NOTCH pathway mutation contributes to inferior prognosis in HBV-infected chronic lymphocytic leukemia

Yue Li[1], Chun Yu Shang[1], Jia Zhu Wu[1], Hao Rui Sheng[1], Hua Yin[1], Jin Hua Liang[1], Hua Yin[1], Li Wang[1], Jian Yong Li[1], Wei Xu[1]

1. Department of Hematology, the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital, Nanjing, China, 210029

Background

Chronic lymphocytic leukemia (CLL) patients with hepatitis B virus (HBV) infection have a poor prognosis, underlying mechanism remains unclear. NOTCH mutations are frequent in CLL and associated with disease progression and drug resistance. It is also reported to be associated with hepatitis infection in lymphoid malignancies.

Objectives

In order to investigate the relation between NOTCH pathway and HBV-associated CLL, we studied 98 previously untreated HBV positive CLL patients and 244 HBV-negative CLL.

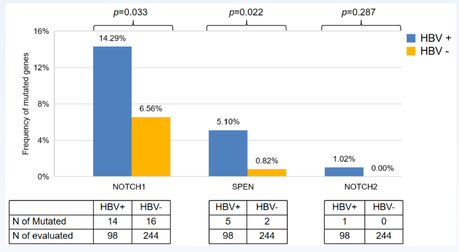
Methods

A total of 342 treatment naïve patients diagnosed with CLL at the First Affiliated Hospital of Nanjing Medical University from 01 Jan 2010 to 31 Oct 2021 were enrolled in our study. The mutation hotspots of NOTCH pathway genes were analyzed by Next Generation Sequencing (NGS) of DNA that used PCR for the identification of genomic mutation. Fisher exact and χ2 tests were used to assess the correlation between HBV infection and clinical, demographic factors in CLL patients. Survival curves were generated by Graphpad 9.5.

Results

NOTCH mutations were more frequent in HBV positive CLL subgroup (17.3% vs 7.4%, *p*=0.033). By survival analysis, HBV infection was associated with disease progression and poor survival [*p*=0.0099 for overall survival (OS) and *p*=0.0446 for time-to-treatment (TTT)]. Any lesions of the NOTCH pathway (NOTCH1, NOTCH2 and SPEN) aggravated prognosis. In multivariate analysis, NOTCH mutation retained an independent significance for HBV-infected patients (*p*=0.016 for OS and *p*=0.023 for TTT). However, HBV positive with NOTCH unmutated had no statistical difference in prognosis compared with HBV negative patients (*p*=0.1706 for OS and *p*=0.2387 for TTT), which indicated that NOTCH pathway mutation contributed to inferior prognosis in HBV-infected CLL.

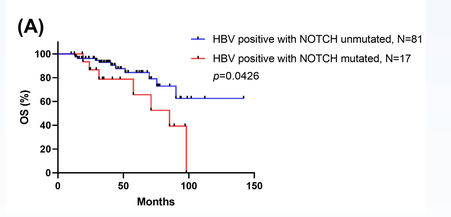
Graph/image title

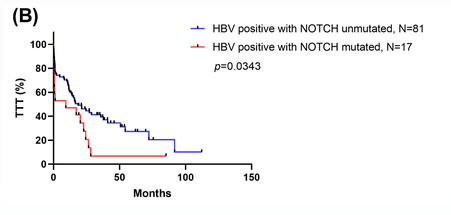


	HBV+	HBV-
N of Mutated	14	16
N of evaluated	98	244

	HBV+	HBV-
	5	2
	98	244

	HBV+	HBV-
	1	0
	98	244





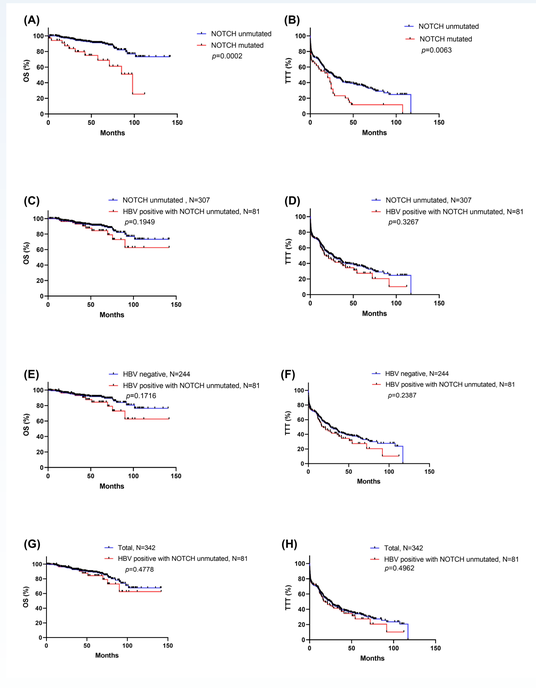


Figure 1. Comparison of NOTCH1, SPEN and NOTCH2 mutation in CLL patients with or without HBV infection.

Figure 2. (A) Among HBV positive subgroup, mutated NOTCH pathway is associated with poor OS. (B) Among HBV positive subgroup, mutated NOTCH pathway is associated with poor TTT.

Figure 3. (A) and (B) NOTCH mutation status is associated with poor CLL survival and disease progression. (C) and (D) HBV positive with NOTCH unmutated subgroup has no prognostic significance among NOTCH unmutated subgroup. (E) and (F) HBV positive with NOTCH unmutated subgroup has no prognostic significance among HBV negative subgroup. (G) and (H) HBV positive with NOTCH unmutated subgroup doesn't confer to poor outcomes compared with overall.

Conclusion

In conclusion, a cohort of CLL patients with HBV positive displayed a worse clinical outcome and the status of NOTCH signaling pathway might play a crucial role.

References

1.Wierda WG, Byrd JC, Abramson JS, et al. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 4.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020;18:185-217.

2.Mahale P, Engels EA, Koshiol J. Hepatitis B virus infection and the risk of cancer in the elderly US population. Int J Cancer. 2019;144:431-439.

3.Tian T, Song C, Jiang L, et al. Hepatitis B virus infection and the risk of cancer among the Chinese population. Int J Cancer. 2020;147:3075-3084.

4.Engels EA, Cho ER, Jee SH. Hepatitis B virus infection and risk of non-Hodgkin lymphoma in South Korea: a cohort study. Lancet Oncol. 2010;11:827-834.

5.Li M, Gan Y, Fan C, et al. Hepatitis B virus and risk of non-Hodgkin lymphoma: An updated meta-analysis of 58 studies. J Viral Hepat. 2018;25:894-903.

6.Innocenti I, Reda G, Visentin A, et al. Risk of hepatitis B virus reactivation in chronic lymphocytic leukemia patients receiving ibrutinib with or without antiviral prophylaxis. A retrospective multicentric GIMEMA study. Haematologica. 2022.