REVIEW

Management of Venous Thromboembolism and Atrial Fibrillation in Patients with Cancer. The Role of Direct Oral Anticoagulants

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ABSTRACT

Cancer is accompanied by an increase of both thrombotic and hemorrhagic complications. Thus, the management of venous thromboembolism (VTE) or atrial fibrillation (AF) presents certain difficulties in oncologic patients. So far, low molecular weight heparins (LMWHs) have been proved the most effective and safe agents for long-term use in the VTE setting. However, the novel oral anticoagulants (Direct Oral Anti-Coagulants-DOACs), which are more friendly to use and begin to displace conventional anticoagulation in non-cancer patients, emerge as an attractive alternative. We present the latest data from randomized trials, meta-analyses of DOACs in oncologic populations and recent recommendation papers, as these agents claim their role in the management of cancer patients. ***Rhythmos 2019;14(1):5-9.***

Key Words: atrial fibrillation; oral anticoagulants; cancer; venous thromboembolism; dabigatran; rivaroxaban; apixaban; edoxaban; heparin; low molecular weight heparin

Abbreviations: AF = atrial fibrillation; DOACs = direct oral anticoagulants; LMWH = low molecular weight heparin; VKA = vitamin K antagonists; VTE = venous thromboembolism

Introduction

Malignant diseases pose an increased thrombotic risk upon patients, reaching a prevalence of 5-10%, which corresponds to a four to seven-fold increase over cancer-free individuals.[1-3] Several factors contribute to this predisposition and a risk score has been developed to assess the thromboembolic risk of patients receiving chemotherapy and guide management (Table 1).[4,5] Moreover, the frequent interventions these patients undergo, the use of anti-cancer therapy with potential vascular toxicity and the concurrent bleeding risk due to the cancer itself or the drug-induced thrombocytopenia further complicates the issue. So far, antithrombotic therapy has been confined to parenteral heparin and low molecular weight heparins (LMWH), but the novel orally administered anticoagulants forcefully seek their place in this clinical scenario offering ease of use and potentially improved compliance. We herein briefly summarize the latest data on the use of direct oral anticoagulants (DOACs) regarding their efficacy and safety in patients with malignancies to determine their emerging role in the prevention and treatment of venous thromboembolism (VTE).

Table 1. The Khorana score [4]

Patient Characteristic	Score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	1
Platelet counts ≥ 350,000 per mm3	1
Leukocyte counts > 11,000 per mm3	1
Hemoglobin< 10 g/dL or use of ESAs	1
BMI ≥ 35 kg/m2	1

High risk: score ≥ 3 / ***Intermediate*** risk: score 1 – 2 / ***Low*** risk: score 0. BMI = body mass index, ESAs = erythropoiesis-stimulating agents

Definitions

Active cancer is defined as: cancer diagnosed within the previous 6 months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer that is not in complete remission [6].

Recent guidelines

Several national and international societies have dealt with the issue of antithrombotic management in active cancer, as it came up shortly after the introduction of the novel oral agents in clinical practice. The European Society of Cardiology recommends the use of LMWH for the first 3-6 months after an acute thrombotic/ thromboembolic episode instead of vitamin K antagonists (VKA).[7,8] The American College of Chest Physicians (ACCP) proposes the use of LMWH over VKA or any of the novel oral agents.[9] The European Society of Medical Oncology (ESMO) recommends unfractionated heparin (UFH) or LMWH in the acute setting and LMWH in chronic basis.[10] The American Society of Clinical Oncology (ASCO) prioritizes LMWH both for prophylaxis and long term treatment.[11] The same suggestions are endorsed by the International Society on Thrombosis and Hemostasis (ISTH), International Initiative on Thrombosis and Cancer (ITAC-CME) and National Comprehensive Cancer Network (NCCN).[12-14]

These statements do not provide robust recommendations on the use of novel oral anticoagulants as extensive evidence at the time of their completion was lacking. They are based on several trials comparing LMWH versus VKAs in patients with malignant disease,[15-18] the most emblematic among them being the CLOT trial,[19] which showed that extended administration of daltaparin was more effective than VKA in reducing the risk of

recurrent thromboembolism in cancer patients, without affecting bleeding rates or mortality.

Contemporary evidence

Since the publication of the aforementioned guiding statements new data have been gathered that deserve discussion. Initially, subgroup analyses of patients with cancer from the population enrolled in the clinical trials of DOACs were performed and showed that all four drugs (dabigatran, rivaroxaban, apixaban, edoxaban) were comparably efficient and safe with warfarin in the subpopulation with active cancer.[20-23]

At the same time, meta-analyses of these large trials, which included a small number of cancer patients, became available. Vedovati et al analyzed 6 trials (AMPLIFY 2013, EINSTEIN-DVT 2010, EINSTEN-PE 2012, HOKUSAI VTE 2013, RECOVER I & II 2013) comparing all four DOACs with conventional anticoagulants. The number of patients with malignancies in the individual studies comprised 2.5%-9.4% of the total study population and in total they reached 1132 patients. DOACs were associated with a non-significant risk reduction for recurrent thromboembolic events and major bleeding when compared with VKA. [24]

Similar results were reported by Brunetti et al who performed a meta-analysis of 9 studies (AMPLIFY 2013, EINSTEIN-DVT 2010, EINSTEN-PE 2012, HOKUSAI VTE 2013, RECOVER I & II 2013, MAGELLAN 2011, ADOPT 2011, RE-MEDY 2103), with the 6 of them being common with the former meta-analysis, while this meta-analysis included two additional studies which compared rivaroxaban and apixaban with LMWH for thromboprophylaxis (MAGELLAN 2011, ADOPT 2011). DOACs showed a non-significant reduction in thromboembolism and bleeding rates in comparison to LMWH followed by VKA. Interestingly, the reduction in hemorrhagic episodes was driven by the difference between DOACs and VKA. When compared to LMWH only, DOACs were associated with a significant rise in bleeding complications.[25]

More recently, another meta-analysis was published, focusing on rivaroxaban. The authors used data from the subgroup analysis of the EINSTEIN-DVT and EINSTEIN-PE trials, along with another three relatively small retrospective studies comparing rivaroxaban to enoxaparin or warfarin in cancer patients. The analysis revealed a non-significant decrease in VTE recurrence and major bleeding in the rivaroxaban group. [26]

In 2018, two randomized clinical trials comparing DOACs with LMWH for the treatment of VTE in cancer patients were published. The Hokusai VTE Cancer trial was a non-inferiority trial which enrolled 1046 patients with active cancer or cancer diagnosed within the previous two years, excluding basal-cell or squamous-cell skin carcinomas, who had symptomatic or incidentally detected pulmonary embolism or deep vein thrombosis in the popliteal vein or above it. [27] They were randomly assigned in a 1:1 ratio to at least 5 days of any LMWH followed by edoxaban 60 mg daily versus dalteparin 200IU/kg daily for 30 days followed by 150 IU/kg daily. Patients with reduced creatinine clearance (30-50 ml/min), low body weight (<60 kg) or on P-glycoprotein inhibitors, would receive edoxaban 30 mg daily. Treatment was continued for at least 6 months and up to 12 months, at the discretion of the attending physician. The primary end-point was a composite of recurrent venous thromboembolism or major bleeding. Recurrent thromboembolism, major bleeding and all-cause death were all included in the secondary end-points. The primary outcome occurred in 12.8% of patients in the edoxaban arm vs 13.5% in the dalteparin arm (hazard ratio - HR, 0.97; $p = 0.006$ for non-inferiority; $p = 0.87$ for superiority). Recurrent thromboembolism and total mortality did not differ. Major bleeding was significantly more common among patients treated with edoxaban (HR, 1.77; $p = 0.04$), a difference driven by upper gastrointestinal bleeding mainly in patients diagnosed with gastrointestinal malignancies. However, severe major bleeding events (hemodynamic instability, intracranial hemorrhage, fatal hemorrhage) were equally distributed between study groups. [27]

The SELECT-D trial allocated 406 patients with active cancer and symptomatic pulmonary embolism (PE), incidental PE, or symptomatic lower extremity proximal deep vein thrombosis (DVT) to dalteparin (200 IU/kg daily for one month followed by 150 IU/kg daily for 5 months) or rivaroxaban (15 mg bid for 3 weeks and then 20 mg per day for a total of 6 months) in a 1:1 fashion.[28] The primary end point was the recurrent VTE during the 6 months of the trial. Safety end points included major bleeding and clinically relevant non-major bleeding. Rivaroxaban was associated with lower VTE recurrence than dalteparin (HR, 0.43), albeit with an increased occurrence of clinically relevant non-major bleeding (HR, 3.76). Major bleeding incidence did not differ between study arms. Most episodes were of gastrointestinal (GI) origin and esophageal or gastric cancer were more commonly involved. [28]

Al Yami et al performed a meta-analysis which included Hokusai VTE cancer study in its analysis, together with RE-COVER I, RE-COVER II, EINSTEIN-DVT, EINSTEIN-PE, RE-MEDY,AMPLIFY, Hokusai-VTE.[29] The authors compared DOACs vs LMWH followed by VKA or LMWH (Hokusai VTE cancer) over

the efficacy outcome of VTE recurrence and safety outcome of major bleeding or clinically relevant non-major bleeding. DOACs decreased VTE recurrence in patients with cancer compared with conventional anticoagulants by 36% (relative risk - RR = 0.64) without any significant influence on bleeding rates (RR = 1.00) [29].

A latest meta-analysis of randomized trials, the majority of which were performed exclusively in patients with active cancer, including the two most recent SELECT-D and HOKUSAI VTE Cancer studies, showed that DOACs reduced VTE recurrence rate by 28% in comparison to LMWH (RR: 0.72) and by 54% in comparison to VKAs (RR: 0.46).[30] Not surprisingly, LMWH was more effective than VKAs (RR: 0.64). There was a trend towards more major bleeding events when DOACs were used vs LMWH (RR: 1.14) and fewer events when DOACs or LMWH were used vs VKAs (RR, 0.85 and RR, 0.75 respectively). The authors concluded that DOACs are probably the most effective while LMWHs are the safest agents. All-cause mortality did not differ between any of the three anticoagulant classes. [30] Similar results were obtained by the meta-analysis of Li et al. [31]

Guidelines update

In view of the latest evidence, the oncology-related scientific societies incorporated the data on DOACs in the updated versions of the relevant guidelines. So far, the ISTH has published recommendations in 2018 where the use of DOACs is recommended for cancer patients with new VTE, low risk of bleeding and no interaction between the anticoagulant and their oncologic medication. Rivaroxaban and edoxaban are the preferred choices as these drugs have been tested in randomized trials. [6]

The Italian Society of Internal Medicine (SIMI) has recently published a comprehensive position paper which recognizes the emerging role of DOACs (presently rivaroxaban and edoxaban) in cancer patients with VTE and low risk for hemorrhage, but still lends its support to the well tested option of LMWH both in the acute phase and in the long-term management. [32]

Imberti et al, in an expert guidance article, recommend the use of DOACs, prioritizing edoxaban, in the management of VTE in patients with cancer and no contraindications. [33]

Atrial fibrillation

In the clinical setting of atrial fibrillation (AF) the evidence regarding oncologic patients is still scarce and is derived mainly from analyses of patients with cancer included in the large randomized trial of DOACs in AF. In an analysis from the ARISTOTLE trial, the efficacy and safety of apixaban compared with warfarin as established in the original study were preserved among the patients with malignant diseases. Apixaban was associated with a better outcome in terms of the composite of stroke/ systemic embolism, myocardial infarction, and death in active cancer (HR 0.30) in comparison to patients without cancer (HR 0.86). This advantage was lost in remote cancer (HR 1.46). [34]

A total of 1153 patients from the ENGAGE AF-TIMI 48 Trial who were diagnosed post-randomization with cancer or recurrence of remote malignancy were analyzed by Fanola et al. The efficacy of edoxaban versus warfarin was consistent regardless of the co-existence of cancer or not in terms of stroke/systemic embolism both in high and low dosing. [35]

Two more studies have addressed the use of DOACs in cancer patients with AF, without however performing any comparison with other anticoagulants. The first study which aimed to assess the thromboembolic and bleeding risk in this population, enrolled 1999 patients without cancer and 289 patients with cancer (active or remote) and non-valvular AF treated with any DOAC their physician would prefer. Thromboembolic events as well as major bleeding were more frequent in cancer patients (2.1% vs 0.8% patient-year, HR 2.58 and 6.6% vs 3% patient-year, HR 2.02, respectively). Thromboembolic risk was highest among patients with active cancer, and the increased incidence of major bleeding in oncologic patients was attributed to gastrointestinal hemorrhage. [36]

The second study was conducted to assess the safety and efficacy of rivaroxaban in patients with active cancer and AF. A total of 163 patients were identified in the medical records. The estimated 1-year cumulative incidence of ischemic stroke was 1.4% and major bleeding was 1.2%. The authors concluded that the efficacy and safety of rivaroxaban in patients with active cancer and AF is comparable to that reported in the general population of the ROCKET-AF trial [37].

Conclusion

More data are obtained every day to help us decide whether and when to use the DOACs in patients with VTE or AF and active malignancies. In the AF setting the information in the literature is still limited. In the management of VTE, so far these drugs seem equally effective in this group of patients as in the general population, without severely compromising safety. A trend towards or a slight increase of bleeding complications in comparison to LMWH is the common finding of randomized trials and meta-analyses. Sobieraj et al. concluded in their meta-analysis that DOACs are probably the most effective and LMWH the safest choice.

Table 2. Ongoing clinical trials testing DOACs in oncologic patients with VTE [38]

Study	ClinicalTrials.gov identifier	DOAC	Comparator
The CAP Study: Apixaban as treatment of venous thrombosis in patients with cancer	NCT02581176	Apixaban	None
ADAM-VTE: A phase III, randomized, open-label study evaluating apixaban safety in subjects with cancer-related venous thrombo-embolism	NCT02585713	Apixaban	Dalteparin
CARAVAGGIO: Apixaban for the treatment of venous thromboembolism in patients with cancer	NCT03045406	Apixaban	Dalteparin
PRIORITY: randomized phase II study to compare the safety and efficacy of dalteparin versus rivaroxaban for cancer associated venous thromboembolism	NCT03139487	Rivaroxaban	Dalteparin
CASTA-DIVA: Cancer-associated thrombosis, a pilot treatment study using rivaroxaban	NCT02746185	Rivaroxaban	Dalteparin
CANVAS: DOACs versus LMWH ± warfarin for VTE in cancer	NCT02744092	Rivaroxaban Apixaban Edoxaban Dabigatran	Dalteparin, enoxaparin, fondaparinux ± warfarin
CONKO-011: Rivaroxaban in the treatment of VTE in cancer patients	NCT02583191	Rivaroxaban	Enoxaparin /Tinzaparin / Dalteparin
COSIMO: A non-interventional study on Xarelto for treatment of VTE and prevention of recurrent VTE in patients with active cancer	NCT02742623	Rivaroxaban Following 4 weeks therapy with LMWH and/or warfarin	Observational
Hong Kong study: A prospective study of dabigatran etexilate as primary treatment of malignancy-associated venous thromboembolism	NCT03240120	Tinzaparin 175 IU/kg daily for 6 days, then dabigatran 150 mg bid from day 6 onward till 6 months after underlying disease remission	Observational

Bleeding is of GI origin mostly and is associated with neoplasms of the GI system. Based on the available evidence, DOACs could constitute a reliable choice in patients at low risk of bleeding, provided that no interactions exist between systemic and anticoagulant therapy, their greatest advantage being the ease of use and improving patient quality of life. However, only two of the DOAC family, namely rivaroxaban and edoxaban, have been tested in randomized trials and more research is warranted. Indeed, several trials are ongoing and the medical community awaits their results with great interest (Table 2). [38] Scientific societies have started to update obsolete guidelines and recommendations to include use of DOACs, and more statements are expected soon in order to establish DOAC's position in the therapeutics of cancer patients.

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