Comment on Slager et al, page 2046

Familial patterns of hematologic precursors

Ola Landgren and Francesco Maura | University of Miami

In this issue of *Blood*, Slager et al report novel results from a large familial screening study including 1045 relatives from 310 families that include a patient with chronic lymphocytic leukemia (CLL).[1]

The aims of their study were to determine patterns of monoclonal B-cell lymphocytosis (MBL) and risk of progression from MBL to CLL. According to large population-based data sets, CLL has one of the highest familial risks among cancers,[2] so it made sense for Slager et al to conduct a study to gain important clinical insights and to advance the field scientifically.

Two large prospective cohort studies, based on the large National Cancer Institute Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial cohort (from more than a decade ago), showed that 2 hematologic malignancies are preceded by precursor conditions. Specifically, prospective data showed that multiple myeloma is consistently preceded by monoclonal gammopathy of undetermined significance (MGUS)[3] and CLL is similarly preceded by MBL.[4] These are clinically and scientifically important observations in that they provide support for clinical monitoring of individuals affected by MGUS and MBL, respectively, and they define a framework for studying risk factors and underlying mechanisms of progressive vs stable precursor disease. Slager et al were motivated to extend current knowledge by studying patterns of progression from MBL to CLL among patients with MBL who are related to patients with CLL.

Slager et al used highly sensitive flow cytometry to prospectively follow relatives of patients with CLL and determined that the baseline prevalence of MBL among those relatives was 22%. After a median follow-up of 8 years among 449 relatives, 12 individuals progressed from MBL to CLL, yielding a 5-year cumulative incidence of about 2%. The authors further dissected their data, and when they considered only the 139 relatives with low-count MBL (absolute clonal B-cell count <500 cells per µL), the 5-year cumulative incidence increased to 6%. Furthermore, during follow-up of 264 individuals who had no MBL at baseline, 60 subsequently developed MBL (2 had high-count MBL [absolute clonal B-cell count ≥500 cells per µL] and 58 had low-count MBL). Overall, this screening cohort of relatives of CLL patients showed an excess of MBL in family members, which is similar to that in previous smaller studies.[2] In addition, among family members of CLL patients, Slager et al found evidence in normal blood of progression from low-count MBL to high-count MBL and then to onset of CLL. The authors estimated that the average rate of progression from low-count MBL to CLL was ~1% per year, which is high compared with the risk of progression in the general population.[5]

Similar to the pathogenesis of other lymphoproliferative disorders,[6-8] that for CLL is characterized by a long evolutionary history and early branching from the most common recent ancestor.[9] In this scenario, most of the key drivers and genomic defining events are acquired several years before progression to CLL, and therefore they are potentially detectable irrespective of the low disease burden (ie, low-count MBL). A comprehensive characterization of these genomic and epigenomic events in CLL and other hematologic malignancies with evidence of early precursors and long evolutionary history[6-8,10] will allow differentiation between progressive and stable entities and potentially allow the development of early interception and preventive strategies.

The novel insights from the clinical epidemiology study by Slager et al suggest that additional molecular investigations are needed to characterize biological mechanisms of progression and to define early genomic signatures of progressors vs non-progressors. For example, such information could be used to translate the observed statistically increased (average) risk of progression among MBL patients who are family members of patients with CLL (vs patients with MBL in the general population) to the absolute risk of progression to CLL in individual cases.

REFERENCES

1. Slager SL, Lanasa MC, Marti GE, et al. Natural history of monoclonal B-cell lymphocytosis among relatives in CLL families. *Blood.* 2021;137(15): 2046-2056.

2. Goldin LR, Landgren O, Marti GE, Caporaso NE. Familial aspects of chronic lymphocytic leukemia, monoclonal B-cell lymphocytosis (MBL), and related lymphomas. *Eur J Clin Med Oncol.* 2010;2(1):119-126.

3. Landgren O, Kyle RA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 2009;113(22):5412-5417.

4. Landgren O, Albitar M, Ma W, et al. B-cell clones as early markers for chronic lymphocytic leukemia. *N Engl J Med.* 2009;360(7):659-667.

5. Fazi C, Scarfò L, Pecciarini L, et al. General population low-count CLL-like MBL persists over time without clinical progression, although carrying the same cytogenetic abnormalities of CLL. *Blood.* 2011;118(25):6618-6625.

6. Maura F, Landgren O, Morgan GJ. Designing evolutionary-based interception strategies to block the transition from precursor phases to multiple myeloma [published online ahead of print 5 August 2020]. *Clin Cancer Res.* doi:10. 1158/1078-0432.CCR-20-1395.

7. Maura F, Rustad EH, Boyle EM, Morgan GJ. Reconstructing the evolutionary history of multiple myeloma. *Best Pract Res Clin Haematol.* 2020;33(1):101145.

8. Rustad EH, Yellapantula V, Leongamornlert D, et al. Timing the initiation of multiple myeloma. *Nat Commun.* 2020;11(1):1917.

9. Gruber M, Bozic I, Leshchiner I, et al. Growth dynamics in naturally progressing chronic lymphocytic leukaemia. *Nature.* 2019; 570(7762):474-479.

10. Gerstung M, Jolly C, Leshchiner I, et al; PCAWG Consortium. The evolutionary history of 2,658 cancers. *Nature.* 2020; 578(7793):122-128.

MYELOID NEOPLASIA

"Mast"ering drug discovery with iPSCs

Adrienne Dorrance | The Ohio State University

In this issue of *Blood*, Toledo et al describe the generation of KIT D186V–induced pluripotent stem cells (iPSCs) from patients with aggressive systemic mastocytosis (SM) to use as patient-specific models for mechanistic studies and drug discovery. Using these iPSCs, the authors identified nintedanib, a US Food and Drug Administration–approved angiokinase inhibitor, as a potential new therapy for SM.[1]

SM is a rare disease involving expansion and organ infiltration of neoplastic mast cells. Initially, SM was thought to be a homogenous disease; however, clinical differences in disease progression and response to therapy, along with the identification of mutations supports the modern premise that SM is a complex heterogenous disease. According to the World Health Organization classification of SM there are several subcategories, including: indolent SM, smoldering SM, aggressive SM (ASM), SM with an associated hematologic neoplasm (involving cell lineages other than mast cells), and mast cell leukemia (MCL). ASM and MCL subgroups have poor outcomes with a median survival for MCL being <1 year.[1-3] Therefore, there is an unmet need for novel therapies for these patients. Although the KIT D816V mutation is found in >80% of patients with SM, it does not appear that the KIT D816V mutation alone is sufficient to induce malignant transformation of mast cells. This mutation contributes to increased proliferation and survival of neoplastic MCs, making it an important therapeutic target for SM.[2,3] The US Food and Drug Administration recently approved midostaurin for the treatment of adults with ASM, SM with an associated hematologic neoplasm, and MCL based on response rates and duration of responses. However, in patients with advanced SM, midostaurin does not induce complete remission.[4]

Advances in our understanding of the biology and treatment of SM have been limited not only by the rarity of the disease, but also by the relatively low number of primary patient cells recovered from patients with SM. Unlike acute myeloid leukemia, where leukemic cells become the dominant cell type within the blood and bone marrow, ASM and MCL present with relatively low levels of MCs in peripheral blood and bone marrow.[2,3] Although human MCL cell lines exist, they do not adequately recapitulate the full spectrum of the human disease. To overcome these limitations, Toledo et al generated iPSCs from patients with ASM and MCL. Importantly, KIT D816V iPSCs derived from patients with SM had important features of the human disease. Specifically, these iPSCs showed increased activation of KIT in the absence of cytokine stimulation and increased proliferation and survival of hematopoietic cells upon iPSC differentiation, compared with KIT unmutated iPSCs. Importantly, iPSCs also displayed patient-specific differences in hematopoietic differentiation capacity, demonstrating that patient heterogeneity is maintained when generating iPSCs. The poor prognosis of SM has also been attributed to the presence of mutations commonly found in other hematologic malignancies such as RUNX1, SRSF2, and TET2 mutations, among others.[5] These cooccurring mutations have not been found in MCL cell lines, but were present in patient-derived SM iPSCs with those additional mutations. This is an important advance because this model reflects more accurately the human disease and its complex biology. Although the authors state that 1 limitation of the model is the persistence of the KIT D816V and associated mutations in the iPSCs, the use of CRISPR/Cas9n would allow for deletion of these mutations within the patient-derived iPSCs to further dissect the contribution of each these mutations in disease progression, similar to what have been done in MDS/acute myeloid leukemia iPSCs.[6]

No longer being limited by cell numbers, Toledo et al used patient-derived iPSCs to perform a drug screen to identify novel SM inhibitors. Nintedanib was found to be a highly potent KIT D816V inhibitor, resulting in decreases in cell viability and KIT activation. Induced fit molecular docking studies confirmed preferential targeting of nintedanib for KIT D816V compared with wild-type KIT, thus possibly eliminating some of the negative off-target drug effects associated with TKIs.[1]

Using patient-derived SM iPSCs, Toledo et al have eliminated critical barriers that prevented large-scale drug screens in a rare subset of hematologic malignancy and identified a potential new treatment of patients with SM with a poor prognosis. This study also demonstrates that the use of patient-specific iPSCs is a valuable tool to investigate other hematologic diseases where primary samples are limited to identify novel targets for therapy.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. Toledo MAS, Gatz M, Sontag S, et al. Nintedanib targets KIT D816V neoplastic cells derived from induced pluripotent stem cells of systemic mastocytosis. *Blood.* 2021;137(15): 2070-2084.

2. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood.* 2017; 129(11):1420-1427.

3. Reiter A, George TI, Gotlib J. New developments in diagnosis, prognostication, and treatment of advanced systemic mastocytosis. *Blood.* 2020;135(16):1365-1376.

4. Valent P, Akin C, Hartmann K, et al. Advances in the classification and treatment of mastocytosis: current status and outlook toward the future. *Cancer Res.* 2017;77(6):1261-1270.