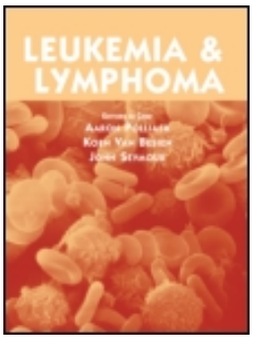

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Paul M. Barr & Clive S. Zent

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COMMENTARY

The ABC of chronic lymphocytic leukemia: Etiology of cytopenias is important in staging and management

Paul M. Barr[1] & Clive S. Zent[2]

[1]*James P. Wilmot Cancer Center, University of Rochester, Rochester, NY, USA and* [2]*Division of Hematology, Mayo Clinic, Rochester, MN, USA,*

Cytopenias are a well-recognized complication of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL). The inferior prognosis of patients with CLL with anemia and thrombocytopenia resulted in the incorporation of these two pivotal criteria into the Rai and Binet staging systems irrespective of the etiology of the cytopenias. However, a number of CLL related and non-CLL related causes must be considered by treating physicians evaluating all cytopenias in patients with CLL. The CLL related causes include bone marrow failure due to infiltration by CLL cells, autoimmune disease, hypersplenism, and treatment related myelodysplastic syndrome and acute myelogenous leukemia. In addition to a clinical assessment, the evaluation of these patients requires testing for hemolysis (direct antiglobulin test, indirect bilirubin, lactate dehydrogenase and reticulocytes), and a bone marrow biopsy and aspirate. The importance of this evaluation has been endorsed in the current International Workshop on CLL modification of the National Cancer Institute guidelines [1].

The most common autoimmune cytopenias complicating CLL are autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP), with lower rates of pure red cell aplasia, and autoimmune granulocytopenia. Observational studies of large populations of patients with CLL report that autoimmune cytopenias occur in 4–9% of patients with CLL, and are diagnosed before or at the same time as the CLL in about 25% of patients [2–5]. Compared to prior reports [6,7], autoimmune cytopenias now appear to occur less frequently, possibly because of the earlier diagnosis of CLL [8]. However, the more widespread use of chemoimmunotherapy combining purine analog and alkylating agents with anti-CD20 antibodies could also have decreased the rates of treatment induced autoimmune cytopenias [9,10].

Observational studies have consistently reported differences in outcomes of cytopenias in patients with CLL according to their etiology. Compared to unselected patients with CLL, autoimmune cytopenias do not necessarily predict for an inferior outcome [4,5]. An important finding was that patients with autoimmune cytopenias have a superior survival compared to those with Rai stage III/IV or Binet C disease caused by marrow failure. However, the patients with CLL with bone marrow failure had a higher rate of adverse biological prognostic factors [2,3], and a positive direct antiglobulin test in the absence of AIHA was associated with an inferior prognosis in a cohort of patients requiring therapy [9]. These findings suggest that patients with CLL with more aggressive biology could be at higher risk of autoimmune complications.

In this issue of ***Leukemia and Lymphoma***, Visco *et al.* report their evaluation of the etiology of cytopenias in a contemporary cohort of 86 patients with CLL who had Binet C disease at diagnosis [11]. Twenty-seven (31%) of these patients had evidence of autoimmune cytopenias, and of these, nine (33%) did not need treatment for progressive CLL. This is an important confirmation of previously reported data, and re-emphasizes the need for a comprehensive evaluation of the etiology of cytopenias in patients with CLL.

The authors then examined the prognostic importance of a diagnosis of autoimmune cytopenias in this small cohort. Consistent with the previous literature, outcomes for Binet C patients with autoimmune cytopenias were superior to those with bone marrow failure. An important finding was that compared to patients with Binet A disease, those patients with low CLL disease burden and autoimmune cytopenia had a worse outcome, which was equivalent to patients with intermediate (Binet B) stage disease. Binet C patients with low burden CLL and autoimmune cytopenias could have a worse outcome than patients with Binet A disease because of independent deleterious effects of autoimmune cytopenias and their treatment, or the association between more aggressive CLL and an increased risk of autoimmune cytopenias. Determining the relationship between CLL and its autoimmune complications is a subject of ongoing research. A better understanding of these interactions

Correspondence: Clive S. Zent, MD, Division of Hematology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905, USA. Tel: 507-284-2511. Fax: 507-266-4972. E-mail: zent.clive@mayo.edu

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could be of benefit both in patient management and in determining the value of autoimmune cytopenias as an independent prognostic factor in patients with CLL.

The study by Visco *et al*. strongly supports the need for a comprehensive evaluation of the etiology of cytopenias in patients with CLL at diagnosis, and their findings are compatible with current recommendations to thoroughly evaluate all cytopenias in patients with CLL. These evaluations are critical for both appropriate therapy and for understanding the prognostic implications of cytopenias. All patients being treated for Binet C (and Rai III–IV) CLL need to be evaluated for bone marrow failure using a bone marrow biopsy and aspirate. While the management of patients with advanced CLL remains challenging, the decision to investigate cytopenias should be as easy as ABC.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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