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632.CHRONIC MYELOID LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Tyrosine Kinase Inhibitor Withdrawal Syndrome in Chronic Myeloid Leukemia Patients Participants of Two Discontinuation Clinical Trials

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Discontinuation of tyrosine kinase inhibitors (TKI) is currently one of the main goals in CML treatment. One of the known adverse events after TKI discontinuation is withdrawal syndrome (WS), which can occur in about 30% of patients (pts), characterized by musculoskeletal pain that begins or worsens weeks after interruption and may be more severe in some cases, but rarely leading to the need for TKI reintroduction. Some studies suggest TKI dose reduction or optimization before stopping treatment may reduce WS rates.

Aims: To estimate the incidence of WS after TKI discontinuation in CML in two clinical trials and to correlate the incidence of these events with patients' characteristics and molecular relapse-free survival (MRFS).

Methods: We analyzed two cohorts of CML patients of two prospective, single-arm, phase II clinical trials: EDI-PIO (Clinicaltrials.gov: NCT02852486) and DES-CML (ReBEC UTN code **:** U1111-1252-7312). In both trials, inclusion criteria were CML in the chronic phase, treated with TKI for at least three years, and with deep molecular response (MR4.5) for two years. In the first trial, TKI was discontinued after using three months of pioglitazone, and in the DES-CML trial, after reducing the dose of the TKI by 50% for six months before discontinuation. TKI was reintroduced if the patient lost MR4.0 (EDI-PIO trial) or major molecular response (MMR) (DES-CML trial). Adverse events related to WS were evaluated until the fourth month after discontinuation. WS was defined as the onset of new musculoskeletal pain and/or an increase in pre-existing pain and/or the need to start any pain medication. The adverse event classification followed the Common Terminology Criteria (CTCAE-Version 4.0), musculoskeletal and connective tissue disorder. The data were collected and stored using the REDcap Platform (by Vanderbilt). MRFS was defined by discontinuation date until the last seen date or loss of MR4.0/MMR. The Kaplan-Meier method was applied for OS, whereas Log-Rank tests were applied to compare its curves. All statistical analysis were done by IBM-SPSS v. 24 and considered significant p-value $< 5\%$.

Results: Between September 2016 and April 2023, we analyzed 63 patients, 32 from the DES-CML study and 31 from the EDI-PIO trial. The median age at discontinuation was 58 years (24-79), 59% male, 52% Sokal low-risk, 35% intermediate, and 13% high; at discontinuation, 94% of the patients were using Imatinib, 3% Dasatinib, 1.5% Bosutinib and 1.5% Nilotinib. The median duration of TKI treatment until discontinuation was 10 years (3-20). Withdrawal syndrome occurred in 41% of cases and was more frequent in females (58% vs. 42%, P=0.02). Fourteen pts from the EDI-PIO study (45%) and 12 (37.5%) from DES-CML developed WS (P=0.61). According to CTCAE, the events were classified as grade 1, 36%, and 33%, while grade 2 was 57% and 58%; and grade 3 was 7% and 8% (P=0.90), respectively, in EDI-PIO and DES-CML trials. Symptoms started at month 1 in 20% of the patients and 73% in months 2 and 3. Seventeen (30%) pts used anti-inflammatory drugs, analgesics, steroids, or muscle relaxants (64% EDI-PIO vs. 66% DES-CML, P=0.90). There was no need to reintroduce TKI for treating WS. Molecular relapse free-survival (MRFS) at 12 months was 72% (95% CI 60-84%), with no difference by protocol (75% DES-CML, 70% EDI-PIO). MRFS at 12 months was 73% and 74% in the group with or without WS, respectively (P=NS).

Conclusions: The incidence and severity of WS were similar in the two trials, corroborating data from the literature. WS was more frequent in females. The dose reduction did not reduce WS rates. However, this condition was self-limited and managed with drugs, without reintroducing TKI. There was no difference in MRFS between the groups with or without WS.

Disclosures Palma: *Pfizer:* Speakers Bureau. **Oliveira:** *Janssen:* Speakers Bureau. **Pontes:** *Pfizer:* Speakers Bureau; *Novartis:* Speakers Bureau. **Pagnano:** *Pintpharma:* Speakers Bureau; *EMS:* Research Funding, Speakers Bureau; *Pfizer:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau.

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