Yttrium-90-Ibritumomab Tiuxetan (Zevalin®) Radioimmunotherapy after Cyto-reduction with ESHAP Chemotherapy in Patients with Relapsed Follicular Non-Hodgkin Lymphoma: Final Results of a Phase II Study

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Keywords

Follicular lymphoma · Indolent non-Hodgkin lymphoma · Phase II trial · Relapsed/refractory lymphoma · CD20

Abstract

Background: Radioimmunotherapy (RIT) is effective in treating relapsed/refractory follicular lymphoma (FL), with durable remissions in first-line consolidation. We hypothesized that RIT with ibritumomab tiuxetan (Zevalin®) would result in durable remissions by eliminating minimal residual disease after cyto-reduction. **Methods:** Patients with FL received 2 cycles of ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) every 28 days, followed by Zevalin 4–6 weeks later if there was no disease progression and bone marrow biopsy showed <25% involvement. **Results:** Twenty-eight patients were treated, with a median age of 61 years, median of 3 prior therapies, 49% high-risk disease (Follicular Lymphoma International Prognostic Index, FLIPI),

and 39% progressive disease. Three patients did not receive Zevalin due to residual bone marrow involvement. The main toxicities were cytopenias, with 11% febrile neutropenia. The overall response rate (ORR) was 72%, with 45% achieving complete response. With a median follow-up of 73 months, 1-year progression-free survival (PFS) was 38%, and median PFS was 10 months, but median overall survival (OS) was not reached. **Conclusion:** The study did not reach its primary endpoint of a 1-year PFS of 67.3%. Reasons for this could include low accrual, high-risk disease, and inadequate debulking provided by 2 cycles of ESHAP. However, this protocol was associated with tolerable toxicity, high ORR, and high OS. Further studies would optimize debulking and focus on high-risk FL patients.

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Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL) and the most common subtype of indolent NHL [1]. FL is incurable but has a variable clinical course. There is no one standard therapy, but most treatment choices utilize an anti-CD20 monoclonal antibody such as rituximab, often combined with chemotherapy [2, 3].

ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) is a salvage regimen used in aggressive NHLs, but has good efficacy in relapsed low-grade lymphomas as well. One study showed a 75% overall response rate (ORR) and 36% complete response (CR) rate in patients with relapsed indolent lymphomas and substantially improved overall survival (OS) compared to DHAP [4]. In another study of 122 patients with relapsed, refractory NHL, ESHAP was associated with an 82% CR rate in indolent lymphoma [5]. Although ESHAP is very active in low-grade NHL, it is not often utilized by community oncologists as a salvage regimen. Therefore, most pretreated patients have not seen these agents and we hypothesized that their lymphomas should be responsive to ESHAP.

Ibritumomab tiuxetan (Zevalin[®]) is a murine anti-CD20 monoclonal antibody conjugated to yttrium-90. In a prospective study of 143 patients with relapsed or refractory NHL where a vast majority of patients had relapsed refractory FL, ibritumomab tiuxetan was associated with a significantly higher response rate compared to rituximab [6]. In a landmark trial, patients with FL who received ibritumomab tiuxetan had a notable increase in PFS [7]. About 20–25% of patients receiving ibritumomab tiuxetan have obtained durable remissions [8].

We postulated that radioimmunoconjugates may significantly improve the outcome for patients with FL, particularly when given for lower disease burden which could likely be achieved after treatment with 2 cycles of ESHAP. We therefore hypothesized that treatment with ibritumomab tiuxetan after 2 cycles of ESHAP would prolong time to progression (TPP), possibly changing the natural history of relapsed disease.

The only difference between ESHAP as originally published and as administered at our institution is the daily intravenous (IV) bolus dosing of cisplatin, instead of continuous infusion. The rationale for continuous infusion of cisplatin originally was to abrogate nephrotoxicity. However, it is well understood that limiting cisplatin doses to <50 mg/m²/dose in combination with IV normal saline-based hydration is sufficient to minimize nephrotoxicity [9]. Cisplatin is amenable to administration via

daily bolus infusion due to cell cycle-independent toxicity and an extracellular half-life of 16–53 h. Importantly, bolus administration results in high intracellular concentrations in lymphocytes [10].

Methods

Patients and Methods

We enrolled patients with histologically confirmed CD20-positive relapsed FL. Patients had bulky stage II, III, or IV disease by Ann Arbor classification. Bulky disease was defined as any tumor measuring 10 cm or greater or occupying more than one third of chest diameter. Patients were required to have at least 1 but less than 4 prior therapies. Patients were older than 18 years of age and required to have ECOG performance status 0–2, measurable disease, signed informed consent, normal serum creatinine, and bilirubin <2.0 × upper limit of normal. Patients with platelet counts ≥150,000 were able to receive 0.4 mCi/kg of ibritumomab tiuxetan; patients with platelet counts 100,000–150,000 received a dose of 0.3 mCi/kg of ibritumomab tiuxetan.

At our institution, ESHAP has been adapted to an outpatient setting, consisting of etoposide 40 mg/m²/day IV bolus on days 1–4 (160 mg/m² per cycle), cisplatin 25 mg/m²/day IV bolus on days 1–4 (100 mg/m² per cycle), methylprednisolone 250 mg IV daily on days 1–4, and cytarabine 2,000 mg/m² IV bolus given once on day 4. Patients were restaged after 2 cycles of outpatient ESHAP, given every 28 days as described. Patients with residual involvement of >25% bone marrow after the 2 cycles of ESHAP were taken off treatment and followed up for TPP and survival. Patients who did not experience progression and had <25% residual bone marrow involvement proceeded to receive ibritumomab tiuxetan 4–6 weeks after completion of the second cycle of ESHAP, with imaging for bio distribution as described originally [11]. Patients were subsequently re-evaluated for response assessment 12 weeks after completion of Zevalin. Thereafter, patients were followed up at 3-month intervals (short-term follow-up) for 2 years, and then every 6 months (long-term follow-up) for an additional 3 years. Once the patients completed long-term follow-up they were followed up on an annual basis (±30 days) for survival and disease status.

Statistical Analysis

The primary objective of this open-label single-arm phase II clinical trial was to evaluate the 1-year progression-free survival (PFS) of patients with relapsed follicular NHL treated with ESHAP chemotherapy for cytoreduction (2 cycles) followed by ibritumomab tiuxetan radioimmunotherapy (RIT), compared to what would be expected historically for patients treated with ibritumomab tiuxetan without prior cytoreduction. Secondary objectives included evaluation of median TTP, ORR, and CR rates.

A 1-year PFS of 67.3% was considered highly encouraging, compared to a historical rate of around 50% [4]. These values corresponded to approximate median TPP of 21 and 12 months, respectively, assuming exponential survival. Fifty-two evaluable patients would be required to test the null hypothesis that the true 1-year PFS is ≤50%, versus an alternative hypothesis that the true rate is ≥67.3% with this therapeutic approach. All patients who received at least one dose of chemotherapy were considered evaluable and included in the analysis. Sample size calculation was com-

puted for 90% power and 10% type I error. Descriptive and summary statistics for demographic and clinical variables were obtained. The incidences of reported adverse events (AEs) were also tabulated. Kaplan-Meier survival analysis for PFS and OS was performed on TPP. All the analyses were performed using Stata [12].

Results

Patient Characteristics

Twenty-eight patients were enrolled in the study, with a median follow-up of 73.0 months (95% CI: 51.6–89.0). The study was closed per institutional mandate for slow accrual. One patient was ineligible due to re-review of pathology showing diffuse large B-cell lymphoma. The median age was 61 years and 36% of the patients were male. More than half the patients had B symptoms, 43% had bone marrow involvement, 39% had elevated β_2 -microglobulin, 44% had elevated lactate dehydrogenase, and none had bulky disease, although 25% of patients had tumors measuring 5 cm or more. The Follicular Lymphoma International Prognostic Index (FLIPI) showed 36% of patients had intermediate-risk and 46% had high-risk disease. The median number of prior therapies was 3 (range 1–4), with 43% of the patients receiving more than one prior regimen. One patient had prior autologous stem cell transplant. Eleven patients (39%) had progressive disease with the last chemotherapy. Table 1 describes additional baseline characteristics of the patients.

Safety

AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs, v3.0, as detailed in Table 2 [13]. AEs were reported in most patients, and 25 patients had grade 3 or higher AE. The most common grade 3 AEs were cytopenias (not prolonged) and fatigue. Notably, the rate of neutropenia was 32% and the rate of febrile neutropenia was 11%, and neuropathy (sensory) was noted in 5 patients. There were 6 serious AEs reported on this study. One patient had a perforated duodenal ulcer, and 1 patient experienced nausea, vomiting, diarrhea, and functional decline. These 2 patients withdrew from the study and were not evaluable for response. Two patients developed myelodysplastic syndrome (MDS) after study completion, with no patients developing acute myelogenous leukemia. One patient had severe thrombocytopenia, leukopenia requiring admission, and transfusion support that qualified as a serious AE. Furthermore, 1 patient had a diagnosis of metachronous colon carcinoma diagnosed after completion of study.

Table 1. Patient characteristics ($n = 28$ patients)

<i>Baseline characteristics</i>	
Median age (SD), years	61 (11.9)
Male	10 (36)
White	27 (96)
Ethnicity (Hispanic)	3 (11)
<i>Clinical characteristics</i>	
Karnofsky performance status	
60	1 (4)
70	4 (14)
80	8 (29)
90	7 (25)
100	8 (29)
Baseline B symptoms	15 (54)
Bone marrow involvement	12 (43)
Prior transplant history	1 (4)
Tumor bulk >5 cm	7 (25)
Elevated β_2 -microglobulin	11 (39)
FLIPI	
0	1 (4)
1	4 (14)
2	10 (36)
3	8 (29)
4	5 (18)
FLIPI-2	
0	4 (14)
1	9 (32)
2	8 (29)
3	5 (18)
4	2 (7)
Prior chemotherapy regimens	
0	0 (0)
1	16 (57)
2	7 (25)
3	3 (11)
4	2 (7)
Response to prior chemotherapy regimens	
CR	9 (32)
PR	4 (14)
SD	1 (4)
PD	11 (39)
UK	3 (11)

Values are n (%) unless otherwise indicated. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UK, unknown.

Efficacy

Twenty-two patients completed the protocol and were evaluable for response. In addition to the 2 patients who withdrew secondary to toxicities, 3 patients were not evaluable for response secondary to bone marrow showing

Fig. 1. Kaplan-Meier survival estimates of all consented patients ($n = 28$). **a** Median progression-free survival (PFS). **b** Median overall survival (OS).

Table 2. Reported adverse events ($n = 28$ patients)

Category	All grades, n (%)	Grade ≥ 3 , n (%)
Any adverse event	27 (96)	25 (89)
Thrombocytopenia	21 (75)	17 (61)
Fatigue	21 (75)	5 (18)
Anemia	21 (75)	4 (14)
Leukopenia	20 (71)	11 (39)
Nausea	19 (68)	1 (4)
Pain	16 (57)	3 (11)
Vomiting	12 (43)	2 (7)
Hair loss/alopecia (scalp or body)	10 (36)	
Neutropenia	9 (32)	2 (7)
Anorexia	9 (32)	
Constipation	7 (25)	
Dyspnea (shortness of breath)	7 (25)	
Diarrhea	6 (21)	1 (4)
Dizziness	6 (21)	
Dehydration	5 (18)	1 (4)
Neuropathy (sensory)	5 (18)	
Weight loss	5 (18)	
Cough	4 (14)	
Tinnitus	4 (14)	
Febrile neutropenia	3 (11)	3 (11)

residual involvement of $>25\%$ that prohibited them from receiving ibritumomab tiuxetan. The ORR for the entire study was 77.3%, with 10 (45%) achieving CR, 32% having partial response (PR) and 14% with stable disease. There was a slight difference in response rates between patients that received one prior regimen (ORR 83%), and those that received more than one prior regimen (ORR

70%). Patients that received one prior regimen achieved 42% CR, while patients with more than one prior regimen achieved 50% CR. Patients with progressive disease with prior therapies had 50% CR and 25% PR, similar to the response in patients with non-progressive disease.

The median follow-up time was 73.0 months (95% CI: 51.6–89.0). In an intent-to-treat analysis, the median PFS was 10.0 months (95% CI: 8.0–18.0) (Fig. 1a), and the median OS was not reached (95% CI: 34.0–not reached) (Fig. 1b). For the 22 evaluable patients, 1-year PFS was 38%, median TTP was 18.0 months (95% CI: 9.2–39.4), median PFS was 10.0 months (95% CI: 8.0–32.0) (Fig. 2a), and median OS was not reached (Fig. 2b) (95% CI: 54.0 months–not reached). Results were best for the patients in CR, with 1-year PFS of 50%, median PFS of 12 months (95% CI: 7.0–54.0), and OS not reached (95% CI: 17 months–not reached) (Fig. 3a, b). Patients treated with one prior regimen had a 1-year PFS of 42%, with a median PFS of 9 months (95% CI: 7.0–32.0), while median OS was not reached. In patients treated with more than one prior regimen, 1-year PFS was 40%, with a median PFS of 11 months (95% CI: 6.0–46.0), and OS was also not reached.

Discussion

FL is a biologically heterogeneous disease with evolving therapeutic options in the relapsed refractory setting [14]. This study was open to accrual prior to the development of novel chemotherapeutic, immunotherapeutic, and targeted agents including bendamustine, idelalisib, venetoclax, and obinutuzumab. Bendamustine in partic-

Fig. 2. Kaplan-Meier survival estimates of evaluable patients ($n = 22$). **a** Median progression-free survival (PFS). **b** Median overall survival (OS).

Fig. 3. Kaplan-Meier survival estimates of evaluable patients who achieved complete response. **a** Median progression-free survival (PFS). **b** Median overall survival (OS).

ular adversely affected accrual in this study, leading to institutionally mandated closure.

ESHAP followed by ibritumomab tiuxetan had tolerable toxicity, with only 11% experiencing febrile neutropenia and no significant renal complications. Only 2 patients withdrew due to toxicity. Two patients did develop MDS, to which ibritumomab tiuxetan could have contributed, but that cannot be separated from the contribution of marrow toxicity from prior chemotherapy regimens [15]. In fact, 1 patient subsequently underwent an allogeneic bone marrow transplant prior to the development of MDS. This is lower than estimates reported in the literature, where the risk of MDS/acute myelogenous leukemia has been estimated to be up to 14% [16]. Further, ESHAP lends itself to combinations nicely [17], and it was not associated with increased nephrotoxicity or neuropathy, thus proving itself as a feasible salvage regimen.

Several factors could have contributed to the trial not reaching its primary endpoint. The trial was closed before reaching its target due to low accrual. It enrolled a high-risk population, with 49% having high-risk disease (FLIPI), and 39% having progressive disease with the last prior therapy. Two cycles of ESHAP may have provided inadequate debulking, evidenced by 3 patients not being able to proceed with ibritumomab tiuxetan due to significant residual bone marrow involvement. Rituximab was not combined with ESHAP so as not to compete with ibritumomab tiuxetan for CD20 binding, and thus interfere with its efficacy [18]

However, the ORR rate of our study was similar to other studies of chemotherapy followed by RIT; for example, Illidge et al. [19] used 3 cycles of R-CHOP or R-CVP prior to ibritumomab tiuxetan in 50 patients. The ORR was 98%, CR was 30% (improving to 44% on follow-up), with

a median PFS of 23.1 months and OS of 77.5% at 5 years. Pisani et al. [20] treated 9 patients with 4 cycles of FCR (fludarabine, cyclophosphamide, rituximab) followed by ibritumomab tiuxetan, with 7 patients achieving CR and 2 PR (converted to CR after ibritumomab tiuxetan). OS or PFS were both 67% at 7.5 years, with 3 patients dying while still in CR. While the majority of chemotherapy-RIT consolidation studies reporting excellent outcomes have been conducted in previously untreated patients [21], in our study there was notably no significant difference in the ORR, PFS, or OS of patients that had received one versus more than one prior regimen, and this protocol also effectively salvaged patients with progressive disease to prior therapies. In two reports, data from the four registration trials of Zevalin were analyzed retrospectively. Long-term responses (TTP ≥ 12 months) were noted in only 37% of 211 patients treated in these trials. The achievement of CR seemed to be the best predictor for achievement of long-term response [22, 23]. This is also noted in our data set, where responders in CR had the best TTP and PFS. Other predictors for durable remissions in a stepwise multivariate logistic regression analysis were tumor size (< 5 cm) and stage I or II disease at the time of RIT [22, 23]. In our study, at least half the patients had bone marrow involvement and one fourth had tumors > 5 cm, which may have adversely affected the response rates and PFS.

Another paradigm shift in the landscape of FL has been the recent realization of a high-risk group of patients that progress within 24 months after therapy, especially following an anthracycline-based therapy (R-CHOP) [24]. Our study enrolled and accrued prior to this discovery.

In summary, while we report a negative trial with respect to the primary endpoint of 1-year PFS with 2 cycles of ESHAP followed by Zevalin, this protocol was associated with low toxicity, good ORR, and good OS, regardless of the number of prior lines of therapy. Future directions of study would include conducting this trial in a high-risk patient population of FL such as that with event-free survival < 24 months, and optimizing debulking with ESHAP to improve subsequent clearance of lymphoma from the bone marrow space prior to treatment with Zevalin.

Statement of Ethics

All subjects who participated gave their informed consent to this study protocol which was approved by the institute's committee on human research.

Disclosure Statement

Dr. Anwer has received personal fees from Seattle Genetics and Incyte. Dr. Persky has received research funding from Merck and Spectrum Pharmaceuticals. Dr. Puvvada has received personal fees from Pharmacyclics, AbbVie, Gilead, and Seattle Genetics and research funding from Takeda, Spectrum, AbbVie, and Genentech Pharmaceuticals.

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