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Racial differences in chronic lymphocytic leukemia: Digging deeper

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Abstract

While it has been well established that there are significant racial differences in lymphoid malignancies, registry-based studies have been limited by incomplete or missing data on stage, race, important clinical and laboratory prognostic factors, treatment, treatment response, and follow-up. To overcome some of these limitations, the authors conducted a retrospective cohort study of consecutive patients with a confirmed diagnosis of chronic lymphocytic leukemia (CLL) receiving care at MD Anderson Cancer Center and Duke University Medical Center. The authors identified 84 AA patients with untreated CLL who more commonly presented with poor-risk biological features such as unmutated IGHV gene, ZAP70 expression, and chromosome 17p or 11q deletion. . When compared to a group of non-black patients, the AA group had significantly shorter median event-free survival and overall survival. These results corroborate the findings of prior studies of CLL, but forward the field by providing additional clinical details to understand the nature of these racial disparities.

Age, gender, race and ethnic background remain the key demographic data that are collected and reported in cancer statistics and cancer outcomes research. While it has been well established that there are significant racial differences in lymphoid malignancies[1, 2] few studies have investigated the relationships between race, the patterns of presentation for chronic lymphocytic leukemia (CLL) /small lymphocytic lymphoma (SLL), treatment selection, and clinical outcomes with modern therapies. A Surveillance, Epidemiology and End Results (SEER) registry study comparing 27,703 white and 2,059 black patients with CLL/SLL diagnosed in the United States from 1992 to 2007 showed that black patients presented at younger age, more advanced stage, and had worse survival than white patients.[3] However, all registry-based studies have been limited by lack of uniform pathology review,[4] disagreement in coding systems for lymphoid malignancies that have changed over time,[5] and incomplete or missing data on stage, race, important clinical and laboratory prognostic factors, treatment, treatment response, and follow-up. Moreover, prior institutional studies and even some population based studies have had insufficient numbers of African American (AA) patients to perform comparisons across racial groups.

To overcome some of these limitations, the authors conducted a retrospective cohort study of consecutive patients with a confirmed diagnosis of CLL receiving care at two major

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academic medical centers in the United States.[6] They identified via retrospective review 84 AA untreated patients referred to MD Anderson Cancer Center and Duke University Medical Center and constructed a comprehensive dataset with complete ascertainment of demographic, clinical data, and treatment information in order to assess the impact of race on disease presentation, treatment selection, and outcomes. This group was compared to 1,571 untreated non-black (NB) patients referred to the same institutions. The manuscript describes the clinical characteristics, response to therapy and survival of AA patients and describes comparison with NB patients. The study indicates that there are racial differences in CLL patterns of presentation and outcomes. AA patients with CLL presented with lower median hemoglobin levels, higher beta2-microglobulin levels (β2-m), and more commonly presented with unmutated IGHV gene (65% vs. 47%), ZAP70 expression (58% vs. 32%), and chromosome 17p or 11q deletion (28% vs. 17%), all of which are associated with worse outcomes. AA patients in this sample more commonly required first-line therapy during the period of follow-up and had a markedly shorter median time to initiation of therapy (14 months vs. 57 months). When compared to a group of 487 NB patients matched to the AA cohort based on treatment regimens, the AA group, despite having similar overall response rates, had significantly shorter median event-free survival (36 vs. 61 months, $p = .007$) and overall survival (152 months vs. not reached, $p = .0001$). In multivariate analyses, race was an independent predictor of shorter event-free and overall survival. Moreover, these racial differences in survival persisted across different levels of β2-m, IGHV gene mutational status (mutated or unmutated), and cytogenetic abnormalities. These results corroborates the findings of a prior study of CLL/SLL in 13 SEER registries suggesting that AA patients in the US present with more advanced stage disease and have worse survival, but forward the field by providing additional clinical details to understand the nature of these racial disparities.

Despite its size this study was limited by the relatively smaller number of black patients as is the case with nearly all US-based and European lymphoma population studies that predominantly have examined white patients. In this academic center-based retrospective study, AA patients comprised 5.1% of the study population. Another limitation of this study is the lack of central pathology review across the two institutions. Changes in the World Health Organization classification of lymphoid malignancies over the time period studied also could potentially complicate the adjudication of diagnoses across eras.[2, 7] However, the change in diagnosis definitions over time is unlikely to influence the findings here because these academic institutions involved expert hematopathologists in the determination of CLL/SLL and there is no reason to suspect that there was differential misclassification of cases of CLL across racial categories over time. A greater challenge for this manuscript and many other studies of racial disparities is that the coding of race in clinical dataset using patient self-report or “observed” definitions from various health professionals can mask numerous factors, such as inherited traits, health education, income, health insurance status, and other psychosocial forces that may influence differences in cancer incidence across racial categories and disparities in cancer outcomes. Improved methods for coding race in clinical environments and capturing salient features of race that influence clinical outcomes are greatly needed if we wish to disentangle the factors that influence outcomes and to develop strategies that improve survival based on a revised understanding of racial disparities.

Other potential limitations of this retrospective study design could include missing or incomplete data on: staging, race, and treatment, or exclusion of cases with missing data. This study did not exclude patients, had stage information for all patients, and reported on all patients with untreated disease at the two centers. The amount of missing data and the patient characteristics at baseline in this setting appear comparable to registry data with the exception that the age at diagnosis for both groups was similar and younger than the typical age of onset for CLL. Several other studies have demonstrated that AA patients tend to

present with lymphoid malignancies at a younger age than white patients, and the lymphoid malignancies including CLL in the NB population have a median age at diagnosis in the seventh decade.[3, 8] The authors attribute these differences in age at diagnosis to the nature of referrals to academic medical centers which is plausible and has been observed in other studies of racial disparities in lymphoid malignancies. Despite these potential shortcomings, this dataset had the critical advantage of collection of important laboratory and treatment data beyond what occurs in typical cancer registries, which will be essential to improving our understanding of racial difference in treatment response outcomes as patients in these cohorts continue to be followed.

While the observations of racial differences in cancer outcomes including CLL unfortunately are not new, the demonstration that these differences in survival persist even when similar therapies are administered for CLL is a novel finding and suggests that AA may have different disease biology than NB patients. Other studies have suggested that there are racial and socioeconomic differences in the use of therapies for lymphoid malignancies in the United States.[9–11] Developing interventions to address the broader disparities in treatment selection and treatment outcomes identified in claims-based cohort studies requires improved understanding of the context in which cancer treatments are selected for patients across racial groups.[12, 13] Socioeconomic factors and health education are others mediators that may contribute to poorer outcomes for AA cancer patients. These and other factors may prohibit or limit access to care leading to disparities. As the authors point out that in this study, time from diagnosis to referral was shorter for AA than NB patients, making referral delay an unlikely cause of worse prognosis for the AA patients included in this analysis. Although this does not rule out the possibility that delays in diagnosis could have occurred before referral to the academic center. These results suggest that additional effort to identify specific therapies that are more likely to benefit AA patients (and others) with poor-risk CLL may be needed after improved access to care is achieved.

At present, there is limited understanding of the racial differences in CLL biology and the factors that influence the poor outcome in the AA population. As a result, there is substantial need for prospective studies aiming at identifying clinically predictive factors that can aid in treatment selection for AA patients with CLL and other lymphoid malignancies. Focused disparities research studies are necessary to determine whether differences in underlying genetic predisposition or exposures exist among black and white patients with CLL which might explain the differences in relative incidence, predisposition to poor risk disease, and reduced survival.

The current work provides meaningful information regarding the role of known prognostic factors and baseline characteristics across racial groups and provides data on the impact of these characteristics on the outcomes of therapy for AA CLL patients. This represents the largest study performed of this type with detailed clinical data and is supported by a similar study in diffuse large B-cell lymphoma that also suggests that racial differences in survival may persist even when black and white patients receive the same treatment.[12] In the future, developing significant clinical research studies of disparities in leukemia will require collection of biological specimens as well as clinical data to examine the racial differences in the molecular and biologic markers and their impact on racial differences in leukemia presentation and outcomes. Future studies in CLL can use this work as cornerstone for investigating racial disparities in this disease.

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