When Two Roads Diverge: Genetically inspired prognostic scoring system (GIPSS) outperforms DIPSS in myelofibrosis patients where the two risk models widely differ

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Introduction

- Prognostic risk models are increasingly incorporating molecular information.
- The Genetically Inspired Prognostic Scoring System (GIPSS) for myelofibrosis (MF) was recently published and relies solely on genomic information.
- The potential for disagreement between “new” and “old” prognostic models increases as overlap decreases between the prognostic inputs.
- In cases where prognostic models widely differ, risk stratification and patient counseling can be difficult.

Objectives

- To validate GIPSS in an independent cohort of MF patients.
- To identify the frequency of disagreement between GIPSS and DIPSS model.
- To analyze the cases in which significant disagreement occurs and assess the performance of GIPSS and DIPSS in these cases.

Methods

- MF patients annotated for GIPSS and DIPSS modeling identified from large institutional MF database.
- Cases with ‘widely differing’ risk scores defined when GIPSS and DIPSS disagreed by ≥ 2 risk groups (i.e. int-1 by GIPSS and high risk by DIPSS, etc.)
 - GIPSS-up-staged = ‘GUS’
 - DIPSS-up-staged = ‘DUS’
- Overall survival (OS) and leukemia-free survival (LFS) measured from date of diagnosis

GIPSS Validation

Figure 1. Overall survival (A) and Leukemia-Free Survival (B) based on GIPSS prognostic system in independent cohort of MF patients

Patient Characteristics

Patient Characteristics	DIPSS up-staged (DUS)	GIPSS up-staged (GUS)
	n (%)	n (%)
	n = 19	n = 20
Median age at diagnosis (y)	71	66
Male sex	9 (47)	10 (50)
Primary myelofibrosis	12 (63)	16 (80)
Constitutional symptoms	11 (58)	4 (20)
Anemia (Hgb < 10 g/dL) or transfusion	18 (95)	2 (10)
Leukocytosis (WBC > 25,000/ μ L)	10 (53)	4 (20)
Circulating blasts $\geq 1\%$	14 (74)	5 (25)
Thrombocytopenia (<100,000/ μ L)	4 (21)	4 (20)
Monocytosis (>1,000/ μ L)	3 (16)	6 (30)
Median adjusted LDH (LDH/U/LN)	2.9	2.2
Splenomegaly	14 (74)	15 (75)
JAK2 V617F mutated	7 (37)	14 (70)
MPL mutated/MPL wt	0 (0)	1 (5)
Type 1 CALR mutated	12 (63)	0
Type 2 CALR mutated	0 (0)	2 (10)
“Triple-Negative” (JAK2, MPL, CALR v	0 (0)	3 (15)
ASXL1 mutated	2 (11)	9 (45)
SRSF2 mutated	0	10 (50)
U2AF1 Q157 mutated	0	2 (10)
≥ 2 mutations (ASXL1, SRSF2, U2AF1 C	0 (0)	7 (35)
Cytogenetics Risk Group		
Very High Risk	0 (0)	7 (35)
Unfavorable	0 (0)	4 (20)
Favorable	19 (100)	9 (45)

Discordance in Risk Models

Figure 3. Discordance of risk-stratification between GIPSS and DIPSS. Stars highlight groups where risk scores differ by ≥ 2 groups.

Conclusions

- Intra-patient prognostic variability has become increasingly prevalent as common inputs from risk models have decreased.
- GIPSS was shown to be valid in our cohort of MF patients.
- GIPSS appeared to outperform DIPSS in cases where the two models disagreed.
- Consideration of allogeneic hematopoietic cell transplant (AHCT) is reasonable based on high-risk molecular features alone.

References

- Tefferi A, Guglielmelli P, Nicolosi M, et al: GIPSS: genetically inspired prognostic scoring system for primary myelofibrosis. *Leukemia*, 2018

Outcomes in Cases where GIPSS and DIPSS disagree

Figure 2. OS (A) of GUS and DUS cohorts overlaying OS by DIPSS. LFS (B) for DUS and GUS patients.