the RIC is

administered several days prior to chemotherapy.

On the other hand, RIT may serve as a practical and convenient consolidation treatment after induction chemotherapy. Such a use offers several advantages. First, full recovery of blood counts is assured at the time RIT treatment. Second, the cytoreduction achieved by chemotherapy usually results in amelioration of bone marrow disease, so that the likelihood of considerable bone marrow involvement exceeding 25% is extremely low. This translates in reduced severity and duration of cytopenia, which correlates with the extent of bone marrow involvement. The observed lack of increased risk of myelodysplasia or acute leukemia with RIT permits its inclusion in a front-line regimen.⁴² The rate of development of antibodies against the RIC (HAMA) may be less compared to unmanipulated immune system, which may be particularly relevant in the case of ¹³¹I-T. Furthermore, the impact of RIT in measurable residual disease could be quantified, i.e. one could know how many partial responses could be converted to complete ones. However, this should be viewed with caution, since ongoing shrinkage of involved nodes may occasionally occur for several months after conventional treatment as well so that the true impact could only be assessed in the context of a randomized study which fortunately is underway. Prolongation of disease free survival (DFS) is expected. Alternatively, because of the documented activity of RIT for indolent NHL, one could envision its use as a chemotherapy-sparing agent, so that patients receive less cycles of chemotherapy followed by RIT.

Several of the ongoing chemotherapy-followed-by-RIT studies utilize rituximab as part of the induction regimen. The use of rituximab could be argued against, fearing that it will engage the CD20 epitopes of the lymphoma cells so that the RIC may not reach its target. On the other hand, the interaction of the antibody with its target should be viewed as a dynamic process of equilibrium with constant detachment of molecules and replacement by others. It should not be forgotten that the RIC is always stoichiometrically much smaller quantity compared to the amount of naked anti-CD20 antibody given with it. In addition, RIT is known to be active even in the presence of measurable rituxan levels, as shown in the study of Zevalin in rituximab-refractory patients, supporting the use of RIT even in the presence of rituximab.³⁷

The strategy of consolidation with RIT has gained acceptance as a research question, as discussed below, supported by the favorable results obtained with the use of rituximab as consolidation. Nevertheless, there are certain theoretical concerns for indiscrete consolidation treatment with RIT. By design, the ratio of beneficial radiation versus radiation deposited to surrounding tissue depends on the size of the lymphomatous mass and the path length of the radioisotope used. Since radiation is delivered within a sphere with radius of a few mm whose center is the radioactive material, if one assumes micrometastatic single cell disease, most of the

radiation emitted by the lymphoma-attached radioconjugate will be delivered to the surrounding tissue. In such sense, there will be a waste of most of the radiation energy delivered. On the other hand, the definition of complete response may still include patients with small lymphomatous aggregates in "normal size" lymph nodes, so that there may still be benefit from the crossfire effect in complete responders. This is more true if the response to preceding chemotherapy was not complete; in such case, RIT may be an ideal agent to treat remaining involved nodes, from the point of view of radiation physics, because of the cross-fire effect. More importantly perhaps, there may be temporal synergy of RIT with chemotherapy, i.e. the cells exposed to RIT may be damaged from the preceding chemotherapy cycles which may have rendered them more susceptible to cell death. Another theoretical concern would be whether the relative resistance of lymphomatous cells to chemotherapy preventing a complete response to it also predisposes to radioresistance. Based on evidence of significant activity of RIT in patients with chemoresistant disease,^{37,58,68} it appears that RIT is still expected to be of benefit. Another concern of the consolidation use is whether a bone marrow in the process of recovering and regenerating from the effects of recent myelotoxic chemotherapy can sustain safely the effect of RIT, and if there is a minimum safe period separating the preceding chemotherapy with the subsequent RIT. Completed studies seem to indicate that an interval period of 4-6 weeks is sufficient for safe administration of RIT without unexpected toxicity, particularly myelosuppression.

It can be reasonably expected that the addition of RIT given after a standard chemotherapy regimen will prolong the duration of the remission and time to progression. Whether the preemptive treatment with RIT of the residual disease may be more beneficial in terms of overall survival compared to reserving its use for the inevitable progression of the indolent lymphoma will remain an important question to be answered in the subsequent years. If the hypothesis of "temporal synergy" as discussed above is true, then consolidation use ought to be more beneficial than subsequent Zevalin treatment upon progression.

Recently, studies documenting activity of RIT in aggressive lymphoma types has led to the development of consolidation studies in such histologies as well. Given the observed improvement of DFS when standard chemotherapy is combined with antibody-based treatment, one can not exclude a significant benefit in such patients.

RADIOIMMUNOTHERAPY CONSOLIDATION

Indolent NHL

The largest experience of using consolidation RIT has been produced by the Southwest Oncology Group (SWOG)

large phase II study, of 90 patients with untreated follicular lymphoma.⁶⁹ After an initial full course CHOP chemotherapy, responding patients received ¹³¹I-T as consolidation. The mean time between the end of chemotherapy and the treatment with RIT was 35 days. RIT was well tolerated without excessive myelotoxicity, and 57% of the patients achieving less than a CR, improved their remission with RIT. Thus the overall response rate was 90% including 67% complete responses, and the 2-year progression-free survival was estimated at 81%. This sequential regimen (CHOP-¹³¹I-T) is now tested in a randomized fashion against CHOP-rituximab. The same RIC was tested after an abbreviated 3-cycle course of fludarabine⁷⁰ again as first-line treatment. The sequence induced a complete response in 83% of the 35 evaluable patients. Grade IV neutropenia or thrombocytopenia was noted in 34% and 29% respectively.

Several studies are underway in the USA and Europe involving ⁹⁰Y-IT consolidation after chemotherapy. In the Sarah Cannon Cancer Center, a short 3-chemotherapy cycle regimen of CHOP-rituximab or CVP-rituximab is followed by ⁹⁰Y-IT, which is thus used as a chemotherapy sparing agent.⁷¹ ⁹⁰Y-IT was given 5-7 weeks after the last chemotherapy cycle. Among the 22 reported responding patients who completed the whole protocol, there were 13 partial responders to chemotherapy, 10 of which converted to complete response after ⁹⁰Y-IT, for an overall complete response rate of 86%. Limited grade IV neutropenia or thrombocytopenia was seen (18% and 0% respectively). Results of Zevalin consolidation following fludarabine-mitoxantrone followed by Zevalin consolidation has been reported suggestive of similar effect.⁷²

The above observations have led to a large ongoing multicentered randomized phase III Europe-based study, testing the role of ⁹⁰Y-IT as consolidation therapy. Patients with stage III and IV follicular NHL receive a first line induction regimen of the choice of the site investigators. Three hundred sixty responders have been randomized to either receive ⁹⁰Y-IT consolidation or just be observed, with primary end point being the disease free survival. Preliminary information (May 2007) was released regarding the positivity of the study, although details are not available. It is expected that this study, as well as the SWOG randomized study, will help more precisely define the value of adding RIT consolidation to standard treatment. As rituximab maintenance after chemoimmunotherapy is gaining acceptance, a subsequent multicenter randomized study is underway, comparing the emerging standard of care of chemoimmunotherapy followed by rituximab maintenance to chemoimmunotherapy plus Zevalin consolidation followed by rituximab maintenance. This study will address the question of the possible benefit of Zevalin added to a rituximab maintenance setting. Clearly the bar is set higher for Zevalin in this study given the improved outcome of the control arm, and the results of this study will help

shape clinical practice.

Aggressive NHL

The documentation of considerable activity of ⁹⁰Y-IT in patients with relapsed or refractory diffuse large B-cell lymphoma⁷³ as well as the hope for further improvement of the overall survival in such group of patients led to the initiation of consolidation studies which are in progress. In relapsed aggressive NHL unsuitable for high dose chemotherapy, the use of ⁹⁰Y-IT following salvage ifosfamide-carboplatin-etoposide-rituximab (R-ICE) is being explored. Finally a European study assesses the role of Zevalin as consolidation after completion of full course R-CHOP in patients with aggressive lymphoma. Such studies will answer the possible benefit of Zevalin consolidation in terms of overall survival, which is hoped.

It is intriguing to consider RIT as a possible substitute of external beam irradiation in limited disease. Two ongoing phase II studies are exploring its consolidative use instead of external beam radiation after an abbreviated course of either CHOP (SWOG), or CHOP-rituximab (Mayo Clinic), in patients with early stage aggressive lymphoma. It may also be interesting to conceive the use of RIT with external beam irradiation in refractory cases. Based on personal anecdotal experience, involved nodes can be treated with both ⁹⁰Y-IT and external irradiation without apparent additive toxicity

Mantle Cell Lymphoma

The sequence CHOP-rituximab followed by ⁹⁰Y-IT consolidation has been tested as first line treatment of mantle cell lymphoma by the Eastern Cooperative Oncology Group (ECOG). The outcome of 56 patients, the larger series of this kind was reported as ASCO 2006;⁷⁴ After 4 cycles of R-CHOP, the overall response rate and the complete response rate were 72% and 14% respectively. Similar to their consolidation studies, after administration of ⁹⁰Y-IT the responses increased respectively to 84% and 45%. A similar approach employing the combination of fludarabine, mitoxantrone, cyclophosphamide and rituximab (FCM-R) as induction regimen followed by ⁹⁰Y-IT consolidation was reported to induce CR in 19 out of 20 patients with untreated mantle cell lymphoma and with an excellent so far freedom from progression (FFP).⁷⁵ However, for relapsed mantle cell lymphoma, the same regimen induced a CR of 40% and TTP of 7 months in a small group of patients. At MD Anderson Cancer Center, ⁹⁰Y-IT is given as consolidation after standard HyperCVAD/rituximab regimen, but there have been no reports so far. It emerges from the above studies, that ⁹⁰Y-IT may be particularly helpful as consolidation after first line chemotherapy, but its usefulness in relapsed disease, either as monotherapy or as consolidation is limited.

Stem Cell Transplant

The studies at University of Washington have since long documented the feasibility of escalating the doses of RIT in order to maximize the anti-tumor efficacy and rescuing from the ensuing myeloablation with infusion of autologous stem cells. Several years ago, Press and colleagues reported on the administration of ^{131}I -B1 anti-CD20 antibody (tositumomab) at myeloablative, dosimetry-based, doses of 345-785 mCi in 22 patients with relapsed follicular lymphoma, inducing a CR in 16/21 of them and a 62% progression free survival (PFS) at 2 years.⁷⁶ In subsequent analysis of this cohort expanded to 29 patients, a 42% 5-year progression-free survival is reported; Reversible acute cardiopulmonary toxicity was noted in 2 patients as dose-limiting toxicity, whereas 60% developed elevated thyroid stimulating hormone.⁷⁷ Although these results compare favorably with historical controls⁷⁸ the inconvenience of the administration of high doses of iodine-131 seems to have prevented the wide-spread use of such treatment. In addition to the above study that involved single agent escalated RIT, studies combining ^{131}I -T with 60 mg/kg of etoposide and 100 mg/kg of cyclophosphamide showed that the maximum tolerated dose would be such that delivers 22-25 Gy to critical organs, inducing a 68% progression-free survival.⁷⁹ A similar approach was used in a small cohort of patients with relapsed mantle cell lymphoma with frequent long remissions.⁸⁰ A different group at the University of Nebraska recently reported a phase I study of up to standard doses of ^{131}I -T followed by high dose BEAM (BCNU, etoposide, ara-C, melphalan) showing feasibility and promising DFS.⁸¹

Several studies have been conducted or are underway exploring the use of ^{90}Y -IT in the context of autologous stem cell transplant. The first report was from the City of Hope in California, demonstrating the safety and feasibility of the administration of standard dose ^{90}Y -IT 2 weeks prior to the infusion of stem cells, in conjunction with high dose chemotherapy.⁸² Several European studies are currently exploring the role of standard dose ^{90}Y -IT as addition to high dose chemotherapy and autologous stem cell transplant. Perhaps the largest study are from the GELA group with 76 patients recently analyzed, and with no serious or unexpected toxicity noted, confirming the safety of this relatively uncomplicated design (Christian Gisselbrecht, personal communication). The efficacy outcomes are awaited. The same strategy of standard dose ^{90}Y -IT followed by BEAM megatherapy and stem cell transplant was tested in a cohort of refractory aggressive lymphoma of poor prognosis.⁸³ Of the 21 evaluable patients, 76% achieved a complete response for an estimated 64% 2 year overall survival, exceeding expectations. If these outcomes are confirmed in larger randomized studies which are underway, they speak to a synergistic activity of RIT and chemotherapy, achieved with temporal proximity of the deliv-

ery of these two treatment modalities.

The field of stem cell transplantation allows the exploration of higher than standard doses of RIT, since myelosuppression ceases to be the dose-limiting toxicity. When ^{90}Y -IT is administered, the organ of concern is the liver, because of the non-specific uptake of the administered radioactivity. The first reports of increased dose ^{90}Y -IT as part of the conditioning regimen was presented by researchers at City of Hope.^{84,85} In an escalated ^{90}Y -IT study, increased dose of ^{90}Y -IT was administered so that the liver received a predetermined dose of 1,000 cGy of radiation, as estimated using ^{111}In -IT imaging. A week later, patients received high dose etoposide and cyclophosphamide, followed by the infusion of autologous stem cells on the 14th day after ^{90}Y -IT. The median dose of ^{90}Y -IT was 71 mCi (2.6 GBq), more than twice the standard (range 37-105 mCi). Thus ^{90}Y -IT served as substitute for historically used total body irradiation. Over 40 patients have been treated so far. Excellent disease-free survival of 80% at 2 years was noted in this selected group of patients with diverse histologies. At Northwestern University, a careful dose escalation of ^{90}Y -IT starting at doses below the conventional one has been performed in conjunction with the BEAM regimen, proving the feasibility of the combination in multiply relapsed B-cell lymphoma.⁸⁶ Cohorts of patients received as much ^{90}Y -IT prior to BEAM so that critical organs received predefined escalating doses of radiation. Dosimetry was performed using ^{111}In -IT. The doses of ^{90}Y -IT differed widely per cohort (0.5-0.75 mCi/kg for the 1,100 cGy cohort). There was no unexpected toxicity, whereas a case of transient venoocclusive disease was noted. All patients engrafted and had a 50% 3-year DFS. An ECOG phase I study of escalated myeloablative ^{90}Y -IT was based on dosimetry, increasing in successive cohorts radiation exposure to the liver.⁸⁷ Following cyclophosphamide-rituximab mobilization for stem cell collection, patients received up to 143 mCi of ^{90}Y , delivering up to 28 Gy to the liver followed by high dose chemotherapy. The treatment was generally well tolerated. Several studies of escalated RIT are ongoing in Europe. Vanazzi *et al.* have reported on a cohort of 18 patients who received escalated ^{90}Y -IT monotherapy followed by stem cell transplant.⁸⁸ The escalation involved the per kg ^{90}Y dose. Patients received up to 1.5 mCi/kg (up to 150 mCi, median dose of 95 mCi). There was one death from hepatitis C reactivation, and one engraftment failure. It is remarkable in this study that the median age of the participants was 66 years. Several groups pursue similar strategies.

At MD Anderson, a study using ^{90}Y -IT prior to reduced-intensity conditioning regimen with a fludarabine-cyclophosphamide combination followed by allogeneic stem cell transplant is underway.⁸⁹ Preliminary results indicate a survival of 5 out of 7 patients with a variety of haematologic malignancies. Although it is too early to comment on the results, this study follows the very exciting data obtained

using rituximab with the same regimen and may be proven to be useful for refractory B-cell malignancies.

It should be pointed out that in all of those studies, there has been no adverse effect on stem cell engraftment and the recovery from the high dose therapy induced aplasia. In most studies, time to neutrophil engraftment was 10 days as expected. All designs allow a minimum of 14 days between the administration of RIT and the infusion of stem cells, which seems to be a safe period given the half life of the isotope. The use of RIT did not seem to increase other organ toxicity, although the studies need to mature before definitive conclusions can be derived.

FUTURE DIRECTIONS

RIT for cancer is a novel treatment modality, which poses several challenges to the health care providers and receivers. First, it requires even closer collaboration between the clinical haematologist - oncologist and the physician licensed to handle the radioactive materials involved, usually a nuclear medicine specialist. Communication requires both the transfer of medical information determining eligibility (bone marrow biopsy results, blood counts, histologic diagnosis, and weight) as well as precise coordination of the timing of the treatment, since the infusion of the naked antibody is handled by the haematologist - oncologist but the subsequent injection of the RIC is done on the same day under the supervision of the licensed physician. As ^{90}Y had not been in clinical use, its handling may require an extension of the license, as well as relevant training of the physicians and other scientists responsible for the preparation of the drug and the administration. Since the conjugation of the isotope to the antibody is made on the spot, familiarity with the preparation procedure, and the testing of the product are essential. Other logistical barriers that had to be overcome were at certain instances the establishment of distinct charging codes for RIT, reimbursement or other pharmacoeconomic issues.

There is no question that RIT monotherapy provides anti-lymphoma results at least equivalent to chemotherapy, if not better. Therefore, it can be used as an alternative to chemotherapy in the treatment sequence of low-grade lymphoma patients. In fact, the lack of typical chemotherapy-associated side effects such as hair-loss, and the overall brevity of the treatment may make it preferable to repetitive cycles of combination chemotherapy for the treatment of relapsed disease. This use can be supported by the feasibility of subsequent chemotherapy treatments, the lack of association with myelodysplastic syndrome development, the low infectious risk, the safety in the older population and the high efficacy, particularly the higher rate of long-lasting response rates associated with earlier use.

A wide range of clinical trials have been designed, reflecting the ambition of the investigators to maximize the

clinical benefit conferred by RIT. The studies designed in the latter years, are result of the realization that RIT is adequately safe, and may add to chemotherapy an non-overlapping anti-lymphoma effect. Rather than considering RIT merely as palliative therapy for multiply pretreated patients, the studies envision it as a dynamic new treatment suitable for early administration to patients, thus exploiting to the maximum its efficacy. In that sense, incorporation in a multiagent therapeutic sequence with chemotherapy, antibodies or other biologicals may be important. For example, it is quite probable that if RIT is given as consolidation after full or abbreviated course of chemotherapy, it may produce longer response duration, and it is not inconceivable that this could translate into better overall survival. Relevant trials are addressing this important question. Many studies target off-label indications such as mantle cell and aggressive lymphoma, seeking to improve clinical outcomes and perhaps augment the cure rate. In fact we are fortunate to expect very soon results from randomized consolidation studies in first line follicular lymphoma and to expect in the future results of randomized studies of consolidation use in conjunction with rituximab maintenance in indolent NHL and of the consolidation use in aggressive NHL. A multitude of studies have already shown that at standard or escalated doses it can be included in stem cell transplant protocols with encouraging results. Additionally, RIT monotherapy upfront, seems to be particularly effective, although not tested in randomized function. It is probably a reasonable approach for selected patients when chemotherapy is undesirable. In that sense, RIT seems to present an attractive option since compared to rituximab monotherapy seems to produce more reliable responses.

As is frequently the case, the impact of such agents on survival and the associated cost-effectiveness will be very difficult to assess. However, there is no question that patients have already experienced significant clinical benefit from RIC, occasionally with long remissions and with preservation of quality of life. RIT is a patient-friendly additional therapeutic alternative that expands the therapeutic armamentarium against B-cell lymphomas and offers the gratification of the clinical success of a targeted anti-cancer approach. Eagerly awaiting study outcomes will help define its precise role in the management of lymphoma.

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