Radioimmunotherapy of Heavily Pre-treated, Non-Hodgkin’s Lymphoma Patients: Efficacy and Safety in a Routine Setting

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Abstract. The aim of the present study was to assess efficacy and safety of radio-immunotherapy with Zevalin® (RIT-Z) in heavily pre-treated, rituximab-refractory patients. Patients and Methods: We studied 12 patients with indolent lymphoma and 7 with aggressive lymphoma. The median number of prior rituximab-containing treatments was 2; overall, 3 therapies had been previously given. Ten patients received RIT-Z as salvage therapy, 9 at high risk of relapse received RIT-Z as consolidation. Staging and follow-up were obtained by positron-emission tomography. Outcomes assessed were failure-free survival (FFS) and time to next treatment (TTNT). Results: Overall FFS and TTNT were 5 and 11 months, respectively; median follow-up 13 months. Major findings were i) no long-term remissions observed in 7 patients who had not responded to their most recent therapy and ii) lack of association between any pre-therapy variables analysed and outcomes. Different subgroups showed no difference in terms of toxicity. Conclusion: We encourage the use of RIT-Z as a consolidation for pre-treated patients with both indolent and aggressive lymphoma.

The use of monoclonal antibodies (MoAB) directed against B-cell membranes has changed the management of patients with non-Hodgkin’s lymphomas (NHL). Since the late 1990s, the chimerical anti-CD20 antibody rituximab has been included in induction as well in salvage chemotherapeutic protocols for indolent and aggressive lymphomas with an improvement in survival (1). In the last few years, two different MoAB, ibritumomab and tositumomab, were labelled with $^{90}$Y and $^{131}$I, respectively, and approved by the U.S. Food and Drug Administration (FDA) for radioimmunotherapy (RIT) of refractory/relapsing low grade, follicular (FL) or transformed B-cell lymphomas (2-4). Both RIT agents have shown comparable efficacy and toxicological profiles when used as a single therapy (5, 6). However, the only agent available in Europe is ibritumomab, a murine anti-CD20 MoAB directed against the same epitope as rituximab, linked to $^{90}$Y by means of the chelator tiuxetan (Zevalin®) (7). Zevalin® has lead to 70-80% overall response rates (ORR) and 30-40% durable complete confirmed or unconfirmed responses (CR/CRu) in patients with indolent NHL (2, 3, 8).

The addition of β- emitting radioisotopes, such as $^{90}$Y and $^{131}$I, to anti-CD20 antibodies has proven to be an effective tool for treatment, by increasing the therapeutic efficacy of MoAB alone (9-10). Indeed, the proposed ‘cross-fire effect’, due to beta particles, seems to overcome some of the mechanisms underlying resistance to MoAB. Nevertheless, the efficacy of RIT in patients previously treated with rituximab-containing therapeutic regimens has not been extensively studied.

Due to its relative lack of toxicity, administration of RIT is particularly suitable for older or heavily pre-treated patients: haematological toxicity is usually transient and promptly recovers after 8 to 12 weeks. To date, no non-haematological toxicities have been observed at standard doses (11-13).

RIT with Zevalin® (RIT-Z) has been also tested in histologically aggressive B-cell lymphomas. Myeloablative therapies followed by autologous stem cell infusion (ASCT) are the best choice for patients with aggressive lymphomas at first relapse who are sensitive to salvage chemotherapy (14). Refractory patients with diffuse large B-cell lymphoma (DLBCL) not suitable for ASCT have been treated with RIT-Z in a large trial, resulting in ~50% ORR and 25-40% CR/CRu rates in patients without prior exposure to rituximab. Lower response rates (19% ORR and 12% CR/CRu) were associated with prior exposure to rituximab (15). In former years, patients were often assigned to RIT late in their treatment course. Recently, long-term follow-up of registration trials demonstrated an increased efficacy with its earlier utilization and the rationale for a consolidation
therapy with Zevalin® has already been tested in patients with indolent lymphoma (16-19). We hypothesized that patients with aggressive lymphoma may also benefit from an earlier administration of RIT therefore, in our institution, RIT-Z is frequently administered as a consolidation therapy in FL as well as in DLBCL patients, even in cases of previous subsequent relapses. To our knowledge, no previous studies report on this approach.

With this study, we analysed the variables affecting efficacy of RIT-Z in a population of patients who had been all pre-treated with rituximab-containing chemotherapy regimens with the following aims: i) to verify whether patients who failed to respond to immediately prior therapy maintain the likelihood of a complete and durable response, as affirmed by long-term follow-up of clinical trials (8) and ii) to address the role of RIT consolidation in patients with indolent as well as in those with aggressive lymphoma. Toxicity of RIT in patients considered at high risk for severe haematological toxicity was a secondary end-point.

Patients and Methods

Patient eligibility and RIT administration. All consecutive patients, not included in clinical trials, assigned to RIT at Sant’ Andrea University Hospital of Rome between July 2006 and May 2008 were retrospectively analysed. Patients were assigned to RIT-Z in any of the following cases: i) FL with refractory/relapsed disease after at least one rituximab-containing chemotherapy regimen; ii) chemosensitive relapse of DLBCL or FL unsuitable for ASCT; iii) DLBCL or FL with resistant relapse. Platelet count ≥100,000/μl and neutrophil ≥1,500/μl were required for RIT. Pre-therapy staging of lymphoma was obtained by combining clinical, anatomical and metabolic findings. Pre-RIT staging included: positron-emission tomography (PET/CT) scan and/or a contrast enhanced CT within 1.5 month prior to RIT, bone marrow trephine biopsies, physical examination, peripheral blood cell counts.

Ibritumomab tiuxetan was labelled with 90Y according to the specifications of the producer. The labelling yield was assessed with silica gel Instant Thin Layer Chromatography (ITLC) (Pal Life Sciences, USA) in saline and analysed with Chromatoscan (BioRad, USA). More than 95% labelling yield was accepted as appropriate. Therapeutic doses of 90Y-Zevalin® were chosen according to patient platelet counts and body weight.

Data collection. For all patients included, the following pre-therapy variables were recorded and analysed: age at RIT, time from diagnosis to RIT, time from the beginning of most recent therapy to RIT, time from the end of the most recent therapy to RIT, number of previous therapies, histological grade and stage at RIT, response to most recent therapy. External beam radiotherapies (EBRT) were not counted in the number of prior therapies. As regards sensitivity to prior therapies, patients who received RIT-Z in complete response (CR) or partial response (PR), i.e. the so called ‘sensitive relapses’, and untreated relapses which reached a CR after their last therapy were categorized as ‘responders’ to the most recent therapy. Patients with stable disease (SD) or progressive disease (PD), i.e. ‘resistant relapses’ after salvage therapy, were classified as ‘non-responders’.

Efficacy assessment. Response to RIT-Z was evaluated three months after treatment by means of PET/CT, according to the criteria recently developed by the consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma (20). Although the patients had been prescribed RIT-Z for routine treatment and not for a research protocol, two nuclear physicians independently assessed the PET scans and the PET-based restaging was assessed with consensus. Responses were definitively established by the referring haematologists, according to the criteria revised by Cheson and colleagues (21). Two parameters were used to assess long-term efficacy of RIT-Z: failure-free survival (FFS) and time to next treatment (TTNT). FFS was determined from the date of RIT-Z until the date of any documented adverse event (i.e. relapse, progression, next treatment or death). Patients without any adverse event were censored at the date of the last follow-up. The achievement of only partial response (PR) was considered to be a failure since all such patients underwent further antilymphoma treatment within three/four months from response evaluation. TTNT was calculated from the date of RIT-Z to the beginning of a subsequent treatment for lymphoma.

Toxicity analysis. Haematological toxicity was a secondary endpoint of this retrospective study and was assessed from laboratory values obtained within the first 12 weeks after RIT-Z. Duration of thrombocytopenia, neutropenia and anaemia were measured from the date of the first laboratory value in grade 3 or 4 toxicity to the date of the first value in grade 1 or 2. All adverse events, growth factor and/or erythropoietin utilization, platelets and/or blood transfusions, were assessed from clinical reports. Subgroup of patients considered at high risk for haematological toxicity were analysed separately.

Statistical analysis. SAS version 8.1 for Windows (SAS Institute, Cary, NC, USA) was used to analyse the data. Variables on study were analysed in univariate as well as in bivariate models for efficacy. In univariate analysis, Kaplan-Meier and Cox regression methods were used in case of dichotomised and continuous variables, respectively. Bivariate analyses were performed with Cox regression method. P-values <0.05 were considered statistically significant.

Results

Patient characteristics. We treated 19 patients: 12 with FL (8 grade 2, 4 grade 3a) and 7 with de novo or transformed FL 3b (n=2) or DLBCL (n=5). Patient characteristics are summarised in Table I. Seven patients were females and 12 were males. Their median age was 59 years (range 33-76), 9 were older than 60 years, 10 younger. The median time from diagnosis was 40 months (range 5-252). The median time from the beginning and from the end of the most recent therapy was 6 months (range 2-25), and 2 months (range 1-18), respectively.

The median number of previous lines of therapy was 3 (range 1-11). All patients had received prior anthracyclines, all had prior alkylators, 7 had been treated with purine analogues. The median number of prior rituximab-containing treatments was 2 (range 1-4). Four patients (2 grade 2 FL, 1 grade 3b FL, 1 DLBCL) had previously undergone a
myeloablative therapy followed by ASCT; 5 had prior EBRT; and 3 had received both ASCT and EBRT.

PET/CT was performed before RIT-Z to evaluate response to salvage therapy in 18 out of 19 patients: PET/CT was performed immediately before RIT-Z in 13 patients, and during salvage treatment in 5. One patient had only contrast-enhanced CT scan before PET. Bone marrow biopsies were performed in 14/19 patients prior to RIT-Z. The remaining 5 patients had no history of bone marrow involvement, thus biopsies were not mandatory.

At time of RIT-Z, 5 patients were stage 4, 2 patients were stage 3, 4 were stage 2, and 8 patients, who were complete responders to salvage therapy, had no evidence of disease. Due to the necessity to dichotomize patients with or without evidence of disease at time of RIT-Z, stage was deemed to add no additional information to subsequent analysis with respect to the variable ‘response to the most recent therapy’.

According to their response to their most recent therapy, 12 patients were classified as responders [8 sensitive relapses in CR (5 grade 2 FL, 1 grade 3b FL, 2 DLBCL), 1 partial response (1 DLBCL), 3 untreated relapses (2 grade 2 FL and 1 grade 3a FL)]; and 7 as non-responders [7 progressive diseases (1 grade 2 FL, 3 grade 3a FL, 1 grade 3b FL and 2 DLBCL)]. The median number of previous therapeutic lines was 3 (range 2-4) in sensitive relapses. All patients were unsuitable for ASCT. All patients had a PET/CT 3 months after RIT-Z to evaluate response.

Response evaluation. Response to RIT-Z was evaluated 3 months later by PET/CT in 17 out of 19 patients. Two patients with DLBCL died without undergoing post-therapy PET/CT. Overall, response evaluation gave the following results: 9 CR, 1 PR and 9 PD. All sensitive relapses, who underwent RIT-Z in CR, were scored as CR; the three patients with untreated relapse experienced a CR, PR and PD, respectively. In the patient with PD, new sites developed, although disease had disappeared in previous sites. All patients with resistant relapse progressed.

Survival analysis. Seventeen patients are still alive after a median follow up of 13 months (range 2 to 29 months). One patient died 2 months after RIT-Z during hospitalization for severe diarrhoea and fever. Although autopsy was not performed, the death was probably attributable to haematological toxicity in a patient with progressive disease with two bulky pulmonary lesions and multiple hepatic localizations. In another patient, the progression was clinically assessed and a subsequent treatment was started 20 days later; death occurred 4 months after RIT-Z.

The median FFS and TTNT were 5 and 11 months, respectively, with 42% (95% CI 0.19905-0.64306) and 44% (95% CI 0.18478-0.68704) projections at 1 year, respectively. Kaplan-Meier curve of FFS is shown in Figure 1. Continuous variables such as age at RIT-Z, time from diagnosis to RIT-Z, time from the beginning of most recent therapy to RIT-Z, and time from the end of most recent therapy to RIT-Z did not significantly affect FFS and TTNT (data not shown).

Although non significant, a trend was observed for the number of previous therapies in predicting both FFS (HR 1.25; 95% CI 0.98-1.60 p=0.063) and TTNT (HR 1.35; 95% CI 0.987-1.848 p=0.06).
One-year FFS was not significantly different (p=0.58) in patients with indolent and aggressive lymphoma (See Figure 2); 41.7% (95% CI 0.14-0.70) vs. 42.8% (95% CI 0.06-0.80). The one-year probability of being treatment free (TTNT) was not significantly different in the same subgroups of patients (p=0.64); 41.5% (95% CI 0.11-0.72) vs. 51% (95% CI 0.11-0.91).

In patients who had responded to their most recent therapy, the one-year FFS was 67% (95% CI 0.40-0.93; p=0.0003, log rank test) vs. 0% in non responders. Kaplan-Meier-estimated median FFS was 14 and 3 months, respectively (See Figure 3).

The one-year TTNT was 64% (95% CI 0.36-0.93; p=0.007, log rank test) vs. 0% in the same subgroups of patients, respectively. Kaplan-Meier-estimated median TTNT was not yet reached in responders and was 6 months in non responders. In non-responders to the most recent therapy, FFS and TTNT dropped to 0% after 4.5 and 10 months, respectively.

At a subsequent pivotal analysis, the variable ‘response to most recent therapy’ was tested in multiple bivariate models together with all other pre-therapy characteristics, always retaining its independent and statistically significant prognostic value (data not shown). Notably, in the bivariate model, together with histological grade, response to most recent therapy retained its statistical significance in predicting both FFS (HR 11.5; 95% CI 2.5-51.7; p=0.0014) and TTNT (HR 8.4; 95% CI 1.6-43.8; p=0.011). The proportionality hazards assumption was investigated by graphic analysis of Schoenfeld residuals. However, this analysis did not allow us to obtain any useful indications.

**Haematological toxicity.** Seventeen patients had at least one weekly complete blood count (complete blood count/differential/platelets) for the first six weeks after RIT-Z and at least one every two weeks for the subsequent six weeks.

Two patients were followed up with laboratory tests until subsequent anticancer treatment (20 days after RIT-Z) and until death (2 months after RIT-Z), respectively. As mentioned above, death was presumably due to haematological toxicity in the patient with a severe underlying progressive disease. This patient had neither received prior purine analogues nor ASCT.

Grade 1-2 thrombocytopenia occurred in 11 patients, while 8 patients experienced grade 3-4 thrombocytopenia, 3 of whom required platelet transfusions. Ten patients had grade 1-2 neutropenia, while grade 3-4 neutropenia occurred in 9 patients, 4 of whom required the administration of colony-stimulating factors (CSF).

Only mild anaemia (grade 1-2) was observed. Median nadirs of platelet and neutrophil counts were reached 35 and 41 days after RIT-Z, respectively. Median durations of severe (grade 3-4) thrombocytopenia and neutropenia were 20 and 35 days, respectively. All grade 3 or 4 toxicities had recovered to grade 1 or 2 within 12 weeks after RIT-Z.

Grade 3-4 thrombocytopenia and/or neutropenia occurred in 4 patients with prior purine analogues (3 patients with both grade 3-4 neutropenia and thrombocytopenia, and 1 with only grade 3 neutropenia) and in 8 patients without prior purine analogues (3 patients with grade 3-4 thrombocytopenia, 3 with grade 3-4 neutropenia and 2 with both). In the subgroup treated previously with purine analogues, two patients with grade 4 thrombocytopenia and neutropenia required CSF administration, accompanied by platelet transfusion in one case. Two patients required both CSF and platelet transfusions in the subgroup of patients not previously treated with purine analogues.

Of the four patients treated previously with ASCT, one had grade 4 neutropenia and thrombocytopenia requiring CSF and
platelet transfusions, one had only a grade 3 neutropenia, and two had only grade 2 neutropenia and thrombocytopenia. Notably, one patient who had been treated previously with both ASCT and purine analogues had only grade 2 neutropenia and thrombocytopenia. This patient underwent a successful allogenic transplantation 28 months after RIT-Z.

Thirteen patients who had received the full dose (0.4 mCi/Kg), and 6 patients who had received the reduced dose (0.3 mCi/Kg) were analysed separately. Only 1 out of 7 patients treated previously with purine analogues received the reduced dose; all 4 patients who had undergone ASCT received the full dose. In patients receiving the full dose, grade 3-4 thrombocytopenia and neutropenia occurred in 5 and 7, respectively (concomitant grade 3-4 thrombocytopenia and neutropenia in 4 patients). In patients receiving the reduced dose, grade 3-4 thrombocytopenia and neutropenia occurred in 3 and 2, respectively (concomitant grade 3-4 thrombocytopenia and neutropenia in one patient only).

Discussion

The present study reports on a single centre experience of RIT-Z, administered to patients with indolent follicular as well as with aggressive DLBCL. To date, few data about the efficacy of RIT-Z in a routine setting have been available (6). In our study, we included patients with refractory/relapsed disease after at least one rituximab-containing chemotherapy, untreated relapse, resistant relapse or chemosensitive relapse unsuitable for ASCT. In the latter subgroup, RIT-Z was therefore administered as a consolidation therapy. The role of RIT-Z administered as a consolidation of a first-line therapy has recently been investigated by the large Follicular Indolent Lymphoma (FIT) Trial showing a significant prolongation of progression free survival (16). It is noteworthy that whereas the FIT trial was designed for patients who had received only one prior therapy, we performed consolidation with RIT-Z in heavily pre-treated patients with indolent as well as aggressive lymphoma. To our knowledge, there are no other published studies that address the role of RIT consolidation in these categories. Seven out of eight patients received the consolidation RIT after more than one (2 to 4) previous lines of therapy. Another patient, with a diagnosis of DLBCL, received RIT-Z to consolidate a PR lasting more than 1 month after first-line treatment.

The first finding of our work was the strong and statistically significant association between sensitivity to the most recent therapy and outcomes. This association was independent of any other tested variables, as shown by multiple bivariate Cox regression analyses. A longer survival in the subgroup of responders was predictable, most of those patients being treated in CR after salvage therapy. Conversely, it was somehow unexpected that in the eight non-responders, the FFS never exceeded 4.5 months.

These results are in agreement with those of an international bi-centre experience, recently published in an abstract form (21). In contrast, they failed to confirm one of the breakthroughs of the Zevalin® clinical registration trials. Taken together, these trials obtained 37% of long-term responses (LTR), defined as CR lasting more than 12 months; according to the authors, “whether the patient had responded to his or her last previous therapy had no effect on the likelihood of an LTR”, the achievement of a CR/CRu being the best predictor of an LTR (8). In our study, no complete and durable responses were achieved in patients who were refractory to their most recent therapy.

The disagreement between our observations and the results of the clinical registration trials may be due to the characteristics of our cohort and to the systematic use of PET/CT. The systematic use of PET/CT could have influenced our results in terms of a more confident, although strict, pre- and post-therapy evaluation of the disease, partially explaining the high failure rates found in our population. In this analysis, indeed, patients were staged and re-staged on the basis of PET/CT, which has higher positive and negative predictive values than CT alone, used to assess response in past clinical trials. As regards the characteristics of our cohort, all patients studied had received rituximab as part of their previous chemotherapeutic regimes. With respect to what has so far been published about Zevalin®, this is relatively uncommon. As a matter of fact, all the clinical trials that have been carried out failed to provide definitive results about the efficacy of Zevalin® in patients who were previously heavily pre-treated with MoAb. Only 57 out of 211 refractory patients enrolled in the registration trial had previously received rituximab, whereas the recently published FIT trial enrolled only 27 and 32 patients who had been treated with rituximab-containing regimens in the treatment and control arm, respectively (13.2% and 15.6% of the overall population). As regards aggressive lymphomas, in the largest published study, all patients included had previously received only one therapeutic regimen, and the ‘rituximab-refractory’ subgroup included only 28 patients (25% of the overall population). Among these 28 patients, efficacy of Zevalin® was poor (15).

The second peculiarity of this cohort is, in our opinion, the absence of strict exclusion criteria. Patients were not excluded from RIT if they were rapidly progressive, nor if they had concluded their most recent treatment within the last month before RIT-Z. A third difference from other series was the high median number of prior therapeutic lines and the presence of patients who had had prior ASCT (21%), prior EBRT (26%) or both (16%), which have often been exclusion criteria (23, 24).

As a final remark, we believe that the similar short-term outcome of patients with indolent and high-grade lymphoma needs to be discussed. In fact, the histological grade was not related to FFS or TTNT. Of the four aggressive lymphoma
patients treated with RIT-Z as consolidation, one had PET/CT-documented focal relapse seventeen months after RIT-Z and two are still in complete remission after nineteen and nine months, respectively. Only the patient with PR after first-line therapy relapsed after three months. Thus, RIT-Z can be proposed as a consolidation of chemosensitive aggressive lymphomas.

Haematological toxicity has been also investigated in this study. In patients considered at high risk, no significant increased haematological toxicity was observed, although the relatively short follow-up was not sufficient to determine the incidence of secondary leukaemias. In particular, full doses of RIT-Z were well tolerated by patients who had had prior ASCT and prior purine analogues.

In conclusion, our study showed response to the most recent therapy to be the strongest predictor of RIT-Z failure, irrespective of tumour biological aggressiveness. We are aware that the diverse population studied, the small sample and number of events make it difficult to draw definitive conclusions. However, our preliminary findings identify patients with both FL and DLBCL chemosensitive relapses and FL untreated relapses as the preferred candidates for RIT-Z. Patients with resistant relapse are unlikely to experience complete and durable responses. In these patients, the indication for RIT-Z might be questionable.

Consolidation with RIT-Z for indolent as well as aggressive lymphoma is a promising therapy, leading in most cases to long failure-free intervals, even in cases of prior relapses. Nevertheless, the lack of a control group does not allow definitive conclusions to be drawn as to an additive benefit of RIT-Z with respect to salvage therapy alone.

References


