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A Phase 2 Study of Concurrent Fludarabine and Rituximab for the Treatment of Marginal Zone Lymphomas

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SUMMARY

The marginal zone lymphomas are a recently defined group of related diseases likely arising from a common cell of origin, the marginal zone B cell. Data on therapy for subtypes other than gastric MALT has been largely limited to retrospective case series. We therefore undertook this prospective phase 2 study of fludarabine and rituximab for the treatment of marginal zone lymphomas. 26 patients were enrolled, 14 with nodal MZL, 8 with MALT lymphomas and 4 with splenic MZL; 81% were receiving initial systemic therapy. Only 58% (95% CI 37–77%) of patients completed the planned six cycles, due to significant hematologic, infectious and allergic toxicity. Four late toxic deaths occurred due to infections (15% (95% CI 4.3–35%), two related to delayed bone marrow aplasia and two related to MDS. Nonetheless, the ORR was 85% (95% CI 65–96%), with 54% CRs. The progression-free survival at 3.1 years of follow-up is 79.5% (95% CI, 63–96%). We conclude that although concurrent fludarabine and rituximab given at this dose and schedule is a highly effective regimen in the treatment of marginal zone lymphomas, the significant hematologic and infectious toxicity observed both during and after therapy is prohibitive in this patient population, emphasizing the need to study marginal zone lymphomas as a separate entity.

Keywords

fludarabine; rituximab; marginal zone lymphoma; bone marrow aplasia; myelodysplasia

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INTRODUCTION

The marginal zone lymphomas (MZLs) have been recently defined as a group of related diseases likely arising from a common cell of origin, the marginal zone B cell. Although extranodal or mucosa-associated lymphoid tissue (MALT) lymphomas have been recognized for some time, splenic and nodal marginal zone lymphomas have been identified more recently as sharing the same monocytoid features and immunophenotype (Matutes, *et al* 2008, Melo, *et al* 1987, Nathwani, *et al* 1999, Sheibani, *et al* 1986).

The clinical presentation and disease course of each subtype varies. The non-MALT marginal zone lymphomas have been subcategorized in a large natural history study as nodal only, splenic only, disseminated (nodal and splenic), and leukemic only (Berger, *et al* 2000). Although the median time to progression of the splenic and leukemic subtypes was >5 years, the median TTP was only about one year for the nodal and disseminated subtypes, despite combination chemotherapy (Berger, *et al* 2000). Although median survival was greater than five years for all subtypes, the rapidity of progression of the nodal and disseminated subtypes suggested the potential for a more aggressive clinical course. Furthermore a recent prognostic model identified a subgroup of splenic MZLs with a five year cause specific survival of only 50% (Arcaini, *et al* 2006).

Given the recently developed classification of MZLs, data on therapy has necessarily been limited and almost entirely retrospective. These retrospective studies have found complete response rates with alkylating agent-based therapies, either single agent or CHOP-like regimens, to vary between 30 and 60% (Parry-Jones, *et al* 2003, Thieblemont, *et al* 1997, Thieblemont, *et al* 2000). Purine analogs have appeared more promising, with initial reports of not infrequent complete remissions in patients refractory to alkylators (Bolam, *et al* 1997, Matutes, *et al* 2008, Mulligan, *et al* 1991, Troussard, *et al* 1996, Yasukawa, *et al* 2002). More recent series have suggested that single agent rituximab is also highly active, particularly in splenic MZLs (Kalpadakis, *et al* 2007, Tsimberidou, *et al* 2006).

To date, only three disease-specific prospective studies have been reported and these enrolled only MALT lymphoma patients. The first looked at daily oral cyclophosphamide or chlorambucil in mostly stage I (with about a third stage IV) MALT lymphoma patients and found a 75% CR rate after one year (Hammel, *et al* 1995). The second reported a 84% CR rate with cladribine in chemotherapy-naïve MALT lymphoma patients, with median progression-free survival not yet reached at 27 months (Jaeger, *et al* 2002). The most recent reported that rituximab alone had an ORR of 87% with PFS 22 months in chemotherapy-naïve MALT patients, and ORR 45% with PFS 12 months in previously-treated MALT patients (Conconi, *et al* 2003). These studies suggest significant activity of a variety of chemotherapy agents in mostly early stage MALT lymphoma patients, but the efficacy of these regimens in advanced disease and the expected duration of response remain unclear. Furthermore, no prospective chemotherapy studies have been reported in other subtypes of marginal zone lymphomas. We therefore decided to undertake this disease-specific prospective study, combining the purine analogue fludarabine with rituximab, in an effort to prolong progression-free survival compared to rituximab in this patient population.

METHODS

Eligibility

This prospective study was performed at the Dana-Farber Cancer Institute, University of Rochester James P Wilmot Cancer Center, Massachusetts General Hospital and Beth Israel Deaconess Medical Center between January 2004 and June 2007. Patients were enrolled who had newly diagnosed or relapsed, histologically confirmed MALT lymphoma, nodal or

splenic marginal zone lymphoma, or a CD5 / CD10 negative low-grade B cell lymphoproliferative disorder which the hematopathologists were unwilling to definitively subclassify. However, the latter patients were assigned a subtype of MZL on clinical grounds, and patients with pathologically or clinically identifiable lymphoplasmacytic lymphoma or Waldenstrom's macroglobulinemia were excluded. Enrolled patients could not be candidates for potentially curative local radiation or antibiotic therapy. Prior therapy with rituximab or radiation was permitted, but patients who had received prior fludarabine-based therapy were excluded. All patients were required to have normal renal function prior to enrollment.

Treatment Program

The planned therapy included 6 cycles of fludarabine at the standard dose of 25 mg/m² on days 1–5 with rituximab 375 mg/m² on day 1 of a 28 day cycle (Czuczman, *et al* 2005). The rituximab dose in the 1st cycle was split between days 1 and 3 for patients with absolute lymphocyte counts greater than 10,000 / μ l. During the first cycle all patients also received allopurinol and intravenous hydration. All patients received infectious prophylaxis with trimethoprim-sulfamethoxazole (or equivalent) for *Pneumocystis jiroveci* (PCP) pneumonia and acyclovir (or equivalent) for varicella zoster virus reactivation. These drugs were continued for a minimum of one month after therapy. After significant allergic hypersensitivity and/or rash were seen in the first several patients, the protocol was modified to require daily administration of a prophylactic antihistamine, preferably diphenhydramine but nonsedating antihistamines were also permitted.

In order to receive the next cycle of therapy, hematologic recovery with absolute neutrophil count (ANC) greater than 1500 / μ l and platelets greater than 75,000 / μ l was required. Subjects who experienced grade 3 or 4 neutropenia received myeloid growth factors in subsequent cycles. Those subjects whose hematologic recovery did not meet the above criteria had delay of their therapy, and in subsequent cycles received myeloid growth factors. If treatment delay continued despite myeloid growth factors, or for those patients experiencing grade 3 or 4 thrombocytopenia, dose reductions of fludarabine to 80% dose and then to 60% dose were required. A delay greater than 6 weeks in initiating the next cycle resulted in mandatory removal from the study.

Study Evaluations

Screening evaluation included CT scans of the chest / abdomen / pelvis, bone marrow biopsy, and histology review for confirmation of diagnosis. Fluorescence in situ hybridization (FISH) for BCL-6, trisomy 3, MALT1 and chromosome 1 rearrangements (using probes for 1p36 and 1q25) was performed on paraffin-embedded diagnostic tissue biopsies or bone marrow biopsies when possible (n=19 available tissue biopsies). Karyotypes from tissue biopsies were not routinely available but deletion of 7q was identified in one case. CT scans were repeated after 3 cycles of therapy and again after 6 cycles of therapy or at the time of removal from study. Response evaluation was based on the Cheson criteria for all patients (Cheson, *et al* 1999a). A bone marrow biopsy was repeated at the conclusion of therapy only if the initial biopsy was involved with lymphoma. Patients were followed with clinic visits, laboratory evaluation and CT scanning every 6 months for four years following therapy.

Statistical Methods

Overall survival (OS) is defined as the time from initiation of study therapy to death from any cause. Progression free survival (PFS) is defined as the time from initiation of study therapy to the first reported outcome event. Outcome events include progression of disease or death from any cause. PFS and OS curves were obtained using the Kaplan-Meier method,

with 95% confidence intervals calculated using Greenwood's formula (Kaplan and Meier 1958, Mantel 1966). The effects of potential prognostic factors for PFS and OS were assessed using Cox multivariable regression models.

RESULTS

Patient Characteristics

26 patients were enrolled on this prospective phase 2 study between January 2004 and June 2007. The characteristics of the patients are detailed in Table 1. All patients had marginal zone lymphomas, with nodal predominating (N = 14) followed by MALT (N = 8). The sites of extranodal involvement of MALT lymphomas included lung (4), gastric (2), orbital adnexae (1), and skin (1). The predominant cytogenetic abnormalities involved chromosome 3, seen in 37% of evaluable patients, including 5 nodal and 1 splenic MZL. Four patients (21%) had co-existent lesions of chromosomes 3 and 1. Two patients, one with MALT and one with nodal MZL, had rearrangements of MALT1.

The great majority of the patients were previously untreated, with stage IV disease. Six of the eight patients with MALT lymphoma had stage IV disease, and none were candidates for local therapy. Three of the four splenic marginal zone lymphoma patients had recurrent disease after prior splenectomy. Five of the 26 patients had received prior systemic therapy, although prior fludarabine-based therapy was an exclusion criterion. The study therapy was the second regimen for two patients (R-CVP or rituximab previously), the third regimen for two patients (rituximab x 2 for one, chlorambucil then cyclophosphamide-rituximab for the other), and the final patient had had CVP, rituximab twice, and R-CHOP and ESHAP followed by BEAM-autologous stem cell transplantation.

Planned Therapy

Although the planned therapy included 6 cycles of fludarabine and rituximab, only 58% (95% CI 37–77%) of patients were able to complete the planned therapy. The majority discontinued therapy due to unacceptable toxicity (N = 9, 35%), with one additional patient removed at the site investigator's discretion (for confusion likely unrelated to therapy) and a second additional patient removed to receive therapy for a newly diagnosed but pre-existing second malignancy. Of those who discontinued therapy for toxicity, the majority did so for hematologic toxicity (6), two for unacceptable or recurrent rash (2), and one for a delayed hypersensitivity reaction to rituximab (1). After the addition of daily prophylactic antihistamine therapy to the protocol requirements, the frequency of rash and hypersensitivity reactions declined significantly.

Toxicity

The overall rate of grade 3–4 toxicities was significant and is enumerated in Table II. 77% of patients experienced at least one grade 3 or higher toxicity, and 42% of patients experienced at least one grade 4 or higher toxicity. All grade 4 toxicities were hematologic, including 38% of patients who experienced grade 4 neutropenia at some point in their course and 12% of patients who experienced grade 4 thrombocytopenia. The use of myeloid growth factors after the 1st cycle of therapy was at the discretion of the treating physician. 18 of 26 patients received myeloid growth factors at some point during the study (69%). Despite this, over half of the patients had at least one treatment delay (14 of 26; 54%), and 31 out of a total of 126 cycles of therapy were delayed (25% of cycles), most frequently due to neutropenia. Seven patients were treated with fludarabine at reduced dose, with three receiving 80% dose, and one of those and four others receiving 60% dose; in all, 14 of 126 cycles (11%) were given with reduced doses of fludarabine.

Significant delayed infectious toxicity was also observed. The protocol required that all patients receive prophylaxis against PCP during therapy and for at least one month afterward; nonetheless, one patient who continued prophylaxis for six months after therapy developed confirmed PCP nine months after therapy. A second patient was treated for presumed PCP (without confirmation of diagnosis) at four months after therapy, and recovered. An additional patient developed *Nocardia pneumonia* at 4.5 months after completion of protocol therapy.

Delayed hematologic toxicity was also evident. Two patients developed bone marrow aplasia in the first months after completing therapy. The first patient, whose sixth and final cycle of therapy started on 11/5/07, was admitted with fever and neutropenia on 3/11/08 and died the following day of gram negative sepsis. Bone marrow biopsy was severely hypocellular, without evidence of lymphoma, and cytogenetics showed a normal karyotype. The second patient, whose last cycle of therapy was on March 7, 2005, went on to develop a cold agglutinin hemolytic anemia concomitant with bone marrow aplasia, and ultimately died of sepsis in the setting of neutropenia in January 2006. Her bone marrow biopsy performed on 12/2/05 showed a markedly hypocellular marrow (<5% cellular) consistent with aplastic anemia, with insufficient cells for cytogenetic analysis but FISH analysis did not reveal deletion or monosomy of chromosomes 5 or 7.

Two other patients have subsequently developed biopsy-proven myelodysplasia, specifically refractory cytopenia with multilineage dysplasia (RCMD). The first had developed progressive lymphoma for which a course of single-agent rituximab was given, which was complicated by multiple infections and worsening pancytopenia. Bone marrow biopsy performed 38 months after conclusion of study therapy was consistent with RCMD, with complex cytogenetics including monosomy 5 and monosomy 7. The second patient, who had been previously treated with R-CVP but who had had no additional therapy after completing study therapy in 2/2005, presented with rapid onset pancytopenia in 7/2008 and bone marrow biopsy revealed RCMD, with complex cytogenetics including 5q deletion. Both of these patients succumbed to infection shortly after their diagnoses of MDS.

Thus four patients of 26 (15%; 95% CI 4–35%) developed significant delayed bone marrow toxicity which led to their deaths in all four cases. These patients had received nearly full-dose therapy with minimal to no growth factor exposure (three received 6 full-dose cycles and the fourth 5 cycles; two did not receive any myeloid growth factors while the other two each received a single dose of pegfilgrastim). Two had received no prior therapy, one had been previously treated with two courses of single-agent rituximab and the fourth had received prior R-CVP. Development of grade 5 delayed bone marrow toxicity was not significantly associated with a history of therapy prior to this study, with the number of cycles of FR received, or with grade 4 hematologic toxicity during the study therapy.

Treatment Outcomes

Despite the shortened course of therapy for many patients, fludarabine and rituximab was highly effective, with 14 patients achieving CR/CRu and 8 patients achieving PR (Table III). The objective response rate was 85% (95% CI 65–96%), with 54% CRs. Only one patient progressed on therapy. With a median follow-up of 3.1 years (range 1.0 – 4.7), three additional patients have relapsed, at 13 months, 33 months and 38 months after therapy. The progression-free survival at 3.1 years of follow-up is therefore 79.5% (95% CI, 63.4% to 95.6%; Figure 1).

Six deaths have occurred, none due to lymphoma. As detailed above, four patients have died of infections in the setting of bone marrow disorders, two with aplasia and two with myelodysplasia. Two additional deaths were due to lung cancers, neither of which appeared

to be related to study therapy. One lung cancer was present prior to the start of study therapy, while the other was diagnosed 29 months after completion of study therapy, in a patient with a history of asbestos exposure. The overall survival at 3.1 years of follow-up is therefore 87.4% (95% CI, 74.0% to 99%; Figure 1). No significant difference in PFS or OS was observed based on the time from diagnosis to treatment, subtype of marginal zone lymphoma, or number of treatment cycles received.

DISCUSSION

The provisional description of marginal zone lymphomas as a group of indolent lymphomas separable from follicular lymphomas and CLL/SLL has been recent, and data on natural history and treatment response have therefore been very limited. SWOG found through pathologic review that MZL patients actually represented about 10% of advanced stage indolent lymphoma patients enrolled on their older upfront CHOP studies (Fisher, *et al* 1995). The MZLs had similar outcomes to the other indolent lymphomas on those studies, albeit with some heterogeneity (Fisher, *et al* 1995). Since then the advent of rituximab has impacted the natural history of follicular lymphoma significantly (Fisher, *et al* 2005, Marcus, *et al* 2005, van Oers, *et al* 2006), yet little to no data are available to address whether the natural history of MZLs has changed, given improved supportive care and the significant activity of rituximab in MZL (Conconi, *et al* 2003, Kalpadakis, *et al* 2007, Tsimberidou, *et al* 2006).

Our goal in this study was to improve upon the progression-free survival of single-agent rituximab in MALT lymphomas, by investigating the safety and efficacy of combining rituximab with fludarabine in patients with more aggressive MZLs. In this paper we report the first prospective treatment study enrolling exclusively MZLs and including subtypes other than extranodal MALT lymphomas. We have found that although the FR regimen is highly effective, its short and long-term hematologic and infectious toxicity is prohibitive in this patient population. Although cytopenias have been significant in all studies, the toxic death rate of 15% that we observe is meaningfully greater than the 0% toxic death rate reported for FR in both follicular lymphoma (Czuczman, *et al* 2005) and CLL/SLL (Byrd, *et al* 2003).

The patient population targeted by this study was the subset with advanced stage aggressive MZL, and in fact that subgroup was well-represented among the patients treated. Most of the patients had nodal MZL or stage IV MALT lymphomas, and 75% of the splenic MZLs had recurred with disseminated disease after splenectomy. Despite this patient population, we found that the FR combination was a highly effective therapy in this disease subgroup, resulting in a 85% response rate and a 79.5% three-year progression free survival, with only three relapses. This high efficacy is similar to that reported in previous studies of FR in other low-grade lymphomas (Czuczman, *et al* 2005, Savage, *et al* 2003), CLL (Byrd, *et al* 2003, Schulz, *et al* 2002), and Waldenström's macroglobulinemia (Treon, *et al* 2008), and does represent an improvement over prior studies in marginal zone lymphomas (Conconi, *et al* 2003, Hammel, *et al* 1995, Jaeger, *et al* 2002).

However these results came at a significant cost: hematologic and allergic toxicity, as well as a high rate of infections during and shortly after therapy. Although the rate of grade 3 or 4 neutropenia during therapy in this study was approximately comparable to other studies (58% vs 70–80% (Byrd, *et al* 2003, Czuczman, *et al* 2005, Treon, *et al* 2008), the occurrence of treatment-related rash requiring discontinuation of therapy has not been reported in other series and may therefore be more common in patients with MZL. Furthermore, although the overall rate of grade 3 or 4 fever or infection in this study (27% including 3 fevers, 1 pulmonary infection during therapy and 3 shortly after) was similar to

two prior studies (Byrd, *et al* 2003, Czuczman, *et al* 2005), both of these prior studies included in their total infection rate a significant number of dermatomal varicella zoster infections and localized herpes simplex infections, which did not occur in this study due to the incorporation of antiviral prophylaxis. The rate of other serious fever or pulmonary infection in those studies was 6–10%, significantly lower than observed in this patient population.

Of particular concern, however, was the occurrence in this study of delayed neutropenia several months after completion of therapy, which led directly to two infectious deaths. Although grade 3–4 neutropenia is commonly seen during therapy, neutropenia occurring outside the usual post-therapy window but earlier than expected for secondary myelodysplasia has not been reported in prior studies of FR (Byrd, *et al* 2003, Czuczman, *et al* 2005, Savage, *et al* 2003, Schulz, *et al* 2002) or in long-term follow-up studies of the rate of secondary myelodysplasia and AML (Cheson, *et al* 1999b, McLaughlin, *et al* 2005, Morrison, *et al* 2002). Both of these patients had aplastic bone marrow affecting all lineages but without evidence of cytogenetic abnormalities associated with MDS. The natural history of this apparent aplastic anemia is unknown because both patients died of infectious complications; their bone marrow might have recovered spontaneously with time, remained unchanged, or progressed to MDS.

Two other patients of the 26 treated were in fact subsequently diagnosed with MDS. Although multiple cases of MDS/AML occurring after fludarabine have been reported, systematic studies have suggested that the risk is low. A recent retrospective study in Waldenstrom macroglobulinemia patients treated with nucleoside analogs reported a 1.6% rate of MDS/AML (Leleu, *et al* 2009). However, long-term follow-up of 724 CLL patients treated with fludarabine on NCI protocols identified 1 case of AML (Cheson, *et al* 1999b). On CALGB 9011, only one of 188 patients (0.5%) receiving fludarabine alone developed MDS/AML, as compared to 5 of 142 (3.5%) patients treated with fludarabine and chlorambucil (Morrison, *et al* 2002). Similarly, the MD Anderson has reported that 8 of 202 low-grade lymphoma patients (4%) treated with fludarabine, mitoxantrone and dexamethasone developed MDS between 1 and 5 years later (McLaughlin, *et al* 2005). Another recent report on 137 patients treated with fludarabine and cyclophosphamide-containing therapies in Australia found that previously untreated patients had MDS rates of 2.5%, compared to 9.3% for previously treated patients (Tam, *et al* 2006). These reports strongly suggest that fludarabine may induce MDS at higher rates when combined with cytotoxic chemotherapy, but rituximab would not be expected to produce this effect. In fact, the only other report of MDS/AML occurring after FR has just been published, with 3 cases occurring in 43 patients enrolled on a prospective study of FR in Waldenstrom macroglobulinemia (Treon, *et al* 2008). This variability in rates of MDS/AML may suggest that certain lymphoma patient populations have unique susceptibility.

We conclude that although fludarabine-rituximab has been reasonably well-tolerated in CLL and other low-grade lymphomas, in this study restricted to patients with marginal zone lymphomas we have found that the regimen results in significant allergic, infectious, and particularly hematologic toxicity, leading to a toxic death rate of approximately 15%. These findings underscore the importance of performing disease-specific prospective trials whenever possible, and suggest that future studies in MZL patients could focus on alkylating agents in combination with rituximab, which have not been formally studied in this disease, or alterations in dose and schedule to reduce the toxicity of FR, which remains a highly effective regimen in this patient population.

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Figure 1. Progression-Free and Overall Survival

At a median follow-up of 3.1 years, 79.5% (95% CI, 63.4% to 95.6%) of patients remain in ongoing remission. 87.4% (95% CI, 74.0% to 99%) of patients are alive. No deaths have occurred due to lymphoma.

Table I**Patient Characteristics**

N	26
Median age (range)	63.7 (31.4–84.0)
Median Time from Diagnosis to Treatment	1.6 mos (0.5, 75.2)
Previously Untreated	21 (81%)
Histology	
Nodal Marginal Zone Lymphoma	14 (54%)
MALT	8 (31%)
Splenic Marginal Zone Lymphoma	4 (15%)
Stage	
IE	1 (4%)
II	2 (8%)
III	5 (19%)
IV	18 (69%)
BM Involvement	
Yes	8 (31%)
No	13 (50%)
Unknown	5 (19%)

Table II**Treatment-Related Toxicities**

Toxicities	Patients
Any Grade 3	9 (35%)
Any Grade 4	11 (42%)
Neutropenia	15 (57%)
Grade 3	5 (19%)
Grade 4	10 (38%)
Febrile Neutropenia	2 (8%)
Thrombocytopenia	7 (27%)
Grade 3	4 (15%)
Grade 4	3 (12%)
Rash	2 (8%)
Grade 3 Toxicities Seen Once:	7 (26%)
Allergic Reaction	
Confusion	
Myositis	
Fever	
Anorexia	
Dehydration	
Upper Resp / Pulm Infection	
Delayed Toxicities	
Pneumonia	
Nocardia	1 (4%)
Pneumocystis jiroveci Confirmed + presumed	1 + 1 (4–8%)
Hematologic	
Aplastic anemia	2 (8%)
MDS (Refractory cytopenia w multilineage dysplasia)	2 (8%)

Table III**Patient Outcomes**

ORR (N = 26)	22 (85%; 95% CI 65–96%)
CR / CRu	14 (54%)
Relapses	1 PD and 3 relapses
Deaths	6 (Two lung cancers; four infections, two with MDS and two with delayed bone marrow aplasia)