RESPONSE

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TO THE EDITOR:

Should we move to a genomic classification of neutrophilic myeloid neoplasms?

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We were very interested to read the letter by Tremblay et al[1] entitled "CNL and aCML are prognostically distinct: a large National Cancer Database analysis" and the discussion in relation to our recent article "CNL and aCML should be considered as a single entity based on molecular profiles and outcomes."[2] Our study, which focused on a relatively large cohort of atypical chronic myeloid leukemia (aCML, n = 30, now renamed myelodysplastic syndrome [MDS]/myeloproliferative neoplasm [MPN] with neutrophilia in the fifth World Health Organization [WHO] classification[3]) and chronic neutrophilic leukemia (CNL, n = 23), highlighted the similarities with regard to genetic profiles, clinical characteristics, and outcomes between these 2 entities. Consequently, we suggested that CNL and aCML may be better classified as a single entity within the MDS/MPN grouping and further subclassified for prognosis and potential therapy according to their genetic profile.

In their letter, Tremblay et al expressed concern about our proposal based on the morphological differences between these 2 entities (mainly the dysplastic features associated with aCML) but more importantly, on their own observations of differences in overall survival (OS) between aCML and CNL based on National Cancer Database (NCDB) data (aCML, n = 702, OS = 15.2 months vs CNL, n = 294, OS = 23.1 months; $P = .00074$). Tremblay et al pointed out that their observed OS estimates are consistent with those of previously published studies; however, these studies are based on a very small number of cases (eg, only 12 for the study cited for CNL) and thus have wide margins of error.[4] Importantly, we would like to highlight that our molecular-risk classification was able to differentiate patients with a median OS of 42.8 months from those with a median survival of 13.0 months, which is clearly superior to the comparison of CNL and aCML thus supporting molecular-based risk scores.[2,5]

In addition, Tremblay et al population-based analysis captures a very impressive number of cases; however, as the authors point out, the molecular data are very limited and there are no morphological data in NCDB, so it is not possible to check whether the diagnostic criteria of CNL/aCML are really met, which is of utmost importance given the difficulty in classifying these patients. The fact that a surprisingly high proportion of patients (18.8% with aCML and 15.3% with CNL) presented *JAK2* mutations suggests that some cases were wrongly classified. Although Tremblay et al confirmed a survival difference when *JAK2*-mutated cases were excluded, it seems unlikely that any misclassification was limited to individuals with *JAK2* mutations. For example, *CSF3R* mutations were not described until 2013, whereas 40% of the NCDB cases were diagnosed before that date.[1,6] A significant proportion of these cases could have been confused with a neutrophilic reaction to a plasma cell disorder, confounding and probably lengthening the estimated survival of CNL.[7-10] In the case of aCML, the absence of cytogenetic information prevents the exclusion of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions, which were not recognized until the 2008 WHO classification (16% of Tremblay et al aCML cases were diagnosed before that date).[1,11] In this regard, because we had extensive clinical, hematological, and molecular data

Submitted 28 July 2023; accepted 2 September 2023; prepublished online on *Blood Advances* First Edition 6 September 2023; final version published online 2 November 2023. https://doi.org/10.1182/bloodadvances.2023011103.

Data are available on request from the corresponding author, Gonzalo Carreño-Tarragona (gonzalo.carreno@salud.madrid.org).

on all our patients, we were able to exclude 6 cases after the initial review because of a preexisting myeloid neoplasm or a likely incorrect diagnosis. In addition, 21 cases were reviewed centrally by microscopic evaluation of bone marrow trephines or by re-evaluation of pathology reports and case histories by an expert hematopathologist. This resulted in the exclusion of 2 further cases that were initially considered to have aCML but were subsequently considered to have primary myelofibrosis or chronic myelomonocytic leukemia. A total of 8 of 69 cases (12.3%) were misclassified at their centers of origin, which emphasizes the difficulty of diagnosing these entities.

We fully agree on the importance of histomorphologic information in the diagnosis and prognosis of myeloid diseases, which must invariably be complemented by molecular information. We welcome further debate and data on the classification of neutrophilic myeloid neoplasms[12,13] and accept that some people consider that there is currently insufficient evidence to definitively conclude that aCML and CNL should be consolidated into 1 disease at this time. An international registry that includes all relevant information would be of great value in advancing our understanding of these rare but fascinating disorders.

Contribution: G.C.-T., A.Á.-L., J.C.H.-B., R.A., and N.C.P.C. analyzed the data and wrote and reviewed the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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