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ABSTRACT N. PO13

MONITORING OF ANTI-FACTOR XA ACTIVITY LEVELS IN PATIENTS TREATED WITH DIRECT ORAL ANTICOAGULANTS AND CONCOMITANT TYROSINE KINASE INHIBITORS AGENTS: A MONOCENTRIC EXPERIENCE.

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Background and Aims:
Direct oral anticoagulants (DOACs) are increasingly used in patients with haematological malignancies for the treatment of venous thromboembolism (VTE) and for primary prophylaxis in non-valvular atrial fibrillation (NVAF). Tyrosine kinase inhibitors (TKIs), frequently prescribed for specific myeloid and lymphoid neoplasms, share the CYP3A4 metabolic pathway with DOACs, raising concerns about potential drug-drug interactions. These concerns are particularly relevant in the haematological setting, where clinical data remain limited. This study aimed to evaluate the safety and efficacy of DOAC therapy when administered concomitantly with TKIs, using anti-factor Xa (anti-Xa) activity monitoring to assess potential pharmacokinetic interactions and guide dose adjustments.

Methods:
We conducted a monocentric retrospective-prospective study including 18 patients with haematological malignancies treated with both DOACs and TKIs between November 2022 and September 2024. Anti-Xa activity was measured via chromogenic assay after a median of 13 months (range 0.13–53.3) of concomitant therapy, and results were used to guide DOAC dose adjustments. Adverse events (AEs) were classified as bleeding (B-AEs) or thrombotic (T-AEs).

Results:
Among the study population (Table 1), 9/18 patients (50%) were receiving DOACs for VTE and 9/18 (50%) for NVAF. Five NVAF patients (56%) were on reduced-dose DOACs due to advanced age, renal impairment, low body weight, or prior bleeding events. Anti-Xa activity was in-range in 13/18 patients (72%), above-range in 4/18 (22%), and below-range in 1/18 (6%). B-AEs occurred in 2/13 patients (15%) with in--range levels and in 2/4 (50%) with above-range levels. The patient with below-range anti-Xa activity experienced a T-AE while on reduced-dose DOAC for secondary VTE prophylaxis and was subsequently managed with dose escalation. Notably, this patient did not develop any B-AEs after the dose increase, despite concomitant clopidogrel therapy.
Following assay results, DOAC doses were reduced in all patients with above-range anti-Xa levels, regardless of bleeding history. No major B-AEs or T-AEs were reported during a median post-assay follow-up of 5 months (range 1.1–20.4). Two minor B-AEs occurred in patients receiving Bruton Tyrosine Kinase inhibitors (BTKis), despite in-range anti-Xa levels, and required only temporary BTKi interruption. One patient, initially treated with apixaban 5 mg twice daily and ruxolitinib, maintained therapeutic anti-Xa activity but developed supratherapeutic levels after switching to fedratinib, a moderate CYP3A4 inhibitor, necessitating DOAC dose reduction.

Conclusions:
Combination of DOACs and TKIs appears generally safe, with most patients achieving appropriate anti-Xa levels. Dose adjustments following anti-Xa assays helped prevent adverse events and maintain treatment efficacy, highlighting the potential need for anti-Xa activity assessments in managing complex drug interactions. Furthermore, patients on BTKis demonstrated a higher incidence of minor B-AEs compared to those on other TKIs (p=0.002), likely due to the off-target effects of BTKi. Ongoing research and further studies with larger patients' cohorts and extended follow-up are needful to validate these findings and enhance safety protocols for prescribing DOACs alongside TKIs.

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patients' characteristics at the time of the anti-Xa activity chromogenic assay

CHARACTERISTICS	N (%)
Patients	18 (100)
Sex, male / female	7 / 11 (39 / 61)
Median age, years (range)	72 (52.7 – 85.2)
Median treatment (*) time before the assay, months (range)	13 (0.5 – 53.3)
Median follow-up time after the assay, months (range)	5.0 (1.1 – 20.4)
Anticoagulant treatment:	
- Edoxaban	4 (23)
- Apixaban	11 (61)
- Rivaroxaban	3 (16)
- Dabigatran	0 (0)
Reason for anticoagulant treatment:	
- Acute treatment of VTE	0 (0)
- Long-term treatment of VTE	4 (23)
- Secondary prophylaxis of VTE	5 (27)
- NVAF	9 (50)
Concomitant hematological disease:	
- JAK2+ mieloproliferative disorders	8 (45)
- Chronic myeloid leukemias	5 (27)
- Non-Hodgkin Lymphomas and Chronic Lymphatic Leukemias	3 (17)
- Ph+ acute lymphoblastic leukemias	2 (11)
Concomitant TKI treatment (**):	
JAK2 inhibitors:	**9 (48)**
- Ruxolitinib	8 (43)
- Fedratinib	1 (5)
BTK inhibitors:	**3 (15)**
- Acalabrutinib	2(10)
- Ibrutinib	1 (5)
BCR/ABL inhibitors:	**7 (37)**
- Imatinib	4 (22)
- Nilotinib	2 (10)
- Asciminib	1 (5)

(*) Concomitant DOAC and TKI administration

(**) A total of 19 anti-Xa activity assays were performed in 18 patients. One patient underwent two assays due to a change in TKI therapy during follow-up.

Abbreviations: DOAC, Direct oral anticoagulants; TKI, Tyrosine kinase inhibitors; VTE, venous thromboembolism; NVAF, Non-valvular atrial fibrillation; JAK2, Janus kinase-2; BTK, Bruton Tyrosine Kinase; BCR/ABL, Breakpoint Cluster Region / Abelson murine Leukemia