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Interaction table of oral factor Xa inhibitors with oral anti-cancer drugs

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Introduction

Patients with active cancer are generally considered at increased risk for thrombosis, which is typically manifested as a deep vein thrombosis and/or pulmonary embolism. This risk depends on many factors, e.g. cancer site, cancer stage or type of treatment [1,2]. For secondary prevention of thromboembolism or in presence of other co-morbidities (e.g. atrial fibrillation), the anticoagulation therapy in these patients is warranted. On the other hand, due to the chemo- or radiotherapy, cancer type and location (e.g. gastro-intestinal tumours) and concomitant anticoagulation, the bleeding risk increases. If anticoagulation is required, the direct oral anticoagulants represent an effective, safe and convenient therapeutic option, compared with low-molecular-weight heparins or vitamin K antagonists. Prescribing direct oral anticoagulants in patients concomitantly treated with oral anti-cancer drugs represents a challenge for the clinicians. The metabolic pathways often interfere, which can lead to clinically relevant drug-drug interactions (DDI) and thus either to increased risk of bleeding or to decrease of oral factor Xa inhibitors efficacy and increased risk of thromboembolism. Scientific evidence for the clinical management of these DDI is emerging, but the robust real-world data is still lacking. Our clinical pharmacy team in cooperation with the in-house Clinic for medical oncology and haematology developed a tool – an interaction table of the oral factor Xa inhibitors (apixaban edoxaban, rivaroxaban) with the commonly prescribed anti-cancer drugs [3,4,5].

Methods

We screened the main metabolic pathways of 67 oral anti-cancer drugs, focusing primarily on CYP3A4, P-gp and BCRP as they are often involved in the metabolism of the oral factor Xa inhibitors. For every drug, the product information (EMA/Swissmedic/FDA) was consulted. In case of lack of data on metabolism, we searched in other sources (e.g. UpToDate, DrugBank). Furthermore, a PubMed search concentrating on the management of the potential DDI was performed. Based on these data we propose the management of the possible DDI by considering dose reduction, switching to other drug within the therapeutic class or avoiding the combination. Moreover, our table mentions increased bleeding risk caused by the drug itself, if applicable [5,6,7,8,9,10,11]. The interaction table was double-checked by another clinical pharmacist and then reviewed by the chief clinical pharmacist and the chief haemato-oncologist.

Results

Oral anti-cancer drug	Oral factor Xa inhibitors			Increased bleeding risk by the oral anti-cancer drug itself?
	Apixaban	Edoxaban	Rivaroxaban	
Abiraterone		preferred		
Afatinib				
Alectinib		preferred		
Anagrelide				
Anastrozole		preferred		vaginal bleeding
Axitinib		preferred		
Bicalutamide		preferred		
Bosutinib		preferred		
Brigatinib				
Cabozantinib	Dose reduction 25%	preferred		
Capecitabine				
Capmatinib	Dose reduction 25%	preferred		
Ceritinib	Dose reduction 50%	preferred		
Chlorambucil				thrombocytopenia
Cobimetinib		preferred		
Crizotinib	Dose reduction 25%	preferred		
Cyclophosphamide		preferred		thrombocytopenia
Dabrafenib		preferred		with trametinib
Dasatinib				
Dexamethasone		preferred		
Entrectinib				
Enzalutamide				thrombocytopenia
Erlotinib		preferred		
Everolimus		preferred		
Exemestane		preferred		vaginal bleeding
Gefitinib		preferred		
Hydroxyurea (Hydroxycarbamide)				
Ibrutinib	Dose reduction 25%	preferred		
Idelalisib	Dose reduction 50%	preferred		
Imatinib		preferred		
Ixazomib		preferred		thrombocytopenia
Lapatinib	Dose reduction 25%	preferred		nosebleed with letrozole
Larotrectinib		preferred		
Lenalidomide				
Lenvatinib		preferred		
Letrozole		preferred		vaginal bleeding
Lorlatinib				
Melphalan				thrombocytopenia
Methotrexate				thrombocytopenia
Nilotinib		preferred		
Niraparib				
Olaparib	Dose reduction 25%	preferred		thrombocytopenia
Osimertinib	Dose reduction 25%	preferred		
Palbociclib	Dose reduction 25%	preferred		thrombocytopenia
Pazopanib	Dose reduction 25%	preferred		
Pomalidomide		preferred		
Ponatinib	Dose reduction 25%	preferred		
Pralsetinib	Dose reduction 25%	preferred		
Prednisolone		preferred		gastrointestinal tract
Prednisone		preferred		gastrointestinal tract
Procarbazine		preferred		
Regorafenib		preferred		
Ruxolitinib		preferred		
Selpercatinib	Dose reduction 25%	preferred		thrombocytopenia
Sorafenib	Dose reduction 25%	preferred		
Sotorasib				
Sunitinib		preferred		
Tamoxifen		preferred		vaginal bleeding
Temozolomide				
Tepotinib	Dose reduction 25%	preferred		
Thalidomide				
Topotecan		preferred		thrombocytopenia
Trametinib				with dabrafenib
Vemurafenib				
Venetoclax	Dose reduction 25%	preferred		
Vinorelbine		preferred		thrombocytopenia
Vismodegib		preferred		

	Clinically relevant interaction not expected or manageable by dose reduction (if applicable)
preferred	Oral anti-cancer drug is a substrate of CYP3A4: interaction with Edoxaban not expected and it is a preferred choice
	Concomitant use not recommended (not necessarily a contraindication); LMWH is the 1st choice) - if injection refused by patient, contact Clinical Pharmacy service
	Bleeding risk by the anti-cancer drug itself; detailed description, if applicable

Table download

Conclusion

Our interaction table provides clinicians with an easy-to-use decision support tool for the management of the possible DDI in cancer patients on oral anti-cancer drugs with indication for the anticoagulation. Our main aim is to increase the safety of the medication therapy on one hand and to simplify the decision-making process of the clinicians on the other hand. This is already a second version of the table, which is periodically updated in accordance with the emergence of new scientific data and/or new therapies. For the future, the next step could be an implementation into the clinic information system or a web-based tool and certainly a regular update of the table based on the latest data.

Literature

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