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Cancer-associated thrombosis (CAT) - Section 3

Direct oral anticoagulants for the treatment of venous thromboembolism in patients with cancer

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Take home meessages

- Venous thromboembolism is a frequent complication of cancer.
- Low-molecular-weight heparins (LMWH) have been proven more effective than vitamin K antagonists for the treatment of cancer associated thrombosis.
- Two direct oral anticoagulants: edoxaban and rivaroxaban have been shown to be more effective than LMWH for the treatment of cancer-associated thrombosis, but their use has been associated with an increase in the risk of major bleeding, especially in patients with gastrointestinal cancers.
- Other studies comparing LMWH and direct oral anticoagulants are in progress.

Introduction

Venous thromboembolism (VTE) is a frequent complication of cancer. In a large prospective cohort of patients with active cancer, VTE was diagnosed in 6% of the patients during 6 months of follow-up.[*1] Cancer-associated thrombosis (CAT) carries higher risks of bleeding and recurrent VTE than thrombosis occurring in the absence of cancer.

In the landmark CLOT study, prolonged low-molecular-weight heparin (LMWH) treatment was associated with a significant and major reduction in the risk of recurrent VTE as compared to vitamin K antagonists (VKA).[*2] Of note, this was not accompanied by a reduction in the risk of major bleeding and this result, obtained in the context of an open-label trial has not been reproduced so far, although several meta-analyses have confirmed a 40% relative risk reduction in the risk of recurrent VTE with the use of LMWH.[*3]

Current state of the art

Prolonged treatment with LMWH is not without inconvenience, it is associated with the need of daily subcutaneous injections, bruising at injection site and a higher cost than VKA. Direct oral anticoagulants (DOACs) may be appealing in patients with CAT. They have a large therapeutic window and are associated with less bleeding complications than VKA in patients with VTE, they have less drug interactions than VKA and do not need monitoring. The efficacy and safety of DOACs in patients with CAT have been evaluated in subgroup analyses of the large phase III trials comparing VKA and DOACS and in several cohort studies of patients with CAT; finally, randomized comparisons with LMWH are now available and allow a direct comparison of DOACs with the reference treatment of patients with CAT.

DOACs have been compared to LMWH overlapped and followed by VKA in 6 randomized trials including over 26,000 patients with VTE.[*4] A total of 1164 of these patients had underlying cancer.[*3] In this subgroup, DOACs were associated with a non-significant reduction in the risk of recurrent VTE (RR, 0.65, 95%CI, 0.38 to 1.09) and bleeding (RR, 0.67, 95% CI, 0.31 to 1.46) as compared with VKA.[*3] Of note, cancer patients in these trials had less advanced cancer, a smaller proportion received anticancer treatment and the mortality was lower than in the trials comparing LMWH and VKA in patients with CAT ().

Several cohort studies reporting the use of DOACs in patients with CAT have been summarized in a systematic review.[5] Most studies reported lower rates of recurrent VTE with DOACs than with LMWH. Patients were not randomized and the treatment groups were not comparable. In 2 studies that only included gastrointestinal and gynecological cancers, the rate of major bleedings was higher in patients receiving a DOAC.[5]

Two randomized controlled trials comparing DOACs with LMWH in patients with CAT have been reported recently.[*6,7] The Hokusai VTE cancer study was an open-label, noninferiority trial

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Table 1

Summary of the Hokusai-cancer VTE study and the Select-D study comparing DOACs with LMWH in patients with cancer-associated thrombosis.

Study	Patients (n)	Comparator	Experimental treatment	Outcomes	Results
Raskob et al	1046	Dalteparin 200 IU/kg 1 month followed by 150 IU/kg for at least 5 months	LMWH for at least 5 days followed by edoxaban 60 mg o.d. (total for at least 6 months)	Recurrent VTE or major bleeding at 12 months Recurrent VTE at 12 months Major bleeding at 12 months	12.8% (edoxaban), 13.5% (dalteparin); HR, 0.97; 95% CI, 0.70 to 0.36; p= 0.006 for noninferiority 7.9% (edoxaban), 11.3% (dalteparin) (difference, −3.4%, 95% CI, −7.0 to 0.2) 6.9% (edoxaban), 4.0% (dalteparin) (difference, 2.9%; 95% CI, 0.1 to 5.6).
Young et al	406	Dalteparin 200 IU/kg for 1 month followed by 150 IU/kg for 5 months	Rivaroxaban 15 mg b.i.d for 3 weeks followed by 20 mg o.d (total of 6 months)	Recurrent VTE at 6 months Major bleeding at 6 months	11% (dalteparin), 4%, (rivaroxaban); HR, 0.43 (95% CI, 0.19 to 0.99). 4% (dalteparin), 6% (rivaroxaban); HR, 1.83 (95% CI, 0.68 to 4.96).

DOAC = direct oral anticoagulants, LMWH = low-molecular-weight heparin, VTE = venous thromboembolism.

that randomized 1050 patients with cancer and acute VTE to receive LMWH for 5 days, followed by oral edoxaban or dalteparin.[*6] Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of recurrent VTE or major bleeding during 12 months after randomization and occurred in 12.8% of patients allocated to edoxaban and 13.5% of patients allocated to dalteparin (hazard ratio [HR], 0.97; 95% CI, 0.70 to 1.36; p=0.006 for noninferiority). Recurrent VTE occurred in 7.9% and in 11.3% of patients allocated to edoxaban and dalteparin, respectively (difference in risk, −3.4%; 95% CI, −7.0 to 0.2). Major bleeding occurred in 6.9% and in 4.0% of patients receiving edoxaban and dalteparin, respectively (difference in risk, 2.9%; 95% CI, 0.1 to 5.6). Treatment duration was longer with edoxaban. The risk of major bleeding was higher in patients with gastrointestinal cancer receiving edoxaban. The Select-D study was a prospective, randomized, open label, pilot trial that randomized 406 patients with CAT to receive either rivaroxaban or dalteparin, for 6 months.[7] The main outcome of recurrent VTE at 6 months occurred in 11% (95% CI, 7% to 16%) of the patients receiving dalteparin and in 4% (95% CI, 2% to 9%) of patients in the rivaroxaban group (HR, 0.43; 95% CI, 0.19 to 0.99). Major bleedings occurred in 4% (95% CI, 2% to 8%) of the patients receiving dalteparin and in 6%; (95% CI, 3% to 11%) of those receiving rivaroxaban (HR, 1.83; 95% CI, 0.68 to 4.96). Patients with cancer of the esophagus or gastroesophageal junction were excluded from enrollment in this trial after the data safety monitoring board reported a non-significant difference in major bleeding in these patients.[7]

In summary, the Hokusai VTE cancer study suggests that edoxaban is non-inferior to dalteparin for the combined outcome of recurrence and bleeding.[*6] Both the Hokusai VTE cancer and Select-D trials suggest a better efficacy but a higher bleeding risk of the DOACs.[7] Patients with gastrointestinal tumors appear to be at higher-risk of bleeding when receiving a DOAC. Other studies are currently assessing rivaroxaban and apixaban in patients with CAT.[8]

Future perspectives

The differences observed between DOACs and LMWH may allow to select patients at high risk of recurrent VTE for a DOAC and patients with a high bleeding risk and/or patients with gastrointestinal cancers for a LMWH. Such an approach is currently limited by the lack of validated tools for estimating these risks and the fact that bleeding and recurrent VTE share some common risk-factors.

Additional trials comparing other DOACs with LMWH are ongoing. Pending these results, patients with CAT who have a perceived high-risk of recurrent VTE or those who do not tolerate subcutaneous injections, may represent good candidates for receiving a DOAC as opposed to a LMWH, provided they do not have gastrointestinal cancers or a high perceived risk of bleeding. Although, risk of recurrent VTE and bleeding have been identified in patients with CAT, formal and validated tools for estimating the bleeding risk are needed to individualize the anticoagulant treatment in these difficult to treat patients.

Disclosures

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