Ibrutinib Restores Tumor-specific Adaptive Immunity in Chronic Lymphocytic Leukemia

Clive S. Zent

SUMMARY

Chronic lymphocytic leukemia (CLL) is characterized by early and profound immune suppression and reversal of these effects is essential to improve patient outcome. Targeted therapy with small-molecule inhibitors such as ibrutinib is highly effective and tolerable. Emerging data suggest that patients with CLL responding to ibrutinib therapy can recover anti-CLL adaptive immune cytotoxicity.

See related article by Baptista et al., p. 4624

In this issue of *Clinical Cancer Research*, Baptista and colleagues report phenotype and in vitro functional data from analysis of circulating CD8$^+$ T cells from patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) responding to ibrutinib therapy. (1) CLL, the most prevalent lymphoid malignancy in the United States, causes early onset and often severe adaptive and innate immune dysfunction resulting in considerable morbidity and mortality (2). Immune dysfunction in patients with CLL increases risk of infections, additional malignancies, and autoimmune disorders. In addition, immune dysfunction could facilitate both initial disease progression and relapse after effective treatment. Patients with CLL treated with chemoimmunotherapy incur additional therapy induced immunosuppression, and even those achieving durable minimal residual disease (MRD) negative complete remissions (CR) have limited recovery of immune competence. The development of highly effective small-molecule targeted inhibitors has resulted in a paradigm shift in CLL therapy. The Bruton tyrosine kinase inhibitor (BTKi) ibrutinib can achieve deep and durable remissions in most patients with minimal iatrogenic immune suppression. This has provided an opportunity to determine whether patients achieving remission can recover from CLL induced immunosuppression. To date, major clinical improvements in innate or adaptive immune function have not been observed, and patients with CLL in remission after treatment with ibrutinib continue to be at increased risk of complications of immune suppression.

Cure of patients with CLL requires elimination of all clonal CLL cells, a goal that is not yet achievable. Alternatively, patients could have a functional "cure" if the tumor burden can be reduced by therapy and the residual clonal CLL cells controlled by reconstitution of durable adaptive immunity. This can currently only be achieved by allogenic hematopoietic stem cell transplantation (AHSCT), a treatment with high risk of serious morbidity and mortality. However, the advent of less toxic and highly effective targeted therapy for CLL provides an opportunity to study the potential for recovery of autologous anti-CLL immune cytotoxicity, which could provide data to design safer interventions to prolong remission duration.

CD8$^+$ T cells in patients with CLL have increased rates of functional exhaustion, which is more apparent in cells obtained from lymphoid tissue compared with those in the circulation (3). Baptista and colleagues show that CLL remissions are associated with reversal of CLL induced changes in the composition of the T-cell population and improvement in cytotoxic CD8$^+$ T-cell function that could potentially lead to improved immune control of their CLL clone (**Fig. 1**; ref. 1). Their study confirms earlier reports that patients with CLL have increased circulating CD8$^+$ and CD4$^+$ T-cell counts prior to treatment, and these counts normalized after successful ibrutinib treatment, and then increased with progressive disease (3). They then show that attainment of remission on ibrutinib was associated with an increase in both the number of unique CD8$^+$ T-cell receptor (TCR) clones and the prominence of these clones (measured as increased clonality) in most patients. Increased clonality was stable in patients with sustained remission but was lost on disease progression. Increased TCRβ clonality associated with ibrutinib therapy manifested as expansion of private cytotoxic CD8$^+$ T-cell clonotypes, suggesting that these clones target specific CLL cell neoantigens. In autologous T cell–CLL cell cocultures, T cells had high granzyme B levels and were effective at killing CLL cells. These data suggest that patients with CLL responding to ibrutinib could recover tumor-specific cytotoxic T-cell function which could improve and maintain their remissions.

These interesting and exciting data need to be interpreted in the context of the limitations of the study design and patient population. Following initiation of therapy, all patients were studied while continuing on ibrutinib therapy. This study is thus not informative about the relative contribution of decreased CLL tumor burden versus the effects of ibrutinib therapy (inhibition of BTK and off-target kinases) to the observed changes in T cells. In addition, the generalizability of reported results to treatment of patients with CLL could be limited by the selection of high risk and older treatment-naïve patients, inclusion of patients with relapsed/refractory disease, and biases in collection of follow-up specimens.

Potentially curative CLL therapy with AHSCT requires allogeneic graft versus lymphoma immune activity. The report by Baptista and colleagues that successful treatment of CLL with ibrutinib increases the number of cytotoxic CD8$^+$ T cells, and that these cells are functional *in vitro* and include a population that targets autologous private CLL neoantigens, provides a starting point for future studies to determine if this autologous immunity can improve and prolong remission. If these cytotoxic CD8$^+$ T cells contribute to the depth and durability of

Wilmot Cancer Institute and Department of Medicine, University of Rochester Medical Center, Rochester, New York.

Corresponding Author: Clive S. Zent, Wilmot Cancer Institute and Department of Medicine, University of Rochester Medical Center, Rochester, New York. Phone: 585-273-3258; E-mail: clive_zent@urmc.rochester.edu

Clin Cancer Res 2021;27:4465–7

doi: 10.1158/1078-0432.CCR-21-1589

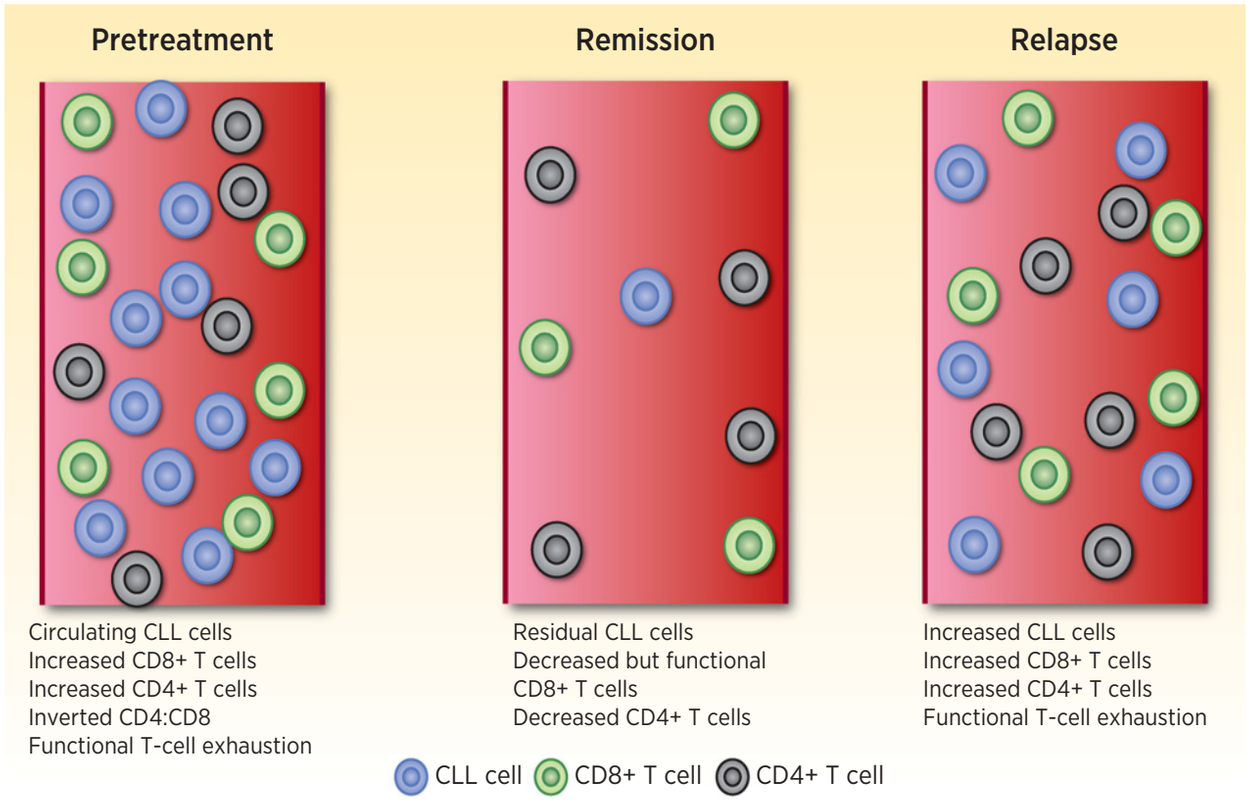

Figure 1.
Effect of ibrutinib on circulating lymphocytes in CLL.

response, this finding could lead to the development of interventions with the potential to further improve treatment of CLL and related diseases.

This study is not informative on how ibrutinib causes the observed changes in circulating T cells. One possible explanation is that decreasing the CLL cell tumor burden removes the direct and indirect immunosuppressive effects of CLL cells, resulting in recovery of immune competence. If this is correct, other B-cell–targeted therapies with minimal deleterious effects on non–B-cell immune cells would be expected to have similar beneficial effects. Alternatively, ibrutinib could cause the observed changes in cytotoxic $CD8^+$ T cells by altering their signaling pathways or indirectly by altering the function of follicular helper or regulatory $CD4^+$ T cells, monocytes or macrophages (3). These effects could be mediated by ibrutinib inhibition of BTK or off-target kinases. The potential role of off-target kinase inhibition by ibrutinib is supported by evidence that covalent binding and inhibition of IL2-inducible T-cell kinase (ITK) by ibrutinib contributes to the observed decreases in T-cell count and increased TCR repertoire in patients with CLL responding to ibrutinib treatment (4). Understanding these interactions and the effect of ibrutinib on $CD4^+$ T-cell subgroups and function are required for a more comprehensive understanding of BTKi and off-target effects on recovery of adaptive immune tumor surveillance and cytotoxicity in patients with CLL. These data would also be important in choosing between ibrutinib and more targeted BTKi (e.g., acalabrutinib and zanabrutinib) in the treatment of B-cell lymphomas. Recovery of immune surveillance could also be important for decreasing the risk of complications of CLL including infection and additional nonclonally related malignancies.

In conclusion, Baptista and colleagues have provided important new data on the changes in circulating cytotoxic $CD8^+$ T-cells following successful therapy of CLL with ibrutinib monotherapy. These data advance our knowledge of the potentially beneficial effects of ibrutinib therapy on recovery of adaptive cellular immunity and suggest that ibrutinib induced remissions could result in better autologous T-cell control of malignant CLL cells. Their data also raise important questions that could be the subject of future research with the potential to generate data leading to incremental improvements in the management of CLL.

Author's Disclosures

C.S. Zent reports grants from Acerta/AstraZeneca and TG Therapeutics outside the submitted work. No other disclosures were reported.

Received May 14, 2021; revised May 25, 2021; accepted May 28, 2021; published first June 9, 2021.

References

1. Baptista MJ, Baskar S, Gaglione EM, Keyvanfar K, Ahn I, Wiestner A, et al. Select antitumor cytotoxic CD8(+) T clonotypes expand in patients with chronic lymphocytic leukemia treated with ibrutinib. Clin Cancer Res 2021;27:4624–33.
2. Forconi F, Moss P. Perturbation of the normal immune system in patients with CLL. Blood 2015;126:573–81.
3. Roessner PM, Seiffert M. T-cells in chronic lymphocytic leukemia: Guardians or drivers of disease? Leukemia 2020;34:2012–24.
4. Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood 2013;122:2539–49.