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Where does ^{90}Y-ibritumomab tiuxetan radioimmunotherapy fit? Selecting the right patient

Martin Bentz

II. Medizinische Klinik, Städtisches Klinikum Karlsruhe, Academic Teaching Hospital of the University of Freiburg, Germany

Corresponding author:
Martin Bentz
Email: martin.bentz@klinikum-karlsruhe.de

A B S T R A C T

Radioimmunotherapy (RIT) with targeted monoclonal antibodies that emit ionising radiation is an effective treatment modality for B-cell non-Hodgkin's lymphoma (NHL). RIT is designed to elicit anti-tumour effects through immunological and radiolytic mechanisms of action, and B-cell lymphomas are particularly ideal targets as they are inherently sensitive to radiation and express cell-surface antigens suitable for targeting. Yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin®), an anti-CD20 murine monoclonal antibody linked to the radionuclide ^{90}Y, is the only form of RIT commercially available in Europe. ^{90}Y-ibritumomab tiuxetan is licensed by the European Medicines Agency for therapy of adult patients with rituximab-relapsed or refractory CD20$^+$ follicular B-cell NHL. Treatment with ^{90}Y-ibritumomab tiuxetan comprises a short-course regimen that involves only a single dose of radioactive antibody. In a randomised phase III trial in rituximab-naïve patients with relapsed or refractory low-grade follicular or transformed CD20$^+$ NHL, the overall response rate to ^{90}Y-ibritumomab tiuxetan therapy was 80%, compared with 56% in patients treated with rituximab. ^{90}Y-ibritumomab tiuxetan has also demonstrated efficacy in patients with multiple prior therapies and bulky tumours, along with elderly patients. The use of ^{90}Y-ibritumomab tiuxetan is restricted to patients with <25% bone marrow infiltration by lymphoma cells, with reversible myelosuppression, manifesting clinically as cytopenias, as the dose-limiting toxicity. Because ^{90}Y is a pure β-emitter with a short half-life, clinical therapy with ^{90}Y-ibritumomab tiuxetan can be administered in an outpatient setting and patients released immediately afterwards unlike gamma radiation forms of RIT. Despite the nominal price of ^{90}Y-ibritumomab tiuxetan, a single dose comprises an entire course of treatment and, as a third-line therapy, offers favourable cost-effectiveness when compared with that of rituximab.

Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of related haematological neoplasms, predominantly of B-cell origin.[1] In contrast to most types of cancer, the incidence of NHL and its associated mortality have been steadily increasing over the past few decades, for reasons that remain to be fully elucidated.[2]

As a result of advances over the past 20 years, a range of treatments is currently available for the various types and stages of NHL, including external beam radiotherapy, high-dose chemotherapy, stem cell transplant and immunotherapy.[3] The

most recent development is the emergence of radioimmunotherapy (RIT) in the form of B-cell–targeted monoclonal antibodies conjugated with radioisotopes that emit ionising radiation. RIT is a particularly attractive approach for the treatment of B-cell lymphomas because these tumour types (a) are inherently more sensitive to radiation than many other tissues in the body and (b) express cell-surface antigens ideal for targeting.

Two major attractions of RIT are the targeted delivery of radioactive particles to the cancerous cells, and the *cross-fire effect*.[4] Targeted delivery of radiation should enhance the antitumour activity of a radioimmunoconjugate beyond that achieved by its equivalent unlabelled monoclonal antibody through mechanisms such as complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity, and apoptosis. Furthermore, the continuous delivery of radiation, compared with the intermittent doses administered by external-beam radiotherapy, may be more effective for preventing repair of radiation-damaged DNA in tumour cells.[4] The cross-fire effect, in which radiation from radioimmunoconjugate-bound tumour cells reaches those neighbouring cells without bound antibody, can kill cells in a tumour that either do not express the target antigen or which the monoclonal antibody cannot physically reach. Thus, the cross-fire effect may be particularly relevant for treating patients with tumours that are bulky and poorly vascularised, and/or have heterogeneous expression of target antigen.

Yttrium-90 (^{90}Y)-ibritumomab tiuxetan (Zevalin®) is currently the only RIT commercially available in Europe for therapy of NHL. ^{90}Y-ibritumomab tiuxetan was registered by the European Medicines Agency (EMEA) in January 2004 and is indicated for the treatment of adult patients with rituximab-relapsed or refractory CD20^{+} follicular B-cell NHL. ^{90}Y-ibritumomab tiuxetan had previously been licensed in the US in February 2002 for the treatment of patients with relapsed or refractory low-grade, follicular or transformed B-cell NHL, including those with rituximab-refractory follicular NHL.

As a consequence of its recent emergence as a treatment modality for NHL, haematologists and oncologists are challenged with managing the use of ^{90}Y-ibritumomab tiuxetan to achieve optimal outcomes for patients. In general, potential barriers to the use of RIT in the treatment of NHL include: the occurrence of myelosuppression; the costs of treatment and management of adverse events; the need for hospitalisation, dosimetry and shielding with some isotopes; and the risks of radiation exposure to healthcare workers, patients and their families. This paper will discuss how these general issues relate to the selection of NHL patients most suitable for treatment with ^{90}Y-labelled immunotherapy.

Physical characteristics and administration of ^{90}Y-ibritumomab tiuxetan

^{90}Y-ibritumomab tiuxetan consists of ibritumomab, a murine IgG1 monoclonal antibody directed against the CD20 antigen, covalently linked to tiuxetan, a metal-binding group that stably chelates the radioisotope ^{90}Y.[5] The CD20 antigen is expressed almost exclusively on the surface of mature B lymphocytes, including normal and malignant cells. Ibritumomab is the murine parent of the human chimeric monoclonal antibody rituximab, whose role in immunotherapy of B-cell NHL is now well established.[6] The ^{90}Y radionuclide has a half-life of only 64 hours and decays to zirconium-90 (^{90}Zr) in a process that releases high-energy , particles only. The cross-fire potential of ^{90}Y-ibritumomab tiuxetan stems from the effective path length of the emitted β particles, 5.3 mm in soft tissue,

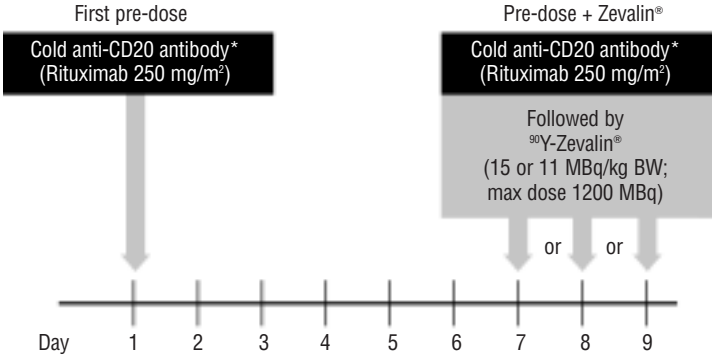

Figure 1: The ^{90}Y-ibritumomab tiuxetan therapeutic regimen. *Dose of cold anti-CD20 monoclonal antibody to optimize biodistribution of Zevalin® BW, body weight.

enabling their penetration of a tissue layer approximately 100 to 200 cells thick.[7]

Whereas iodine-131 (^{131}I), the other main radioisotope employed in RIT, emits penetrating gamma (γ) rays as well as , particles, ^{90}Y is a pure β-emitter, which offers safety advantages in terms of preparation and administration, and reduced risk of radiation exposure to individuals interacting with the patient.7 During preparation of radiolabelled immunoconjugate from *cold* ibritumomab tiuxetan, and subsequent administration of the labelled antibody, plastic and acrylic materials can be used for shielding healthcare workers and patients, as approximately 1 cm of such materials absorbs all emitted , particles.

Administration of ^{90}Y-ibritumomab tiuxetan

A course of treatment with ^{90}Y-ibritumomab tiuxetan spans 7 to 9 days (Figure 1). On day 1, a 10-minute intravenous (IV) infusion (*push*) of rituximab 250 mg/m^2 is administered to enhance the subsequent delivery of ^{90}Y-ibritumomab tiuxetan to tumour sites. By blocking the most accessible CD20 sites in peripheral blood, rituximab inhibits non-tumour-specific uptake of the immunoconjugate by the reticuloendothelial system. On day 7, 8 or 9, an identical repeat dose of rituximab is followed immediately by a 10-minute IV push of ^{90}Y-ibritumomab tiuxetan.[5] The dosage of ^{90}Y-ibritumomab tiuxetan is calculated on the basis of the patient's body weight and baseline platelet count.7 Dosages of 14.8 MBq/kg (0.4 mCi/kg) or 11.1 MBq/kg (0.3 mCi/kg) are administered to patients with pretreatment platelet counts of ≥150×10^9/L or 100-149×10^9/L, respectively, up to a maximum dose of 1,184 MBq (32 mCi). Dosimetry, via imaging with indium-111-labelled ibritumomab tiuxetan on day 1 following the rituximab dose, is generally not required for determining the therapeutic dose in patients meeting the eligibility criteria of <25% bone marrow infiltration by lymphoma cells.

The absence of penetrating γ-emissions associated with ^{90}Y-ibritumomab tiuxetan means that it can be routinely administered on an outpatient basis,[7] provided it is allowed by law. In contrast, treatment with ^{131}I-based RIT has traditionally necessitated hospitalisation, often in specialised, shielded facilities.4 Virtually all the radioactivity from a therapeutic dose of ^{90}Y-ibritumomab tiuxetan is retained within the body, with the main clearance mechanism of urinary excretion eliminating only approximately 7% of the administered dose over the following 7 days.[8] The risk of radiation exposure to family members and acquaintances of treated patients in the week following treatment with ^{90}Y-ibritumomab tiuxetan is in the range of background radiation.[9] Because the amount of radioactivity contained in bodily fluids of treated patients is very small, no additional measures beyond standard universal precautions for handling body fluids are needed to minimise exposure

Table 1: Key criteria for ^{90}Y-ibritumomab tiuxetan (Zevalin®) treatment (Zevalin Prescribing Information).

Inclusion
Adult patients with rituximab relapsed or refractory CD20$^+$ follicular B-cell NHL
≤25 bone marrow involvement by NHL
absolute neutrophil count (ANC) >1500/μL platelets >100,000/μL
Exclusion
Prior myeloablative therapy
Prior external-beam radiation to >25% of active bone marrow
Pregnancy and lactation
Platelet counts <100,000/μL, neutrophil counts <1500/μL
Children and adolescents under 18 years of age

to acquaintances of outpatients or hospital caregivers of individuals receiving inpatient treatment for medical reasons.[7] In contrast to patients who have been treated with ^{131}I-RIT, there is no need to determine activity limits or dose rate limits before discharge of patients treated with ^{90}Y-labelled immunotherapy.

Patient selection criteria

Patient selection is the key to achieving optimal outcomes with ^{90}Y-ibritumomab tiuxetan. Myelosuppression is the dose-limiting toxicity associated with ^{90}Y-ibritumomab tiuxetan and the risk of grade 4 cytopenias is proportional to the amount of lymphoma penetration in the bone marrow. These side effects would appear to be a consequence of the targeting of CD20$^+$ cells by ^{90}Y-ibritumomab tiuxetan; i.e. greater numbers of CD20$^+$ NHL cells within the marrow lead to more ^{90}Y-ibritumomab tiuxetan distributing into this tissue compartment and hence more associated myelotoxicity.[10] Consequently, patients with adequate bone marrow reserves and limited involvement of lymphoma with bone marrow are the optimal candidates for ^{90}Y-ibritumomab tiuxetan therapy. Selection of patients should, therefore, encompass the criteria detailed in Table 1. Based on an acceptable safety and efficacy profile demonstrated in elderly patients in clinical trials,[11,12] ^{90}Y-ibritumomab tiuxetan can be administered to patients aged ≥65 years.[5]

Tolerability of ^{90}Y-ibritumomab tiuxetan

An analysis of safety data pooled from five separate clinical trials involving 349 outpatients with relapsed, refractory, or transformed CD20$^+$ B-cell NHL has showed ^{90}Y-ibritumomab tiuxetan to be generally well tolerated.[10] Associated toxicity was primarily haematologic and reversible. Nadir blood counts occurred at 7 to 9 weeks following administration of radioactive dose and persisted for a further 1 to 4 weeks. Grade 4 neutropenia, thrombocytopenia, and anaemia occurred in 30%, 10%, and 4% of patients, respectively. Overall, 279 of 349 patients (80%) experienced non-haematologic adverse events associated with ^{90}Y-ibritumomab tiuxetan treatment, which were generally attributed to the rituximab component of the regimen. The majority of non-haematological adverse events were grade 1 or 2, with the most frequent being asthenia (35%), nausea (25%), chills (21%) and fever (13%) (Figure 2). Grade 3 or 4 non-haematologic adverse events occurred in 39 patients (11%). Grade 3 or 4 infection occurred in 16 patients (5%). To date, no infusion-related acute hypersensitivity reactions to ^{90}Y-ibritumomab tiuxetan itself have been documented,[13] although rare cases have been reported with rituximab infusion.

Efficacy of ^{90}Y-ibritumomab tiuxetan

Several clinical trials have demonstrated that ^{90}Y-ibritumomab tiuxetan is an effective therapy for NHL.[14-17] In a pivotal randomised phase

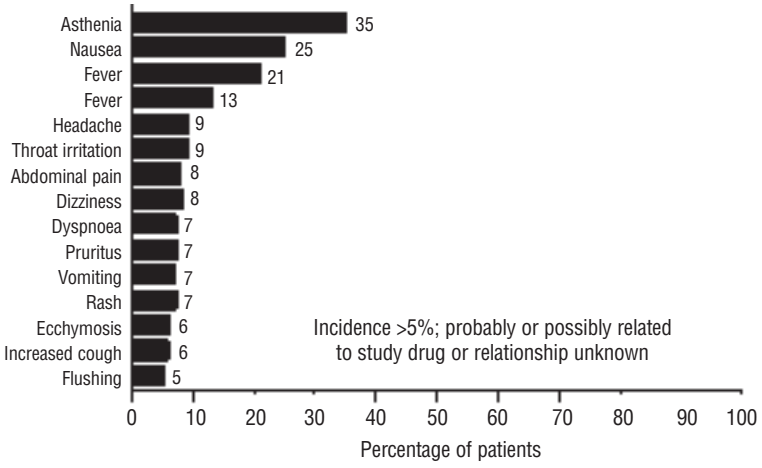

Figure 2: Non-haematologic adverse events following treatment with ^{90}Y-ibritumomab tiuxetan (n=349).[10]

III trial in 143 rituximab-naïve patients with relapsed or refractory low-grade follicular or transformed CD20$^+$ NHL, ^{90}Y-ibritumomab tiuxetan exhibited greater efficacy than rituximab.[15] In this study, overall response rate (ORR), the primary efficacy endpoint, was 80% in the ^{90}Y-ibritumomab tiuxetan-treated group, compared with 56% in the rituximab-treated group (p=0.002). Complete responses (CR) were achieved by 30% of the ^{90}Y-ibritumomab tiuxetan-treated group, compared with 16% of rituximab-treated patients (p=0.04). Although the study was not powered to detect differences in time-to-event variables, long-term follow-up at a median of 44 months revealed trends towards longer time-to-progression (TTP), duration of response, and time-to-next therapy in patients treated with ^{90}Y-ibritumomab tiuxetan.[17] In patients who achieved either a complete response (CR) or unconfirmed CR (CRu), the median TTP was 24.7 months in those treated with ^{90}Y-ibritumomab tiuxetan, compared with 13.2 months in rituximab recipients (p=0.41). The greatest differences in time-to-event variables were in patients with follicular lymphoma, who comprised 79% of the study population.

^{90}Y-ibritumomab tiuxetan has also demonstrated efficacy in rituximab-refractory patients. In a pivotal trial in 54 patients with follicular NHL who had failed prior therapy with rituximab, treatment with ^{90}Y-ibritumomab tiuxetan elicited an ORR of 74%, comprised of CR and partial response (PR) in 15% and 59% of patients, respectively.[16] Furthermore, in a phase II trial, the low dose of ^{90}Y-ibritumomab tiuxetan was shown to be effective in patients with mild thrombocytopenia.[14] In this study, 30 patients with advanced, relapsed or refractory, low-grade, follicular, or transformed B-cell NHL, and a platelet count of 100–149×10^9/L, received a dose of 11.1 MBq/kg (0.3 mCi/kg). The ORR was 83% and comprised 37% CR, 6.7% CRu and 40% PR.

An analysis of data pooled from several clinical trials has found that ^{90}Y-ibritumomab tiuxetan elicited long-term responses in patients with relapsed or refractory B-cell NHL.[18] Durable remission, defined as TTP of ≥12 months, was achieved by 37% of all patients, including 39% of patients with follicular lymphoma. Separate analyses of the pooled clinical trial data found that ^{90}Y-ibritumomab tiuxetan appeared most effective when administered early in the treatment continuum,[19] with the highest response rates achieved in second-line therapy.[20] Furthermore, in a study in 10 patients with previously untreated low-grade follicular lymphoma, therapy with ^{90}Y-ibritumomab tiuxetan

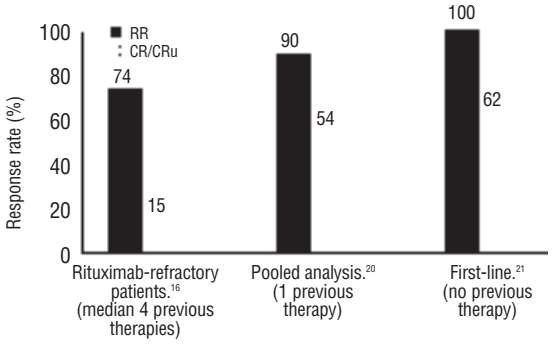

Figure 3: Response rates with ^{90}Y-ibritumomab tiuxetan in 3 studies with decreasing numbers of previous therapies.[16,20,21]

elicited an ORR of 100% (CR 62%, PR 38%),[21] indicating its potential as a first-line therapy. Response rates from the Witzig,[16] Emmanouilides,[20] and Sweetenham[21] studies shown in Figure 3 clearly demonstrate this relationship. Given the cross-fire effect of ^{90}Y-ibritumomab tiuxetan, its efficacy in treatment of bulky disease remains of great interest. In a multivariate analysis of pretreatment prognostic variables, the ORR in patients with bulky tumours (≥5 cm) was significantly lower than in patients with tumours <5 cm, but deemed acceptable at 68%.[22]

Cost-effectiveness of treatment with ^{90}Y-ibritumomab tiuxetan

Although information on the cost-effectiveness of RIT is limited, an economic analysis of ^{90}Y-ibritumomab tiuxetan therapy concluded that it appears to be a cost-effective third-line treatment strategy for follicular lymphoma, when compared with rituximab.[23] This study analysed data on drug price, related costs and clinical outcomes. Efficacy data derived from two published clinical trials with similar patient populations: the phase III trial of ^{90}Y-ibritumomab tiuxetan versus standard rituximab treatment (4 weekly doses),[17] and a phase II trial of prolonged rituximab therapy (eight weekly doses).[24] In both studies, treated patients had received a median of 2 prior chemotherapies. The mean total cost of treatment with ^{90}Y-ibritumomab tiuxetan was estimated to be approximately €17,332, which was higher than the estimated mean total cost of a standard 4-dose course of rituximab (€9,797) but lower than that of an eight-dose rituximab regimen (€19,993). In terms of health benefits, the average number of disease-free months per patient treated was highest for ^{90}Y-ibritumomab tiuxetan at 14.4 months followed by 11.4 months for the eight-dose rituximab regimen and 6.2 months for the four-dose rituximab regimen. Thus, on average, third-line treatment with ^{90}Y-ibritumomab tiuxetan instead of standard rituximab therapy would cost an additional €7,536 but would result in each patient experiencing an extra 8.2 disease-free months. Furthermore, ^{90}Y-ibritumomab tiuxetan therapy would not only be cheaper than extended treatment with rituximab but would also result in an extra 3 disease-free months. When the estimates of health benefit were combined with costs, the mean cost per month in remission was lowest for ^{90}Y-ibritumomab tiuxetan, estimated at €1,207, followed by €1,590 for four doses of rituximab therapy, and €1,760 for eight doses of rituximab (Table 2). Given that the cost-effectiveness of ^{90}Y-ibritumomab tiuxetan compared favourably with rituximab in this study, it is interesting that a cost-comparison of several treatments for follicular lymphoma, excluding ^{90}Y-ibritumomab tiuxetan, found that rituximab was less expensive than options such as stem cell transplant and IV fludarabine.[25]

Place of ^{90}Y-ibritumomab tiuxetan in therapy

Based on the combined evidence from clinical trials of ^{90}Y-ibritumomab tiuxetan and other RIT, a treatment algorithm for advanced

Table 2: Summary of inputs and outputs of cost-effectiveness analysis (€).

Input / output	*^{90}Y-ibritumomab tiuxetan*	*4-dose rituximab*	*8-dose rituximab*
Total mean per-patient costs of therapy	17332.63	9796.67	19993.26
Effectiveness in terms of *average disease-free months*	14.4	6.2	11.4
Effectiveness in terms of *average year in remissions*	1.20	0.51	0.95
Cost per *disease-free* month	1206.84	1590.37	1759.66
Cost per year in remission	14482.08	19084.42	21115.92

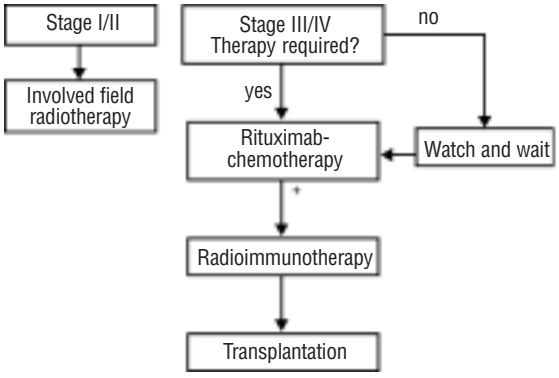

Figure 4: Proposed treatment algorithm for low-grade follicular lymphoma.[26]

low-grade follicular lymphoma has been proposed that integrates RIT between rituximab-based chemoimmunotherapy and stem cell transplant (Figure 4).[26] The optimal use of ^{90}Y-ibritumomab tiuxetan may prove to be as a first-line therapy.[21] Furthermore, several clinical trials are in progress analyzing the potential of ^{90}Y-ibritumomab tiuxetan as part of the conditioning regime in autologous transplantation for B-cell lymphomas.

Despite previous concern that the myelosuppression associated with RIT might have implications for the tolerability of subsequent treatments, patients who have previously been treated with ^{90}Y-ibritumomab tiuxetan do not appear to have an increased risk of adverse reactions to other NHL therapies.[27,28] As a consequence, patients who fail ^{90}Y-labelled immunotherapy can be candidates for other treatment modalities.

Conclusions

In order to place the clinical benefits of ^{90}Y-ibritumomab tiuxetan into context, it is important to note that patients in the target population have incurable disease, are symptomatic and require treatment. The ^{90}Y-ibritumomab tiuxetan treatment regimen is efficacious and well tolerated, and is convenient for both the NHL patient and health care workers, with therapy able to be completed within a week in an outpatient setting with minimal shielding requirements, and very few special precautions following discharge. The key to achieving optimal outcomes with ^{90}Y-ibritumomab tiuxetan is selecting the appropriate patient, namely those with limited involvement of disease with bone marrow and adequate marrow reserves. At this stage, the best time to use ^{90}Y-ibritumomab tiuxetan appears to be following first relapse. Overall, ^{90}Y-ibritumomab tiuxetan is a valuable addition to the therapeutic armamentarium for follicular NHL.

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