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Utilization of Radioimmunotherapy (RIT) and Hematopoietic Stem Cell Transplantation (HSCT) in B-cell Non-Hodgkin's Lymphoma (NHL): 10 Year Experience of a Single Community Cancer Center

Nibal Saad[1*], Kleanthe Kolizeras[2], Susan M Szpunar[3] and Ayad Al-Katib[2]

[1]*Department of Hematology/Oncology, State University of New York Upstate Medical University, Syracuse, NY, USA*

[2]*Van Elslander Cancer Center, Grosse Pointe Woods, Michigan, USA*

[3]*Graduate Medical Education, St John Hospital & Medical Center, Detroit, USA*

[*]**Corresponding Author:** Nibal Saad, Department of Hematology/Oncology, State University of New York Upstate Medical University, Syracuse, NY, USA, Tel: 313 706 6607; Fax: 315 464-8279; E-mail: nibalsaad@yahoo.com

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Abstract

After Yttrium (Y^{90}) Ibritumomab tiuxetan (Zevalin) and Iodine (^{131}I) tositumomab (Bexxar) were approved by the FDA, the improved response of B-cell NHL to this novel RIT makes it a promising alternative to more aggressive treatment like HSCT. In this study, we describe the experience of a single community-based cancer center with RIT and HSCT in patients with B-cell NHL in terms of response, survival and toxicity. Retrospectively, we reviewed 75 patients with B cell NHL who were treated with either RIT (N=50) or HSCT (N=25) between 2003 and 2013. Choice of treatment modality, i.e. RIT *vs.* HSCT was based on discretion of treating Oncologist taking into consideration patient's age, performance status, comorbidity and preferences. RIT-treated patients were older. HSCT was more likely to be used in aggressive lymphoma and as a consolidation of primary therapy. RIT was used mainly in indolent lymphoma and as salvage treatment. Overall response rates were better in HSCT-treated patients (100% *vs.* 76%). Median overall survival was higher in HSCT-treated patients (221 *vs.* 79.4 months). Similar results were obtained when we compared OS in patients younger than 60 years (221 *vs.* 79.4 months) and in patients with aggressive lymphoma (221 *vs.* 59.7 months). PFS was not met in HSCT, while it was 16.2 months in RIT. Myelodysplastic syndrome (MDS) occurred in both groups (12% HSCT *vs.* 2% RIT). Thrombocytopenia was more prevalent with RIT. All other toxicities were significantly more common with HSCT. This study shows that, in clinical practice, younger patients with aggressive B-cell NHL and without significant comorbidity are more likely to be offered HSCT. On the other hand, RIT was offered to older patients with indolent histology. Our results show that RIT is a reasonable alternative salvage treatment modality for B-cell NHL patients who are not candidates for HSCT.

Keywords: Radioimmunotherapy; B-cell lymphoma; Hematopoietic stem cell transplantation; Non-Hodgkin's lymphoma

Introduction

The incidence of non-Hodgkin's Lymphoma (NHL) in the United States was estimated at 71,850 cases in 2015 [1]. Death rates for both men and women, declining since the late 1990s, decreased at a rate of 2.4% per year from 2006 to 2010, reflecting improvements in treatment. Survival varies widely by cell type and stage of disease. For NHL, the overall 1 year and 5 year relative survival rates are 81% and 69%, respectively.

Lymphoid neoplasms are classified into four WHO categories: precursor lymphoid neoplasms, mature T cell or NK cell lineage, Hodgkin lymphoma, and mature B cell neoplasms. Mature B cell neoplasms consist of a heterogeneous group of diseases, divided into: indolent and aggressive groups [2,3]. Therapeutic approaches to NHL are based on the specific lymphoma subtype, stage of the disease, physiologic status of the patient, and prognosis. While chemotherapy, immunotherapy, immunochemotherapy and/or radiotherapy are curative in some patients, many with primary or relapsed disease remain refractory to conventional treatments. HSCT is effective as salvage treatment [4] but its many limitations make it a less desirable treatment. Age of the patient, long term toxicity, availability of donors, and relapse are the most significant limitations to HSCT.

In 2002 and 2003, the US FDA approved Yttrium (Y^{90}) Ibritumomab tiuxetan (Zevalin) and Iodine (^{131}I) tositumomab (Bexxar) for treatment of relapsed and refractory follicular lymphoma [5]. Those radioimmunotherapy agents achieved good response compared to immunotherapy and chemotherapy [6,7]. At St. John Hospital and Medical Center, we offer RIT to many types of B cell NHL patients and follow-up to patients who were referred to other institutions for HSCT. Iodine (^{131}I) tositumomab (Bexxar) was offered to the patients until its production was discontinued on February 2014, due to decline in demand. Yttrium (Y^{90}) Ibritumomab tiuxetan (Zevalin), however has been in use since its FDA approval. We sought to describe our experience as a community-based cancer center with the response rate, overall survival, progression free survival and toxicity of RIT and HSCT as treatment modalities for B-cell NHL over 10 years.

Patients and Methods

Patient population

The study included Van Elslander Cancer Center patients with either aggressive or indolent B cell NHL who were treated with RIT

(Bexxar or Zevalin) at our center or by HSCT at another institution and followed up at the Van Elslander Cancer Center. All patients were older than 18 years old. Patients were excluded if they were treated with both modalities, or if they had other malignancies at the time of diagnosis.

Methods

We retrospectively reviewed the database of NHL patients treated at the Lymphoma Clinic of the Van Elslander Cancer Center between 2003 and 2013. Data for patients who received RIT at Van Elslander Cancer Center or were treated at St. John Hospital and Medical Center were retrieved from our Lymphoma database. Transplant data for patients who were referred to transplant centers were obtained through follow-up correspondence from those facilities and subsequent follow-up at our institution.

Treatment selection

HSCT was offered as second line treatment for aggressive NHL and as a consolidation treatment for high risk aggressive lymphoma. It is also one of the treatment choices for relapsed and/or refractory indolent NHL. Patients were referred for HSCT whenever indicated at the discretion of the treating Oncologist. RIT was used for patients who were not candidates for HSCT; or opted for RIT rather than HSCT.

Pre-treatment evaluation for patients who were candidates for RIT included imaging and bone marrow (BM) aspiration and biopsy according to the consensus conference report on RIT [8]. Unless dictated by the patient's renal function, bladder control status and ability to comply with post treatment radiation safety requirement, the type of RIT (Zevalin® or Bexxar®) was up to the discretion of the referring Oncologist. For Bexxar®-treated patients, dosimetry imaging was done at 48 and 120 hours. Therapy dose, on day 8, was calculated to deliver 75 cGy to the total body. Zevalin® imaging was done at 48 h and a therapeutic dose of 0.4 mCi/kg or 0.3 mCi/kg was given depending on platelet counts (≥ 150 K/μL or 100 K/μL to 149K/μL, respectively) on days 7, 8, or 9.

For HSCT patients, the stem cells were most commonly harvested from peripheral blood but bone marrow (BM) was also used in a few cases. Four patients had allogeneic stem cell transplants, three from peripheral blood. The transplant conditioning regimen for those patients was BEAM (Dexamethasone, BCNU [Carmustine], Etoposide, Ara-C, Melphalan), and FLU+BU (Fludarabine, Busulfan): R-BEAM was used for the patient with bone marrow stem cell transplant.

Twenty patients received autologous peripheral blood stem cell transplantation. Multiple conditioning regimens were implemented: two patients were treated with (CVB) Cyclophosphamide-Etoposide-Carmustine; one patient with CVB with Rituximab; R -BEAM (Rituximab - Dexamethasone, BCNU [Carmustine], Etoposide, Ara-C, Melphalan) was the conditioning regimen for 9 patients; a TBI/Cyclophosphamide conditioning regimen was used for 3 patients and (RICE) Rituximab, Ifosfamide, Carboplatin, Etoposide for one patient. We were unable to retrieve the regimens for 4 other patients.

Post treatment follow-up

HSCT and RIT Patients were monitored for toxicity (National Cancer Institute-Common Terminology Criteria for Adverse Events, NCI-CTC v4.03) and evaluated for response after 12 weeks of therapy according to the Revised Response Criteria for Malignant Lymphoma [9]. Complete blood count and a basic metabolic panel were ordered weekly until week 12 and then every three months or as clinically indicated. After two years of remission, RIT and HSCT patients were followed up every 6 months.

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 were assessed initially using chi-squared analyses and Student's t-test or ANOVA as appropriate. Kaplan-Meier method was used to study the difference in duration of response between different patient sub-groups. Toxicities were assessed using Student's t-test and repeated measures ANOVA. All data analyses were conducted using SPSS v. 19.0 and a p-value of 0.05 or less was considered to indicate statistical significance. This project was approved by the St. John Hospital and Medical Center Institutional Review Board.

Results

Patient characteristics

RIT and HSCT patient distribution and characteristics are shown in Table 1. RIT patients were older, with a mean age 67.5 years compared to 53.9 years for HSCT ($p<0.0001$). HSCT was used in 19 patients with aggressive lymphoma, accounting for 76% of all HSCT treatment, in 3 (12%) transformed lymphoma patients, and in 3 (12%) individuals with indolent lymphoma. RIT was used in 17 (34%) patients with aggressive lymphoma, in 23 (46%) indolent lymphoma patients, and in 10 (20%) patients with transformed lymphoma; Difference in the distribution of patients between the two treatment groups was significant ($P<0.002$).

Demographics	RIT	SCT	Total	p- Value
Number of patients	50	25	75	
Mean age	67.56	53.92	58.01	0.0001
Race				
White (%)	45 (90)	22 (88)	67 (89)	
Black (%)	4 (8)	2 (8)	6 (8)	0.879
Others (%)	1 (2)	1 (4)	2 (3)	
Gender				
Male (%)	21 (42)	13 (52)	34 (45)	0.412
Female (%)	29 (58)	12 (48)	41 (55)	
Treatment				
SCT Auto (%)	NA	20 (80)	20 (80)	
SCT Allo (%)	NA	4 (16)	4 (16)	
SCT Lost data (%)	NA	1 (4)	1 (4)	
RIT Bexxar (%)	33 (66)	NA	33 (66)	
RIT Zevalin (%)	17(34)	NA	17 (34)	

Stage of Disease				
Early (%)	9 (18)	2 (8)	11 (15)	
Late (%)	36 (72)	15 (60)	51 (68)	0.712
Missed data (%)	5 (10)	8 (32)	13 (17)	
Histology				
Aggressive (%)	17 (34)	19 (76)	36 (48)	
Indolent (%)	23 (46)	3 (12)	26 (35)	0.002
Indolent to aggressive (%)	10 (20)	3 (12)	13 (17)	
Bone Marrow Involvement				
Yes (%)	10 (20)	2 (8)	12 (17)	
No (%)	40 (80)	20 (80)	60 (80)	0.253
Missed data (%)	0	3 (12)	3 (4)	
Response to Regimen prior to Treatment				
CR/PR (%)	35 (70)	19 (76)	54 (72)	
SD/PD (%)	14 (28)	5 (20)	19 (25)	0.341
Missed data (%)	1 (2)	1 (4)	2 (3)	
Mean Duration of response from last regimen to relapse before SCT/RIT in months				
	361	538		0.03
Treatment as Consolidation vs. Salvage				
Relapsed (%)	50 (100)	7 (28)	57 (76)	
Consolidation (%)	0	17 (68)	17 (23)	0.0001
Missed data (%)	0	1 (4)	1 (1)	

Table 1: Demographic and clinical characteristics of patients.

HSCT was used as consolidation treatment in 17 patients (70%), autologous in 13 patients and allogeneic in 4 patients. RIT was used as treatment for relapsed or refractory disease in all 50 patients (100%); p<0.001. The duration of response from the last regimen to the time of relapse before treatment (RIT or HSCT) was significantly longer in HSCT patients (p=0.03). Otherwise the two groups were comparable. Due to these different patient characteristics, Statistical comparison was not sought, and we present the results as descriptive data.

Response to RIT and SCT

The initial assessment of response after HSCT or RIT (after 12 weeks of treatment) was categorized into overall response rate (ORR) [which included complete (CR) and partial remission (PR)], and stable/progressive disease (SD/PD). ORR was observed in all HSCT patients (100%; 23 response-evaluable patients): 18 patients (78.3%) achieved CR and 5 patients (21.7%) PR. Thirty-five out of forty-six patients (76.08%) who were treated with RIT achieved ORR: 22 patients (47.8%) achieved CR, and 13 patients (28.3%) PR. The rest of the patients had stable [2 patients (2.9%)], or progressive disease [9 patients (13%)]. Two HSCT and four RIT patients were lost to follow-up after treatment. Results favor HSCT as they are summarized in Table 2.

Response	ORR=CR/PR	SD/PD	Total	Missed data
SCT (%)	23 (100)	0 (0)	23 (100)	2
RIT (%)	35 (76)	11 (16)	46 (100)	4

Table 2: Response to RIT and HSCT.

Overall survival

Median overall survival was 221 months for the HSCT group and 79.4 months for the RIT group (Figure 1A). The data were sub-analyzed based on age and histology. There were 21 patients younger than 60 years in each group. Median survival was 221 months for HSCT subgroup, and 79.4 months for RIT subgroup (Figure 1B). There were 4 patients older than 60 in the HSCT group and 28 in the RIT group. Median overall survival was not met in the HSCT subgroup of patients older than 60 years, and was 80 months in the RIT subgroup. Twenty-two patients with aggressive lymphoma were treated with HSCT and 27 patients with RIT. Median overall survival was 221 months in the HSCT group and 59.7 months in the RIT treated patients (Figure 1C). In indolent lymphoma, 3 patients were treated with HSCT and 22 patients with RIT. Median overall survival was not met in the HSCT subgroup, and was 81.8 months in the RIT subgroup.

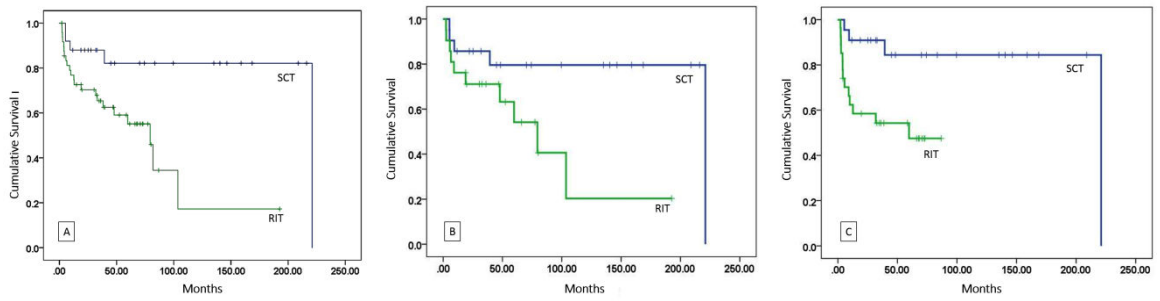

Figure 1: A. Overall Survival, all patients; HSCT compared with RIT; B. Overall Survival in patients younger than 60; HSCT compared with RIT; C. Overall Survival in aggressive NHL; HSCT compared with RIT.

Progression free survival

Median PFS was not reached in HSCT patients, the total number of patients was 20; we were not able to define the disease status of 5 patients. Median PFS for RIT patients was 16.2 months (n=45 patients, 5 patients lost follow-up) (Figure 2A). As with OS, PFS data was sub-analyzed based on age and histology. The number of patients in each subgroup and the PFS are shown in Table 3. Figure 2A-2E shows those PFS curves.

Subgroups	Sub class	Pt number	Median PFS (Months)
HSCT 20	Age<60	16	Not met
(5 pt data missed)	Age>60	4	Not met
RIT 45	Age<60	21	56.4
(5 pt data missed)	Age>60	24	14.8
HSCT 20	Aggressive	17	Not met
(5 pt data missed)	Indolent	3	Not met
RIT 45	Aggressive	24	13.2
(5 pt data missed)	Indolent	21	35.9

Table 3: PFS in subgroups of RIT and HSCT patients.

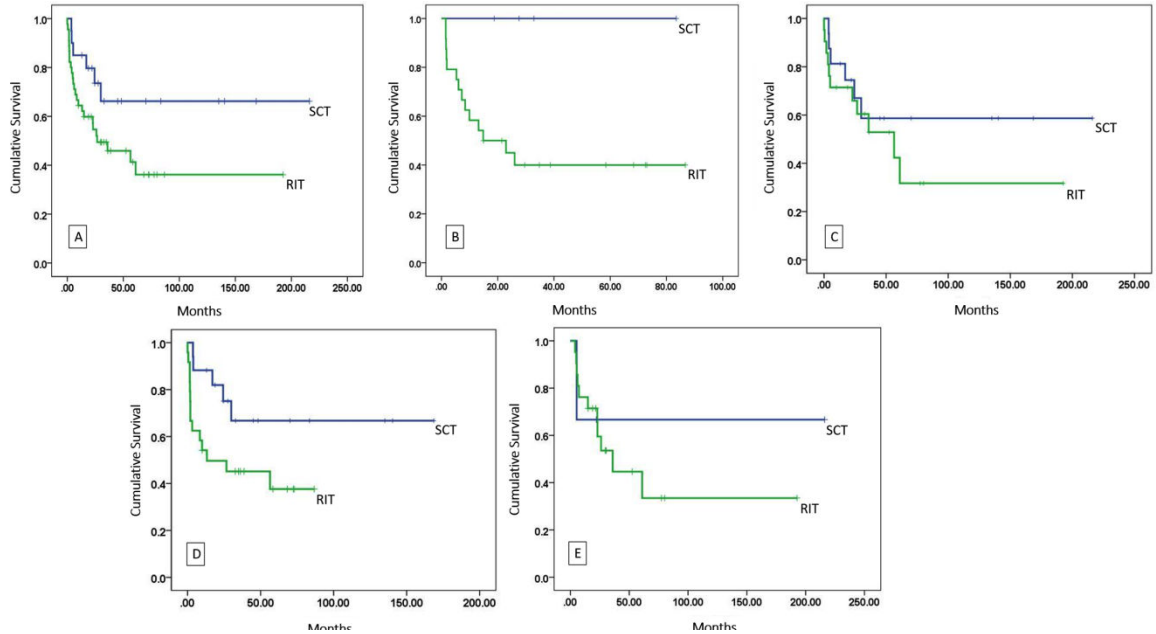

Figure 2: A. PFS all patients; B. PFS in patients older than 60; C. PFS in patients younger than 60; D. PFS in aggressive NHL; E. PFS in indolent NHL.

Toxicity

Treatment toxicity, in general, was higher in HSCT than in RIT-treated patients (Tables 4 and 5).

Toxicities included myelodysplastic syndrome (MDS), opportunistic infections, secondary malignancy, electrolyte abnormalities, neurologic, gastrointestinal (GI), skin, cardiovascular, and urinary side effects. Only thrombocytopenia was more common in RIT compared with HSCT.

Discussion

In this retrospective study, we describe the outcome of HSCT and RIT in NHL patients. RIT is shown to be an effective treatment with fewer side effects and easier to administer compared with HSCT. RIT was especially effective in relapsed refractory indolent NHL, and in elderly patients with significant morbidity. Many studies on Zevalin® reported an overall response rate (ORR) of 74% to 84% with complete remission (CR) in 15% to 44% of patients with relapsed or refractory indolent lymphoma, [10-12] transformed B cell NHL and rituximab refractory follicular NHL [12]. In these studies, time to progression

(TTP) was 6.8 months to 15 months. Bexxar® was studied in relapsed, transformed NHL as well as in rituximab refractory indolent NHL and demonstrated ORR of 57% to 81% and CR of 20% to 50%. Median progressive free survival in those studies was 9.9 months to 22 months [6,13-16]. These results are compatible with ours where the ORR was 78.3% and the CR rate was 47.8% for both kinds of RIT therapy; median PFS was 16.2 months [17].

When compared with single agent Rituximab, RIT achieved better overall and CR rates in relapsed or refractory NHL [16]. Also, the response to RIT, when compared to historical data, was equal to or better than the response to conventional chemotherapy regimens like ESHAP (Etoposide, Methylprednisolone (Solumedrol), High-Dose Cytarabine (Ara-C) and Cisplatin) which achieved 31.3% CR, 53.1% ORR, and 8.6 months median survival. Conventional cytotoxic regimens, however, exhibited higher toxicity [18]. The RIT data also compares favorably with other salvage regimens like mini BEAM (BCNU, VP16, Ara-C, and Melphalan) which achieved 37% ORR, and 18% 4 year survival for the patients who did not get HSCT [19]. Safety data from clinical trials using Zevalin® indicate that most of the non-hematological adverse events reported were mild to moderate in severity with nausea, asthenia, and chills being the most common [20,21]. Grade 3 and 4 non-hematologic side effects were reported 11% of the time. Those were transient and needed primary supportive care. Myelosuppression, the primary dose limiting toxicity, usually develops by week 4-6, reaches a nadir by week 7-9 and starts to recover before 12 weeks.

Similar results were found with Bexxar®. Grade 3 or 4 anemia, neutropenia, and thrombocytopenia were observed in 5%, 45%, and 32% of patients, respectively [22]. Secondary MDS and acute leukemia were reported in <1% of those patients. Higher incidence of MDS/AML (2.6% to 6.3%) was reported with Bexxar®. 5 of 38 patients developed elevated thyroid-stimulating hormone with Bexxar [13,22]. In our study, grade 3 and 4 toxicities were hematologic: thrombocytopenia (16%), neutropenia (17%) and anemia (7%). All other side effects were minimal and needed mild supportive care. We treated 33 patients with Bexxar® with no reported thyroid dysfunction. Other than thrombocytopenia, RIT was a safer treatment with fewer side effects than HSCT (Tables 4 and 5).

Systemic Side effects		HSCT (%)	RIT (%)	Total
MDS	Yes	3 (12)	1 (2)	4
Opportunistic Infections	Yes	3 (12)	0 (0)	3
Sec Malignancy	Yes	4 (16)	0 (0)	4
Electrolytes Abnormality	Yes	6 (24)	0 (0)	6
	No	18 (72)	49 (98)	67
	Not reported	1 (4)	1(2)	2
Neurologic	Yes	9 (36)	0 (0)	9
	No	15 (60)	50 (100)	65
	Not reported	1 (4)	0	1
GI	Yes	9 (36)	0 (0)	9
	No	15 (60)	50 (100)	65
	Not reported	1 (4)	0	1
Skin	Yes	4 (16)	0 (0)	4
	No	20 (80)	50 (100)	70
	Not reported	1 (4)	0	1
Cardiovascular	Yes	3 (12)	0 (0)	3
	No	21 (84)	50 (100)	71
	Not reported	1 (4)	0	1
Urinary	Yes	3 (12)	0 (0)	3
	No	21 (84)	50 (100)	71
	Not reported	1 (4)	0	1

Table 4: Systemic Side effects of RIT and HSCT.

Grade of Toxicity		0 (%)	1 (%)	2 (%)	3 (%)	4 (%)	Total reported (%)	Missed data
Neutropenia	SCT	10 (58)	2 (12)	2 (12)	2 (12)	1 (6)	17 (100)	8
	RIT	8 (20)	6 (15)	9 (23)	9 (23)	8 (20)	40 (100)	10
Thrombo-cytopenia	SCT	10 (56)	5 (28)	1 (6)	2 (11)	1 (5)	19 (100)	6
	RIT	2 (5)	15 (38)	7 (18)	15 (38)	1 (3)	40 (100)	10
	SCT	7 (39)	8 (44)	3 (17)	0 (0)	0 (0)	18 (100)	7
Anemia	RIT	11 (28)	22 (55)	3 (8)	2 (5)	2(5)	40 (100)	10

Table 5: Hematologic side effect of RIT and HSCT.

The group of HSCT patients in our study was heterogeneous and included aggressive and indolent lymphoma as well as autologous and allogeneic transplants. Rituximab was used in many conditioning regimens as well as in some of the treatments prior to transplant. In these patients, ORR to HSCT was 100% with CR rate of 78.3%. Median overall survival was 221 months and median PFS was not met.

It is well known that response to transplant depends on the type of lymphoma. Autologous HSCT is recommended for refractory follicular lymphoma [23] with a 5-year survival of more than 90% [24]. However, autologous HSCT did not improve OS compared with immunochemotherapy when used as consolidation [25]. In relapsed or refractory DLBCL, autologous HSCT achieves 86% ORR, (13% PR, and 53% 3-year PFS) [26]. Autologous HSCT was found to have a role in mantle cell lymphoma as consolidation with 3 year PFS and OS of 89% and 88% respectively [27] Allogeneic HSCT was also recommended for relapsed and/or refractory mantle cell lymphoma with 5 years OS of 37-49% [28,29].

As far as we know no randomized studies have been conducted comparing RIT and HSCT. In this study, the heterogeneity of NHL and the introduction of RIT only when HSCT was not an option made comparison of two modalities difficult, especially that several other factors favor HSCT, like longer previous response period, being used as consolidation rather than salvage, younger patient population, and less comorbidity. The imbalance in patient characteristics between the two treatment modalities reflects the state of oncology practice during the study period. Our study, however, demonstrates the feasibility of administering RIT in a community setting as a safe and effective outpatient procedure. Importantly, as the PFS curves show, we demonstrate durable responses and plateau in the survival curve after about 2 years of follow-up in patients older than 60 who are not transplant candidates.

Over the last few years, more novel agents were introduced to treat relapsed refractory indolent NHL including Idelalisib, a PI3-kinase delta inhibitor (FDA approved in 2014), and Bruton tyrosine kinase (BTK) inhibitor, Ibrutinib which was FDA approved in 2013 for treatment of CLL/SLL, Waldenstrom Macroglobulinemia and mantle cell lymphoma. More monoclonal antibodies targeting malignant cells have also been developed, like Ofatumomab for CLL/SLL and Obinutuzomab for CLL/SLL and relapsed follicular lymphoma. These options for therapy provide an opportunity to tailor the treatment to the individual patient based on age, histology of lymphoma, comorbid conditions and patient lifestyle.

In summary, our data demonstrate that during the study period (2003-2013), physician practice was to offer HSCT as salvage or consolidation therapy to eligible patients with relapsed/refractory B-cell NHL. This practice yielded superior results, albeit with higher toxicity compared with RIT. RIT, on the other hand is an appropriate alternative option whenever HSCT is not feasible. It is not clear if RIT will yield equivalent results to HSCT if applied to the same group of B-cell NHL patients. Decision on most appropriate salvage therapy for B-cell NHL is likely to evolve over time as new targeted agents are introduced to Oncology practice. In the absence of prospective randomized trials comparing different treatment options, studies like ours can provide objective data to gauge physician practices in the community at large.

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