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Radioimmunotherapy for lymphoma – analysis of clinical trials and treatment algorithms

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Abstract

Ibritumomab, an ^{90}Yttrium (^{90}Y) labelled radioimmunoconjugate, is registered in Europe to treat follicular lymphomas. Its mode of action combines the selectivity of monoclonal antibodies with the efficiency of radiotherapy, making it a unique and useful therapeutic agent. This paper is for haemato-oncologists with a decent practice in lymphoma therapy, who have not yet used ibritumomab themselves. It summarizes clinical trials with radioimmunotherapy, indicating clinical situations where it may be specifically useful.

Key words: radioimmunotherapy, ibritumomab, ^{90}Y-ibritumomab tiuxetan (Zevalin), lymphoma

Introduction

Monoclonal antibodies have changed the treatment and prognosis of B cell Non Hodgkin Lymphoma (NHL). Until recently, it was generally accepted that "aggressive" lymphomas are potentially curable, while "indolent" lymphomas tend to have a progressive course with multiple relapses. Chemotherapy is effective against most dividing cells, but relatively inefficient against tumours with a low proliferation fraction. Classical radiotherapy has an established role in treating localized disease; however, in advanced clinical stages only total body irradiation (TBI), one of the transplant conditioning regimens, is applicable. Both monoclonal antibodies registered in Europe for treatment of B cell lymphomas (Rituximab and ibritumomab tiuxetan) are capable of damaging non proliferating tumour cells in patients with disseminated disease, enhancing the efficiency of chemotherapy and improving its results. Rituximab is a 'naked' monoclonal antibody exercising its action through complement mediated cytotoxicity (CMC), antibody dependent cellular cytotoxicity (ADCC) and synergism with chemotherapy. Conversely, immune mechanisms play a limited role in radiolabelled antibody (ibritumomab — tiuxetan), which is in fact a clever way to deliver an isotope to the clusters of lymphoma cells. While most haemato-oncologists know and widely use Rituximab, their experience with ibritumomab is rather limited. Radioimmunoconjugates have a different mode of action than "naked" monoclonal antibodies. Understanding their strength and limitations is essential in order to treat lymphoma patients most efficiently.

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Differences between radioimmunoconjugates and "naked" monoclonal antibodies

Rituximab, an anti CD 20 monoclonal antibody, was a true revolution in the treatment of B cell lymphomas, and chemoimmunotherapy became the 'golden standard' in diffuse large B cell lymphoma (DLBCL) [1] and follicular lymphoma (FL) [2]. Rituximab in maintenance therapy [3] in FL has recently been registered in Europe and its final approval in chronic lymphocytic leukaemia (CLL) is expected later this year. Chemoimmunotherapy improves the outcome of other subtypes of B cell malignancies (i.e. mantle cell lymphoma — MCL or marginal zone lymphoma — MZL); however, they are not frequent enough to allow proper registration studies.

So, is there any possibility for further improvement? Monoclonal antibodies are relatively big molecules, poorly penetrating grossly enlarged, partly fibrosed lymph nodes (Table 1). Hundreds of Rituximab particles have to be bound to the cellular surface to damage it. It works very well in "liquid tissues", like bone marrow (BM) or peripheral blood (PB), in which the cells are easily acces-

Table 1. Comparison between rituximab and ibritumomab tiuxetan

	Rituximab — "naked" MoAb	Ibritumomab tiuxetan — radioimmunoconjugate (^{90}Y)
Phase of drug development	Well established, based on several IIIrd phase clinical trials	The ideal place and dose schedules to be established
Dose	375 mg/ m^2, 4–8 doses, usually with concomitant chemotherapy or later as a maintenance	~ 1 mg/m^2, usually as a single dose, either in monotherapy or as a consolidation strategy
Mechanism of cellular damage	Complement mediated, ADCC, direct damage/apoptosis, synergism with chemotherapy	Radiotherapy
Haematological toxicity	Literally none	Dose limiting
Registration	FL & DLBCL chemoimmunotherapy, maintenance of FL	Rituximab relapsing or refractory FL or transformed FL, the only approved therapy for use after Rituximab failure
Most effective	In "liquid tissue": bone marrow and blood partly fibrosed	In moderately enlarged LN, even when enlarged,
Limitations	Large, fibrosed, poorly vascularised LN	Extensive BM (> 25%) or blood involvement
Why it should be used	Proven EFS and OS benefit a standard element of first line therapy of DLBCL/ FL/ MCL	Best palliation method in low-grade lymphoma patients failing several previous treatment lines If used early in the course of the disease, may prevent further relapses in FL, resulting in a survival plateau

MoAb — monoclonal antibodies; ADCC — antibody dependent cell mediated cytotoxicity; DLBCL — diffuse large cell lymphoma; EFS — event free survival; OS — overall survival; MCL — mantle cell lymphoma; BM — bone narrow; LN — lymph nodes

sible. A single ibritumomab-tiuxetan molecule with thousands of ^{90}Y atoms attached is capable of killing several adjacent cells (Figure 1). The average range of Beta particles emitted by ^{90}Y is about 5 mm, so it is effective in lymph nodes and tissue lymphoma infiltrates even if ibritumomab does not reach every cell. Its action is less selective than Rituximab: what is desired in lymph nodes is a disadvantage in bone marrow and haematological toxicity is a dose limiting factor [4]. Radioimmunotherapy (RIT) is contraindicated in patients with a significant bone marrow lymphoma infiltration (> 25%), BM hypoplasia or peripheral cytopenia (leukocytes < 1000/ul, blood platelets < 100,000/ul).

Haematological toxicity of RIT is due to stem cell damage. The period of cytopenia is postponed by 3-5 weeks and prolonged compared to what would have been expected after chemotherapy. Cytostatics either cause an immediate drop in the blood counts (if BM infiltration is important) or a gradual one, 7–10 days later, due to damage of the progenitor cells in the bone marrow (which under normal circumstances would proliferate and become mature cells at that time). Late onset cytopenia after RIT is caused by the direct damage of the early stem cells, usually quiescent, and consequently indestructible by standard dose chemotherapy. Its severity depends on lymphoma subtype, bone marrow involvement and preceding chemotherapy. Stem cell involvement is confirmed by clonogenic capacity studies [5]. Therefore, retreatment with ibritumomab, although possible, should be used with caution.

Rituximab is part of an established standard, and we have a lot of experience with its application. Ibritumomab is registered in Europe for Rituximab relapsing or refractory FL, and it is the only therapy approved for use after Rituximab failure.

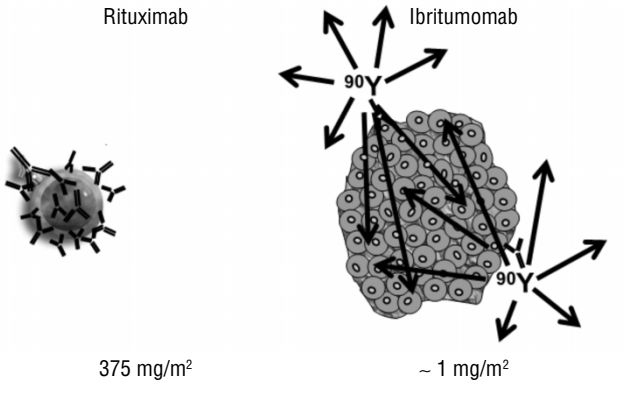

Figure 1. Comparison of the doses and mode of action of monoclonal antibodies: several particles of a "naked" antibody (Rituximab) are necessary to kill a single lymphoma cell, while one particle of radioimmunoconjugate (Ibritumomab tiuxetan) is potentially capable of killing several adjacent cells.

The differences between radioimmunotherapy and classical radiotherapy

Conventional involved field radiotherapy (IFRT) plays an important role in lymphoma treatment as a consolidative approach in localized diseases. An absorbed dose of 30–40 Gy delivered in 20–30 daily fractions is usually sufficient to deal with moderately enlarged lymph nodes within the irradiated areas. Poor vascularisation or heavy fibrosis of the tumour does not impair IFRT effectiveness. Extended field radiotherapy, like mantle field RT, has a limited capacity to deal with advanced disease and is generally abandoned because of the late side effects (increased risk of secondary solid tumours and cardiovascular accidents). Irradiating the whole body at the same time increases the efficiency but is possible only as an element of transplant conditioning procedure. Total body irradiation (TBI) is used in high-risk cases, when the efficiency counts more than late side effects. In TBI procedure 10–12 Gy delivered in 6 fractions, every 12 hours have a similar biological effect to 30 Gy IFRT (where the dose per fraction is smaller, and the longer time interval allows for cellular repair processes). In external beam radiotherapy, apart from some heart and lung shielding, the absorbed dose is equal in all irradiated areas.

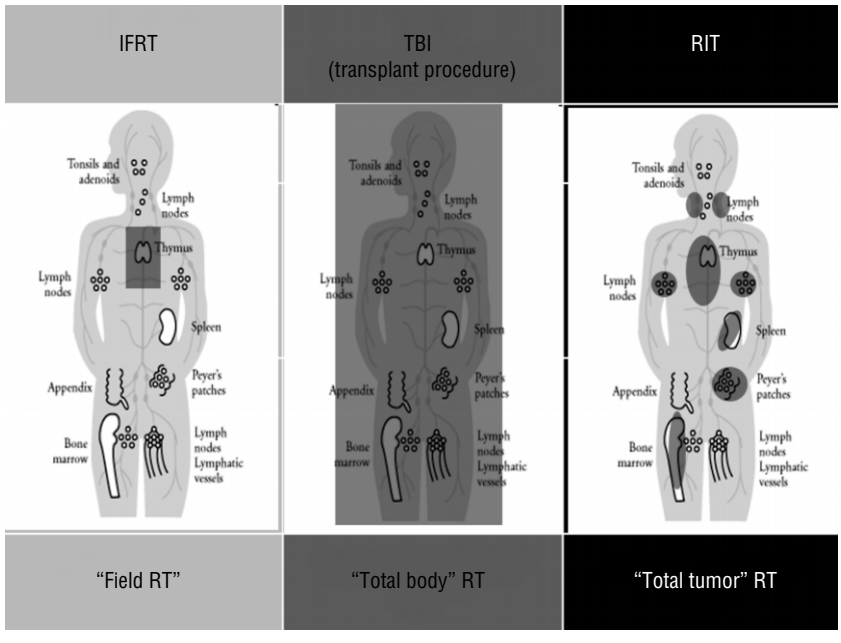

Figure 2. Different ways to deliver radiotherapy. IFRT — involved field radiotherapy; TBI — total body irradiation; RIT — radioimmunotherapy; RT — radiotherapy.

In RIT, radiolabelled monoclonal antibodies are administered intravenously. Ibritumomab is directed against a CD20 (cluster differentiation) molecule, present on most B lymphocytes. Its infusion is preceded by two doses of Rituximab (on day –7 and 0) to saturate all CD20 antigens on circulating B lymphocytes. After a short distribution phase, most radiolabelled antibodies are bound to the tumour. RIT is therefore a "total tumour radiotherapy", in which the absorbed dose is greater in the lymphoma and smaller in the tissue which is not infiltrated (Figure 2).

Both radioimmunotherapy and conventional external beam irradiation use radiation to destroy malignant cells. The effects of irradiation depend on the distribution and number of ionizations in a cell (which is related to the dose) and biological factors such as the phase of the cell cycle, degree of hydration or oxygenation. The cells are damaged either as a result of several "direct hits" of important structures (i.e. DNA, proteins) or due to the devastating effect of free radicals °OH, e^-_{aq}, °H and H_3O formed during water radiolysis. In RIT, the low dose rate of the radiation delivered constantly exerts a greater anti-tumour activity than an equivalent dose of conventional external beam radiation, in which the cells are able to repair the damage between subsequent fractions. Paradoxically, radioimmunotherapy may work better for tumours which we can measure in millimetres or centimetres than for micrometastases or single cells, as with fewer antibodies attached, the cross-fire effect is less prominent. On the other hand, we should be realistic about the ability of ibritumomab to deal with a very large tumour burden; most of the patients with enlarged lymph nodes exceeding 5–7 cm will have only a partial response.

Radioimmunotherapy in follicular lymphoma

Four registration clinical trials with RIT were performed in heavily pretreated low-grade lymphoma patients having failing several previous treatment lines. Two of them were in fact dose escalation studies, setting 14.8 MBq/kg (not exceeding 1200 MBq/patient) as a standard for patients without cytopenia [6] and 11.1 MBq/kg for those with mild thrombocytopenia [7]. The randomized comparison with Rituximab (n = 147) [8] and the trial in which ibritumomab was given to Rituximab refractory cases (defined as no response or progression in less than six months) [9] demonstrated a higher response rate after radioimmunotherapy. In four trials analyzed together (n = 211), there were 73–83% of responders who achieved 29–47% of complete regression of the disease or complete regression unconfirmed (CR/CRu). The average progression free survival (PFS) was nine months, and the projected five year overall survival (OS) was 53%. All patients with partial responses eventually progressed. PFS duration increased with the quality of response: from 12 months in responding patients to 23 months in CR/CRu cases. There were two papers published on the long time follow-up of these studies, identifying 37% (78/ /211 patients) with continuous remission at 12 months [10, 11]. A third of these patients had been treated with at least three previous therapies, and 37% of them had not responded to their last therapy. Median time to progression was 29 months and projected five year OS was 81%. Ibritumomab has an established role as the best possible palliation, effective also in cases refractory to previous treatments. Most responses are durable — longer than the time to progression after the preceding therapy. There is even a small subgroup of "long time survivors" with a plateau on the Kaplan Meier curve (about 20% of all patients, nearly 40% of those who were in constant CR after the first 12 months). Similar results were confirmed in 250 relapsing/refractory low grade lymphoma patients treated with tositumomab, an anti CD20 ^{131}Iodine labelled radioimmunoconjugate [12]. The integrated analysis of five clinical trials revealed a 47–68% response rate with 20–38% CR and 17% 5-year PFS. Similarly to ibritumomab, 32% (81/250 patients) who were in an on-going remission at 12 months had an excellent prognosis with median PFS of 45 months (Table 2, 3).

Table 2. Radioimmunotherapy as best palliation method in heavily pretreated, low-grade lymphoma patients (summary of nine clinical trials with nearly 500 patients included)

	Ibritumomab tiuxetan (^{90}Y)	Tositumomab (^{131}I)
Number of patients	211 patients included in 4 registration trials	250 patients included in 5 clinical trials
Responders	73–83% (medium PFS–12 months)	47–68% (medium PFS–12.9 months)
CR/CRu	29–47% (medium PFS–23 months)	20–38% (medium PFS–28 months)
At 5 years	53% OS, about 15% PFS	17% PFS

CR/CRu — complete remission or completed remission unconfirmed; PFS — progression free survival; OS — overall survival

Table 3. Long-lasting PFS in heavily pretreated, low-grade lymphoma patients after radioimmunotherapy

	Ibritumomab tiuxetan (^{90}Y)	Tositumomab (^{131}I)
Number of patients	78/211 — 37% of patients included in 4 registration trials	81/250 — 32% of patients included in 5 clinical trials
Group description	33% — after failing > 3 regimens 37% — refractory to previous therapy	33% — after failing > 4 regimens 37% — refractory to previous therapy
Medium PFS	28 months	46 months
At 5 years	81% OS, about 25% PFS	About 40% PFS

PFS — progression free survival; OS — overall survival

A complete response is the single most important condition for long time to progression (TTP). In one of the studies [13] durable responses were observed in 75% of patients with CR confirmed by a masked independent randomized radiology and oncology review (MIRROR) panel. We can increase the CR rate after radioimmunotherapy by: 1) applying it earlier, before the failure of several previous treatment lines, 2) using it as a consolidation strategy after the initial cytoreduction or 3) escalating its dose or retreating patients with partial regression (PR).

Several studies and comparisons [14] demonstrate the increased effectiveness of radioimmunotherapy if used earlier in the course of a disease (Figure 3). The CR/CRu rate is higher (51% vs. 21%, $p < 0.01$) and the time to progression increases (15.4 vs. 9.2 months, $p < 0.05$) in patients treated at first relapse compared with those who received two or more prior therapies [15]. First line ibritumomab with further Rituximab maintenance in advanced stage FL at diagnosis was explored by Sweetenham et al. [100% response rate (RR), 60% CR, n = 10] [16]. A larger study (n = 76) with a longer follow-up was done with tositumomab [17]: RR and CR rates were 95% and 75% respectively; 59% of patients were in a continuous CR at five years with projected medium progression free survival of 6.1 years.

Results were even more encouraging when ibritumomab was used to consolidate an initial response after abbreviated cyclophosphamide, doxorubicin, vincristine, prednisolone-rituximab (CHOP-R) [18] or fludarabine, mitoxantrone (FM) [19] chemotherapy. To investigate this matter further, a phase III study was completed, in which 360 patients with a CR/PR after initial cyclophosphamide, vincristine, prednisolone (CVP) or cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy were randomized to RIT or observation [20]. The final analysis is expected this year during the American Society of Hematology (ASH) meeting.

Hematologic toxicity is a dose-limiting factor. Radioimmunotherapy is not offered more than twice to the same patient. Escalating the dose requires a stem cell support (transplant conditioning regimens, sometimes applied in transformed follicular lymphoma, are described further in the DLBCL section).

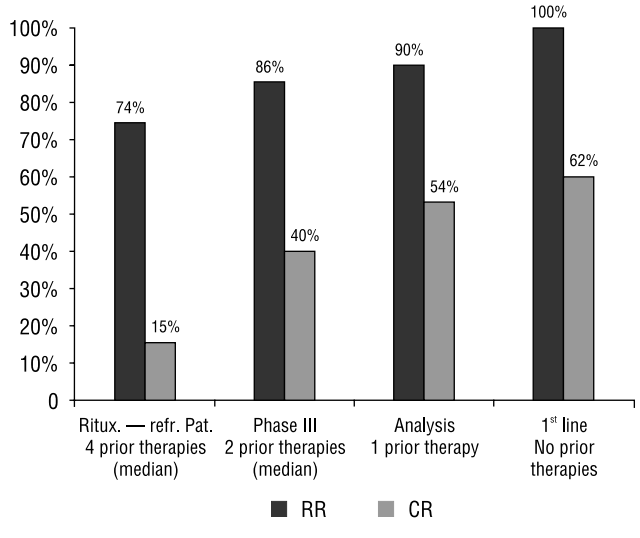

Figure 3. Response rate to radioimmunotherapy in subsequent treatment lines [9, 10, 14, 16]. RR — response rate; CR — complete regression.

German Group has recently published an FL therapy algorithm including RIT [21]. Ibritumomab is recommended as the first line treatment in patients not eligible to chemotherapy and at the first relapse in low risk elderly patients. In first relapse of young patients or high-risk elderly patients, radioimmunotherapy is one of the options following initial chemoimmunotherapy.

Radioimmunotherapy in mantle cell lymphoma (MCL)

The first results of RIT in relapsed patients with a high tumour burden were discouraging, with an average PFS of 3–5 months [22, 23]. Although cytoreduction with chemoimmunotherapy improves

the response rate (RR) and prolongs PFS to 7.5 months [24], ibritumomab is not spectacularly effective in relapsed MCL patients. There are currently two clinical trials with RIT used as a consolidation of first line chemoimmunotherapy in patients unsuitable for dose escalation or stem cell transplants: The Eastern Cooperative Oncology Group (ECOG) study with 4 cycles of cyclophosphamide, doxorubicin, vincristine, prednisolone-rituximab (CHOP-R) regimen [25] and a Polish Lymphoma Research Group (PLRG) study with 3–6 cycles of fludarabine, cyclophosphamide mitoxantrone-rituximab (FCM-R) [26]. The preliminary results suggest a very good response rate (84–100%) with a high proportion of CR (45–85%). Progression free survival rates (PFS) are yet to be determined, but the median was not reached after two years of follow-up. If it is confirmed by longer follow-up, radioimmunotherapy consolidation may become a standard consolidation in elderly MCL patients.

Radioimmunotherapy in diffuse large cell lymphomas (DLBCL)

In DLBCL and transformed FL, ibritumomab monotherapy shows only moderate activity in patients treated earlier with chemoimmunotherapy (20% RR, 4% CR) [27]. At present it is used as a consolidation strategy. In elderly patients it may improve the first line therapy efficacy and reduce its side effects; shortening chemoimmunotherapy reduces the risk of cardiac toxicity risk due to anthracyclines. This approach was initially investigated by Hamlin [28] and Morchauser [29] in first line and relapsed patients, respectively. A randomized comparison which will eventually determine the RIT role of ibritumomab as a consolidation therapy in Aggressive Lymphoma (ZEAL study) in first CR/CRu is currently ongoing.

Dose escalation and stem cell transplants is the treatment of choice in relapsed DLBCL patients and at diagnosis high risk cases at. Ibritumomab may be used as a transplant conditioning regimen in three possible ways:

— instead of TBI, by escalating RIT dose [30];
— combining a standard ibritumomab dose with a carmustine, cytarabine, etoposide, melphalan (BEAM) or cyclophosphamide, carmustine, vinblastine (CBV) chemotherapy [31];
— using both escalating RIT dose and chemotherapy conditioning [32]. Combined conditioning strategies may enhance an anti-lymphoma effect. Although an escalated dose of radioimmunotherapy requires individual dosimetry, it is feasible for elderly patients and allows autologous transplants to be performed as outpatient procedures.

Summary

It is not yet proven that low grade lymphomas may be cured with radioimmunotherapy. Ibritumomab is, however, the best possible palliation in cases relapsing or refractory to several previous chemotherapy lines. Most patients respond, and some of them are a true "long responders" with an evident plateau on survival curves. The proportion of long progression free survivals increases when radioimmunotherapy is applied earlier in the disease course, optimally in the first relapse. Initial cytoreduction is always worth considering in patients with a very large tumour burden, although possibly is not necessary for those with lymph nodes < 5–7 cm in diameter. The role of upfront radioimmunotherapy (i.e. as a consolidation of first line treatment) has to be confirmed in the phase III trials. Most clinical studies were performed in FL patients, although radioimmunotherapy maybe equally efficient in other B-cell low-grade lymphomas.

In aggressive lymphomas, RIT can be used as a consolidation strategy: either as an element of transplant conditioning regimen (in high-risk cases) or in monotherapy (in elderly patients).

Haematological toxicity is the only important side effect of ibritumomab, and the quality of life is superior compared to chemotherapy. In pharmacy-economic analysis, RIT is fully justified when compared to other monoclonal antibodies.

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