Review article

The role of direct oral anticoagulants in the treatment of cancer associated venous thromboembolism

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ABSTRACT

Cancer disease is one of the most significant risk factors for venous thromboembolic complications. In this review features of treatment and unsolved questions of alternative anticoagulant therapy of cancer-associated thromboembolism (CAT) are considered. The modern guidelines advocate the use of low-molecular-weight heparin (LMWH) over a vitamin K antagonist (VKA) for the first 3–6 months after diagnosis of VTE in cancer patients. Few years ago direct oral anticoagulants (DOACs) have been approved for the treatment of venous thromboembolism (VTE). DOACs have demonstrated comparable efficacy and safety with VKA in general population. But efficacy and safety of DOACs as compared with long-term LMWH for the treatment of CAT have not been definitely established. The review focuses on the results of the first two prospective randomized studies (HOKUSAI VTE Cancer and SELECT-D) in which the efficacy and safety of edoxaban and rivaroxaban was compared with low-molecular-weight heparin dalteparin for the treatment of VTE in cancer patients and the latest recommendations from SSC of the ISTH on the feasibility of using DOACs in the treatment of CAT.

Key words: cancer-associated thromboembolism, direct oral anticoagulants

INTRODUCTION

Cancer patients are at high risk for morbidity and mortality due to thrombosis and existing data demonstrate that cancer is associated with a hypercoagulable state [1, 2]. Venous thromboembolism (VTE) including deep venous thrombosis (DVT) and pulmonary embolism (PE) frequently complicates the course of malignancy, particularly in the setting of medical and surgical anticancer treatments [3]. The risk of VTE is fourfold to sevenfold in cancer patients compared to those without [4]. In cancer patients the rate of PE is ~ 9% and PE is the second leading cause of death for patients with cancer [5]. Among all VTE patients the rate of cancer-associated thromboembolism (CAT) is about 20% and 13% in patients receiving chemotherapy.

Both recurrent VTE and bleeding complicate the course of cancer. The risks of recurrent thrombosis and bleeding are higher among patients with cancer than among those without [6]. The CLOT trial [7] and two other studies [8, 9] demonstrated that treatment of cancer-associated VTE with 6 months of LMWH resulted in a significantly lower recurrent rate at 6 months than treatment with warfarin with similar risk of bleeding in both groups. The modern guidelines [10–13] advocates the use of low-molecular-weight heparin (LMWH) over a vitamin K antagonist (VKA) for the first 3–6 months after diagnosis of VTE in cancer patients. Whether the use of LMWH therapy has benefit beyond 6 months is unknown. As it was reported by Khorana et al, 2016 [14] only about 50% of patients with CAT adhere to long-term treatment with LMWH and one of the reasons which limit its adoption is daily subcutaneous injections.

THE RESULTS OF THE DOACS EFFECTIVENESS STUDY

Direct oral anticoagulants (DOACs) have been approved for the treatment of VTE. Four DOACs: dabigatran, rivaroxaban, apixaban, edoxaban have demonstrated comparable efficacy and safety with VKA in general population [15–20]. But efficacy and safety of DOACs as compared with long-term LMWH for the treatment of CAT was not established. Meanwhile the meta-analyses based on indirect comparison suggest that DOACs may also have similar efficacy and safety to LMWH for the treatment VTE in cancer patients.

Two randomized trials (Hokusai VTE Cancer and SELECT-D) evaluating DOACs in CAT patients have been published in 2018 year. At the beginning of 2018 year the results of first direct comparison DOAC (edoxaban) and LMWH (dalteparin) in Hokusai VTE Cancer study were published. The aim of this study was to compare the oral factor Xa inhibitor edoxaban with subcutaneous dalteparin for the treatment of patients with cancer-associated thromboembolism. The study was randomized and open-label [21].

VTE Cancer

Eligible patients were randomized by interactive Web-based system in 1 : 1 ratio to receive either edoxaban or dalteparin. Edoxaban was started after ≥ 5 days period of treatment with low-molecular-weight heparin which was chosen by treating physician. Edoxaban was administrated orally at a fixed dose of 60 mg per day. In patients with creatinine clearance of 30 to 50 ml/min or a body weight ≤ 60 kg or in those receiving potent P-glycoprotein inhibitors a lower dose of edoxaban (30 mg per day) was administrated. Dalteparin was administrated subcutaneously at a dose of 200 IU/kg of body weight once daily (maximal daily dose 18 000 IU) for 30 days. After 1 month of treatment daily dose of dalteparin has been reduced to 150 IU/kg. In both groups treatment was to be continued for at least 6 months and up to 12 months.

The primary outcome was a composite of recurrent VTE or major bleeding in accordance with criteria of International Society on Thrombosis and Haemostasis (ISTH). Secondary outcomes included recurrent VTE and major bleeding analyzed separately and survival free of recurrent VTE or major bleeding. All outcomes were independently adjudicated by committe without knowledge of treatment allocation.

A total of 1050 adult patients with active cancer and symptomatic or incidentally detected VTE involving the popliteal, femoral, iliac or inferior vena cava and/or acute confirmed pulmonary embolism (PE) were enrolled in the trial.

The types of cancer in edoxaban and dalteparin groups: colorectal 15,9 and 15,1%; lung 14,8 and 14,3%; genitourinary 12,5 and 13,5%; breast 12,3 and 11,5%; pancreatic or hepatobiliary 9,4 and 7,6%; gynecological 9,0 and 12,0%; upper gastrointestinal 6,3 and 4,0%; hematological malignancy 10,7 and 10,5%; other 9,2 and 11,5%; respectively. Anticancer drug therapy continuing after randomization in edoxaban and dalteparin groups: antimetabolites 23,8 and 22,5%; platinum-based chemotherapy 20,1 and 20,4%; monoclonal antibodies 8,0 and 9,3%; taxanes 7,7 and 9,0%; hormonal therapy 7,9 and 7,1%; topoisomerase inhibitors 5,7 and 9,2%; respectively. Alkylating agents, anthracyclines, vinca alkaloids, kinase inhibitors, immunomodulating agents, proteasome inhibitors, antitumor antibiotics received ≤ 5% of patients of both groups. Patients could receive more than one anticancer drug. Anticancer treatment included drugs initiated before randomization.

The baseline characteristics of the patients were similar in dalteparin (n = 524) and edoxaban (n = 522) groups. Mean age was about 64 years, creatinine clearance of 30–50 ml/min had 7% of patients, platelet count of 50 000–100 000 per µl had 5% of patients and about 23% of patients met criteria to receive lower dose of edoxaban. Pulmonary embolism (PE) with or without deep venous thrombosis (DVT) was observed in 62,8%, DVT only in 37,2% of patients. Active cancer had 98% of patients and 53% of patients had metastatic disease. Cancer treatment within previous 4 weeks had 72% of patients. Previous VTE had about 10% of patients, 0/1/2/ ≥ 3 risk factors for bleeding (surgery within 2 weeks before randomization, the use of antiplatelet agents, primary or metastatic brain tumor, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer and treatment with bevacizumab within 6 weeks before randomization) accordingly had 18/28/31 and 22% of patients in both groups.

The median duration of assigned treatment was 211 days (IQR 76 to 357) in edoxaban group and 184 days (IQR 85 to 341) (p = 0,01) in dalteparin group. In patients of edoxaban and dalteparin groups the duration of study treatment < 3 months was observed in 26,6 and 26,1%; from 3 months to ≤ 6 months in 15,3 and 19,5% and more than 6 months in 58 and 54,4%, respectively. The death was the reason for permanent study drug discontinuation in 16,5% of patients in edoxaban and 19,1% of patients in dalteparin group.

The primary outcome occurred in 12,8% in edoxaban group and in 13,5% of patients in dalteparin group (HR 0,97; 95% CI 0,70–1,36; p = 0,006 for noninferiority; p = 0,87 for superiority). Among secondary outcomes recurrent VTE were observed in 7,9% patients in edoxaban group and in 11,3% in dalteparin group (HR 0,71; 95% CI 0,48–1,06); p = 0,09. Recurrent DVT observed in 3,6% patients in edoxaban group and in 6,7% in dalteparin group (HR 0,56; 95% CI 0,32–0,97); recurrent PE in 5,2% and 5,3% (HR 1,00; 95% CI 0,59–1,69), respectively.

There were more major bleeding in the edoxaban than in dalteparin group: 6,9% vs. 4,0% (HR 1,77; 95% CI 1,03–3,04); p = 0,04. Death occurred in 206 patients (39,5%) in the edoxaban group and in 192 patients in the dalteparin group. The most frequent was cancer related death: 181 patients (34,7%) in the edoxaban group and in 172 patients (32,8%) in the dalteparin group. Six deaths in each group were related to either venous thromboembolism or bleeding.

Subgroup analyses have demonstrated that there were no statistically significant interactions between subgroups and treatment except for the patients with gastrointestinal cancer at the time of randomization. Patients with gastrointestinal cancer in edoxaban group were more likely to have an increase in the risk of bleeding during treatment than patients in dalteparin group. The most common adverse event in both groups was progression of neoplasm (13%).

Hokusai VTE Cancer study demonstrated that in patients with CAT edoxaban was more effective than dalteparin to prevent recurrent VTE but was associated with significantly increased risk of major bleeding. In Hokusai VTE Cancer study the rate of recurrent VTE at 6 months in dalteparin group was similar with the rate observed in the CLOT study [7], but the rate of major bleeding at 6 months (3,2%) was lower than previously reported with dalteparin [7]. Thus, for the treatment of cancer associated VTE edoxaban was more effective than dalteparin to prevent recurrent VTE but was associated with increased risk of major bleeding. The difference in major bleeding was mainly due to the higher rate of upper gastrointestinal bleeding.

Hokusai VTE Cancer study had some limitations: open-label design, the number of primary outcomes was lower than expected. Median duration of treatment was shorter with dalteparin than with edoxaban.

SELECT-D

The results of second prospective, randomized, open-label, multicenter SELECT-D study were published in 2018 year, July [22]. In this trial 406 cancer patients with acute VTE were recruited. Eligible patients were randomized by telephoning Warwick Clinical Trials Unit at a one-to-one ratio using a computer-based minimization algorithm with stratification by stage of disease, platelet count, type of VTE (symptomatic VTE or incidental PE) and risk of clotting by tumor type. For patients assigned to dalteparin the drug was prescribed as well as in the Hokusai Cancer study. For patients assigned to rivaroxaban, 15-mg tablets were administered orally with food twice daily for first 3 weeks, followed by 20-mg tablets once daily for a total of 6 months. Rivaroxaban was discontinued if platelet counts were < 50 000/mm^3. A dose reduction or discontinuation of rivaroxaban was specified for levels of renal impairment.

All patients were assessed at 3-month intervals until month 12 and then at 6-month interval until month 24. The primary outcome was VTE recurrence. Secondary outcomes included major bleeding and clinically relevant nonmajor bleeding (CRNMB).

A total of 406 patients with active cancer and VTE were enrolled in the trial and 203 patients were allocated to each trial arm. The

types of primary tumor in rivaroxaban and dalteparin groups: colorectal 27 and 23%, lung 11 and 12%, esophageal/gastroesophageal 5 and 9%, gastric 2 and 3%, bladder 5 and 2%, ovarian 6 and 9%, gynecologic 3% in both groups, pancreatic 9 and 5%, lymphoma 5 and 6 %, breast 10% in both groups, multiple myeloma 1 and 2%, kidney 1 and 3%. Currently receiving cancer treatment in rivaroxaban and dalteparin groups: chemotherapy 81 and 85%; radiotherapy 4 and 7%; target therapy 15% in both groups; endocrine therapy 11% in both groups. Patients could receive more than one anticancer drug.

The baseline characteristics of patients were comparable between treatment groups. Age (median) was 67 years. A symptomatic DVT or PE was observed in 193 patients (48%) and incidental PE in 213 patients (52%). A metastatic disease was observed in 48% of patients. The median duration of treatment was 5,8 months (IQR 3,0–6,0 months) for dalteparin and 5,9 months (IQR 2,5–6,0 months) for rivaroxaban.

The 6-month rates of recurrent VTE were 11% (95% CI 7–16%) and 4% (95% CI 2–9%) for patients receiving dalteparin and rivaroxaban, respectively. Site of primary tumor (stomach or pancreas vs. other – HR 5,5 (95% CI 1,97–15,66) and VTE type (symptomatic VTE vs. incidental PE – HR 2,78 (95% CI 1,2–6,41) predicted for VTE recurrence.

The 6-month cumulative major bleeding rates were 4% (95% CI 2–8%) for dalteparin and 6% (95% CI 3–11%) for rivaroxaban; CRNMB rates were 4% (95% CI 2–9%) and 13% (95% CI 9–29%), respectively HR. Most major bleedings were GI there were no CNS bleedings. Gastric/esophageal cancer patients were especially at risk for major bleeding (4 of 11 patients receiving rivaroxaban vs. 1 of 19 receiving dalteparin) and these patients were excluded towards the end of the study. Overall survival at 6 months was 70% (95% CI 63–76%) in dalteparin group and 75% (95% CI 69–81%) in rivaroxaban group. Main limitations of the study were slow recruitment and only 6-months period of treatment.

The cumulative rate of VTE recurrence and major bleed at 6 months in Hokusai VTE Cancer [21], SELECT-D [22] and CLOT [7] trials are presented in table 1. The 6 month cumulative risk of recurrent VTE in dalteparin groups in Hokusai VTE Cancer and SELECT-D trials was consistent with what had been postulated based on CLOT trial. Patients receiving edoxaban and rivaroxaban had a lower 6-month rate of recurrent VTE but a higher major bleeding rate.

Meta-analysis results

A lot of the observational cohort studies describing initial experiences in cancer patients have been published after approval of DOACs for the treatment of VTE. The most of them reported that the durations of DOACs treatment were longer than that of LMWH and the rate of recurrent VTE was lower in patients receiving DOACs. The rates of major and CRNMB were heterogeneous across studies. This may reflect the physician's bias in selection of patients with CAT.

A meta-analysis of two randomized controlled trials (Hokusai VTE Cancer and SELECT-D) [23] demonstrated that DOACs patients had a lower 6-month rate of recurrent VTE (42/725) than patients receiving LMWH (64/727) (RR 0,65, 95% CI 0,42–1,01). However, patients receiving DOACs had a higher major bleeding rate (40/725) than patients receiving LMWH (23/727) (RR 1,74, 95% CI 1,05–2,88) and higher CRNMB rate (RR 2,31, 95% CI 0,85–6,28).

The increase in major bleeding episodes related to edoxaban and rivaroxaban seems to be limited to the upper gastrointestinal tract. This data are consistent with results of previous studies of DOACs [20]. In SELECT-D study [22] enrolling patients with gastroesophageal cancers was premature stopped due to more than expected gastrointestinal bleeding. Patients with gastrointestinal cancer and VTE receiving DOACs may be at the highest risk for bleeding and these drugs should be used with cautions in these patients. It remains unclear if these findings can be extrapolated to dabigatran or apixaban. Therefore DOACs should be used very carefully in patients with gastrointestinal cancer because of the highest risk for bleeding. Future studies should focus on investigation of other DOACs (apixaban, dabigatran) as well as appropriate selection of cancer VTE patients for safe treatment with DOACs.

TABLE 1.
The cumulative rate of VTE recurrence and major bleed at 6 months in Hokusai VTE Cancer, SELECT-D and CLOT trials.

	Hokusai VTE Cancer trial		SELECT-D trial		CLOT trial	
	Dalteparin	Edoxaban	Dalteparin	Rivaroxaban	Dalteparin	VKA
The cumulative VTE recurrence rate at 6 months	8,8%	6,5%	11%	4%	9%	17%
The cumulative major bleed rate at 6 months	3,2%	5,6%	4%	6%	6%	4%

SUMMARY

The benefits of DOACs (oral administration, no monitoring, lower recurrent VTE) need to be considered in CAT patients in context their negative attributes (increased bleeding and possible drug--drug interaction). Unfortunately patients with CAT have a lot special unsolved problems. The one of them is absence of score for bleeding assessment in cancer patients receiving DOACs. It is difficult to take into account all drug-drug interaction in rapidly evolving anticancer therapy. We know nothing about bleeding risk of DOACs in patients received immunotherapy which complicate with autoimmune colitis. We need more information about efficacy and safety of DOACs among different types of tumor and regimens of anticancer therapy.

Taking into account all mentioned above, experts from SSC of ISTH in 2018 [24] recommend to individualized treatment regimens after shared decision-making with patients. They suggest the use of DOACs for cancer patients with acute VTE, low risk of bleeding and no drug-drug interaction with systemic therapy. LMWHs constitute an acceptable alternative. Edoxaban and rivaroxaban are the only that have been compared with LMWH in RCTs in cancer patients. A final recommendation should be made taking into account the preferences of the patient, informed about the advantages and disadvantages of DOACs.

For cancer patients with acute VTE and high risk of bleeding (luminal gastrointestinal cancer with an intact primary, cancer at risk of bleeding from genitourinary tract, bladder or nephrostomy tubes, patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis or colitis) experts suggest the use of LMWH. Edoxaban and rivaroxaban are acceptable alternatives if there is no drug-drug interaction with current systemic therapy. A final recommendation should be made after shared decision-making with patient regarding a potential reduction in recurrence but higher bleeding rates with DOACs, incorporating patient preferences and values.

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