ELSEVIER

Blood 142 (2023) 4543–4544

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Final Report: Somatic Mutations and HMGCLL1 Haplotype Are Not Associated with Molecular Relapse-Free Survival in Patients with Chronic Myeloid Leukemia Who Attempt Treatment-Free Remission

Maria Agustina Perusini, MD[1], *Katia Pagnano, MD PhD*[2], *Carolina Pavlovsky, MD*[3], *Beatriz Moiraghi, MD*[4], *Ana Varela, MD*[4], *Michele Bianchini*[5], *Carmen Fava, MDPhD*[6], *Jiří Mayer, MD*[7], *Daniela Žáčková, MD*[8], *Anežka Kvetková, MD*[9], *Tomáš Jurček, PhD*[9], *Ivana Ježíšková, PhD*[9], *Ana Beatriz Pascoal Lopes*[2], *Gislaine Borba Oliveira, MD Msc*[10], *Carmino De Souza, MD PhD*[10], *Amirthagowri Ambalavanan*[11], *Anthea Travas*[11], *Jaeyoon John Kim*[12], *Danielle Pyne*[11], *Jessie Medeiros*[11], *Sagi Abelson*[13], *Dennis Dong Hwan Kim, MD PhD*[14]

[1] Princess Margaret Cancer Centre / University Health Network, Toronto, Canada
[2] Hematology and Hemotherapy Center, University of Campinas, Campinas, Brazil
[3] FUNDALEU, Buenos Aires, Argentina
[4] Hospital Jose Maria Ramos Mejia, Buenos Aires, Argentina
[5] CIO-FUCA, Instituto Alexander Fleming, Buenos Aires, Argentina
[6] Department of Clinical and Biological Sciences, University of Turin, Torino, Italy, Orbassano, Italy
[7] University Hospital Brno and Masaryk University, Brno, Czech Republic
[8] Dpt. of Internal Medicine Hematology and Oncology, University Hospital Brno and Masaryk University, Brno, Czech Republic
[9] Dpt. of Internal Medicine Hematology and Oncology, University Hospital Brno and Masaryk University, Brno, Czech Republic
[10] Hematology and Hemotherapy Center, University of Campinas, Campinas, Brazil
[11] University Health Network, Toronto, Canada
[12] Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada
[13] University Health Network, Princess Margaret Cancer Centre, Toronto, Canada
[14] Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

Background

Chronic myeloid leukemia (CML) is a clonal hematopoietic stem cell disorder resulting from the *BCR::ABL1* rearrangement. Patients with CML have a comparable life expectancy to that of age-matched individuals in the general population when they achieve an optimal response with tyrosine kinase inhibitor (TKI) therapy. With the aim of improving the quality of life of patients who are significantly affected by drug-related adverse events and financial burden, the practical goal of CML treatment has shifted to treatment-free remission (TFR), defined as the successful discontinuation (DISC) of TKI therapy without losing leukemia control. TKI treatment DISC is a safe procedure but requires appropriate candidate selection and frequent molecular monitoring. Several biomarkers were investigated, but no definite biomarker has yet been successfully identified and validated. We have investigated somatic mutations before TKI discontinuation and HMGCLL1 haplotype as a potential biomarker for TFR, given that they were previously described as predictors of CML outcomes.

Patients and methods

A total of 155 patients who attempted TKI discontinuation for TFR from 5 countries were included: Canada (n=71), Brazil (n=30), Argentina (n=28), Italy (n=23), and the Czech Republic (n=3). We applied our in-house single molecule-molecular inversion probe (smMIP) panel which is a barcoded error-corrected DNA-based sequencing with a limit of detection up to 0.2%. The panel encompasses 40 genes with 332 amplicon probes: epigenetic modifiers (n=7), activation signaling (n=12), myeloid transcription factor (TF; n=5), spliceosome (n=3), tumor suppressor (n=3), cohesion (n=4), miscellaneous (n=3) and 8 HMGCLL1 single nucleotide polymorphisms (SNPs). Two groups were constructed based on these eight SNPs: group 1: CTCAGGCA (C- haplotype) or group 2: ACGTAATG (A-haplotype). Samples were collected prior to TKI DISC when patients met the criteria for TFR attempt. Molecular relapse-free survival (mRFS) was calculated from the date of TKI DISC to the date

of confirmed loss of deep molecular response (DMR). Loss of DMR includes single-time loss of major molecular response (MMR) or two consecutive episodes of loss of molecular response 4 log or deeper response (MR4). Kaplan-Meier survival estimate was used to evaluate mRFS and Cox's proportional hazard regression model was applied.

Results

The median MR4 duration prior to TKI DISC was 7.2 years (range 4.7-9.3), while overall TKI treatment duration was 8.5 years (range 6.0-11.6). With a median follow-up of 831 days (range: 460-1,415), out of the 155 patients, 68 (43.9%) lost response, among whom 6 lost MMR only, 12 lost MR4 only, and 50 lost MMR and MR4, both. Median time to MMR loss was 95 days (range 83.5-137). A total of 71 mutations were detected in 51 patients (32.9%). *TET2* mutation was the most frequent mutation, detected in 17 cases (24%) followed by *ASXL1* (n=14; 20%) and DNMT3A (n=12; 17%). When grouped by relevant biological pathways involved, mutations in epigenetic genes (n=42, 61%) were the most frequently involved. mRFS rate was 64% (95% CI [55.8-71.1%]) and 56% [48.2-64.0%] at 6 and 12 months, respectively. During the univariate analysis, no significant difference was observed in mRFS according to the presence, number, or type of somatic mutations, or the HMGCLL1 haplotype. Additionally, there were no significant differences in mRFS based on age, sex, Sokal risk group, line of TKI therapy, or TKI drug type prior to TKI DISC. However, MR4 duration prior to TKI DISC was associated with mRFS rate: patients with≥7.3 years (n=71) showed higher mRFS: 74.09% [62.05-82.82%] compared to those <7.3 years (n=74) with mRFS rate of 44.36% [32.54 -55.51] (p <0.01, HR 0.36 [0.21-0.63]). In addition, a longer duration of TKI treatment before TKI DISC was associated with higher mRFS: patients with ≥ 8.3 years of treatment (n=85) showed 71.8% mRFS [60.4-80.4], compared to 42.5% mRFS [30.5-54.0%] in those with <8.3 years (n=71) (p<0.01, HR 0.48 [0.31-0.74]). Multivariate analyses for mRFS confirmed that MR4 duration and the total duration of TKI treatment before TKI DISC were associated with TFR outcomes, but not the presence of epigenetic mutations, any mutation, or HMGCLL1 haplotype (Table1).

Conclusion

In CML, somatic mutations before attempting TFR are frequently observed. However, our current study does not support their prognostic significance as TFR-predictive biomarkers.

Disclosures Pagnano: *Novartis, Pfizer, EMS, Pintpharma:* Speakers Bureau; *Novartis, Pfizer:* Honoraria. **Pavlovsky:** *Pfizer:* Speakers Bureau; *Novartis:* Speakers Bureau; *Bristol Myers Squibb:* Speakers Bureau. **Moiraghi:** *Novartis:* Speakers Bureau; *Pfizer:* Speakers Bureau; *Takeda:* Speakers Bureau. **Mayer:** *BeiGene:* Research Funding; *MSD:* Research Funding. **Žáčková:** *Astra Zeneca:* Other: travel grant; *Pfizer:* Honoraria, Other: travel grant, Speakers Bureau; *Angelini Pharma:* Consultancy, Honoraria, Other: travel grant, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel grant, Speakers Bureau. **Oliveira:** *Janssen:* Speakers Bureau. **Kim:** *Pfizer:* Consultancy, Honoraria, Research Funding; *Paladin:* Consultancy, Research Funding; *BMS:* Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding.

Table 1	Univariate analysis			Multivariate analysis
	mRFS at 1 year, % (IC95)	p	HR (IC 95%)	HR (IC 95%), p
Male (n=73) Female (81)	58.96 (46.31-69.58) 55.07% (43.55-65.17)	0.34	1.00 1.26 (0.77- 2.04)	
Age =<65 (n=119) >65 (n=35)	54.51% (44.92-63.13) 61.87% (43.54 -75.79)	0.60	1.03 (0.744-1.44) 1.00	
Sokal risk score Low (n=64) Intermediate (n=31) High (n=11)	61.54% (30.83-81.84) 57.76% (44.14-69.19) 43.64% (14.70-69.86)	0.76	1.00 1.03 (0.744-1.44)	
First line TKI (n=115) **>First line TKI (n=40)**	54.36% (44.68-63.06) 62.79% (45.32-76.06)	0.31	1.00 1.02 (0.60-1.73)	
Imatinib (n=134) **2GTKI (n=21)**	53.16% (43.26-62.09) 54.78% (34.16-71.37)	0.95	1.00 1.01 (0.56- 1.83)	
HMGCCL1 Haplotype A (72) C (67)	58.52% (46.08-69.03) 58.81% (45.91-69.62	0.78	1.00 1.46 (0.80-2.66)	1.46 (0.80-2.66), p=0.21
Any mutation (51) **No mutation (104)**	63.20% (48.12 -74.99) 53.25% (43.03 -62.45)	0.46	1.00 0.76 (0.43- 1.36)	0.93 [0.52-1.67], p= 0.82
Epigenetic mut, N= 42 **No epigenetic mut, N=113**	57.78 (40.60-71.62) 56.09% (46.37-64.72)	0.72	1.00 1.10 (0.64-1.88)	1.20 (0.68-2.13), p= 0.51
TKI duration <8.3 years (n=71) >=8.3 years (n=85)	42.50% (30.49-53.99) 71.83% (60.41-80.47)	<0.01	1.00 0.48 [0.31-0.74]	0.84 [0.77-0.91], p<0.01
MR4 duration <7.3 years (n=74) >=7.3 years (n=71)	44.36% (32.54 -55.51) 74.09% (62.05-82.82)	<0.01	1.00 0.36 [0.21-0.63]	0.81 [0.74-0,90], p <0.01

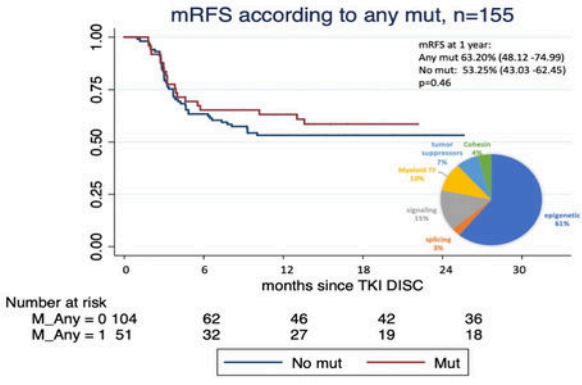

Figure 1

https://doi.org/10.1182/blood-2023-189797