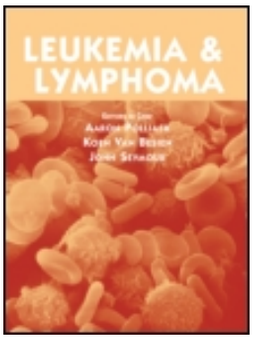

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COMMENTARY

Gastric mucosa-associated lymphoid tissue lymphoma resistant to *Helicobacter pylori* eradication: what's the best option?

Jennifer R. Brown

Department of Medical Oncology, Dana-Farber Cancer Institute, and Department of Medicine, Harvard Medical School, Boston, MA, USA

Extranodal mucosa-associated lymphoid tissue (MALT) lymphomas frequently occur in the setting of inflammation that may arise from infection, as in gastric MALT lymphoma, or from autoimmune disease, as with salivary gland or thyroid MALT lymphoma. The strongest evidence for an etiologic link between infection or inflammation and MALT has certainly come from gastric MALT, which is associated with *Helicobacter pylori* infection in 89% of cases [1]. In fact, first-line therapy for gastric MALT lymphoma associated with *H. pylori* infection is eradication of *H. pylori* with antibiotics and proton pump inhibitors. A recent systematic review of 32 studies found that the remission rate with antibiotics is 77.5% [1]. In further follow-up analysis of 994 patients, lymphoma relapse occurred in only 7.2% of patients over 3253 patient years of follow-up, or 2.2% per year [1]. Another large study found that the freedom from treatment failure and overall survival at 10 years were 90% and 95% [2]. These results with just antibiotics as first-line therapy are obviously excellent. Despite this obvious dependence of many gastric MALT lymphomas on *H. pylori*, a subset of gastric MALT lymphomas are negative for *H. pylori*. Furthermore, approximately 25% carry t(11;18), which fuses the *API2* gene on chromosome 11 with the *MALT1* gene on chromosome 18 and leads to activation of nuclear factor κB (NFκB) [3]. The presence of this translocation is associated with *H. pylori* negativity [4] and has also been identified in many studies as a key risk factor for lack of response to *H. pylori* eradication, which works only 22–25% of the time in these patients [5,6].

The treatment of localized gastric MALT lymphoma that is either *H. pylori* negative or fails eradication therapy therefore remains controversial. A recent consensus statement on the subject suggested that either localized radiotherapy or systemic therapy are valid options with curative potential [3]. In this issue of ***Leukemia and Lymphoma***, Levy and colleagues report the outcomes of a single-center prospective observational study in which they compare outcomes of rituximab alone and chlorambucil with rituximab in these patients [7]. In previous work they have found that the response to oral alkylating agents varies dramatically based on the presence or absence of t(11;18), with an 89% ongoing remission rate at 7 years in patients without t(11;18) but only 8% with t(11;18) [8]. They have therefore sought to improve on the latter results by adding rituximab, which has been reported to have a 77% response rate in gastric MALT resistant to or ineligible for *H. pylori* eradication therapy [9]. Response to rituximab has also been reported to be preserved regardless of t(11;18), with a 75% overall response rate (ORR) with translocation and 69% ORR without [9].

The current study enrolled 49 patients and included 16 *H. pylori* positive patients who failed to remit with antibiotics, as well as 33 *H. pylori* negative patients, nine of whom had failed to respond to chlorambucil previously and 24 of whom were undergoing their first-line therapy. Patients were initially started on rituximab alone with four weekly infusions followed by four monthly infusions. If disappointing results were seen with rituximab alone, chlorambucil was added. Therapy was not randomized but was selected by a multidisciplinary committee, and ultimately 30 patients received rituximab with chlorambucil and 21 received rituximab alone.

In the overall group, response was quicker but not ultimately better with the addition of chlorambucil. The interesting findings of this study are really in the differential response of the patients with and without t(11;18). The patients without t(11;18) showed no difference with the addition of chlorambucil, suggesting that these patients do very well with rituximab alone. However, the patients with t(11;18) showed a significantly greater response to rituximab–chlorambucil than to rituximab alone at all time points [7], suggesting perhaps some synergy of response, given the authors' own prior data on the limited efficacy of chlorambucil alone and their current relatively poor response with rituximab alone.

Prior work investigating the effect of t(11;18) on treatment response has suggested poor response with oral alkylating agents [8], but preserved response with either cladribine [3] or rituximab [9]. Perhaps the best long-term chemotherapy

Correspondence: Jennifer R. Brown, MD, PhD, Director, CLL Centre, Assistant professor of medicine, Department of Medical Oncology, Dana-Farber Cancer Institute, Department of Medicine, Harvard Medical School, 450 Brookline Avenue, Boston, MA 02215, USA. Tel: 617-632-4564. Fax: 617-582-7909. E-mail: jbrown2@partners.org

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data are with cladribine, but concerns about cytopenias and long-term risks of myelodysplasia remain. The study published here suggests that rituximab–chlorambucil may be a better tolerated alternative even in t(11;18) positive patients. Radiotherapy also remains a well-tolerated alternative, with high response rates and long-term complete remissions in patients who fail *H. pylori* eradication and/or chemotherapy [10], but few data exist on its efficacy in the setting of t(11;18). A randomized trial comparing surgery to radiotherapy to CHOP/CVP (cyclophosphamide, doxorubicin, vincristine, prednisone/cyclophosphamide, vincristine, prednisone) chemotherapy was done in the era prior to *H. pylori* therapy [11], but radiotherapy and current systemic therapy options have not been compared.

Overall the results of this study as well as the accumulating data suggest several questions for investigation. The emerging body of data demonstrating differential treatment response based on t(11;18) status suggests that certainly in clinical trials t(11;18) should be determined prior to therapy to track response, and in randomized trials should be a stratification factor if possible. The optimal choice of systemic therapy may depend on t(11;18), with patients without the translocation doing well with most options, and those with the translocation needing stronger therapy, perhaps chlorambucil with rituximab as described here or cladribine. Finally, the question of whether systemic therapy or radiotherapy will result in better outcomes over long-term follow-up also remains open, and the time is certainly right for a controlled clinical trial of systemic therapy versus radiotherapy, controlling for t(11;18) status. Although controlled trials are difficult in this disease given its rarity, their outcome would be informative in guiding therapeutic selection and definitively establishing the role of t(11;18) in therapeutic selection. Fortunately, despite these uncertainties and the time required to complete studies in this disease, overall patient outcomes remain excellent with all these options.

Potential conflict of interest: A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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