Cancer is a pathological condition in which an assemblage of cells display uncontrolled growth, invasion, and sometimes metastasis. Journal of Cancer Science & Therapy aims to provide most authentic and complete source of information on current developments in the field of cancer science and therapies and intends to exploit the scientific benefit to cancer patients flowing from public/private funded cancer research globally.

The Journal of Cancer Science & Therapy (JCST) is an Open Access publication which encompasses a high quality of original research pertaining human and animal related cancer diseases, and made available to the readers aware of the threats posed by assorted neoplasm.
Saerly and Efficacy of Radioimmunotheapy with $^{90}$Yttrium-rituximab in Patients with Relapsed CD20+ B cell Lymphoma: A Feasibility Study

M Vaes*, D Bron1, DJ Vugts2, M Paesmans3, N Meuleman1, G Ghanem4, T Guitot5, B Vanderlinden6, K Thielemans7, GAMS van Dongen8, P Flamen9 and K Muylle1

1Department of Clinical Hematology, Institute Jules Bordet, Université Libre de Bruxelles, Bld de Waterloo 121, 1000 Brussels, Belgium
2Department of Nuclear Medicine and PET Research, VU University Medical Centre, De Boelelaan 1107, 1081 HV Amsterdam, The Netherlands
3Data Centre, Institute Jules Bordet, Université Libre de Bruxelles, Bld de Waterloo 121, 1000 Brussels, Belgium
4Department of Radiophysics, Institute Jules Bordet, Université Libre de Brussels, Bld de Waterloo 121, 1000 Brussels, Belgium
5Department of Nuclear Medicine, Institute Jules Bordet, Université Libre de Bruxelles, Bld de Waterloo 121, 1000 Brussels, Belgium
6Department of Immunology-Physiology, Faculty of Medicine, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium
7Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, De Boelelaan 1107, 1081 HV Amsterdam, The Netherlands
8Department of Nuclear Medicine, Institute Jules Bordet, Université Libre de Bruxelles, Bld de Waterloo 121, 1000 Brussels, Belgium and Faculty of Medicine, Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium

Abstract

Purpose: Both anti-CD20 antibodies (ibritumomab; ZEVALIN® and tositumomab; BEXXAR®) currently used for radioimmunotherapy of B cell non-Hodgkin’s lymphoma are murine immunoglobulins. The aim of this feasibility study was to evaluate the safety and efficacy of radioimmunotheraphy with a human chimeric anti-CD20 antibody labelled with Yttium-90 ($^{90}$Y-rituximab) in patients with B cell lymphoma.

Methods: Patients with CD20+ B-cell lymphoma in partial remission or with progressive disease after at least one line of therapy were included. $^{90}$Y-rituximab was administered at a similar schedule as currently approved by the European Medicines Agency for the treatment with $^{90}$Y-ibritumomab tiuxetan (ZEVALIN®): a first infusion of rituximab 250 mg/m² is repeated one week later and directly followed by the injection of $^{90}$Y-rituximab (14.8 MBq/kg). $^{18}$FDG-PET/CT was performed before treatment and repeated 3 months after for response assessment.

Results: Twenty-six patients were treated with $^{90}$Y-rituximab. Disease histologies included mainly follicular lymphomas (53%), Toxicity was primarily haematological. The incidence of grade 3-4 neutropenia, thrombocytopenia and anemia were 34%, 38%, and 8% respectively, with spontaneous recovery in all but one patient that needed autologous stem cell transplant for refractory thrombocytopenia. Among the relevant long-term side effects, one patient developed secondary myelodysplasia 2 years after the treatment. The overall response rate was 88% (95% CI: 70%-98%), including 65% complete metabolic responses and 23% partial metabolic responses. After a median follow-up of 29.6 months, the Kaplan-Meier estimated median progression-free survival was 9.1 months (95% CI 6.1-17.9). Median time to next treatment was 24 months (95% CI: 12.8-28).

Conclusion: Radioimmunotherapy with $^{90}$Y-rituximab in patients with relapsed CD20+ B-cell lymphomas is safe, well tolerated and effective when the ZEVALIN® treatment schedule is used.

Keywords: CD20+; Radioimmunotherapy; Non Hodgkin’s Lymphoma; Rituximab;Yttrium-90; Monoclonal antibody

Abbreviations: RIT: Radioimmunotherapy; NHL: Non-Hodgkin’s Lymphoma; ANC: Absolute Neutrophil Count; HAMA: Human Anti-Murine Antibodies; HACA: Human Anti-Chimeric Antibodies; ORR: Overall Response Rate; PFS: Progression-Free Survival; DR: Duration of Response; OS: Overall Survival; CR: Complete Response; PR: Partial Response; TTNT: Time to Next Treatment; MDS: Myelodysplastic Syndromes; AML: Acute Myeloid Leukemia; EBRT: External Beam Radiation Therapy; NLPHL: Nodular Lymphocyte Predominant Hodgkin’s Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index; ASCIT: Autologous Stem Cell Transplant

Introduction

Radioimmunotherapy (RIT) is a targeted molecular radiotherapy in which radiation from radionuclides is delivered selectively to tumours by using monoclonal antibodies directed to tumour-associated antigens. The most widely studied radioimmunoconjugates for treatment of B cell Non-Hodgkin’s Lymphoma (NHL) are murine anti-CD20 monoclonal antibodies radiolabelled with Yttium-90 ($^{90}$Y-ibritumomab tiuxetan; ZEVALIN®) or Iodine-131 ($^{131}$I-tositumomab; BEXXAR®). Several studies have shown the efficacy of these radioimmunoconjugates in patients with B cell NHL, as a single agent in indolent lymphoma and in combination with chemotherapy in both indolent and aggressive lymphoma [1-6]. In Europe, only $^{90}$Y-ibritumomab tiuxetan (ZEVALIN®) has been approved, and this radioimmuno conjugate is used in combination with unlabeled rituximab.

Rituximab (RITUXAN® or MABTHERA®), a chimeric IgG1 Kappa monoclonal antibody, targets the same epitope on the CD20 antigen.
as its murine counterpart, ibritumomab. Rituximab has delivered an increased survival both in low grade and aggressive lymphoma’s and is currently part of the standard of care in NHL, mostly in combination with chemotherapy regimens [7-10]. Using antibody structures with human characteristics may potentially increase immune-based anti-tumour activity, improve pharmacokinetics and reduce immunogenicity. RIT with iodine-131 (131I)–labelled rituximab has been evaluated in patients with relapsed or refractory indolent NHL, revealing an acceptable toxicity profile and efficacy [11]. Yttrium-90 (90Y) is a pure β-emitting isotope with the potential to emit particles that deliver 5 times more energy to the tumour site than 131I (2.3 MeV versus 0.6 MeV β energy), with a longer path length (5.3 mm versus 0.8 mm) and a shorter half-life (2.7 days versus 8 days) [12,13]. Its longer path length may provide an advantage, particularly for bulkier tumours or those with poor antibody penetration. As 90Y has no coexisting gamma radiation (in contrast to 131I), radiation safety precautions are minimal and RIT may be delivered on an outpatient basis [12,13].

Study Objectives

The primary objective of the study was to assess the safety of radioimmunotherapy with 90Y-rituximab in patients with CD20+ B cell lymphoma in partial remission or relapse. Secondary endpoints included the Overall Response Rate (ORR), Progression-Free Survival (PFS), Duration of Response (DR) and Overall Survival (OS). Additional efficacy endpoints were Complete Response (CR) rate, Partial Response (PR) Rate and Time to Next Treatment (TTNT). To our knowledge, this is the first report of treatment with 90Y-rituximab.

Methods

Patient selection

In this prospective, single-center feasibility study, 26 patients were enrolled between June 2007 and December 2011. Eligible patients had histologically confirmed CD20+ B-cell lymphomas in progressive disease or partial remission after at least one line of treatment. Patients had to be at least 18 years old, have lesions measurable on 18FDG-PET/CT, World Health Organization classification (WHO) or those with poor antibody penetration. As 90Y has no coexisting gamma radiation (in contrast to 131I), radiation safety precautions are minimal and RIT may be delivered on an outpatient basis [12,13].

Evaluation of response

18F-FDG-PET/CT was performed for response assessment 3 months after the treatment or when progressive disease was clinically suspected, using the International Workshop Response Criteria for malignant lymphoma [16]. During follow-up, 18F-FDG-PET/CT was repeated (until disease progression) every 3 months during the first year and every 6 months during the second year or when progressive disease was suspected.

Evaluation of toxicity

For the purpose of collecting safety data, the treatment period was defined as the time from registration to 14 weeks afterwards. The basic follow-up period within the study started after the treatment period until disease progression or up to 2 years after registration. After this follow-up period within the study, a further follow-up based on clinical
reports provides additional information about late toxicity, PFS, TTNT and OS.

All adverse events from study during the treatment period were reported according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0. Adverse events after this period, which were considered to be possibly or probably related with study drug, were also recorded. Laboratory assessments included complete blood count (differential and platelet count) and serum chemistry and were performed weekly during the treatment period and every 3 months during the follow up period.

**Statistical methods**

Statistical analysis includes descriptive analysis of baseline characteristics, response to treatment, safety variables (median and range for continuous variables, frequency tabulations for categorical variables). Time-to event distributions were estimated using the Kaplan-Meier method. Median follow-up was estimated using the reverse Kaplan-Meier method (i.e. considering as censored a patient who died). Overall survival was measured from treatment administration (90Y-rituximab infusion) until death, any cause. Progression free survival was defined as the time interval between treatment administration and documented progression or death. For time to next treatment, death or initiation of a new treatment were considered as events. Duration of response was considered only for responding patients and was defined as the time elapsed between date of response assessment and progression or death. Logistic regressions models have been used to assess the impact of baseline characteristics on response or on toxicity. For the toxicity, the modelled probability is the occurrence of grade III-IV event. A P value of<0.05 was considered statistically significant. All statistical analyses were performed by using the software SAS 9.2.

**Results**

Patient's characteristics

A total of 26 patients were included in the study between June 2007 and December 2011. Patient demographics and baseline characteristics are listed in table 1. Median age was 61 years old (range 29-73) and main disease histology included follicular lymphomas (53%). Ninety-two percent of patients were in progressive disease and 62% of patients had a disease stage III/IV at study entry. Patients were treated previously with a median of 2 therapy regimens (range 1-7), with 97% patients had a disease stage III/IV at study entry. Patients were treated with 90Y-rituximab. The patient recovered a platelet count>20.000/µl and an ANC>1000/µl respectively 21 days and 12 days after stem cell rescue. However, bone marrow reserve remained poor and no febrile neutropenia. One patient with chronic bronchial infections developed fever and sputum the day before 90Y-rituximab administration. One patient experienced grade 4 pancytopenia, with severe thrombocytopenia (platelets<3000/µl) and neutropenia (ANC<500/µl) refractory to platelet transfusions and growth factors respectively. A rescue autologous stem cell transplant was administered 52 days after the treatment with 90Y-rituximab. The patient recovered a platelet count>20.000/µl and an ANC>1000/µl respectively 21 days and 12 days after stem cell rescue. However, bone marrow reserve remained poor requiring intermittent injections of Granulocyte-Colony Stimulating Factor (G-CSF) and with platelet counts varying from 35.000 to 100.000/µl. Despite a prolonged pancytopenia, no infectious episode or severe bleeding occurred. Aside from this patient, hematologic toxicity was transient and reversible in all patients, with one patient requiring 3 units of red blood cell transfusions and another patient requiring one platelet administration. There occurred no major bleeding event and no febrile neutropenia. One patient with chronic bronchial infections developed fever and sputum the day before 90Y-rituximab administration and was treated with amoxicillin-clavulanate for one week.

Logistic regression analysis demonstrated that baseline absolute neutrophil count was significantly associated to the occurrence of grade 3-4 neutropenia (OR=0.38 (95% CI: 0.15-0.85) for an increase of baseline neutrophils of 1000 cells/µl; P=0.02). In contrast, baseline platelet count was not predictive for grade 3-4 thrombocytopenia and

**Statistical analysis**

The software SAS 9.2 was used for statistical analysis. Descriptive analysis included median and range for continuous variables, frequency and percentage for categorical variables. Time-to event distributions were estimated using the Kaplan-Meier method. Median follow-up was estimated using the reverse Kaplan-Meier method (i.e. considering as censored a patient who died). Overall survival was measured from treatment administration (90Y-rituximab infusion) until death, any cause. Progression free survival was defined as the time interval between treatment administration and documented progression or death. For time to next treatment, death or initiation of a new treatment were considered as events. Duration of response was considered only for responding patients and was defined as the time elapsed between date of response assessment and progression or death. Logistic regression models have been used to assess the impact of baseline characteristics on response or on toxicity. For the toxicity, the modelled probability is the occurrence of grade III-IV event. A P value of<0.05 was considered statistically significant. All statistical analyses were performed by using the software SAS 9.2.

**Table 1: Characteristics of all patients (n=26).**

| Variable | Number | % |
|----------|--------|---|
| Age | Median (range) | 61 (29-73) |
| Sex | Male | 18 | 69 |
| | Female | 8 | 31 |
| Histology | Follicular | 14 | 53 |
| | Transformed follicular | 2 | 8 |
| | NLF | 3 | 12 |
| | Marginal zone lymphoma | 2 | 8 |
| | Mantle cell lymphoma | 2 | 8 |
| | DLBCL | 2 | 8 |
| | Small lymphocytic | 1 | 3 |
| Disease Stage at study entry | I/II | 10 | 38 |
| | III/IV | 16 | 62 |
| Disease Status at study entry | Partial remission | 2 | 8 |
| | Progressive disease | 24 | 92 |
| Follicular lymphoma (n=14) | FLIPI low (0-1) | 9 | 64 |
| | FLIPI intermediate (2) | 2 | 14 |
| | FLIPI high (>2) | 3 | 22 |
| Prior therapies | Median (range) | 2 (1-7) |
| | <1 | 16 | 62 |
| | >2 | 10 | 38 |
| Prior rituximab therapy | 24 | 92 |
| Prior ASCT | 7 | 27 |
| Bone marrow infiltration | 4 | 15 |

*ASCT: Autologous Stem Cell Transplant*
there were not enough anemia events to allow the analysis of baseline hemoglobin and anaemia occurrence. No other factor were found to significantly affect the occurrence of grade 3-4 hematologic toxicity. The following factors were assessed: age, sex, disease stage, number of prior regimens (1 versus>1), bone marrow infiltration, prior external beam radiation therapy, prior autologous stem cell transplant.

There were no grade 3-4 non hematologic adverse events reported, in particular no infusion-related adverse events. Asthenia was the most common type of grade 1-2 non hematologic adverse events. No clinically significant chemistry abnormalities were associated with the treatment. None of the patients had significant reductions in immunoglobulin levels following treatment. Among the relevant long-term side effects, one patient previously treated with 2 prior treatment regimens (including alkylating agents, Total Body Irradiation, and autologous stem cell transplant) developed secondary myelodysplasia 27 months after the treatment and subsequently died.

**Response-efficacy**

An ORR of 88% (95% CI: 70%-98%) was achieved based on International Workshop Criteria. A CR was achieved in 65% of patients (95% CI: 44%-83%) and PR in 23% patients. Patients with follicular histology (n=14) had an ORR of 100% with 79% of CR (Table 3).

Progression-free survival (PFS) was estimated by Kaplan-Meier analysis: the median PFS was 9.1 months (95% CI: 6.1-17.9) after a median follow up of 29.6 months (Figure 1). The estimated rate of patients without progression at 2 years is 26%. Responders had an estimated median response duration of 8.7 months (95% CI: 3.1-15.5) for all patients and of 10.6 months among patients with follicular lymphoma (Figure 2). Median time to next treatment (TTNT) was 24 months (95% CI: 12.2-28) with 43% of patients without a treatment at 2 years of follow-up. Median OS was not reached (Figure 3).

Logistic regression analysis did not identify any prognostic factor for ORR. The following factors were assessed: age, sex, disease stage, disease histology, number of prior regimens, medullary infiltration, prior external beam radiation therapy, prior autologous stem cell transplant.

Among the 23 responding patients, response duration lasted for

---

### Table 2: Hematologic toxicity.

| Hematologic Parameter | Baseline | Nadir | Time to nadir (weeks) | Time to recovery (weeks) |
|-----------------------|----------|-------|-----------------------|-------------------------|
| Hemoglobin (g/dl)     | 13.5 (9.7-15.8) | 12.1 (7.2-14.2) | 7.5 (1-13) |                       |
| Platelets (cells/µl)  | 249.000 (150.000-405.000) | 63.000 (3000-206.000) | 6 (4-9) | 2 (1-7) |
| ANC (cells/µl)        | 3260 (1240-5520) | 1090 (50-2760) | 7 (4-12) | 1 (1-4) |

*All values are expressed in median (range)*

### Table 3: Response rates.

| Lymphoma Type | N | % | N | % |
|---------------|---|---|---|---|
| All lymphoma’s (N=26) | 23 | 88% | 14 | 100% |
| Complete response | 17 | 65% | 11 | 79% |
| Partial response | 6 | 23% | 3 | 21% |
| Stable disease | 1 | 4% | 3 | 21% |
| Progressive disease | 2 | 8% | 2 | 8% |

---

![Figure 1: Progression-free survival in all patients and in patients with follicular lymphoma.](image1)

![Figure 2: Response duration in all patients and in patients with follicular lymphoma.](image2)
patients received the standard dose (14.8 MBq/kg) of 90Y-rituximab and grade 4 neutropenia, thrombocytopenia and anemia occurred in 19%, 15% and 0% of patients; grade 3 toxicities in 15%, 23% and 8% respectively. Median time to recover from neutropenia and thrombocytopenia was 1 and 2 weeks respectively and recovery was not due to heavy use of hematopoietic growth factors as only one patient was treated with growth factors during the study. Those results are comparable with toxicities observed with 99mTc-ibritumomab tiuxetan, as evaluated in an integrated safety analysis of data from five clinical trials with 99mTc-ibritumomab tiuxetan: toxicity observed was primarily hematologic and lasting approximately 1 to 4 weeks [17]. Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 30%, 10%, and 3% of patients respectively, and these grade 3 toxicities occurred in 30%, 53% and 13% respectively [17].

One of our patients developed grade 4 pancytopenia refractory to platelet transfusions and growth factors, requiring an autologous stem cell transplant 52 days after the treatment with 90Y-rituximab. She had been treated with 2 prior chemotherapy regimens (EBVP-epirubicine, bleomycine, vinblastine, prednisone- and BEACOPP) and an autologous stem cell transplant 5 months before RIT. Anti-platelet antibodies and several anti-HLA class I antibodies were identified, accounting for refractoriness to platelet transfusions. Stem cell collection before RIT revealed poor culture with 5 CFU-GM (Colony Forming Unit-Granulocyte, Monocyte) and 0 BFU-E (Burst Forming Unit-Erythroid) for 2 × 105 cells, reflecting a poor bone marrow reserve before RIT treatment [18,19].

Despite 34% of grade 3-4 neutropenia and no prophylactic use of antibiotics, no serious infections were observed. This is probably due to non disruption of gastrointestinal mucosal barriers, the fact that T-cells are unaffected by rituximab and maintained serum immunoglobulin concentrations, despite B-cell depletion. Other side effects reported with 99mTc-ibritumomab tiuxetan are flu-like symptoms, including chills, fever, abdominal pain, and allergic reactions. Those were most linked to rituximab preload [17]. No infusion reaction has been observed in our study, probably due to the fact that premedication was administered before rituximab and infusion was performed during 4 hours.

The development of treatment-related myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) is a potential concern for patients receiving radioimmunotherapy. An extensive analysis of 746 patients who had received 99mTc-ibritumomab tiuxetan demonstrates that there does not seem to be an increased incidence of secondary MDS or AML: 2.5% MDS/AML occurred, 1.9 year after RIT, which is expected for this heavily pre-treated patient population [20]. In our study, one patient developed MDS (4%) 2 years after the treatment, but he had prior Total Body Irradiation for autologous stem cell transplant and chemotherapy with alkylating agents, which is known to be a risk factor for MDS [21].

The safety of the 99mTc-ibritumomab tiuxetan treatment schedule in NHL has been proven in various studies, with myelosuppression being the most important observed toxicity [1,17,22]. Radioimmunotherapy with rituximab labelled with Iodine-131 have also been well tolerated in a phase II study [11]. The available safety data for 99mTc-ibritumomab tiuxetan on one hand and the safety data of 131I-rituximab on the other hand justify performing no dose-escalating study, particularly in patients with a majority of low grade lymphomas in their early course of disease.

Both 99mTc-ibritumomab tiuxetan and 131I-tositumomab are contraindicated in following conditions: bone marrow involvement of more than 25%, external beam radiation therapy (EBRT) of >25% of active marrow, prior autologous stem cell transplant. In our study, those patients were not excluded, because of the availability of stem cells collection for rescue transplant in case of severe or prolonged toxicity. No significant increase in toxicity was observed in the 7 patients with prior autologous stem cell transplant or in the 4 patients with bone marrow infiltration, neither in the patients with prior EBRT. However 3 of the 4 patients with bone marrow infiltration experienced reversible grade 4 neutropenia and thrombocytopenia, so the absence of significant differences could be attributable to the small number of patients.

In contrast, our study revealed that lower baseline neutrophil count significantly augments the risk of developing grade 3-4 neutropenia. Indeed some patients had already grade 1-2 neutropenia at baseline. These results suggest that baseline neutrophil count, as a surrogate of the bone marrow reserve, could be a predictive factor of toxicity complementary to bone marrow infiltration. No correlation was found...
between baseline platelet count and thrombocytopenia as all patients had baseline platelets>150,000/µl.

Hematological toxicity not only depends on bone marrow reserve and infiltration degree, but also on bone marrow absorbed dose and subsequently on radiotracer’s biodistribution. Inter-patient variabilities of radiotracer’s biodistribution can vary with the spleen size, the amount of circulating B cells and the tumour load. Performing imaging with monoclonal antibody labelled with a positron emitting isotope such as Zirconium-89 in combination with PET scanning could be useful to visualize individual radiotracer’s biodistribution and eventually define patients at high risk for toxicity [23,24].

Using the treatment schedule of 90Y-ibritumomab tiuxetan for 90Y-rituximab administration, we obtained an ORR of 88% with 65% of CR, assessed by 18FDG-PET/CT 3 months after treatment. For note, in the different trials using 90Y-ibritumomab tiuxetan in NHL, ORR ranged from 67% to 80% with CR rates from 15% to 30% [1,22,25]. For 131I-rituximab, ORR of 76% with 53% of CR was obtained in 91 patients with relapsed or refractory indolent NHL [11]. However, no comparison can be made between trials with different treatment schedules, patient selection, radiotracers and imaging techniques used for response assessment. In our study response assessment was performed by 18FDG-PET/CT at 3 months in comparison to CT scan at 1 month in the 90Y-ibritumomab tiuxetan trials and at 3 months in the 131I-rituximab trial.

No clinical factor was found to be significantly correlated with the response rate, but the small number of patients and the high response rate limit the analysis. Although, clinical efficacy was particularly prominent in the subgroup of patients with follicular histology (ORR of 100% with 79% of CR), a small number of patients with other histologies, like nodular lymphocyte predominant Hodgkin’s lymphoma, mantle cell lymphoma or diffuse large B cell lymphoma did respond well, showing the interest to further explore RIT in those diseases.

For a median follow up of 29.6 months, the median PFS in our study was 9.1 months and median DR in responders was 8.7 months. No comparison can be done with 90Y-ibritumomab tiuxetan trials or 131I-rituximab trials as progression was assessed on 18FDG-PET/CT in our study and not by CTscan. Median time to next treatment was 24 months, which is a better surrogate of the clinical efficacy of 90Y-rituximab, particularly in follicular lymphomas, as small and asymptomatic lesions detected on periodically PET/CT wouldn’t be diagnosed with a standard clinical follow up.

As there is no universally accepted definition of what constitutes a long-term durable response, we have defined as long-term responders the patients with duration of response of 12 months or more. As a reminder, duration of response was defined as the time elapsed between date of response assessment (3 months after treatment administration) and progression or death. Forty-three percent of the responding patients experienced durable response and their disease histology was mainly follicular lymphomas (70%), with two NLPHL and one transformed follicular lymphoma. All but one patient who had a PR relapsed within 12 months, confirming that induction of a CR is key to achieve a long-term durable response. This has been observed with 90Y-ibritumomab tiuxetan [26] and 131I-rituximab [27]. 90Y-ibritumomab tiuxetan has also been shown to be more effective when administered early in the course of disease [28]. In our study the proportion of patients with only one prior treatment was higher in the long-term responders than in the short-term responders. Among long-term responders, 40% responded less than 12 months to their most recent therapy.

Conclusion

In conclusion, this prospective trial revealed that radioimmunotherapy with 90Y-rituximab in patients with relapsed CD20+ B-cell lymphoma is safe, well tolerated and effective when the 90Y-ibritumomab tiuxetan treatment schedule is used, while preserving quality of life.

Acknowledgment

This trial was financially supported by Belgian Cancer Plan, Télévie and Les Amis de l’Institut Bordet (AIB). M. Vaes is currently a research fellow financially supported by Télévie-Fond de la Recherche Scientifique (FNRS). We also acknowledge all our patients and their referring physicians.

References

1. Witzig TE, Gordon LI, Cabanilles F, Czuczman MS, Emmanouilides C, et al. (2002) Randomized controlled trial of yttrium-90-labeled ibritumomab tiuxetan radioimmunotherapy versus rituximab immunotherapy for patients with relapsed or refractory low-grade, follicular, or transformed B-cell non-Hodgkin’s lymphoma. J Clin Oncol 20: 2453-2463.

2. Buchegger F, Antonescu C, Delaoye AB, Helg C, Kovacsovics T, et al. (2006) Long-term complete responses after 131I-tositumomab therapy for relapsed or refractory indolent non-Hodgkin’s lymphoma. Br J Cancer 94: 1770-1776.

3. Witzig TE, Molina A, Gordon LI, Emmanouilides C, Schilder RJ, et al. (2007) Long-term responses in patients with recurring or refractory B-cell non-Hodgkin lymphoma treated with yttrium 90 ibritumomab tiuxetan. Cancer 109: 1804-1810.

4. Kaminski MS, Tuck M, Estes J, Kolstad A, Ross CW, et al. (2005) 131I-tositumomab therapy as initial treatment for follicular lymphoma. N Engl J Med 352: 441-449.

5. Press OW, Unger JM, Braeli RM, Maloney DG, Miller TP, et al. (2006) Phase II trial of CHOP chemotherapy followed by tositumomab/iodine-I-131 tositumomab for previously untreated follicular non-Hodgkin’s lymphoma: five-year follow-up of Southwest Oncology Group Protocol 59911. J Clin Oncol 24: 4143-4149.

6. Morschhauser F, Radford J, Van Hoof A, Vitoio U, Sobeyran P, et al. (2008) Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma. J Clin Oncol 26: 5156-5164.

7. Marcus R, Imre K, Solal-Celigny P, Catalanov JV, Dmoszynska A, et al. (2008) Phase III trial of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26: 4579-4586.

8. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilley H, et al. (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346: 235-242.

9. McLaughlin P, Grillo-López AJ, Link BK, Levy R, Czuczman MS, et al. (1998) Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 16: 2825-2833.

10. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, et al. (2005) Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 106: 3725-3732.

11. Leahy MF, Seymour JF, Hicks RJ, Turner JM (2006) Multicenter phase II clinical study of iodine-131-rituximab radioimmunotherapy in relapsed or refractory indolent non-Hodgkin’s lymphoma. J Clin Oncol 24: 4418-4425.

12. Illidge T, Morschhauser F (2011) Radioimmunotherapy in follicular lymphoma. Best Pract Res Clin Haematol 24: 279-293.
13. Ivanov A, Swann R, Illidge T (2008) New insights into the mechanisms of action of radioimmunotherapy in lymphoma. J Pharm Pharmacol 60: 987-998.

14. Perk LR, Visser GW, Vosjan MJ, Stigter-van Walsum M, Tijink BM, et al. (2005) (89)Zr as a PET surrogate radioisotope for scouting biodistribution of the therapeutic radiometals (90)Y and (177)Lu in tumor-bearing nude mice after coupling to the internalizing antibody cetuximab. J Nucl Med 46: 1898-1906.

15. Perk LR, Visser OJ, Stigter-van Walsum M, Vosjan MJ, Visser GW, et al. (2006) Preparation and evaluation of (89)Zr-Zevalin for monitoring of (90)Y-Zevalin biodistribution with positron emission tomography. Eur J Nucl Med Mol Imaging 33: 1337-1345.

16. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, et al. (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25: 579-586.

17. Witzig TE, White CA, Gordon LI, Wiseman GA, Emmanouilides C, et al. (2003) Safety of yttrium-90 ibritumomab tiuxetan radioimmunotherapy for relapsed low-grade, follicular, or transformed non-Hodgkin’s lymphoma. J Clin Oncol 21: 1263-1270.

18. Hénon P, Sovalat H, Becker M, Arkam Y, Ojeda-Uribe M, et al. (1998) Primordial role of CD34+ 38- cells in early and late trilineage haemopoietic engraftment after autologous blood cell transplantation. Br J Haematol 103: 568-581.

19. Demirer T, Buckner CD, Bensinger WI (1996) Optimization of peripheral blood stem cell mobilization. Stem Cells 14: 108-116.

20. Czuczman MS, Emmanouilides C, Darif M, Witzig TE, Gordon LI, et al. (2007) Treatment-related myelodysplastic syndrome and acute myelogenous leukemia in patients treated with ibritumomab tiuxetan radioimmunotherapy. J Clin Oncol 25: 4285-4292.

21. Lillington DM, Micallef IN, Carpenter E, Neat MJ, Amess JA, et al. (2001) Detection of chromosome abnormalities pre-high-dose treatment in patients developing therapy-related myelodysplasia and secondary acute myelogenous leukemia after treatment for non-Hodgkin’s lymphoma. J Clin Oncol 19: 2472-2481.

22. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, et al. (1999) Phase III trial of IDEC-123b radioimmunotherapy for treatment of relapsed or refractory CD20(+) B-cell non-Hodgkin’s lymphoma. J Clin Oncol 17: 3793-3803.

23. van Dongen GA, Vosjan MJ (2010) Immuno-positron emission tomography: shedding light on clinical antibody therapy. Cancer Biother Radiopharm 25: 375-385.

24. Rizvi SN, Visser OJ, Vosjan MJ, van Lingen A, Hoekstra OS, et al. (2012) Biodistribution, radiation dosimetry and scouting of 90Y-ibritumomab tiuxetan therapy in patients with relapsed B-cell non-Hodgkin’s lymphoma using 89Zr-ibritumomab tiuxetan and PET. Eur J Nucl Med Mol Imaging 39: 512-520.

25. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, et al. (2002) Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin’s lymphoma. J Clin Oncol 20: 3282-3289.

26. Gordon LI, Molina A, Witzig T, Emmanouilides C, Raubitschek A, et al. (2004) Durable responses after ibritumomab tiuxetan radioimmunotherapy for CD20+ B-cell lymphoma: long-term follow-up of a phase 1/2 study. Blood 103: 4429-4431.

27. Leahy MF, Turner JH (2011) Radioimmunotherapy of relapsed indolent non-Hodgkin lymphoma with 131I-rituximab in routine clinical practice: 10-year single-institution experience of 142 consecutive patients. Blood 117: 45-52.

28. Emmanouilides C, Witzig TE, Gordon LI, Vo K, Wiseman GA, et al. (2006) Treatment with yttrium 90 ibritumomab tiuxetan at early relapse is safe and effective in patients with previously treated B-cell non-Hodgkin’s lymphoma. Leuk Lymphoma 47: 629-636.

Submit your next manuscript and get advantages of OMICS

Unique features:
- User-friendly/feasible website-translation of your paper to 50 world’s leading languages
- Audio Version of published paper
- Digital articles to share and explore

Special features:
- 200 Open Access Journals
- 15,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: www.editorialmanager.com/cancerscience/