

Treatment Outcome of Mucosa Associated Lymphoid Tissue (MALT) Marginal Zone Non-Hodgkin's Lymphoma. Single Institutional Experience

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ABSTRACT

Purpose: To evaluate the treatment outcome in patients with mucosa associated lymphoid tissue (MALT) lymphoma in terms of response to treatment, progression-free and overall survivals as well as prognostic factors.

Patients and Methods: Between 1995 and 2002, 40 patients with clinical stages (CS) I-IV MALT lymphoma were treated at NEMROCK. The progression free survival (PFS) and overall survival (OAS) were calculated using the Kaplan Meier technique. Thirty-one patients (77.5%) had CS I-II and 9 (22.5%) had CS III-IV disease. Twenty of the 31 CS I-II patients received radiation therapy alone, five patients received chemotherapy, while three patients were treated by triple therapy (Amoxicillin, Omeperazole, Clarithromycin). Among the 9 CS III-IV patients, treatment included chemotherapy alone (6 patients), chemoradiation (2 patients) and surgery (one patient). The median follow-up period was 40 months.

Results: 19 out of twenty patients with CS I-II treated by radiation therapy alone had a 95% response rate (CR 85% - PR 10%). Among the study population (40 patients), the 5 year OAS and PFS were 86% and 66%, respectively. The 5 year OAS was 86% and PFS was 72% among CS I-II patients; the corresponding estimates in CS III-IV patients were 70% and 28%, respectively. Using multivariate analysis, there was a significant correlation between the stage of the disease, site of presentation (non GIT) and the overall survival.

Conclusion: Modest doses of radiation therapy provide better local control in patients with early stage MALT lymphoma. The poor PFS in advanced staged disease suggests the need for further clinical trials evaluating novel drug approaches taking into consideration the biological behavior and the indolent nature of such disease entity.

Key Words: Non Hodgkin's lymphoma - Mucosa associated lymphoid tissue (MALT) - Overall survival (OAS) - Progression-free survival (PFS) - Treatment outcome.

INTRODUCTION

One quarter of non-Hodgkin's lymphomas arise from tissues other than lymph nodes and even from tissues that normally contain no lymphoid tissue. These lymphomas are referred to as primary extranodal lymphomas [1].

Lymphoma arising from mucosa-associated lymphoid tissue (MALT) was first recognized by Isaacson and Wright in 1983 when a distinctive type of extranodal low grade B cell lymphoma with unique morphologic, immunophenotypic and clinical features was described [2].

MALT lymphoma was later recognized as a distinct clinico-pathologic entity among the marginal zone B lymphomas in 1994 in the Revised European-American Lymphoma (REAL) classification [3].

Transformation of low to high grade MALT lymphoma is heralded by the increased number of transformed blast cells which form sheets of clusters and grow to confluence effacing any preceding low grade tumor [4].

The cells of low grade MALT lymphomas express all mature B-cell antigens and may be CD43 +ve but are CD5 -ve and CD10 -ve. Like marginal zone cells, they also express CD21 and CD35. In most cases, MALT lymphomas synthesize surface and cytoplasmic IgM and rarely IgA and IgG. BCL2 protein expression is usually positive [3].

Clinically, MALT lymphomas tend to arise in extranodal sites. The most common site of

presentation is the gastrointestinal tract [5,6]. Other common sites include conjunctiva, orbit, salivary glands, lungs and breast [7,8].

Certain MALT lymphomas are associated with preceding chronic inflammation or autoimmune disease as the association between *Helicobacter pylori* gastritis and gastric MALT [9], Hashimoto's thyroiditis and MALT lymphoma of the thyroid gland [10].

Most cases of MALT lymphoma present as localized disease. They behave indolently and respond favorably to local therapy including surgery and radiation therapy. Recent studies have demonstrated that involved field irradiation may be adequate for patients with localized MALT lymphoma [11], while systemic chemotherapy is usually of value for advanced or disseminated disease [12].

The aim of this study is to analyze and review the clinicopathologic profile of patients with MALT lymphomas treated at NEMROCK during the period 1995 through 2002 (inclusive). Also, the treatment outcome as regards the overall response, progression free and overall survivals, as well as different prognostic factors will be assessed.

PATIENTS AND METHODS

This is a retrospective study including 40 patients diagnosed as MALT lymphomas who presented at NEMROCK during the period 1995-2002 (inclusive).

Work-up and staging:

Between January 1995 and September 2002, 40 patients with clinical stages I-IV MALT/Marginal zone lymphoma were treated at NEMROCK.

All patients had pathological documentation of MALT lymphoma. Staging work-up included bone marrow aspirate and biopsy, chest X-ray abdomino-plevic CT scan, upper endoscopy for those with GI symptoms and all routine laboratory investigations including renal and liver profiles.

Treatment by stage:

Treatment received was stratified according to the disease stage as shown in Table (2). Among the 31 patients with clinical stages I-II disease, 20 patients (64.5%) received local radiation

therapy alone, 5 patients (16%) had chemotherapy alone, 3 patients (9.6%) had surgery alone and the remaining 3 patients (9.6%) received triple therapy only.

For patients receiving locoregional irradiation, the median dose was 30 Gy/20 fractions/4 wks. The dose ranged from 2500cGy to 3500cGy (except for one patient with orbital MALT lymphoma who received 20Gy).

Among the 9 patients with clinical stages III and IV, six patients (66.6%) received chemotherapy alone as initial treatment, two (22.2%) received combined chemoradiation while the remaining patient (11.1%) had surgery alone. Chemotherapy regimens used include cytoxan, 600mg/m² iv d1, vincristine 1.4 mg/m² iv d1 and prednisone 100mg po d1-d5 (CVP) in six patients; chlorambucil 4mg/m² bid d1-d5 in 3 patients especially those with low grade superficial MALT. Patients presenting with aggressive high grade MALT lymphoma were treated with CHOP regimen (4 patients): cyclophosphamide 750 mg/m² iv d1, vincristine 1.4 mg/m² iv d1, adriamycin 50 mg/m² iv d1 and prednisone 100mg/po d1-d5. All cycles were to be repeated every 3-4 weeks provided hematological recovery was achieved.

Statistical analysis:

The endpoints in this study included response rate, overall and progression free survivals and prognostic factors.

Progression free survival was calculated from the date of remission till progression or death. Overall survival was calculated from the date of diagnosis till death or last follow-up.

The Kaplan Meier statistical method was used to calculate survival using SPSS version 9 statistical package. Significance was measured at the 0.05 level where a *p*-value less than 0.05 was significant [13].

Using multivariate analysis, correlation between the different prognostic factors and survival was presented using multiple regression analysis.

Response assessment:

Complete response: Complete disappearance of all known disease for at least 4 weeks with no new lesions developing.

Partial response: Reduction of 50% of all measurable lesions for at least 4 weeks with no new lesions developing.

No change response: Less than 50% regression but less than 25% progression for 4 weeks.

Progressive disease: $\geq 25\%$ increase in the overall measurable disease for 4 weeks.

RESULTS

The relative frequency incidence of MALT lymphoma to all NHL patients who attended NEMROCK during the study period was 3.35%, while MALT lymphoma constituted 9.95% of extranodal lymphoma cases.

The patients' characteristics (40 patients) are listed in Table (1). Twenty seven patients (67.5%) were males. The median age at presentation was 51.5 years. Patients were clinically staged using the Ann Arbor staging system, where 31 patients (77.5%) had CS I-II and 9 patients (22.5%) had CS III-IV.

Twenty patients (50%) had gastrointestinal involvement while the other twenty patients (50%) had non GIT involvement with the nasopharynx as the main site, representing 22.5%.

The enrolled patients in this study were treated by different treatment modalities (Table 2). Thirty one patients (77.5%) achieved complete remission (CR), seven patients (17.5%) had partial response (PR) with an overall response of 95%. The remaining two patients (5%) had disease progression (Table 3).

There was a statistically significant impact of the received treatment modality and the CR achieved, where 85% (17/20 patients) treated by irradiation achieved CR versus 54.5% (6/11 patients) for those treated by chemotherapy ($p = 0.026$). However, the overall response achieved in both treatment groups was comparable, 95% vs 90.9% respectively, with no statistically significant difference ($p = 1.06$) (Table 4).

The 5-year rates of progression free survival and overall survival for the whole group (40 patients) were 66% and 86%, respectively (Figs. 1,2).

The 5-year progression free survival in CS I-II patients (31 patients) was 72% vs 28% for those with CS III-IV (9 patients) with a statistically significant value ($p < 0.003$) (Fig. 4). The

corresponding 5 year overall survival (OAS) rates were 86% and 70%, respectively, with no statistically significant difference ($p = 0.62$) (Fig. 3).

Clinical stage I-II patients:

Among the thirty-one patients with early stage disease, 10 patients had relapse and two patients had persistent disease after initial treatment. The median time to relapse was 18 months with a range of 0-98 months.

Seventeen of the twenty patients who received radiation therapy as initial treatment had a local control (85%). However, six patients out of these seventeen relapsed outside the sites of initial presentation. Local control was achieved in 4 out of 6 patients who received further treatment, mainly systemic chemotherapy, while the other two patients still had disease at the time of analysis.

Of the 3 patients treated with surgery alone, two relapsed at other sites. However, they were alive and free of disease after further treatment.

Two patients out of the 5 who received chemotherapy alone relapsed locally. Salvage with local irradiation was successful.

Also, among the 10 patients with CS I-II with pathologic documentation of disease at time of relapse, 3 (30%) patients developed transformation to diffuse large cell lymphoma.

Clinical stage III-IV patients:

Among the 9 evaluable patients with advanced stage disease, 5 patients failed to achieve CR while the remaining 4 patients achieved CR to initial therapy. However, two patients developed relapse. The median time to relapse was 8 months (range 3-16 months).

Of the 6 patients who received chemotherapy alone as initial treatment, two patients achieved CR, two had PR and two had progressive disease.

The two patients who received combined chemo-radiation as initial treatment achieved CR and remained disease free at 35 and 41 months, respectively. The patient treated by surgery entered in PR.

Using multivariate analysis for prognostic factors, there was a significant correlation between the overall survival, site of disease (non GIT) and the clinical stage (Table 5).

Table (1): Patients characteristics n = 40.

	No.	%
<i>Gender:</i>		
Male	27	67.5
Female	13	32.5
<i>Age (years):</i>		
Median	51.5±7.6	
Range	19-68	
<i>Clinical stage:</i>		
I	20	50
II	11	27.5
III	6	15
IV	3	7.5
<i>Sites:</i>		
<i>GIT:</i>		
Stomach	11	27.5
Duodenum	4	10
Small intestine	4	10
Colorectal	1	2.5
<i>Non-GIT:</i>		
NPX	9	22.5
Orbit	3	7.5
Lung	2	5
Thyroid	3	7.5
Parotid	2	5
Lip	1	2.5
<i>Performance status:</i>		
0-2	30	75
3	10	25
<i>B symptoms:</i>		
+ve	12	30
-ve	28	70
<i>LDH:</i>		
Normal	25	62.5
Elevated	15	37.5

Table (2): Treatment by stage in 40 patients with MALT lymphoma (NEMROCK 1995-2002).

	No.	%
<i>Stage I:</i>		
Total	20	50
Radiotherapy	14	35
Chemotherapy	2	5
Surgery	1	2.5
Triple therapy	3	7.5
<i>Stage II:</i>		
Total	11	27.5
Radiotherapy	6	15
Chemotherapy	3	7.5
Surgery	2	5
<i>Stage III-IV:</i>		
Total	9	22.5
Chemotherapy	6	15
Chemoradiation	2	5
Surgery	1	2.5

Table (3): Treatment response of 40 patients with MALT lymphoma (NEMROCK 1995-2002)

Response	No.	%
Complete response (CR)	31	77.5
Partial response (PR)	7	17.5
Disease progression (DP)	2	5

Table (4): Treatment response of 40 patients with MALT lymphoma according to treatment received (NEMROCK 1995-2002).

Response	Treatment received									
	RTX		Chemo		S		Chemorad		Triple	
	No.	%	No.	%	No.	%	No.	%	No.	%
CR	17	85	6	54.5	3	75	2	100	3	100
PR	2	10	4	36.4	1	25	0	-	-	-
DP	1	5	1	9.1	0	-	0	-	-	-
Total	20	100	11	100	4	100	2	100	3	100

RTX = Radiotherapy.

S = Surgery.

Triple = Antibiotic therapy.

Table (5): Multivariate analysis of actuarial survival of 40 patients with MALT lymphoma in relation to different prognostic factors (NEMROCK 1995-2002).

Variable	Regression coefficient	Standard error	t. significance	p-value
Sex	11.9	21.6	1.657	0.26*
Performance	-5.11	5.71	-0.896	0.39*
B-symptoms	26.2	15.6	1.684	0.11*
Site (non GIT)	8.59	3.65	2.353	0.03**
Stage	-25.2	8.39	-3.003	0.01**
Treatment	12.7	25.8	1.867	0.28*
Response	15.6	2.74	3.412	0.16*

* Not significant.

** Significant.

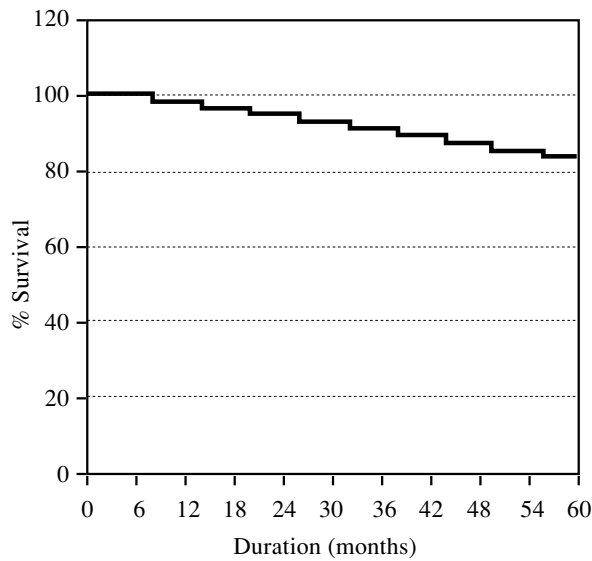


Fig. (1): Overall survival for the 40 patients with MALT lymphoma NEMROCK 1995-2002.

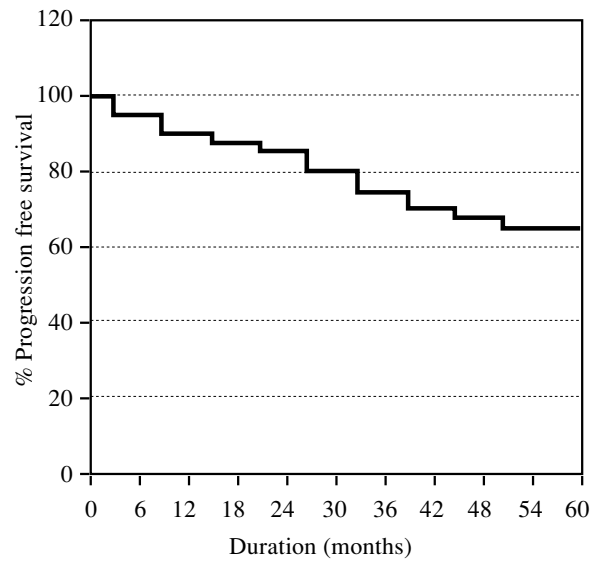


Fig. (2): Progression free survival for the 40 patients with MALT lymphoma NEMROCK 1995-2002.

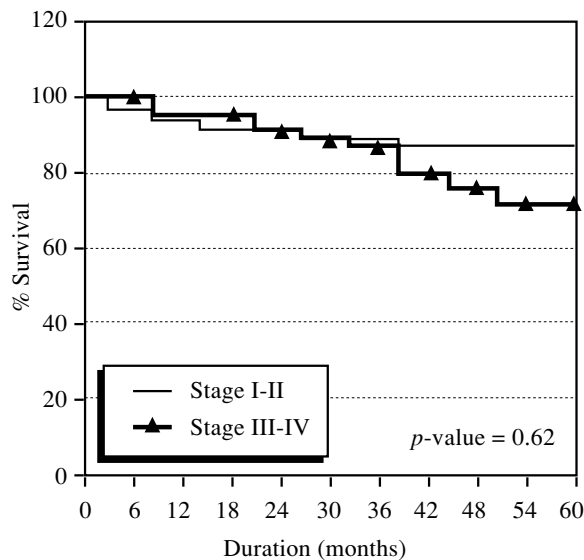


Fig. (3): Overall survival in 40 patients with MALT lymphoma according to clinical stage (NEMROCK 1995-2002).

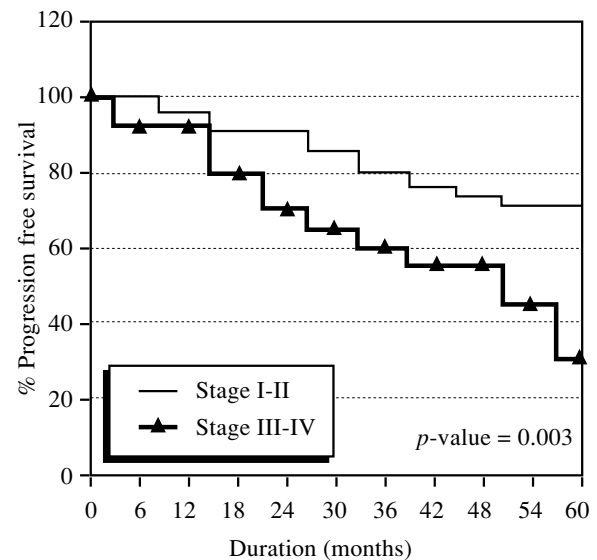


Fig. (4): Progression free survival for the 40 patients with MALT lymphoma according to clinical stage (NEMROCK 1995-2002).

DISCUSSION

MALT lymphoma was first described by Isaacson and Wright [2] in 1983 as an extranodal lymphoma arising in the marginal zone of the mucosa-associated lymphoid tissue and became nowadays popular among investigators due to its indolent behavior and complete curability of early stage by non-cytotoxic drugs.

MALT lymphoma comprised 3.35% of the total number of cases presenting at NEMROCK during the study period between 1995-2002;

compared to 7.6% in the literature [14]. This may be attributed to the lack of an integrated interdepartmental cooperation, the non-specific presenting symptoms of gastro-intestinal MALT which may be misdiagnosed as simple gastritis and lastly, the discrepancy in pathologic sub-classification of MALT into low and high grade subtypes.

In the present study, the clinical characteristics at presentation are in agreement with those that have been reported by others [8,12,15]. There

was a male predominance with a mean age of 51.5 years \pm 7.6 SD. The majority of cases were localized at presentation with 77.5% of cases presenting with stage I-II disease. The most frequent sites of involvement were the gastrointestinal tract (50%) followed by nasopharynx, orbit and thyroid gland. This was confirmed by the published data on anatomical distribution of MALT being commonest in the stomach followed by small intestine and lungs [6].

Unlike most low grade B cell lymphomas, MALT lymphomas are usually localized. Bone marrow involvement is very rare and occurs late in the course of disease. In a series of 93 patients [16] with low grade gastric MALT, 7.5% had stage IV disease because of bone marrow involvement compared to no bone marrow involvement in our study, as most patients (77.5%) presented with early stage disease.

Many clinical studies have shown that the cure of *Helicobacter pylori* infection is associated with complete remission in ~80% of patients in early clinical stage [9]. In our series, the three patients, with positive H.P infection on top of gastric MALT, achieved complete remission following the triple therapy with no relapse till the time of data analysis.

In this study the stratification of patients into clinical stages I-II versus clinical stages III-IV demonstrated significant differences in progression free survival (PFS) and overall survival (OAS) rates between the two groups.

An excellent 5 year OAS rate of 86% and a lower 5 year PFS rate of 66% were found in our study. Similar results have been observed by other investigators. Zinzani et al. [8] reported on 75 patients with non-gastrointestinal MALT lymphoma that, with a median follow-up time of 42 months, the 5-year OAS rate was estimated at 95% while the failure free survival rate was 70%. Also, Thieblemont et al. [12] reported on 158 patients with MALT lymphoma that, with a median follow-up time of 48 months, the 5-year OAS rate was 86% while the PFS rate was ~50%. In both series, as in our study, about two-thirds of the patients had clinical stage I-II disease.

In the current study, a 95% local control rate was achieved in patients who received radiation therapy. The median dose of radiation therapy used was 30 Gy. Somewhat higher doses were

used in earlier years, based on doses typically used to treat localized follicular lymphomas. In a series from Memorial Sloan Kettering Cancer Center, 17 patients with stage I-II gastric MALT were treated with radiation therapy [11]. The median dose of radiation used was 30 Gy. At a median follow-up period of 27 months, the PFS rate was 100%. On the other hand Tsang et al. [17] reported an overall local control rate of 97% at a median follow-up of 4.2 years.

In the present study, at a median follow-up time of 40 months, six patients out of twenty patients controlled by radiation therapy, relapsed outside the sites of initial presentation. Longer follow-up time is needed to determine whether the relapse at other sites continues to occur over time after initial local therapy. Nevertheless, it is reassuring that the likelihood of disease control in patients with local relapses remains excellent where 4 out of 6 patients who relapsed at other sites and received further therapy, were able to attain second remission.

Although reasonable PFS and OAS rates were achieved in patients with early stage MALT lymphoma, yet much lower rates were noted in patients with advanced stage disease.

The majority of the advanced stage patients in this study (6/9) received systemic chemotherapy as part of their initial treatment. As is the case with follicular lymphoma, the currently available systemic therapeutic regimens appear to have limited success in providing durable remission in MALT lymphoma.

Despite the poor PFS in patients with advanced stage disease (28%), the OAS rate in these patients (70%) is still favorable which is in accordance with the known indolent behavior of MALT lymphoma and its overall excellent prognosis.

Using multivariate analysis, there was a significant correlation between the stage of disease, site of presentation and the overall survival (Table 5). Thieblemont et al. [12] reported that shorter overall survival was associated with poor performance status, stage, low albumin and anemia while shorter time to progression was associated with non-gastrointestinal MALT lymphoma.

Although the number of studied patients is small, together with the different affected sites,

the heterogeneity in treatment options and the relative short period of follow-up, yet we can still conclude that a dose of 30 Gy to involved regions (e.g, entire stomach, ipsilateral parotid or orbit) is advisable for the treatment of localized MALT lymphoma.

Future trials using alternative systemic therapy and immune modulation are needed to help to improve the disease response and the long term disease control rates in patients with disseminated MALT lymphoma.

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