Safety and Efficacy of Combination Therapy with Fludarabine, Mitoxantrone, and Rituximab Followed by Yttrium-90 Ibritumomab Tiuxetan and Maintenance Rituximab as Front-Line Therapy for Patients With Follicular or Marginal Zone Lymphoma

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Abstract

Better survival outcomes in indolent lymphomas are needed. 22 patients withfollicular/marginal zone lymphoma were enrolled in a phase II clinical trial to receive chemoimmunotherapy followed by radioimmunotherapy consolidation and rituximab maintenance. This regimen was safe, obtaining high complete remission rates and durable responses. This approach warrants further investigation as it may provide a survival advantage in indolent lymphomas.

Background: We conducted a single-institution phase II clinical trial evaluating the safety and efficacy of combination chemoimmunotherapy followed by radioimmunotherapy consolidation and rituximab maintenance as front-line treatment in indolent lymphomas. **Patients and Methods:** We enrolled 20 patients with intermediate- to high-risk follicular lymphoma and 2 patients with marginal zone lymphoma. Treatment consisted of 4-6 cycles of FM (fludarabine 25 mg/m^2 on days 1-3, mitoxantrone 12 mg/m^2 on day 1 of each 28-day cycle). The protocol was amended after enrolling the first 4 patients to include rituximab 375 mg/m^2 on day 1. After 6-8 weeks, responders received ^{90}Y-ibritumomab tiuxetan (Zevalin) followed by maintenance rituximab (375 mg/m^2 weekly $\times$ 4 doses, repeated every 6 months for 2 years). **Results:** After R-FM, the overall response rate was 95% with a complete response rate (CR) of 45% (n = 10), a partial response (PR) rate of 50% (n = 11), and stable disease in 1 patient. Nineteen patients received ^{90}Y-ibritumomab tiuxetan with a 60% conversion rate of PR to CR, resulting in an improved CR of 79% (n = 15) and a PR of 21% (n = 4). Fifteen patients proceeded to rituximab maintenance resulting in 3 patients with PR converting to CR. At median follow-up of 49.6 months, median progression-free survival (PFS) was 47.2 months and median overall survival (OS) was not reached in an intent-to-treat analysis. The most common adverse effects were hematologic, with 2 patients experiencing treatment-related myelodysplastic syndrome (MDS), evolving to acute myelogenous leukemia (AML) in 1 patient. **Conclusion:** R-FM with ^{90}Y-ibritumomab tiuxetan consolidation and rituximab maintenance is well tolerated, improving CR rates and maintaining durable responses in patients with untreated indolent lymphomas.

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Introduction

Non-Hodgkin lymphomas (NHLs) are a diverse group of lymphoid neoplasms that collectively rank fifth in cancer incidence and mortality in the United States.[1-2] Among all NHLs, follicular lymphoma (FL) is the second most frequent subtype worldwide.[3] Although FL is generally considered an indolent disorder, survival duration is heterogeneous.

There is currently no specific standard of care for front-line treatment of indolent NHL, with widely disparate approaches. Attempts to treat B-cell malignancies with monoclonal antibodies reactive against B-cell antigens began more than a decade ago.[4-5] In FL, the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy yields high response rates (overall response rate [ORR], 100%; complete response [CR], 87%, and partial response [PR], 13%) [6-7] and molecular remission rates (eradication of *bcl-2*$^+$ cells from the peripheral blood and bone marrow).[8]

Similar if not better outcomes are seen with rituximab in combination with fludarabine, a purine analogue that produces response rates of 30%-50% as a single agent in relapsed FL.[9] Combination fludarabine-rituximab in patients with treatment-naive and relapsed indolent lymphoma/FL achieves an ORR of 90% (CR 80%) and a molecular remission rate of 88%.[10] Several phase II studies have since evaluated regimens incorporating fludarabine and mitoxantrone (FM) with rituximab,[11-12] reproducibly yielding ORRs approaching 100%, with CR rates between 89% and 98%.

Despite high initial response rates with advancing treatment strategies, the prognosis of indolent lymphomas remains virtually unchanged, with the majority of patients relapsing and durations of response diminishing with each subsequent treatment.[13-17] In an attempt to improve response rates, and potentially survival, strategies such as radioimmunotherapy consolidation and rituximab maintenance are being vigorously explored.

Radioimmunotherapy provides greatest efficacy (higher ORR and CR, longer progression-free survival [PFS]) when used earlier in the treatment sequence of FL.[18-21] Kaminski et al reported an ORR of 95%, with CR of 75% using radioimmunotherapy in the front-line therapy for FL.[22] Furthermore, debulking with chemotherapy (or chemoimmunotherapy) before radioimmunotherapy consolidation potentially improves treatment efficacy by reducing the overall tumor burden. This is supported by the FIT (First Line Indolent Trial), which reported the superiority of ^{90}Y-ibritumomab tiuxetan (Zevalin) consolidation vs. observation in patients with advanced-stage FL after induction chemotherapy.[21]

The established efficacy and tolerance of rituximab induction therapy in FL has led to the evaluation of various rituximab maintenance schedules.[23,24] The recent interim analysis of the PRIMA (Primary Rituximab and Maintenance) trial demonstrated a 2-year PFS advantage in patients who received rituximab maintenance after induction chemoimmunotherapy (68% vs. 82%, $P < .001$) validating this approach.[24]

In view of these findings, we sought to investigate the safety and efficacy of a novel strategy combining induction chemoimmunotherapy with FM and rituximab followed by consolidation with ^{90}Y-ibritumomab tiuxetan and maintenance rituximab in patients with previously untreated intermediate- or poor-risk indolent NHL.

Materials and Methods

Patient Eligibility

Patients with biopsy-proven, untreated, bidimensionally measurable stage II/IV (graded according to the Ann Arbor Staging System) FL expressing the CD20 antigen, with an intermediate to high Follicular Lymphoma International Prognostic Index (FLIPI) score were eligible for this trial. The protocol was later amended to include 2 patients with a FLIPI of 1 who fit criteria to initiate treatment and 2 patients with marginal zone lymphoma (MZL) with an intermediate- to high-risk International Prognostic Index (IPI). Diagnostic biopsies were reviewed by an institutional hematopathologist to confirm the diagnosis of FL or MZL according to the World Health Organization (WHO) classification. All patients underwent a 2-step registration process. The first registration was conducted at initial enrollment, and the second took place before the administration of radioimmunotherapy. For the first registration, inclusion criteria were age $\geq$18 years, expected survival $\geq$ 3 months, WHO performance status of 0 to 2, and acceptable hematologic status within 2 weeks before patient registration. Acceptable hematologic status was defined by an absolute neutrophil count $\geq$ 1500 cells/mm^3, platelet count $\geq$ 100,000 cells/mm^3, and no reduction in bone marrow precursors in any cell lines. Patients were excluded if they had prior history of treatment for a lymphoproliferative disorder, presence of central nervous system lymphoma, HIV- or AIDS-related lymphoma, abnormal liver function (total bilirubin level $>$ 2.0 mg/dL), abnormal renal function (serum creatinine level $>$ 2.0 mg/dL), previous external beam radiation therapy to $>$ 25% of active bone marrow (involved field or regional), previous growth factor support within 2 weeks of treatment, a cardiac ejection fraction of $<$ 45%, or positive hepatitis A or B antigen studies.

All eligible patients were required to undergo a full medical history, physical examination, computed tomography (CT) scan of the neck, chest, abdomen, and pelvis, and bilateral bone marrow biopsies and aspiration for histologic examination, flow cytometry, and cytogenetic analysis within 4 weeks before the first registration. An attempt was made to assay bone marrow cells and/or peripheral blood at baseline and after radioimmunotherapy with polymerase chain reaction for t(14;18) translocations in which the *bcl2* gene is juxtaposed with the immunoglobulin heavy-chain locus. However testing was inconsistent and no conclusions could be drawn regarding molecular response to our treatment strategy. Blood chemistry panels were also performed (including liver function tests and creatinine, uric acid, lactate dehydrogenase, and β_2-microglobulin levels).

Patients were restaged 4 to 6 weeks after their fourth cycle of R-FM chemotherapy by physical examination, blood testing, CT scans, and bone marrow aspiration and biopsy. Partial responders with $>$ 25% bone marrow involvement received 2 additional cycles of R-FM. Patients who achieved at least a PR after 4 to 6 cycles of R-FM were eligible for consolidation with ^{90}Y- ibritumomab tiuxetan provided that their granulocyte count was $>$ 1500 cells/mm^3, their platelet count was $>$ 100,000 cells/ mm^3, and their bone marrow examination had $\leq$ 25% involvement with lymphoma.

All patients were notified of the investigational nature of this study and gave informed consent in accordance with institutional guidelines, including the Declaration of Helsinki. The study was approved by the hospital institutional review board.