ELSEVIER

Blood 142 (2023) 5915–5917

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

615.ACUTE MYELOID LEUKEMIAS: COMMERCIALLY AVAILABLE THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

Clonal Dynamics and Deterministic Clinical Fate Mapping of Patients with Myelodysplastic Neoplasms and Acute Myeloid Leukemia with *TP53* Disruption

Shyam Ajay Patel, MDPhD[1], *Benjamin Tanenbaum, MD*[2], *Asiri Ediriwickrema, MD*[3], *Jan Cerny, MDPhD*[2], *Lloyd Hutchinson*[2], *Xiuling Meng*[2], *William K Gerber*[2], *Salwa Khedr, MD*[2], *William Selove*[4], *Bruce Woda, MD*[2], *Jonathan M. Gerber, MD*[2]

[1] Department of Medicine - Hematology/Oncology, UMass Chan Medical School, Worcester, MA
[2] UMass Chan Medical School, Worcester, MA
[3] Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA
[4] UMass Memorial Medical Center, Whitinsville, MA

Background: Myelodysplastic neoplasms (MDS) and acute myeloid leukemia (AML) with multi-hit *TP53* comprise the highest risk subgroup of all myeloid malignancies. *TP53* aberration is recognized as a diagnostic category in the 2022 International Consensus Classification (ICC) and the 5 th edition of the WHO. However, these systems do not discern among the subtypes of *TP53* aberrations regarding response to therapy. In this study, we explore the clonal dynamics that underlie such prognostic heterogeneity within distinct subgroups of *TP53*-aberrant MDS and AML, with a specific focus on the effect of hypomethylating agent (HMA) vs. araC-based chemotherapy on *TP53* variant allele frequency (VAF).

Methods: The UMass Leukemia Registry from the UMass Data Lake identified 76 patients harboring *TP53* aberration(s) plus ICD-10 code of either D46.9 (MDS and its subentities) or C92.00 (AML and its subentities) between 2011-2023. Data was integrated with hematopathology records. *TP53* exome sequencing was performed with coverage depth 500X to 6500X, and VAFs were adjusted for copy number variation (CNV), as previously described (Patel SA *et al.*, *Leuk Lymphoma* 2021; 62: 3348-60). Patients with serial bone marrow biopsy samples were included. We defined multi-hit *TP53* status as per the ICC: two or more distinct *TP53* mutations with VAF $\geq$ 10%, or a single *TP53* mutation plus one of the following abnormalities: (1) del(17p13.1), (2) *TP53* VAF >50%, (3) copy-neutral loss-of-heterozygosity, or (4) any complex karyotype. Clonal dynamics were assessed for MDS vs. AML and for varying *TP53* allelic states as a function of therapeutic intervention. Clinical fate mapping was performed based on management decisions at various points of clinical care.

Results: For patients with *TP53*-aberrant MDS, 17 patients underwent serial bone marrow biopsies during treatment. Of these, 11 (64.7%) had multi-hit status. Eight patients (47.1%) underwent hematopoietic cell transplant (HCT), and 7 of these 8 patients had received HMA-based front-line therapy. For patients with MDS, we assessed the effect of HMA-based therapy on *TP53* VAF. The mean *TP53* VAF (sum of VAFs) was significantly lower after HMA-based treatment (35% vs. 12.6%) ($p = 0.0075$) **(Panel A)**. For patients with *TP53*-aberrant AML, 19 patients underwent serial bone marrow biopsies. Of these, 14 (73.7%) had multi-hit status. Only 2 patients (10.5%) underwent HCT. Five patients (26.3%) received araC-based induction, while 11 patients (57.9%) initially received HMA-based induction. For patients with AML with multi-hit *TP53*, we assessed the effect of HMA-based vs. araC-based front-line therapy on *TP53* VAF. HMA therapy led to mean fold reduction in *TP53* VAF (pre-treatment to post-treatment) of 11.7 $\pm$ 5.8 ($p = 0.019$), while araC-based therapy actually led to mean fold increase (but not statistically significant) in *TP53* VAF (pre-treatment to post-treatment) of 2.6 $\pm$ 1.05 ($p = 0.319$) **(Panel B)**. HMA-based treatment resulted in significantly greater reduction in the VAF in aberrant clones and subclones compared to araC-based treatment. Compared to AML, most patients with MDS (62.9%) proceeded with palliative intent therapy at the time of diagnosis. Although patients with AML (53.7%) attempted to proceed with curative intent at the time of diagnosis, only 14.6% eventually proceeded with HCT, largely due to clinical decompensation or disease progression during front-line therapy. Among HCT recipients for MDS (n =10), 7 (70%) remained in remission. Among HCT recipients for AML (n = 6), 4 (66.7%) remained in morphologic leukemia-free state.

Conclusion: There is limited literature on clonal and subclonal diversity in patients with MDS or AML with *TP53* aberrations. Such considerations constitute an important therapeutic issue, as certain interventions may only eliminate a fraction of a patient's mutant cells. In our study, HMA- and araC-based regimens had differential effects on various subclones: HMA was

more effective in reducing the *TP53* mutational burden and increasing patient ability to proceed with HCT. AraC-based therapy appeared less effective, perhaps due to selection pressure in favor of *TP53*-mutant cells. Prospective trials are required to identify optimal regimens that lead to the best long-term outcomes, and single-cell resolution might assist with more definitively assessing dynamics of clonal response to treatment.

Disclosures Patel: *UMass Center for Clinical and Translational Science (CCTS) Pilot Project Program grant (NIH / NCATS Grant UL1TR001453:* Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Cerny:** *MERIT CRO:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Actinium Pharmaceuticals:* Current holder of *stock options* in a privately-held company; *BlueBird Bio, Inc:* Current holder of *stock options* in a privately-held company; *Cellectar Sciences:* Current holder of *stock options* in a privately-held company; *Dynavax Technologies:* Current holder of *stock options* in a privately-held company; *Gamida Cell:* Current holder of *stock options* in a privately-held company; *Atyr Pharma:* Current holder of *stock options* in a privately-held company; *Novavax Inc:* Current holder of *stock options* in a privately-held company; *Ovid Therapeutics Inc:* Current holder of *stock options* in a privately-held company; *Sorreto Therapeutics:* Current holder of *stock options* in a privately-held company; *Veru Inc:* Current holder of *stock options* in a privately-held company; *Viridian Therapeutics:* Current holder of *stock options* in a privately-held company; *Vaxart Inc:* Current holder of *stock options* in a privately-held company; *2Seventy Bio Reg SHS:* Current holder of *stock options* in a privately-held company; *Bristol Myers Squibb:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *ICON- Prolacta:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *ICON- Allovir:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Gerber:** *AbbVie:* Divested equity in a private or publicly-traded company in the past 24 months; *Novartis:* Honoraria, Research Funding; *Hutchmed:* Research Funding; *Bristol Myers Squibb:* Research Funding; *Stemline Therapeutics, Inc.:* Research Funding.

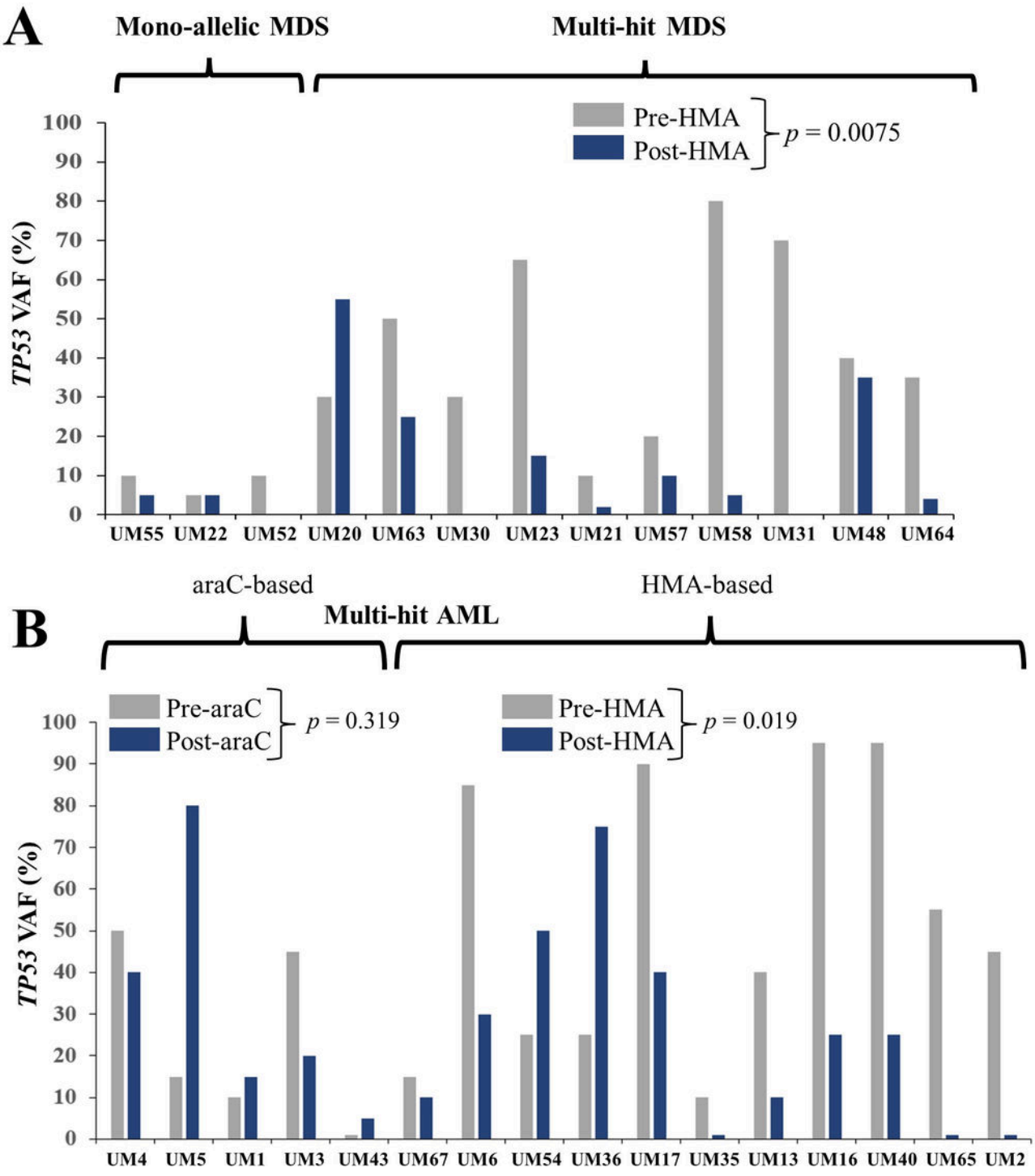

Figure 1

https://doi.org/10.1182/blood-2023-181945