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Blood 142 (2023) 3241–3242

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

Prognostic Relevance of Truncating *ASXL1* Mutations and *ASXL1*-Integrated Molecular Models in Proliferative CMML

Clifford M Csizmar, MD PhD[1], *Mark Gurney, MB, BCh, BAO*[1], *Terra L Lasho, PhD*[1], *Rashmi Kanagal-Shamanna, MD*[2], *Kelly S. Chien, MD*[3], *Danielle E. Hammond, MD*[3], *Christy M Finke*[1], *Abhishek A Mangaonkar, MBBS*[4], *Aref Al-Kali, MD*[5], *Naseema Gangat, MBBS*[5], *Ayalew Tefferi, MD*[5], *Hassan Alkhateeb, MD*[5], *Guillermo Garcia-Manero, MD*[3], *Guillermo Montalban-Bravo, MD*[3], *Mrinal M. Patnaik, MD MBBS*[1]

[1] Division of Hematology, Department of Medicine, Mayo Clinic, Rochester, MN
[2] Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX
[3] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[4] Mayo Clinic, Rochester, MN
[5] Division of Hematology, Mayo Clinic, Rochester, MN

Introduction

Chronic myelomonocytic leukemia (CMML) can be classified into dysplastic (dCMML) and proliferative (pCMML) subtypes based on a white blood cell count (WBC) $\geq 13 \times 10^9$/L for pCMML. Though this cutoff may seem arbitrary, there is evidence that pCMML is a unique biological entity with a distinct molecular profile and worse outcomes (Carr RM, *et al. Nat Commun.* 2021). We hypothesized that contemporary CMML prognostic scoring systems - such as the Mayo Molecular Model (MMM; Patnaik MM, *et al. Leukemia.* 2014) and the CPSS-Molecular Model (CMM; Elena C, *et al. Blood.* 2016) - would not adequately risk-stratify pCMML patients. Moreover, while truncating *ASXL1* mutations are considered a high-risk feature in CMML, their prognostic relevance in pCMML is unknown.

Methods

After IRB approval, we compiled a large (n = 888), molecularly-annotated database of CMML patients seen at two US medical centers (Mayo Clinic and MD Anderson) via retrospective chart review. All statistical analyses considered the clinical and laboratory parameters obtained at the time of presentation. The cohort was divided into dCMML and pCMML subgroups, which were analyzed independently alongside the entire cohort. Categorical variables were compared by Fisher exact or Pearson χ^2 tests and continuous variables by Mann-Whitney U tests. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. Survival was assessed via the Kaplan-Meier method. *P*-values < 0.05 were considered significant. Calculations were performed using the BlueSky Statistics (v10.3.1) interface for R.

Results

We identified 474 (54%) dCMML cases and 410 (46%) pCMML cases with median age 71 years and 67% males. Patients with pCMML were more likely to have higher AMC (5.1 vs 1.5 x 10^9/L, $p < 0.0001$), circulating immature myeloid cells (IMC; 65% vs 36%, $p < 0.0001$) and abnormal karyotypes (37% vs 30%, $p = 0.0187$). They were also overrepresented in higher-risk categories of the MMM and CMM compared to dCMML ($p < 0.0001$ for each model). The number of somatic mutations was higher in pCMML than dCMML (mean 3.0 vs 2.6, $p = 0.0050$). Mutations in *ASXL1* (53% vs 39%), *NRAS* (21% vs 11%), *CBL* (18% vs 12%), *SETBP1* (14% vs 7%), *JAK2* (10% vs 3%), *CEBPA* (5% vs 2%), *GATA2* (3% vs 0%), and *FLT3* (3% vs 1%) were more frequent while mutations in *TET2* (38% vs 48%), *SF3B1* (2% vs 8%), *ZRSR2* (2% vs 8%), and *NPM1* (1% vs 3%) were less frequent in pCMML compared to dCMML, respectively ($p < 0.05$ for all).

Though the MMM and CMM effectively stratified the dCMML group, they did not provide meaningful risk stratification in the pCMML group (MMM $p < 0.05$ overall but could not distinguish between low and intermediate-1/2 or intermediate-1 and high risks; CMM $p > 0.05$). Likewise, there was no difference in the median overall survival (OS) or leukemia free survival (LFS) when pCMML patients were stratified by truncating *ASXL1* mutations(**Figure 1A**).

We then sought to better risk stratify pCMML. Univariate analysis identified increasing age, male gender, abnormal karyotype, and elevated WBC, ANC, and AMC as adverse predictors for OS. In addition, the presence of IMC and peripheral blood (PB) blast % were adverse factors for LFS, while age was not significant for LFS. None of the aforementioned mutations were significant in the univariate model for OS, whereas *GATA2* and *NPM1* mutations were significant for LFS. In multivariate

analysis for OS, only male gender and AMC ≥ 10 x 10^9/L retained significance. In multivariate analysis for LFS, male gender, AMC ≥ 10 x 10^9/L, and peripheral blasts ≥ 5% remained significant; *GATA2* and *NPM1* mutations were not significant. These variables risk-stratified pCMML patients based on the presence of 0, 1, or ≥ 2 risk factors (**Figure 1B**). In comparison, OS was 40.7 months (95% CI 35.2 - 50.1 mo.) for dCMML patients, 20.1 months (95% CI 18.2 - 22.7 mo.) for pCMML patients, and 31.8 months (95% CI 28.4 - 33.5 mo.) for the entire cohort. At last follow up, 586 deaths (66%) and 168 AML transformations (19%) were recorded in the cohort. Deaths in dCMML vs pCMML were 294 (62%) vs 291 (71%; p = 0.0067), with AML transformations in 83 (18%) vs 84 (21%; p = 0.2055) patients, respectively.

Conclusions

Truncating *ASXL1* mutations, along with *ASXL1*-mutation weighted CMML prognostic models failed to effectively risk stratify pCMML patients. In pCMML, male gender and AMC ≥ 10 x 10^9/L, effectively risk stratified for OS, while these factors along with PB blasts ≥ 5% effectively risk stratified for LFS.

Disclosures Chien: *AbbVie:* Consultancy; *Rigel Pharmaceuticals:* Consultancy. **Alkhateeb:** *Mayo Clinic:* Current Employment. **Garcia-Manero:** *Genentech:* Research Funding; *Bristol Myers Squibb:* Other: Medical writing support, Research Funding; *AbbVie:* Research Funding. **Montalban-Bravo:** *Rigel:* Research Funding; *Takeda:* Research Funding. **Patnaik:** *Epigenetix:* Research Funding; *Kura:* Research Funding; *CTI BioPharma:* Membership on an entity's Board of Directors or advisory committees; *StemLine:* Research Funding.

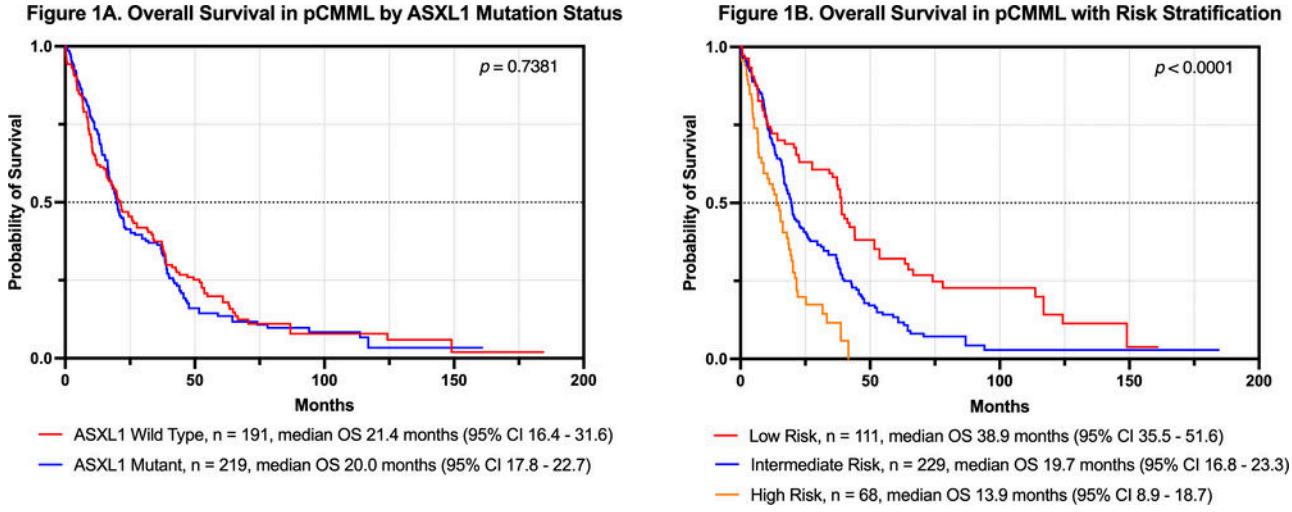

Figure 1

https://doi.org/10.1182/blood-2023-186881