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Iodine-131 Rituximab Radioimmunotherapy: Durable Control of Follicular Lymphoma

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Abstract

Aims: We evaluated the response and toxicity, after long-term follow up of Iodine-131 rituximab radioimmunotherapy in patients with follicular lymphoma under the routine clinical care of a single hematologist over a period of 12 years.

Materials and methods: Patients received ^{131}I-rituximab radioimmunotherapy according to a standard, personalized dosimetry protocol predicated upon a prescribed whole body radiation absorbed dose of 0.75Gy. Four doses of maintenance rituximab were subsequently administered over 12 months.

Results: Response rate was 97% with 24(77%) patients experiencing a complete remission confirmed on ^{18}F-fluorodeoxyglucose positron emission tomography-computerized tomography scan. The cohort of 3 patients with duodenal lymphoma all achieved complete remission lasting 4-5 years.

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Conclusion: ^{131}I-rituximab radioimmunotherapy is an effective, safe, affordable, repeatable treatment which does not compromise future therapy options upon relapse. It is practical, being administered on an outpatient basis, and referring physicians maintain governance of their patients.

Keywords: Iodine-131-rituximab radioimmunotherapy; Duodenal lymphoma; /Indolent NHL

Introduction

Follicular lymphoma (FL) is the most common form of indolent B cell non-Hodgkin lymphoma (NHL) and accounts for approximately 20% of lymphomas in adults [1,2]. The Follicular Lymphoma International Prognostic Index (FLIPI) prognostication scheme predicts survival based on the factors age >60 years, Ann-Arbor stage ≥ 3, nodal sites ≥ 5, hemoglobin <120g/L, and increased lactate dehydrogenase [3]. Asymptomatic patients may be simply observed in the first instance, since systemic therapies are not recognised as curative [1,4,5]. As time progresses, remissions post-treatment become shorter and the disease may transform to high grade lymphoma [6,7]. Overall, the median survival of FL ranges from 8 to 12 years [5].

Radioimmunotherapy is an effective and practical treatment option for relapsed/refractory FL given the inherent radiosensitivity of lymphoma. The mechanism of action after systemic administration of a radioimmunoconjugate which binds to the CD20 positive cells, delivers targeted cytotoxic radiation to the lymphoma cell. In addition the 200-cell diameter range of beta rays from Iodine-131 irradiates tumor cells in proximity, even if they do not express the CD20 antigen [8]. We have administered iodine-131 rituximab radioimmunotherapy (^{131}I-rituximab RIT) to treat patients with relapsed or refractory indolent non-Hodgkin lymphoma, most of whom had follicular lymphoma, with an objective overall response rate of 76% with a 4 year actuarial survival rate of 59% ± 10% with minimal toxicity [8]. We reported our clinical experience of the same treatment in 142 consecutive patients with relapsed low grade non-Hodgkin lymphoma, predominantly FL, where objective response rate (ORR) of 67%, complete remission rate (CR) of 50%, and 8 year overall survival (OS) of 48% were observed [9]. We have also treated a cohort of 68 FL patients first-line with 131I-rituximab radioimmunotherapy achieving 98% ORR and 89% CR in a prospective Phase II clinical trial [10].

We describe here the long-term follow-up of patients with FL treated with ^{131}I-rituximab RIT, coupled with maintenance rituximab, under the routine clinical care of a single hematologist.

Patients and Methods

All patients had histologically confirmed FL, an Eastern Co-operative Oncology Group performance status of less than 3, life expectancy of more than 3 months and had received no rituximab within the 6 months prior to ^{131}I-rituximab RIT. Rituximab was administered to saturate non-specific binding sites. Radioimmunotherapy with ^{131}I-rituximab RIT was then administered on an outpatient basis according to the standard personalised

dosimetry protocol predicated upon a whole body radiation absorbed dose of 0.75Gy [8]. Four doses of maintenance rituximab were administered at 3 month intervals following 131I-rituximab RIT. All patients remained under the governance of the referring Hematologist and the role of the Nuclear Medicine Physician was to perform the dosimetry and to administer the radioimmunotherapy. Administration of 131I-rituximab RIT was performed under Compassionate Patient Use provisions of the Special Access Scheme of the Therapeutic Goods Administration of the Commonwealth Government of Australia on the written informed consent of each patient in accordance with protocols approved by the Human Research Ethics Committee of Fremantle Hospital in conformity with the Declaration of Helsinki and NH&MRC guidelines. Response to treatment was assessed with 18F-fluorodeoxyglucose positron emission tomography scan combined with computerized tomography scan (^{18}F-FDG-PET-CT) at 3-6 months.

The primary outcome of this study was to assess toxicity, response to treatment, and survival by OS and progression free survival (PFS). Kaplan-Meier methodology was used to estimate median OS and PFS.

Results

Thirty one patients with FL presenting in the course of routine clinical practice of a single Hematologist were referred for treatment with 131I-rituximab RIT between 2001 and 2013. Baseline patient and disease characteristics are shown in Table 1. There were 14 male and 17 female patients with a median age of 54 years (range 30-74). Sites of disease included nodal disease only; 18/31(58%), nodal plus extranodal disease; 10/31(32%), and duodenal disease only; 3/31(10%). Ann-Arbor stage III-IV disease was evident in 18 patients (58%). The FLIPI Score was 0 in 7/31(23%), 1 in 13/31(42%), 2 in 4/31(13%), 3 in 6/31(19%), and 4 in 1/31(3%). The median time from diagnosis to 131I-rituximab RIT was 39 months (range 2-354). Seven patients had 131I-rituximab RIT as first-line treatment. Twenty-four patients had had treatment prior to 131I-rituximab RIT, and the median number of prior lines of therapy was two. Prior therapy modalities included radiation only in 1(3%) patient, with the others having a variety of combination chemotherapy regimens, including rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP), rituximab, fludarabine, mitoxantrone, dexamethasone (R-FMD), cyclophosphamide, etoposide, vincristine, prednisolone (CEOP), prednisolone, chlorambucil, cyclophosphamide. One patient had had previous myeloablative chemotherapy and autologous hematopoietic stem cell transplantation (ASCT). Treatment was indicated in every patient as per the Groupe pour l'Etude de Lymphome Folliculaire (GELF) criteria [11], being symptomatic in 30/31 (97%), 8/31(26%) had high tumour bulk, and 4/31(13%) had a lactate dehydrogenase above the upper limit of normal.

Parameter	**n(%)**
Gender	male 14(45%), female 17(55%)
Main site	
Lymph node disease only Lymph node plus other site Duodenum only	18(58%) 10(32%) 3(10%)
FLIPI	
0 1 2 3 4	7(23%) 13(42%) 4(13%) 6(19%) 1(3%)
Time from diagnosis to 131I-rituximab RIT (months)	median 39, range2-354
Number of patients given prior treatment	24(77%)
Number of prior lines of therapy	
1 2 3	13 10 1

Table 1: Patient and disease characteristics at diagnosis. FLIPI – follicular lymphoma international prognostic index; ^{131}I-rituximab RIT – iodine-131 rituximab radioimmunotherapy.

At the time of writing, 30/31(97%) patients are alive. Table 2 summarises treatment outcomes. The median OS has not been reached after a median follow up of 65 months. The median PFS is 71 months (range 6-152) (Figure 1). The ORR was 30/31(97%), CR confirmed on 18F-FDG-PET-CT in 24/31(77%), partial response (PR) in 4/31(13%). Unconfirmed complete remission (CRu) was seen in 2/31(7%), and progressive disease (PD) in 1/31(3%). There were no acute hypersensitivity reactions during the infusion of 131I-rituximab RIT and no infections or episodes of bleeding requiring hospital admission. Grade III-IV neutropenia (defined as absolute neutrophil count <1x109/L) occurred in 4/31(13%) patients. Grade III-IV thrombocytopenia (defined as platelets <50x109/L) occurred in 1/31(3%) patient. Subclinical hypothyroidism occurred in 4/31(13%) patients and was treated. Myelodysplasia occurred in only one patient.

Parameter	**n(%)**
Response to ^{131}I-rituximab RIT	
CR on ^{18}F-FDG-PET-CT CRu PR on ^{18}F-FDG-PET-CT PD	24(77%) 2(7%) 4(13%) 1(3%)
Toxicity	
Atypical infection Neutropenia <1x109/L Thrombocytopenia <50x109/L Hypothyroidism Myelodysplasia	0(0%) 4(13%) 1(3%) 4(13%) 1(3%)
PFS (months)	median 71, range 6-152
OS (months)	Not reached after a median follow up of 65 months, range 9-152

Table 2: Response to treatment, toxicity, survival. CR – complete remission; CRu – unconfirmed complete remission; PR – partial response; 18F-FDG-PET-CT – Fluorine-18-fluorodeoxyglucose positron emission tomography combined with computerized tomography; PD – progressive disease; PFS – progression-free survival; OS – overall survival.

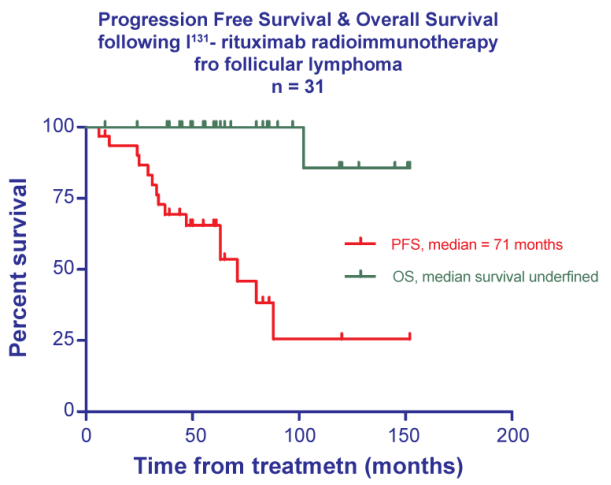

Figure 1: Kaplan-Meier plot of progression free survival (PFS) and overall survival (OS) for 31 patients following 131I-rituximab radioimmunotherapy for follicular lymphoma.

Discussion

The choice of treatment modality of NHL depends in part upon the stage of disease and the patients' ability to tolerate it. Radiation therapy is effective for stage I-II disease and can lead to long lasting remissions [12]. Anti-CD20 monoclonal antibody therapy such as rituximab either alone or with combination chemotherapy is effective for stage III-IV disease [13]. Chemoimmunotherapy with R-CHOP is still widely used as efficacy is established with an overall response rate of approximately 90%. Newer agents such as bendamustine are emerging but have yet to be proven [2]. Some prefer to withhold anthracyclines, so that it is available later in the event of disease transformation. Autologous or allogeneic hematopoietic stem cell transplantation is reserved for selected patients in high risk situations such as relapsed/refractory or transformed disease [2,4]. The survival of patients with FL is improving as a result of the sequential application of effective therapies, particularly rituximab, including 131I-rituximab RIT, and improved supportive care [4].

Reporting a cohort of NHL patients from a single hematologist experience has obvious limitations but is representative of real-world clinical practice over a decade. Our patients represent a heterogeneous group and there was variation in the timing of 131I-rituximab RIT (first-line vs salvage therapy), and the stage of disease. All patients required treatment according to GELF criteria (single lesion>7cm, three nodal sites >3cm, splenomegaly, cytopenias, effusions, organ compression). Over one third (13/31) of our patients have achieved more than 5 years relapse-free survival. The choice of 131I-rituximab RIT as the main therapy was taken after meticulous in-house development, calculation of individual dosimetry, and extensive published evidence of efficacy [8,9,10,14].

Radioimmunotherapy is a relatively recent therapeutic modality for FL and has the potential to change the approach to the management of this heterogeneous disease. Commercially available murine antibody based agents yttrium-90 ibritumomab-tiuxetan and iodine-131 tositumomab have been approved for the treatment of relapsed and refractory FL and show potent single-agent activity; 131I-tositumomab treatment had an ORR of 95%, CR 75%, actuarial 5-year PFS 59%, and median PFS 6.1 years in a phase II study of 76 consecutive patients with previously untreated grade I-II, Ann-Arbor stage III-IV FL [15]. However, sale of this agent, was discontinued and marketing approval withdrawn in the United States in February 2014, consequent on poor sales attributed to physician reimbursement issues rather than any proven lack of efficacy [16]. Yttrium-90 ibritumomab-tiuxetan treatment had an ORR of 87%, CR or CRu 56%, and after a median follow-up of 30.6 months the median PFS for all patients was 25.9 months and median OS had not been reached in patients with previously untreated FL [17]. Furthermore, 90Y-ibritumomab-tiuxetan treatment produces statistically significant higher ORR and CR compared to rituximab alone in patients with relapsed or refractory low-grade FL [18]. However, toxicity in clinical practice has been reported to be relatively high with grade 3-4 neutropenia in 55% and thrombocytopenia in 56% [19]. In clinical practice rates of response to treatment with 90Y-ibritumomab tiuxetan and ^{131}I-tositumomab are at the lower range of those reported in the literature for various reasons, with an overall response rate of 47% and complete response rate 13% [19]. On the contrary, our group of patients in routine clinical practice achieved an ORR of 97% and CR (confirmed on ^{18}F-FDG-PET-CT) of 77% post^{131}I-rituximab RIT.

Duodenal FL without nodal disease is rare but occurred in 3 of our patients who all had symptoms attributable to bowel wall lymphoma. All achieved CR confirmed on ^{18}F-FDG-PET-CT. These patients continue to be asymptomatic at 44, 55, and 60 months follow-up post 131I-rituximab RIT and four doses of maintenance rituximab, and none have required further treatment. This cohort has achieved excellent response, but this should be interpreted with caution as it seems to be a remarkably indolent FL variant more likely than nodal FL to present with early stage disease [20]. Duodenal FL has different features from nodal FL, including grade 1/2 histology, no marginal zone or plasmacytic differentiation, no reactive germinal centres, and the t(14;18)(q32;q21) positive B-cells do not acquire further karyotypic changes thus they have a low malignant potential [20]. The gene expression profile shows upregulation of Chemokine ligand 20 (CCL20) and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) which is downregulated in nodal FL and may play a role in molecular pathogenesis which is presently unclear [21].

As FL is highly treatable but ultimately incurable, it is essential to treat patients with effective therapies which are tolerable. Rituximab is an attractive monoclonal antibody as it preferentially treats B cell lymphoma without affecting T cell function. Other advantages of ^{131}I-rituximab RIT are the ability to repeat administration in the event of relapse, given the lack of potential for human anti-mouse antibody formation, which may occur in 131I-tositumomab radioimmunotherapy [22]. Outpatient administration of 131I-rituximab RIT is safe and the median radiation exposure is within the limits recommended by international guidelines [23]. Patient and carer issues with outpatient radiation safety of 131I-rituximab RIT have also been recently addressed in depth [24]. Our treatment constituted full combination radioimmunotherapy, where the patient received treatment with a full course of rituximab immunotherapy at standard dosage, followed by radioimmunotherapy and maintenance rituximab. Potential toxicity of ^{131}I-rituximab RIT includes self-limited neutropenia and thrombocytopenia, and subclinical hypothyroidism. In our reported experience of 142 consecutive patients, grade IV neutropenia occurred in 10%, grade IV thrombocytopenia in 6%, and grade IV anemia in 1% [9]. In the

current single physician study, toxicity included grade III-IV neutropenia in 13%, grade III-IV thrombocytopenia in 3%, which compares favourably with conventional R-CHOP chemotherapy regimen [25]. One of our patients was diagnosed with myelodysplasia on a bone marrow aspirate and trephine after becoming pancytopenic 8 years post 131I-rituximab RIT. Cytogenetic analysis of bone marrow aspirate showed an abnormal complex and mosaic karyotype consistent with myelodysplasia, most likely due to prior chemotherapy with chlorambucil-prednisolone, melphalan- cyclophospamide-prednisolone, 4 cycles R-CHOP. Compromise of hematopoietic stem cell collection in patients treated with prior radioimmunotherapy may be a potential concern, which can be addressed by a second and/or salvage harvest. In our small experience, stem cell collection has not been impaired after ^{131}I-rituximab RIT and patients have undergone autologous stem cell transplantation with no significant difference in engraftment kinetics when compared to patients treated with prior chemotherapy [10,26].

Conclusion

In real life clinical practice, epitomized by a single hematologist's clinical experience, durable control of FL by ^{131}I-rituximab RIT is achievable without significant toxicity in non-selected patients, including those pretreated with chemotherapy. Subsequent therapeutic options are not compromised upon relapse and outpatient ^{131}I-rituximab RIT is practical, affordable, and preserves quality of life.

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