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DOACs in Cat

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Abstract

The risk of VTE in patients with malignancy is high when compared to the normal population. This obviously increases morbidity in already sick patients and is a leading secondary cause of mortality. The choice of anticoagulant in these patients ischallenging due tohigh risk of bleeding(presence of GI malignancy and intracranial metastasis), associated co morbidities, current FDA approvals and increased risk of recurrence. Hence In this mini review wewill attempt to discuss the mechanism of action, pharmacokinetics and updated evidence regarding DOACS in treatment of VTE in cancer patients and how it contrasts with the use of LMWH.

Keywords: *CAT cancer associated thrombosis, VTE venous thromboembolism, DOAC direct oral anticoagulant, LMWH low molecular weight heparin, VKA vitamin K antagonist.*

Introduction

LMWH has been the mainstay of treatment of VTE in cancer patients since most of the guidelines from ACCP, NCCN and ASCO societies for years have recommend LMWH over warfarin. These guidelines have been based on Clot study. In the Clot study cancer patients with symptomatic VTE were assigned to either warfarin or dalteparin treatment groups andduring their 6 month follow up it was found that patients in thedalteparin group had decreased recurrence of clotswith no increase in incidence of bleeding compared to warfarin group. [1] The commercially available LMWHs in USA are enoxaparin and dalteparin.

DOACs, Direct oral anticoagulants previously known as NOACs (Novel oral anticoagulants) are the oral alternatives used to treat VTE. Dabigatran, apixaban , rivaroxaban and edoxaban are the currently available DOAC s in USA. They have been studied in the past few years in the treatment of CAT. The outcomes were measured in terms of recurrent VTE and clinically relevant bleeding in cancer patients taking DOACs vs VKA. AMPLIFY-EXT cancer subgroup study proved apixaban to be noninferior to VKA in CAT.[2] Also EINSTEIN DVT/PE with cancer subgroup showed comparable efficacy with rivaroxaban and VKA but higher rates of bleeding in active cancer with rivaroxaban. [3] Lower incidence of VTE recurrence was noticed with edoxaban compared to VKA in HOKUSAI trial. [4] Interestingly none of the DOACs were compared head to head with LMWH until recently which we will subsequently discuss in the article.

Mechanism of Action

Coagulation cascade is a fine-tuned mechanism that is important to maintain hemostatic stability in the body. The reason DOACs are called direct is because they act directly on a single factor in the coagulation pathway. Apixaban, Rivaroxaban and Edoxaban act on factor Xa (activated) and dabigatran actson factor lla or thrombin. They inhibit the corresponding factors and prevent formation of fibrin or clot formation in the cascade. (fig 1)

DOACs have little interaction with food or drugs, so they usually are prescribed in a fixed dose. They do not need frequent laboratory monitoring. [5] DOACs have shorter half life compared to VKA and reach peak plasma concentrations quickly. Dabigatran is the only DOAC available as a pro-drug and becomes active after drug metabolization. Dabigatran is eliminated from the body primarily renally, whereas Factor Xa inhibitors are mainly eliminated by the biliary-fecal route. The drug interactions of DOACs are mainly limited to drugs that act on P-glycoprotein for

dabigatran and on P-glycoprotein and/or cytochrome P3A4 for rivaroxaban, apixaban and edoxaban[6] Because Xa inhibitors are substrate of both the CYP 3A4/5 hepatic isoenzyme system and P-gp efflux transporter system, they are subject to numerous drug interactions. [7] Drugs such as phenytoin, St. John's Wort, carbamazepine and rifampin should not be co administered with these anticoagulants. [6]Edoxaban is contraindicated in nonvalvular atrial fibrillation (NVAF) patients with a creatinine clearance (CrCl) greater than 95 mL/minute because of an increased risk of ischemic stroke compared to warfarin .(11)

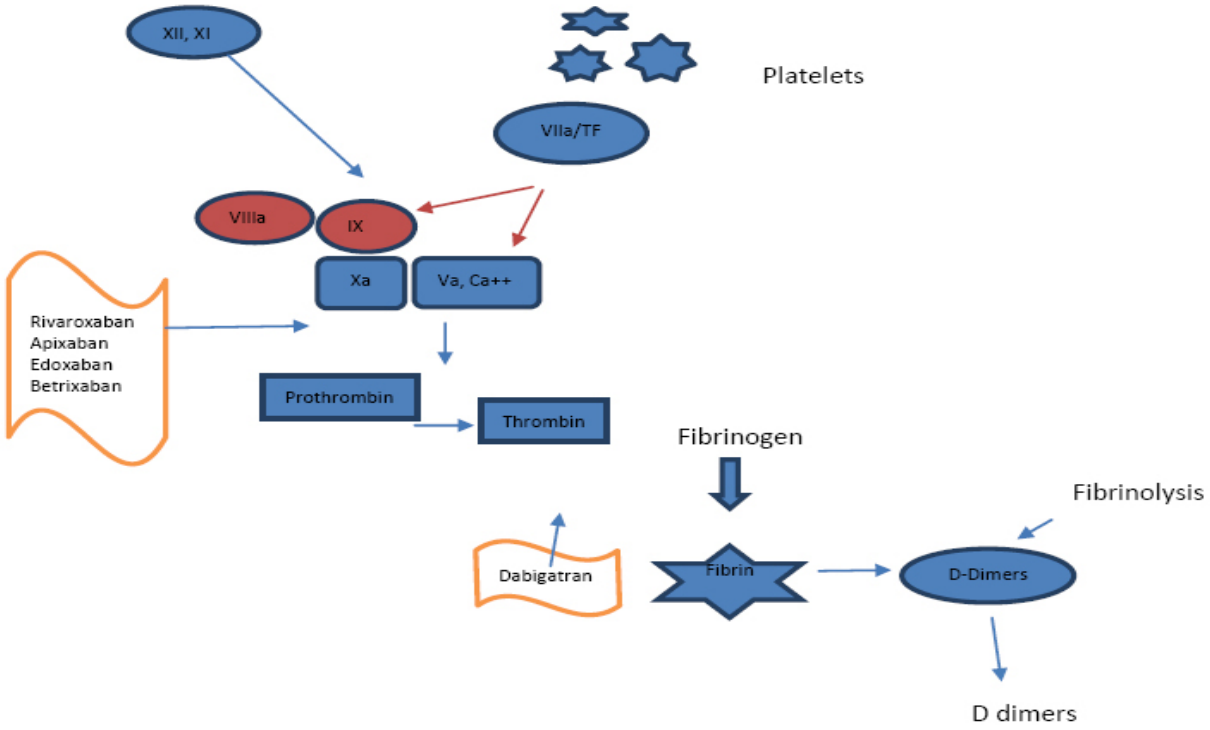

Figure 1. *Mechanism of action of DOACs*

Interestingly idarucizumab [praxibind] obtained FDA approval for use to reverse dabigatran (direct Thrombin inhibitor} on October 16, 2015. For other DOACS, which have intrinsic factor Xa inhibitor activity, 4 factor prothrombin complex is recommended as reversal agent. Andexanet has been studied to reverse the effect of factor Xa inhibitors as outlined in the study published in 2016 in NEJM. (6). With initial bolus and subsequent 2 hour infusion the anti-Factor X a activity was shown to be significantly reduced in major bleeding in patients taking rivaroxaban and apixaban, and effective hemostasis attained in 79% cases. The US Food and Drug Administration (FDA) has approved Andexxa (coagulation factor Xa [recombinant] inactivated-zhzo) to reverse the anticoagulation effects of factor Xa inhibitors when needed due to life-threatening or uncontrolled bleeding, Portola Pharmaceuticals has announced[8].

Table for DOACs

Agent	LMWH	Dabigatran	Rivaroxaban	Apixiban	Edoxaban
Dose	1mg/kg bid	150 mg bid	15mg bid x3 wk, then 20 mg daily	10 mg bid x 1wk then 5 mg bid	6o mg daily after 5 days of parenteral
Dose Adjustment per renal function	no	yes	yes	no	yes
admin	s/c	oral	oral	oral	oral

MOA	Xa and Thrombin inhibitor	Thrombin inhibitor	Xa inhibitor	Xa inhibitor	Xa inhibitor
Safety >75 old, obese, GFR[30-50]	No	yes	yes	Yes	Yes, C/I CrCl>95mL/m
FDA approval for CAT	yes	no	no	no	no
P glycoprotein CYP3A4 interaction	no	Potent P-gp inhibitors, inducer rifampin	Potent dual CYP3A4 and P-gp inhibitors or inducer	Potent dual CYP3A4 and P-gp inhibitors or inducers	Potent P-gp inhibitors and P-gp/CYP3A4 dual inducer rifampin
Antidote	Protamine sulphate	Idaruxizumab	adnexxa	adnexxa	adnexxa

Evolution of Guidelines, FDA Approval and Recent Data for Treatment of CAT

ASCO (American Society of Clinical Oncology) 2013 clinical update suggests use of LMWH in CAT and clearly mentions that DOACs are not recommended as preferred agents. NCCN (National Comprehensive Cancer Network) clinical guidelines 2015 emphasize the use of LMWH as the preferred agent for VTE treatment in cancer patients. Interestingly ACCP(American College of Chest Physicians) updated its guidelines in 2016 and not only suggested LMWH over VKA for treatment of CAT (grade 2B) but also recommended dabigatran , rivaroxaban, apixaban and edoxaban, all, as grade 2C evidence for use in VTE in cancer patients. Of note, to date only LMWH and that too only Dalteparin is FDA approved for treatment of VTE in cancer patients.

But recently published studies have focused on DOACs compared to LMWH which has been the standard of treatment of CAT so far. According to the systematic review and metanalysis published in Thrombosis Research [9], DOACs have a lower 6 month VTE recurrence (42/725) compared to LMWH (64/725) but had more clinically significant bleeding (40/725) than LMWH group (23/725). The absolute risk differences were small (2–3%) for both primary outcomes, though clinically significant.This is the first systematic review and metanalysis to summarize the incidence of recurrent VTE and majorbleeding episodes in over 5000 patients with CAT managed with DOACs when directly compared with LMWHs. The largest study referenced in the meta-analysis was the Hokusai cancer trial which used edoxaban as its DOAC of choice . Most of the other studies have used rivaroxaban. Dabigatran and apixaban have not been well studied in CAT. The bleeding episodes seen in patients taking DOAC were most of the time limited to the upper gastrointestinal tract in the Hokusai-Cancer study, as studied in the group meta-analysis. Edoxaban treatment and increased major bleeding in patients with gastrointestinal cancers was also noticed in a subgroup analysis. [10] One of the main reasons suggested for decrease in recurrence rate of CAT is good adherence to DOAC by patientsdue to ease of administration of DOAC in real world compared to parenteral LMWH. Only 50 percent of patients adhere to LMWH. [11]

Select-d was the first randomized trial for treatment of VTE, investigating the use of direct oral anticoagulants vs low molecular weight heparin in patients with cancer as they enrolled patients in April 2016.It is prospective, randomized, open label, multicentre pilot trial comparing dalteparin and rivaroxaban for cancer patients with VTE – symptomatic and incidental pulmonary embolism and or Deep vein thrombosis, with a second placebo-controlled randomization (rivaroxaban vs placebo). At end of 6 months VTE rate was 4 % with rivaroxaban vs 11 % with LMWH. Major bleeding however was 4 % wit LMWH vs 6 % with rivaroxaban. (10)

The latest study comparing DOAC with LMWH has been published in 2018. This is anopen label,non-inferiority trial published in New England Journal of Medicine in which active cancer patients with acute VTE were treated with Dalteparin vs Edoxaban for 6 to 12 months[10]. Active cancer was defined as cancer diagnosed within last 6 months.

Acute VTE could be symptomatic or incidentally discovered deep vein thrombosis and or pulmonary embolism. Patients were divided to receive either LMWH for 5 days and then followed by edoxabanin a dose of 60 mg or they received dalteparin 200 U per kg subcutaneouslyfor 30 days and a tailored dose for next 6 to 12 months. The patients were followed for 6 to12 months . Recurrence of VTE was noticed to be 7.9 % with Edoxaban vs Dalteparin(11.3%) P=0.09, but the bleeding rate was higher (6.9)% as compared to Dalteparin group (4%) P=0.04 This difference was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban .Hence in this trial involving patients with CAT, edoxaban was noninferior to dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. (fig 2)

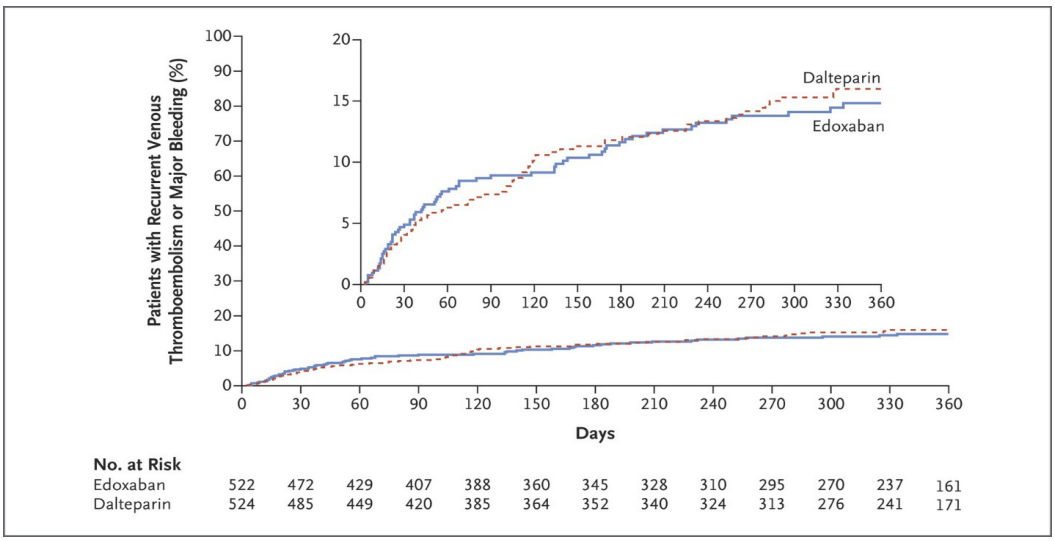

Figure 2. *Kaplan–Meier Cumulative Event Rates for the Primary Outcome*

Conclusion

There are various factors affecting the choice of anticoagulation in VTE in cancer patients. Oral intake along with lack of frequent laboratory monitoring contributes to better adherence to DOAC by patients. But thrombocytopenia and presence of intracranial tumorsare limiting factorswhich increase the chance of clinically significant bleeding. Upper GI malignancy and use of P glycoprotein and CYP3A4 inhibitors prevent the absorption of anticoagulants.The cost of medication is also important factor in determining the choice of anticoagulant.Absence of antidote for these oral anticoagulants have been one of the main limiting factoras well in their widespread usage in the past. But with new trials and wider insurance coverage and antidote availability patients with cancer may have better oral choices available for their management.

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