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Current evidence of rivaroxaban in cancer-associated thrombosis

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Abstract

Patients with cancer have a high risk of developing cancer-associated thrombosis (CAT). Current guidelines suggest preferential use of low molecular weight heparins (LMWH) in CAT. The real-world data show that compliance with recommended LMWH therapy in cancer patients is low. Many patients discontinue injectable anticoagulants prematurely, in some cases even after a month, despite a high recurrence rate in this population. In recent years an increasing number of cancer patients are treated with direct oral anticoagulants, mainly rivaroxaban. Recent data confirming the safety and efficacy of rivaroxaban are starting to emerge and support the growing trend of using direct oral anticoagulants in cancer patients. If positive results of the recently completed SELECT-D trial are confirmed in the upcoming trials and registries of CALLISTO project, the guidelines for the treatment of CAT will have to be revised in favour of DOAC use in cancer-associated thrombosis.

Key words: venous thromboembolism, cancer, cancer-associated thrombosis, direct oral anticoagulants, low molecular weight heparins, vitamin K antagonists

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Introduction

Cancer-associated thrombosis is a complex problem in oncological patients who have significantly higher risk of developing venous thromboembolism (VTE) when compared with the general population [1, 2], the risk is estimated to be up to 7 times higher than in patients without cancer [3–6]. Between 4 and 20% of them will be affected with CAT [7–9], as the cancer itself is a hypercoagulable state [10, 11]. Additionally, reduced mobility, dehydration, cachexia are frequent in this population. Other factors facilitating thrombosis include chemotherapy agents, indwelling venous catheters and surgical procedures. Chemotherapy leads to a 2–6 fold increase in the likelihood of VTE compared with the risk in the general population [3, 12]. VTE is the second leading cause of death in this population [7, 13] and has a significant impact on morbidity and mortality [14].

According to the 2016 edition of the American College of Chest Physicians (ACCP) guidelines, the preferred antithrombotic agents are low-molecular-weight heparins (LMWH) [15]. In practice, many patients with VTE and cancer either do not receive this treatment or it is too short or they are treated with VKA instead.

The duration of treatment with LMWH should last 3 to 6 months and is recommended both by general [15] and oncology guidelines [14, 16], it should be extended beyond 6 months in patients with cancer and a high risk of recurrence, inoperable malignancy and low bleeding risk.

Venous thromboembolism in cancer patients

The risk of VTE is the highest in the first months after diagnosis, but the risk of recurrence afterwards is never negligible and reaches the peak within the first 6–12 months [17]. The treatment of CAT is associated with a 3-fold higher rate of recurrent thrombosis than

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in non-cancer patients [2, 18–22]. While antithrombotic treatment is an imperative in CAT, anticoagulant-induced bleeding risk should be always kept in mind, as it is increased in this population by 2.5 to 6 fold [2, 11]. A similar pattern has been observed with rivaroxaban [23].

VTE is one of the leading causes of death in this population, and negatively impacts treatment outcome [24–28]. The survival in cancer patients and diagnosed with VTE is lower (up to three times) when compared with cancer patients with no thrombosis [8, 29]. The highest rates of VTE are seen in patients with cancer of the brain, pancreas (especially metastatic), stomach, kidney, bladder, uterus, lung, or ovary [8, 9, 30, 31] and it is very likely to occur during the first year of the follow-up.

A recent meta-analysis reported on the incidence rates of venous thrombosis in cancer patients, stratified by background risk of venous thrombosis. They constitute an inhomogeneous group with the of the risk of developing VTE varying from 13 per 1000 person-years to 68 in high-risk patients (metastatic and high-grade cancer) [4].

Treatment of venous thromboembolism in cancer patients

Warfarin in no longer the standard of care in CAT due to its multiple interactions with other drugs, unpredictable INR and impaired oral drug intake due to vomiting, mucositis, and diarrhoea that often accompany cancer. VKA treatment in cancer patients is characterised with higher rates of major bleeding and recurrence in comparison with heparin [32, 33]. The VKA therapy is often suboptimal, even selected and closely monitored patients in pivotal trials had untherapeutic INR time (47% in CATCH and 46% in CLOT trial respectively).

The CLOT trial was the largest study favouring the use of dalteparin over warfarin in CAT [34]. It has shown the superiority of dalteparin in comparison to warfarin in preventing VTE recurrence and LMWHs have become standard of care for cancer-associated thrombosis. Ten years later, similar CATCH trial, which enrolled 900 patients, and compared tinzaparin to warfarin, failed to demonstrate a significant reduction of recurrent VTE for patients treated with LMWH for CAT (7.2% recurrent VTE for tinzaparin vs. 10.5% for warfarin). There were no differences in major bleeding between the arms of the study [35].

Both Einstein trials demonstrated noninferiority of rivaroxaban compared to standard therapy in general population [36, 37]. In consequence, this new standard has been endorsed by 2016 ACCP guidelines. The results of CAT treatment from both EINSTEIN-DVT and EINSTEIN PE studies signalled favourable treatment results in this subgroup of patients [38]. Recurrent VTE occurred in 7% of patients treated with LMWH and vitamin K antagonists (VKA) and in 5% of patients treated with rivaroxaban, while clinically relevant bleeding was observed in 14% of patients in the rivaroxaban arm and in 16% of patients receiving LMWH/VKA. Major bleeding occurred in 2% of patients on rivaroxaban and in 5% of patients LMWH/VKA. Patients with active cancer constituted only 5% of the studied population (6% in EINSTEIN-DVT and 4.6% in EINSTEIN PE), therefore the results could not be generalised. The details of malignancies in EINSTEIN trials were not collected, which has limited the adoption of rivaroxaban in clinical practice in cancer patients, also the subset of patients with cancer was too small to extrapolate the results of both studies to the population of cancer patients.

According to the 2016 ACCP guidelines, LMWHs are the preferred treatment for CAT. The efficacy and positive safety profile of rivaroxaban in CAT led to further studies (head-to-head comparison of LMWH vs. rivaroxaban in CAT) which will be discussed later in the article.

Overview of VTE treatment in cancer according to clinical guidelines

Specific national and international guidelines for VTE treatment in CAT were published or updated by a number of societies in recent years. American College of Chest Physicians, the American Society of Clinical Oncology, the National Comprehensive Cancer Network and other societies updated their guidelines in the management of CAT between 2015 and 2016 [14, 15, 39]. Due to the lack of data from the cancer-specific randomised trials, LMWHs are recommended as the first-line treatment for CAT, both in the acute phase and in long-term treatment. Oral anticoagulants were reserved for patients unable or unwilling to use long-term parenteral therapy. ACCP recognises DOACs as an alternative for LMWH based on grade 2C evidence (the same as for VKA). With regard to VTE prevention in ambulatory cancer patients, thromboprophylaxis is not recommended or there are no specific recommendations. In March of 2018 new guidelines from the International Society of Thrombosis and Hemostasis have been issued, based on 2 available RCTs in CAT population (Hokusai Cancer and Select-D). It has been highlighted that only rivaroxaban and edoxaban have been subjected to randomised trials in CAT population. It has been suggested that those two drugs should be preferentially used in cancer patients when the risk of bleeding is low, in those where the bleeding is high (gastroesophageal cancer, gastritis, mucositis) LMWH are still the best choice [40].

Are current guidelines implemented? Prescription patterns versus guidelines

Due to poor compliance with LMWHs, a growing number of cancer patients are receiving rivaroxaban for the treatment of CAT. Among 1.7 million US patients diagnosed with cancer and treated for CAT between 2009 and 2014, warfarin was prescribed in the 50% of patients despite recommendations, 40% were treated with LMWH and only 10% with other drugs [41]. In 2014 half of them were treated with LMWH, warfarin use fell below 30% and rivaroxaban use increased to 20%. Less than 1% of patients were treated with apixaban or dabigatran. The percentage of patients on rivaroxaban increased in the final year of the study, surpassing warfarin [41].

Compliance for LMWH was low, as many as 44% of patients discontinued therapy in less than a month, including patients with advanced cancer [42]. After 6 months only 13% of patients remained on LMWH. The data reflect patients' dissatisfaction with injectable anticoagulants and preference for oral drugs of which warfarin is nowadays less often prescribed in favour of rivaroxaban. The prescription patterns among patients in the US reflect poor implementation of the recent guidelines and preference for oral anticoagulants versus injectable anticoagulants in cancer patients.

Direct oral anticoagulants for cancer-associated thrombosis

All recent pivotal trials with rivaroxaban (Einstein) , apixaban (AMPLIFY) and edoxaban (Hokusai) included small samples of cancer patients [36, 37, 43, 44]. None of those trials targeted specifically cancer population. The indirect comparison of direct oral anticoagulants (DOAC) efficacy and safety of versus VKA in patients with CAT was assessed in a recent meta-analysis including 19 060 patients [45]. The publication revealed similar efficacy and a non-significant relative risk favouring improved safety with DOACs. Other data confirm that DOACs can be as effective and safe as traditional LMWH/VKA combination [46], the data are supported by other publications, it has also been found that VKA is responsible for more bleeding events than LMWH [47, 48]. Another meta-analysis evaluating 3242 patients found that recurrence rate and bleeding rates were comparable between DOACs and LMWH [49]. This finding has been confirmed by other retrospective, single-centre studies [23, 50].

A retrospective cohort study from the US covering the period between 2007 and 2015 found that the median duration of therapy with LMWH was only 1 month versus 3 months and 3.5 months for rivaroxaban and warfarin respectively. Risk of bleeding was similar between three agents, but the recurrence of VTE was the lowest for rivaroxaban [51]. Randomised controlled trials data comparing rivaroxaban with LMWH for long-term treatment are starting to emerge. Select-D is one of nine studies planned as a part of a bigger CALLISTO project, which will examine the use of rivaroxaban in people with active cancer. The goal of the project is to accumulate and analyse data of 4000 patients, both in randomised trials and registries.

The programme will research not only treatment but also prevention of VTE and additionally patient preference with regard to different anticoagulation regimens used for VTE treatment.

The ongoing CONCO-011 trial will report both the traditional endpoints (safety and efficacy) and also the satisfaction of patients treated with rivaroxaban versus LMWH. The trial is expected to be completed in 2018.

Select-D randomised trial

Select-D was the first prospective randomised trial comparing the efficacy and safety of rivaroxaban versus dalteparin in cancer patients presenting with the first symptomatic VTE including PE. Patients from 58 centres in Great Britain were followed between 2013 and 2016, the study randomised 406 patients (203 in each arm). Patients presented with locally advanced disease (38%), metastatic disease (59%), or haematological malignancies (3%). Recurrent VTE occurred in 4% (95% CI 2–9%) in the rivaroxaban group and 11% (95% CI 7–17%) in the dalteparin group. There were no differences between major bleeding in groups (both at 3–4%), clinically relevant bleeding was significantly higher with rivaroxaban (17%; 95% CI 12–22%) than with dalteparin (5%; 95% CI 3–9%). There were no intracranial bleedings. The authors concluded, that rivaroxaban is characterised by a very low VTE recurrence rate at 6 months in CAT, with a similar number of major bleeds reported across both trial arms, but more clinically relevant non-major bleeds [52].

CONCLUSIONS

There is an unmet need for anticoagulation therapy with an acceptable benefit-risk profile, offering therapy that patients with cancer are willing to comply with, both in the acute and in the long-term phase of VTE treatment.

The current evidence for DOACs in patients with CAT is favourable. Despite the lack of updated recommendations, increasing numbers of patients are treated with rivaroxaban for CAT, because too many of them do not comply with prescribed LMWH therapy. Lack

of long-term acceptance for injectable anticoagulants must be taken into account when initiating therapy in such patients. More data are needed with regard to the type of cancer and its stage versus DOACs efficacy and safety in upcoming trials. Oral anticoagulants may play a limited role in patients with gastrointestinal bleeding, active gastrointestinal malignancy, nausea and vomiting. LMWHs still will be preferred and will be more predictable in those patients.

Incidences of recurrent VTE and major bleeding among rivaroxaban-treated CAT patients seen in meta-analysis of real-world studies are similar to those seen with DOACs (rivaroxaban and edoxaban) in recently published randomised clinical trials for general population. However, the pooled incidence of all-cause mortality in this analysis was lower than seen in CAT trials, suggesting that rivaroxaban may preferentially be prescribed by clinicians to CAT patients with less severe cancer. With many trials underway, the paradigm of treating CAT preferentially with LMWH will be challenged soon. There is probably no class effect for DOACs, therefore each new drug has to be studied separately and results from one study with a specific DOAC cannot be extrapolated to another oral anticoagulant. Lack of recognition of DOAC for cancer patients is a reflection of data paucity from cancer-specific trials in 2015 and 2016 when many guidelines were updated. In 2018 we can demonstrate data proving that rivaroxaban can be offered as an alternative to selected cancer, or even the first choice therapy in patients unwilling to take injectable anticoagulants. Finally, it is worth mentioning that rivaroxaban in the only DOAC available in Poland where the summary of product characteristics does not forbid its use in cancer patients.

Conflict of interest

None.

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