XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026 Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P022

Chronic myeloid leukemia

# FOURIER-TRANSFORM INFRARED SPECTROSCOPY ANALYSIS OF PLASMA-DERIVED EXTRACELLULAR VESICLES AS A TOOL TO DETECT TKI-RELATED TOXICITY IN CHRONIC MYELOID LEUKEMIA PATIENTS: A PRELIMINARY STUDY

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Chronic myeloid leukemia (CML) is effectively treated with several tyrosine kinase inhibitors (TKI) now widely available. As patients who achieve an optimal response now reach near-normal life expectancy, maintaining quality of life (QoL) during the often-lifelong therapy has become increasingly important, as symptom burden strongly affects not only QoL but also treatment adherence and therapeutic outcomes. TKI intolerance leads to a switch in therapy in about 20% of patients within the first three years of treatment. Therefore, early detection of TKI-related toxicity or adverse effects (AEs) can be crucial to prevent severe complications and enable timely management. Yet, AEs are often assessed in trials where survival or disease control are the primary endpoints, resulting in many symptoms being underreported. In this context, extracellular vesicles (EV) might emerge due to their ability to transfer bioactive molecules between cells, acting as molecular messengers. EV are released by virtually all cell types, mirroring systemic physiological and pathological condition and potentially providing insights into TKI-related AEs. To analyze EV heterogeneity, Fourier-transform infrared spectroscopy (FTIR-S) offers a label-free and rapid approach to uncover their molecular composition. In this work, we employed FTIR-S to detect subtle differences in EV composition on a preliminary cohort of CML patients (pts).

EV were isolated from plasma samples via commercial kit, including 52 pts under TKI treatment who had achieved at least a major molecular response, 7 pts at diagnosis, and 10 healthy controls. For FTIR-S, 3 µL of sample was deposited onto a diamond window and dried with nitrogen. Spectra were recorded in three technical replicates and analyzed using principal component analysis (PCA) to identify patterns and differences in EV composition.

**Results:** show that PCA effectively discriminates EV from pts at diagnosis and healthy controls, confirming its potential in the CML setting. Moreover, healthy subjects and pts at diagnosis cluster separately from those under TKI therapy. Figures indicate that some TKI-treated pts may overlap with the healthy cluster, particularly those treated with ponatinib or bosutinib. However, it should be noted that AEs are shared across different TKI and are often patient-specific, potentially influencing EV composition and the resulting clustering patterns.

In this work we confirm the potential of FTIR-S as a powerful tool for the analysis of plasma-derived EV. This approach may enable the detection of differences in EV composition that reflect TKI-related toxicity, without the need for complex sample preparation. These are preliminary results that require validation in a larger and well-characterized cohort to verify whether the technique can discriminate samples not based on the administered TKI, but rather on the onset of specific AEs or toxicities, with the ultimate goal of assessing its potential for early detection.

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| Therapy | |
|---|---|
| Imatinib | 14/52 (27%) |
| Dasatinib | 11/52 (21%) |
| Nilotinib | 15/52 (29%) |
| Bosutinib | 7/52 (13%) |
| Ponatinib | 5/52 (10%) |