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Treatment of venous thromboembolism in patients with cancer: What news from clinical trials?

Melina Verso*, Laura Franco, Michela Giustozzi, Cecilia Becattini, Giancarlo Agnelli

Internal Vascular and Emergency Medicine - Stroke Unit, University of Perugia, Perugia, Italy

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ABSTRACT

About 15% of patients with cancer experience one or more episodes of venous thromboembolism (VTE) during the course of their disease. In patients with cancer, VTE has a substantial impact on the quality of life and care.

Current guidelines recommend low-molecular-weight heparin (LMWH) as first choice therapy for long-term anticoagulation in cancer patients with VTE. However, there are several practical issues concerning the long-term use of these anticoagulants.

In the last years, several direct oral anticoagulants (DOACs) have emerged as alternatives to heparins and vitamin K antagonists for the treatment of VTE, but data regarding both efficacy and safety of DOACs in the subgroup of patients with cancer treatments were limited. The results of two studies evaluating the clinical benefit of treatment of VTE with direct oral anticoagulants in patients with cancer have been recently presented. Several studies comparing DOACs with LMWH are currently ongoing.

1. Introduction

About 15% of patients with cancer experience one or more episodes of VTE during the course of their disease [1]. On the other hand, about 15% of patients with VTE are affected by cancer at the time of presentation of the thrombotic event [2]. About 4% of patients with VTE are newly diagnosed with cancer at the time of thrombotic event or in the year thereafter [3]. If affected by VTE, patients with cancer have a high risk of recurrence and bleeding related to anticoagulant therapy [4,5].

In patients with cancer, VTE has a substantial impact on the quality of life and care. VTE exposes cancer patients to the risk of anticoagulant treatment and may lead to otherwise unnecessary hospitalization. Annual health care costs in cancer patients with VTE were reported to be significantly higher than in cancer patients without VTE [6,7].

International guidelines [6–12] recommend low-molecular-weight heparin (LMWH) as first choice therapy for initial and long-term anticoagulation in cancer patients with VTE. However, there are several practical issues concerning the long-term use of these agents. LMWHs needs daily subcutaneous injection, weight-adjustment of the dose and can be associated with heparin-induced thrombocytopenia. These issues influence the quality of life of patients, in particular those with cancer.

Direct oral anticoagulants (DOACs) have several potential favorable features as an easier administration (oral administration and fixed dose regimens) half-lives similar to that heparins, predictable anticoagulant effect and poor drug interactions.

The results of two studies [13,14] evaluating the clinical benefit of treatment of VTE with direct oral anticoagulants in patients with cancer have been recently presented. Several studies with the same design are currently ongoing.

2. Epidemiology of VTE in cancer patients

In cancer patients, the risk for VTE is particularly high during the first months after the diagnosis of cancer, mainly due to surgery and chemotherapy, and at the end-stage of the disease, mainly due to the progression of cancer and the poor performance status.

The risk factors for VTE associated with cancer may be categorized as related to the patient and to the site, histology and extension of cancer. Patient risk factors are high BMI, high ECOG score and recent diagnosis of cancer [15]. Cancer of pancreas, brain, lung, gastrointestinal and genitourinary tract are more commonly associated with VTE [16]. A recent review reported higher rates of VTE in patients with different types of cancer with “metastatic disease” in comparison with patients with localized disease [16].

Cancer chemotherapy amplifies the prothrombotic effect of cancer cells and causes direct damage to the vascular endothelium [17]. Cisplatin is associated with about 2-fold increase in the risk of VTE when compared with non–cisplatin-based chemotherapy [18]. The combination therapy with platinum compounds and gemcitabine was reported

* Corresponding author at: Internal Vascular and Emergency Medicine –Stroke Unit, University of Perugia, Via Gerardo Dottori # 1, 06100 Perugia, Italy.
E-mail address: melina.verso@unipg.it (M. Verso).

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to be associated with a particularly high rate of VTE [19]. An association between antiangiogenic agents, such as bevacizumab, and anti-EGFR agents with an increased risk of VTE was initially reported [20] but not confirmed by more recent data [21].

A detrimental effect of VTE on survival was reported in patients with cancer and confirmed after adjusting for type and stage of cancer and co-morbid conditions. The estimated risk of death at two years in cancer patients who experienced VTE was reported to be about double in comparison with cancer patients without VTE [22,23]. This reduced survival was found in patients with several types of cancer [24–27] and it seems to be more pronounced if VTE occurs in patients with less extensive disease [12,24,25] or, regardless to cancer stage, in the first 3 months after cancer diagnosis [22]. In addition to patients with symptomatic VTE, a reduced survival was also observed in cancer patients with incidental VTE, detected by routine contrast-enhanced computed tomography scans performed for cancer staging [10].

3. Treatment of VTE in patients with cancer

Current guidelines recommended LMWH as first choice therapy for initial and long-term anticoagulation in cancer patients with VTE [6–12]. In the CLOT study, treatment for 6 months with dalteparin resulted in a significant reduction of about 50% in the risk of recurrence in comparison with the conventional treatment (dalteparin followed by INR-adjusted warfarin) from 17% to 9% [28]. The superiority of LMWH over conventional treatment in reducing recurrences was confirmed by a meta-analysis [29]. The more recently published CATCH trial showed a statistically non-significant risk reduction of 35% tinzaparin (at a dose of 175 UI/kg daily) in reducing the risk of overall recurrence of VTE [30]. In this study, a similar risk of major bleeding was seen in patients treated with tinzaparin or conventional treatment. At variance from the CLOT study, in the CATCH study no dose reduction was planned after the first month of treatment. The difference between the two studies could be explained by the lower recurrence rate in the CATCH study compared to the CLOT study. Fewer patients with metastatic disease (55% vs. 67%), ECOG performance status of 2 (23% vs. 36%), previous history of thrombosis (6% vs. 11%) or receiving chemotherapy (53% vs. 78%) were included in the CATCH trial as compared with the CLOT trial.

The optimal dose of LMWH for long-term treatment of VTE in cancer patients is not clearly defined. Dalteparin is recommended at full therapeutic doses during the first month and then at 75% of the initial dose for the remaining treatment period. The optimal duration of the anticoagulant treatment has been not investigated. Current guidelines recommend that the antithrombotic treatment should be administered for at least 3–6 months [6–12]. A prolongation of anticoagulation should be considered in patients with clinical evidence of active disease and/or in those receiving anticancer treatment, although the benefit of such extension remains unclear and should be balanced against the risk of bleeding [31]. A risk assessment model for predicting recurrent VTE in cancer patients (the Ottawa score) was been proposed [32].

In the last years, several direct oral anticoagulants (DOACs) have emerged as alternatives to heparins and vitamin K antagonists for the treatment of VTE [33–39]. Subgroup analyses [40,41] and meta-analyses [42,43] of subgroup of patients with history of cancer or active cancer included in six phase III trials evaluating DOACs for long-term treatment of VTE (about 5% of overall population) suggested that in these patients DOACs have efficacy and safety profiles similar to those observed in patients without cancer. The patients with cancer included in phase III clinical trials also had lower rates of metastatic disease and lower mortality than those included in the CATCH and CLOT trials, with limited data regarding active cancer treatments which could affect both efficacy and safety of DOACs.

3.1. Recent studies comparing LMWH with DOACs

Results from two studies [13,14] specifically evaluating the clinical benefit of treatment of VTE with DOACs in patients with cancer have been recently presented.

The recently published Hokusai VTE cancer [13] was a randomized, open-label, PROBE, non-inferiority trial comparing the efficacy and safety of edoxaban with dalteparin as monotherapy in the treatment of symptomatic or incidental venous thromboembolic events in patients with history of cancer or active cancer disease. In this trial patients with cancer were randomly assigned to receive either LMWH for at least 5 days followed by oral edoxaban at the dose of 60 mg once daily (edoxaban group) or subcutaneously dalteparin at the dose of 200 UI/kg once daily for 1 month followed by dalteparin at the dose of 150 UI/kg once daily (dalteparin group). Edoxaban was administered at the dose of 30 mg once daily in patients with a creatinine clearance of 30 to 50 ml per minute or in case of a body weight of 60 kg or less or in case of concomitant administration of potent P-glycoprotein inhibitors. The treatment was given for at least of 6 months and up to 12 months. The primary outcome was the combination of recurrent VTE and major bleeding at 12 months. This trial, that enrolled 1050 patients with VTE and cancer, showed an incidence of the composite of recurrent VTE and major bleeding of 12.8% in the edoxaban group and 13.5% in the dalteparin group (Hazard Ratio, 0.97; 95% CI 0.70 to 1.36; $p = 0.006$ for non-inferiority). Recurrence rates of 7.9% and 11.3% in the edoxaban and dalteparin groups respectively were observed. The VTE recurrence rate of 6 months of 8.8% in the dalteparin group is consistent with the rates reported with dalteparin in the CLOT end in the CATCH trials [28,30]. The rates of major bleeding were 6.9% in the edoxaban group and 4.0% in the dalteparin group, (hazard ratio, 1.77; 95% CI 1.03 to 3.04; $p = 0.004$). The difference in the rates of major bleeding was mainly due to the gastrointestinal bleeding in the edoxaban group that in largely occurred in patients who had gastrointestinal cancers. Of note, the median duration of assigned treatment was longer with edoxaban than with dalteparin (211 days versus 184 days, respectively). No statistical significant difference in terms of mortality at 12 months was observed between two treatment groups (36.6% versus 39.5%, in edoxaban and dalteparin groups, respectively).

The recently presented pilot Select-D study [14] is a randomized, open-label, trial comparing rivaroxaban (at a dose of 15 mg bid for 21 days, followed by 20 mg od) with dalteparin (200 IU/kg for the first 1 month followed by 150 IU/kg od) for the treatment of VTE in 406 patients with active cancer. After 6 months of treatment, patients with residual thrombosis were randomized to receive placebo or continue rivaroxaban for extended period of further six months. The main outcomes of this pilot study are to assess rates of major and clinically relevant non-major bleeding and to evaluate the extended anticoagulation treatment beyond 6 months in selected patients. The results showed a 6-month VTE recurrence rate of 11% in the dalteparin group and 4% in the rivaroxaban group. The rates of major and non-major clinically relevant bleeding were 17% and 6% in the rivaroxaban and dalteparin group, respectively. Of note, about 50% of included patients were affected by an incidental pulmonary embolism. Finally, the difference in 6-month overall mortality observed in this study was not statistically significant (70% and 75% in the dalteparin and rivaroxaban group, respectively).

3.2. Ongoing studies comparing LMWH with DOACs

Several trials aimed at improving the anticoagulant treatment in patients with cancer-associated VTE by comparing DOACs with LMWH are currently ongoing.

The Caravaggio study [44] is an investigator-initiated, multinational, prospective, randomized, open-label with blind end-point evaluation (PROBE), non-inferiority clinical trial (NCT03045406). The study has been planned to be conducted in 140 centers in ten European

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