MALT Lymphomas

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Opinion statement

Mucosa-associated lymphoid tissue (MALT) lymphomas occur in a variety of organs, including the orbit, conjunctiva, salivary glands, skin, thyroid gland, lungs, stomach, and intestine. These tumors are often localized and of indolent clinical behavior. Diagnosis is made by pathologic evaluation of a tissue biopsy. Careful staging is mandatory and tailored to the initial presentation. Staging includes a history and physical, chemistries, computed tomography scan, and bone marrow biopsy. This information is supplemented with an ear, nose, and throat consultation, esophagogastro-duodenoscopy, colonoscopy, endoscopic ultrasound of the stomach, and cytogenetic/immunohistochemical analysis of the tumors. Treatment is tailored to organ involvement and stage at presentation. Eradication of *Helicobacter pylori* using a triple anti-*H. pylori* regimen approved by the US Food and Drug Administration is standard therapy for all *H. pylori*-positive gastric MALT lymphomas. Endoscopic ultrasound- and computed tomography-staged gastric MALT stage IE tumors will achieve a complete response with this approach in approximately 60% to 90% of patients (the more superficial the tumor [T1/T2], the better the response). Patients with tumors that are T4 node-positive Musshoff stage IIE1 and IIE2 or tumors with adverse cytogenetics should receive radiotherapy or surgery with or without radiotherapy. Tumors with a significant high-grade component or large cell tumors with a minor low-grade MALT component should receive CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)-based chemotherapy. Localized MALT lymphomas of the orbit, conjunctiva, salivary glands, and thyroid gland are treated successfully with radiotherapy. Surgery as first-line therapy for gastric MALT lymphomas was replaced by attempts at organ preservation. In the past, margin-free surgical excision or tumor debulking followed by radiation therapy and chemotherapy has been highly effective for gastric MALT lymphomas. Therefore, surgical excision of large cell or bulky tumors of the stomach, thyroid, lung, and salivary gland, followed by adjuvant radiotherapy or chemotherapy, may still be an important consideration in selected patients. Surgery still has a role for patients with relapsed or refractory low-grade disease and life-threatening hemorrhage. Disseminated MALT lymphomas are incurable and are treated primarily with chemotherapy according to symptoms.

Introduction

Lymphomas of mucosa-associated lymphoid tissue (MALT) are mostly indolent B-cell–derived neoplasms that occur in a variety of organs [1••,2•,3••,4]. Gastric MALT lymphomas that are associated with *Helicobacter pylori* infection are separated from extragastric MALT lymphomas. Similar to other types of lymphoma, staging is important and similar to other low-grade B-cell neoplasms because the extent of disease determines curability [5]. Because of the indolent nature of MALT lymphomas, treatment decisions should be of low morbidity, and unless treatment is administered with curative intent, it should mostly involve symptomatic patients [6]. Progress in the understanding of the biology of these neoplasms is steady, and in the case of cytogenetics, has important implications for treatment.

Treatment

Gastric low-grade mucosa-associated lymphoid tissue lymphoma

- Multiple biopsies should be analyzed carefully for a possible high-grade component. Biopsies taken through endoscope are more often graded as low-grade MALT lymphomas compared to surgical specimen, indicating an important shortcoming of this commonly used diagnostic procedure [7]. The exact number and histologic arrangement of large cells that portend poor response to *H. pylori* eradication therapy remains unclear. Some studies suggest that clustered large cells comprising 10% or more of the tumor portend a lower cause-specific survival [7,8].
- The *H. pylori* status of the patient should be determined by the urea breath test or *H. pylori* serology (both tests are 90% sensitive). Alternatively, biopsies of the stomach obtained during endoscopy can be analyzed with the urease test. Most patients with gastric MALT lymphomas are *H. pylori*-positive. Cytogenetics should be determined because 40% of MALT lymphomas harbor translocations, including t(11;18)(q21;q21), t(1;14)(p22;q32), and t(1;2)(p22;p12). These tumors are frequently locally advanced and unresponsive to *H. pylori* eradication therapy [9,10••]. In addition, strong nuclear Bcl-10 staining predicts for advanced disease and treatment failure.

Diet and lifestyle

- Acquisition of *H. pylori* seems to occur through ingestion of contaminated sources and may be more common in socioeconomically underprivileged countries. Infection with *H. pylori* in these countries is commonly acquired during childhood. Inhabitants of industrialized nations often acquire the organism in adulthood. There is no evidence for zoonotic transmission.

Pharmacologic treatment

H. pylori-positive low-grade gastric mucosa-associated lymphoid tissue lymphomas

- All *H. pylori*-positive MALT lymphomas of the stomach should be treated with *H. pylori* eradication therapy [11–13,14••,15,16]. In the United States, 14-day treatment courses are considered standard therapy. There are nine treatment options approved by the US Food and Drug Administration for first-line *H. pylori* eradication. *H. pylori* eradication success rates of greater than 80% can be expected. Primary resistance to clarithromycin and metronidazole significantly impacts cure rates.
- Recommended drug combinations include a proton pump inhibitor, clarithromycin, and metronidazole or amoxicillin; ranitidine bismuth citrate, clarithromycin, and metronidazole or amoxicillin, or tetracycline; or a proton pump inhibitor, bismuth, metronidazole, and tetracycline for 2 weeks each. *H. pylori* eradication treatment failures should ideally be treated with a 14-day drug regimen based on susceptibility testing. Empiric therapy should use a four-drug regimen containing a proton pump inhibitor and bismuth-based triple therapy with high-dose metronidazole [14••].
- The complete response (CR) rate for patients with gastric stage IE MALT lymphomas was reported at 60% to 90%. Tumors confined to the mucosa and submucosa respond the best to these treatments, whereas tumors with serosal involvement (T3) or extension beyond the stomach wall (T4) have a worse response rate in most studies [17•–19•]. Tumor location may also influence response rates with distal stomach tumors achieving higher CR

rates than proximal tumors. The reported CR rates for patients with stage IIE1 disease and higher range from 0% to 60%, with the high response rate shown in only one trial. It is thought that patients who are node positive have poor CR rates with primary *H. pylori* eradication therapy.

- The time to achieving CR varies widely between reports, but it often occurs within 2 to 12 months. Regular endoscopic monitoring is mandatory during therapy. Patients not achieving CR and patients with resistant or progressive disease should be treated with radiotherapy or surgery, although stable disease without further therapy was documented.
- Approximately 50% of the patients in CR will remain positive for a B-cell clone, which is assessed by polymerase chain reaction (PCR). The clinical significance of PCR-positivity after achieving CR is unclear [20,21,22•]. The relapse rate of patients treated exclusively with *H. pylori* eradication therapy is also unclear. These important questions are the subject of ongoing clinical trials.

Clarithromycin

Standard dosage	500 mg twice or three times daily.
Contraindications	Hypersensitivity to any of the macrolide antibiotics.
Main drug interactions	Multiple interactions. Concomitant use with drugs metabolized by the hepatic microsomal enzyme cytochrome P450 3A4 may increase concentrations of drugs, including carbamazepine, digoxin, and hydroxymethylglutaryl-coenzyme A reductase inhibitors.
Main side effects	Gastrointestinal (*eg*, diarrhea, nausea, and abnormal taste [3%]), headache (2%), and overgrowth of nonsusceptible bacteria causing *Clostridium difficile* colitis.
Special points	Primary *H. pylori* resistance decreases efficacy of therapy by approximately 50%. Some *H. pylori* isolated from patients receiving clarithromycin and acid suppressive agents demonstrate an increase in clarithromycin minimum inhibitory concentrations over time, demonstrating decreased susceptibility and increasing resistance to drugs.
Cost effectiveness	The cost for 14 days of therapy is $11.

Amoxicillin

Standard dosage	1 gram twice or three times daily.
Contraindications	History of beta-lactam antibiotic allergy.
Main drug interactions	Concomitant use of estrogen-containing oral contraceptives will decrease efficacy of contraceptives.
Main side effects	Hypersensitivity reactions, including anaphylaxis, rash (0.4%–10%), gastrointestinal (nausea and vomiting 2%; diarrhea 9%–17%), epigastric distress, gastritis, and anorexia.
Special points	Patients initiated on amoxicillin should be questioned regarding history of reactions to other beta-lactam antibiotics.
Cost effectiveness	The cost for 14 days of therapy is $26.

Metronidazole

Standard dosage	250 mg four times daily.
Contraindications	Hypersensitivity and concomitant alcohol use.
Main drug interactions	Use with alcohol can cause a disulfiram-like reaction, including flushing, headache, nausea, vomiting, sweating, and abdominal cramps. Use with warfarin can potentiate anticoagulation effects of warfarin.
Main side effects	Gastrointestinal (*eg*, nausea, diarrhea, and abdominal discomfort), headache, dry mouth, anorexia, and metallic taste.

Special points Resistance frequently develops when *H. pylori* eradication is not achieved. Regimens containing metronidazole should not be used in patients with known or suspected resistant isolates because of reduced efficacy.

Cost effectiveness The cost for a 14-day course is $3.

Ranitidine bismuth citrate/ranitidine

Standard dosage 400 mg twice daily of ranitidine bismuth citrate or ranitidine 150 mg twice daily.

Contraindications Hypersensitivity to any histamine-2 (H2) receptor antagonist and history of acute porphyria.

Main drug interactions Minimal. Interactions are less common compared to other H2 antagonists.

Main side effects Side effects are infrequent and mild. Gastrointestinal effects include nausea, constipation, and abdominal pain. Bismuth products can cause the patient's tongue and stool to be black, although this side effect is harmless.

Cost effectiveness The cost for a 14-day course is $44.

Tetracycline

Standard dosage 500 mg four times daily.

Contraindications Hypersensitivity to any tetracycline derivatives. Avoid during pregnancy.

Main drug interactions Use with aluminum, calcium, or magnesium products may decrease absorption of tetracycline. Warfarin effects may be potentiated. Concomitant use of estrogen-containing oral contraceptives will decrease efficacy of contraceptives.

Main side effects Dose-related gastrointestinal (*eg*, nausea, vomiting, diarrhea, anorexia, flatulence, and abdominal discomfort), photosensitivity, onycholysis, and discoloration of nails.

Special points None.

Cost effectiveness The cost for a 14-day course is $11.

Omeprazole, lansoprazole, esomeprazole

Standard dosage Omeprazole 40 mg daily, lansoprazole 30 mg twice to three times daily, and esomeprazole 40 mg daily.

Contraindications Hypersensitivity.

Main drug interactions Omeprazole is a cytochrome P450 inhibitor and may prolong the elimination of agents, such as phenytoin, warfarin, and diazepam.

Main side effects Side effects are infrequent and mild, mainly involving the gastrointestinal tract (1%–5%). Headaches and dizziness are reported.

Special points None.

Cost effectiveness The cost for a 14-day course (based on omeprazole) is $38.

Therapy of localized nongastric mucosa-associated lymphoid tissue lymphomas

- Pulmonary MALT lymphomas (bronchus-associated lymphoid tissue) are unilateral in approximately 75% of patients and bilateral in 25% [23,24]. Single or multiple masses appear equally common, but interstitial spread occurs and nearly 50% of carefully staged patients present with stage III or IV disease [25,26]. Mediastinal lymph nodes are involved in approximately 40% of patients when pathologic specimens are analyzed carefully. Nonetheless, bronchus-associated lymphoid tissue is an indolent disease. Chemotherapy or surgery is the primary treatment modality. Depending on disease activity, purine analogs, oral cyclophosphamide or chlorambucil, and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CVP (cyclophosphamide, vincristine, and prednisone) chemotherapy regimens can be used. Radiotherapy can be used to consolidate the patient after surgery.

- Conjunctival tumors can be treated with radiotherapy, but promising results were obtained with conjunctival interferon-α2a injections [27•].
- Thyroid MALT lymphomas have an excellent prognosis and seem to respond well to radiation therapy or chemotherapy. We recommend primary radiation therapy, but bulky tumors may first require thyroidectomy followed by consolidation radiotherapy.
- Mucosa-associated lymphoid tissue lymphomas of the skin are often stage III or IV at diagnosis [28]. Careful staging is mandatory. Local therapy with surgery or radiotherapy is followed by chemotherapy for symptomatic patients.

Interferon-α2a

Standard dosage	1.5 million international units (IU) subconjunctivally inside the lesion three times per week for 4 weeks, then 1 million IU three times weekly for 4 weeks, followed by maintenance 1 million IU every 15 days for four times.
Contraindications	None.
Main drug interactions	Minimal.
Main side effects	Reports of mild transient adverse effects (*eg*, local irritation and blurriness). This drug should have minimal systemic absorption, thus not having reported systemic effects.
Special points	This therapy is still experimental.
Cost effectiveness	The cost for an initial 4-week cycle is $230.

Advanced stage low-grade mucosa-associated lymphoid tissue lymphoma

- Patients with advanced stage MALT lymphoma with multiple sites of involvement should be treated with chemotherapy. It may be that extragastric MALT lymphomas are more often multifocal than gastric tumors.
- Multiple chemotherapy regimens used for low-grade lymphomas are available. A small study used cladribine for a maximum of six cycles in patients with MALT lymphomas of gastric or extragastric location [29]. In addition, patients with gastric lymphoma received *H. pylori* eradication therapy. CR rates were above 80% for the entire cohort, with gastric MALT lymphomas responding better than extragastric cases. It is unlikely that true cures can be achieved with this approach, but durable remissions were shown with a median follow-up time of 32 months.
- Single-agent oral chemotherapy with cyclophosphamide or chlorambucil was investigated in a mixed patient population of patients with stage I and stage IV disease [30]. The median follow-up time was 45 months and CR was achieved in 75% of patients. However, approximately 30% of these patients subsequently relapsed. The role of single-agent oral alkylator therapy for disseminated MALT lymphoma is restricted to palliation.
- Patients with more aggressive clinical presentation should be treated with CVP, CHOP, or rituximab plus CHOP for six cycles.

Cladribine

Standard dosage	0.12 mg/kg intravenously for 5 consecutive days every 4 weeks for a maximum of six cycles.
Contraindications	Hypersensitivity.
Main drug interactions	None.
Main side effects	Dose-limiting severe bone marrow suppression, including neutropenia (70%) and thrombocytopenia (12%), and prolonged lymphopenia, causing infectious complications. Rash (27%), fatigue, and nausea.
Special points	Efficacy based on a small number of treated patients.
Cost effectiveness	The cost for one cycle is $2813.

Cyclophosphamide

Standard dosage	100 mg by mouth every day.
Contraindications	None.
Main drug interactions	Medications that inhibit cytochrome P450 3A4 may increase the toxicity of cyclophosphamide.
Main side effects	Severe bone marrow suppression, hemorrhagic cystitis, bladder cancer, nephrotoxicity, and nausea.
Special points	Efficacy based on a small number of treated patients.
Cost effectiveness	The cost for a 1-month supply is $249.

Chlorambucil

Standard dosage	6 mg by mouth every day.
Contraindications	Hypersensitivity.
Main drug interactions	Barbiturates may increase chlorambucil toxicity by inducing hepatic activation of chlorambucil.
Main side effects	Dose-limiting bone marrow suppression, myelodysplasia, focal and generalized seizures, nausea, and rash. If rash develops, the agent should be discontinued immediately.
Special points	Use with caution in patients with a history of seizures or head trauma.
Cost effectiveness	The cost for a 1-month supply is $178.

Radiation therapy

- Malt lymphomas are radiosensitive. Localized MALT lymphomas of the orbit, conjuctiva, salivary glands, thyroid, and stomach can be treated successfully with primary radiotherapy [31–33]. With a median follow-up time of 27 months, disease-free survival rates of up to 100% were reported [34]. Highest cure rates are reported for gastric and thyroid MALT lymphomas [35].
- Gastric MALT lymphomas with adverse prognostic features for successful outcome with primary *H. pylori* eradication therapy, including node-positive patients (stage IIE1 and IIE2), tumors with t(11;18), and tumors with serosal and subserosal extension, should be treated with primary radiotherapy. *H. pylori*-negative patients and patients not achieving CR with anti-*H. pylori* therapy should be treated with primary radiotherapy.
- Some evidence exists that bulky tumors are treated less successfully with single-modality therapy. Therefore, bulky tumors should be considered for treatment with combined modality therapy with surgery followed by radiotherapy or chemotherapy followed by radiotherapy.

Gastric mucosa-associated lymphoid tissue lymphoma

Standard dosage	No clearly defined standard dose exists. Reported doses range from 28.5 to 50.4 Gy to the stomach and adjacent lymph nodes, with most patients receiving 30 to 35 Gy. Whole abdominal radiotherapy with 20 Gy with a boost to the stomach and adjacent lymph nodes of an additional 20 Gy was reported. A review of the published data justifies doses of 30 Gy as sufficient therapy. Multiple-field techniques to minimize left kidney damage should be used.
Contraindications	Relative contraindication: stage IV disease unless it is needed for local control or bleeding.
Main side effects	Gastric perforation and gastric bleeding (incidence 1%–5%; more likely in advanced stages or bulky lesions), renal toxicity, hypertension, and secondary cancers.

Nongastric mucosa-associated lymphoid tissue lymphoma

Standard dosage	Involved-field radiotherapy is standard. No clearly defined standard dose exists. Reported doses range from 17.5 to 40 Gy, with lower doses used for conjunctival and orbital adnexal disease. In one retrospective analysis, a median of 33.30 Gy was used for parotid tumors. Two reports describe the use of 25 Gy and 30 to 36 Gy for orbital adnexal disease, respectively.
Contraindications	Relative contraindication: stage IV disease unless needed for local control.
Main side effects	Secondary cancers, sicca syndrome, cataracts and radiation dermatitis, and retinal damage.
Special points	Parotid: radiation field to include parotid gland and ipsilateral upper cervical nodes. Patients with Sjögren's syndrome with parotid MALT lymphoma have a high incidence of sicca syndrome after radiation. Tumor recurrence in the radiation field is uncommon, but extranodal recurrences in other MALT lymphoma sites are frequent.

Diffuse large B-cell lymphoma plus or minus areas of marginal zone/mucosa-associated lymphoid tissue lymphoma (World Health Organization classification)

- Patients with a predominant large-cell component and a minor low-grade component pose a difficult treatment decision. The optimal treatment of these patients has not been defined. The growing attempt at organ preservation has lessened the role for first-line surgery [36].
- All patients who are *H. pylori*-positive should undergo *H. pylori* eradication therapy. Cases of superficial high-grade lymphomas treated successfully with *H. pylori* eradication therapy were reported [37,38]. This approach, although provocative, should be restricted to clinical trials until more data on effectiveness become available.
- Chemotherapy with six cycles of the CHOP regimen with or without rituximab could be considered first-line therapy for patients with stage III and IV disease. Carefully staged patients with stage 1E and IIE2 disease can be treated with three to six cycles of rituximab plus CHOP, followed by consolidation with involved field radiotherapy.
- The contemporary role of surgery in the management of gastric large cell lymphoma arising from low-grade MALT is unclear [39–41]. Patients with stage I disease localized to the mucosa, submucosa, or muscularis propria had high cure rates with total gastrectomy alone. The value of adjuvant chemotherapy for patients with stage I disease remains uncertain. In some retrospective analysis, adjuvant chemotherapy benefited surgically treated patients with subserosal or more advanced tumor involvement, but it showed little benefit in patients with tumors confined to the gastric wall [42]. Serosal or subserosal involvement or stage IIE1 and IIE2 disease significantly reduces the effectiveness of surgery as sole treatment. These patients were treated with surgery, followed by adjuvant chemotherapy, with excellent 5-year survival rates.
- Because patients with stage I disease can be treated successfully with sequential chemoradiotherapy, the role of surgery is restricted to large tumors, patients at high risk for perforation and massive bleeding, and medical conditions preventing effective nonsurgical therapy.
- A prospective trial comparing surgery plus chemotherapy with chemotherapy alone or chemotherapy followed by consolidation radiotherapy has not been reported.

Rituximab

Standard dosage	375 mg/m^2 intravenously on day one of every cycle.
Contraindications	Hypersensitivity.
Main drug interactions	None.
Main side effects	Side effects are experienced by 75% of patients during first infusion and decline markedly with following infusions. Reactions considered severe have an incidence of 10%. Infusion-related reactions range from mild to severe and fatal (*eg*, fevers, chills, rigors, asthenia, nausea, rash, pruritus, angioedema, hypotension, headache, bronchospasm, acute respiratory distress syndrome, and systemic inflammatory response syndrome). These reactions should be managed by decreasing the infusion rate and administering supportive care. Tumor lysis syndrome, cardiac abnormalities including arrythmias, in addition to neutropenia and thrombocytopenia were reported.
Special points	None.
Cost effectiveness	The cost is $3693 per cycle.

Cyclophosphamide

Standard dosage	750 mg/m^2 intravenously on day 1.
Contraindications	None.
Main drug interactions	Medications that inhibit cytochrome P450 3A4 may increase the toxicity of cyclophosphamide.
Main side effects	Myelosuppression, hemorrhagic cystitis and other bladder irritation, nephrotoxicity, alopecia, nausea, vomiting, anorexia, and mucositis.
Cost effectiveness	The cost is $444 per cycle.

Doxorubicin

Standard dosage	50 mg/m^2 intravenously on day 1.
Contraindications	Pre-existing cardiomyopathy.
Main drug interactions	None.
Main side effects	Dose-limiting cardiomyopathy, myelosuppression (primarily leukopenia), nausea, vomiting, alopecia, change of urine and tears to orange-color, mucositis, and risk of extravasation.
Special points	Dose modification with liver dysfunction.
Cost effectiveness	The cost is $822 per cycle.

Vincristine

Standard dosage	1.4 mg/m^2 intravenously, with a maximum dose of 2 mg on day 1.
Contraindications	Pre-existing neuropathy.
Main drug interactions	Medications that are inhibitors of cytochrome P450 3A4 may increase the toxicities of vincristine.
Main side effects	Peripheral neuropathy, autonomic toxicity including constipation and abdominal cramping, muscle weakness, alopecia, and risk of extravasation.
Special points	Dose modification needed with liver dysfunction. Patients should be placed on a bowel regimen.
Cost effectiveness	The cost is $63 per cycle.

Prednisone

Standard dosage	100 mg by mouth daily days 1 to 5.
Contraindications	None.
Main drug interactions	Corticosteroids are metabolized by cytochrome P450 3A4. Concomitant medications that are inducers, inhibitors, or substrates for this enzyme may alter the metabolism of prednisone.

Main side effects Gastrointestinal irritation, insomnia, anxiety, mental status, changes, fluid retention, hypertension, hyperglycemia, and increased risk of infection.
Special points Consider concomitant H2-receptor antagonist or proton pump inhibitor to reduce gastrointestinal irritation.
Cost effectiveness The cost is $62 per cycle.

Imaging

Endoscopic ultrasound

Standard procedure Endoscopic ultrasound.
Contraindications High risk for perforation, active bleeding, and unstable cardiac arrhythmias.
Complications Esophageal perforation, cardiac arrhythmias, and aspiration (all < 1%).
Special points Best technique for gastric MALT lymphoma staging.

Surgery

Gastrectomy

Standard procedure Gastrectomy.
Contraindications Patients with high operative mortality and early stage IE gastric MALT lymphomas.
Complications Mortality 5%, morbidity 20%, dumping syndrome, fistulas, and reductions in quality of life.

Emerging therapies

- The gastric MALT lymphoma relapse rate after histologically confirmed complete tumor regression is unknown. Longer follow-up of prospective trials is necessary to answer that question.
- The role of maintenance therapy with oral clorambucil 6 mg/m^2 by mouth daily for 14 of every 28-day cycle for a total of six cycles is being investigated in a large international cooperative study [22•]. Patients in histologic CR after primary *H. pylori* therapy will be randomized to observation or oral chlorambucil. Mature results from this trial are not expected for several years.
- The role for rituximab in the initial therapy of these lymphomas or as consolidation therapy is unclear and should be defined through clinical trials.

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