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 10^5 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
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 higher Binet stage at diagnosis, progress more rapidly, and have worse outcome.[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.[51] 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.[40] In studies of zanubrutinib, 4 of 90 subjects at-risk had HBV-reactivation resulting in the recommendation to give entecavir prophylaxis.[43] 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.[44] 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 chemoinmunotherapy 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 predominantly 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 predominantly 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.

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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.

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