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631.MYELOPROLIFERATIVE SYNDROMES AND CHRONIC MYELOID LEUKEMIA: BASIC AND TRANSLATIONAL

Interleukin 10 (IL10) and IL15 Significantly Decreased in Chronic Myeloid Leukemia Patients Presenting with Tyrosine Kinase Inhibitor (TKI) Withdrawal Syndrome (TWS). Results from the Prospective, Explorative and Multicenter « Kiwis » Study Designed for TWS. *Clinicaltrial.Gov ID: NCT03996096; Study Number: 18-206*

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Aims

Treatment-free remission (TFR) has been included in practice guidelines as a new management goal for chronic myeloid leukemia (CML) patients, implying discontinuation of tyrosine kinase inhibitors (TKI). Paradoxically, TKI discontinuation gives rise to musculoskeletal pain and/or flushing, known as TKI withdrawal syndrome (TWS), in approximately 25% of patients with a reported median time of occurrence of 6 weeks. This syndrome is assumed to be caused by cytokine release, mast cell regrowth, or reactivation of an underlying inflammatory state. The KIWIS trial aimed at assessing these hypotheses by prospectively dosing biological markers before and after TKI discontinuation looking for any significant variation to be correlated to TWS. The secondary objectives were: description of the manifestations of TWS, assessment of TFR. Here, we will only focus on the primary objective.

Methods

The KIWIS study (*Clinicaltrial.govID:* NCT03996096) was a multicenter prospective cohort of adult CML patients who had been treated with TKIs for at least 5 years, with a minimum of 2 years in deep molecular response (MR4.5). Patients with a history of inflammatory disease, those taking steroids, or those unable to complete the short form of the Brief Pain Inventory (BPI) were not included. BPI was used to assess pain severity and its impact on daily functioning. The arithmetic mean of the four severity items was used to score the severity of pain at different time points and identify patients with TWS. Blood samples were collected at baseline (M0), 1 month (M1), 2 months (M2), and 3 months (M3) post-discontinuation of TKI. We explored the following biomarkers: CRP, Rheumatoid Factor, tryptase, calcium, phosphate, Creatin Kinase, IL2, IL6, IL10, TGFβ, TNFα, IFNΥ, VEGF, PDGFβ, IL15, Crosslaps (CTX), Collagen pro-peptide type 1 (PINP1), and parathormone. Each patient served as their own control, and any variation of a biomarker by 20% from baseline was considered clinically significant. The BPI form

was completed at the same time points as BCR-ABL follow-up: M0, M1, M2, M3, M4, M5, M6, M8, M10, and M12 following TKI withdrawal. The study was powered to include 50 patients.

Results

Out of the 50 patients, 16 (32%) developed TWS within the first 3 months, with a median onset time of 2 months. Patients' characteristics are displayed in table1. The baseline characteristics of patients in the TWS and non-TWS groups were similar. The duration of CML treatment was significantly longer in TWS patients compared to non-TWS patients (median: 9, Interquartile Range (IQR) [7-13] vs 7, IQR [6-8], p=0.039, respectively). No predictive factor for developing TWS were observed considering patients' characteristics and BPI scores at M0 in the univariate analysis. At M0, there were no significant differences between the two groups in terms of the concentration of each specific biomarker. In the TWS group, IL10, IL15, and IFNϒ levels decreased between inclusion and the M3 time point. For IL10, the median was 0.18 pg/ml (IQR: 0.12; 0.31) vs. 0.12 (IQR: 0.08-0.17), p=0.002; for IL15, 2.30 pg/ml (IQR: 1.77; 2.92) vs. 1.81 (IQR: 1.48; 2.25), p=0.026; and for IFNϒ, 5.92 pg/ml (IQR: 4.17; 12.49) vs. 4.24 pg/ml (IQR: 2.64; 7.99), p=0.036. In the non-TWS group, no significant differences were found. Changes in IL10 were positively correlated with changes in IL15 from M0 to M3 in all patients: r=0.42, p=0.009. No significant variations were observed in the two patient groups regarding the other biomarkers.

Figure 1 exemplifies the evolution of IL10 (A: in TWS patients; B: in non-TWS patients) at M0 and M3. One patient missed the M3 time point sample.

Conclusion

This is the first study designed to prospectively investigate biomarkers associated with TWS. Our results suggest that TWS is not a cytokine-release-like syndrome but a distinct entity significantly associated with a decrease in IL10, IL15, and IFNϒ concentrations. It is worth noting that IL10 is an anti-inflammatory cytokine known to reduce pain; the role of IL15 and IFNϒ remains to be clarified. We hope that this study will pave the way for further investigations to fully understand the pathophysiology of TWS.

Disclosures Johnson-Ansah: *GILEAD:* Consultancy; *PFIZER:* Consultancy; *NOVARTIS:* Consultancy, Honoraria. **Damaj:** *Takeda, Blueprint Medicines Corporation, and Thermo Fisher:* Consultancy, Other: Advisory Role; *Takeda, AbbVie and Pfizer:* Other: Travel and Accommodation Expenses. **Nicolini:** *INCYTE BIOSCIENCES:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Novartis:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *SUN pharma:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BMS:* Honoraria, Membership on an entity's Board of Directors or advisory committees. **Berger:** *NOVARTIS:* Consultancy, Research Funding; *NOVARTIS:* Research Funding; *PFIZER:* Consultancy, Research Funding; *INCYTE:* Research Funding.

Table1: patients' characteristics

	All (n=50)	TWS (n=16)	No-TWS (n=34)	p-value
Baseline characteristics				
Male, n(%)	31 (62)	10 (62)	21 (62)	0.97
Age (years), median (IQR)	62 (53 - 68)	56 (47 - 75)	64 (57 - 69)	0.20
Score de Sokal, n(%)				
Low risk	13 (35)	5 (38)	8 (33)	
Intermediate risk	8 (22)	2 (15)	6 (25)	0.83
High risk	16 (43)	6 (46)	10 (42)	
Type of TKI at the time of discontinuation, n(%)				
Imatinib	27 (54)	9 (56)	18 (53)	
Dasatinib	9 (18)	2 (12)	7 (21)	
Nilotinib	10 (20)	3 (19)	7 (21)	0.74
Bosutinib	3 (6)	2 (12)	1 (3)	
Ponatinib	1 (2)	0 (0)	1 (3)	

Figure 1

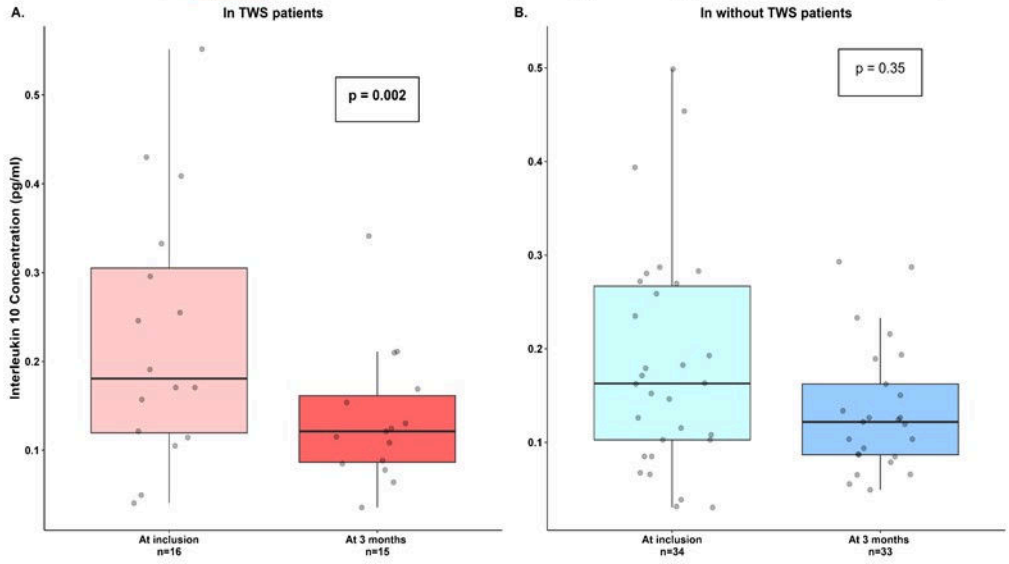

Figure 1

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