A Phase I/II Trial of High-Dose Yttrium $^{90}$ ibritumomab tiuxetan in Combination with 
High-Dose Etoposide and Cyclophosphamide Followed by Autologous Stem Cell 
Transplant in Patients with Poor-Risk or Relapsed Non-Hodgkin’s Lymphoma (NHL)

Running title: High-dose Yttrium $^{90}$ ibritumomab tiuxetan and autologous stem cell transplant for 
NHL

Auayporn Nademanee, MD1, Stephen Forman, MD1, Arturo Molina, MD5, Henry Fung MD1, 
David Smith, PhD2, Andy Dagis, MS2, Cheuk Kwok, PhD3, Dave Yamauchi, MD4, Anne-Line 
Anderson, MS3, Peter Falk, MD1, Amrita Krishnan, MD1, Mark Kirschbaum, MD1, Neil Kogut, 
MD1, Ryotaro Nakamura, MD1, Margaret O’Donnell1, MD, Pablo Parker1, MD, Leslie 
Popplewell, MD1, Vinod Pullarkat, MD1, Roberto Rodriguez, MD1, Firoozeh Sahebi, MD1, 
Eileen Smith, MD1, David Snyder, MD1, Anthony Stein, MD1, Ricardo Spielberger, MD1, 
Jasmine Zain, MD1, Christine White MD5, and Andrew Raubitschek MD3

1. From the Division of Hematology and Hematopoietic Cell Transplantation, 
2. Division of Information Services, 3. Department of Radioimmunotherapy, 4. Division of 
Diagnostic Radiology, City of Hope National Medical Center, Duarte CA; and 
5. Biogen Idec Inc., Cambridge, MA and San Diego, CA.

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Corresponding author: Auayporn Nademanee, MD, City of Hope National Medical Center, 1500 
E. Duarte Road, Duarte, CA 91010, Phone: 626 256-4673, ext 62691, FAX: 626 930-5446, 
Email: anademanee@coh.org
ABSTRACT

We conducted a phase I/II trial of high-dose \(^{90}\)Y ibritumomab tiuxetan in combination with high-dose etoposide (VP16) 40-60 mg/kg (day-4) and cyclophosphamide (CY) 100 mg/kg (day-2) followed by ASCT in 31 patients with CD 20 + NHL. Patients underwent dosimetry (day -21) with 5 mCi \(^{111}\)In-ibritumomab tiuxetan following 250mg/m\(^2\) rituximab, followed a week later by \(^{90}\)Y ibritumomab tiuxetan to deliver target dose of 1000 cGy to highest normal organ. Bone marrow biopsy was done on day-7 to estimated radiation dose and stem cells were re-infused when radiation dose was estimated to be <5 cGy. The median \(^{90}\)Y ibritumomab tiuxetan dose was 71.6 mCi (range, 36.6-105). Histology included follicular lymphoma (n=12), diffuse large B-cell (n=14) and mantle cell (n=5). Median number of prior chemo was 2. The treatment was well tolerated. Median time to reach ANC >500/\(\mu\)l and platelet>20,000/\(\mu\)l was 10 days and 12 days, respectively. There were two deaths and 5 relapses. At a median follow-up of 22 months, the 2-year estimated overall survival and relapse-free survival are 92% and 78%, respectively. We conclude that high-dose \(^{90}\)Y ibritumomab tiuxetan can be combined safely with high-dose etoposide and cyclophosphamide without increase in transplant-related toxicity or delayed engraftment.

INTRODUCTION

Despite the use of aggressive combination chemotherapy regimens, approximately 30-40% of the patients with aggressive non-Hodgkin’s lymphoma (NHL) do not achieve a complete remission (CR) or experience a relapse after attaining a remission.\(^1,1\) High-dose chemotherapy or chemo/radiotherapy followed by autologous stem cell transplantation (ASCT) has been shown to induce long-term disease control in about 10-50% of patients with relapsed or refractory
aggressive lymphoma. The benefit of high-dose therapy and ASCT has been proven to be superior to conventional salvage chemotherapy in a large randomized study of patients with chemo-sensitive relapsed NHL. Thus, high-dose therapy with ASCT has become a potential curative modality for patients with relapsed aggressive lymphoma. However, not all the patients derive long-term benefit from this treatment and recurrent disease remains the single most common cause of treatment failure after ASCT. New therapeutic approaches that decrease relapse rates after ASCT are therefore needed.

Since NHL is radiosensitive, preparative regimens for ASCT have included chemotherapy augmented by total body irradiation (TBI). Results of Phase I and II studies of fractionated TBI 12.0 Gy, etoposide 60 mg/kg and cyclophosphamide 100 mg/kg have shown that this regimen is effective in patients with lymphoid malignancies. The 5-year progression-free survival (PFS) was 52% with a relapse rate of 42% for 134 patients with relapsed NHL who underwent ASCT utilizing this regimen. These results have been confirmed in the Southwest Oncology Group (SWOG) cooperative trial. Despite its effectiveness, a relapse rate of 30% - 50% remains considerably high. In addition, most relapses occur at previous sites of disease suggesting that targeted therapy may decrease relapse.

Radioisotope-labeled monoclonal antibodies combine the targeting properties of monoclonal antibodies with the proven ability of radiation to safely induce cellular damage in target and neighboring cells. In addition, high-energy beta particles can kill tumor cells, including those in
bulky or poorly vascularized tumors, within range even without direct binding of the antibody, by creating a crossfire effect.  

Two radioisotope-labeled monoclonal antibodies have been approved by the FDA for treatment of relapsed or refractory NHL: $^{90}$Y-labeled ibritumomab tiuxetan (Zevalin®) and $^{131}$I-labeled tositumomab (Bexxar). In an attempt to deliver targeted radiation to tumor sites, radioimmunotherapy (RIT) has been evaluated in myeloablative trials with and without high-dose chemotherapy. Press et al. pioneered the use of high-dose RIT in conjunction with ASCT in two different trials. The first trial used high-dose $^{131}$I tositumomab with autologous bone marrow rescue in 43 patients with B-cell lymphoma in relapse. In this study, 19 patients received therapeutic infusion of 234 – 777 mCi of $^{131}$I-labeled antibodies followed by autologous marrow infusion. Sixteen patients achieved a CR, two had a partial response and one had a minor response. Nine of 16 complete responders have remained in CR for 3 to 53 months. Toxicities included myelosuppression, nausea, infection and two episodes of cardiopulmonary toxicity. In a second study, Press et al. evaluated the combination of high-dose $^{131}$I tositumomab, etoposide and cyclophosphamide in conjunction with ASCT in 38 (26 low-grade; 12 aggressive) NHL patients. Of the 37 evaluable patients, 33 (89%) were alive and 29 (78%) were progression-free after a median follow-up of 1.5 years. Toxicities included grade 4 myelosuppression in all patients, grade 2-3 nausea in 26 (70%), pulmonary infiltrate in 4 and grade 3 veno-occlusive disease (VOD) in 2 patients. These results indicate the feasibility of delivering high-dose RIT in combination with high-dose chemotherapy in an ASCT setting for NHL.
\( {}^{90}Y \) Ibritumomab tiuxetan is formed by the conjugation of ibritumomab (a murine monoclonal antibody directed against the antigen CD20) to tiuxetan, a metal chelator. Tiuxetan is a second-generation chelator that can bind with high affinity to \( {}^{90}Y \) for therapy, or indium 111 (\(^{111}\)In) for imaging purposes. It is approved for treatment of patients with relapsed or refractory low-grade, follicular, or CD20+ transformed B-cell NHL, and follicular NHL which has failed rituximab.\(^{11}\) In the pivotal, Phase III, randomized, controlled trial comparing \( {}^{90}Y \) Ibritumomab tiuxetan with rituximab, overall response rate was 80% and 56%, respectively.\(^{12}\) \( {}^{90}Y \) Ibritumomab tiuxetan has been shown to an effective therapy for diffuse large B-cell lymphoma (DLBCL) with a response rate of 58 %.\(^{13}\) \( {}^{90}Y \) Ibritumomab tiuxetan therapies is well tolerated with dose limiting toxicity being myelosuppression.

Given the relatively high-risk of relapse with TBI based conditioning regimens and the safety and feasibility of \( {}^{90}Y \) ibritumomab tiuxetan to directly deliver radiation to tumor sites, we conducted a phase I/II study utilizing high-dose \( {}^{90}Y \) ibritumomab tiuxetan instead of TBI in combination with high-dose etoposide and cyclophosphamide followed by ASCT in patients with poor-risk or recurrent CD 20+ B-cell NHL.

**MATERIALS AND METHODS**

**Eligibility**

Eligible patients were required to be at least 18 years of age and younger than 60 years. Patients were to have histologically confirmed, relapsed, refractory or poor risk low- or intermediate-grade CD20+ B-cell NHL including follicular small cleaved, follicular mixed,
follicular large cell, diffuse small cleaved, diffuse mixed, diffuse large cell, immunoblastic lymphoma, mantle cell lymphoma and transformed low-grade. Patients were to have a platelet count ≥ 150,000/mm³ and ≤ 10% lymphomatous involvement of bone marrow at the time of stem cell collection. Patients were required to have normal renal function (serum creatinine ≤ 1.5 mg/dl or creatinine clearance of ≥ 60 ml/min); adequate pulmonary function (FEV1 > 65% of predicted or a DLCO ≥ 50% of predicted; cardiac ejection fraction of > 50% by echocardiogram and adequate liver function (bilirubin of ≤ 1.5 x normal and SGOT or SGPT ≤ 2 x normal). In addition, patients were to be HIV negative, have no active or history of CNS disease, have ECOG performance status of 0 or 1, or Karnofsky Performance status > 80%. Patients were to be at least four weeks from prior radiation or chemotherapy. All patients had autologous peripheral blood stem cells (PBSC) harvested and cryopreserved before study entry. No in-vitro purging was used. Patients were excluded from treatment if they had received prior radioimmunotherapy, had human anti-mouse antibody (HAMA) or anti-chimeric antibody (HACA) levels, were unable to provide adequate number of CD34+ cells (≥ 3 x 10⁶ cells/kg), displayed abnormal cytogenetics on bone marrow aspirate, had received prior bone marrow transplantation, experienced prior malignancies or showed evidence of active hepatitis B or C infection or were positive for hepatitis B surface antigen. All patients gave written informed consent to participate in the protocol, which was approved by the institutional review boards and radiation safety committees of the City of Hope Comprehensive Cancer Center.
Study Design

This phase I-II, open-label, study was designed to assess the safety and efficacy of a new preparative regimen consisting of $^{90}$Y ibritumomab tiuxetan, high-dose etoposide and cyclophosphamide followed by autologous stem cell support in patients with relapsed, refractory and poor risk CD 20+NHL. In addition, it was designed to determine the maximum tolerated dose (MTD) of $^{90}$Y ibritumomab tiuxetan that can be given with high-dose etoposide and cyclophosphamide followed by ASCT, however, the dose was capped at 100 mCi for practical consideration.

The treatment plan is shown in Schema Figure 1. Prior to study initiation, PBSCs were collected via apheresis after mobilization with chemotherapy and growth factor or growth factor alone. The dosimetry study for high-dose $^{90}$Y ibritumomab tiuxetan are quite complicated and more detailed than with conventional dose $^{90}$Y ibritumomab tiuxetan. The patient underwent a dosimetric study with $^{111}$In ibritumomab tiuxetan one week (Day-21) prior to the administration of the therapeutic dose of $^{90}$Y ibritumomab tiuxetan on day -14). Serial gamma camera images were obtained at approximately 0 (i.e. end of infusion), 24, 48, 72-96, 120 and 144 hours post-infusion. At each time point, one whole body and 4 spot planar scans were acquired with a dual head gamma camera. In addition, two SPECT images were obtained at 24 and 48-72 hour time points. Nuclear medicine (NM) images were used to estimate the distribution of activity in various organs, especially liver, lungs, kidney, heart and spleen. Blood samples were be obtained at approximately 0, 2, 4-6, 24, 48, 72-96, 120 and 144 hours post-infusion of the antibody to determine antibody clearance and to estimate radiation dose to the bone marrow.
Urine samples were collected daily for 6 days for dosimetry study to determine radioisotope clearance. The detailed dosimetry study for high-dose $^{90}$Y Ibritumomab tiuxetan will be published in a separate manuscript.

Patients were eligible for treatment if tumor dose was greater than any normal organ, except spleen and bone marrow, i.e. liver, lung, kidney. For patients in CR at time of transplantation, no specific tumor localization was required as long as FDG-PET scan was negative. Tumor dose was calculated from multiple gamma camera images and blood/urine pharmacokinetic profile. If the patient showed favorable biodistribution, the therapeutic dose was administered on day -14.

$^{90}$Y Ibritumomab tiuxetan was administered on study day –14 at a dose designed to achieve a maximum absorbed dose of 1000 cGy to any normal organ excluding the spleen and bone marrow. The maximum administered dose was capped at 100 mCi. Patients were hospitalized overnight for observation after $^{90}$Y ibritumomab tiuxetan administration and for intravenous hydration. Bone marrow biopsy was done on study day-7 to estimate radiation dose and determine when it was safe to give PBSC. The dose of etoposide, given on study day –4, was initiated at 40 mg/kg in Cohort 1 and escalated to 60 mg/kg for Cohort 2. Cyclophosphamide was administered on day –2 at a fixed dose of 100 mg/kg ideal body weight. PBSC were reinfused on study day +1 when the radiation absorbed dose to the stem cells was estimated to be < 5 cGy. Granulocyte-colony stimulating factor (G-CSF) 5 μcg/kg was given intravenously daily beginning after PBSC infusion.
Complete blood counts and platelet counts, chemistry profile and safety evaluations for toxicity were conducted on all treatment days, and additionally on Study Day 7, 14, 30, 60, 100, 180 and at year 1 and 2. Serum for HAMA/HACA testing was obtained at Study Day 60, 100 and Year 1. Toxicities were graded according to the NCI Common Toxicity Criteria (CTC) version 2 with the addition of BMT complex/Multi-Component Events. Toxicities were summarized in terms of type, severity, nadir or maximum values for laboratory measures, time of onset, duration and reversibility or outcome.

**Response Evaluation and Statistical Methods**

Computerized tomography evaluations were planned at 1, 3, 6 and 12 months then every 6 months for two more years and then yearly. FDG-PET scan was recommended if it was abnormal before transplant or when CT abnormalities were noted. Bone marrow aspiration and biopsy were performed at 6 months post-transplant and yearly thereafter. Bone marrow aspirates underwent cytogenetic analysis, immunophenotyping and gene rearrangement studies.

Response was determined in comparison with disease status at the time of study entry. Complete response (CR) was defined as complete disappearance of all measurable evidence of disease on physical examination or radiographic evidence of tumor, all disease-related symptoms, and appearance of no new lesions. Partial response (PR) was defined as a 50% or greater reduction in tumor size from baseline in the sum of the products of perpendicular diameters of all measurable lesions with no progression of evaluable disease and no new lesions. Progressive disease was defined as > 25% increase in the sum of the products of all measurable lesions over
The product-limit method of Kaplan-Meier was utilized to estimate time-to-event endpoints such as RFS, OS, time to relapse and time to engraftment. Each time-to-event endpoint was calculated from the date in which the patient went on-study. Standard statistical methods were used to estimate events such as the incidence of infection and therapy-related MDS, estimated as binomial proportions with exact 95% confidence intervals. Survival curves were estimated by the method of Kaplan-Meier.

RESULTS

Between May 2000 and November 2003, 41 patients were enrolled and 31 completed the treatment and are included in this report. Ten were not able to proceed with treatment due to lack of tumor imaging in five, unfavorable biodistribution with increase splenic uptake in one, progressive disease prior to receiving $^{90}$Y ibritumomab tiuxetan in two, allergic reaction to rituximab immediately prior to imaging dose in one and allergic reaction to $^{90}$Y ibritumomab tiuxetan during imaging dose infusion in one. Six patients were treated in cohort 1 and 25 in cohort 2. The plan for dose escalation of $^{90}$Y ibritumomab tiuxetan in cohort 3 was stopped since the dose of $^{90}$Y ibritumomab tiuxetan was capped at 100 mCi and patients in both cohort 1 and 2 had received this dose.
Patient characteristics are shown in Table 1. There were 17 males and 14 females with the median age of 51 years (range, 25-59.6). Lymphoma histology was follicular grade (FL) I/II in 8, follicular large cell (FLC) in four, diffuse large B-cell (DLBCL) in 14, and mantle cell lymphoma (MCL) in five. Fifty-five percent of patients had bone marrow involvement at diagnosis. The median number of prior chemotherapy regimens was 2 (range, 1-6). Twenty-nine patients had received rituximab either alone (8), or in combination with salvage chemotherapy (21). Seven patients were transplant during first CR/PR including four with MCL and three patients with DLBCL with persistent nodal mass with positive FD6 – PET Scan. Ten were transplanted in ≥ 2nd CR, while 9 were transplanted in relapse. Five had primary progressive disease but had responded to salvage therapy before transplant. None of the patients had received prior radiotherapy.

The median dose of $^{90}$Y ibritumomab tiuxetan delivered was 71.6 mCi (range: 36.6-105). The 6 patients in cohort 1 were treated with 40 mg/kg VP-16 and the 25 patients in cohort 2 were treated with 60 mg/kg VP-16. All patients received cyclophosphamide at a fixed dose of 100 mg/kg.

**Hematopoietic Recovery**

Peripheral blood stem cells were infused as scheduled on day +1 in 26 patients. Five patients had a delay in PBSC infusions for 24-48 hours due to high estimated bone marrow radiation dose of >5 cGy. The median CD $^{34+}$ cells infused was $6.87 \times 10^6$/kg (range, 3.1-33.5 $\times 10^6$/kg). One patient failed to engraft. This patient received a very high number of PBSC that were collected
at another institution. For the 30 evaluable patients, the median time to absolute neutrophils count $> 0.5 \times 10^9/L$ and $> 1.0 \times 10^9/L$ were both 10 days (range, 8-17). The median time to platelet count $> 20 \times 10^9/L$ and $50 \times 10^9/L$ were 12 days (range, 9-24) and 19 days (range 13-178), respectively. Patients received a median of 4 (range, 1-19) red cell transfusions and 5 (range, 2-37) platelet transfusions. One patient with MCL developed mild pancytopenia at 3 months post-transplant. Bone marrow examination showed hypocellular marrow without lymphoma involvement or any sign of myelodysplasia or abnormal cytogenetics. She remained mildly pancytopenic without needing a transfusion and relapsed at 12 months with peri-orbital soft tissue mass.

**Toxicity**

$^{90}$Y Ibritumomab tiuxetan was well tolerated at this high dose with no adverse events or allergic reactions attributed to the RIT therapeutic regimen. Transplant regimen-related toxicity is summarized in Table 2. Mucositis (81%), neutropenic sepsis (81%), nausea (84%) occurred in most patients, but these conditions were usually mild to moderate in severity (grade I-II). One patient had engraftment syndrome at recovery of white blood cell count, which resolved after administration of corticosteroid. Three patients had grade 3 cardiac toxicity including two with atrial fibrillation; one was associated with sepsis and the other with history of atrial arrhythmia before transplant developed AF after etoposide-induced hypotension. Both were treated successfully with anti-arrhythmic agents. One other patient developed cardiomyopathy and congestive heart failure at 2 months post-transplant. Cardiac function returned to normal 6 months later after appropriate cardiac medications. Four patients had grade 3 pulmonary toxicity due to volume overload (2), congestive heart failure (1) and moderate pleural effusion (1). One
patient developed idiopathic interstitial lung disease at 2 years post-transplant. This patient was given rituximab post-transplant because of minimal residual disease noted on bone marrow flow study. Lung biopsy showed bronchiolitis obliterans. His symptoms and radiology abnormality resolved after outpatient treatment with short course of corticosteroids. There were two grade 3 liver toxicities. One patient developed reactivation of hepatitis B infection at 6 months post-transplant. His hepatitis B serologies were negative before transplant and the abnormal liver function test returned to normal and viral load were negative after treatment with lamivudine (Epivir®). Another patient developed skin rashes, angioedema with abnormal liver function at day +34 post transplant. By exclusion, diagnosis of drug allergy and drug induced hepatitis was made. Her symptoms resolved and her liver function returned to normal after a short course of corticosteroid. There were two deaths. One patient died at day +164 from alcohol induced liver failure documented on liver biopsy. Another patient died from graft failure at day +44 post transplant.

All patients had serial testing for HAMA/HACA but none has developed antibodies. There have been no significant changes in cardiac ejection fraction or pulmonary function study at 6 months and at one year after transplant.

The toxicity profiles observed in this study are similar to toxicity observed in patients receiving TBI, etoposide and cyclophosphamide at our center. The transplant-related mortality of 3% is in keeping with current experience with other high-dose regimens. All patients have normal marrow cytogenetic studies before transplant and so far none has developed any clonal disorders.
on serial follow-up bone marrow biopsies post-transplant. However, the follow-up time is still too short to draw a firm conclusion.
Response Evaluation

All 13 patients with active disease achieved complete remission except one had a persistent positive FDG-PET scan. An example of response seen in a patient with refractory relapsed DLBCL is shown in figure 2. Five patients received involved field radiation to sites of prior bulky mass > 5 cm following ASCT in keeping with our current practice for post-transplant radiation therapy. Involved field radiation was well tolerated except one patient developed transient neutropenia and thrombocytopenia during mediastinal radiation that required growth factor support.

Relapse

Five patients had relapsed at 3, 11, 12, 13 and 24 months after transplant. All relapses were documented on tissue biopsy. One patient with MCL relapsed with a peri-orbital soft tissue mass at 12 month. Two relapses occurred in patients with FLC, both had extensive prior treatment 3 and 6 regimens before transplant. One patient with primary refractory DLBCL relapsed at 3 months at a prior site of disease and was treated successfully with salvage radiotherapy and rituximab. Another patient with DLBCL relapsed in the bone marrow at 11 months even though she never had bone marrow involvement. None of the patients with follicular lymphoma grade I/II have relapsed to date. It should be noted that the biology of relapsed diseases seem to be less aggressive since all relapsed patients are still alive after salvage therapy with rituximab alone with or without radiation and without the need for systemic chemotherapy.
Survival

Twenty-four of 31 patients are alive in remission at a median follow up of 22 months (range, 2 – 44). The Kaplan-Meier estimated 2-years RFS and OS is 78% (95% confidence interval [CI], 61%-96%) and 92% (95% CI, 82%-100%), respectively and is shown in Figure 3. Since most patients with FLC had areas of DLC in their biopsy specimens, we combined the FLC with DLBCL for the purpose of this analysis. The 2-year RFS and OS is both 100% for patients with follicular grade I and II. The 2-year RFS and OS for combined FLC and DLBCL is 74%(95%CI, 47%-100%) and 93% (95%CI, 81% -100%), respectively. For MCL the 2-year RFS and OS is 50% (95%CI, 1% -99%), and 75%(95% CI, 33% -100%), respectively. The DFS and OS based on histology are shown in Figure 4 and 5.

DISCUSSION

This study demonstrates the feasibility of administering high-dose $^{90}$Y ibritumomab tiuxetan with high-dose etoposide and cyclophosphamide followed by ASCT without additional toxicity. The preliminary results are encouraging and the toxicity profiles are very similar to other high-dose regimens. Our results are comparable to the study reported by Press et al using $^{131}$I tositumomab in combination with identical doses of etoposide and cyclophosphamide followed by ASCT in 52 patients with relapsed B-cell NHL. In their study, the estimated 2-year OS and PFS was 83% and 68%, respectively. In addition to the difference in radioisotope used, the two studies have some different design features to note. First, the MTD of $^{131}$I tositumomab that can be given safely to dose-limiting normal organs, especially the heart and lung, with 60 mg/kg of etoposide and 100 mg/kg of cyclophosphamide was 2500 cGy. Our study initially planned to escalate dose of $^{90}$Y Ibritumomab tiuxetan to deliver 1000, 1250, 1500…2000-2500 cGy to
normal organ. Initially the $^{90}$Y Ibritumomab tiuxetan was capped at 100 mCi for practical reason relating to isotope and antibody formulation. The cap was continued when it became evident that we would not be able to increase based on protocol restructure for marrow infusion which was set at projected integrated dose of 5 cGy without significantly delaying the stem cell infusion. In fact five patients had slow marrow clearance and had a delay in stem cell infusion for 24-48 hours. Since patients in cohort 1 and 2 received the maximum dose 100 mCi of $^{90}$Y ibritumomab tiuxetan, further dose escalation was not carried out. All patients in our study received $^{90}$Y Ibritumomab tiuxetan dose that delivered 1000 cGy to normal organ. Therefore we are unable to determine the MTD of $^{90}$Y Ibritumomab tiuxetan, which can be given with high-dose etoposide/cyclophosphamide in our study. The lower dose of radiation in our study may explain why we observed less pulmonary toxicity than did Press et al (four patients in the $^{131}$I-tositumomab/VP/CY study developed delayed interstitial pneumonitis at 2 to 8 months after transplant). Second, the inclusion criteria are different. Press et al study only included relapsed patients with measurable or evaluable diseases and excluded those in remission. In contrast, our study included both patients in relapsed and in remission, 17 patients in our study were in complete remission at transplant. Third, patients in Press et al study were more heavily pretreated with a median of 3 prior regimens compared to median of 2 prior regimens in our study. Lastly, while most patients (73%) in Press et al study had follicular lymphoma, 45% of our patients had de novo DLBCL. The experience of $^{90}$Y Ibritumomab tiuxetan in relapsed DLBCL is limited, however, our results suggest that it may be an effective therapy for DLBCL and in a high-dose setting $^{90}$Y Ibritumomab tiuxetan may even overcome chemotherapy-resistance in patients with relapsed/refractory DLBCL.
Ibritumomab tiuxetan was chosen for this study since it possess several unique properties favorable for use in the transplant setting compared to an I-labeled radioimmunoconjugate. The pure β emission allows the mCi dose of ibritumomab tiuxetan to be increased without causing significantly increased doses to the hospital personnel caring for the patient, with the high doses being capable of being administered in a standard private room compared to the lead lined facilities required for the high dose I therapies. Most of patients in our study do not require hospitalization although we normally keep them overnight for observation and hydration. The 2.67 day half-life of the radioisotope allowed for re-infusion of the marrow in a timely manner as we have documented in our study. The ibritumomab tiuxetan protocols incorporated rituximab as the unlabeled antibody, an active therapeutic agent which can be combined with other cytotoxic drugs as were planned in the administration of the transplant regimens. The residual rituximab circulating after the conditioning regimen was felt to be potentially advantageous in treating any CD20 positive cells in the re-infused product.

The necessity of incorporating a higher dose of RIT with high-dose chemotherapy in the ASCT setting remains to be confirmed. Other investigators have added escalated doses of I tositumomab or Y ibritumomab tiuxetan to high-dose BEAM (carmustine, etoposide, Cytarabine and melphalan) regimen followed by ASCT. Vose et al. conducted a phase I/II study evaluating the addition of standard outpatient dose of I tositumomab in 4 doses cohorts (30, 45, 60 and 75 cGy) to the BEAM regimen in 23 patients with chemotherapy refractory aggressive NHL (FLC=4, DLC=14, and MCL=5). The hematologic and non-hematologic toxicities were similar to historical patients receiving BEAM alone and there were no treatment related deaths. At a median follow-up of 38 months (27 to 60), the 3-year event-free survival
OS was 39% and 55%, respectively. Winter et al added escalating dose of $^{90}$Y Ibritumomab tiuxetan to deliver 100, 300, or 500 cGy to normal organ to BEAM in 14 patients with relapsed B-cell NHL.\textsuperscript{16} The median total dose of $^{90}$Y Ibritumomab tiuxetan was 21 mCi or 0.24 mCi/kg. There was no delay in hematopoietic recovery; however, all but two patients experienced asymptomatic decreases in diffusion capacity. The 2-year OS and PFS was 75% and 54%, respectively. Encouraging data were reported by Fung et al. where standard dose $^{90}$Y Ibritumomab tiuxetan (0.4 mCi/kg) was added to BEAM in older patients with poor-risk or relapsed aggressive B-cell NHL.\textsuperscript{17} The results from these studies suggest that standard dose of RIT can be added to myeloablative regimens and this approach may allow dose intensification without significant additional toxicity. In addition, it may be easier to deliver this therapy than a higher dose RIT, making it more suitable for older patients or those who are unable to receive total body irradiation.

Patients with FL have an indolent clinical course and are not cured by current treatment approaches. High-dose therapy with ASCT has been shown to improve increase the duration of remission in some patients with relapsed low-grade NHL.\textsuperscript{18,19} However, because of the long natural history and the continued pattern of relapse post ASCT in some studies, the role of high-dose therapy with ASCT as a potential curative treatment for patients with relapsed low-grade lymphoma has not been clearly established. Since both $^{131}$I tositumomab\textsuperscript{20} and $^{90}$Y Ibritumomab tiuxetan\textsuperscript{21} have been shown to be an effective salvage therapy for relapsed FL and transformed lymphoma, incorporating RIT into high-dose regimen may potentially improve the outcome of high-dose therapy and ASCT in relapsed and transformed lymphoma. Gopal et al conducted a retrospective multivariable comparison of 125 patients with relapsed FL who
received either high-dose RIT using $^{131}$I tositumomab (n=27) or conventional high-dose therapy (n=98). The patients’ characteristics were similar except more patients treated with high-dose RIT had elevated LDH pre-transplant and were in high international prognostic risk group. They found that patients treated with high-dose $^{131}$I tositumomab experienced improved OS (p= .02) and PFS (p= .03) when compared to patients treated with conventional high-dose therapy. The estimated 5-year OS and PFS were 67% and 48%, respectively for high-dose $^{131}$I tositumomab and 53% and 29%, respectively, for conventional high-dose therapy. Our results with high-dose $^{90}$Y ibritumomab tiuxetan, albeit in a small number of patients, are very encouraging. None of the patients with FL grade I and II has relapsed and they are all alive in remission. The results from these two studies suggest that incorporating RIT into high-dose regimen may lead to improve outcome of ASCT for relapsed and transformed FL. Further studies are therefore required to determine the curative potential of this approach.

Given the poor prognosis of MCL with median survival of 3 years and no cure with current treatment approaches, high-dose therapy and ASCT have been performed during first and subsequent remission in patients with MCL. Unlike aggressive NHL, high-dose therapy and ASCT has failed to improved prognosis in relapsed MCL. Using ASCT as consolidation treatment during first complete remission has improved DFS and remission duration in some studies but relapse continues to occur. Encouraging results were reported by Gopal et al using high-dose $^{131}$I tositumomab in combination with etoposide and cyclophosphamide and ASCT in 16 patients with relapsed MCL. Although most patients were heavily pre-treated (median of 3 prior regimens) and 7 had chemotherapy-resistant disease, the 3-year OS and DFS was 93% and 61%, respectively. The feasibility of a dose-escalated $^{131}$I chimeric anti-CD
antibody C2B8 (rituximab) with ASCT for relapsed MCL has also been demonstrated in another study. Although further study is required, these results suggest again that high-dose RIT may help overcome chemotherapy–resistance, in this case in MCL. Given encouraging results with high-dose $^{131}I$ tositumomab, we plan to continue to evaluate the role of high-dose $^{90}Y$ ibritumomab tiuxetan in the autologous stem cell transplant setting in MCL.

This phase I/II study demonstrates that high-dose $^{90}Y$ ibritumomab tiuxetan can be safely given combination with high-dose etoposide and cyclophosphamide in an autologous stem cell transplant setting for NHL without additional transplant-related toxicity. This regimen is effective in patients with relapsed or poor-risk B-cell NHL. Further studies and longer follow-up are required to determine whether this approach provide longer duration of remission and possible cure and to assess the long-term toxicity of high-dose $^{90}Y$ ibritumomab tiuxetan when given in combination with high-dose chemotherapy. The feasibility of incorporating $^{90}Y$ ibritumomab tiuxetan in the stem cell transplant setting should allow this study to be extended to other institution for cooperative group trial.

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  Emily Krupka, RN and Jill Land RN

Nurse Coordinator/Radioimmunotherapy:
Phyllis Broene, RN, OCN and Preeyarat Kloythanomsup, RN

Manuscript preparation:

Amy Stillings-Farris
Reference List


(23) Hiddemann W, Unterhalt M, Herrmann R et al. Mantle-cell lymphomas have more widespread disease and a slower response to chemotherapy compared with follicle-center


Figure 1

-14 -7 -4 -2 +1-21
111In Zevalin Imaging
90Y Zevalin Therapy
BD Bx
VP-16
CTX
TRANSPLANT

Daily NM Scans/Blood/Urine (Dosimetry)

Close Observation

Follow-Up 30, 60, 100 Days, Every 6 mos for 2.5 yrs, Yearly Thereafter

Pre-Study: Screening w/MD, Stem Cell Collection, Testing

Figure 2

FDG-PET
111In-Zevalin
FDG-PET

Prior to HSCT
Post HSCT
Figure 3

Figure 4
Figure 5

[Graph showing disease-free survival over time for different types of cells.]
### Table 1. Patients Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>51 (25-59.6)</td>
</tr>
<tr>
<td>Male: Female</td>
<td>17 : 14</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Follicular Grade I</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Follicular Grade II</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Follicular Grade III</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Diffuse Large B-Cell</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>B symptoms at Diagnosis</td>
<td>12 (38%)</td>
</tr>
<tr>
<td>Stage at Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Stage I-II</td>
<td>6 (19%)</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>25 (81%)</td>
</tr>
<tr>
<td>Extranodal involvement at diagnosis</td>
<td>19 (61%)</td>
</tr>
<tr>
<td>Bone marrow involvement at Diagnosis</td>
<td>17 (55%)</td>
</tr>
<tr>
<td>Prior chemo regimen, median (range)</td>
<td>2 (1-6)</td>
</tr>
<tr>
<td>Prior Rituximab</td>
<td>29 (94%)</td>
</tr>
<tr>
<td></td>
<td>8 alone, 21 with chemotherapy</td>
</tr>
</tbody>
</table>
### Disease status at ASCT

<table>
<thead>
<tr>
<th>Status</th>
<th>Count (Percentage)</th>
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</thead>
<tbody>
<tr>
<td>First CR/PR</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>≥ Second CR</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>Induction failure</td>
<td>5 (16%)</td>
</tr>
</tbody>
</table>

### Table 2. Toxicity of High-Dose $^{90}$Y-Zevalin, etoposide and CY followed by ASCT in patients with poor-risk and relapsed B-Cell NHL

<table>
<thead>
<tr>
<th>Organ</th>
<th>Grade 1 (Percentage)</th>
<th>Grade 2 (Percentage)</th>
<th>Grade 3 (Percentage)</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rashes</td>
<td>5 (16%)</td>
<td>7 (23%)</td>
<td>4 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>5 (16%)</td>
<td>12 (39%)</td>
<td>9 (29%)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3 (10%)</td>
<td>11 (35%)</td>
<td>11 (35%)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>1 (3%)</td>
<td>23 (74%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>6 (19%)</td>
<td>0</td>
<td>3 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>10 (32%)</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2 (6%)</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic</td>
<td>19 (61%)</td>
<td>4 (13%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

CY = cyclophosphamide, ASCT = autologous stem cell transplant
A Phase I/II Trial of High-Dose Yttrium 90 ibritumomab tiuxetan in Combination with High-Dose Etoposide and Cyclophosphamide Followed by Autologous Stem Cell Transplant in Patients with Poor-Risk or Relapsed Non-Hodgkins Lymphoma (NHL)