Unmask the genetic backbone of ibrutinib-relapsed chronic lymphocytic leukemia progression and Richter transformation

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Comment on: Kadri S, Lee J, Fitzpatrick C, *et al.* Clonal evolution underlying leukemia progression and Richter transformation in patients with ibrutinib-relapsed CLL. Blood Adv 2017;1:715-27.

Submitted Apr 05, 2018. Accepted for publication May 21, 2018.
doi: 10.21037/atm.2018.05.34
View this article at: http://dx.doi.org/10.21037/atm.2018.05.34

In the issue of *Blood Adv*, Kadri *et al.* (1) reported a cohort of nine chronic lymphocytic leukemia (CLL) ibrutinib-relapsed patients with leukemia progression and Richter transformation. With the next-generation sequencing (NGS) and single-nucleotide polymorphism (SNP) array, 18p deletion [del(18p)], together with del(17p)/*TP53* mutations was found in CLL tumor cells in five out of nine patients before ibrutinib administration. The frequency of del(18p) and del(17p) in *de novo* CLL population is much lower than that in this cohort. This may be attributed to that the CLL treated with ibrutinib in this cohort is mostly relapsed ones. Although del(17p) involving *TP53* gene may undermine the DNA repair system and predispose tumor cells to further mutation, the clone harbored *TP53* gene mutation is killed and diminished upon ibrutinib treatment. Among the novel mutation gained in ibrutinib-relapsed disease, *BTK* are the predominant genetic aberrations, and mutation of *IRF4* and *MPL* gene involved individual case. Besides the BTK mutation, another recurrent relapse-specific mutation was found: *PCLO* gene was found in two relapsed disease. However, *PLCG2* gene mutation was not identified in this series. Additionally, this study tried to delineate the difference mutation profile between CLL leukemia progression and Richter transformation (histological progression). Unlike the identification of recurrent mutations involving Notch pathway and cell cycle in Richter transformation of CLL treated with cytotoxic therapy (2), none of the recurrent mutation, which may be uniquely responsible for Richter transformation, was found in this ibrutinib treated cohort. Nonetheless, different kind of BTK mutations were identified in the tumor cells in peripheral blood and in the Richter transformation tissue. This demonstrated that CLL tumor cells mutated divergently in the peripheral blood and tissue microenvironment.

CLL is a hematological neoplasm featuring non-apoptosis tumor cells accumulating in the immune organ such as lymph node, bone marrow and spleen. Meanwhile, the CLL tumor cells circulating between tissue microenvironment and peripheral blood, resulting lymphocytosis. The therapeutic strategy of CLL in immune-chemotherapy era requires stratifying patients into different risk groups to administrate chemotherapy. However, some high-risk patients, such patients with 17p deletion, response poorly to the standard therapy and, the prognosis of patients with relapsed disease is ominous. As the recognition of the role of B-cell receptor (BCR) signaling in B-cell tumor including CLL, targeting BCR signaling with small molecular inhibitor provides the CLL patients with a novel therapeutic option. With the advances of ibrutinib treatment, overall survival and progression-free survival of CLL patients were remarkably improved (3). Unfortunately, CLL patients with ibrutinib exposure will develop resistant disease eventually, and even progressed into large B-cell lymphoma (Richter transformation) (4). Previous studies reported that mutation in BTK, which encodes the target of ibrutinib, and mutation in *PLCG2*, which encodes the PLCγ2, the downstream of BTK, were involved in the mechanism of ibrutinib resistance (4,5). However, these mutations failed to account for all relapsed

or resistant disease, indicating the necessity of more comprehensive study.

The study conducted by Kadri *et al.* used the deep target sequencing with a large panel to profile regular tumor driven genes in serial CLL samples exposure to ibrutinib. This methodology not only covers a more comprehensive gene set but also provide a satisfactory sequencing depth to identify minor mutation clone. Besides these, copy number variation was revealed by single nucleotide polymorphism assay. The most exciting finding in this clonal evolution study is the identification of BTK *T316A* mutation, instead of the BTK *C481S* mutation, which undermines the binding activity of ibrutinib to BTK protein (5). Additionally, 18p deletion was highlighted as a possible genetic hit responsible for ibrutinib resistance, yet the specific gene involved by 18p deletion is still unknown.

This clonal evolution study suggested that mutation in TP53 and BCR signaling genes may mainly account for ibrutinib resistance in CLL. As mutations in BCR downstream signal pathway such PI3K and NF-κB were not found, drugs targeting these signal pathways may represent an alternative therapy in relapsed patients. Studies from other groups (4-8) together with the current one demonstrated genetic aberration only accounts for a fraction of resistance disease, indicating the other mechanisms including epigenetic abnormality and microenvironment mechanisms. Thus, future studies focusing these areas will improve the therapeutic strategy of the CLL patients.

Acknowledgements

None.

Cite this article as: Wang WG, Zhou XY, Li XQ. Unmask the genetic backbone of ibrutinib-relapsed chronic lymphocytic leukemia progression and Richter transformation. Ann Transl Med 2018;6(11):234. doi: 10.21037/atm.2018.05.34

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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