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by Christopher J. Gibson and John Koreth

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Molecular assessment and the current limits of post-transplant prognostication for chronic myelomonocytic leukemia

Christopher J. Gibson and John Koreth
Division of Hematologic Malignancies, Dana-Farber Cancer Institute
450 Brookline Ave., Boston MA 02215

Chronic myelomonocytic leukemia (CMML) is the best known and most thoroughly characterized myeloid overlap syndrome.[1] It combines the disorganized hematopoiesis of myelodysplastic syndromes with features of a myeloproliferative neoplasm, specifically an excess of monocytes. CMML has a wide range of prognostic heterogeneity, but like other myeloid stem cell disorders, it can only be cured by allogeneic hematopoietic cell transplantation (HCT).[2]

While CMML has clearly defined pathologic criteria for diagnosis, it is a rare entity.[3] Moreover, given its distinctive features, it is often excluded from prospective clinical studies of both MDS and MPN. As a result, our understanding of CMML's biology and clinical behavior remains limited, particularly for patients who require transplant.

In this issue, Mei et al present the largest molecular assessment of CMML patients undergoing HCT published to date.[4] Among 313 patients, they identified pathogenic somatic mutations in 93%. While there was substantial overlap with mutations recurrently identified in other myeloid disorders, the spectrum and frequency of mutations in this cohort had distinctive features. Compared with a large study of MDS transplant patients,[5] CMML patients had more frequent mutations in *ASXL1* (61% vs 20%), TET2 (35% vs 12%), SRSF2 (31% vs 6%), and *KRAS/NRAS* (33% vs 6%), and fewer mutations in *TP53* (3% vs 19%) and *SF3B1* (3% vs 10%). Compared with a different study of patients undergoing transplantation for myelofibrosis,[6] CMML patients had less frequent mutations in *JAK2* (6% vs 62%), *CALR* (<1% vs 16%), and *MPL* (<1% vs 5%). These findings confirm that CMML has distinctive genetic features compared with other myeloid disorders, which likely contribute to both its myeloid lineage bias and its relatively poor prognosis.

Even when incorporating non-molecular disease features, the rarity of CMML has precluded the publication of a single definitive study of clinical outcomes. Consequently, at least five different prognostic scoring systems have been proposed[7–11] (Table 1). Each of these incorporates a different combination of overlapping clinical and, in some cases, molecular features. None of these systems were developed in transplant-only cohorts, and indeed the authors found that both the GFM and MMM systems

categorized a disproportionate number of patients in this cohort as high-risk, thereby limiting those systems' prognostic value in this setting.

On the other hand, both the CPSS and the newer CPSS-Mol systems retained prognostic value here, but primarily because they accurately predicted treatment-related mortality; both systems performed poorly in predicting post-transplant relapse. For the CPSS, the rate of relapse in the lower three risk groups was nearly identical. Although the rate of relapse was elevated for the high-risk group, this group was comprised of only 13 patients. For the CPSS-Mol, there was no appreciable association between risk group and the rate of relapse, which was highest in the intermediate-1 group and relatively similar in the low, intermediate-2, and high-risk groups. The limited prognostic capacity for post-transplant relapse may reflect the fact that both tools were developed to predict overall survival, not just relapse. It may also reflect the fact that both tools were trained on non-transplant cohorts and therefore may not include variables that are specifically prognostic in the setting of allogeneic transplantation.

The combination of clinical and molecular disease features has proven to have powerful prognostic value in other myeloid diseases, and the authors reasonably hypothesized that the comprehensive molecular profiling of this cohort would improve the accuracy of existing prognostic tools. This proved not to be the case: the CPSS-Mol, which incorporates mutations in 4 genes that are prognostic in the non-transplant setting,[10] was no better at predicting post-transplant outcomes than the CPSS. At face value this is counterintuitive.

On further consideration, however, this finding is not wholly surprising. In other myeloid neoplasms, mutations that confer high risk in unselected patients do not always retain prognostic significance in transplant-only cohorts. This may reflect the higher average risk of patients who require transplantation, as well as the additional heterogeneity introduced by the many clinical variables associated with transplantation. Alternatively, it may indicate that neoplasms with these mutations retain sensitivity to the graft-versus-leukemia effect of transplant, in contrast to other mutations (such as *TP53,* which is rare in CMML) that confer a poor prognosis in both the transplant and non-transplant settings.

A central goal of retrospective risk-stratification studies is the generation of hypotheses to guide future clinical trials and treatment strategies, but there has been a disconcerting lack of agreement among previous studies of CMML transplant patients. No one existing prognostic system has proven consistently superior to the others, and while each has effectively stratified survival in some cohorts, none has been very accurate in predicting other outcomes, particularly relapse. As a registry-based

assessment, the current study has clear advantages over previous single- or even multi-institution studies. Nevertheless, there is still room for future larger collaborative studies to better refine post-transplant risk stratification for this rare, high-risk hematologic malignancy.

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	Year	N	Variables								
			Hbg[a]	WBC or component[b]	Immature myeloid cells	Platelets < 100 x 10^9/L	Marrow Blasts[c]	Cytogenetics[d]	Point mutations[e]	Age > 65	FAB & WHO designations
MDAPS	2002	213	■	■	■		■				
GFM	2013	312	■	■		■			■	■	
MMM	2013	226	■	■	■	■					
CPSS	2013	558	■					■			■
CPSS-Mol	2016	214	■	■			■	■	■		

Table 1. Summary of CMML risk stratification scoring systems. Shown are the variables included in the MD Anderson Prognostic Scoring System (MDAPS),[7] the Groupe Française de Myélodysplasies (GFM) system,[8] the Mayo Molecular Model (MMM),[9] the CMML-specific scoring system (CPSS),[10] and the clinical/molecular CPSS (CPSS-Mol),[11] as well as the year each system was published, and the number of patients (N) included in the respective training cohorts. Hbg: hemoglobin; WBC: white blood cell; FAB: French-American-British classification; WHO: World Health Organization classification.

[a]Hemoglobin < 12 g/dl (MDAPS), ≤ 10 g/dl (GFM, MMM), or transfusion dependency (CPSS, CPSS-Mol)
[b]Total WBC ≥ 15 x 10^9/L (GFM) or ≥ 13 x 10^9/L (CPSS-Mol), absolute lymphocyte count ≥ 2.5 x 10^9/L (MDAPS), or absolute monocyte count ≥ 10 x 10^9/L (MMM)
[c]Marrow blasts ≥ 5% (CPSS-Mol) or 10% (MDAPS)
[d]CMML-specific cytogenetics
[e]*ASXL1* mutations (GFM); *ASXL1*, *NRAS*, *RUNX1*, or *SETBP1* mutations (CPSS-Mol)