Screening for clinically relevant drug-drug interactions between direct oral anticoagulants and antineoplastic agents: A pharmacovigilance approach

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INTRODUCTION

- Use of direct oral anticoagulants (DOACs) in patients with cancer remains suboptimal due to the concern regarding potential drug-drug interactions (DDIs) with antineoplastic treatments. However, the clinical relevance of these DDIs is unknown.
- In this study, we examined the reporting risk of bleeding and stroke for concurrent use of DOACs and antineoplastic agents proposed by previous pharmacokinetic studies

METHODS

- Study design and data source: retrospective analysis FDA Adverse Events Reporting System (FAERS) from 2004 to 2021.
- Main exposure: AE reports containing DOACs (including dabigatran, rivaroxaban, apixaban, edoxaban) in combination with antineoplastic agents [kinase inhibitors (KIs), chemotherapy, hormone therapy, immunomodulating agents (IMAs)] with CYP3A4/P-gp inhibitory or inducing activity suggested by *in vitro* studies
- Outcome: bleeding and stroke events by Standardized MedDRA Queries
- Statistical analysis:
  - Primary analysis: disproportionality analyses (DPA), logistic regression model (LR), and Multi-item Gamma-Poisson Shrinker (MGPS) to identify disproportionate reporting of potential DDIs between DOACs and antineoplastic agents by therapeutic class (5 combinations) and by individual drugs (63 combinations). MGPS was used as the main approach.
  - Disproportionality measures: ROR and 95% CI (DPA and LR), EBGM (EB05-EB09) (MGPS).
  - Sensitivity analyses: (1) restricting the analyses to AE reports from 10/19/2010 (2) refining outcome definition by clinician (3) using warfarin as reference group in DPA and LR.
  - Analysis was conducted using SAS and R.

RESULTS

- A total of 36,066 AE reports with both DOAC and antineoplastic agents were obtained from FAERS database in 2010-2021. Overall, there was an increase in trends in AE reports with PK-suggested DDIs by therapeutic class (**Figure 1**).
- The highest bleeding rates in each drug class were the combination of DOACs with neratinib (39.08%, n=34), tamoxifen (21.22%, n=104), irinotecan (20.54%, n=83), and cyclosporine (19.17%, n=227). The highest rate of stroke was DOAC-prednisolone combination (2.43%, n=113) (**Table 1**)
- DOACs-neratinib was the only signal detected [EBGM (EB05-EB95) = 2.71 (2.03-3.54)]. No elevated signal was found for other combinations by therapeutic class and individual drugs (**Table 1**). Sensitivity analyses showed consistent findings.

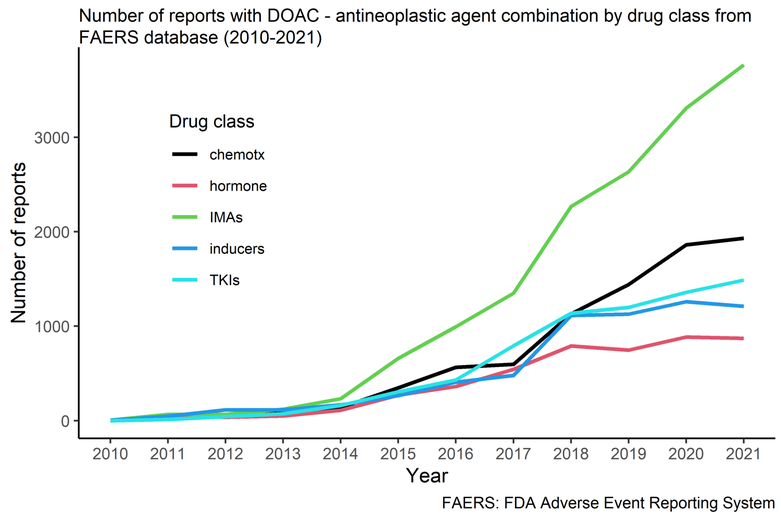

Figure 1. Number of reports with DOAC-antineoplastic agent combination by therapeutic class from FAERS (2010-2021).
chemotx: chemotherapy, TKIs: kinase inhibitors, IMAs immunomodulating agents

CONCLUSION

- Most DOAC-antineoplastic DDIs do not appear be clinically relevant. The exception may be DOAC-neratinib.
- Our findings may help clinicians narrow the "watch list" of DDIs when managing anticoagulation therapy in patients with concomitant cancer.
- Due to limitations of spontaneous reporting systems, the findings should be interpreted with caution and confirmed by future research.

REFERENCES AND ADDITIONAL INFO

SCAN ME

Table 1. Main analysis of signal detection for drug-drug interactions between DOACs and antineoplastic agents

Combination	Number of reports with events	DPA ROR (95% CI)	Logistic regression ROR (95% CI)	MGPS EGBM (EB05, EB95)
DOACs-KIs (N=7006)	944 (13.36)	0.30 (0.28-0.32)	0.24 (0.23-0.26)	1.02 (0.97-1.08)
DOACs-imatinib	83 (25.38)	0.66 (0.51-0.84)	0.46 (0.35-0.59)	1.89 (1.58-2.25)
DOACs-dasatinib	48 (17.39)	0.41 (0.30-0.55)	0.36 (0.26-0.50)	1.30 (1.02-1.63)
DOACs-nilotinib	34 (15.11)	0.34 (0.24-0.49)	0.25 (0.24-0.26)	1.13 (0.85-1.48)
DOACs-lapatinib	16 (15.68)	0.36 (0.21-0.61)	0.48 (0.28-0.82)	1.15 (0.76-1.68)
DOACs-erlotinib	59 (13.98)	0.31 (0.24-0.41)	0.28 (0.21-0.36)	1.05 (0.85-1.30)
DOACs-axitinib	41 (14.44)	0.32 (0.23-0.45)	0.31 (0.22-0.44)	1.08 (0.84-1.38)
DOACs-ceritinib	11 (26.19)	0.68 (0.34-1.36)	0.88 (0.42-1.84)	1.73 (1.06-2.70)
DOACs-trametinib	41 (15.07)	0.34 (0.25-0.48)	0.29 (0.20-0.41)	1.12 (0.87-1.44)
DOACs-sunitinib	108 (27.48)	0.73 (0.59-0.91)	0.34 (0.27-0.43)	2.05 (1.75-2.39)
DOACs-neratinib	34 (39.08)	1.24 (0.80-1.90)	1.06 (0.65-1.72)	2.71 (2.03-3.54)
DOACs-sorafenib	30 (24.79)	0.63 (0.42-0.96)	0.30 (0.20-0.46)	1.79 (1.32-2.37)
DOACs-ponatinib	32 (16.16)	0.37 (0.25-0.54)	0.29 (0.19-0.43)	1.20 (0.90-1.59)
DOACs-vemurafenib	20 (14.49)	0.33 (0.20-0.52)	0.31 (0.19-0.51)	1.08 (0.75-1.52)
DOACs-cobimetinib	23 (15.97)	0.37 (0.23-0.57)	0.25 (0.16-0.40)	1.18 (0.84-1.63)
DOACs-gefitinib	9 (14.75)	0.33 (0.16-0.68)	0.22 (0.11-0.45)	1.07 (0.62-1.74)
DOACs-afatinib	31 (27.19)	0.72 (0.48-1.09)	0.51 (0.33-0.78)	1.94 (1.44-2.58)
DOACs-hormone (N=4728)	763 (16.14)	0.37 (0.34-0.40)	0.30 (0.27-0.32)	1.22 (1.15-1.30)
DOACs-letrozole	211 (14.72)	0.33 (0.29-0.38)	0.21 (0.18-0.25)	1.12 (1.00-1.25)
DOACs-anastrozole	173 (20.69)	0.50 (0.43-0.59)	0.38 (0.32-0.45)	1.56 (1.37-1.77)
DOACs-abiraterone	94 (14.97)	0.34 (0.27-0.42)	0.39 (0.31-0.49)	1.13 (0.95-1.33)
DOACs-bicalutamide	127 (20.99)	0.51 (0.42-0.62)	0.29 (0.24-0.36)	1.58 (1.36-1.82)
DOACs-tamoxifen	104 (21.22)	0.52 (0.42-0.64)	0.26 (0.21-0.33)	1.59 (1.35-1.86)
DOACs-chemotherapy (N=8236)	1322 (16.05)	0.36 (0.34-0.39)	0.27 (0.25-0.28)	1.22 (1.16-1.27)
DOACs-methotrexate	921 (17.80)	0.41 (0.39-0.45)	0.30 (0.28-0.33)	1.34 (1.27-1.41)
DOACs-vincristine	65 (11.55)	0.25 (0.19-0.33)	0.18 (0.14-0.23)	0.88 (0.71-1.07)
DOACs-irinotecan	83 (20.54)	0.50 (0.39-0.63)	0.28 (0.22-0.36)	1.54 (1.28-1.83)
DOACs-IMAs (N=15475)	1351 (8.73)	0.18 (0.17-0.19)	0.14 (0.13-0.15)	0.66 (0.63-0.69)
DOACs-cyclosporine	227 (19.17)	0.46 (0.40-0.53)	0.31 (0.27-0.36)	1.45 (1.30-1.61)
DOACs-sirolimus	41 (17.60)	0.41 (0.29-0.58)	0.35 (0.25-0.49)	1.31 (1.01-1.68)
DOACs-tacrolimus	200 (15.40)	0.35 (0.30-0.41)	0.25 (0.21-0.29)	1.17 (1.04-1.31)
DOACs-dexamethasone	897 (6.91)	0.14 (0.13-0.15)	0.12 (0.11-0.13)	0.52 (0.50-0.56)
DOACs-inducers (6311)	152 (2.41)	0.36 (0.31-0.43)	0.68 (0.57-0.80)	1.05 (0.90-1.21)
DOACs-dabrafenib	9 (3.78)	0.58 (0.30-1.14)	0.82 (0.41-1.63)	1.54 (0.87-2.55)
DOACs-prednisolone	113 (2.43)	0.37 (0.31-0.44)	0.64 (0.53-0.78)	1.04 (0.87-1.23)

*DOACs: direct oral anticoagulants, KIs: kinase inhibitors, IMA: immunomodulating agents. All combinations not shown, refer to Additional Info and References