

Poorer Clinical Outcomes For Black Patients With AML: A Wake Up Call For Better Data And Greater Understanding Of Cancer Outcomes In All Ethnic Groups.

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In this issue of Cancer Discovery Drs Eisfeld and Bhatnagar show that black patients in the United States with Acute Myeloid Leukemia (AML) have a shorter survival compared to white patients. This is an important paper as it addresses an under researched issue: the complex interaction of race, tumour genetics, socio-economic factors and access to treatment, in defining treatment outcomes for a devastating cancer.

AML is the most common aggressive adult leukemia. There are ~20 000 new cases each year in USA (<https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html>) and in Europe that number is ~18 000 (1). AML is more common as individuals age, like most cancers, with ~70% of patients over the age of 60. It is genetically, and epigenetically, heterogeneous. The landscape of recurrent genetic (2) and cytogenetic changes (3) is well studied, especially in younger patients. Most of the data on clinical outcomes in AML comes from either large national cooperative group studies, or from industry sponsored clinical trials. These data show survival is dependent on two broad categories of factors. The first category encompasses patient factors, such as age, performance status, co-morbidity that determine a patient's ability to cope with the toxicity of intensive chemotherapy and potentially an allogeneic stem cell transplant, which is the only curative option for chemoresistant disease. The second category are prognostic recurrent AML cytogenetic changes and genetic mutations that provide the basis for international prognostic scoring systems as the European Leukaemia Net risk classification (4) and the US NCCN national guidelines (https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf). For example, mutation in the *NPM1* gene is associated with a good response to chemotherapy. In contrast, a high variant allele frequency *FLT3-ITD* mutation confers a poorer prognosis. Moreover, as the two mutations often co-occur, co-occurrence of a high variant allele frequency mutation in *FLT3-ITD* reduces the favourable prognostic impact of an *NPM1* mutation (4).

However, it has been known for some time that recruitment to the clinical studies on which these treatment recommendations are based has an over-representation of the Caucasian

population. This then begs the question of how representative these data are of non-Caucasian populations, and whether the recommendations on which they are based are appropriate for all ethnic groups.

Previous studies analysing data from both US **Cancer and Leukemia Group B** (CALGB) cooperative group trials (5) and registries (**S**urveillance **E**pidemiology and **E**nd **R**esults, SEER, and US state cancer registries) (6-8) have shown differences in frequencies of risk cytogenetic groups in African American patients compared to white patients (more African American patients had both favourable and adverse risk cytogenetics and less intermediate risk cytogenetics). Importantly, when treated on uniform protocols, African American patients had lower complete remission rates and overall survival compared to all other patients when known risk factors were taken into account (5). Similarly, registry data confirmed the worse overall survival of African American and Hispanic AML patients (7). In African Americans this was true even when corrected for age and cytogenetic risk group (8) and could only be partially explained by access to treatment (6,9) and socio-economic factors (6).

It is in this light that Drs Eisfeld and Bhatnagar now provide additional, thought provoking insight (10). They and their colleagues initially conducted a more in depth analysis of SEER data and showed that of the 1356 African American and 8074 non-Hispanic white patients under the age of 60 African American patients were found to have a 27% higher risk of death compared with non-Hispanic white patients ($P < 0.001$) after adjustment for age, sex, metropolitan area residential status, a measure of poverty and decade of diagnosis. Worryingly, survival of African American patients has significantly shortened compared to non-Hispanic white patients in the two decades since 1995, hinting at a widening disparity in outcome, rather than improvements with time.

For the first time, the authors also conducted mutation analysis on 81 genes on AML diagnostic samples from 1339 patients (1244 non-Hispanic white and 95 African American) entered into CALGB trials. In general, the mutation profile of African American AML patients is very similar to white patients. However, there were significantly fewer *NPM1* and *WT1* mutations and more *IDH2* and *PIK3CD* mutations in African American patients. The novel finding the authors suggest is that beyond socio-economic factors and access to treatment, AML genetics, attributable to race, accounts in part for poorer outcomes. This rests on poorer clinical response in patients with *NPM1* and *IDH2* mutations. Though this the largest study of mutational analysis in AML and the relationship between mutation profile, ethnicity and clinical outcome, unsurprisingly the numbers of samples studied from African American patients with mutations in *NPM1* (26) and *IDH2* (16) are small. Thus, caution must be exercised in interpreting this data until it is validated through meta-analysis from other large cooperative group datasets, or in the case of *NPM1* mutant patients, the kinetics of molecular *NPM1*

measurable residual disease (MRD) vary between African American and non-Hispanic white patients after intensive anthracycline and cytosine arabinoside induction and consolidation chemotherapy.

Nevertheless, if the observations that African American patients with *NPM1* and *IDH2* mutation do worse are correct then this may lead to a change in practice, for example, a greater emphasis on monitoring of MRD so patients at risk of relapse can be identified earlier and receive salvage therapy, including allogeneic transplantation. These findings also encourage the field more broadly to conduct robust analyses of clinical outcome that include ethnicity as a variable. If, as I suspect, ethnicity is an independent biological variable determinant of clinical outcome, then mechanistic analyses to understand why this is the case may give a deeper insight into therapy response and resistance. Potential mechanisms could include germline variation regulating drug handling or anti-cancer immune responses. So in summary, this work is a timely wake call not only for the AML field, but more broadly for other cancers as well, that our research needs to take into account the complex variable that is ethnicity, so we can serve all our diverse communities.

References

1. Miranda-Filho A, Pineros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. *Lancet Haematol* 2018;**5**(1):e14-e24 doi 10.1016/S2352-3026(17)30232-6.
2. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, *et al.* Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med* 2016;**374**(23):2209-21 doi 10.1056/NEJMoa1516192.
3. Grimwade D, Hills RK, Moorman AV, Walker H, Chatters S, Goldstone AH, *et al.* Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood* 2010;**116**(3):354-65.
4. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, *et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017;**129**(4):424-47 doi 10.1182/blood-2016-08-733196.
5. Sekeres MA, Peterson B, Dodge RK, Mayer RJ, Moore JO, Lee EJ, *et al.* Differences in prognostic factors and outcomes in African Americans and whites with acute myeloid leukemia. *Blood* 2004;**103**(11):4036-42 doi 10.1182/blood-2003-09-3118.

6. Byrne MM, Halman LJ, Koniaris LG, Cassileth PA, Rosenblatt JD, Cheung MC. Effects of poverty and race on outcomes in acute myeloid leukemia. *Am J Clin Oncol* 2011;**34**(3):297-304 doi 10.1097/COC.0b013e3181dea934.
7. Patel MI, Ma Y, Mitchell BS, Rhoads KF. Understanding disparities in leukemia: a national study. *Cancer Causes Control* 2012;**23**(11):1831-7 doi 10.1007/s10552-012-0062-3.
8. Patel MI, Ma Y, Mitchell BS, Rhoads KF. Age and genetics: how do prognostic factors at diagnosis explain disparities in acute myeloid leukemia? *Am J Clin Oncol* 2015;**38**(2):159-64 doi 10.1097/COC.0b013e31828d7536.
9. Patel MI, Ma Y, Mitchell B, Rhoads KF. How do differences in treatment impact racial and ethnic disparities in acute myeloid leukemia? *Cancer Epidemiol Biomarkers Prev* 2015;**24**(2):344-9 doi 10.1158/1055-9965.EPI-14-0963.
10. Bhatnagar B, Kohlschmidt J, Mrózek K, Zhao Q, Fisher JL, Nicolet D, *et al.* Poor Survival and Differential Impact of Genetic Features of Black Patients with Acute Myeloid Leukemia. *Cancer Discovery* 2021.