Chinese Medical Journal®

Chronic lymphocytic leukemia in China

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Chronic lymphocytic leukemia (CLL) is 10- to 20-fold less common in Han Chinese in China compared with persons of predominately European descent translating to incidences of 0.2 to 0.6 per 10E+5 population/year *vs.* 4.6 per 10E+5 population/year.[1-3] Reason(s) for this markedly lower incidence and therefore prevalence in China is unknown but is shared with the other Asian nationalities including Japanese, Koreans, and others.[4-6] Studies of large cohorts of Chinese with CLL are relatively rare and there are no population-based studies in the mainland of China. Several seeming differences between CLL in Chinese and persons of predominately European descent are reported such as younger age at diagnosis, different background genotypes, increased frequency of *IGHV* mutation, different stereotype use and different mutation topographies.[7] However, in general, most cases of CLL in Han Chinese are like CLL in persons of predominately European descent.

Why is CLL uncommon in Chinese

Surveillance

Most people with CLL are asymptomatic. Consequently, the diagnosis of CLL is often made when a complete blood count (CBC) is done in the course of evaluating a synchronous or metachronous medical condition or in the context of a routine CBC for insurance coverage of a new job, etc. There is no population-based registry of CLL in the mainland of China. Data from a registry covering 46 geospaces from 1986 to 1988 reported an age-adjusted incidence of 0.05 per 10^5 population, most likely a substantial underestimation because of the unavailability of multi-parameter flow cytometry in that interval.[8] In a single-center retrospective study from 2011 to 2016, we reported a dramatic increase in new cases of CLL.[9] Often the diagnosis was based on an abnormal CBC done for another medical disorder or for other reasons unrelated to signs or symptoms of CLL such as an employment exam. Median age and early stage at diagnosis is consistent with an increased frequency of CBCs done for other medical conditions in older persons. These data support the notion that ascertainment bias is one reason why CLL seems uncommon in China. However, this is only a partial explanation because CLL is also uncommon in Asians in resource-rich countries like Japan and Korea.[10,11] It is also 5- to 10-fold lower in Asians living in the US where there are high-quality incidence registries.[12]

We recently probed additional reasons for this seeming increase in CLL incidence in China and identified three considerations: (1) decentralization: wider availability for CLL testing in resource-poor geospaces; (2) centralization: increased health insurance coverage and ability to access tertiary medical centers in large cities; and (3) increased accessibility of routine health examinations and willingness to visit physicians for health-related issues (Yang S, Chen S).

Genetics

Chinese and other Asian immigrants to the US and Canada have a markedly decreased incidence of CLL compared with persons of predominately European descent in these countries.[1,12] HapMap analyses showed high-risk single-nucleotide variants weakly associated CLL risk in persons of predominately European descent are uncommon in Han Chinese and other Asian populations.[13,14] The increased familial risk of CLL described in persons of European descent has not been reported in Han Chinese but this may reflect surveillance biases.

Several mutations are common in CLL. del(13q14) is considered an initiating event in some cases and it can be used to establish CLL in mice. However, del(13q14) is detected in only about one-half of Chinese and Europeans with CLL.[15,16] Other abnormalities such as trisomy 12 and mutations in *ATM*, *NOTCH1*, *TP53*, *BIRC3*, and *SF3B1* are associated with CLL progression or chemotherapy resistance. Chinese with CLL have a lower

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001811

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Chinese Medical Journal 2022;135(8)

Received: 04-08-2021; **Online:** 11-10-2021 **Edited by:** Peng Lyu

frequency of *SF3B1* mutations and an increased frequency of *MYD88* and *KMT2D* mutations compared with persons of predominately European descent.[17,18]

IGHV mutation state, gene usage and stereotype between Chinese with CLL and persons of predominately European descent are presented with an increased frequency of mutated *IGHV* in Chinese. Lower frequencies of *IGHV* 1 to 69 and *IGHV* 1 to 2 use and a lower frequency of stereotyped receptors are reported.[19] Frequency of subset eight stereotype is significantly higher and subset two is significantly lower in Chinese with CLL compared with Europeans.[19] We hypothesize a pathogen exposure might explain clonal selection within the B-cell *IGHV* repertoire *(vide supra)*.

Environmental factors

Data from population-based Taiwanese of China and Korean cancer registries reported recent increases in CLL incidence which the authors attributed to changing lifestyles.[11,13] A US study reported a higher incidence of CLL in Asians born in the US *vs*. those born in Asia.[20] These data suggest a possible environmental impact on CLL incidence such as diet. We think this explanation unlikely. Studies of associations between environmental exposures such as ionizing radiations, UV exposures, obesity, pesticides, and herbicides have low, if any, increased risk of CLL.[21-24] The A-bomb survivors had marked increases in risks of developing acute lymphoid and myeloid leukemias (acute lymphoblastic leukemia and acute myeloid leukemia) and chronic myeloid leukemia but only a slight increase in CLL which was detected after 70 years.[25]

Comparing CLL in Chinese and Europeans

CLL in Han Chinese and persons of predominantly European descent are mostly similar. However, there is an impression that Chinese and other Asians with CLL are younger, are more likely to have a higher stage at diagnosis, progress more rapidly, and have worse outcomes. Studies in the mainland of China report that a median age of diagnosis is about 60 years with 45% to 60% having Binet stage B or C at diagnosis. Median age at diagnosis in Europeans is about 65 to 70 years with 20% to 40% with Binet stage at diagnosis.[26-29] We found that more older persons in an early stage were diagnosed when more CBCs were done for routine physical hospital visits or when investigating an unrelated medical condition. Most of these differences can be explained by the surveillance biases that we discussed above.

Current studies

Several studies of Bruton tyrosine kinase (BTK)-inhibitors such as ibrutinib, zanubrutinib, and orelabrutinib were done in China and approved by the National Medical Products Administration. Most data suggest safety and efficacy profiles like those in Europeans.[30-35] However, in a study of ibrutinib, we found that the overall response rate (ORR) was not a good progression-free survival (PFS) surrogate in Chinese compared with Europeans (*vide infra*).[30] We also found that ibrutinib was associated with a lower risk of reactivation of latent hepatitis B-virus (HBV)-infection compared with rituximab. A study of pirtobrutinib recently started enrollment (NCT04849416) and a study of ArQ 531 is planned. Venetoclax is under the study in persons with advanced CLL with del(17p) or failing BTK-inhibitors (NCT02966756). Chinese drug companies are developing new Bcl-2 inhibitors (NCT03913949, NCT04682808, NCT04494503, and NCT04356846).

CLL therapy in China

Chlorambucil was the only CLL therapy in China for many years. People often received chlorambucil, cyclophosphamide, vincristine, and prednisone (Cyclophosphamide, Oncovin, Prednisone) or cyclophosphamide, doxorubicin, vincristine, and prednisone (Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone)-like regimens before purine-analogue, fludarabine was available. Rituximab became available in China in 2000 and fludarabine in 2001. Response rates to fludarabine and cyclophosphamide or fludarabine, cyclophosphamide, and rituximab (FCR) in Chinese are like those reported in Europeans.[36-39] Ibrutinib became available in 2013, and zanubrutinib and orelabrutinib in 2020.

Study C3002 compared ibrutinib *vs*. rituximab in subjects with advanced CLL and those unable to tolerate fludarabine-based therapy.[40] Most subjects were Chinese. The ibrutinib ORR was 61% (95% confidence interval [CI], 50–71%), lower than that reported in Europeans. However, 30-month PFS was 66% (56–75%) and survival, 84% (75–91%), similar to Europeans.[30,32-34] These data suggest that ORR may not be an accurate PFS or survival surrogate in studies of ibrutinib. A study of zanubrutinib in advanced CLL reported 1-year event-free survival of 87% (78–93%) like results in Europeans.[31] A study of orelabrutinib reported rapid, deep responses in Chinese with advanced CLL.[41]

There is a high prevalence of latent HBV-infection in China.[42] Subjects with CLL and latent HBV-infection (HBsAg-negative, anti-HBc positive, and HBV-DNA negative) were included in the C3002 study of ibrutinib *vs*. rituximab. We reported a lower rate of HBV-reactivation with ibrutinib.[30] In studies of zanubrutinib, 4 of 90 subjects at-risk had HBV-reactivation resulting in the recommendation to give entecavir prophylaxis.[31] Chinese with CLL should be screened for latent HBV-infection pretherapy.

Ibrutinib and zanubrutinib are covered by public insurance but not all Chinese can afford these drugs, and therapy interruptions are associated with worse PFS.[43] Because of this, there is a considerable interest in fixed duration therapy such as with ibrutinib combined with FCR or bendamustine and rituximab in some clinical trial (NCT03980002).

Venetoclax was studied in Chinese with CLL. A global study of limited duration acalabrutinib and venetoclax with or without obinutuzumab compared with chemoimmunotherapy is ongoing (NCT03836261). A study

of limited duration therapy with ibrutinib and new Bcl-2 inhibitors is registered in Clinicaltrials.gov (NCT04494503). There is currently no access to ofatumumab, obinutuzumab, or alemtuzumab in China. There are 21 studies of CAR-T-cells and three studies of CAR-NK-cells recruiting subjects with CLL registered in Clinicaltrials.gov.

Conclusions

CLL is uncommon in Han Chinese compared with persons of predominately European descent with a 10- to 20-fold lower incidence. This decreased incidence is shared with other Asians living in Asia or elsewhere consistent with a predominately genetic basis for this lower incidence. CLL in Chinese is mostly like CLL in Europeans but there are some differences including younger age at diagnosis, different background genotypes, increased frequency of *IGHV* rearrangement, hypermutation, different stereotype use and different mutation topographies. A recent seeming increase in CLL in China seems predominately related to increased ascertainment. Research is focused on defining the genetic background on which CLL develops to explain the deficit of CLL in Chinese. We hypothesize that an infectious agent present in Asia about 45,000 years ago was a selective pressure for resistance to and/or decreased susceptibility to developing CLL. The fast development of new drugs dramatically benefits Chinese with CLL. More progress is expected.

Acknowledgements

Dr. Shenmiao Yang (Peking University People's Hospital) contributed greatly to developing this typescript and provided important data and comments.

Funding

RPG acknowledges support from the National Institute of Health Research (NIHR) Biomedical Research Centre funding scheme.

Conflicts of interest

RPG is a consultant to BeiGene Ltd., Fusion Pharma LLC, La Jolla NanoMedical Inc., MingSight Pharmaceuticals Inc., CStone Pharmaceuticals, NexImmune Inc., and Prolacta Bioscience; advisor to Antengene Biotech LLC, Medical Director, FFF Enterprises Inc.; partner, AZCA Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd.

References

1. Mak V, Ip D, Mang O, Dalal C, Huang S, Gerrie A, *et al*. Preservation of lower incidence of chronic lymphocytic leukemia in Chinese residents in British Columbia: a 26-year survey from 1983 to 2008. Leuk Lymphoma 2014;55:824–827. doi: 10.3109/10428194.2013.827785.
2. Ko BS, Chen LJ, Huang HH, Chen HM, Hsiao FY. Epidemiology, treatment patterns and survival of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) in Taiwan, 2006–2015. Int J Clin Pract 2021;75:e14258. doi: 10.1111/ijcp.14258.
3. Fabbri G, Dalla-Favera R. The molecular pathogenesis of chronic lymphocytic leukaemia. Nat Rev Cancer 2016;16:145–162. doi: 10.1038/nrc.2016.8.
4. Mahlich J, Okamoto S, Tsubota A. Cost of illness of Japanese patients with Chronic Lymphocytic Leukemia (CLL), and budget impact of the market introduction of ibrutinib. Pharmacoecon Open 2017;1:195–202. doi: 10.1007/s41669-017-0024-5.
5. Choi Y, Lee JH, Jung CW, Jo JC, Kim JS, Kim I, *et al*. Treatment outcome and prognostic factors of Korean patients with chronic lymphocytic leukemia: a multicenter retrospective study. Korean J Intern Med 2021;36:194–204. doi: 10.3904/kjim.2019.210.
6. Wells R, Lau KS. Incidence of leukaemia in Singapore, and rarity of chronic lymphocytic leukaemia in Chinese. Br Med J 1960;1:759–763. doi: 10.1136/bmj.1.5175.759.
7. Yang S, Varghese AM, Sood N, Chiattone C, Akinola NO, Huang X, *et al*. Ethnic and geographic diversity of chronic lymphocytic leukaemia. Leukemia 2021;35:433–439. doi: 10.1038/s41375-020-01057-5.
8. Yang C, Zhang X. Incidence survey of leukemia in China. Chin Med Sci J 1991;6:65–70.
9. Yang S, Gale RP, Shi H, Liu Y, Lai Y, Lu J, *et al*. Is there an epidemic of chronic lymphocytic leukaemia (CLL) in China? Leuk Res 2018;73:16–20. doi: 10.1016/j.leukres.2018.08.011.
10. Chihara D, Ito H, Matsuda T, Shibata A, Katsumi A, Nakamura S, *et al*. Differences in incidence and trends of haematological malignancies in Japan and the United States. Br J Haematol 2014;164:536–545. doi: 10.1111/bjh.12659.
11. Lee SJ, Tien HF, Park HJ, Kim JA, Lee DS. Gradual increase of chronic lymphocytic leukemia incidence in Korea, 1999–2010: comparison to plasma cell myeloma. Leuk Lymphoma 2016;57:585–589. doi: 10.3109/10428194.2015.1068307.
12. Gale RP, Cozen W, Goodman MT, Wang FF, Bernstein L. Decreased chronic lymphocytic leukemia incidence in Asians in Los Angeles County. Leuk Res 2000;24:665–669. doi: 10.1016/s0145-2126(00)00038-2.
13. Wu SJ, Huang SY, Lin CT, Lin YJ, Chang CJ, Tien HF. The incidence of chronic lymphocytic leukemia in Taiwan, 1986–2005: a distinct increasing trend with birth-cohort effect. Blood 2010;116:4430–4435. doi: 10.1182/blood-2010-05-285221.
14. Lan Q, Au WY, Chanock S, Tse J, Wong KF, Shen M, *et al*. Genetic susceptibility for chronic lymphocytic leukemia among Chinese in Hong Kong. Eur J Haematol 2010;85:492–495. doi: 10.1111/j.1600-0609.2010.01518.x.
15. Lai YY, Huang XJ. Cytogenetic characteristics of B cell chronic lymphocytic leukemia in 275 Chinese patients by fluorescence in situ hybridization: a multicenter study. Chin Med J 2011;124:2417–2422.
16. Döhner H, Stilgenbauer S, Benner A, Leupolt E, Kröber A, Bullinger L, *et al*. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910–1916. doi: 10.1056/NEJM200012283432602.
17. Xia Y, Fan L, Wang L, Gale RP, Wang M, Tian T32, *et al*. Frequencies of SF3B1, NOTCH1, MYD88, BIRC3 and IGHV mutations and TP53 disruptions in Chinese with chronic lymphocytic leukemia: disparities with Europeans. Oncotarget 2015;6:5426–5434. doi:10.18632/oncotarget.3101.
18. Yi S, Yan Y, Jin M, Xiong W, Yu Z, Yu Y, *et al*. High incidence of MYD88 and KMT2D mutations in Chinese with chronic lymphocytic leukemia. Leukemia 2021;35:2412–2415. doi: 10.1038/s41375-021-01124-5.
19. Marinelli M, Ilari C, Xia Y, Del Giudice I, Cafforio L, Della Starza I, *et al*. Immunoglobulin gene rearrangements in Chinese and Italian patients with chronic lymphocytic leukemia. Oncotarget 2016;7:20520–20531. doi: 10.18632/oncotarget.7819.
20. Clarke CA, Glaser SL, Gomez SL, Wang SS, Keegan TH, Yang J, *et al*. Lymphoid malignancies in U.S. Asians: incidence rate differences by birthplace and acculturation. Cancer Epidemiol Biomarkers Prev 2011;20:1064–1077. doi: 10.1158/1055-9965.EPI-11-0038.
21. Zablotska LB, Lane RSD, Frost SE, Thompson PA. Leukemia, lymphoma and multiple myeloma mortality (1950–1999) and incidence (1969–1999) in the Eldorado uranium workers cohort. Environ Res 2014;130:43–50. doi: 10.1016/j.envres.2014.01.002.
22. Slager SL, Benavente Y, Blair A, Vermeulen R, Cerhan JR, Costantini AS, *et al*. Medical history, lifestyle, family history, and occupational risk factors for chronic lymphocytic leukemia/small lymphocytic lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014;2014:41–51. doi: 10.1093/jncimonographs/lgu001.

23. Castillo JJ, Reagan JL, Ingham RR, Furman M, Dalia S, Merhi B, *et al*. Obesity but not overweight increases the incidence and mortality of leukemia in adults: a meta-analysis of prospective cohort studies. Leuk Res 2012;36:868–875. doi: 10.1016/j.leukres.2011.12.020.
24. Hourigan CS, Gale RP, Gormley NJ, Ossenkoppele GJ, Walter RB. Measurable residual disease testing in acute myeloid leukaemia. Leukemia 2017;31:1482–1490. doi: 10.1038/leu.2017.113.
25. Hsu WL, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, *et al*. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. Radiat Res 2013;179:361–382. doi: 10.1667/RR2892.1.
26. Li H, Yi SH, Xiong WJ, Liu HM, Lyu R, Wang TY, *et al*. Chronic lymphocytic leukemia prognostic index: a new integrated scoring system to predict the time to first treatment in Chinese patients with chronic lymphocytic leukemia. Chin Med J 2017;130:135–142. doi: 10.4103/0366-6999.197978.
27. Qin S, Fan L, Liang J, Gale R, Miao Y, Wu Y, *et al*. Definition of disease-progression risk stratification in untreated chronic lymphocytic leukemia using combined clinical, molecular and virological variables. Hematol Oncol 2018;36:656–662. doi: 10.1002/hon.2520.
28. Baumann T, Moia R, Gaidano G, Delgado J, Condoluci A, Villamor N, *et al*. Lymphocyte doubling time in chronic lymphocytic leukemia modern era: a real-life study in 848 unselected patients. Leukemia 2021;35:2325–2331. doi: 10.1038/s41375-021-01149-w.
29. Gentile M, Shanafelt TD, Mauro FR, Laurenti L, Rossi D, Molica S, *et al*. Comparison between the CLL-IPI and the Barcelona-Brno prognostic model: analysis of 1299 newly diagnosed cases. Am J Hematol 2018;93:E35–E37. doi: 10.1002/ajh.24960.
30. Yang S, Zhu R, Li N, Feng Y, Zuo R, Gale RP, *et al*. Ibrutinib in advanced chronic lymphocytic leukaemia/small lymphocytic lymphoma: lower risk of hepatitis-B-virus reactivation. Acta Haematol 2022;145 1:54–62. doi: 10.1159/000518398.
31. Xu W, Yang S, Zhou K, Pan L, Li Z, Zhou J, *et al*. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. J Hematol Oncol 2020;13:48. doi: 10.1186/s13045-020-00884-4.
32. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, *et al*. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213–223. doi: 10.1056/NEJMoa1400376.
33. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, *et al*. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood 2015;125:2497–2506. doi: 10.1182/blood-2014-10-606038.
34. Byrd JC, Hillmen P, O'Brien S, Barrientos JC, Reddy NM, Coutre S, *et al*. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. Blood 2019;133:2031–2042. doi: 10.1182/blood-2018-08-870238.
35. Tam CS, Trotman J, Opat S, Burger JA, Cull G, Gottlieb D, *et al*. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood 2019;134:851–859. doi: 10.1182/blood.2019001160.
36. Xu M, Fan L, Miao KR, Liu P, Xu W, Li JY. Comprehensive assessment of prognostic factors predicting outcome in Chinese patients with chronic lymphocytic leukemia treated with fludarabine and cyclophosphamide. Med Oncol 2012;29:2102–2110. doi:10.1007/s12032-011-0054-2.
37. Li H, Xiong WJ, Liu HM, Yi SH, Lu R, Wang TY, *et al*. Efficacy of rituximab for patients with chronic lymphocytic leukemia. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2017;39:800–805. doi: 10.3881/j. issn.1000-503X.2017.06.011.
38. Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, *et al*. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17:928–942. doi: 10.1016/S1470-2045(16)30051-1.
39. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, *et al*. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376:1164–1174. doi: 10.1016/S0140-6736(10)61381-5.
40. Huang X, Qiu L, Jin J, Zhou D, Chen X, Hou M, *et al*. Ibrutinib versus rituximab in relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma: a randomized, open-label phase 3 study. Cancer Med 2018;7:1043–1055. doi: 10.1002/cam4.1337.
41. Xu W, Song Y, Li Z, Yang S, Liu L, Hu Y, *et al*. Safety, tolerability and efficacy of orelabrutinib, once a day, to treat Chinese patients with relapsed or refractory chronic lymphocytic leukemia/small cell leukemia. Blood 2019;134:4319. doi: 10.1182/blood-2019-123331.
42. Wang F, Xu RH, Han B, Shi YX, Luo HY, Jiang WQ, *et al*. High incidence of hepatitis B virus infection in B-cell subtype non-Hodgkin lymphoma compared with other cancers. Cancer 2007;109:1360–1364. doi: 10.1002/cncr.22549.
43. Yang S, Zhu R, Li N, Feng Y, Zuo R, Huang X. Impact of treatment pattern on survival in Chinese patients with relapsed/refractory chronic lymphocytic leukemia or small lymphocytic lymphoma receiving ibrutinib or rituximab treatment. EHA 2020. Abstract EP720.

How to cite this article: Gale RP. Chronic lymphocytic leukemia in China. Chin Med J 2022;135:883–886. doi: 10.1097/CM9.0000000000001811