

## EDITORIAL



# CALR mutations possess unique prognostic relevance in myelofibrosis—before and after transplant

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The prognostic relevance of karyotype and mutations in acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS) has long been recognized and continues to be heavily promoted [1]. The same is turning out to be true for myelofibrosis (MF), which is a related stem cell-derived myeloid neoplasm with shared genetic signature [2]. Mutations in primary MF (PMF) can be practically organized into three prognostic categories: (i) favorable (*CALR* type 1/like), (ii) unfavorable with karyotype-independent impact (*ASXL1*, *SRSF2*, *U2AF1-Q157*), and (iii) unfavorable with impact that might not be independent of karyotype or other high molecular risk (HMR) mutations (*EZH2*, *IDH1*, *IDH2*, *CBL*, *KRAS*, *NRAS*, *TP53*) [3–7]. These mutations have been incorporated into formal risk models for PMF, including the mutation-enhanced international prognostic systems, MIPSS70 [6] and MIPSS70+ version 2.0 (MIPSSv2) [3], and the genetically inspired GIPSS [8]; the first two include clinical risk factors while GIPSS is based on karyotype and mutations, only. The prognostic relevance of *ASXL1* mutation was more recently reiterated in PMF but not in post-essential thrombocythemia (ET) or post polycythemia vera (PV) MF [9], while *SF3B1* mutation was associated with shortened survival in post-ET/PV but not primary MF [10]. In addition, *EZH2* mutation was recently implicated in leukemic transformation [11] while RAS-pathway mutations were associated with poor response to ruxolitinib therapy [7].

In transplant-eligible patients with PMF (age 70 years or younger), the presence or absence of MIPSS70/v2-recognized mutations, along with other risk factors, enables identification of higher or lower risk disease, with respective 10-year survival rates of 0–10% and 50–86% (Fig. 1) [3, 6]. Based on these estimates, the risk of transplant-related mortality (TRM) from allogeneic hematopoietic stem cell transplantation (AH SCT) is generally considered justified, in patients with higher risk disease, and might also be the case for intermediate-risk disease, if one were to risk early TRM in exchange for the possibility of long-term survival benefit [12]. AH SCT is currently the only treatment modality in MF with the potential to prolong survival, with a large retrospective study reporting 3-year survival, relapse, and non-relapse mortality rates of 58%, 22% and 29%, respectively [13]. Fortunately, the procedure is becoming more and more feasible in older patients and in those without HLA-identical sibling donor [13]. A small number of retrospective studies in MF have also suggested that AH SCT might overcome prognostic adversity from HRM mutations and unfavorable karyotype [14, 15]. The possibility of mutation impact on post-transplant survival in MF has also been suggested and incorporated into the clinical-molecular myelofibrosis transplant scoring system (MTSS), which was derived from patients with either primary or secondary MF, and included *ASXL1* mutation as unfavorable and *CALR* or *MPL* mutations as favorable risk mutations [16].

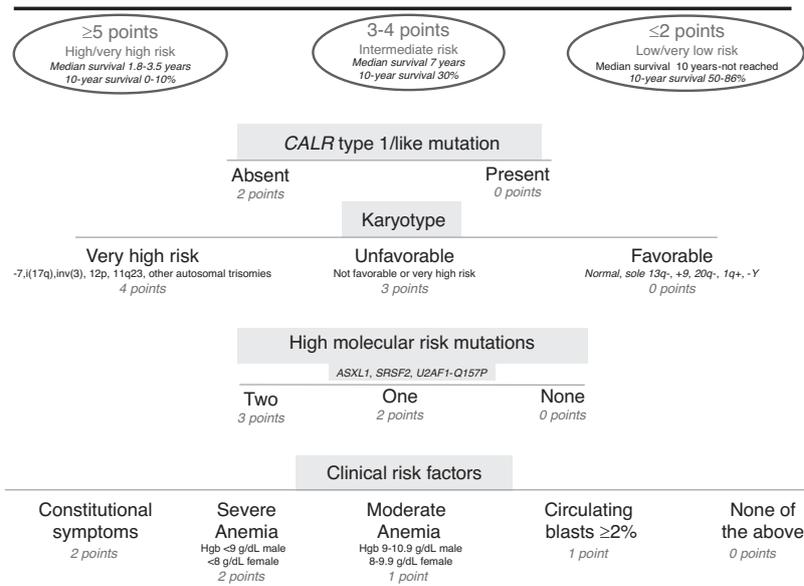
In the current edition of *BMT*, Hernandez-Boluda and colleagues report the European bone marrow transplant (EBMT) centers' experience on 346 relatively young (median age 57.4 years) *CALR*-mutated patients with MF who received AH SCT at multiple European centers between 2010 and 2019 and followed for a median of 40 months [17]; 5-year survival was 63% (vs 50% in the *JAK2*-mutated comparative cohort) and even better at 71% in those receiving busulfan-containing conditioning regimens; comparison to a *JAK2*-mutated cohort revealed better outcome in terms of overall survival, non-relapse mortality (NRM), and relapse rate; in multivariate analysis, older age was the only variable associated with inferior survival, which is noteworthy considering the older age distribution of the comparator *JAK2*-mutated cohort. As an explanation for the post-transplant survival difference between *JAK2* and *CALR* mutated cohorts, the authors entertained the possibility of higher frequency of HMR mutations in the former [18]. In a much smaller study of *MPL*-mutated MF patients undergoing AH SCT ( $N = 18$ ) [19], 5-year survival rate of 84% and 1-year TRM of 17% were reported; the only patient who relapsed in the study harbored HRM mutations (*ASXL1* and *EZH2*); furthermore, among 5 patients in whom post-transplant molecular monitoring was performed, 4 achieved complete clearance of *MPL* mutation, at time of engraftment, with the 5th patient achieving the particular milestone by day 100; the molecular remissions were accompanied by full donor chimerism [19].

The study by Hernandez-Boluda et al. [17] is molecularly truncated by its lack of distinction between type 1/like (*CALR*-1) and type 2/like (*CALR*-2) *CALR* mutations and information on HMR mutations, including *ASXL1*, *SRSF2*, *U2AF1-Q157* and others. This is not a trivial oversight, considering the fact that *CALR*-1-mutated MF patients live significantly longer, compared to their *CALR*-2 and *JAK2*-mutated counterparts [20–22]. Furthermore, the presence of *CALR* mutation, in general [23], and *CALR*-1 mutation, in particular [24], has been shown to attenuate but not erase the prognostic gravity of HMR mutations and unfavorable karyotype [24]. Accordingly, HMR mutations and karyotype should always be accounted for during survival analysis of *CALR*-mutated MF. In addition, collection of molecular data during monitoring of measurable residual disease (MRD) and at time of overt, cytogenetic, molecular, or chimerism relapse, is highly advised, in order to gauge their relevance and vulnerability to therapeutic interventions, including donor lymphocyte infusions (DLI) [25–27]. In a recent study of 37 MF patients who received DLI after either molecular ( $N = 17$ ) or hematologic ( $N = 20$ ) relapse, complete molecular response was achieved in 88% vs 60% of those with molecular vs hematologic relapse and 6-year survival rates were 77% and 32%, respectively; these observations underline the importance of post-transplant molecular monitoring and early therapeutic intervention at the time of molecular relapse.

At present, non-transplant treatment options in MF are palliative in scope and should not distract from aggressively pursuing AH SCT, when it is indicated. The presence of *CALR*-1 in MF portends a

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Mutation/karyotype-enhanced international prognostic scoring system for primary myelofibrosis (MIPSSv2)



**Fig. 1 Risk stratification in primary myelofibrosis.** Mutation and karyotype enhanced international prognostic system for primary myelofibrosis.

relatively less aggressive disease tempo, characterized by progressive splenomegaly and anemia, which appear to be sensitive to treatment with JAK2 inhibitors [28]; however, we are inclined to favor transplant in the presence of unfavorable karyotype or HMR mutations [29], as reflected in our current treatment algorithm for MF [2]. To that effect, we acknowledge the possibility of a more favorable post-transplant outcome in CALR vs JAK2 mutated patients with MF [16, 17]. A particularly worrisome scenario involves the presence of multi-hit TP53, where AHSCT might not overcome its detrimental effect on survival; in a recent communication, 6-year post-transplant survival rates were 25% for multi-hit vs 56% single-hit vs 64% wild-type TP53 [30]; in the particular study, CALR mutations were reported in 17% of 58 patients with multi-hit TP53 but information on further distinction between CALR-1 and CALR-2 was not available. Regardless, additional studies with larger number of informative cases are needed to accurately determine the impact of CALR-1 mutation on post-transplant survival, in the setting of multi-hit TP53 and/or other HMR mutations.

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#### AUTHOR CONTRIBUTIONS

Both authors were involved in writing this editorial.

#### COMPETING INTERESTS

The authors declare no competing interests.

#### ADDITIONAL INFORMATION

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