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United for success against non-Hodgkin's lymphoma: role and responsibilities of the nuclear medicine department

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A B S T R A C T

Yttrium-90 (^{90}Y) ibritumomab tiuxetan is an immunotherapeutic agent that has recently been approved for the treatment of relapsed or refractory low-grade, follicular, or CD20^{+} transformed non-Hodgkin's lymphoma (NHL). ^{90}Y-ibritumomab tiuxetan has delivered highly encouraging responses in clinical studies and represents a major advance in the management of patients with difficult forms of NHL. This agent is notable for its emission of β radiation only, which minimizes or eliminates the need for radiation safety precautions normally associated with radiopharmaceuticals and permits treatment to be carried out in an outpatient setting. Moreover, dosimetry is not required prior to therapy for approved usage in the European Union, and preparation of the radiolabeled monoclonal antibody is straightforward and easily learned.

Traditionally, nuclear medicine physicians have been solely responsible for the management of patients undergoing radiotherapy, but logistic, patient selection, and haematological safety considerations call for a multidisciplinary team approach to optimize outcomes with ^{90}Y-ibritumomab tiuxetan. The team should include the haemato-oncologist or haematologist, immunopathologist, clinical nurse specialist, nuclear medicine physician, radiopharmacist, radiation protection specialist, and other nurses, junior and administrative staff, as appropriate. The team approach draws on a wide range of specialist skills and early data from a major UK institution show that treatment benefits are maximised when treatment is administered on a collaborative basis. Thus, ^{90}Y-ibritumomab tiuxetan represents a significant therapeutic advance, and provides new opportunities for optimizing therapeutic outcomes through the multidisciplinary approach to patient care.

Introduction

Monoclonal antibodies labeled with yttrium-90 (^{90}Y) that target CD20 represent a relatively novel group of immunotherapeutic agents that are currently under investigation for the treatment of non-Hodgkin's lymphoma (NHL). New agents for the management of relapsed or refractory, low-grade, follicular, or transformed NHL are especially welcome because therapeutic options for these forms of the disease are limited. For example, patients with advanced-stage follicular lymphoma cannot be cured with current treatments,[1] and consistent rates of relapse are seen over time, even in patients who have initially achieved complete responses.[2]

The inherently high radiosensitivity of follicular lymphoma and the expression of antigens that

present potential targets have provided promising new means of approaching this and other forms of NHL that are difficult to treat. Radioimmunoconjugates target the CD20 antigen on B-cell lymphomas and induce radiolysis in both targeted and adjacent cells. This is achieved via a radiation *crossfire* effect, which is particularly useful for treating bulky and poorly vascularized tumours and those expressing more than one type of antigen.[1]

Most clinical experience so far with radioimmunoconjugates has been gained with ^{90}Y-radiolabeled murine monoclonal antibody ibritumomab and iodine-131–radiolabeled tositumomab. ^{90}Y-ibritumomab is a pure high energy β emitter with a half-life of only 64 hours, which renders it suitable for use in outpatient departments.[3] In contrast, ^{131}I-tositumomab emits both β and γ radiation and has a half-life of 8 days. Thus, radiation isolation is necessary during treatment with ^{131}I-tositumomab, and must be maintained for several days until total body radioactivity decreases to acceptable levels.[4] Conversely, radiation safety requirements with ^{90}Y-ibritumomab are considerably less burdensome for both healthcare professionals and patients than those for ^{131}I-tositumomab.

^{90}Y-ibritumomab tiuxetan consists of ibritumomab, a murine monoclonal antibody from which rituximab, a therapeutic anti-CD20 agent that promotes B-cell lysis, is derived, and tiuxetan, a compound that chelates ^{90}Y for therapy and indium-111 (^{111}In) for imaging purposes. This novel antibody-targeted agent has proven effective in clinical trials, and has produced response rates of over 80% in patients with relapsed refractory low grade, follicular, or CD20$^+$ transformed NHL.[5-8] A very encouraging 83% overall response rate and median time to progression of 9.4 months with a reduced-dosage regimen was obtained in a study in 30 patients with relapsed or refractory NHL and mild thrombocytopenia.[6]

The clinical successes achieved with radionuclide therapy highlight the need for healthcare providers to ensure that their systems for administration of these radioactive materials are optimized. The coordination and timing of treatment regimens requires the cooperation of all medical, nursing, nuclear medicine, and pharmacy staff, and other healthcare workers who are involved in the preparation and administration of, for example, ^{90}Y-ibritumomab tiuxetan. All staff must also be familiar with the safety measures involved, and patients should understand how their treatment differs from conventional chemotherapy and what they must do to prevent the unnecessary exposure to radiation of persons around them.

Principles of ^{90}Y-ibritumomab tiuxetan immunotherapy

^{90}Y is a pure β emitter that decays to zirconium-90 (^{90}Zr). Its effective path length of 5.3 mm infers that 90% of its high β energy is absorbed with a sphere of radius 5.3 mm, which corresponds to 100 to 200 cell diameters. It is this property that confers the broad crossfire effect that has delivered promising results in clinical trials when ^{90}Y is conjugated with a monoclonal antibody such as ibritumomab.[9] The crossfire effect is believed to increase tumour killing by the irradiation of tumour cells that are not bound to the antibody, and it is this that gives ^{90}Y-ibritumomab tiuxetan its particular clinical utility in patients with bulky or poorly vascularized tumours.

The amount or activity of ^{90}Y-ibritumomab tiuxetan to be given to each patient is calculated according to the person's bodyweight and baseline platelet count. Dosimetry was originally deemed to be an important part of therapy with ^{90}Y-ibritumomab tiuxetan for patients with low grade NHL, with a tracer dose of ibri-

tumomab labeled with γ-emitting ^{111}In being used to predict distribution within the body of the subsequently intended dose of ^{90}Y-ibritumomab tiuxetan. Wiseman et al.[10] carried out dosimetry in a phase I/II clinical trial in patients with histologically confirmed relapsed or refractory low-grade, intermediate-grade, or mantle cell NHL who had failed to respond to chemotherapy. The tumour-to-normal organ ratio of absorbed radiation dose was 7:1, which indicated acceptable radiation delivery to normal tissues and thus allowed the full therapeutic dose of ^{90}Y-ibritumomab tiuxetan to be given to all patients. Moreover, no correlation was found between haematological toxicity and the estimated radiation-absorbed dose to the red marrow, which implies that such toxicity cannot be predicted by dosimetry but is determined by the status of the patient's bone marrow reserves. These findings were confirmed by dosimetry data from a phase III clinical study,[11] in which lack of correlation between dosimetric or pharmacokinetic parameters and severity of haematological nadirs in 72 heavily pretreated patients with dosimetric data showed that it is safe to give ^{90}Y-ibritumomab tiuxetan in this type of population without pretreatment with ^{111}In-ibritumomab tiuxetan radiation dosimetry.

The original regimen recommended for treatment with ^{90}Y-ibritumomab tiuxetan consisted of an intravenous dose of rituximab 250 mg/m^2 followed within 4 hours by 185 MBq (5 mCi) ^{111}In-ibritumomab tiuxetan (1.6 mg total body dose). Rituximab is needed to clear circulating B-cells that might attach to radiolabeled antibody and reduce or minimize levels of radioactivity available for the destruction of lymphoma. Whole-body gamma camera imaging was then performed at 2 to 24 hours and again at 48 to 72 hours, with an optional third scan at 90 to 120 hours. This was followed by further treatment with rituximab 250 mg/m^2 and ^{90}Y-ibritumomab tiuxetan. However, investigators have now concluded that ^{90}Y-ibritumomab tiuxetan can be given safely on the basis of bodyweight and baseline platelet counts, with activities of 0.4 mCi/kg (15 MBq/kg) recommended for persons with counts of 150×10^9/L or higher, and 0.3 mCi/kg (11 MBq/kg) for those with counts below this level down to 100×10^9/L. Thus, the modified schedule now recommended in the European Union (EU) consists of two intravenous infusions of rituximab 250 mg/m^2, the first on day 1 and the second between days 7 and 9, followed by a 10-minute infusion of ^{90}Y-ibritumomab tiuxetan.[12] This regimen is suitable for patients with pretreatment platelet counts as indicated above and with less than 25% bone marrow involvement as indicated by biopsy. Dosimetry is required when ^{90}Y-ibritumomab tiuxetan is being given in an investigational setting that differs from that defined by the clinical trials upon which registration was based in patients with low grade NHL.

Radiolabeling of ibritumomab tiuxetan can be easily and reliably carried out in the nuclear medicine department, usually within 1 hour, with minimal radiation safety precautions. The relatively short half-life of ^{90}Y makes centralized radiolabeling before delivery impractical and excessively costly, unlike the situation pertaining to ^{131}I-labeled products,[13] and preparation is therefore carried out by radiopharmacy staff on-site. Plastic and acrylic vial and/or syringe shields are most appropriate for shielding; primary lead shielding should be avoided because of the potential exposure risk posed by the production of bremsstrahlung radiation. Bremsstrahlung production is proportional to the atomic number of an element, and is therefore low for the materials present in plastics and acrylic compounds. For ^{90}Y, the proportion of β energy that is converted to bremsstrahlung after passage through a material of atomic number of 7.9 is only 0.6%, and the effective atomic numbers of polyethylene and acrylic

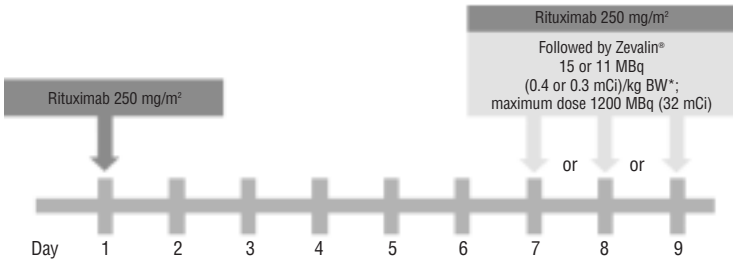

Figure 1: Administration regimen recommended for ^{90}Y-ibritumomab tiuxetan in the European Union. *15 MBq (0.4 mCi)/kg body weight (BW) in patients with a platelet count ≥150,000/μL or 11 MBq (0.3 mCi)/kg BW in patients with a platelet count of 100,000–<150000/μL. The maximum dose is 1200 MBq (32 mCi). All MBq values are rounded up.

are both lower than this.[14,15] In contrast, if lead (with its atomic number of 8216) or leaded glass were to be used, this would paradoxically necessitate the use of thicker shielding than would normally be expected because of the high energy bremsstrahlung that would be produced.

The labeling of ^{90}Y-ibritumomab tiuxetan is straightforward and easily taught. The product is supplied as a kit containing all nonradioactive components, with shipping of ^{90}Y chloride solution being arranged as appropriate according to local procedures. Radiolabeling is carried out aseptically, with the reaction vial held in a suitable dispensing shield as described above. The volume of ^{90}Y chloride equivalent to 40 mCi (1480 MBq) of activity is calculated on the basis of the stock solution supplied. Sodium acetate is then used to adjust the pH for the radiolabeling reaction which is subsequently terminated with a formulation buffer. After preparation in the reaction vial, the volume required for each patient is calculated using a dose calibrator in the usual way on the basis of the platelet count.[17] Before release from the radiopharmacy, testing for radiochemical purity is carried out by instant thin layer chromatography. This ensures that at least 95% of ^{90}Y has been chelated by the antibody-tiuxetan complex. The entire procedure is suitable for pharmacy- or technician-based laboratories, and subjects operators to less than 1/400 of the acceptable annual dose of finger radiation.

^{90}Y-ibritumomab tiuxetan can be administered routinely in the outpatient department (Figure 1) because, although β radiation and low-level bremsstrahlung are produced, there are no γ emissions. This minimizes risk to healthcare workers and to family members, who receive no greater exposure than they would from background radiation. This has been shown in a study carried out to quantify radiation exposure among family members with unrestricted contact with patients who had been treated with ^{90}Y-ibritumomab tiuxetan.[18] There is also no need to determine activity or dose rate limits before patients are released back into the community, as is the case with patients who have received treatment with radiopharmaceutical agents containing ^{131}I. The typical radiation dose from ^{90}Y-ibritumomab tiuxetan is at least a thousand times less than that required to exceed outpatient exposure limits as recommended by the US Nuclear Regulatory Commission,[19,20] so it is clear that requirements for outpatient treatment will always be satisfied in patients receiving this agent.

In the above radiation exposure study,[18] in which no patient shielding of any kind was used, the only recommendations to family members were to avoid contact with body fluids such as saliva, blood, urine and stools. Dosimetric monitoring of the family member with closest contact with each patient showed exposure to be within the range normally expected for background radiation over a 7-day period, and the usual precautions pertaining to the minimization of duration of expo-

sure, maximization of distance from source, and the use of shielding were shown to be unnecessary after treatment with ^{90}Y-ibritumomab tiuxetan.

Multidisciplinary teamwork in the administration of ^{90}Y-ibritumomab tiuxetan

Many nuclear medicine physicians are accustomed to supervising and administering all treatments and follow-up to patients undergoing ^{90}Y labeled immunotherapy. This, however, may not be the optimum approach for this novel form of treatment because of the haematological safety considerations and because of logistic issues and matters pertaining to patient selection. Many nuclear medicine physicians are not specifically trained in the follow-up of haematology patients, and a team approach is recommended to ensure the best possible outcomes. ^{90}Y-ibritumomab tiuxetan is easy to administer when nuclear medicine specialists, haematologists, and oncologists work together, and the benefits of combining the knowledge, backgrounds, and specializations of these persons can result in treatment outcomes that are well worth the additional logistical and administrative efforts involved.

The multidisciplinary radioimmunotherapy team may consist typically the following:

- haemato-oncologist or haematologist
- immunopathologist
- clinical nurse specialist
- junior doctors and nurses working in the chemotherapy suite
- nuclear medicine physician
- radiopharmacist
- radiation protection specialist
- other nurses and reception and administrative staff as appropriate.

The exact makeup of the team will be determined by the skill mix available at any particular centre, and the precise nature of the role(s) taken by each member.

The team is needed because this approach recognizes that each member possesses different skill sets that are unlikely to be fully attainable in full by a single individual. The haematologist is initially needed as a diagnostic specialist to establish that the patient has relapsed or refractory follicular NHL, to determine bone marrow involvement, and to confirm that each individual is eligible for ^{90}Y labeled immunotherapy. The immunopathologist confirms the patient's CD20 status, and the nuclear medicine physician directs the course of treatment after referral of the patient by the haematologist. The nuclear medicine physician also needs to confirm that the center is able legally to hold and store ^{90}Y, to administer and dispose of radiolabeled materials at the activity levels required, to give the radiopharmaceutical on an outpatient basis (this will depend on local and national regulatory requirements), and to ensure that all necessary permissions and licenses are held.

Treatment with ^{90}Y-ibritumomab tiuxetan requires coordination, particularly if patients are traveling from other areas. Ideally, one team member should oversee administrative issues involved with treatment, including patient selection and liaison, reagent supply and delivery, treatment timing and follow-up, and reimbursement. The haemato-oncology specialist nurse is a logical choice as a central reference, and should be responsible for ensuring that funding for treatment is secured. This may be an issue in countries where state subsidy is not necessarily guaranteed, or where treatment is to be funded at least partially from private sources. The specialist nurse also contacts patients to make sure that they are fully aware of procedures and timings of treatment, and to ensure that dates for attendance at the clinic suit both the patient and the nuclear medicine department. Continuity between the ordering of reagents and their preparation, and

Table 1: Treatment sequence requirements for administration of ^{90}Y-ibritumomab tiuxetan on *Z-day*.

Time	*Procedures*
10 days before administration (Z-day –10)	Recheck patient eligibility in terms of bone marrow involvement (lymphoma involvement <25% of bone marrow)
	Check platelets >100,000/mL
	Weigh patient and check still happy to proceed with treatment
	Order ibritumomab tiuxetan and ^{90}Y
7 days before administration (Z-day –7)	Recheck eligibility
	Give first dose of rituximab 250 mg/m^2
	Confirm time and date of therapy
Z-day	Admit patient to day unit: check weight, height and general health
	Take blood sample and measure full blood count. Confirm eligibility and report to nuclear medicine department with estimated time of completion of rituximab infusion
	Give rituximab 250 mg/m^2. Inform nuclear medicine department 20 minutes before end of infusion
	Take patient to nuclear medicine with maintained IV access when rituximab infusion complete
	Prepare ^{90}Y-ibritumomab tiuxetan and undertake quality control check. Administer 0.4 mCi/kg (15 MBq/kg) or reduce to 0.3 mCi/kg (11 MBq/kg) if platelets <150 000/mL (do not treat if platelets <100,000/mL)
	Infuse ^{90}Y-ibritumomab tiuxetan over 10–20 minutes; reduce rate in event of adverse reactions (e.g. chills, bronchospasm)
	After completion of infusion, remove IV cannula, collect waste for β disposal, advise patient on post-treatment effects, and allow patient to go home. Advise haemato-oncology department
After Z-day	Haemato-oncology department undertakes follow-up

administration to the patient, is critical. This is normally overseen by the person responsible for radiolabeling, which in most cases will be the radiopharmacist.

When a patient has been deemed eligible for treatment with ^{90}Y-ibritumomab tiuxetan, a treatment timetable is set up and coordinated through the nuclear medicine department, with the day of administration of ^{90}Y-ibritumomab tiuxetan being designated *Z-day*. The requirements for each treatment step (outlined in Figure 1) are summarized in Table 1.

The need for the team approach is underlined by the efficacy of this new type of treatment. Previous advances in radionuclide treatment with ^{131}I for thyroid cancer achieved only palliation of symptoms and occasional tumour shrinkage, but ^{90}Y-ibritumomab tiuxetan is the first potentially curative therapy of this type. Issues such as patient selection, logistics, and haematological safety necessitate the formation of a treatment team to ensure that the full potential of therapy is realized.

Experience with ^{90}Y-ibritumomab tiuxetan in the outpatient setting

A review of the first 18 months' experience with ^{90}Y-ibritumomab tiuxetan at a major UK institution after the product's introduction for routine clinical use has illustrated the success

that can be achieved when this type of immunotherapy is administered with a team approach.[21]

A total of 13 patients (six men and seven women aged 42 to 72 years) referred from six different institutions were treated by the nuclear medicine and haematology departments of The Royal Free Hospital in London between December 2003 and July 2005. Follow-up data were available for all 13 patients, of whom ten remained alive. Complete response to ^{90}Y-ibritumomab tiuxetan therapy was achieved in six patients (46%), with partial response or stable disease in two each (15%). Three (23%) had progressive disease: one of these individuals had large volume disease at the time of treatment, and all have since died. At the time of reporting, five patients maintained complete remission, while the sixth showed disease progression at 6 months. One of the partial responders developed progressive disease at 12 months. Stable disease has been maintained in two patients, and one awaits a decision on funding for a second cycle of treatment.

Bronchospasm was observed in one patient during intravenous infusion of ^{90}Y-ibritumomab tiuxetan, and a further patient reported nausea and vomiting 4 days after treatment. Severe pancytopenia was seen in three patients, two of whom needed blood or platelet transfusions.

These very encouraging data are in accordance with previously reported randomized trial findings in larger groups of patients with NHL. Witzig et al.[7] reported a 15% complete response rate (74% overall response) in 54 patients with rituximab-refractory follicular NHL, with median time to progression of 6.8 months in responders. Moreover, complete responses were achieved in 30% of 73 patients who received ^{90}Y-ibritumomab tiuxetan in a further study (overall response 80%).[8] Median time to progression was 11.2 months.

More recently, Wiseman and Witzig have reviewed long-term durable responses in 211 patients with relapsed, refractory, or transformed indolent CD20$^+$ B-cell NHL who were treated with ^{90}Y-ibritumomab tiuxetan.[22] Time to progression of at least 12 months was noted in 78 patients (37%) with median age 58 years. Two or more prior treatment regimens had been received by 59% of patients, and 37% had failed to respond to the therapy given immediately prior to ^{90}Y-ibritumomab tiuxetan. Notably, the median duration of response was 29.3 months, and an impressive 53.9 months in patients with an ongoing response to treatment (range to 82+ months). It is therefore clear that ^{90}Y-ibritumomab tiuxetan confers durable long-term responses in patients with relapsed or refractory NHL, and that failure of prior therapy does not preclude the achievement of a long-term response with this agent.

Conclusions

NHL is a highly radiosensitive malignant disease, and ^{90}Y labeled immunotherapy allows effective doses of radiation to be targeted via a monoclonal antibody. The advance represented by this type of treatment also presents logistic and organizational issues, however, and these are best addressed by the adoption of a multidisciplinary and collaborative approach to the patient. Data are now emerging to demonstrate the benefits that can be achieved when ^{90}Y labeled immunotherapy is administered by a clinical team focused around the nuclear medicine department.

Radiation precautions with ^{90}Y-ibritumomab tiuxetan are minimal, and do not require patients to make any significant changes to their daily routines. Therapy can be administered safely on an outpatient basis, and dosimetry is not necessary in the EU for patients with low-grade NHL. Radioimmuno-

therapy with ^{90}Y-ibritumomab tiuxetan represents a significant step forward for a group of patients with a disease considered difficult to treat effectively. It also provides new opportunities for optimizing therapeutic outcomes through the multidisciplinary approach to patient care, which draws on the combined experience of a team of healthcare professionals in order to maximize clinical benefit.

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