HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

Clin Cancer Res. 2016 April 1; 22(7): 1547–1549. doi:10.1158/1078-0432.CCR-15-3106.

Arresting the Inflammatory Drive of Chronic Lymphocytic Leukemia with Ibrutinib

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Summary

The clinical success of agents targeting the B cell receptor (BCR) signaling pathway in chronic lymphocytic leukemia (CLL) may also derive from disrupting the CLL microenvironment. Investigation of the immunomodulatory effects of these agents illuminates the unique immunobiology of CLL and highlights potential targets for dismantling the chronic inflammatory drive.

In this issue of *Clinical Cancer Research*, Niemann and colleagues systematically dissect the extracellular effects of an intracellular BCR signaling inhibitor in CLL(1). The incurability of CLL, outside of allogeneic stem cell transplantation, has motivated the search for molecular pathways integral to CLL survival. One prominent example is the BCR signaling pathway and as a result, multiple small molecules targeting various downstream components of this pathway have entered clinical trials where significant clinical benefit has accrued across the various CLL clinicogenetic subgroups(2). Ibrutinib, an orally bioavailable small molecule developed as a Bruton's tyrosine kinase inhibitor, is an FDA-approved therapy for relapsed/refractory CLL and was recently shown to improve overall survival as a frontline regimen as well(3).

In vitro studies have shown ibrutinib to induce only modest levels of apoptosis in CLL cells, strongly suggesting a non-autonomous mechanism to its clinical potency(4). Indeed, ibrutinib is known to bind other kinases related to BTK, notably those in the TEC family such as ITK, expressed in T cells. Ibrutinib inhibits T cell activation-induced cytokine secretion *in vitro*, and *in vivo* drives an anti-tumor Th1 polarization effective in both solid and hematologic malignancies(4-6). However, the effects of ibrutinib on other cell types in the CLL microenvironment remain unclear.

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Disclosure of Potential Conflicts of Interest

C.J. Wu is a consultant/advisory board member for Neon Therapeutics. No potential conflicts of interest were disclosed by the other author.

This understanding may be critical for CLL therapy given the vital role played by the microenvironment on CLL pathogenesis. Strikingly, transcriptional signatures of BCR activation, nuclear factor-kappa B (NF-kB) signaling, proliferation and activation have been already prominently observed in CLL cells from bone marrow and lymph nodes whereas CLL cells in peripheral blood exhibited more quiescent signatures and increased apoptotic priming(7). As malignant counterparts of normal B cells, CLL cells display a remarkable ability to recruit and co-opt immune cells into providing inflammatory 'nourishment' that bankrolls CLL expansion (8)(**Figure 1, top**). These include the secretion of factors that recruit (e.g. CCL3/4) and induce the differentiation (e.g. HMGB1) of CD68+ nurselike cells (NLCs) from monocytes(9). This cell population facilitates CLL cell survival and chemoresistance partly through secretion of CXCL12 and CXCL13 – chemokines that in turn induce CLL chemotaxis and activation. In addition to monocytes, T cells also aid and abet CLL expansion through expression of CD154, the ligand for the CD40 receptor found on B and CLL cells(8). *In vivo* survival and proliferation of patient-derived CLL cells in xenograft models require robust expansion of autologous CD4+ T cells(10). Importantly, T cells from CLL patients further exhibit profound dysfunction, with features of exhaustion and an inability to form immunological synapses(11). Given the clinical potency of ibrutinib in CLL, investigating its off-target and off-tissue effects may highlight inflammatory pathways to which CLL is addicted.

Niemann and colleagues exploit a robust sample collection protocol from a phase 2 study of single agent ibrutinib in 80 patients with CLL, treated with ibrutinib 420 mg orally once daily until disease progression or intolerance. The study cohort comprised patients with CLL requiring therapy, either treatment naïve or with relapsed/refractory disease. All patients had age≥65 and/or *TP53* aberrations. The authors meticulously characterized the *in vivo* changes associated with ibrutinib treatment in 1) chemokines and cytokines previously implicated in CLL biology; 2) T cell numbers, subtypes, and activation states; and 3) macrophage-CLL relationships, both spatial and paracrine in nature, demonstrating the ability of this drug to arrest critical tumor-host interactions (**Figure 1, bottom**).

First, serum chemokine and cytokine profiling revealed significant decreases in 13 of 20 analytes tested, with 4 of 10 chemokines demonstrating rapid decreases within the first 24 hours of treatment. Second, both quantitative and qualitative changes in T cell subsets and activation states were described. Circulating CD3+, CD3+CD4+, and CD3+CD8+ T cells significantly decreased upon ibrutinib treatment; importantly, these decreases constituted a normalization of T cell numbers to baseline values rather than T cell lymphopenia. In addition to quantitative changes in T cells, the authors report qualitative effects. Ibrutinib treatment was associated with significant decreases in T cell activation, proliferation and 'pseudoexhaustion' as measured by HLA-DR, Ki-67 and PD-1 positivity, respectively. The phenomenon of 'pseudoexhaustion' has been recently described as a state of T cell dysfunction in CLL similar to exhaustion with functional deficits in T cell proliferation and cytotoxicity but with a twist: the capacity to produce inflammatory cytokines is retained(11). Th17 T cells were found to be significantly reduced after ibrutinib treatment; and the authors established the cell-autonomous nature of this effect by demonstrating that ibrutinib significantly impairs the *in vitro* differentiation of murine CD4+ T cells into Th17 cells in a

dose dependent manner. Finally, the authors utilize bone marrow specimens to carefully observe that ibrutinib disrupts macrophage (CD68+) extensions physically contacting CLL cells. This dismantling of the “macrophage embrace” is accompanied by reductions in both marrow-derived CXCL13, a macrophage secreted CLL-chemoattractant, and CLL cell migration towards autologous marrow supernatant.

Taken together, these data bolster the view that BCR inhibitors not only affect intracellular circuitry but also rewire the carefully constructed, supportive microenvironmental network of the CLL cell. The study is limited by lack of causation – is this off-target inhibition of other TEC family kinases (notably ITK) necessary for the clinical efficacy of ibrutinib? Will other, more selective BTK inhibitors falter? Recent clinical data suggests that acalabrutinib, a more selective, irreversible BTK inhibitor that does not bind alternative kinases and has additional favorable pharmacokinetic features, has an extraordinarily high rate of durable remissions among patients with high-risk CLL(12). Nevertheless, BCR signaling blockade has yet to result in complete eradication of the disease – implying that further investigation of the chronic inflammatory drive will be vital for designing novel therapeutic combinations.

The implications of this study also extend beyond CLL. Ibrutinib synergizes with PD1 blockade to induce tumor regression in preclinical murine models of a B cell lymphoma and myeloma insensitive to ibrutinib(6). Remarkably, this synergy applied to both colon and breast carcinoma models as well. The efficacy was dependent upon host T cells, associated with induction of tumor-specific T cells, and generation of a memory response(6). Indeed, ibrutinib is currently being tested in clinical trials of multiple solid malignancies. Performing similar analyses to Niemann and colleagues in patients with BTK-deficient malignancies treated with ibrutinib should clarify which immunomodulatory effects are directly mediated by off-target effects as opposed to downstream consequences of BTK inactivation.

As corruptions of normal hematopoiesis, leukemias and lymphomas co-opt the physiologic circuitry of immune cells – subverting homeostatic signals to drive expansion of the malignant clones. CLL serves as a quintessential example of this process – residing in lymph nodes and the bone marrow niche and embraced by a diverse assortment of inflammatory but dysfunctional T cell subtypes and macrophages. Given the vast array of novel therapies in CLL, correlative studies that examine the microenvironment *in vivo* in patients should be incorporated into all clinical trials so that the inflammatory drive can be systematically dissected, understood and subsequently dismantled.

Acknowledgments

The authors thank Noelia Purroy and Romain Guieze for helpful discussions.

Grant Support

P. Bachireddy is supported by the Damon Runyon Physician-Scientist Training Award and the Conquer Cancer Foundation Young Investigator Award. C.J. Wu is supported by the Blavatnik Family Foundation, the National Heart, Lung, and Blood Institute (RO1HL103532 and RO1HL116452), the NCI (RO1CA155010 and U10CA180861), and the Leukemia & Lymphoma Society Translational Research Program Award.

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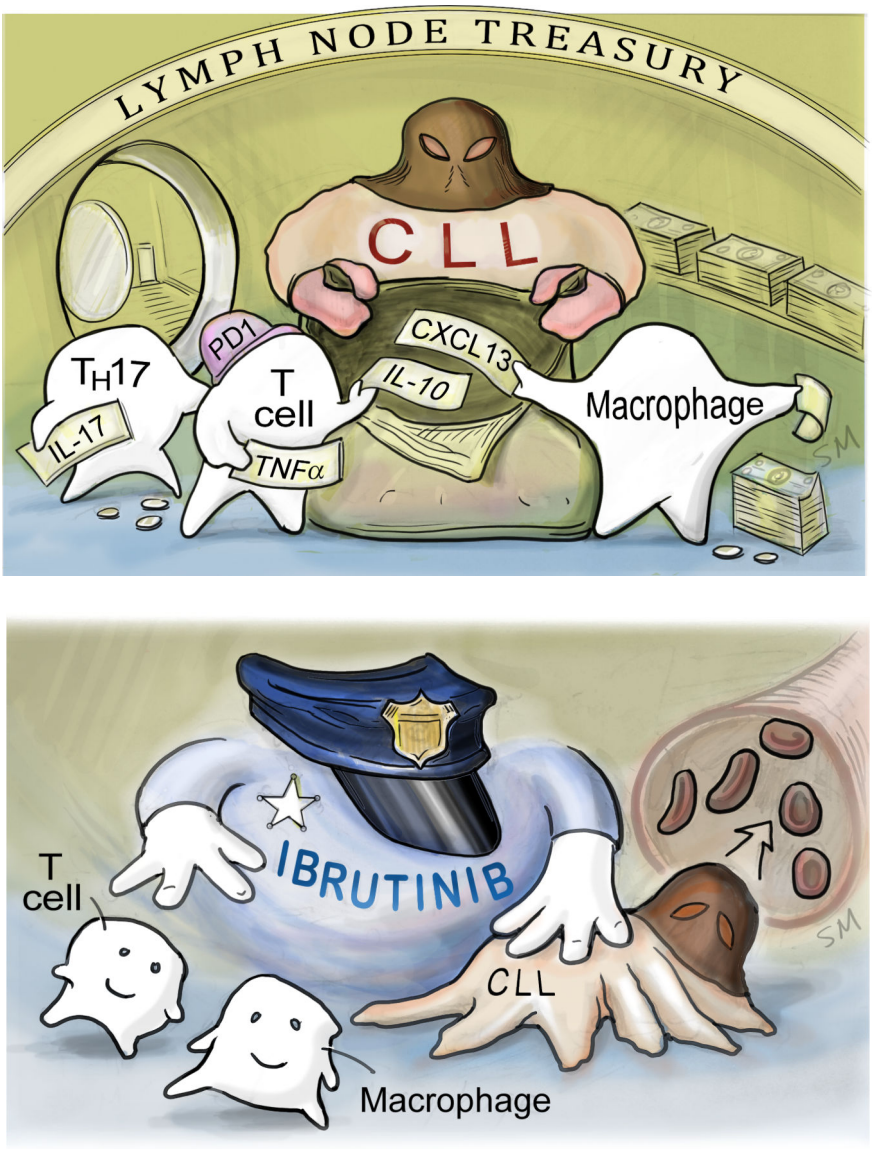

Figure 1.

Ibrutinib arrests the chronic inflammatory drive supporting CLL. Within the lymph node, the bi-directional interactions between the CLL cell and inflammatory immune populations (e.g. macrophages, PD1+ T cells, Th17 cells) aid and abet CLL maintenance and expansion (top). Ibrutinib revokes the inflammatory milieu, normalizing immune activation states and exiling CLL from the lymph node (bottom). Image courtesy of Steven Moskowitz.