High Relapse Rate in Patients with MALT Lymphoma Warrants Lifelong Follow-up

Markus Raderer,[1,5] Berthold Streubel,[2] Stefan Woehrer,[1] Andreas Puespoek,[3] Ulrich Jaeger,[1] Michael Formanek,[4] and Andreas Chott[2]

Abstract

Background: B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) is thought to be an indolent disease, with a good prognosis following various forms of treatment. Little, however, is known about the rate and pattern of relapse following successful treatment.

Patients and Methods: We have analyzed time to and pattern of relapse in patients with MALT lymphoma, along with investigation of t(11;18) (q21;q21), t(1;14) (p22;q32), and t(14;18) (q32;q21) involving *IGH*/*MALT1*, trisomy 3, and trisomy 18. Eighty-six patients achieving complete remission (CR) after initial therapy with sufficient follow-up data were available. Primary site of disease was the stomach (n = 36), salivary gland (n = 19), ocular adnexa/orbit (n = 12), lung (n = 8), thyroid (n = 5), breast (n = 3), liver (n = 2), and skin (n = 1).

Results: Thirty-two patients (37%) relapsed between 14 and 307 months (median 47 months) after initial CR. Ten relapses were local, whereas the remaining patients relapsed in a distant organ. Eight of 36 gastric versus 24 of 50 nongastric MALT lymphomas (P = 0.02) relapsed. Five patients had a second recurrence 26 to 56 months after a second CR. Relapse rates were not related to forms of initial treatment. Chromosomal aberrations were detected in 14 of 28 (50%) relapsing patients, and chromosomal alterations were identical at diagnosis and relapse. No significant association of any of the genetic changes investigated with relapse was found. Interestingly, patients with t(11;18) (q21;q21) had a significantly longer median time to relapse (76 months) than patients without this translocation (29 months; P = 0.012).

Conclusions: In view of the late relapses seen in our series, lifelong observation of all patients treated for MALT lymphoma seems to be required.

Extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) is a disease predominantly affecting the gastrointestinal tract (1–3), especially the stomach, but is also common in the salivary glands, the ocular adnexa/orbit, and the lung (2–4). Interestingly, MALT lymphomas originate in acquired MALT rather than physiologic mucosal lymphoid tissue as exemplified by the Peyer's patches (5).

MALT lymphoma irrespective of origin is thought to be an indolent disease as reflected by the good general prognosis of patients (6). There is widespread consensus that MALT lymphomas remain localized to their mucosal environment for a prolonged period of time (2, 3) due to exclusive interaction between lymphoma cells and mucosal adhesion molecules (7, 8). This immunologic trafficking nevertheless seems to be slightly different for mucosal sites within the gastrointestinal tract as opposed to nongastrointestinal sites (8).

In the past, local therapies including surgery and radiation have preferentially been applied. Although resulting in good local control, distant relapses have repeatedly been reported in the literature, in some cases even after decades following initial treatment (9–11). To date, there are no data on the relapse pattern of MALT lymphomas and the optimal duration of follow-up after successful therapy. Therefore, we have analyzed all patients with MALT lymphoma treated at our institution who achieved complete remission (CR) following initial therapy. In addition, we have investigated samples from all patients for chromosomal aberrations common in MALT lymphoma including t(11;18), t(1;14), and t(14;18) involving *IGH/MALT1*, trisomy 3, and trisomy 18 to assess whether these changes might influence relapses.

Patients and Methods

A retrospective analysis of patients with MALT-lymphoma diagnosed and treated at our institution was done. Only patients who had undergone extensive staging according to our standard protocol (12), who had achieved CR after therapy, and in whom follow-up data of at least 24 months after initial treatment were available, were included. Histologic diagnosis of MALT-lymphoma was done according to the criteria outlined in the WHO classification (13), and histologic (re-) assessment was done by a reference hematopathologist (A.C.). Immunologic phenotyping on paraffin sections was done for

Authors' Affiliations: [1]Clinical Division of Oncology, Departments of Medicine I, [2]Pathology, [3]Medicine IV, and [4]Otorhinolaryngology Medical University Vienna, and [5]Center of Excellence in Clinical and Experimental Oncology (CLEXO), Vienna, Austria

Received 11/8/04; revised 2/3/05; accepted 2/10/05.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Markus Raderer, Division of Oncology, Department of Medicine I, Medical University Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria. Phone: 43-1-40400-2296; E-mail: markus.raderer@meduniwien.ac.at.

demonstration of light-chain restriction and the phenotype CD20+CD5−CD10−cyclinD1−, which, in context with the microscopic appearance, is consistent with MALT lymphoma.

Information extracted from patients' charts and analyzed included diagnosis and localization on initial presentation, extent of staging, treatment, response to treatment, duration of response (calculated from CR to histologic diagnosis of relapse), site of relapse, and time to relapse. In all patients referred to our institution for relapsing MALT lymphoma, the original biopsies were also reassessed, and patients were only included if these, along with information on initial treatment, staging, and response, were available.

t(11;18)(q21;q21) involving *API2* and *MALT1* was assessed by reverse transcription-PCR, t(14;18)(q32;q21) involving *IGH* and *MALT1*, t(1;14)(p22;q32) involving *BCL10* and *IGH*, and trisomies 3 and 18 were investigated by fluorescence *in situ* hybridization as previously published (14). These genetic studies were carried out on representative biopsies both at diagnosis and at relapse in all patients.

Results

A total of 86 patients with MALT lymphoma treated at our institution and achieving CR were identified for our analysis. The large majority of patients (n = 36) had gastric lymphoma; the remaining primary sites of disease were salivary gland (n = 19), ocular adnexa/orbit (n = 12), lung (n = 8), thyroid (n = 5), breast (n = 3), liver (n = 2), and skin (n = 1).

Different forms of treatment (or combinations thereof) including surgery, radiation and chemotherapy, and *Helicobacter pylori* eradication were applied (see Table 1). Treatment modalities applied did not differ between the group of patients with relapse and those without recurrence (data not shown).

A total of 32 patients (37%) relapsed: 8 relapses occurred in patients with an initial diagnosis of gastric MALT lymphoma, 9 in parotid, 5 in lacrimal, 5 in pulmonary lymphoma, 3 in MALT lymphoma of the breast, and 1 each in conjunctival and cutaneous MALT lymphoma. Four of these 32 patients (12%) had been referred to our institution after relapse had been diagnosed. Due to the accessibility of the original lymphoma sites, regular bioptical follow-up had only been done in patients with gastric lymphoma. In these patients, 6 to 14 gastroscopies with negative histologic results had been done before diagnosis of relapse.

Taken together, 8 of 36 patients with gastric lymphoma versus 24 of 50 nongastric MALT lymphomas (P = 0.02) relapsed. Only one of our patients showed transformation to diffuse large B-cell lymphoma on relapse (see Table 1). Ten relapses were local, whereas the remaining patients relapsed in a distant organ. The large majority of these recurrences occurred in another MALT organ, as only three patients developed recurrent disease in lymph nodes (for details, see Table 1), and only one had (additional) bone marrow involvement.

In total, seven patients have died: two of three relapsing patients from lymphoma progression (including the patient with transformation) and one from myocardial infarction, whereas four have died in CR from causes unrelated to lymphoma.

The median follow-up was 56 months (range, 30-315) in relapsing patients and 53 months (range, 33-130) for the nonrelapsing patients. The median time to relapse was 47 months, ranging from 14 to 307 months. Five of these 31 patients had another relapse following a second CR; these relapses occurred 26, 43, 49, and 56 months (in two patients) after the first recurrence. The occurrence of relapses and their pattern, however, seemed not to be influenced by the treatment modality employed for reaching CR (P > 0.2, data not shown).

Analysis of chromosomal aberrations could be carried out successfully in 28 of 32 relapsing patients. No chromosomal aberrations were detected in 14 of 28 relapsing patients (50%). A total of seven relapsing patients (25%) had evidence of t(11;18)(q21;q21), which was the sole aberration in all cases. Two cases were found positive for t(14;18)(q32;q21) along with trisomy 3; an additional three patients harbored trisomy 3 as the sole aberration; and two patients had both trisomy 3 and trisomy 18. Taken together, trisomy 3 was present at the same frequency (25%) as the t(11;18)(q21;q21) in our cohort of relapsing patients. No differences were found between genetic changes present in the initial samples and material obtained on relapse in the 32 patients developing recurrences.

In the patients in continuous CR during follow-up, aberrations could be investigated in 43 of 55 cases. A t(11;18)(q21;q21) was found in 7 of 43 (16%), and trisomy 3 was present in 8 cases (18.6 %). The differences between relapsing and nonrelapsing patients, however, were not statistically significant for both t(11;18)(q21;q21) (P = 0.822) and trisomy 3 (P = 0.732). Interestingly, t(11;18)(q21;q21)+ patients had a significantly longer median time to relapse (76 versus 29 months, P = 0.012) as compared with patients without this translocation.

Due to the small sample size in various localizations, comparative analysis was done only in gastric lymphoma, where sufficient material for analysis of genetic changes was available in 29 patients. In total, 9 of 29 (31%) were found positive for t(11;18)(q21;q21), including 4 of 8 (50%) relapsing and 5 of 21 (24%) nonrelapsing patients (P > 0.2). Trisomy 3 was present in only 2 of 21 patients (in one case accompanied by trisomy 18) in continuous CR as opposed to 0 of 8 gastric lymphoma patients with recurrence.

Discussion

This is the first series to systematically address the rate and pattern of relapse in patients with MALT lymphoma achieving CR after initial therapy. Judging from our data, the rate of recurrences seems to be substantial, with the median time to relapse being 47 months (range, 14-307 months). Only 4 of the 32 patients (12%) with relapse had been referred to our institution after recurrence had been diagnosed. This relatively small percentage suggests that our data do indeed reflect a real clinical phenomenon in patients with MALT lymphoma rather than being caused by a referral bias.

Eight of 36 patients with gastric lymphoma versus 24 of 50 nongastric MALT lymphomas (P = 0.02) relapsed, suggesting a higher risk of relapse for extragastric MALT lymphoma. This is also in keeping with previous results documenting a higher rate of initial multiorgan involvement in MALT lymphomas arising outside the stomach (12). The large majority of these recurrences occurred in another MALT organ, which is in keeping with the notion of a common mucosal immunity and homing of MALT lymphoma cells within their original environment (2, 8) and again underscores the importance of extensive staging of patients with MALT lymphoma (12). In addition, only one patient developed transformation to diffuse large B-cell lymphoma, suggesting that the risk of subsequent transformation is small in patients with MALT lymphoma. This

Table 1. Characteristics of relapsed patients

Sex/Age	Therapy	Site of presentation	Genetics	Site of relapse	TTR1 (mo)	Site of 2nd relapse	TTR2 (mo)	FUT
F/63	A, CHOP	Stomach	t(11;18)	Stomach	69			81
F/63	A, 2CdA	Stomach	t(11;18)	Stomach	18	Stomach	49	49
F/55	CHOP	Stomach, bladder, spleen	Neg	Lacrimal	47			51
M/30	A, CHOP, R	Stomach	Neg	Stomach	52			52
M/61	S	Stomach	t(11;18)	Colon, stomach	307			315
F/64	S	Stomach	Neg	Parotid bilat, lung	131			141
M/64	A, 2CdA	Stomach, jejunum	Neg	Stomach	29			41
M/76	S	Stomach	t(11;18)	Lung, stomach, bone marrow	231			233
F/63	R-CHOP	Parotid, local LNN	+3	Parotid, lung	26			26
F/68+	R	Parotid bilat	Neg	Stomach, lung[t]	23			30
F/45	MCP, R	Parotid	Neg	Parotid contralat	29			37
F/51+	R	Parotid	Tri3	Stomach	81			81
M/31	R, MCP	Parotid, local LNN	Neg	Colon, LN cervical	27			38
F/67	R	Parotid	nd	LNN abdom	64			69
F/48	R	Parotid	Neg	Lacrimal	50			58
M/35	R	Parotid	Neg	LN cervical	33	Colon, cervical LN	26	59
F/46	R	Parotid	Tri3	Parotid contralat	14	LNN	43	57
M/44	S	Lung	t(11;18)	Lung	63	Orbit, parotid bilat, stomach	56	119
F/75	S	Lung	t(11;18)	Lung	76			76
M/64	S	Lung	t(11;18)	Lung	127			127
F/56	MCP	Lung bilat	Neg	Lung	40			48
M/76	S, MCP	Lung	Neg	Pharynx	21			39
M/85	2CdA	Lacrimal + lung	Tri3, Tri18	Orbit	18			29
F/35	R	Lacrimal	Tri3	Lacrimal	16			31
M/76	2CdA	Lacrimal bilat	t(14;18), Tri3	Lacrimal	49			52
F/70	R	Lacrimal	t(14;18), Tri3	LNN abdom	43			49
F/82+	R	Conjunctiva	nd	Skin	23			38
F/71	R	Lacrimal	Neg	Lacrimal	16			26
F/77	R	Mamma	nd	Mamma, spleen	64			64
F/53	R	Mamma	Neg	Mamma bilat, orbit	71	Subcutis	56	127
F/54	R	Mamma + lacrimalis	Tri3, Tri18	Parotid	49			49
M/79+	Cyclo	Skin	nd	Lacrimal	25			37

NOTE: +, dead.
Abbreviations: TTR, time to relapse; FUT, follow-up time; R, radiation; A, antibiotic treatment; S, surgery; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP, rituximab + CHOP; MCP, mitoxantrone, chlorambucil, prednisone; Cyclo, oral cyclophosphamide; t, transformation to diffuse large cell lymphoma; nd, not done; Tri3, trisomy 3; Tri18, trisomy 18; LN, lymph node; LNN, lymph nodes.

fact has already been reported for MALT lymphomas harboring the t(11;18)(q21;q21), which seem to have a relatively stable karyotype with a lack of transformation (15). Judging from our data, the apparent risk for transformation to diffuse large cell lymphoma is also extremely low for cases without this specific translocation.

In our cohort of patients, the relapse rate was not related to the initial stage of the disease or to the treatment modality applied for reaching CR. As with other series available in the literature (3), however, interpretation of this finding is impaired by the fact that no uniform treatment strategies were applied in our patients due to the different localizations of the lymphoma and the absence of a standard chemotherapeutic regimen.

Genetic changes commonly found in patients with MALT lymphoma could be investigated in the large majority of patients (28 of 32 relapsing patients and 43 of 55 patients in ongoing CR), and sufficient material was available for genetic assessment in the 28 relapsing patients also from the time of initial diagnosis. Of interest is the fact that no differences were found between genetic changes present in the initial samples and material obtained on relapse in the 28 evaluable patients developing recurrences. These data are the first indication that relapses in MALT lymphoma are not triggered/accelerated by accumulation of additional MALT lymphoma-associated genetic changes in the course of the disease. It has to be emphasized, however, that only a very limited number of genetic aberrations were investigated.

None of the aberrations investigated were predictive of relapse, as differences between relapsing and nonrelapsing patients, however, were not statistically significant for both t(11;18)(q21;q21) ($P = 0.822$) and trisomy 3 ($P = 0.732$). Interestingly, t(11;18)(q21;q21)+ patients had a significantly longer median time to relapse (76 versus 29 months, $P = 0.012$) as compared with patients without this translocation. This finding is in contrast to recent results which have associated t(11;18)(q21;q21)+ MALT lymphomas at least of gastric origin with more advanced stage, suggestive of a more aggressive clinical course (16). Our data are the first to suggest that MALT lymphomas with t(11;18)(q21;q21) might run a more indolent clinical course and might be characterized by a significantly longer time to relapse.

Taken together, our findings suggest that patients with MALT lymphoma should undergo lifelong follow-up after successful initial treatment irrespective of treatment modality or genetic changes present on diagnosis.

References

1. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas: Part 1. Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol 1997;8:727–37.
2. Isaacson PG. Gastric MALT-lymphoma: from concept to cure. Ann Oncol 1999;10:637–45.
3. Raderer M, Isaacson PG. Extranodal lymphoma of MALT-type: Perspective at the beginning of the 21st century. Expert Rev Anticancer Ther 2001;1:53–64.
4. Zucca E, Roggero E, Bertoni F, Conconi A, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 2: Head and neck, central nervous system and other less common sites. Ann Oncol 1999;10:1023–33.
5. Isaacson PG, Norton AJ. Malignant lymphoma of the gastrointestinal tract. In: Extranodal lymphomas. Isaacson PG, Norton AJ, editors. Edinburgh: Churchill Livingstone; 1994. p. 15–65.
6. Thieblemont C, Bastion Y, Berger F, et al. Mucosa-associated lymphoid tissue gastrointestinal and non-gastrointestinal lymphoma behavior: Analysis of 108 patients. J Clin Oncol 1997;15:1624–30.
7. Dogan A, Du M, Koulis A, Briskin MJ, Isaacson PG. Expression of lymphocyte homing receptors and vascular addressins in low-grade gastric B-cell lymphomas of mucosa associated lymphoid tissue. Am J Pathol 1997;151:1361–9.
8. Brandtzaeg P, Farstad I, Haraldsen G. Regional specialization of the mucosal immune system: primed cells do not always home along the same track. Immunol Today 1999:20:267–77.
9. Graziadei G, Pruneri G, Carboni N, et al. Low-grade MALT-lymphoma involving multiple mucosal sites and bone marrow. Ann Hematol 1998;76:81–3.
10. Kawamata N, Miki T, Fukuda T, et al. Determination of a common clonal origin of gastric and pulmonary mucosa-associated lymphoid tissue lymphomas presenting five years apart. Intern Med 1995;34:220–3.
11. Stephen MR, Farquharson MA, Sharp RA, et al. Sequential MALT lymphomas of the stomach, small intestine and gall bladder. J Clin Pathol 1998;51:77–9.
12. Raderer M, Vorbeck F, Formanek M, et al. Importance of extensive staging in patients with mucosa-associated lymphoid tissue (MALT)-type lymphoma. Br J Cancer 2000;83:454–7.
13. Isaacson PG, Müller-Hermelink HK, Piris MA, et al. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. World Health Organization classification of tumours: tumours of haematopoietic and lymphoid tissues. Lyon: IARC Press; 2001. p. 157–60.
14. Streubel B, Simonitsch-Klupp I, Müllauer L, et al. Variable frequencies of MALT lymphoma-associated genetic aberrations in MALT lymphomas of different sites. Leukemia 2004;18:1722–6.
15. Rosenwald A, Ott G, Stilgenbauer S, et al. Exclusive detection of the t(11;18)(q21;q21) in extranodal marginal zone B-cell lymphomas (MZBL) of MALT-type is in contrast to other MZBL and extranodal large B-cell lymphomas. Am J Pathol 1999;155:1817–21.
16. Ye H, Liu H, Attygalle A, et al. Variable frequencies of t(11;18)(q21;q21) in MALT lymphomas of different sites: significant association with CagA strains of *H pylori* in gastric MALT lymphoma. Blood 2003;102:1012–8.