Assorted B-Cell Lymphomas

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Updated May 2008*

Updates: Minor changes only

WHO Classification [1]

- Marginal Zone B-cell lymphomas
  - Splenic marginal zone lymphoma with or without villous lymphocytes
  - Extra-nodal marginal zone lymphoma of mucosa-associated lymphoid tissue i.e. MALT lymphoma
  - Nodal marginal zone lymphoma with or without monocytoid B-cells
- Hairy cell leukemia
- Mediastinal (Thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma

Marginal Zone B-Cell Lymphoma ❖

Introduction

Marginal zone lymphomas are a group of lymphomas with a characteristic morphologic and immunophenotypic appearance [2]. Three major types are identified: extranodal or MALT lymphoma, nodal or monocytoid B-cell lymphoma, and splenic lymphoma with or without villous lymphocytes. Together these entities account for approximately 9-10% of B-cell lymphomas [3].

Diagnosis

Marginal zone lymphomas are characterized by cellular heterogeneity, including marginal zone (centrocyte-like) cells (small atypical cells resembling small cleaved follicular cells, but with more abundant cytoplasm), monocytoid B-cells, small lymphocytes, and plasma cells. Occasional large cells are present in most cases [2]. Tumor cells express surface Immunoglobulin, B-cell antigens (CD19, CD20) and are usually $CD5^-$, always $CD10^-$, and $CD23^-$. Immunophenotyping studies are helpful in excluding B-CLL ($CD5^+$), mantle cell ($CD5^+$, Cyclin D1+), and follicular lymphoma ($CD10^+$) [1, 2, 4].

Baseline Investigations

The following investigations are indicated for most patients with marginal zone lymphoma:

- Pathology review
- CBC, differential blood film
- Serum electrolytes and creatinine
- Liver function tests
- Serum LDH
- Serum uric acid
- Hepatitis C serology
- Chest x-ray
- CT chest, abdomen and pelvis
- Unilateral bone marrow biopsy (if localized)

*Original treatment policy prepared by Dr. Kevin Imrie; updated in 2005 & 2008 by Dr. Eugenia Piliotis

HIV Serology

As marginal zone lymphoma is not typically associated with HIV infection, HIV testing should be limited to patients at risk of infection, especially if choice of treatment would be affected.

Hepatitis C Serology

Given a documented association between Hepatitis C and splenic marginal zone and MALT lymphomas [5, 6]. Hepatitis C serology should be routinely ordered.

Cardiac Assessment

A cardiac assessment should be performed in all patients potentially eligible for anthracycline-based chemotherapy (such as CHOP). MUGA scan or 2D-echocardiogram should be performed in all patients with a history of:

- Age > 60
- Hypertension
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Angina
- Cardiac arrhythmia
- Myocardial infarction

Gallium Scans

Gallium scans are not routinely recommended, but may be required for patients on experimental therapy.

Staging & Prognosis

Patients with marginal zone lymphoma should be staged according to the Ann Arbor staging system [7]. Stage and location have been found to have important prognostic significance [8]. The International Prognostic Factor staging system has not been validated in this type of lymphoma in large trials, but appears to be predictive of outcome [3].

Ann Arbor Stage

The Ann Arbor staging system continues to be used in marginal zone lymphoma. This system provides limited prognostic information, but is of use in determining patients eligible for treatment with combined modality therapy. All patients should have an Ann Arbor stage assigned.

Stage Definition

Stage I	Involvement of a single lymph node region or a single extranodal site.
Stage II	Involvement of two or more lymph nodes on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site and one or more lymph nodes on the same side of the diaphragm.
Stage III	Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by involvement of the spleen or by localized involvement of an extra lymphatic organ or site or both.
Stage IV	Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

The absence or presence of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding admission are to be denoted in all cases by the suffix A or B respectively.

Splenic Marginal Zone Lymphoma with or without Villous Lymphocytes

Introduction

Splenic marginal zone lymphoma is a rare disorder comprising less than 1% of all lymphoid malignancies with a median age of presentation of 60-65 years [9]. Patients typically present with splenomegaly and bone marrow involvement. Involvement of peripheral blood with villous lymphocytes is variable. Autoimmune hemolytic anemia or thrombocytopenia may complicate the clinical course [1, 10, 11]. An association between splenic marginal zone lymphoma and Hepatitis C infection has been documented, as well as regression in splenic lymphoma with antiviral treatment, therefore patients should have hepatitis serology performed at diagnosis [5].

Diagnosis

The red pulp of the spleen is infiltrated with sheets and nodules of small cells with the typical morphology of marginal zone lymphocytes. When the abnormal lymphocytes are found in the blood they usually display short polar villi [1, 11]. The immunophenotype is typical of marginal zone lymphomas. The most common genetic abnormalities in splenic marginal zone lymphoma involve deletions or translocations of the long arm of chromosome 7 (q21-31), which is found in 40% - 60% of patients. Trisomy 3 (or gain in 3q) is also found in 20% - 40% of patients. Loss of p53 expression (chrom 17q) can be rarely found, and may impart a more aggressive disease course [10-12].

Prognosis

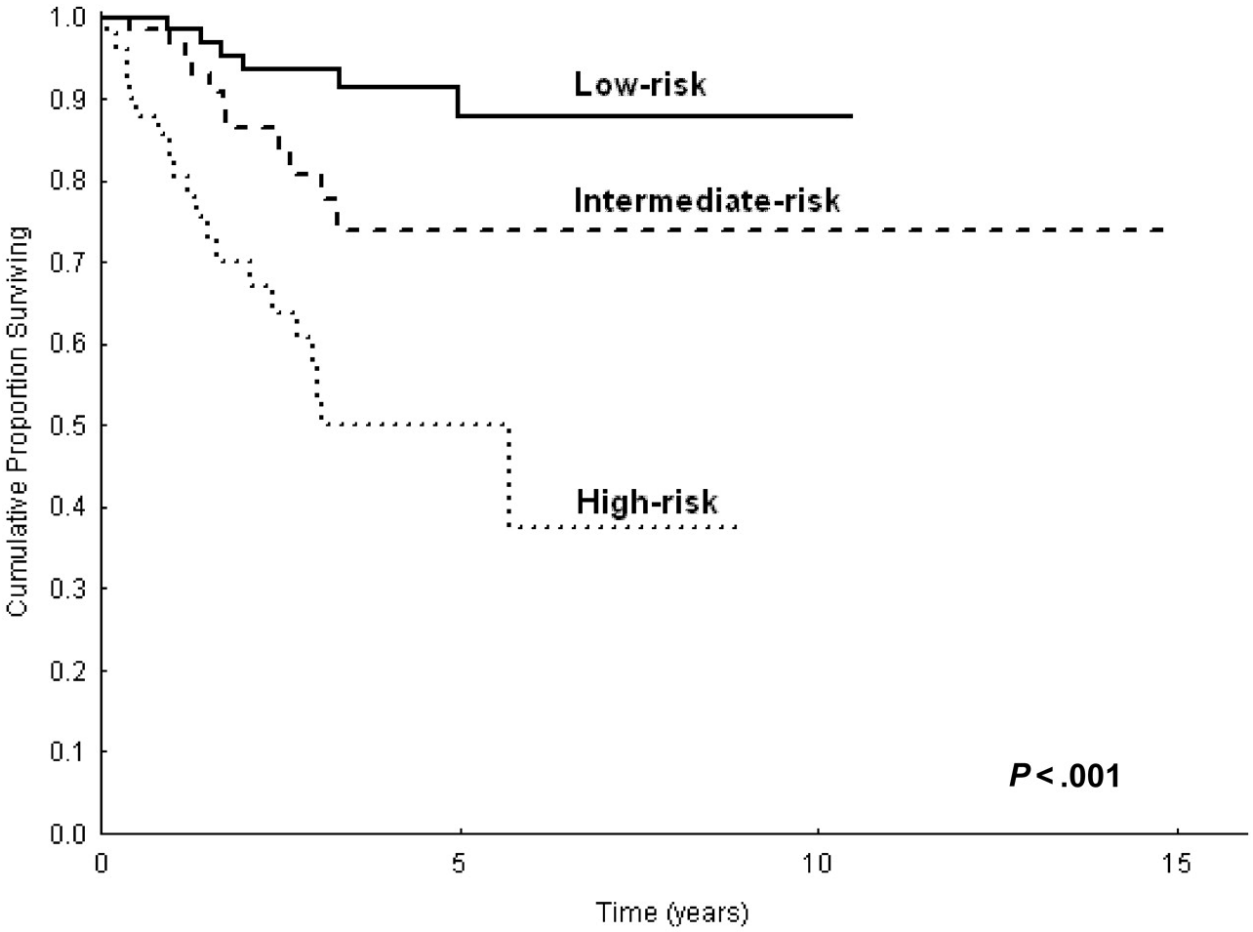
Splenic marginal zone lymphoma is a very indolent disease with an average survival of 8-10 years. Patients who fail to achieve a complete response to first-line therapy, or have a poor performance status have an inferior prognosis [10, 11]. Arcani et al. recently derived a prognostic model using three variables; Hb < 120 g/L, albumin < 35 g/L and elevated LDH based on a multivariate analysis on 309 patients with splenic marginal zone lymphoma. Patients were divided into low risk; no risk factors (41%), intermediate risk; 1 risk factor (34%), or high risk; 2 or 3 risk factors (25%). The 5-year cause specific survival for the three risk groups were found to be 88%, 73% and 50% respectively [13]. **See graph on page 4**.

Treatment

Most patients can adopt a “watch and wait” approach at initial presentation. Once patients become symptomatic with cytopenias, immune complications or symptomatic splenomegaly, the first treatment of choice is splenectomy. If systemic treatment is required they should be treated similarly to **Nodal Marginal Zone Lymphoma** [10, 11]. If patients are found to be positive for Hepatitis C they should be referred to a hepatologist for consideration of antiviral therapy.

Figure 1

CSS of 233 patients with splenic MZL according to the 3 categories of the prognostic model



MALT Lymphoma; Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue

Introduction

MALT lymphomas comprise 7-8% of all lymphoid malignancies, and up to 50% of all primary gastric lymphomas. MALT lymphomas appear to arise due to chronic antigenic stimulation. This stimulation drives lymphoid proliferation, and predisposes to the development of a malignant clone, often with cytogenetic abnormalities. There is usually a history of chronic inflammation such as *H. pylori* induced gastritis, or autoimmune disorders such as Sjögren's syndrome and Hashimoto thyroiditis. Association with Hepatitis C infection has also been documented more commonly with splenic marginal zone lymphoma, as well rarer cases of Borrelia burgdorferi in cutaneous MALT, Chlamydia psittaci in ocular MALT and Campylobacter jejuni in immunoproliferative small intestine disease (IPSID) [6]. The majority of MALT lymphomas arise in the stomach, however, they can also be found in the head and neck, ocular, lung, skin, intestinal tract, thyroid, breast and genitourinary tract [1, 14]. Low-grade MALT lymphomas are usually very indolent, often with no progression over years without treatment. Sixty-eight percent present with stage IE - IIE, 32% with stage IV and 17% have bone marrow involvement [1, 15].

Diagnosis

The pivotal feature of low-grade MALT lymphoma is the presence of 'lymphoepithelial lesions' with unequivocal invasion and partial destruction of glands. Early borderline cases may be confused with HP-related follicular gastritis and therefore a scoring session has been devised to enhance the diagnostic criteria [16]. The lymphocytes have the characteristic morphology and immunophenotype of marginal zone lymphs. Plasmacytic differentiation is often seen. The lymphocytes appear to be derived from post germinal center memory B-cell with evidence of immunoglobulin gene rearrangement and somatic mutation of variable region [17]. Chromosomal abnormalities are often found in MALT lymphoma. Trisomy 3 is found in 60% and t(11;18)(q21;q21) is found in 25-50% of MALT lymphomas. The translocation of t(11;18) fuses API2 (inhibitor of apoptosis) to MALT1, a caspase like protein. The fusion protein significantly increases NFκB activation, which is anti-apoptotic. The translocation t(1:14)(p22;q32) is less commonly found, however its fusion protein also up-regulates NFκB via over-expression of Bcl 10 on chromosome 1 [14, 17, 18].

Staging

Initial work-up for MALT lymphomas should include endoscopy and multiple biopsies of both normal and involved mucosa. Endoscopic ultrasound can also be used for regional staging of patients with more limited disease to differentiate between superficial and infiltrative MALT based on gastric wall thickness, however this modality is not universally available [19].

Staging System Proposed for GI Lymphoma [15]

Stage I	Tumor confined to the GI tract Single primary sites or multiple non-contagious lesions
Stage II	Tumor extending in abdomen from primary GI site Nodal involvement: II_1 Local (Paragastric or para-intestinal) II_2 Distant (Mesenteric, para-aortic, para-caval, pelvic, inguinal)
Stage IIE	Penetration of serosa to involve adjacent organ tissue
Stage IV	Disseminated extranodal involvement or a GI-tract lesion with supradiaphragmatic disease

H. Pylori Testing

There are several diagnostic tests available for H. Pylori including:

1. Invasive – endoscopic biopsy with:	2. Non-invasive:
❖ Histology (multiple sites) ❖ Culture ❖ PCR (polymerase chain reaction) ❖ Rapid urease tests	❖ 13C – urea breath test ❖ Stool sample & fecal antigen testing ❖ Serology (IgG-ELISA)

Most diagnostic approaches have a sensitivity and specificity of > 90% in experience hands. Since our patients all require endoscopy, we recommend a combination of at least one invasive and one non-invasive diagnostic test. Once endoscopic surveillance is completed patients can be followed with either urea breath test or fecal sampling [20].

Of note:

1. PCR testing and rapid urease testing on biopsy samples can be less sensitive in some circumstances (i.e. bleeding ulcer)
2. Serology is not appropriate for follow-up post ulcer eradication

Prognosis

MALT lymphomas are indolent lymphomas that typically remain localized, and have an excellent prognosis with survival 80-90% at 5 years [14, 21]. See Fig. 2 & 3 Survival Curves – Marginal Zone lymphoma, MALT Type.

Figure 2

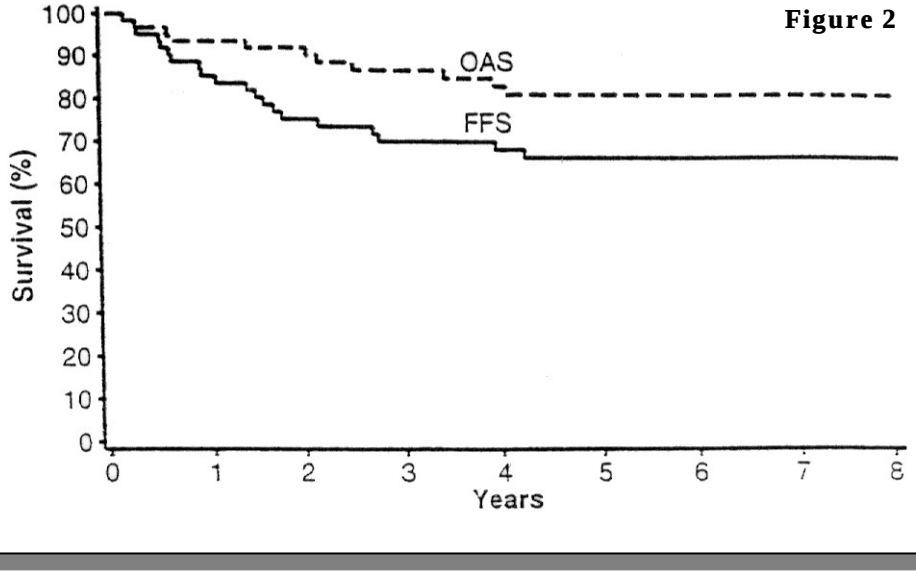
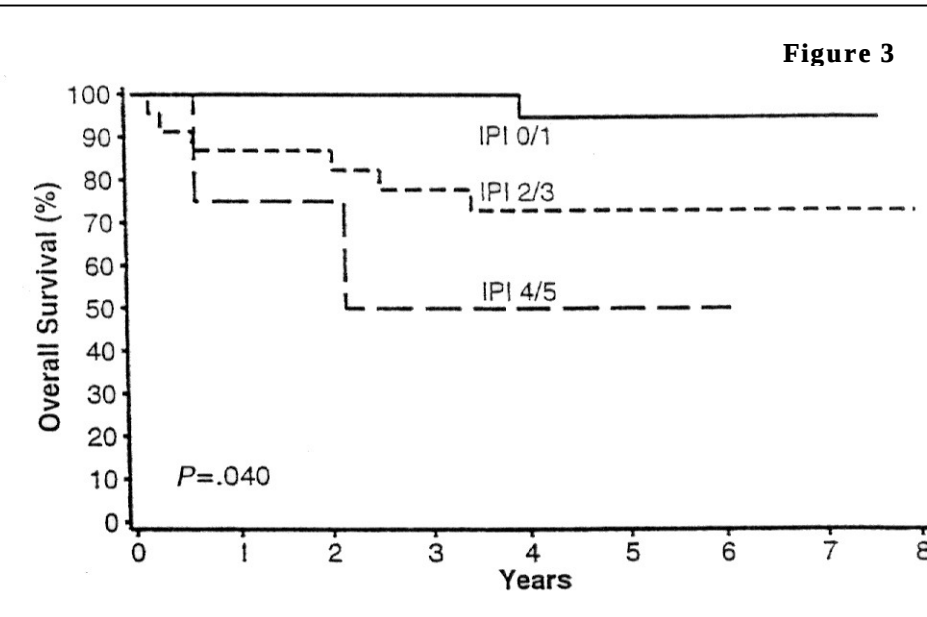


Figure 3



Management of Localized Disease

Patients with localized disease have typically been treated with radiation +/- chemotherapy. More recently, *H. Pylori* eradication has been reported to induce complete histologic remission in 61-95% of patients who are *H. Pylori* positive, [22-26]. These remissions can take up to 18 months (median 3-5 months), therefore repeated endoscopy and biopsy is required [25, 27]. Biopsy specimens may remain positive by PCR for up to 2 years post-antibiotic treatment, and some patients may remain molecularly positive indefinitely with no evidence of histologic relapse, however close monitoring is necessary [28-32]. Antibiotic therapy appears to be less effective in patients with high-grade MALT, those with regional lymph node involvement (Stage II), and those with deep involvement on endoscopic ultrasound. MALT lymphomas that harbor the t(11:18) translocation have also been shown less responsive to *H. Pylori* eradication alone [30, 31, 33].

Recommendations

All patients with biopsy proven MALT lymphoma should be offered *H. Pylori* eradication. Patients with non-gastric malt or patient with negative *H. Pylori* serology should also be offered eradication therapy.

Option A	Option B
❖ Amoxicillin 1 g twice daily for 10 days ❖ Clarithromycin 250 mg twice daily for 10 days ❖ Omeprazole 20 mg twice daily for 10 days	❖ Bismuth 302 mg four times daily for 14 days ❖ Metronidazole 500 mg three times daily for 14 days ❖ Tetracycline 500 mg four times daily for 14 days ❖ Omeprazole 20 mg twice daily for 14 days

Patients who are *H. Pylori* positive with localized gastric MALT lymphoma, stage I confined to the mucosa can be offered the choice of:

- *H. Pylori* eradication alone, with strict endoscopic surveillance with multiple biopsies at 2 months, 6 months and every 6 months thereafter for 2 years
- *H. Pylori* eradication and local irradiation **(3000 cGy in 15 fractions)** without the need of endoscopic surveillance.

Patients who have failed antibiotic therapy after 18 months should receive local irradiation **(3000 cGy in 15 fractions)**.

Patients with locally advanced MALT lymphoma who are *H. Pylori* negative, or have either deep involvement of the muscularis, or nodal involvement (Stage II) should be treated with local irradiation **(3000 cGy in 15 fractions**). Patients found to have the t (11:18) should also be considered for first line local irradiation[33-35].

Surgical resection of gastric MALT lymphomas is not recommended as primary therapy. Patients who have undergone resection should receive H. Pylori eradication and may be considered for local irradiation.

Management of Disseminated Gastric MALT Lymphoma

Patients with advanced stage marginal zone lymphoma have a survival similar to patients with advanced stage follicular lymphoma [3]. A “watch and wait” approach like that used with follicular lymphoma is appropriate for most patients **(see Follicular Lymphoma)**. Patients with life threatening organ involvement should be treated with CVP+ rituximab, while other symptomatic patients can receive chlorambucil with or without rituximab. Anthracycline based chemotherapy and purine analogs will be reserved for relapse.

Non-Gastric MALT

MALT lymphomas have been found to occur in the intestine, orbit, lung, skin, parotid gland, thyroid, breast, and pancreas [36]. Non-gastrointestinal MALT lymphomas may have a higher rate of dissemination and relapse. Initial management in published series involves surgery, local radiation, as well as chemotherapy.

Patients with localized non-gastric MALT should be treated with local radiation to a dose of **2400 cGy in 12 fractions - 3600 cGy in 18 fractions**, depending on site and bulk of disease. Patients will not routinely receive adjuvant chemotherapy. Those not eligible for local radiation, or who progress should be treated similarly to Disseminated Gastric MALT Lymphoma.

Transformed MALT Lymphoma

Patients with large cell lymphoma arising on a background of marginal zone lymphoma or with "high-grade" MALT or marginal zone lymphoma should be treated in the same way as Diffuse Large B-Cell Lymphoma **(see Diffuse Large B-Cell Lymphoma)**.

Nodal Marginal Zone Lymphoma with or without Monocytoid B-Cells

Introduction

Nodal marginal zone lymphomas comprise 1-2% of all lymphoid malignancies [9]. This diagnosis is made when patients present with primarily nodal disease, without evidence of extranodal or splenic involvement. Bone marrow can be occasionally involved.

Diagnosis

The morphology and immunophenotype is consistent with marginal zone lymphomas in general. Genetic abnormalities have not been well studied in this subtype of marginal zone lymphomas, however they do not appear to have the same frequency of trisomy 3 and t(11;18) as seen in the splenic and MALT subtypes [1].

Prognosis

Marginal zone lymphomas as a group are considered low-grade lymphomas with a median survival of approximately 9 years, and a time to progression of 3.8 years. There is however considerable variation depending on the subtype and clinical presentation. Coiffier et al. looked at 124 patients with marginal zone lymphoma. Patients presenting with splenic marginal zone lymphoma have a very indolent course with TTP of approximately 7 years and a median survival of 9 years. Leukemic marginal zone lymphoma is also very indolent, and may represent an early phase of splenic marginal zone lymphoma with villous lymphocytes. Nodal and disseminated marginal zone lymphoma have very short TTP of 1.3 and 1.1 years respectively, with a median survival of approximately 5 years [4]. **See graphs on page 9-10.**

Treatment

Nodal marginal zone lymphomas should be treated similarly to other low-grade lymphoid malignancies. An initial "watch and wait" approach is appropriate if patients are asymptomatic. Once patients are symptomatic there are several treatment options available for systemic therapy. There is a paucity of clinical trials in nodal marginal zone lymphoma, however the agents used in follicular lymphoma have similar efficacy. Patients should be offered enrollment in clinical trials where available.

Oral alkylators such as chlorambucil are the treatment of choice for first line therapy. CVP + rituximab may be considered if patients present with significant bulk or symptoms, when more rapid control of the disease is desired. There is no proven benefit to the addition of anthracyclines to first-line therapy.

Second-line & Subsequent Therapy

Nodal marginal zone lymphomas have not been extensively studied in isolation due to their rarity, however they are often included in trials of low-grade lymphomas, and are felt to behave similarly to follicular lymphoma, therefore we recommend a similar approach (**see Follicular Lymphoma**). Of note, according to CCO guidelines all low-grade B-cell lymphomas, including Marginal Zone lymphomas, are eligible for maintenance Rituxan after treatment with combination Rituxan chemotherapy.

R-chlorambucil or R-CVP → Fludarabine (F) or FC (+/- R) → CHOP-(R) → Radioimmunoconjugates

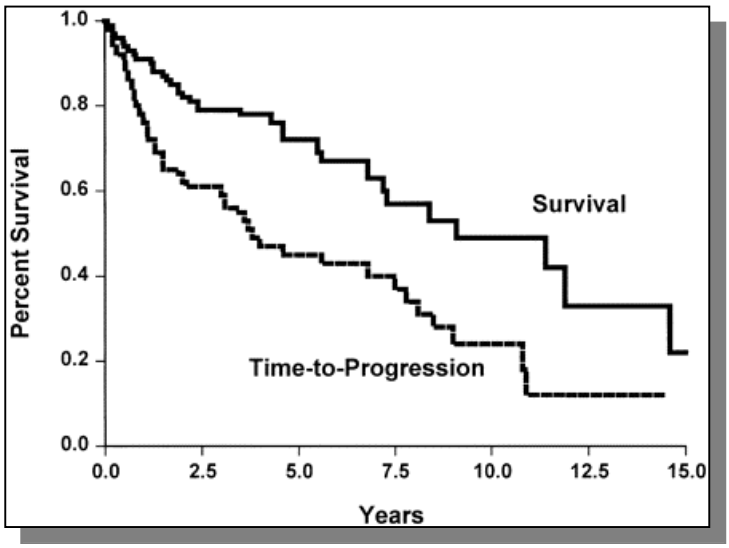


Figure 4. Overall survival and time to progression of the 124 patients with marginal zone lymphoma

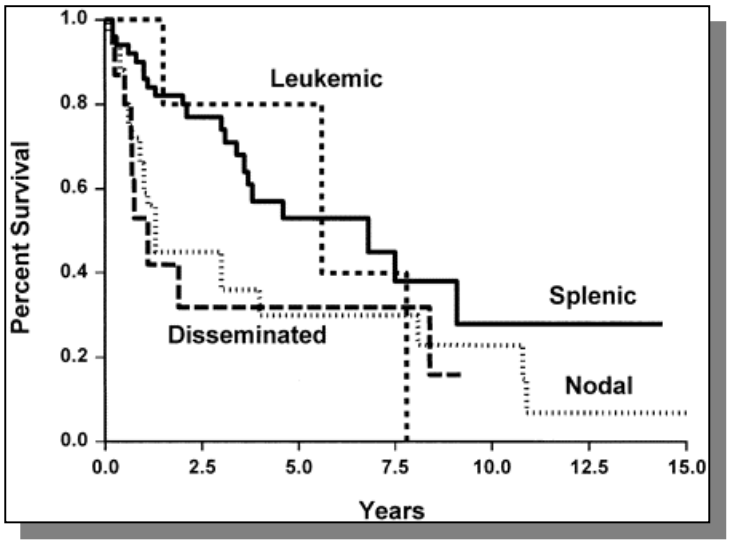


Figure 5. Time to progression of the 124 patients with marginal zone B-cell lymphoma according to clinical subtypes

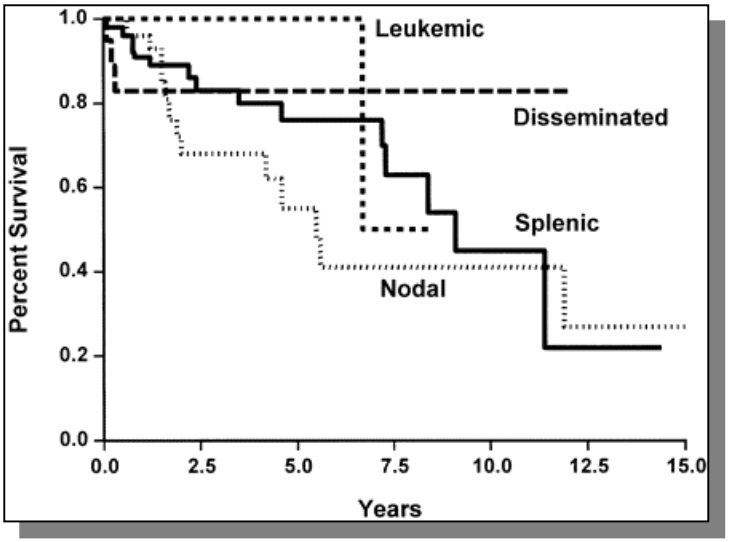


Figure 6. Overall survival of the 124 patients with marginal zone B-cell lymphoma according to the clinical subtype

Hairy Cell Leukemia

Introduction

Hairy cell leukemia is a rare disorder comprising 2% of all lymphoid leukemias. It is an indolent lymphoproliferative disorder that typically presents with pancytopenia and splenomegaly in middle-aged adults. The outcome has improved markedly over the past 5-10 years with most patients enjoying prolonged survival with purine analog therapy [1, 37].

Diagnosis

Hairy cell leukemia is characterized morphologically by proliferation of small lymphoid cells with an oval or bean-shaped nucleus, chromatin slightly less clumped than that of a normal lymphocyte, and abundant pale cytoplasm with “hairy” projections on smear preparations [2]. The bone marrow is always involved and reticulin is generally increased, resulting in a dry tap. The diagnosis is best made by bone marrow biopsy. The tumor cells are Sig^+, $CD5^-$, $CD10^-$, CD19+, CD20+, $CD23^-$, $CD25^+$(strong), CD 103+, and $FMC7^+$. Other clinical features include monocytopenia, vasculitis and opportunistic infections [1].

Staging & Prognosis

No staging system is commonly applied to patients with hairy cell leukemia. The Ann Arbor system is unhelpful as all patients have stage IV disease and the IPI has not been examined in this patient population. The four-year survival in most series exceeds 90% [38-41]. Adverse prognostic factors reported by some groups include age > 50, presence of adenopathy, and white blood cell count > 15 $x10^9$/L [42]. Even in patients with adverse features, prognosis appears to be excellent.

Treatment

Although the outcome of patients with purine analog therapy appears to be excellent, it remains unclear whether treatment is curative as even patients who achieve a complete clinical remission can have disease detected by sensitive molecular methods. Patients who are asymptomatic and have normal blood counts can be observed without treatment. Patients who are symptomatic or have hemoglobin < 100g/L, ANC < 1.0, or platelets < 50 should be started on therapy. First-line therapy is cladribine (2-Chlorodeoxyadenosine, 2-CDA) given as a single 7-day infusion of 0.1 mg/kg/day via infusion pump. The response rate to 2-CDA exceeds 80% in most published series [36, 38-43]. Several groups have shown similar efficacy with a more convenient 5-day 2 hour IV infusion protocol of 2-CDA [44-46]. Patients without sulfa allergy should receive Septra prophylaxis for at least 2 years following treatment [43, 47].

Assessment of Response & Follow-up

The majority of patients with hairy cell leukemia will respond to 2-CDA. Survival and relapse rate do not appear to be worse in patients with a partial response to treatment [38, 39]. For this reason re-staging with bone marrow aspiration and biopsy is not routinely warranted following therapy. Patients who are asymptomatic following therapy and have acceptable blood counts (Hb > 100g/L, ANC > 1.0, PLT > 50) should be followed at 3-month intervals by clinical assessment with CBC and differential. Chadha et al. recently published long-term follow-up of patients treated with 2CDA reporting 54 % PRF at 12 yrs and 87% OS at 12 yrs. This reflects the fact that most patients who relapse are either asymptomatic or are likely to respond to second-line therapy [43]. There does appear to be an increased risk of second malignancies in patients treated for hairy cell leukemia, therefore patients should be encouraged to pursue routine primary screening [43, 48].

Management of Relapse

Approximately -30% of patients who respond to 2-CDA will relapse [42]. Patients have been re-treated with 2-CDA at relapse with response rates of 70-80% with the majority of patient achieving a second CR [39-42]. Anecdotal reports of second-line treatment with splenectomy, interferon, or CHOP have been generally disappointing [39, 41, 42]. Preliminary results from small series suggest rituximab may be of benefit [49, 50].

Mediastinal (Thymic) Large B-Cell Lymphoma

Introduction

Primary mediastinal large B-cell lymphoma (PMBCL) is a newly described entity that is a subtype of diffuse large B-cell lymphoma. It comprises approximately 2% of all non-Hodgkin's lymphomas, and occurs in younger patients (third to fifth decade) with a female predominance. Patients present with a large, locally invasive anterior mediastinal mass which may be complicated with superior vena cava obstruction. In disseminated or relapsed disease, extranodal involvement of skin, CNS, kidney, and liver is common [1, 2, 9, 51, 52].

Diagnosis

The diagnosis of primary mediastinal large B-cell lymphoma should be considered in patients who present with a large mediastinal mass and histologic features of a large B-cell lymphoma (DLBCL) [2]. The tumor is thought to arise from thymic B-cells, thus there is often evidence of thymic remnants. There is also often dense fibrosis. The lymphoma cells are large, with variable nuclear features. The tumor cells are often Ig^-, but express B-cell-associated antigens (CD19, CD20, CD22, CD79a). There may be clusters of CD30 positive Reed

Sternberg like cells, which may make differentiation from Hodgkin's disease difficult [1, 3]. The genetic abnormalities in primary mediastinal large B-cell lymphoma include hyperdiploidy such as over expression of chromosome 2p (MAL and REL gens), as well as gains in chromosome 9p corresponding to the Janus Kinase 2 location which are quite specific for PMBCL and found in up to 75% of cases. These mutations are distinct from classic DLBCL, and the more typical bcl-2 and bcl-6 mutations are notably absent [1, 52]. Interestingly, the gene expression profiles of PMBL tumors are found to be more similar to Hodgkin's disease than other cases of DLBCL, however currently PMBL is still considered a subtype of DLBCL [52-54].

Baseline Investigations

Most patient with primary mediastinal large B-cell lymphoma should have the following investigations:

- CBC and differential
- Electrolytes, BUN, creatinine, urate
- Serum LDH
- CT chest, abdomen, pelvis, head
- Bone marrow aspirate and biopsy, unilateral

Gallium Scans

A total body gallium scan should be performed in all patients being treated with curative intent, particularly those who would be considered for salvage therapy and stem cell transplantation if not in complete remission after initial therapy.

HIV Serology

B-cell lymphoma is the most common malignancy associated with HIV infection. As HIV lymphoma is treated differently and risk factor assessment is imperfect in identifying HIV positive patients, most patients with primary mediastinal large B-cell lymphoma should undergo HIV serology testing at diagnosis.

Cardiac Assessment

A cardiac assessment should be performed in all patients potentially eligible for anthracycline-based chemotherapy (such as R-CHOP). MUGA scan or 2D-echocardiogram should be performed in all patients with a history of:

- Age > 60
- Hypertension
- Congestive heart failure
- Peripheral vascular disease
- Cerebrovascular disease
- Angina
- Cardiac arrhythmia
- Myocardial infarct

Assessment of Central Nervous System

Patients with primary mediastinal B-cell lymphoma may have an increased incidence of CNS involvement, particularly intraparenchymal brain involvement [55]. For this reason, all patients should have both a CT head (with contrast) and a lumbar puncture with 10 cm^3 sent for cytology.

Staging & Prognosis

The clinical behavior of primary mediastinal large B-cell lymphoma is somewhat unclear. Most authors find the outcome of patients with this disorder similar to diffuse large B-cell lymphoma, however, some authors report inferior outcomes, while others find outcome to be better. Response rates vary from 55-90% + and long-term survival rates range from 45-93%. This discrepancy may result in part from the small numbers of patients in most series, differing patient characteristics in different series, as well as differences in therapy. Both the Ann Arbor stage and International Prognostic Factor Index have been shown to be predictive of prognosis however given most patients are young, have limited stage and high LDH, the IPI may not as useful to differentiate patients as it is in other Non Hodgkin's lymphoma subtypes [3, 51, 52, 56-58].

Ann Arbor Stage

The Ann Arbor staging system continues to be used in primary mediastinal B-cell lymphoma.

Stage Definition

Stage I	Involvement of a single lymph node region or a single extranodal site.
Stage II	Involvement of two or more lymph nodes on the same side of the diaphragm or localized involvement of an extra lymphatic organ or site and one or more lymph nodes on the same side of the diaphragm.
Stage III	Involvement of lymph node regions on both sides of the diaphragm that may also be accompanied by involvement of the spleen or by localized involvement of an extra lymphatic organ or site or both.
Stage IV	Diffused or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

The absence or presence of fever > 38.5 °C, drenching night sweats, and/or unexplained weight loss of 10 percent or more body weight in the six months preceding admission are to be denoted in all cases by the suffix A or B respectively.

The International Prognostic Factor Index

The International Prognostic Factor Index (IPI) provides more precise and reproducible prognostic information than the Ann Arbor stage, but does not distinguish patients eligible for combined modality therapy for localized disease [59]. The IPI stage is dependent on five prognostic factors: Age, Ann Arbor stage, Performance status, LDH and number of extranodal sites **(see Diffuse Large B-Cell Lymphoma)**.

Management of Localized Disease

Most patients with primary mediastinal B-cell lymphoma will present with bulky disease confined to the thoracic cavity. Most published series report the results of anthracycline-based multi-agent chemotherapy with or without radiation. There is some evidence in the literature that the more dose intense regimens such as MACOP-B, VACOP-B and NHL-15 may be superior to standard CHOP chemotherapy with OS rates of 85-90% with 5 year OS rate of 85-95%. Unfortunately most of these series are retrospective, have often over represented favourable risk patients and have had variable use of consolidative radiotherapy. There is only one published prospectively controlled trial from Mexico which compared CEOP-Bleo to megaCEOP-Bleo in 68 patients [51, 53, 56, 58, 60-70]. There was no difference in response, but a statistically increased OS and FFS in the more intense arm [60]. It is important to emphasize that none of these dose intense regimens have been compared to Rituxan plus CHOP which is the current standard of care [51-53, 56, 58, 60-73], and furthermore, more intensive combination chemotherapy regimens have not been demonstrated to be superior

to CHOP in large randomized trials in other aggressive histology lymphomas and are typically more toxic. For these reasons, we recommend the use of R-CHOP rather than more intensive regimens.

The role of consolidative radiotherapy is also controversial in patients with PMBCL. Most centres offer radiation to all patients as part of their standard protocol, however there is some evidence that chemotherapy alone is effective in achieving excellent responses and long-term survivals in patients with PMBCL. Furthermore there is the potential of long-term toxicities of mediastinal radiation in a predominantly younger and female population of patients. Unfortunately there are no randomized trials addressing this subject and the data available is even more difficult to decipher than the chemotherapy literature as residual disease post chemotherapy is difficult to interpret given the bulky fibrotic masses at presentation and the lack of functional imaging post chemotherapy in most series [52, 63, 74]. Given the lack of guidance from the literature we recommend all patients with limited stage disease receive involved field radiation post chemotherapy. Patients who are female and younger than 25 years of age should be considered on an individual basis.

Patients with limited stage disease should receive combined modality therapy with R-CHOP for 6 cycles followed by mediastinal irradiation. Involved field radiotherapy is recommended for all patients. Patients achieving a complete response to chemotherapy will be treated to a dose of **3000 cGy/15 fractions**. Patients achieving a partial response will be treated to a dose of **3600 cGy/18 fractions**. All other patients will be considered for radiation on an individual basis.

Management of Advanced Stage Disease

A significant minority of patients will present with advanced stage disease. Patients who are felt to have advanced stage disease solely on the basis of pleural or pericardial effusions should be treated as if they have limited stage disease, particularly if cytology is negative for malignant cells. Patients who have documented **advanced stage disease** should receive R-CHOP for 6 cycles. Patients who achieve a complete response may be considered for consolidative radiotherapy to sites of bulky disease including the mediastinum. Radiation will be limited to **3000 cGy/15 fractions**.

Assessment of Response and Follow-Up

Patients with primary mediastinal B-cell lymphoma who achieve a complete remission with either chemotherapy alone or with combined modality therapy appear to have an excellent prognosis with relapse rates less than 10%. Furthermore the incidence of late relapses beyond 2 years is very rare in comparison to DLBCL [2, 3, 52, 72, 73, 75]. The size of residual abnormalities on chest x-ray, however, does not appear to be predictive [57]. A baseline gallium scan is of particular importance in patients with primary mediastinal B-cell lymphoma [63, 74].

Patients who have significant shrinkage of tumor size on CT scan and become gallium negative will be considered to have a major response. Patients who are gallium-negative at baseline and who achieve a significant reduction in tumor size may be re-biopsied or simply followed. There is no indication for surveillance CT scans during well follow-up visits. PET scans have not been used extensively in this patient population and have not been validated in clinical trials. Ideally PET scans should be used in assessing response within a setting of a research protocol.

Treatment of Patients with CNS Involvement

All patients should be evaluated for CNS involvement at diagnosis with a contrast CT scan of the head and a lumbar puncture.

Patients with positive CSF cytology should be treated with CHOMP chemotherapy, including both intrathecal and intravenous high dose methotrexate. Patients failing to clear their CSF of malignant cells by the end of chemotherapy should be treated with craniospinal irradiation to a dose of **2400 cGy/12 fractions**.

Patients presenting with focal leptomeningeal lesions of the brain, base of skull or spinal cord on CT scan or MRI scan should be treated with combined modality therapy, including involved field radiation to gross sites of disease to a dose of **3600 cGy/18 fractions**.

Management of Refractory or Relapsed Disease

Patients who fail to respond to initial therapy or who relapse, have a poor prognosis. Patients under age 60 with a good performance status should be considered for salvage chemotherapy and autologous stem cell transplantation [76]. Patients not eligible for transplantation should be treated palliatively with regimens such as oral VP-16 and prednisone.

Intravascular Large B-Cell Lymphoma

Introduction

Intravascular large B-cell lymphoma is a very rare subtype of non-Hodgkin's lymphoma, where the lymphoma cells are only found in the lumina of small vessels. Patients typically present disseminated disease at diagnosis with multiple organs involved including bone marrow, lung, skin and CNS. Peripheral blood involvement has been documented, but is rare. Patients tend to be elderly with poor performance status, B symptoms, anemia and elevated LDH [1, 77].

Diagnosis

The diagnosis depends on an expert hematopathologist, as the morphology can be very subtle. The lymphoma cells are typically large with vesicular nuclei and prominent nucleoli with frequent mitotic figures. The immunophenotype is typically CD19+, CD20+, and CD5+/-. There have also been rare cases of T-cell Intravascular large cell lymphoma reported [1]. Despite this being a very rare entity there are some notable geographic variations. Patients from Western countries tend to present with more skin and CNS involvement, in contrast to patients from Asian countries who present with more multi-organ involvement with bone marrow, spleen/liver, cytopenias and hemophagocytic syndrome [77].

Baseline Investigations

Same as Mediastinal Large B-cell Lymphoma **(page 12)**

Prognosis

This is a very aggressive lymphoma, which is typically rapidly fatal with multi-system failure, hemophagocytic syndrome and DIC. This entity is often diagnosed on autopsy. There may however be a more benign form of Intravascular B-cell lymphoma, which presents with mainly skin involvement [1, 78].

Treatment

Due to its rarity and its rapid course there is no consensus on optimal management, therefore we recommend 6-8 cycles of R-CHOP chemotherapy. High dose MTX should be incorporated into the drug regimen if CNS disease is identified.

Primary Effusion Lymphoma

Introduction

This is a very rare NHL subtype that typically presents in patients who are immunocompromised, most notably in patients with advanced HIV infection with very low CD4 counts. Patients usually present with serous effusions without detectable organomegaly or lymphadenopathy. This type of lymphoma is invariably associated with human herpes virus 8 (HHV8)/Kaposi sarcoma herpes virus (KSHV). Up to one third of patients have pre-existing Kaposi's sarcoma lesions. Co-infection with EBV is also commonly seen [1, 79].

Diagnosis

The diagnosis is dependent on the appropriate clinical scenario. The lymphoma cells are very pleomorphic in appearance ranging from anaplastic, to immunoblastic, to plasmacytoid. The majority of cells are large and occasionally with vacuolated cytoplasm. Some cells can resemble Reed-Sternberg cells. The cells are usually of B-cell origin with evidence of immunoglobulin gene rearrangement, they are typically positive for the leukocyte common antigen CD45, however they are usually negative for B-cell markers and thus are described as having a Null phenotype. T-cell PEL has also been described, plasma cell related markers such as CD30, CD38 and CD138 are often positive. HHV-8/KSHV viral genomes are present in all cases. There are no consistent genetic abnormalities [1, 79].

Baseline Investigations

Patients with primary effusion lymphoma should receive the following:

- CBC and differential
- Serum electrolytes and renal function
- Liver profile
- Uric acid
- LDH
- CT chest, abdomen and pelvis
- Unilateral bone marrow aspiration and biopsy
- Tap of effusion with cytology, flow cytometry,
- PCR testing for HHV8 viral genome on malignant cells from effusion sample
- HIV serology, CD4 count and viral load

Gallium scans are typically not indicated.

CSF analysis should be performed in patients with clinical evidence of CNS disease, as primary effusion lymphoma has been only rarely associated with CNS involvement [80].

Cardiac assessment should be performed according to the guidelines in **Mediastinal Large B-Cell Lymphoma**.

Prognosis

Primary effusion lymphoma is a very aggressive disease with a median survival of five months, however there have been a few documented long term remissions using conventional chemotherapy and antiviral therapy [79, 81].

Treatment

Given the rarity of this disorder there is no consensus on the optimal management. From the few cases of long term remissions in the literature it appears that a multifaceted approach is necessary [81, 82].

1. Control of HIV viral load is essential, however not sufficient on its own to produce remissions. Combination antiviral therapy should be initiated as soon as possible or adjusted appropriately in order to gain control of the viral load and CD4 counts.

2. Treatment of HHV8 is also indicated, with cidofovir, alpha interferon, broad-spectrum antivirals, or a combination of some or all of the above.

3. Traditional lymphoma based chemotherapy such as CHOP in combination with 1) and 2) should also be offered. Currently patients with HIV associated aggressive lymphoma are not routine given Rituxan in combination with standard chemotherapy due to evidence of increased toxicity due to infectious complications [83].

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