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ORIGINAL ARTICLE

Non-gastric marginal zone B cell lymphoma: clinicopathologic features and treatment results

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Abstract The optimal treatment strategy and outcome of non-gastric marginal zone lymphoma (MZL) remains undefined. The role of rituximab and fludarabine in MZL has not been critically appraised and compared with conventional chemotherapy. We retrospectively analyzed 81 consecutive patients with non-gastric MZL (mucosa-associated lymphoid tissue lymphoma, n=66; splenic MZL, n=11; nodal MZL, n=4). As a group, the treatment results were favorable, with an overall response rate of 87% and a complete response (CR) rate of 73%. The CR rate was similar for conventional chemotherapy, and rituximab- and fludarabine-containing regimens. However, the relapse rate was significantly decreased in rituximab- and fludarabine-containing regimens. The use of rituximab and fludarabine was associated with acceptable side effects. For splenic MZL, splenectomy was significantly associated with a superior CR rate. Early stage, good performance status, and low international prognostic index risk scores significantly impacted on CR rate and survivals. Rituximab and fludarabine were safe for non-gastric MZL and resulted in more durable remissions.

Keywords Non-gastric marginal zone lymphoma · Mucosa-associated lymphoid tissue · Splenic marginal zone lymphoma · Rituximab · Fludarabine

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Introduction

The World Health Organization (WHO) classification of lymphoid malignancies distinguishes between three different subtypes of marginal zone B cell lymphomas: splenic B cell marginal zone lymphoma (splenic MZL) [1], extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) [2], and nodal marginal zone lymphoma (nodal MZL) [3]. MZLs are derived putatively from memory B cells that have passed through the germinal center (post-germinal center memory B cells) [4]. The lymphoma cells, similar to their putative normal counterparts, possess a remarkable capability to home to sites where they have undergone antigenic stimulation, including MALT, the spleen, and lymph nodes [5], accounting for the formation of lymphomas in these sites. However, despite a common cell origin, MZL originating at different anatomical sites have distinct clinicopathologic features and treatment outcome [1–3].

Infections or chronic inflammation may provide the antigenic stimulation in the initial stages of lymphomagenesis. Relevant infections include *Helicobacter pylori* in gastric MALT lymphoma, *Campylobacter jejuni*, *Borrelia burgdorferi*, and *Chlamydia psittaci* in extranodal MZL, and hepatitis C virus in splenic MZL [6]. Chronic inflammation due to autoimmune diseases, commonly involving Sjögren syndrome and Hashimoto thyroiditis, also predisposes to extranodal MZL [6].

MZLs are considered low-grade lymphomas. Gastric MALT lymphoma is the most common MZL. The efficacy of *H. pylori* eradication and the subsequent therapeutic strategies for gastric MZL have been well defined [7]. For non-gastric MZL, however, the optimum

treatment is less well established because most large series contained a mixture of gastric and non-gastric MZL and rarely analyzed these disease entities separately.

Two classes of drugs, rituximab and purine analogues (including fludarabine and 2-chlorodeoxyadenosine), have made a major positive impact on the treatment outcome of low-grade lymphomas, particularly follicular lymphoma. However, their efficacy in the management of MZL has only recently been examined [8–11], although their role in comparison with other conventional regimens is still undefined.

In this study, we retrospectively analyzed a consecutive cohort of patients with non-gastric MZL in order to define the clinicopathologic features and the role of rituximab and the purine analogue fludarabine in comparison with alkylating agents in the treatment of these lymphomas. Although there is as yet no definitive evidence that non-gastric MZL, splenic MZL, and nodal MZL are distinctive diseases, increasing evidence suggests that they have different clinicopathologic features and treatment outcome. Therefore, they were also both analyzed individually and together as a group in this study.

Materials and methods

Patients

Consecutive patients with non-gastric MZL diagnosed between January 1998 and January 2010 were analyzed. There were no exclusion criteria. The diagnoses were based on the WHO classification criteria of MZL [1–3].

Investigations and treatment

Standard staging procedures including bilateral bone marrow trephine biopsies were adopted. Computerized tomography, magnetic resonance imaging, or positron emission tomography/computerized tomography was used for the detection of organ or tissue involvement at the primary site, thorax and abdomen. Treatment regimens were determined at the discretion of the attending physicians.

Statistical analysis

Response to treatment was determined by standard criteria [12]. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Disease-free survival (DFS) was calculated from the date of achievement of complete response to date of death, disease relapse/progression, or date of last follow-up. Difference between treatment groups was calculated by chi-square test. Prognostic factors for complete response (CR) and mortality were identified with logistic regression analysis. Five-year OS and DFS were estimated through the Kaplan–Meier method, and comparisons between treatment regimens were performed using Cox regression analysis.

Results

Patients

Eighty-one patients were identified (Table 1). There was no gender preference, with a median age of presentation at 57 (15–86)years. MALT lymphomas were most prevalent, followed by splenic and nodal MZL. Patients predominantly presented with early-stage disease, with good performance status and no B symptoms. Therefore, the majority of patients had favorable International Prognostic Index (IPI) scores. Paraproteins were present in 15 of 81 (18%) patients. About 20% of patients had a known underlying autoimmune disease. Chronic hepatitis B virus infection was found in 17% of patients, which was comparable with the general population. Hepatitis C infection was only found in one patient. Notably, two of the patients were siblings, having splenic and nodal MZL, respectively.

Non-gastric MALT lymphoma

Sixty-six patients had MALT lymphomas (Table 2). Early-stage (stage I/II) disease was found in 80% of patients. The most common sites of presentation were ocular and ocular adnexal structures (29%), followed by the salivary glands (20%). Multiple sites of involvement were found in eight patients (12%). None of the patients with ocular MALT lymphoma had autoimmune disorders. However, seven patients with salivary gland (11%) and two patients with thymic involvement (4%) had underlying Sjögren syndrome. All four patients with thyroid MALT lymphoma had autoimmune thyroiditis with hypothyroidism. Autoimmune thyroid disease was also found in a patient with skin MALT lymphoma. Other associations were mixed connective tissue disease in a patient with submandibular involvement and Graves' disease in a patient with conjunctival involvement. Therefore, the frequency of autoimmune diseases in this group of patient was 24% (16/66). A monoclonal paraprotein was detected in 12 patients (18%). Whereas immunoglobulin (Ig) M and G were found in MALT lymphoma in various sites, IgA was detected only in two patients with thymic involvement.

Table 1 Clinicopathological features of 81 patients with marginal zone lymphoma

Clinicopathological features	Number (%)
Gender	
Male	38 (47)
Female	43 (53)
Median age (range), years	57 (15–86)
Diagnosis	
Non-gastric MALT lymphoma	66 (81)
Splenic marginal zone B cell lymphoma	11 (14)
Nodal marginal zone lymphoma	4 (5)
Ann Arbor stage	
I	41 (51)
II	13 (16)
III	5 (6)
IV	22 (27)
Presence of B symptoms	6 (7)
Performance status	
0	46 (57)
1	21 (26)
2	11 (13)
3	3 (4)
4	0 (0)
International prognostic index	
Low (0 or 1)	35 (43)
Low/intermediate (2)	23 (28)
Intermediate/high (3)	16 (20)
High (4 or 5)	7 (9)
Lactate dehydrogenase	
Increased	65 (80)
Normal	14 (17)
Not available	2 (3)
Paraprotein	
Immunoglobulin G	4 (5)
Immunoglobulin M	6 (7)
Immunoglobulin A	2 (2)
Two monoclonal antibodies	3 (4)
Not present	60 (74)
Not available	6 (7)
Hepatitis B virus infection	
Positive	14 (17)
Negative	64 (79)
Not available	3 (4)
Concomitant autoimmune disorders	
Present	18 (22)
Absent	63 (79)

Splenic MZL

Eleven patients (nine men, two women) had splenic MZL (Table 3). Moderate splenomegaly (median size 10 cm

Table 2 Clinicopathological features of 66 patients with non-gastric MALT lymphoma

Clinicopathological features	Number (%)
Gender	
Male	27 (41)
Female	39 (59)
Median age (range), years	57 (15–86)
Primary site(s) of presentation	
Ocular and ocular adnexae	19 (29)
Salivary gland	13 (20)
Buccal mucosa	2 (3)
Nasopharynx	1 (2)
Cricoid	1 (2)
Tonsils	1 (2)
Thyroid gland	4 (6)
Thymus	1 (2)
Lungs	6 (9)
Intestine	5 (8)
Omentum	1 (2)
Testes	1 (2)
Cutaneous	3 (5)
Two or more anatomical sites	8 (12)
Ann Arbor stage	
I	41 (62)
II	12 (18)
III	4 (6)
IV	9 (14)
International Prognostic Index	
Low (0 or 1)	55 (83)
Low/intermediate (2)	9 (14)
Intermediate/high (3)	2 (3)
High (4 or 5)	0 (0)
Paraprotein	
Immunoglobulin G	3 (5)
Immunoglobulin M	4 (6)
Immunoglobulin A	2 (3)
Two monoclonal antibodies	3 (5)
Not present	49 (74)
Not available	5 (8)
Associated autoimmune diseases	
Sjögren syndrome	9 (14)
Parotid MALT lymphoma	4 (6)
Submandibular MALT lymphoma	1 (2)
Minor salivary gland MALT lymphoma	2 (3)
Thymic MALT lymphoma	1 (2)
Multifocal MALT lymphoma involving also the thymus	1 (2)
Autoimmune thyroiditis with hypothyroidism	5 (8)
Thyroid MALT lymphoma	4 (6)
Cutaneous MALT lymphoma	1 (2)
Mixed connective tissue disease	1 (2)
Submandibular MALT lymphoma	1 (2)
Graves' disease	1 (2)
Conjunctival MALT lymphoma	1 (2)

Table 3 Clinicopathologic features and treatment results of 11 patients with splenic marginal zone lymphoma

Parameters	Number (%)
Gender	
Male	9 (82)
Female	2 (18)
Median age (range), years	50 (35–80)
B symptoms	3 (27)
Splenomegaly	11 (100)
Median size (range), cm below left costal margin	10 (5 25)
Hepatomegaly	2 (18)
Hematological parameters	
Anemia (Hb <11 g/dL)	7 (64)
Lymphocytosis (>4 × 10^9/L)	5 (45)
Neutropenia (<2 × 10^9/L)	2 (18)
Thrombocytopenia (<100×10^9/L)	5 (45)
Leukemic phase	5 (55)
Marrow infiltration	11 (100)
Paraproteinemia	
IgG	1 (9)
IgM	1 (9)
International prognostic index	
Low (0 or 1)	1 (9)
Low/intermediate (2)	3 (27)
Intermediate/high (3)	5 (45)
High (4 or 5)	2 (18)
Treatment and outcome	
Splenectomy + chemotherapy[a]	3 (27)
CR	2/3 (67)
PR	1/3 (33)
Splenectomy + rituximab + chemotherapy[a]	2 (18)
CR	2/2 (100)
Chemotherapy[a]	5 (45)
CR	1/5 (20)
NR	4/5 (80)
Chemotherapy[a] + rituximab	1 (9)
PR	1/1 (100)

Ig immunoglobulin, *CR* complete response, *PR* partial response, *NR* no response

[a] Chemotherapy included chlorambucil, FND (fludarabine, mitoxantrone, dexamethasone), CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), CEOP (cyclophosphamide, epirubicin, vincristine, prednisolone), and M-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone)

below costal margin) was found in all the cases. There were varying degrees of peripheral blood cytopenias. Although neoplastic infiltration of the marrow was observed in all patients, circulating lymphoma cells were detectable in only six patients (55%). Monoclonal immunoglobulin was detected in two patients (18%). One patient was positive for lupus anticoagulant. In one patient, the lymphoma cells were positive for CD5 with an absolute lymphocytosis of 10.8×10^9/L at presentation.

Nodal MZL

There were four patients (two men, two women) with NMZL. IgM monoclonal protein was detected in one patient. In one patient, there was coexisting autoimmune hemolytic anemia, vitiligo, and common variable immunodeficiency diagnosed prior to the occurrence of NMZL.

Treatment outcome of non-gastric MZL

Local therapy (excision with or without involved field radiotherapy) was administered in 17 patients (26%). Twenty-seven patients (41%) received systemic chemotherapy. Twelve patients (18%) received rituximab-containing chemotherapeutic regimens. Eight patients (12%) received rituximab alone. The response rates for this group of patients were presented in Table 4.

Splenic MZL

The treatment regimens and responses for this group of patients were presented in Table 3. Splenectomy was performed in five patients, which was followed by chemotherapy in three patients and rituximab and chemotherapy in two patients. Six patients received chemotherapy without splenectomy, one of whom received rituximab as well. The CR rate was significantly better in patients who were splenectomized as compared with those who were not (CR: 4/5 splenectomized versus 1/6 non-splenectomized, $P=0.035$).

Nodal MZL

Two patients were treated with the regimen fludarabine, mitoxantrone, dexamethasone (FND): one patient with R-FND (rituximab 375 mg/m^2 before each course of FND) and one patient with chlorambucil followed by rituximab (375 mg/m^2 given weekly for four doses). CR was achieved in two patients and partial response (PR) in one patient.

Relapse characteristics and transformation

The features and outcome of relapsed cases of the non-gastric, splenic, and nodal MZL were presented individually in Table 5. Fifteen patients with non-gastric MALT lymphoma relapsed, three with high-grade histological transformation. Ten patients underwent further treatment,

Table 4 Treatment and outcome of 66 patients with non-gastric MALT lymphoma

Treatment and outcome	Number (%)
Refused treatment or defaulted	2 (3)
Local resection only	11 (17)
CR	8/11 (73)
PR	0/11 (0)
NR	3/11 (27)
Radiotherapy alone	3 (5)
CR	3/3 (100)
PR	0/3 (0)
NR	0/3 (0)
Local resection + radiotherapy	3 (5)
CR	3/3 (100)
PR	0/3 (0)
NR	0/3 (0)
Rituximab ± local treatment	8 (12)
CR	7/8 (88)
PR	1/8 (12)
NR	0/8 (0)
Chemotherapy ± local treatment	27 (41)
CR	20/27 (74)
PR	5/27 (19)
NR	2/27 (7)
Rituximab + chemotherapy ± local treatment	12 (18)
CR	10/12 (83)
PR	2/12 (17)
NR	0/12 (0)

CR complete response, *PR* partial response, *NR* no response

with nine (90%) achieving a second CR. The only patient who did not respond to treatment had small bowel and pleural involvement, which at relapse showed transformation into diffuse large B cell lymphoma. Of the nine cases achieving CR2, two patients had subsequent relapses, presenting as transformation into high-grade follicular lymphoma and diffuse large B cell lymphomas. Both patients died ultimately of refractory lymphoma despite intensive chemotherapy and hematopoietic stem cell transplantation. Three patients with splenic MZL relapsed, two of whom showed high-grade histological transformation. Only one patient achieved a CR2 after intensive chemotherapy and allogeneic hematopoietic stem cell transplantation. One patient with nodal MZL relapsed as a high-grade lymphoma and achieved CR after chemotherapy and ibritumomab tiuxetan therapy.

Toxicity of treatment

Grade 4 neutropenia and febrile neutropenia was encountered in 14 (17.3%) and 13 (16%) patients, respectively (Table 6). Treatment-related mortality due to sepsis occurred in two cases (2.5%). Therapy-related acute myeloid leukemia developed in one patient with parotid MALT lymphoma 6 years after diagnosis.

Prognostic factors

Treatment results of the entire group were shown in Table 7. The overall response rate was 87% (69/79 patients) with a CR of 73% (58/79 patients). Various regimens designed for indolent lymphomas were used (Table 8). Fludarabine regimens and non-fludarabine regimens did not impact on CR rates. However, relapses were significantly reduced in patients receiving fludarabine regimens as compared with those receiving non-fludarabine regimens (3/23, 13% versus 9/22, 41%, $P=0.03$). Interestingly, rituximab-containing regimens and non-rituximab regimens also did not impact on CR rates. However, relapses were significantly decreased in patients receiving rituximab-containing regimens as compared with those receiving non-rituximab regimens (2/21, 10% versus 10/24, 42%, $P=0.015$). Similarly, when these regimens were analyzed according to whether fludarabine and/or rituximab were used, the CR rates were comparable. However, relapse rates were significantly lower in patients receiving both rituximab and fludarabine as compared with patients receiving none ($P=0.008$), while patients receiving either rituximab or fludarabine showed intermediate results (Table 8). The impact of stage, performance status, and IPI risk score on response rates was evaluated using logistic regression. Favorable prognostic factors for CR were early-stage (stage I/II) disease (OR=3.11, $P=0.039$), good performance status (≤1, OR=9.36, $P<0.001$), and low IPI risk score (<3, OR=4.17, $P=0.011$). These factors, nevertheless, did not impact on the relapse rates.

Survivals

The 5-year OS for the whole cohort was 84.6% (95% confidence interval, CI=0.73–0.92; Fig. 1a) and the 5-year DFS was 82.2% (95% CI=0.70–0.90; Fig. 1b). During the follow-up period, 14 patients (non-gastric MZL, $n=9$; splenic MZL, $n=5$) died: ten from refractory diseases, two from treatment-related causes, one from therapy-related leukemia, and one from unrelated causes. Prognostic factors associated with a lower mortality included stage I/II disease (odds ratio=0.08, $P<0.001$) and IPI risk score <3 (odds ratio=0.09, $P<0.001$). No differences in survival or mortality were observed between different treatment regimens.

Discussion

In this study, we have analyzed a cohort of MZL patients separately according to whether they had non-gastric,

Table 5 Clinicopathological features and outcome of 19 patients with relapsed non-gastric marginal zone lymphoma

Clinicopathological features and outcome	Number (%)
Non-gastric MALT lymphoma	15/66 (23)
Site of relapse	
Same	8 (53)
Different	7 (47)
Pattern of relapse	
Locoregional	8 (53)
Advanced/disseminated	7 (47)
Transformation	
None	63/66 (95)
Diffuse large B cell lymphoma	2/66 (3)
High-grade follicular lymphoma	1/66 (2)
Treatment and outcome	
Radiotherapy alone	1
CR	1/1 (100)
Radiotherapy+FND	1
CR	1/1 (100)
Excision+radiotherapy+rituximab	1
CR	1/1 (100)
Excision+R-COPP	1
CR	1/1 (100)
FND	2
CR	2/2 (100)
CEOP	1
CR	1/1 (100)
NOPP	1
NR	1/1 (100)
CEOP followed by autologous PBSCT consolidation	1
CR	1/1 (100)
DHAP followed by autologous PBSCT consolidation	1
CR	1/1 (100)
Splenic marginal zone lymphoma	3/11 (27)
Site of relapse	
Same	3 (100)
Pattern of relapse	
Advanced/disseminated	3 (100)
Transformation	
Diffuse large B cell lymphoma	1/11 (9)
T cell-rich B cell lymphoma	1/11 (9)
Treatment and outcome	
FND	1
PR	1/1 (100)
CEOP	1
NR	1/1 (100)
DHAP followed by matched sibling allogeneic BMT	1
CR	1/1 (100)
Nodal marginal zone lymphoma	1/4 (25)
Site of relapse	
Same	1 (100)
Pattern of relapse	
Advanced/disseminated	1 (100)
Transformation	1/4 (25)
Diffuse large B cell lymphoma	1/4 (25)
Treatment and outcome	
R-CEOP followed by ^{90}Y-irbitumomab tiuxetan consolidation	1
CR	1/1 (100)

CR complete response, *PR* partial response, *NR* no response, *FND* fludarabine–mitoxantrone–dexamethasone, *CEOP* cyclophosphamide–epirubicin–vincristine–prednisolone, *NOPP* mitoxantrone–vincristine–procarbazine–prednisolone, *DHAP* dexamethasone–cytarabine–cisplatin, *COPP* cyclophosphamide–vincristine–procarbazine–prednisolone, *PBSCT* peripheral blood stem cell transplantation, *BMT* bone marrow transplantation, *R* rituximab at 375 mg/m^2 before each course of chemotherapy

splenic, and nodal disease and also as a group for their responses to treatment. The reason for analyzing three MZL as a group with respect to treatment outcome is because similar drugs and strategies are often employed in their treatment. This series showed features characteristic of MZL. There was a slight female predominance (women/men=1.4:1), probably related to a higher frequency of autoimmune diseases in women, which predisposes to MZL. In fact, the association of non-gastric MALT lymphomas with autoimmune diseases was clearly observed [13, 14], including salivary gland and thymic MALT lymphomas with Sjögren's syndrome and thyroid MALT lymphomas with autoimmune thyroiditis. The most common primary site was ocular and ocular adnexal structures, followed by salivary glands and lungs, similar to previously reported findings [15, 16]. About 30% of patients had stage IV disease at presentation, often with multiple sites of involvement, which is in contrast to gastric MALT lymphomas that are usually localized [17].

For the whole cohort, treatment results were favorable, with CR achieved in 73% of patients. The impact of surgical removal of the lymphoma, particularly in localized non-gastric MALT lymphomas in the salivary and thyroid glands, has not been fully evaluated. We showed that splenectomy, even in our small series of splenic MZL, had a significantly favorable impact on CR. Splenectomy has traditionally been considered to be an important first-line treatment for splenic MZL [18]. However, with the advent of effective drugs including rituximab and fludarabine, the role of splenectomy has

Table 6 Therapy-related toxicities in 81 patients with non-gastric marginal zone lymphomas

Toxicity	Number (%)
Anemia	
Grade 1	10 (12)
2	6 (7)
3	3 (4)
4	2 (3)
Neutropenia	
Grade 1	5 (6)
2	4 (5)
3	10 (12)
4	14 (17)
Thrombocytopenia	
Grade 1	1 (1)
2	3 (4)
3	4 (5)
4	8 (10)
Intracranial hemorrhage	1 (1)
Febrile neutropenia	13 (16)
Bacteraemia	9 (11)
Invasive fungal infections	1 (1)
Reactivation of tuberculosis	1 (1)
Localized herpes zoster	1 (1)
Disseminated herpes zoster	1 (1)
Reactivation of hepatitis B virus infection	1 (1)
Therapy-related acute myeloid leukemia	1 (1)
Miscellaneous[a]	4 (5)
Therapy-related mortality	2 (3)

[a] Including two cases of vincristine-related neuropathy, one case of chlorambucil-related liver function derangement, and one case of acute graft-versus-host disease of the skin after matched sibling bone marrow transplantation

been questioned [19]. In a recent series of splenic MZL, the purine analogue 2-chlorodeoxyadenosine with or without rituximab has been reported to result in a CR rate of only 52%, very few of the patients having undergone a splenectomy [11]. The role of splenectomy might be clarified by a trial comparing splenectomy + immunochemotherapy versus immunochemotherapy alone. However, such a study is unlikely to be performed because of the rarity of splenic MZL and the general reluctance of using surgery to treat lymphoma patients. Hence, it may not be unreasonable to start treatment with a combination of rituximab and a purine analogue and reserve the more invasive splenectomy for patients with unsatisfactory responses or relapses after immunochemotherapy.

Similarly, although rituximab has significantly improved the outcome of aggressive [20] and indolent [21] B cell lymphomas, its role in MZL has not been critically appraised. If fact, data of the impact of rituximab on the outcome of MZL have not been well documented. Likewise, whereas purine analogues have improved the treatment outcome of low-grade lymphomas [22], their therapeutic efficacy has only recently been examined in MZL. Combination treatment with rituximab and fludarabine had been reported in two series [9, 23] comprising only 36 patients with non-gastric MZL. The CR rate varied from 54% to 80%. In another series of 82 patients with non-gastric MZL, the purine analogue 2-chlorodeoxyadenosine ± rituximab resulted in a CR rate ranging from 60% to 73% [24]. However, none of these studies compared their results with conventional regimens containing alkylating agents. Therefore, whether rituximab and purine analogues actually resulted in better outcome than alkylating agents could not be determined. In fact, the European

Table 7 Treatment results of 79 patients with non-gastric marginal zone lymphomas

Treatment	Number	OR	CR	PR	SD	PD	Relapse
Local treatment alone	17	14/17 (82%)	14/17 (82%)	0/17 (0%)	2/17 (12%)	1/17 (6%)	5/14 (36%)
Systemic chemotherapy							
Fludarabine containing	28	25/28 (89%)	23/28 (82%)	2/28 (7%)	1/28 (4%)	2/28 (7%)	3/23 (13%)
Non-fludarabine containing	34	28/34 (82%)	22/34 (65%)	6/34 (18%)	3/34 (9%)	3/34 (9%)	9/22 (41%)
Rituximab							
Rituximab ± chemotherapy	25	23/25 (92%)	21/25 (84%)	2/25 (8%)	1/25 (4%)	1/25 (4%)	2/21 (10%)
Non-rituximab-containing chemotherapy	37	30/37 (81%)	24/37 (65%)	6/37 (16%)	3/37 (8%)	4/37 (11%)	10/24 (42%)
Fludarabine and rituximab							
Fludarabine + rituximab containing	11	10/11 (91%)	10/11 (91%)	0/11 (0%)	0/11 (0%)	1/11 (9%)	0/10 (0%)
Fludarabine, non-rituximab containing	17	15/17 (88%)	13/17 (76%)	2/17 (12%)	1/17 (6%)	1/17 (6%)	3/13 (23%)
Rituximab, non-fludarabine containing	14	13/14 (93%)	11/14 (79%)	2/14 (14%)	1/14 (7%)	0/14 (0%)	2/11 (18%)
Non-fludarabine, non-rituximab	20	15/20 (75%)	11/20 (55%)	4/20 (20%)	2/20 (10%)	3/20 (15%)	7/11 (64%)

OR overall response, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 8 Impact of pretreatment characteristics on outcome in non-gastric marginal zone lymphomas

Pretreatment characteristics	Number	OR	CR	PR	SD	PD	Relapse
Disease stage							
Stage I/II disease	52	50/52 (96%)	44/52 (85%)	6/52 (12%)	1/52 (2%)	1/52 (2%)	13/44 (30%)
Stage III/IV disease	27	19/27 (70%)	14/27 (52%)	5/27 (19%)	4/27 (15%)	4/27 (15%)	6/14 (43%)
Performance status							
≤1	65	60/65 (92%)	53/65 (82%)	7/65 (11%)	2/65 (3%)	3/65 (5%)	13/53 (25%)
>1	14	9/14 (64%)	5/14 (36%)	4/14 (29%)	3/14 (21%)	0/14 (0%)	1/5 (20%)
IPI score							
<3	56	53/56 (95%)	46/56 (82%)	7/56 (13%)	2/56 (4%)	1/56 (2%)	15/46 (33%)
≥3	23	16/23 (70%)	12/23 (52%)	4/23 (17%)	3/23 (13%)	4/23 (2%)	4/12 (33%)

OR overall response, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

Society for Medical Oncology guideline has stated that for gastric MALT lymphoma at least, no clear evidence in the literature exists to indicate the superiority of any of these drugs [7].

Our study was retrospective so that treatment regimens were very heterogeneous. Therefore, firm conclusions are not possible. However, we had the opportunity of comparing rituximab, fludarabine, and alkylating agent-containing regimens in the treatment of MZL. We also showed that CR rates were not different between regimens containing alkylating agents, rituximab, fludarabine, and rituximab + fludarabine. The CR rates in our study varied from 65% to 91%, comparable with data reported previously from regimens containing rituximab and purine analogues [9, 10, 24]. However, we showed that relapse rates were significantly different, with regimens containing rituximab and fludarabine giving significantly fewer relapses. The results suggested that the depth of remission, reflecting the extent of clearance of lymphoma cells, might be better with rituximab- and fludarabine-containing regimens.

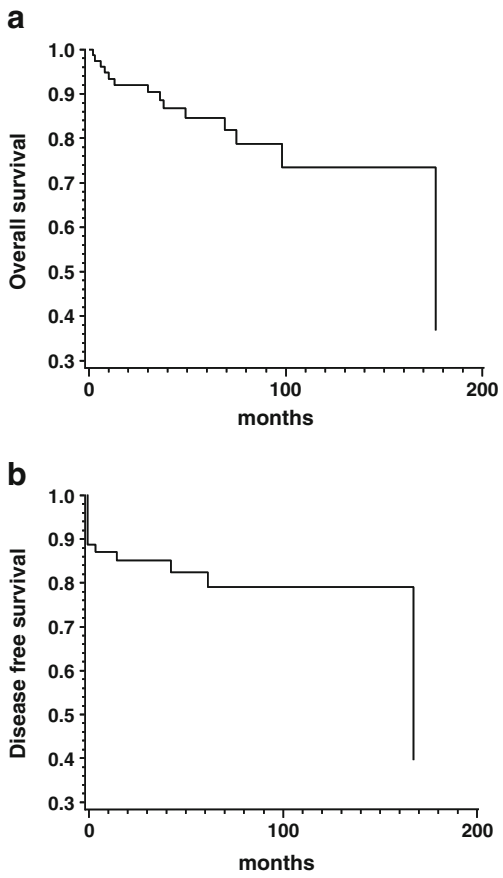

Fig. 1 Survival of patients with marginal zone lymphoma. **a** Overall survival. **b** Disease-free survival

Concerns have been expressed over the use of rituximab and purine analogues in MZL. In one study, the combined use of rituximab and fludarabine resulted in significant hematologic toxicities (grade III, 77%; grade IV, 42%), with 15% of patients developing delayed marrow toxicity that resulted in death [9]. In this study, however, grade IV toxicity appeared to be acceptable at about 15%, with treatment-related-mortality at only 2%. Therefore, rituximab + fludarabine appeared to be safe in our patient population, in accordance with experience of the use of this combination in chronic lymphocytic leukemia. Another issue is the possibility of myelodysplastic syndrome related to the use of purine analogues [7], particularly fludarabine [25]. One patient in our series developed acute myeloid leukemia 6 years after receiving FND. Hence, it is important that patients who have received fludarabine should have life-long follow-up.

In conclusion, we showed that non-gastric MZL as a group showed favorable response to treatment. The use of rituximab and fludarabine reduced the relapse rate as compared with conventional chemotherapy. Therapy with rituximab and fludarabine was associated with acceptable side effects. These data obviously have to be interpreted in light of the heterogeneity of patients and treatment in this

series. Therefore, the combination of rituximab and fludarabine should be fully evaluated systemically in prospective trials.

Conflict of interests The authors have no conflict of interests to declare.

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