monoallelic deletion (median OS, 60 months) and the cytogenetic abnormality of del(1p32) (median OS, 49 months) in identifying HR NDMM patients. Notably, this finding is observed in a substantial proportion, 11%, of patients at diagnosis. These findings need to be considered in updated risk-stratification criteria, around which prospective risk-adapted clinical trials can be designed. The phase 2 Optimum/Muknine trial for UHR patients included del(1p) in the criteria for eligibility and showed a benefit for an intensified treatment approach using a quintuplet induction (daratumumab, bortezomib, lenalidomide, cyclophosphamide, and dexamethasone), augmented ASCT, and quadruplet (daratumumab, bortezomib, lenalidomide, and dexamethasone) consolidation strategy.[6]

This study also corroborates the negative prognostic impact of multiple HR cytogenetic abnormalities (see figure panel B), adding to the authors' previous work in this area,[7] and suggests that the biallelic deletion of 1p32 may have a similar prognostic impact to biallelic *TP53* mutations, a well-recognized marker of UHR myeloma, in which the median OS is 24 months (see figure panel C).[3] Another key message is the specification of the importance of the locus of del(1p), with only del(1p32) appearing to be useful in prognostication.

An additional important finding from the current analysis includes the equivalence of the different platforms (FISH/SNP arrays/NGS) used, which will help in discussions regarding standardization of methodology and cutoffs; this is essential if cytogenetic and genomic criteria are to be incorporated into risk-adapted treatment strategies outside of clinical trials.

However, it must be noted that this is a retrospective analysis of a large intergroup cohort of patients, with its attendant caveats, including missing data, and, therefore, corroboration of the impact of del(1p32) on outcomes from prospective clinical trial data sets is required, along with analysis of its impact on other known genomic negative prognostic markers, mainly *TP53* mutations and 1q amplification.

It is anticipated that the results of this study will be pivotal in the effort to accurately define HR and UHR myeloma patients at diagnosis and disease progression, adding to data provided by the mSMART, EMC92/SKY92, UAMS GEP70, and CoMMpass criteria.[8] This information will aid the design of prospective risk-adapted clinical trials to eventually improve outcomes for patients in this area of high unmet need.

Conflict-of-interest disclosure: A.K. is a member of the advisory boards of Janssen, Celgene, Amgen, and Kyowa-Kirin, Mundipharma. ■

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https://doi.org/10.1182/blood.2022018967

MYELOID NEOPLASIA

Comment on Schnegg-Kaufmann et al, page 1316

The kids are alright: MDS clones mature

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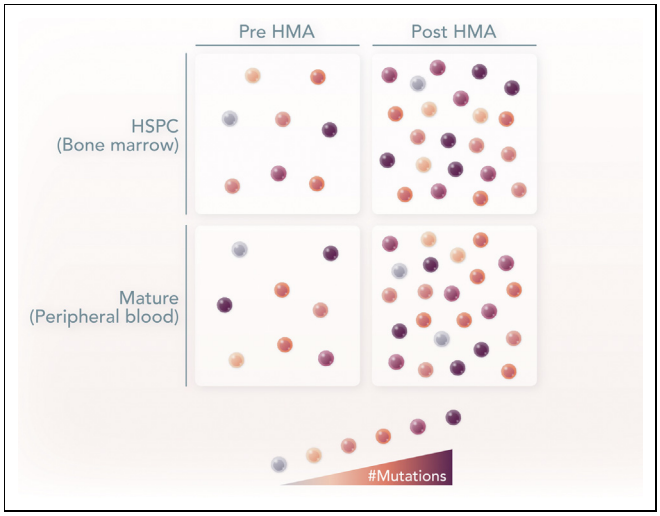
In this issue of *Blood*, Schnegg-Kaufmann et al[1] demonstrate that highly mutated hematopoietic stem and progenitor cells contribute to normal hematopoiesis in myelodysplastic neoplasms (MDS) and chronic myelomonocytic leukemia (CMML) with or without azacytidine (AZA) treatment.

Myeloid malignancies represent a highly diverse set of diseases, including myeloproliferative neoplasms, MDS, and acute myeloid leukemia (AML). Notably, many genetic mutations are shared across different myeloid malignancies (*TET2, TP53*), whereas others are unique to a specific type (*NPM1*[c]). These different mutations ultimately promote abnormal self-renewal of hematopoietic stem and progenitor cells (HSPCs) and/or block their maturation into normal myeloid cells such as granulocytes or monocytes. This block in maturation ultimately results in a major morbidity in MDS/CMML cytopenias, which make patients transfusion dependent.

Importantly, concepts from 1 disease are frequently applied to other myeloid malignancies. For example, minimal residual disease (MRD) measurement in chronic myeloid leukemia is standard of care,[2] and a similar concept for risk stratification is emerging in AML.[3] The fundamental paradigm to emerge from



In MDS and CMML, there is a mixture of normal (white) and abnormal (brown) HSPCs. Brown color gradient represents the mutational burden. In both pre- and post-HMA treatment, the highly mutated HSPCs can differentiate and contribute to the peripheral blood, with slight variance in the clonal architecture. Professional illustration by Somersault18:24.

these 2 diseases is that reduction in disease burden permits unmutated HSPCs to mature, thereby normalizing blood counts. This implies that the mutated HSPCs cannot differentiate with therapy and, therefore, their elimination is vital to disease control. This concept has been applied to other myeloid malignancies such as MDS and CMML. The contradiction is that treatment with DNA hypomethylating agents (HMAs) such as decitabine or AZA can normalize blood counts without a commensurate reduction in disease burden.[4,5] Whether this is because highly mutated HSPCs can mature normally in response to AZA or there is increased output from the remaining normal cells or HSPCs with fewer mutations is an important, unresolved question within the literature.[5]

To address this question, Schnegg-Kaufmann et al used multiple approaches on samples from patients with MDS or the MDS/myeloproliferative neoplasm overlap disease CMML, before and after AZA treatment. The authors initially hypothesized based on in vitro colony-forming assays[5] that highly mutated clones would fail to differentiate into peripheral blood cells. In addition, they hypothesized that normal HSPCs or clones with fewer mutations would mature in response to DNA hypomethylation. As a first step, 2 patients with CMML and 1 patient with MDS, all harboring *TET2* mutations, had stem and progenitor cells fractionated, and quantitative polymerase chain reaction was used to measure the variant allele fraction of different mutations to quantify clonal architecture on both bulk and single-cell populations. Counterintuitively, the authors found that the clonal architecture did not vary as hematopoietic cells differentiated from stem cells to myeloid progenitors and eventually into differentiated cells. These data demonstrate that highly mutated HSPCs can differentiate into mature cells in the absence of treatment.

To understand how HMAs may alter the clonal architecture, a second cohort of 9 MDS patients was analyzed similarly, this time pre– or post–AZA treatment. Again, their results at the single-cell level confirm that highly mutated HSPCs could differentiate into normal mature blood cells. Significantly, the ability of highly mutated HSPCs to differentiate was seen in both AZA responders and non-responders. The only mutation that appeared disfavored during the differentiation process was biallelic mutations in *TP53*; these clones were depleted by AZA. Collectively, this work implies that highly mutated HSPCs can be induced to mature via AZA therapy, and this ability is independent of clinical response. One important caveat is that given the robust, highly detailed molecular studies performed, the number of patients was overall small, and, therefore, more extensive studies are needed to confirm these findings. However, by leveraging single-cell approaches, the authors have addressed a critical question regarding how HMAs can induce clinical responses without altering disease burden in MDS/CMML.

This work has important implications beyond the use of AZA in MDS/CMML. First, it highlights that not all concepts from 1 myeloid malignancy can be applied broadly across the group. Traditionally, MDS and CMML are considered precursor conditions that ultimately transform into AML in a minority of patients. This work would imply that the same paradigms in measuring response to therapy through MRD may not be applicable in MDS, at least in reversing cytopenia(s) and long-term disease control. Given that many MDS patients are older and not eligible for curative therapy with an allogeneic bone marrow transplantation, this work highlights that following MRD may not be a valuable guide for treatment. Second, as people age, clonal hematopoiesis dominates,[6,7] and the bulk of hematopoiesis is driven by a small number of HSPCs with a single mutation. In the case of clonal cytopenia of undetermined significance (CCUS), treatment with HMAs has been proposed and studied.[8,9] Schnegg-Kaufmann et al's work suggests that although HMAs may improve cytopenia(s), they may not alter the clinical trajectory of the disease in terms of progression to MDS or AML. Collectively, this research highlights the need for larger prospective studies in patients with CCUS, MDS, and CMML to contrast their clonal dynamics with distinct myeloid malignancies such as AML (see figure).

Conflict-of-interest disclosure: S.R. declares no competing financial interests. ■

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https://doi.org/10.1182/blood.2022019187

THROMBOSIS AND HEMOSTASIS

Comment on Burdett et al, page 1322

Summiting thrombotic hazards in glioma

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In this issue of *Blood*, Burdett and colleagues describe the first venous thromboembolism (VTE) prediction model following surgical resection of grade 2 to 4, molecularly defined, adult-type diffuse gliomas.[1]

About 10% to 30% of patients with glioma experience a VTE event over the course of their disease.[2] The majority of VTEs in glioma arise in association with surgical resection or while receiving adjuvant therapy.[3] Advanced age, large tumor size, leg paresis, prior VTE, A or AB blood type, and the presence of intratumoral thrombosis have all been identified as thrombotic risk factors.[4] The proposed mechanisms of thrombogenesis in glioma center on tumor production of tissue factor, procoagulant tumor microvesicles (MVs), and podoplanin, a transmembrane sialoglycoprotein believed to increase platelet activation in glioma.[5] Gliomas with mutated *IDH1* status have lower levels of tissue factor expression and may be associated with a lower risk of VTE than gliomas with wild-type *IDH1*—an observation first reported in 2016 by the authors of the present study.[6] Podoplanin production by glioma cells is also downregulated in the presence of mutated *IDH1*.[7]

Despite the strong association of glioma with VTE, no VTE prediction tools are available that accurately gauge VTE risk in this disease. The Khorana score, the most widely used clinical prediction tool for VTE in cancer, did not include sufficient numbers of patients with glioma in its original study design, although modifications to the Khorana score to incorporate glioma have been devised.[8,9] In the absence of accurate VTE prediction tools in glioma, the potential utility of prophylactic anticoagulation in these patients is uncertain, as concerns about hemorrhagic risks from anticoagulation have long dissuaded most practitioners from its use in patients with glioma despite their high VTE risk.[3,10]

In the current prospective, observational study, Burdett and colleagues have developed the first risk prediction model of incident VTE in glioma by analyzing 3 separate cohorts of patients with glioma: a discovery cohort of 393 patients with newly diagnosed or recurrent glioma treated at Northwestern Memorial Hospital in Chicago and 2 validation cohorts from Duke University (157 patients) and UCLA (68 patients). Using their discovery cohort, the authors employed lasso regression to identify 10 risk factors for incident VTE in patients with glioma in their initial discovery cohort. The identified risk factors, in no specific order, included: (1) IDH mutation status, (2) MGMT promoter methylation, (3) glioma grade, (4) prior history of VTE, (5) hypothyroidism, (6) asthma, (7) hypertension, (8) leukocyte count, (9) body mass index, and (10) patient age. These risk factors then in turn informed their Cox proportional hazards model with the continuous outcome of time-to-incident-VTE diagnosis, in the context of a mean follow-up period of 20.5 months across all cohorts. The model was then utilized to evaluate predictive ability for the outcome of interest in the 2 external cohorts. In all, the areas under the receiver operating characteristic curves for each external cohort, aiming to find an ideal balance of the highest specificity and sensitivity, were 0.79 to 0.84 in the discovery cohort and 0.63 to 0.68 and 0.70 to 0.73 in the 2 external cohorts. This is a respectable output in the context of clinical medicine (by comparison, this statistic was 0.7 for the Khorana score as originally reported in 2008). The model is available as an R Shiny application at https://kbellburdett.shinyapps.io/GliomaPredictVTE/.

In addition to the VTE prediction model, the authors also report a number of interesting pathophysiologic insights on VTE development in glioma. In their analysis, patients with wild-type *IDH1/IDH2* showed a trend toward higher levels of circulating tissue factor on tumor MV (TF-MV). Patients with the highest levels of TF-MV activity had the fastest time to VTE and highest cumulative incidence of VTE. Tumor podoplanin had a significant association with development of VTE while circulating podoplanin did not. In a murine inferior vena cava stenosis model of thrombosis, mice with wild-type *IDH1* and high tissue factor expression developed larger thrombi than mice with mutated *IDH1* and low tissue factor expression.

In all, the new established model by Burdett and colleagues, and the pathophysiologic insights they report, represent major steps forward in the field of cancer-associated thrombosis and in the study of patients with glioma. As has been the case with nearly every VTE risk prediction model, future modifications of Burdett's model may be expected by centers across the globe. In particular, a reevaluation of the model in the context of a competing risk framework might improve its performance, as patients without VTE in the current model were censored at last follow-up, inclusive of a possibility of having died; this would constitute a competing risk preventing full capture of VTE events