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Review article

Anticoagulant treatment of cancer associated venous thrombosis

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Abstract Venous thromboembolism is a shadow over the malignant diseases. Many patients experienced venous thrombosis or pulmonary embolism during the course of malignant disease and those complications may precede overt malignant disease for months. The association between malignant disease and venous thrombosis represent malignant potential of disease and usually mean dismal prognosis. Different cancers have different propensity to cause thrombosis and pancreatic, stomach and brain tumors yield the highest risk, however, colonic, lung, prostate and breast cancers are more prevalent and the number of vein thrombosis is predominant in association with these tumors. In the last two years, a strong medical evidence become available from the randomized trials and now, direct oral anticoagulant drugs (rivaroxaban, edoxaban and apixaban) become equally recommended to patients with venous thrombosis as low molecular weight heparins which were the standard therapy. For rivaroxaban and edoxaban, higher prevalence of major bleeding was associated to gastrointestinal carcinomas.

Kew words venous thromboembolism, malignant disease, direct oral anticoagulant drugs

Introduction

Thrombosis, particularly venous thromboembolism (VTE) and hemorrhage are very often presented in patients with malignant diseases. These complications maybe fatal and it is very important that the physicians who treated patients with malignant diseases anticipate the risk for thrombosis and hemorrhage. The features of malignant diseases, characteristics of patients and treatment are three elements which must be estimated for the prediction of risk for both complications. Certain tumors like pancreatic carcinoma, lung adeno and microcellular carcinomas, brain tumors, multiple myeloma have very strong susceptibility for thrombosis caused predominantly by their biology. The presence of a procoagulant microvesicles in circulation, hyperviscosity syndrome, dysregulated immune response, elevated tissue factor production and secretion, and down-regulation of anticoagulant and fibrinolytic systems are behind this procoagulation properties of these tumors[1]. In this case thrombotic process is usually resistant to anticoagulant therapy and spreads despite the various treatment options. Only control of the malignant process can improve thrombosis treatment in these patients, but for many of them it is not possible with the current medical knowledge. The occurrence of thrombosis is the ominous sign and very often represents the malignant potential of the disease with dismal prognosis[2]. Some other malignant diseases may develop thrombosis predominately associated to treatment, like breast, prostate or colon carcinomas. Surgery treatment, especially abdominal and pelvic, care an enhanced risk for post treatment thrombosis and need prophylactic treatment with anticoagulants for weeks. Intravenous catheters are also sights of the thrombotic masses and can cause embolization in patients with malignant disease. On the other side, patients with malignant disease are also prone to hemorrhagic complications. Surgery, mucositis, thrombocytopenia, corticosteroids, other disorders of hemostasis, liver and renal failure are very often present during the course of malignant disease and can cause severe or even fatal bleeding. Because of that, primary prevention of VTE in patients with malignant disease is very complex and generally pharmacology prevention is not recommended.

Anticoagulant therapy for VTE in patients with malignant disease

From 2003 when CLOT trial[3] was published (dalteparin versus dalteparin+vitamin K antagonist after cancer associated VTE) LMWH were recommended anticoagulant therapy for cancer associated VTE. In this trial 676 patients randomly assigned to dalteparin or dalteparin for a short time and vitamin K antagonists for six months. Dalteparin group had almost 50% reduction of recurrent VTE events without excess of bleeding. However, there was no difference in 6-months mortality between two groups. The larger, CATCH trial published almost 10 years later (900 patients with cancer associated VTE) did not have such convincing results with non-significant

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Table 1. Landmark randomized clinical studies with direct oral anticoagulants for the secondary prevention of cancer associated thrombosis

	HOKUSAI VTE Edoxaban (edoxaban vs control)	SELECT-D Rivaroxaban (rivaroxaban vs control)	CARAVAGGIO Apixaban (apixaban vs control)
Number of randomized pts	1050	406	1155
Age (mean)	64	67	67
The most frequent type of Ca	Colorectal, Lung, Genitourinary 53%	Colorectal, Lung, Breast 58%	Colorectal, Lung, Breast -
Metastatic disease	-	-	68%
Locally advanced or metastatic	Composite of recurrent VTE and MB during 12 months	VTE recurrence at 6 months	VTE recurrence at 6 months
Primary end point	12.8 vs 13.5%, p=ns 7.9 vs 11.3%, p=0.09	4.0 vs 11.0%, p<0.05	5.6 vs 7.9%, p=NS (p=0.0001 for noninferiority)
Recurrent VTE	6.9 vs 4.0%, p=0.04	6.0 vs 4.0%, p=NS, but with significantly higher rate of CRNMB	3.8 vs 4.0%, p=0.60
Major bleeding			
Death from any cause	39.5 vs 36.6%, p=NS	25 vs 30%, p=NS	23.4 vs 26.4, p=NS

decrease of VTE recurrence during 6-month therapy with tinzaparin versus tinzaparin plus vitamin K antagonists. In both trials time in therapeutic range for patients treated with vitamin K antagonists was slightly less than 50%, but it very difficult to achieve better INR management in patients with active cancer. Patients in CATCH trial[4] had less pronounced risk factors for recurrent VTE than patients in CLOT trial and there is the most important factor influence the difference in the results between these trials.

Direct oral anticoagulant (DOAC) drugs entered into the treatment of VTE after phase III randomized trials[5-9], which all confirmed that DOACs are not inferior to classical combination of LMWH plus vitamin K antagonists with less intracranial bleeding. Moreover, DOACs are more simple to use than vitamin K antagonists with much less drug-drug and drug-food interactions and without need for laboratory checking and frequently adjustment dosage. Cumulative number of patients with cancer associated VTE in these phase III trials (RECOVER, EINSTEIN DVT and PE trials, AMPLIFY and HOKUSAI-VTE) (5-9) was 1132 and, the meta-analysis of these trial confirmed the basic findings that DOACs are not inferior to LMWH plus vitamin K antagonists in this subgroup of patients with less major bleeding.

It is very difficult to carry out studies for VTE secondary prevention in cancer associated thrombosis patients. Patients are very heterogeneous in so many variables. Kind and stage of the disease, surgery, chemotherapy, radiation, catheters, patient characteristics are very strong confounding variables which can considerable influence to the outcome. It is possible that we need different anticoagulation strategy in different situations. Despite of these limitations, the first step was made. Three landmark randomized studies were published their results regarding secondary prevention of VTE in patients with malignant disease using anti Xa oral anticoagulants (table 1). The comparator for all this studies was the protocol used in CLOT study, dalteparin 200 IU sc daily for one month than 150 IU sc daily till six months. DOACs were used in the same way like in phase III studies where they were introduced. Edoxaban in HOKUSAI-VTE Cancer trial (10) was used 60 mg a day after 5-6 days of initial LMWH therapy. Rivaroxaban in SELECT-D trial[11] was use 15 mg bid, and 20 mg a day for at least 6 months thereafter. In Caravaggio trial[12] apixaban was used as 10 mg bid for 7 days and after that for 5 mg bid for at least 6 months. It is not easy to compare the results of these studies (inclusion and exclusion criteria are not the same, the HOKUSAI trial has different primary end-point and planned longer anticoagulant therapy etc.). In summary, DOACs were not inferior for the prevention of recurrent VTE compare to Dalteparin regime, however, rivaroxaban and edoxaban might cause more frequent bleeding in patients with gastrointestinal carcinoma. All-cause mortality did not change regarding the choice of anticoagulants.

Several professional societies[13,14] introduced the novel data to their guidelines of treatment cancer associated venous thromboembolism. They recommend LMWH or antiXa DOACs for the treatment of CAT since their similar efficacy in preventing recurrent VTE and similar safety at least for non-gastroentestinal or maybe urologic carcinomas which are much more prone to bleeding with edoxaban and rivaroxaban. However, they emphasized that LMWH have very little important drug-drug interactions with very long experience of serving in that indication. Since the possible interactions of DOACs with various chemotherapeutic drugs are still to be estimated in clinical settings, many experts do not recommend DOACs in combination with antineoplastic drugs. Moreover, the combination of LMWH and DOACs maybe an attractive alternative scheme for many CAT patients, where the LMWH would be applied intra-hospital around a chemotherapy and, DOACs would be used out of hospital.

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Sažetak

Antikoagulantna terapija karcinoma povezana sa venskim trombozama

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Venski tromboembolizam je senka koja prati maligne bolesti. Mnogi pacijenti sa malignom bolešću tokom nje dožive venski tromboembolizam i on može prestavljati i prvu manifestaciju bolesti čak nekoliko meseci pre postavljanja dijagnoze. Povezanost maligne bolesti i venske tromboze prestavlja uglavnom maligni potencijal bolesti i označava lošu prognozu. Različiti kanceri imaju različitu predispoziju za nastanak venskog tromboembolizma i tu se posebno izdvajaju tumori pankreasa, želuca i mozga, ali neki drugi tumori koji su mnogo češći u stvari još više doprinose ukupnom broju bolesnika sa venskim tromboembolizmom kao što su karcinomi pluća, prostate, kolona i dojke. U poslednjih nekoliko godina je oblavljeno nekoliko randomizovanih studija koje su pokazale da su direktni oralni antikoagulantni lekovi (rivaroksaban, edoksaban i apiksaban) jednako efikasni ako ne i bolji od nisko-molekularnih heparina u prevenciji rekurentnih tromboemboljskih događaja a da oprez preba da postoji kod carcinoma gastrointestinalnog trakta jer je pokazano da rivaroksaban i edoksaban izazivaju češće krvarenja kod ove grupe bolesnika.

Ključne reči: *vesnki tromboembolizam, maligna bolest, direktni oralni antikoagulantni lekovi*