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

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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. 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). 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.

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. A total of 1164 of these patients had underlying cancer. 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. 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. 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.

Two randomized controlled trials comparing DOACs with LMWH in patients with CAT have been reported recently. The Hokusai VTE cancer study was an open-label, noninferiority trial...
that randomized 1050 patients with cancer and acute VTE to receive LMWH for 5 days, followed by oral edoxaban or dalteparin. 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, 0.1 to 6.9). Major bleeding occurred in 6.9% and in 4.0% of patients receiving edoxaban and dalteparin, respectively (difference, 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. The main outcome of recurrent VTE at 6 months occurred in 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).

Disclosures
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The landmark Hokusai VTE cancer trial comparing for the first time a direct oral anticoagulant and low-molecular-weight heparin for the treatment of cancer-associated thrombosis

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