Nuclear Medicine and Biology 43 (2016) 227–231

Contents lists available at ScienceDirect

Nuclear Medicine and Biology

journal homepage: www.elsevier.com/locate/nucmedbio

Safety and efficacy of radioimmunotherapy (RIT) in treatment of non-Hodgkin's lymphoma in the community setting

Tarik Hadid [a,1], Ali Raufi [b], Zyad Kafri [a], Mary Mandziara [a], John Kalabat [c], Susan Szpunar [d], Kleanthe Kolizeras [a], Mary Steigelman [a], Ayad Al-Katib [a,b,*]

[a] Van Elslander Cancer Center, Grosse Pointe Woods, MI, USA,
[b] Lymphoma Research Laboratory, Wayne State University School of Medicine, Detroit, MI, USA
[c] Department of Radiology, St. John Hospital and Medical Center, Detroit, MI, USA
[d] Graduate Medical Education, St. John Hospital and Medical Center, Detroit, MI, USA

ARTICLE INFO

Article history:
Received 30 November 2015
Accepted 16 December 2015

Keywords:
Radioimmunotherapy
Iodine-131 tositumomab
Yttrium-90 ibritumomab tiuxetan
Follicular lymphoma
Diffuse large B-cell lymphoma

ABSTRACT

Introduction: Radioimmunotherapy (RIT) is a unique therapeutic modality that combines biologic and radiolytic mechanisms to induce tumor kill. RIT is underutilized in the community outpatient setting.
Methods: This is an institutional review of patients treated with RIT at St. John Hospital and Medical Center (SJH&MC) 2003–2011. RIT agents were dosed according to recommended guidelines. Response was assessed using the Revised Response Criteria for Malignant Lymphoma and toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events. The primary aim was to assess overall response rate (ORR) and overall survival (OS). The secondary aim was to assess the impact of variable host and disease factors on the ORR to RIT and OS.
Results: Forty-eight patients were treated with RIT within the specified period at SJH&MC; of which 52% with follicular lymphoma (FL) and 46% with diffuse large B cell lymphoma (DLBCL). The majority of patients had relapsed or refractory disease (98%). Median duration of follow-up was 17 months. The ORR was 73% with 44% complete remission (CR) rate and OS of 48 months. The ORR was 79% with 58% CR rate and OS of 82 months among FL patients. Among DLBCL patients, the ORR was 65% with 30% CR rate and OS of 39 months. Response to last therapy before RIT was the only significant predictor of response to RIT and a significant predictor of OS in multivariate analyses. Prior exposure to EBRT did not predict response or survival in multivariate analyses. Toxicity was manageable and predominantly hematologic.
Conclusions: RIT is effective and feasible for use in the community outpatient setting.
Advances in knowledge and implications for patient care: Patients with B-cell NHL can safely receive RIT close to home. With some coordination of effort, it is not difficult for community-based cancer centers to implement this treatment modality.

1. Introduction

Non-Hodgkin's lymphoma (NHL) comprises a diverse group of diseases with variable behaviors and outcomes. In 2015, it is expected that 71,850 individuals will be diagnosed with NHL, of which 19,790 will succumb to their disease [1]. In the United States, NHL is the sixth most common neoplasm and the leading hematologic malignancy [2].

The discovery of rituximab, an anti-CD-20 monoclonal antibody, has favorably improved the outcomes of patients with NHL, particularly those with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). When added to chemotherapy, rituximab significantly improves the overall response rate (ORR) and survival, both when given at diagnosis and relapse [3,4]. Radioimmunotherapy (RIT) is another therapeutic advancement for treatment of NHL. This modality utilizes radionuclide-labeled anti-CD-20 to deliver β-particles emitted by the radioactive moieties to the tumor cells. As a result, it increases the dose delivered to the tumor cells while keeping the radiation exposure to the normal tissue limited; hence reducing toxicity [5]. There are two RIT agents approved in the United States; ibritumomab tiuxetan (Zevalin®) which delivers yttrium-90 and tositumomab (Bexxar®), which delivers iodine-131. Iodine-131 tositumomab was withdrawn from the market in the United States due to dramatic decline in its use.

* Corresponding author at: 19229 Mack Avenue, Suite 36, Grosse Pointe Woods, MI 48236, USA. Tel.: +1 313 647 3130; fax: +1 313 647 3137.
E-mail addresses: tarik.hadid@stjohn.org (T. Hadid), ayad.al-katib@stjohn.org (A. Al-Katib).
[1] 19229 Mack Avenue, Suite 23, Grosse Pointe Woods, MI, 48236, USA. Tel.: +1 313 647 3245.

http://dx.doi.org/10.1016/j.nucmedbio.2015.12.004
0969-8051/

RIT is underutilized in the community outpatient setting due to concerns about its feasibility and safety [6]. In this study, we review our community-based institutional experience and explore the feasibility and safety of these agents for the treatment of NHL.

2. Methods and materials

2.1. Study population

In this study, all patients with NHL that were treated with RIT at St. John Hospital and Medical Center (SJH&MC), Detroit, Michigan between November, 2003 and February, 2011 were included. Subjects were identified using an institutional database implemented to track all patients with lymphoid disorders diagnosed, evaluated and/or treated at SJH&MC.

2.2. Study design

This study was conducted as a joint effort between the Division of Hematology and Oncology and the Division of Nuclear Medicine at SJH&MC. An approval from the institutional review board was obtained. This retrospective review presents our community-based experience with the use of RIT agents in patients with NHL. Subjects were included in the study if they were treated with RIT for newly diagnosed, relapsed or refractory NHL. Subjects that were younger than 18 years of age at time of RIT treatment or with alternative diagnosis were excluded. The primary aim of the study was to assess the ORR and overall survival (OS) of patients treated with RIT. The secondary aims include assessment of the impact of the histology, International Prognostic Index in the Rituximab era (R-IPI) in patients with DLBCL, Follicular Lymphoma International Prognostic Index (FLIPI) in patients with follicular lymphoma (FL), age at RIT treatment, gender, race, number of prior lines of therapy, RIT agent used, stage, response to last regimen before RIT and prior use of external beam radiation therapy (EBRT) on the ORR to RIT and OS.

2.3. Patient characteristics

Demographic data was collected, including age, gender, race and the type of RIT agent used. Other disease specific characteristics were collected including histology, stage, R-IPI in patients with DLBCL, FLIPI in patients with FL, number of prior lines of therapy, response to last regimen before RIT and prior use of EBRT. All subjects underwent pretreatment imaging and bone marrow aspiration and biopsy according to the recommendations of the consensus conference report on RIT [7].

2.4. Study materials

The choice of RIT agent used was that of the treating physician and was largely based on personal preference. For subjects who received iodine-131 tositumomab, treatment was started with the dosimetric step that consists of intravenous (IV) administration of 450 mg dose of tositumomab over 60 min followed by IV administration of 5 mCi of iodine-131 tositumomab over 20 min. Dosimetry and biodistribution scans were then performed at 48 and 120 h. If biodistribution was acceptable, therapeutic dose would be calculated to deliver 75 cGy to the total body if platelet count was ≥150,000/μL and 65 cGy if the platelet count was between 100,000 and 149,000/μL. Once calculated, an IV administration of 450 mg dose of tositumomab over 60 min was followed by IV administration of the calculated dose of iodine-131 tositumomab over 20 min [8]. For those who received yttrium-90 ibritumomab tiuxetan, therapy was started with rituximab 250 mg/m^2 on day 1. After 4 h, 5 mCi IV injection of indium-111 ibritumomab tiuxetan was administered over 10 min. After 48–72 h, biodistribution imaging was performed and, only if acceptable, treatment would be continued. On day 7, 8 or 9, subjects received an additional dose of rituximab 250 mg/m^2 followed within 4 h with yttrium-90 ibritumomab tiuxetan. The treatment dose was 0.4 mCi/kg if platelet count was ≥150,000/μL and 0.3 mCi/kg if platelet count was between 100,000 and 149,000/μL at the time of administration [9].

2.5. Post-treatment assessment methods

Subjects were assessed for response approximately 12 weeks after therapy was completed using the Revised Response Criteria for Malignant Lymphoma [10]. Toxicity was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events [11].

2.6. Statistical analysis

Descriptive statistics were generated to characterize the study population with respect to demographic and clinical factors. The association between response to treatment and clinical and demographic variables was assessed using chi-squared analyses (or Fisher exact test when appropriate) and Student's *t*-test (or analysis of variance when appropriate). Univariate and multivariate analyses using logistic regression and analysis of covariance were performed to model the effects of treatment while controlling for any potential confounding variables as appropriate. Kaplan–Meier method was used to study the difference in OS between different subgroups. Toxicities were assessed using Student's *t*-test and repeated measures analysis of variance. All data analyses were conducted using SPSS v. 19.0. All statistical tests were two-sided and a p-value of 0.05 or less was considered statistically significant.

3. Results

We identified 25 patients (52%) with FL with or without transformation, 22 patients (46%) with DLBCL, and one patient (2%) with small lymphocytic lymphoma. Among these patients, 34 (71%) received iodine-131 tositumomab and 14 (29%) received yttrium-90 ibritumomab tiuxetan. A summary of the baseline characteristics of the study participants is depicted in Table 1.

Among the study population, the ORR was 73% (33 patients); 44% (20 patients) achieved complete response (CR) and 29% (13 patients) achieved partial response (PR). Response was not assessable in 3 patients (2 with DLBCL and 1 with FL) due to missing information. The ORR among patients with FL was 79% with CR rate of 58%. The ORR among patients with DLBCL was 65% with CR rate of 30%. The ORR was not significantly different between patients with FL and DLBCL ($p = 0.29$). R-IPI was not a significant predictor of response to RIT in patients with DLBCL ($p = 0.2$). Similarly, FLIPI was not a significant predictor of response to RIT in those with FL ($p = 0.79$). Among the study population, lower number of prior lines of therapy, positive response

Table 1
Baseline characteristics of the entire cohort (N = 48).

Demographic feature	Value
Age at diagnosis-years	
Median	60
Range	34–88
Age at RIT administration-years	
Median	68.5
Range	37–89
Female-count (%)	29 (60.4)
Histological diagnosis-count (%)	
DLBCL	22 (45.8)
FL	25 (52.1)
Small lymphocytic lymphoma	1 (2.1)
Disease status-count (%)	
Relapsed/refractory	47 (97.9)
Newly diagnosed	1 (2.1)
RIT agent-count (%)	
Iodine-131 tositumomab	34 (70.8)
Yttrium-90 ibritumomab Tiuxetan	14 (29.2)