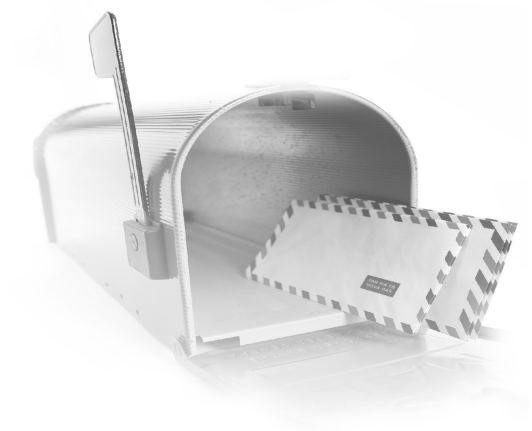

BLOOD RESEARCH
Volume 56 · Number 4 · December 2021

Letters to the Editor

Shared molecular basis, diagnosis, and co-inheritance of alpha and beta thalassemia

TO THE EDITOR: We have read the article entitled "Molecular basis and diagnosis of thalassemia" by Farashi and Harteveld that was recently published in *Blood Research* [1]. We want to express our congratulations to the author for successful publication, and we would also like to provide some input.

The authors described the molecular underpinnings of alpha and beta thalassemia separately in this article. Every facet of the illnesses was addressed, including diagnostic criteria for both, yet there was no mention of their common molecular basis or co-inheritance.

We would like to emphasize this issue by pointing out that other published manuscripts have reported on both types of thalassemia. In a study in Pakistan, in order to establish the prevalence and investigate the spectra of alpha thalassemia gene deletions in patients with beta thalassemia, Shahid *et al.* [2] concluded that alpha thalassemia coexists with beta thalassemia major. This study led to the significant finding that alpha thalassemia deletions (−alpha 3.7, −alpha 4.2) are also the common co-inherited deletions found in beta thalassemia major; however, this link has not been thoroughly researched. Guvenc *et al.* [3] investigated the association of alpha and beta-thalassemia genotypes using the reverse hybridization technique, and demonstrated that the alpha thalassemia mutation is co-inherited with sickle cell anemia. These authors also concluded that interactions between the alpha and beta globin chains may produce moderate to severe phenotypes depending on the molecular defects involved. Both types of thalassemia occur at such high frequencies that it is not uncommon for individuals to inherit the alpha thalassemia trait from one parent and the beta thalassemia trait from the other [4]. In addition, alpha and beta globin genes are inherited on two different chromosomes (the alpha globin gene is on chromosome 16 and the beta globin gene is on chromosome 11). The diagnosis of individuals with both alpha and beta thalassemia is not routinely performed for the individual types, and the simultaneous presence of alpha and beta thalassemia does not appear to interfere with ascertaining beta thalassemia carrier state in routine hematological screening tests [4]. Although restriction endonuclease DNA mapping can detect contemporaneous inheritance of both types of thalassemia, definitive screening criteria are still needed.

The co-inheritance of alpha and beta thalassemia is quite rare; according to Li *et al.* [5] in the Chinese population, the chances of finding an individual with co-inheritance of both is 1:1000. The co-occurrence of both alpha and beta thalassemia reduces the severity of the disease; therefore, these patients present with only mild to moderate symptoms of anemia and are less likely to be found in a hospital-based population [6].

Conclusion

These findings imply that a diagnostic criterion for screening patients with concurrent alpha and beta thalassemia should be developed. Furthermore, prenatal testing and genetic counseling should be undertaken in regions where alpha and beta thalassemia are more common in order to build a controlled and preventative environment that could lead to a lower incidence of co-inheritance of the two diseases.

Govinda Khatri, Abdul Moiz Sahito, Saboor Ahmed Ansari
Department of Internal Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan

Correspondence to: Govinda Khatri
Department of Internal Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Sindh 75500, Pakistan
E-mail: govindakhatri550@gmail.com

Received on Jul. 15, 2021; Revised on Aug. 16, 2021; Accepted on Aug. 25, 2021
https://doi.org/10.5045/br.2021.2021128

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article

were reported.

REFERENCES

1. Farashi S, Harteveld CL. Molecular basis of α-thalassemia. Blood Cells Mol Dis 2018;70:43-53.
2. Shahid S, Nadeem M, Zahid D, Hassan J, Ansari S, Shamsi T. Alpha thalassemia deletions found in suspected cases of beta thalassemia major in Pakistani population. Pak J Med Sci 2017;33:411-6.
3. Guvenc B, Canataroglu A, Unsal C, et al. β-Globin chain abnormalities with coexisting α-thalassemia mutations. Arch Med Sci 2012;8:644-9.
4. Law HY, Chee MK, Tan GP, Ng IS. The simultaneous presence of alpha- and beta-thalassaemia alleles: a pitfall of thalassaemia screening. Community Genet 2003;6:14-21.
5. Li D, Liao C, Li J, Xie X, Huang Y, Zhong H. Detection of alpha-thalassemia in beta-thalassemia carriers and prevention of Hb Bart's hydrops fetalis through prenatal screening. Haematologica 2006;91:649-51.
6. Winichagoon P, Fucharoen S, Weatherall D, Wasi P. Concomitant inheritance of alpha-thalassemia in beta 0- thalassemia/Hb E disease. Am J Hematol 1985;20:217-22.

Tp53 disruptions: is there a marker of poor prognosis in chronic lymphoproliferative disorders?

TO THE EDITOR: We read with great interest the paper by Göçer and Kurtoğlu about a real-life experience of 32 patients with chronic lymphocytic leukemia (CLL, 11/32 cases) or B-cell non-Hodgkin lymphomas (NHL, 21/32 cases) treated with ibrutinib [1]. The authors observed an elevated overall response rate (ORR) and complete response (CR) rate, consistent with available literature data. Overall toxicity was manageable without unexpected adverse events (AE). In all the 11 CLL patients, the deletion of 17p (del17p) mutation was assessed and 4 were positive. Interestingly, a survival curve for overall survival (OS) according to del17p status was performed and showed that in four mutated cases, one had early disease relapse, while the others were disease-free, despite the short follow-up period [1]. We agree with the authors that single-agent ibrutinib is a suitable option for patients with both CLL and NHL, regardless of prior therapies and disease subtype. We strongly appreciate the effort to present a real-world experience on ibrutinib use for NHL patients, including marginal zone lymphoma (MZL), an NHL subtype in which ibrutinib is not approved as treatment in most countries. However, we did not find any mention about del17p or TP53 mutations for NHL cases, even if the TP53 gene could have a prognostic significance in lymphoid malignancies other than CLL. It is interesting to assess TP53 disruptions (17p deletions and/or TP53 mutations) in NHL cases experiencing an early disease progression during or after ibrutinib therapy.

Chronic lymphoproliferative disorders such as MZL are characterized by an indolent course. Rituximab with bendamustine (BR) or alkylating agents as first-line regimens demonstrated long-term efficacy and mild toxicity. However, a small proportion of refractory patients exists and there is a lack of clinical trials to establish the optimal management for this subgroup [2]. Poor prognosis has been associated with TP53 disruptions in many solid tumors and hematological malignancies, including lung cancer and splenic MZL (SMZL) [3]. Noy and colleagues demonstrated the possibility of achieving a durable response with ibrutinib single-agent in relapsed/refractory (R/R) MZL in the PCYC-1121 phase II trial, leading to the Food and Drugs (FDA) approval of ibrutinib for previously treated MZL patients [4, 5]. However, in the PCYC-1121 study, only 14 SMZL cases were enrolled. Göçer and Kurtoğlu also did not specify the MZL subtype in their cohort. Moreover, to our knowledge, only a case of extranodal MZL and 5 cases with central nervous system MZL localization receiving ibrutinb were published. Thus, a real-life experience about SMZL is lacking [1, 4-7].

At our institution, we managed a 17p-deleted, rituximab-refractory SMZL patient with concomitant lung cancer. The patient started first-line therapy with BR and after 4 cycles, CT scan showed normal spleen size and a pulmonary lesion. Histological exam of the lesion after lobectomy demonstrated squamous lung cancer (pT2a-pN0, PDL1-negative, ALK-negative, EGFR not assessed). The patient stopped BR and underwent clinical follow-up for both malignancies. Nine months later, the patient relapsed. Due to this unusual behavior, FISH analysis was performed and revealed a 17p deletion. Karyotype did not show other alterations. We decided to administer a chemotherapy-free regimen using bortezomib and rituximab. A partial response was obtained after 3 cycles; however, CT scan showed lung cancer recurrence. The patient then received platinum-based therapy. However, at oncological restaging, he had lymphocytosis and thrombocytopenia, and CT scan demonstrated stable disease, an increase of spleen size, and enlarged lymph nodes suspicious for a lymphoproliferative disorder. Given the 17p deletion-positive status, we decided to treat the patient with ibrutinib. We obtained the drug for compassionate use after the approval of Institutional Review Board. The patient signed the informed consent form and received 560 mg ibrutinib orally once daily. Spleen size rapidly diminished during the clinical exam and platelet count improved. Although the SMZL clinically improved during the first cycle, the patient developed worsening respiratory failure and underwent sudden death at home, probably due to the concomitant pulmonary neoplasm; autopsy was not performed.

Lymphoproliferative disorders and solid neoplasms with 17p deletion are characterized by poor prognosis with no standard of care, representing an unmet need for clinicians [3, 8]. Interestingly, the presence of TP53 mutations was associated with response to anlotinib, a novel oral multi-targeted antiangiogenic tyrosine kinase inhibitor used in advanced,