Radioimmunotherapy for non-Hodgkin lymphoma: Historical development and current status

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Abstract.—Radioimmunotherapy treatment for lymphoma is a novel targeted therapeutic approach. Several years of development of radioimmunoconjugate compounds came to fruition in February of 2002 when \(^{90}\)Y-ibritumomab tiuxetan (Zevalin, Y2B8) was approved in the USA and later in Europe, for the treatment of relapsed or refractory, low grade or transformed B-cell lymphoma in the USA. \(^{90}\)Y-ibritumomab tiuxetan utilizes a monoclonal anti-CD20 antibody to deliver \(\beta\)-emitting yttrium-90 to the malignant B-cells. Clinical trials have demonstrated its efficacy, with observed clinical responses in the 80 % range. This product has become available in Europe, with simplified administration, for the treatment of relapsed follicular lymphoma. A similar anti-CD20 radiotherapeutic compound, \(^{131}\)I-tositumomab, was subsequently approved in the USA. Promising studies exploring expanded applications of radioimmunotherapy as consolidation, as part of transplant, or in other histologic types have been recently completed or are under way. Radioimmunotherapy has been shown to be an effective and clinically relevant complementary therapeutic approach for patients with lymphoma, bringing the Nuclear Medicine into lymphoma therapeutics.

INTRODUCTION

The introduction of targeted therapeutic approaches has revolutionized the field of cancer treatment. In particular, the use of monoclonal antibodies has been met with considerable success, first for the treatment of lymphoma but also for certain solid tumors. In addition to their therapeutic value, antibodies constitute excellent targeting systems, marking selected cells for the interaction with innate immune effector mechanisms, or by conjugation with drugs or isotopes which are thus locally delivered. In contrast to the mixed results obtained with immunotoxins, radioimmunotherapy (RIT) has been proven to be effective enough, so that the USA Food and Drug Administration (FDA) approved the first ever radioimmunoconjugate (RIC) for the treatment of a malignancy in February of 2002, when ibritumomab tiuxetan (Zevalin\textsuperscript{TM}) was licensed for the treatment of indolent or transformed, relapsed B-cell lymphoma\textsuperscript{1}. Thus, CD20-based radioimmunotherapy for non-Hodgkin lymphoma (NHL) follows the path first paved by the successful application of rituximab (Matthera), an antiCD20 monoclonal antibody widely used against B-cell malignancies. RIT had previously been tried rather unsuccessfully in a variety of tumor 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 tumor 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 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 shedded 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 with Burkitt’s lymphoma cells. 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/m². 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. 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. Among others, it was shown that the kinetics of indium-labelled antibody were similar and could predict the yttrium-labelled antibody distribution, which supported the clinical development of 90Y-ibritumomab tiuxetan (Zevalin) in patients with the same variable region, and is currently commercially available both in the USA and Europe. 131I-tositumomab (Bexxar™) uses the B1 antiCD20 antibody first developed by Nadler et al 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 radioimmunotherapy other than the theoretical concern regarding the development of antimurine 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-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%. Internalisation 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. Favourable 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
Tracer imaging 5 mCi of Pre-infusion dose 250 mg of rituximab 450 mg of tositumomab Pre-infusion antibody chimeric (rituximab) murine (tositumomab) Monoclonal antibody murine (ibritumomab) murine (tositumomab) Urinary excretion minimal Variable Isotope used 90Y Path length 5.3 mm 0.8 mm Isotope T1/2 64 hours 8 days Tracer imaging 5 mCi of 131I-T (ZEVALIN) and 131I-T (BEXXAR) Purpose of tracer 2-3 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

*platelet counts < 100,000/ml.

212Bi or 213Bi and astatium (211At) have been tried but appear to be cumbersome for successful clinical use. 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 mm 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.

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 131I by the thyroid gland mandates the use of saturated potassium iodine solution (SSKI, Lugol) to prevent thyroid irradiation. The biological half-life of 131I RIC varies widely and unpredictably among patients and only partially depends on renal clearance. These issues oblige the use of dosimetry in clinical practice.

As a pure β emitter, 90Y 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 T1/2 of 64 hours compared to 8 days of 131I, 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 131I, 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 gamma component, a surrogate isotope is used for imagine or dosimetry. For that purpose, substitution with 111In has been successfully used to predict the pharmacokinetics of 90Y-labelled antibodies. Both 90Y and 131I have been components of anti-CD20 radioimmunoconjugates (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. 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 $^{111}$In-IT is performed in the USA but not required in Europe, while and dosimetry for $^{131}$I-tositumomab ($^{131}$I-T) is necessary, as described below.

$^{90}$Y-IBRITUMOMAB TIUXETAN (ZEVALIN™)

This is the first RIC approved for the treatment relapsed or refractory low grade or transformed B-cell NHL. Ibritumomab 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 antiCD20 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 $^{90}$Y to the antibody.

During the registrational clinical trials, a meticulous and thorough dosimetry procedure was performed largely using data derived from $^{111}$In-ibritumomab tiuxetan ($^{90}$In-IT) kinetics. The purpose of dosimetry was to eliminate the possibility of excessive radiation exposure of vital organs. Thus, pharmacokinetics (PK) 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 $^{111}$In-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 $^{90}$Y 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 $^{111}$In-IT are similar to those of $^{90}$Y-IT. The validity of this assumption was confirmed in selected patients who underwent PK analysis after $^{90}$Y-IT administration. Patients would be ineligible to proceed with the therapeutic dose of $^{90}$Y-IT if any of the vital organs or unaffected areas would receive a dose exceeding 2000 cGy, a limit that was never reached. In addition to the blood derived PK, 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 $^{90}$Y-IT administration. Based on these, FDA eliminated the requirement for dosimetry in 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 > 1500/µl and a platelet count > 100000/µl. These restrictions emerged from the phase I-II trials and protect from potentially serious myelosuppression. Patients with CNS 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 $^{90}$Y-IT (Zevalin) are as follows: Patients first receive an infusion of 250 mg/m² of rituximab. In the USA only, this is followed by the administration of 5 mCi of $^{111}$In-IT for the purpose of imaging. Subsequently, two gamma camera scans are performed within the first and third 24-hour period. The purpose of the scans is to ascertain optimal biodistribution of the ra-

| Table 2 |
| CONTRAINDICATIONS TO CONVENTIONAL DOSE RADIOIMMUNOTHERAPY |
| - Bone marrow involvement by lymphoma > 25% |
| - Neutrophils < 1.5 x 10⁹/l |
| - Platelets < 100 x 10⁹/l |
| - Myelodysplastic or very hypocellular marrow |
| - Prior high dose chemotherapy* |
| - Circulating B-cells > 5000/µl* |

dioactive antibody (performed visually) and thus protect form the theoretical risk of sequestration in vital organs. Such an occurrence was never observed among 349 patients involved in the clinical trials and the expanded access program. For that reason imaging has been eliminated in Europe. One week after the first administration, patients receive a similar dose of rituximab followed by the therapeutic dose of \(^{90}\text{Y}-\text{IT}\), given at 0.4 mCi/kg, not to exceed 32 mCi. For patients with platelet counts ranging between 100000-150000/\(\mu\text{l}\), the dose is reduced to 0.3 mCi/kg.

Nuclear site permit and initiation are simple and depend on local regulations. Calibration and dose quantitation, is usually required. Occasionally, the RIC has to be prepared on the spot, using the labeling kit, a process of less than an hour. The radioactive antibodies have to be ordered 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 injection over 10 minutes. The amount of antibody injected is less than 5 mg, significantly less than the preinfused rituximab. Plastic or plexiglass 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. 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.

Clinical Trials

All the trials before registration took place in the USA. The phase I/II study of Zevalin included a dose escalation of the rituximab pre-infusion required to optimize the distribution of the radioactive antibody, as well as a dose escalation of the radioactivity of Zevalin, starting at a dose of 0.2 mCi/kg. The optimum dose of rituximab was defined as 250 mg/m\(^2\). Maximum tolerated dose of \(^{90}\text{Y}-\text{Zevalin}\) was determined to be 0.4 mCi/kg for patients with platelet count over 150000/\(\mu\text{l}\) and 0.3 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 responses and 2 partial ones. The median time to progression exceeded one year. The major toxicity was reversible myelosuppression with median ANC 1100/\(\mu\text{l}\) and median thrombocytopenia 49500/\(\mu\text{l}\). It became apparent that the extent of bone marrow involvement by lymphoma and the pretreatment 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.

After these encouraging results, a large randomized study was initiated comparing \(^{90}\text{Y}-\text{IT}\) (Zevalin) to rituximab, involving 143 patients with relapsed or refractory low grade or transformed lymphoma, and similar eligibility criteria as above. 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). The overall response rate and the complete response rate favoured \(^{111}\text{In}-\text{IT}\) 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 9 patients with non-follicular histology. The incidence of HAMA or antichimeric antibody (HACA) was 2 %. Non-haematologic toxicity was not different in the two groups. The time to progression and the duration of response comparison did not reach significance; however the median time to next therapy, based on clinical judgement for need for subsequent treatment, was not reached at the time of analysis for the RIC arm and was 15.2 months for the un-conjugated antibody arm, favouring Zevalin. 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. 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 $^{111}$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 favourably with that of the last chemotherapy regimen. For the whole group 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 plain antibody.

The question of whether mildly thrombocytopenic patients (with platelet count 100000-150000/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. Responses seem to be similar to those reported in other studies with an 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.

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 patients the only factor that predicted for better response was tumour bulk. Patients with nodal masses more than 5 cm had a 68 % response rate and shorter duration of response, whereas those with smaller tumours 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, extra-nodal disease and IPI score failed to correlate with outcome. Responses seem to be somewhat less frequent in small lymphocytic lymphoma or transformed lymphoma.

**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 1000 patients. Geriatric patients up to 85 years of age seem to tolerate the treatment as well with similar response expectations. Myelosuppression is clearly the main and dose limiting toxicity. The median neutrophils count recorded in the registra-

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<tr>
<th>Extent of Bone Marrow (BM) Involvement</th>
<th>Grade IV Cytopenia</th>
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<tr>
<td>Percent BM involvement at Baseline (%)</td>
<td>Neutropenia</td>
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<td>0 (%)</td>
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<td>Neutropenia</td>
<td>23</td>
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<td>Anemia</td>
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<td>Thrombocytopenia</td>
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All p values < 0.05. Grade IV toxicity is defined as neutrophils < 500/µl, Platelets < 100000/µl, Hb < 6.5 g/dl

trational trials was 800/µl; the median haemoglobin 10.3 g % and the median platelet count 37.500/µl. In contrast to chemotherapy, cytopenia nadir occurs 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 % BM involvement, and only 23 % for patients with no obvious disease infiltration (IDEC file). 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 (MDS) and acute myeloid leukaemia (AML) has been reported to date in only 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 incidence of AML/MDS is within the expected range, with an annualised rate of 0.21 % and 0.62 % since initial diagnosis and since RIT respectively. These date do not support an increased risk compared to historical controls.

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 en-
rolled in all preapproval studies, the incidence of hospitalisation for infections was 6.6%, including only 6 cases of febrile neutropenia\textsuperscript{42,43}. 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\textsuperscript{36,43}. 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 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\textsuperscript{44}. Responses were noted in the majority of the patients. Rituximab may also be active for subsequent relapses\textsuperscript{45}. 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 $^{90}$Y-IT.

**Radiation Kinetics and Safety**

In the clinical trials before approval, dosimetry studies were always 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 MIRDOS3 program. In all patients the calculated radiation dose was within the set limit of 2000 cGy or 300 cGy for the bone marrow and in fact the exposure was much lower than these limits. The median T$^{1/2}$ of $^{90}$Y in the blood was 28 hours (range 14-36 hrs)\textsuperscript{32,35}. The median radiation exposure as calculated in the 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\textsuperscript{31,35}. Hence the median liver exposure is in the range of 500 cGy and much less for other organs\textsuperscript{30,35}. 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 BM involvement by disease. In occasional patients, the spleen exposure exceeded the cut-off of 2000 cGy likely due to direct involvement by lymphoma. Such patients received Zevalin uneventfully. Predicted median tumour exposure was 1484-1712 cGy (range 61-24274 cGy). 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 splenomegal$^{30}$. Radiation hazard is minimal with $^{90}$Y-IT. There is only limited amount of secondary $\gamma$ 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. No contact isolation is necessary, but condoms are recommended. 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\textsuperscript{46}.

**Expanded Applications of $^{90}$Y-IT**

The activity of 90Y-IT in aggressive B-cell lymphoma has been documented in the phase I/II study\textsuperscript{32}. 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 progression for the complete responders has not been reached at 35.5 months follow up (2.5-40 months)\textsuperscript{47}. Subsequently a larger multicenter phase II study was performed in Europe demonstrating a 40-58% response in patients with relapsed or refractory, rituximab-naive aggressive lymphoma\textsuperscript{48}.
Patients with non-follicular indolent B-cell lymphoma have been included in the clinical trials or the expanded access trial documenting activity of Zevalin in entities such as small lymphocytic lymphoma, marginal zone lymphoma or Waldenstrom’s macroglobulinaemia. Clinical trials are also underway investigating activity in CLL, mantle cell NHL, CNS lymphoma, or paediatric lymphoma.

However, the optimal incorporation of $^{90}$Y-IT into the therapeutic strategy of NHL has not been clearly defined. Phase I studies using $^{90}$Y-IT for two consecutive treatments, (one standard administration, followed by a reduced, dose escalating dose 3 months later)\(^5\), treatment of post-transplant relapses or repetitive low intensity treatments in patients with excessive bone marrow involvement, with chronic lymphocytic leukemia or consolidation after induction treatment of aggressive or mantle lymphoma are ongoing.

Perhaps the most successful use of Zevalin will be as consolidation treatment after chemotherapy. In a USA study, a short 3-cycle regimen of CHOP-rituximab or CVP-rituximab is followed by $^{90}$Y-IBRITUMOMAB tiuxetan, which is thus used as a chemotherapy sparing agent\(^5\). $^{90}$Y-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 to chemotherapy, 10 of which converted to complete response after $^{90}$Y-IT, for an overall complete response rate of 86 %. Limited grade 4 neutropenia or thrombocytopenia was seen (18 % and 0 % respectively). Studies at Rush Presbyterian Cancer Center and MD Anderson Cancer Center are underway exploring the use of $^{90}$Y-IT after fludarabine-mitoantrone and fludarabine-mitoantrone-rituximab respectively. A study of full course CHOP-rituximab consolidated by Zevalin is explored at the University of Pittsburgh.

The above observations have led to a large ongoing multicentered randomized phase III Europe-based study, testing the role of $^{90}$Y-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 $^{90}$Y-IT consolidation or just be observed, with primary end point being the disease free survival. It is expected that this study will demonstrate a significant advantage in disease-free survival, and thus help define more precisely the value of adding RIT consolidation to standard treatment.

Preliminary studies demonstrate, as cytoreductive prior to HDC or at escalated doses as part of ablative high dose chemoradiation are also explored.\(^5\) It is noteworthy that in such a study incorporating Zevalin in a transplant program, the dose is calculated so that vital organs do not receive more than 1000 rads of exposure. The median dose of $^{90}$Y-IT thus delivered was 74.9 mCi (range 33.6-105 mCi) without unexpected toxicity and with encouraging early results, suggesting that myeloablative higher doses of $^{90}$Y-IT are well tolerated. Alternatively, a classical dose-escalation program is proposed\(^5\). Thus radioimmunotherapy may be replacing total body irradiation in such approaches.

$^{131}$I-TOSITUMOMAB

Iodine-131 tositumomab (Bexxar, Corixa and Glaxo Smith-Kline) consists of the murine IgG2a anti-CD20 antibody anti-BI (tositumomab) that has undergone iodination of tyrosine residues with radioactive $^{131}$I. Although efficacy of the tositumomab in vivo has been reported, it is not currently clinically available. There are certain similarities with Zevalin, including similar eligibility criteria. It is of note that Bexxar has been approved in the USA for rituximab-refractory indolent lymphoma. Similar to Zevalin $^{131}$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 Zevalin, the purpose of dosimetry is to determine the therapeutic dose of $^{131}$I-T. Three whole body $\gamma$-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 different 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. In patients with platelet count over 150000/µl this is set at 75 cGy, but it is 65 cGy if platelets are in the 100000-150000 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. Eventually a dose escalation trial established as MTD the 75 cGy total body dose and 450 mg as the optimal pre-dose of tositumomab (using corrected optical extinction coefficient). 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. Aggressive histology, lower total body dose of radiation, bulky disease and elevation of LDH predicted for inferior chance for response. Four patients have developed myelodysplasia 1.2 to 7.5 years after treatment. Ten patients developed HAMA but some of those had received multiple dosimetric doses or retreatment.

At a subsequent confirmatory multicenter trial conducted at 6 centres 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. The median duration of response was 9.9 months. The mean activity of the delivered therapeutic dose was 88 mCi (range 45 to 177 mCi) and the mean biologic T/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 was haematologic, with five patients reaching a nadir platelet count of less than 10000/µl and two patients ANC of less than 100/µl. The haematologic nadir occurred at 6-7 weeks and was for ANC, haemoglobin and platelets 800/µl, 10.2 g % and 43,000/µl respectively. A smaller trial involving 40 patients refractory to rituximab, 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). Somewhat surprisingly this relatively small study is the basis for its approval in the USA.

A provocative study including previously untreated patients with low grade follicular NHL indicated a higher activity in early disease. 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 %. Since such patients are also less immunocompromised, 63 % were found to develop HAMA, frequently associated with a flu-like syndrome. These 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.

Work by Press and others have demonstrated the feasibility of incorporating “high dose” $^{131}$I-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. The $^{131}$I-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 $^{131}$I-T has satisfactory activity against patients with B-cell lymphoma, attributable to targeted irradiation of the tumour 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 $^{90}$Y-IT suggesting of a “class effect” whereby the isotope used is less important for the antitumour activity, although it dictates the type of radiosafety procedures required. $^{131}$I-T is generally well tolerated. Infusion reactions are generally mild, infrequently requiring infusion rate decrease. The most common immediate events are mild malaise and nausea, probably related to the radioactive component. The predominant toxicity is reversible pancytopenia occurring.
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6-7 weeks after treatment and lasting approximately 2 weeks. 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 TSH elevation occurs in less than 10% of the patients. 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. Development of AML or MDS has been reported in up to 6.3% of the patients with calculated annualized incidence of 3.8%/year\(^{(61)}\). Tumours receive a medium of 1010 cGy (standard deviation 696 cGy) whereas normal organs receive less than 200 cGy in general\(^{(56)}\). 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\(^{(64)}\). Contact with pregnant women or children is to be avoided. Based on radiation activity measurements at 1 meter 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 hr after dosing\(^{(65)}\). 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\(^{(66)}\).

RADIOIMMUNOTHERAPY: INCORPORATION IN CLINICAL PRACTICE AND FUTURE DIRECTIONS

RIT offers an effective convenient and attractive novel treatment for lymphoma. There is no question that RIT 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 since the administration phase lasts only 1 week, 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.

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 and the nuclear medicine physician. Communication requires both the transfer of medical information determining eligibility (bone marrow biopsy results, blood counts, histologic diagnosis, weight) as well as precise coordination of the timing of the treatment, since the infusion of the naked antibody is handled by the haematologist but the subsequent injection of the RIC is done on the same day under the supervision of the licensed physician. On the other hand, the simplicity of administration of a purely beta-emitter product such as Zevalin, makes its implementation particularly rewarding.

Efforts are underway to optimize and expand the use of RIC. Incorporation in a multiagent therapeutic sequence with chemotherapy, antibodies or other biologicals may be important. For example, it is likely that if RIT is given as consolidation after full or abbreviated course of chemotherapy, it may produce longer response duration. Additionally, RIT may eventually become an important component of the preparative regimen prior to transplant. Relevant trials are addressing these important questions. The important issue of feasibility of retreatment is explored in a phase I study with dose escalation of the retreatment 90Y-IT dose. This study has indicated that retreatment doses up to 0.3 mCi/kg may be possible\(^{(51)}\). As mentioned earlier, first line treatment has indicated a high response rate, but it is believed that such an approach should be discouraged outside a trial, until more information regarding the long-term safety of RIT is available. Potential improvement of the therapeutic window of RIC may result from pretargeting of the lymphoma cells, whereby the streptavidin-tagged anti-lymphoma antibody is administered first, the excess is cleared, and subsequently radioactive biotin ligand is infused\(^{(6)}\). RIC may be an excellent agent to replace total body irradiation as part of a myeloablative treatment, since it can provide higher irradiation of the tumour cells for less amount of irradiation to the normal tissues. Such approaches have been developed for both products with early encouraging results.
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 RIT, 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.

REFERENCES

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