Over the past decade, the concept of targeting cytokines to treat autoimmune, rheumatologic, and malignant diseases has evolved at a rapid pace. Currently, there are medicines approved by the US Food and Drug Administration and/or the European Union that target IL-1β, IL-2, IL-5, IL-6, tumor necrosis factor α (TNF-α), interferon gamma (INF-γ), and INF-α.[4] Dozens of medicines that target additional cytokines are in preclinical development and early-phase clinical trials. In some circumstances, these medications are less effective than nonspecific immune suppressants; however, in other situations, they have shown considerable promise. TNF-α inhibitors are very active in rheumatoid arthritis and inflammatory bowel disease.[4] The IL-6 inhibitor tocilizumab may be effective in reversing the cytokine release syndrome seen after novel T-cell activating anticancer therapies, including bispecific T-cell engaging single-chain antibody constructs and chimeric antigen receptor–modified T cells.[5,6] Care is needed and preclinical studies are important before cytokine blockade is used in the clinic, because the cytokine cascade is very complex with positive and negative feedback. For example, IL-10 is markedly elevated in ALPS, leading to the hypothesis that IL-10 inhibition may be effective in ALPS. Yet, in animal models, inhibition of IL-10 caused a worsening of disease.[7]

Further studies are needed to determine the mechanisms underlying the elevated IL-17 levels in ALPS and DALD and to understand the downstream effects of those elevations on different signaling pathways. Signaling through the PI3K/Akt/mTOR pathway can positively regulate Th17 differentiation, and blockade of this pathway by using the mTOR inhibitor sirolimus can downregulate production of proinflammatory cytokines, including IL-17A by Th17 cells in other diseases.[8] Sirolimus is a very active drug in murine and human ALPS, which raises the question: Is part of the benefit of sirolimus in ALPS through inhibition of Th17 and IL-17A? Recent studies have demonstrated that targeting Jak/Stat signaling may be effective in preclinical models of ALPS.[9] Targeting Jak/Stat can impair proinflammatory IL-17 cytokine production, raising another question: Is part of the benefit of Jak/Stat inhibition in ALPS through inhibition of Th17 and IL-17?[10]

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Boggio E, Clemente N, Mondino A, et al. IL-17 protects T cells from apoptosis and contributes to development of ALPS-like phenotypes. *Blood.* 2014; 123(8):1178-1186.
2. Sundrud MS, Trivigno C. Identity crisis of Th17 cells: Many forms, many functions, many questions. *Semin Immunol.* 2013;25(4):263-272.
3. Oliveira JB, Bleesing JJ, Dianzani U, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. *Blood.* 2010;116(14):e35-e40.
4. Miller AV, Ranatunga SK. Immunotherapies in rheumatologic disorders. *Med Clin North Am.* 2012;96(3): 475-496, ix-x.
5. Teachey DT, Rheingold SR, Maude SL, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. *Blood.* 2013;121(26): 5154-5157.
6. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med.* 2013;368(16):1509-1518.
7. Yin Z, Bahtiyar G, Zhang N, et al. IL-10 regulates murine lupus. *J Immunol.* 2002;169(4):2148-2155.
8. Yin H, Li X, Zhang B, et al. Sirolimus ameliorates inflammatory responses by switching the regulatory T/T helper type 17 profile in murine colitis. *Immunology.* 2013; 139(4):494-502.
9. Wang S, Yang N, Zhang L, et al. Jak/STAT signaling is involved in the inflammatory infiltration of the kidneys in MRL/lpr mice. *Lupus.* 2010;19(10):1171-1180.
10. González-Alvaro I, Ortiz AM, Domínguez-Jiménez C, Aragón-Bodi A, Díaz Sánchez B, Sánchez-Madrid F. Inhibition of tumour necrosis factor and IL-17 production by leflunomide involves the JAK/STAT pathway. *Ann Rheum Dis.* 2009;68(10):1644-1650.

● ● ● LYMPHOID NEOPLASIA

Comment on Xochelli et al, page 1199

Clonal B-cell lymphocytosis: a new member?

Maurilio Ponzoni[1] and Paolo Ghia[1,2] [1]SAN RAFFAELE SCIENTIFIC INSTITUTE; [2]UNIVERSITÀ VITA-SALUTE SAN RAFFAELE

In this issue of *Blood*, Xochelli et al have identified, in otherwise healthy individuals with no clinical signs of lymphoproliferative disorders, a circulating clonal B-cell population with an immunophenotype consistent with a marginal zone B-cell population (CBL-MZ).[1] This scenario is reminiscent of monoclonal B-cell lymphocytosis (MBL)[2] of the "CD5-negative type," although the report includes cases with rather prominent B lymphocytosis (up to 34×10^9/L, K. Stamatopoulos, Institute of Applied Biosciences, Thessaloniki, Greece, written communication, December 16, 2013), being above the MBL threshold of 5×10^9 B lymphocytes/L[2].

It is interesting to note that at the time of the original report, the authors found it difficult to identify cases lacking CD5 expression, while $CD5^+$ cases were more easily classified as chronic lymphocytic leukemia (CLL)-like or non–CLL-like (atypical CLL) MBL.[3] The definition of marginal-type MBL was not widely accepted due to the lack of distinct phenotype for marginal zone (MZ) cells, with the diagnosis being made by exclusion of other more disease-specific phenotypes.

Xochelli et al have demonstrated the occurrence of a circulating monoclonal B-cell population with a distinct MZ-like phenotype using a flow-cytometric profile consistent with a MZ origin. The authors conclusively demonstrate that at least a fraction of the so-called CD5-negative (or expressing very weakly) monoclonal B-cell populations can indeed be defined based on the coexistence of immunophenotypical and morphologic features typically associated with MZ lymphomas involving the spleen (SMZL), including expression of CD49d and FMC7, in the absence of GC markers such as CD10 and/or CD38.

Despite the resemblance to SMZL, some features of CBL-MZ are different. Of particular interest and unexpectedly, none of the reported cases were associated with hepatitis C virus infection, a condition that in the past was considered to underlie most $CD5^-$ MBL cases.[4] Thus, the relationship between the CBL-MZL cases described by Xochelli and

collaborators and those arising in the context of viral infections remains to be elucidated.

These entities share with MBL the indolent course and the low propensity to progress to overt malignancy. Among the patients followed for 5 years, only 17% of them progressed to clinically overt, splenic B-cell lymphoma of MZ origin, and only 3 needed treatment over the follow-up time. It is likely that CBL-MZ represents a more heterogeneous group than expected and could include more subgroups, similar to what happens for physiological MZ subsets.

Despite the similarities with MBL, one could still ask whether these monoclonal expansions could be indeed actual neoplasms, and it remains questionable if these conditions could be easily differentiated from bona fide lymphoproliferative disorders, because splenomegaly is not an absolute requirement for the diagnosis of SMZL. On one hand, even the subgroup of "nonprogressing" CBL-MZL seems to fulfill the criteria of neoplastic disease, because 27% of cases carried chromosome 7 abnormalities. On the other hand, it is remarkable that, at the histopathological level, some cases have been reported to display a bone marrow infiltration up to 70% of overall cellularity.

The description of a tissue counterpart of CBL-MZL still needs to be defined. In fact, available data are exclusively based on peripheral blood smear and bone marrow biopsy, while other data on the histopathological examination of extra nodal sites associated with the presence of MZ are not yet available, in contrast to previously published tissue observations in the case of in situ mantle cell lymphoma[5] and follicular lymphoma[6] and proposed also for CLL.[7] Further follow-up as well as the experience of additional groups may help clarify these questions, which involve both diagnostic and clinical aspects. In any case, the features reported by Xochelli et al provide a useful tool to track the characteristics of MZ B-cell lymphoproliferations in their very early stages and can be exploited as an experimental model for the study of the natural history of these diseases.

Finally, this paper brings attention to the contentious issue of overdiagnosis of indolent lymphoproliferative disorders. Performance of blood tests for no specific clinical indications will lead more frequently to the diagnosis of MBL or CBL, generating ethical and medical issues regarding patient management, including what type of diagnosis to communicate. A lot needs still to be done in this "gray zone" between health and disease, but awareness of multiple and, usually, nonprogressive conditions like CBL-MZL is helpful in preventing unnecessary clinical interventions and avoiding risky diagnostic or therapeutic procedures. In this respect, we fully agree with the authors' message of caution, suggesting not to include in the routine workup procedures such as endoscopy or bone marrow examination in the absence of suggestive clinical signs or symptoms.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Xochelli A, Kalpadakis C, Gardiner A, et al. Clonal B-cell lymphocytosis exhibiting immunophenotypic features consistent with a marginal-zone origin: is this a distinct entity? *Blood.* 2014;123(8):1199-1206.

2. Marti GE, Rawstron AC, Ghia P, et al; International Familial CLL Consortium. Diagnostic criteria for monoclonal B-cell lymphocytosis. *Br J Haematol.* 2005; 130(3):325-332.

3. Ghia P, Prato G, Scielzo C, et al. Monoclonal CD5+ and CD5- B-lymphocyte expansions are frequent in the peripheral blood of the elderly. *Blood.* 2004;103(6): 2337-2342.

4. Fazi C, Dagklis A, Cottini F, et al. Monoclonal B cell lymphocytosis in hepatitis C virus infected individuals. *Cytometry B Clin Cytom.* 2010;78(Suppl 1): S61-S68.

5. Carvajal-Cuenca A, Sua LF, Silva NM, et al. In situ mantle cell lymphoma: clinical implications of an incidental finding with indolent clinical behavior. *Haematologica.* 2012;97(2):270-278.

6. Cong P, Raffeld M, Teruya-Feldstein J, Sorbara L, Pittaluga S, Jaffe ES. In situ localization of follicular lymphoma: description and analysis by laser capture microdissection. *Blood.* 2002;99(9):3376-3382.

7. Gibson SE, Swerdlow SH, Ferry JA, et al. Reassessment of small lymphocytic lymphoma in the era of monoclonal B-cell lymphocytosis. *Haematologica.* 2011; 96(8):1144-1152.

● ● ● MYELOID NEOPLASIA

Comment on Woyach et al, page 1207, and on Rushworth et al, page 1229

Boldly Targeting Kinases without mutations

Matthew S. Davids[1] [1]DANA-FARBER CANCER INSTITUTE

In this issue of *Blood*, Woyach et al provide compelling evidence that Bruton's tyrosine kinase (BTK) is a critical target of ibrutinib in chronic lymphocytic leukemia (CLL), and Rushworth et al report data suggesting that BTK may also be a viable therapeutic target in acute myeloid leukemia (AML). These studies exemplify the concept that selectively targeting overactive kinases may be therapeutically useful in neoplasia even in the absence of recurrent genetic mutations in those kinases.[1,2]

The foundation of targeted cancer therapy has been selective inhibition of tyrosine kinases that are constitutively activated by DNA mutations or translocations that are recurrent and fundamental to disease pathophysiology. The story of the tremendous success of imatinib and other ABL kinase inhibitors in chronic myeloid leukemia (CML) is the best known example among hematologic malignancies,[3] and targeted therapy has also shown promise in several solid tumors such as melanoma[4] and lung cancer.[5] Targetable kinase mutations with direct relevance to disease pathogenesis have been identified less frequently in lymphoid neoplasms, making the extension of this paradigm to CLL and related diseases challenging.

Despite this limitation, arguably there is no cancer for which more new promising therapeutic agents are available than for CLL, with the rise of novel agents against a variety of targets such as the B-cell receptor (BCR) pathway[6] and the intrinsic mitochondrial pathway of apoptosis,[7] along with immune-based therapies such as chimeric antigen receptor T cells.[8] None of these therapies depends on the presence of a genetically mutated target. This success in CLL unfortunately has not yet been seen in AML, for which several targeted agents are in