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Direct Oral Anticoagulants and Cancer-Associated Thrombosis Management. Where Do We Stand in 2019?

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Abstract

Direct oral anticoagulants (DOACs) are now widely used for the management of venous thromboembolism (VTE) that now includes cancer-associated thrombosis. This review summarizes recent data on VTE prophylaxis and treatment, new challenges, guidelines, and updates as well as the current place for DOACs on the emerging cancer-associated VTE management landscape.

Keywords

direct oral anticoagulants, cancer, venous thromboembolism

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Introduction

Venous thromboembolism (VTE) is a prevalent global cardiovascular disease, with high-associated mortality. A significant number of patients with cancer develop VTE during the course of their disease.[1] Cancer-associated thrombosis (CAT) increases morbidity, mortality, and costs for patients with malignancy. Cancer-associated thrombosis management is challenging, as standard anticoagulation treatment leads to recurrence rates 2-fold and major bleeding rates 3-fold higher, when compared to noncancer VTE treated.[2] Traditional treatment with low-molecular-weight-heparin (LMWH) followed by vitamin K antagonists (VKA) was frequently inadequate. International normalized ratios were poorly controlled, with unacceptable recurrences and major bleedings rates.[3] In this setting, LMWHs were studied in early 2000 as an alternative to VKA for CAT treatment. Five landmark randomized control trials (RCT) demonstrated that LMWH was more effective than VKA, with similar or superior safety profiles.[4-8] Guidelines issued in 2016 recommend LMWH over VKA for CAT management,[9] but clinicians and oncologists have not fully embraced this practice; patients with cancer do not tolerate daily injections for extended periods of time, resulting in poor compliance and increased recurrence rates. Low-molecular-weight-heparin–associated costs remain a major issue.[10]

Direct oral anticoagulants (DOACs) were primarily developed for stroke prevention in atrial fibrillation patients, but also widely tested for different indications, including VTE prophylaxis and treatment. The pharmacological properties of DOACs offer appealing alternatives to the limitations associated with LMWH and VKAs. Direct oral anticoagulants are administrated orally and have a more rapid onset of action and more predictable pharmacodynamics (PD) than VKA, precluding the need for dose adjustment and routine monitoring. Direct oral anticoagulants are also associated with fewer risks of food–drug and drug–drug interactions compared to VKA, attractive properties for the management of CAT.[11] Recent trials have explored DOACs for VTE prevention and treatment in the cancer landscape. This review summarizes the main findings

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of these pivotal trials and future directions for DOACs in CAT management.

Direct Oral Anticoagulants for VTE Prevention in Patients With Cancer

Venous Thromboembolism Prevention of in-Hospital Patients With Cancer

Direct oral anticoagulants have been evaluated for the prophylaxis of VTE for hospitalized medically ill patients; however, no trials were conducted to evaluate prophylaxis of DOACs for in-hospital patients with cancer. In general, DOACs failed to prevent VTE as compared to enoxaparin in the majority of RCT for the medically ill population, with the exception of betrixaban.[12] Venous thromboembolism prophylaxis in the in-hospital medically ill is challenging. Guidelines recommend parenteral anticoagulants—LMWH—(mainly enoxaparin, based on the MEDENOX trial or fondaparinux based on the ARTEMIS trial) during hospitalization only.[13,14] Both parenteral compounds are effective, providing relative risk reductions (RRR) around 50% when compared to placebo. Direct oral anticoagulants were tested for VTE prophylaxis in the medically ill population, including both in-hospital and an extended out-of-hospital phase (35 days). The Extended Clinical Prophylaxis in Acutely Ill Medical Patients trial with enoxaparin,[15] the Apixaban Dosing to Optimize Protection from Thrombosis trial,[16] the Multicenter, Randomized, Parallel Group—Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin trial,[17] the Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients trial,[12] and the MARINER trial[18] evaluated different strategies to protect patients from VTE events up to 35 days post-discharge. Results were poor: Studies of extended thromboprophylaxis have shown either excess major bleeding (it should be noted that DOACs were given for a longer period of time than LMWH—this may partly contribute to more bleeding) or a benefit that was based mainly on reducing the risk of asymptomatic deep vein thrombosis (DVT), a surrogate end point detected by mandatory venous ultrasound at the end of the treatment period.[12,15-18] Only betrixaban demonstrated benefits in the overall studied population as compared to placebo for extended VTE prophylaxis for medically ill patients. Despite its approval by the Food and Drug Administration in the United States for this indication, betrixaban failed to demonstrate superiority in the initial prespecified cohort of high D-dimer level patients.[12] Moreover, in both ARTEMIS and MEDENOX trials, the planned exposure treatment was 6 to 14 days, whereas with DOACs trial planned exposure was around 30 days. Furthermore, no benefit in the cancer subgroup was identified. Patients with cancer in those studies were underrepresented, intentionally excluded or operationally defined to an extent that interpretations to CAT would not be conclusive. In summary, for in-hospital medically ill patients, current data support the use of parenteral enoxaparin, or fondaparinux, during their hospitalization.[19]

Venous Thromboembolism Prevention in Surgical Patients With Cancer

Direct oral anticoagulants, despite their favorable efficacy and safety profile, as well as their fast onset and offset pharmacokinetics (PK), were never properly tested in an RCT for surgical patients with cancer. Concerns with post-op absorption, leading to unpredictable PK/PD response, affecting efficacy and particularly safety, discouraged the development of such trials. An ongoing trial (PRO-LAPS II) is currently evaluating rivaroxaban or placebo for extended antithrombotic prophylaxis after laparoscopic surgery for colorectal cancer (NCT03055026). Results are not available yet. The standard of care for VTE prevention in surgical patients with cancer, including major thoracic and abdominal surgical procedures are parenteral drugs, such as LMWH and fondaparinux, for at least 30 days postoperative.[19]

Venous Thromboembolism Prevention of Out-of-Hospital Chemotherapy Patients With Cancer

The vast majority of CAT events (approximately 74%) occur in the outpatient setting, particularly in high-risk patients undergoing chemotherapy.[20] Ultra-LMWH (semuloparin) and an LMWH (nadroparin) were tested in 2 large prospective RCTs for primary thromboprophylaxis in ambulatory patients receiving chemotherapy. These parenteral drugs significantly decreased the risk of symptomatic VTE compared to placebo, without increasing the risk of major or clinically relevant nonmajor bleeding (CRNMB).[21,22] A recent meta-analysis showed that primary thromboprophylaxis with LMWH significantly reduced the rate of symptomatic VTE in ambulatory patients with cancer receiving chemotherapy compared to no prophylaxis (RR: 0.54, 95% confidence interval [CI]: 0.38-0.75) without significantly increasing the risk of major bleeding (RR: 1.44, 95% CI: 0.98-2.11).[23] This strategy was however never received approval from regulatory agencies because of the low absolute number of events. In the semuloparin trial, a reduction from 3.4% to 1.2% of symptomatic events led to an RRR = 64% (hazard ratio [HR]: 0.36; 95% CI: 0.21-0.60; $P < .001$), but its absolute reduction of 2.2% of symptomatic events was not compelling enough to warrant approval for this indication. Moreover, ultra-LMWH and LMWH are parenteral compounds which are not well tolerated by patients undergoing chemotherapy.

Direct oral anticoagulants have been tested in CAT management in phase II studies. The phase-II pilot ADVOCATE study randomized 125 patients with cancer treated with systemic anticancer therapy to either receive once daily doses of apixaban (5 mg, 10 mg, or 20 mg), or placebo. No patient receiving any of the 3 doses of apixaban developed symptomatic VTE, compared to 3 (10%) of 29 patients in the placebo group. No major bleeding occurred in the 5- and 10-mg apixaban groups,

2 major bleeding events occurred in the 20-mg apixaban group, and 1 occurred in the placebo group.[24]

Direct oral anticoagulants might be more beneficial in these out-of-hospital settings, if investigators entered patients at high enough VTE risk to demonstrate the absolute benefit of a thromboprophylaxis strategy. Such lessons were learned from previous parenteral trials. The validated Khorana score, which was based on a collection of readily available clinical (type of cancer, body mass index $\geq$ 35 k/m^2) and biological parameters (platelet count > 350 000/L, leukocyte count > 11 000/L, hemoglobin < 10 g/dL or use of erythropoiesis-stimulating agent), was used to assess VTE risk in patients receiving chemotherapy in DOACS trials. This score identifies low VTE-risk patients (score of 0), intermediate VTE-risk patients (score of 1-2), and high VTE-risk patients (score $\geq$ 3), improving the chance to find which chemotherapy patient would benefit the most from anticoagulation strategy.[25] This score has a good negative predictive value but regarding the positive predictive value indeed, most of the cancer VTE cases are outside the high-risk category.[26]

The AVERT trial randomized 574 patients with cancer at intermediate or high risk of VTE (Khorana score $\geq$ 2) who were initiating chemotherapy to receive apixaban (2.5 mg twice daily) or placebo for 6 months. At 6-month follow-up, the rate of objectively confirmed VTE, which was the primary efficacy outcome, was significantly lower in the apixaban arm compared to placebo (4.2% vs 10.2%, HR: 0.41, 95% CI: 0.26-0.65, $P < .001$). Major bleeding, the primary safety outcome, as expected, was significantly higher in the apixaban group compared to placebo (3.5% vs 1.8%, HR: 2.00, 95% CI: 1.01-3.95, $P = .046$). The rate of CRNMB, the secondary safety outcome, did not differ between the 2 treatment arms (7.3% in the apixaban arm vs 5.5% in the placebo arm, HR: 1.28, 95% CI: 0.89-1.84). Rates of death from any cause were similar between the 2 treatment arms (12.2% in the apixaban arm vs 9.8% in the placebo arm, HR: 1.29, 95% CI: 0.98-1.71).[27]

The CASSINI trial randomized 841 patients with cancer (Khorana score $\geq$ 2), initiating chemotherapy to either receive rivaroxaban (10 mg once daily) or placebo for 6 months. Patients with primary or metastatic brain cancer and those at high risk of bleeding were excluded. Over the entire 6-month follow-up, the composite primary end point of DVT, PE, and VTE-related death occurred in 5.95% of patients in the rivaroxaban group and 8.79% in the placebo group (HR: 0.66, 95% CI: 0.40-1.09, $P = .101$, number needed to treat [NNT] = 35). However, during the on-treatment period, a prespecified analysis demonstrated that patients on rivaroxaban experienced fewer primary end point events compared to patients on placebo (HR: 0.40, 95% CI: 0.20-0.80, $P = .007$; NNT = 26). The rate of major bleeding and CRNMB did not differ between the 2 treatment arms (HR: 1.96, 95% CI: 0.59-6.49, $P = .265$ and HR: 1.34, 95% CI: 0.54-3.32, $P = .53$). All-cause mortality rates were similar between groups (20.0% in patients on rivaroxaban vs 23.8% in patients on placebo, HR: 0.83, 95% CI: 0.62-1.11, $P = .213$). Given the severity of the primary disease, the discontinuation of study drug was high (34%), which explains the failure to achieve superiority of the primary end point on the ITT analysis.[28] Both regimens are not yet approved for clinical use.

Direct Oral Anticoagulants for the Treatment of CAT

The RCTs that evaluated DOACs for the long-term and extended treatment of VTE were not designed to evaluate cancer because the comparator was LMWH followed by VKA. Existing guidelines recommend LMWH as monotherapy for CAT. However, a small subset of patients with CAT was included in these studies. A meta-analysis including 6 studies (2 with dabigatran, 2 with rivaroxaban, 1 with edoxaban, and 1 with apixaban), evaluated 1132 patients. Venous thromboembolism recurred in 23 (3.9%) of 595 and in 32 (6.0%) of 537 patients with cancer treated with DOACs and conventional LMWH followed by VKA treatment, respectively (OR: 0.63; 95% CI: 0.37-1.10; I2, 0%). Major bleeding (MB) occurred in 3.2% and 4.2% of patients receiving DOACs and conventional treatment, respectively (OR: 0.77; 95% CI: 0.41-1.44; I2, 0%). These studies suggested that DOACs were at least as efficacious and safe as standard therapy for CAT.[29] A retrospective single-arm cohort study evaluating 400 patients with CAT treated with rivaroxaban showed VTE recurrence of 3.25% with MB occurring in 5.5% during the treatment.[30] These studies set the stage for RCTs comparing DOACs to LMWH.

The investigator-initiated SELECT-D pilot trial randomized 406 patients with cancer with symptomatic or incidental VTE having an Eastern Cooperative Oncology Group (ECOG) Performance Status $\leq$2 to receive rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily—The EINSTEIN program dose regimen)[31] or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily—the CLOT trial dose regimen)[6] for 6 months. At 6-month follow-up, the cumulative rate of recurrent VTE was significantly lower with rivaroxaban compared to dalteparin (4% vs 11%, HR: 0.43, 95% CI: 0.19-0.99). MB was similar between the 2 groups (6% vs 4% in the rivaroxaban and dalteparin arms, respectively, HR: 1.83, 95% CI: 0.68-4.96), while the cumulative rate of CRNMB was significantly higher in patients treated with rivaroxaban compared to dalteparin (13% vs 4%, respectively, HR: 3.76, 95% CI: 1.63-8.69). Overall 6-month survival did not differ between the 2 treatment arms (75% vs 70% in the rivaroxaban and dalteparin arms, respectively). In patients with esophageal or gastroesophageal cancer, major bleeding tended to occur more frequently with rivaroxaban than with dalteparin (36% vs 11%, in the rivaroxaban and dalteparin arms, respectively). Most major bleeding events in the rivaroxaban group (7 of 11) were gastrointestinal. Most CRNMB events occurring in patients treated with rivaroxaban were gastrointestinal (9 of 25) or genitourinary (11 of 25).[32]

The HOKUSAI-VTE cancer trial was a global, prospective, PROBE (Prospective Randomized Open, Blinded End-point) noninferiority trial that compared the safety and efficacy of edoxaban to dalteparin in the treatment of VTE in patients with

CAT for 12 months. Different from other RCTs in CAT, this trial assessed for a composite outcome of recurrent VTE or MB. This was an innovative composite primary efficacy end point, based on the idea that VTE recurrence and MB are the 2 most prominent complications expected in anticoagulation therapy for CAT. Adult patients with CAT (with active cancer) were randomly assigned, in a 1:1 ratio, to receive either edoxaban or dalteparin. Edoxaban was started after a course of therapeutic dose LMWH (not necessarily dalteparin) was given subcutaneously for at least 5 days. Edoxaban was administered orally at a fixed dose of 60 mg once daily, with the dose adjusted to 30 mg if the creatinine clearance was between 30 and 50 mL/min, body weight $\leq$60 kg or concomitant use of P-gp inhibitors. Dalteparin was given subcutaneously at a dose of 200 IU per kilogram of body weight once daily for 30 days, with a maximum daily dose of 18 000 IU. Thereafter, dalteparin was given at a dose of 150 IU per kilogram once daily. In all the patients, treatment with edoxaban or dalteparin was to be continued for at least 6 months and up to 12 months. One hundred forty-six patients were included in the modified intention-to-treat analysis. A primary outcome event (VTE + MB) occurred in 67 (12.8%) of the 522 patients in the edoxaban group as compared with 71 (13.5%) of the 524 patients in the dalteparin group (HR: 0.97; 95% CI: 0.70-1.36; $P = .006$ for noninferiority; $P = .87$ for superiority). Recurrent VTE occurred in 41 (7.9%) patients in the edoxaban group and in 59 (11.3%) patients in the dalteparin group (difference in risk: -3.4 percentage points; 95% CI: -7.0 to 0.2). The rate of major bleeding was significantly higher with edoxaban than with dalteparin. MB occurred in 36 (6.9%) patients in the edoxaban group and in 21 (4.0%) patients in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI: 0.1-5.6). This difference was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban.[33]

These findings are consistent with the results of all studies of DOACs for CAT management. The increase in upper gastrointestinal major bleeding occurred mainly in patients who had entered the trial with gastrointestinal cancer. Despite the increase of bleeding with DOACs, no increase of fatal or intracranial bleeding was observed with these drugs.

The results of the phase-IV ADAM-VTE trial, another investigator-initiated study were presented at the 60th American Society of Hematology annual meeting. Three hundred patients with cancer having an ECOG performance status $\leq$2 with acute symptomatic or incidental VTE were randomized to receive apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily) for 6 months. The primary safety end point (MB) was similar in the 2 treatment groups (0.0% [0 of 145 patients] in the apixaban arm vs 2.1% [3 of 142 patients] in the dalteparin arm, $P = .9956$). The rates of the secondary safety composite end point (major and CRNM bleeding) were also similar for both groups (9%). Venous thromboembolism recurrence rate was significantly lower with apixaban compared to dalteparin (3.4% [5 of 145 patients] vs 14.1% [20 of 142 patients] in the apixaban and dalteparin arms, respectively, HR: 0.26, 95% CI: 0.09-0.80, $P = .0182$). The rates of death did not differ between the 2 treatment arms (15.9% vs 10.6% in the apixaban and dalteparin arms, respectively, HR: 1.36, 95% CI: 0.79-2.35).[34] The ADAM trial is a small study encumbered by the limitations of an exploratory trial. However, its results suggest a trend to a favorable risk–benefit ratio for apixaban in the treatment of CAT. More robust data with apixaban for CAT treatment are expected with the CARAVAGGIO trial (NCT03045406) that is planned to enroll 1200 patients with cancer with acute VTE to receive apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) or dalteparin (200 IU/kg daily for 1 month followed by 150 IU/kg daily) for 6 months. The primary efficacy end point is the rate of recurrent VTE and the primary safety outcome is the rate of MB. Recruitment is nearly complete with results expected later this year.

Based upon the data mainly from the SELECT-D and HOKUSAI cancer trials, the Scientific and Standardization Committee on Hemostasis and Malignancy of the International Society on Thrombosis and Hemostasis (ISTH) recently released a guideline on CAT management. Edoxaban and rivaroxaban are suggested for patients with cancer with established VTE, who are at low risk of bleeding, and who have no potential drug–drug interactions with concurrent systemic anticancer therapy. The guidance emphasizes the importance of physician–patient shared decision-making, which considers patient preferences and values. It also suggests that for high risk of bleeding gastrointestinal CAT patients, LMWHs should still be considered first-line therapy.[35]

Table 1 summarizes the trial characteristics and main outcomes for DOACs in the management of VTE prophylaxis and treatment for CAT.

Unsolved Issues

The pathophysiology of the prothrombotic condition in patients with cancer is multifactorial and involves molecular dysregulation, inflammation, endothelial dysfunction, and a specific alteration in cellular and receptor functions which are dependent on the type and stage of cancer. These processes lead to venous and arterial thrombosis, microvascular abnormalities, and bleeding. At this time several ongoing clinical trials with DOACs in comparison to LMWH are carried out to demonstrate the relative efficacy of these agents in the management of CAT. The DOACs are single target drugs without any effect on the release of tissue factor pathway inhibitor which is a hallmark of heparin and related drugs. Moreover, the heparins exert profound vascular and endothelial modulatory effects, whereas the DOACs do not exhibit these properties, therefore with less endothelial modulatory effects in comparison to heparins.

The main unresolved issues related to the use of DOACs in cancer include drug interactions, renal impairment, and thrombocytopenia. Only in randomized clinical trials, the safety and efficacy of DOACs can be validated, and at this time, the data are limited despite the favorable reduction of thrombotic events in patients with cancer. Risk stratification is also another issue.

Table 1. Direct Oral Anticoagulant (DOAC) for VTE Prophylaxis and Treatment in Patients With Cancer: Data From Prospective Randomized Trials.

	CAT Prophylaxis		CAT Treatment		
Study	CASSINI	AVERT	SELECT – D	HOKUSAI Cancer	ADAM VTE
Molecule	Rivaroxaban	Apixaban	Rivaroxaban	Edoxaban	Apixaban
Date of conclusion	January 2019	April 2018	December 2017	December 2017	November 2019
Countries	Global	Canada	United Kingdom	Global	United States and Canada
Investigator's initiative	No, Janssen Scientific	Yes	Yes	No, Daiichi-Sankyo	Yes
Study design	Double-blind	Double-blind	Open	Open	Open
Blind adjudication	Only with bleeding	Yes	Only with bleeding	Yes	Yes
N	841	574	406	1050	315
Lead-in with LMWH	–	–	3 days before randomization	5 days	5 days
Lead-in Mandatory	No	No	No	Yes	–
LMWH (comparator)	–	–	Dalteparin	Dalteparin	Dalteparin
Objectives	Assess the efficacy and safety of rivaroxaban vs placebo for thromboprophylaxis in ambulatory patients with cancer	Assess the efficacy of apixaban vs placebo for thromboprophylaxis in patients with ambulatory cancer	Provide an estimate of the occurrence of DVT (IC 95%)	Noninferiority of edoxaban vs dalteparin for the outcome	Superiority trial assessing the safety of apixaban versus dalteparin during a 6-month treatment period of cancer-associated VTE
NI margin	–	–	–	1.5	–
Primary outcome	Recurrence of DVT	The first episode of objectively documented major venous thromboembolism and major bleeding	Recurrence of DVT	Recurrence of DVT and major bleeding	Major bleeding
Study follow-up	6 months	7 months	6 months	12 months	6 months
Cancer or brain metastasis	Not allowed	Allowed	Allowed	Allowed	Allowed
Gastrointestinal cancer	Allowed	Allowed	Interrupted throughout the study	Allowed	Allowed
Minimum platelet count	50 000/mm^3	50 000/mm^3	100 × 10^9/L	50 000/mcL	50 000/mm^3
Clinical FUP timelines	2, 4, 6 months	1, 3, 6, and 7 months	3/3 months	1, 3, 6, 9, 12 months	Every month
VTE	2.62% vs 6.41% HR: 0.40, 95% CI: 0.20-0.80 $P = .007$	4.2% vs 10.2% HR: 0.41, 95% CI: 0.26-0.65 $P < .001$	4% vs 11% HR: 0.43, 95% CI: 0.19-0.99 $P =$ NR	7.9% vs 11.3% HR: 0.71, 95% CI: 0.48-1.06 $P = .09$	3.45 vs 14.1% HR: 0.26, 95% CI: 0.09-0.80 $P = .0182$
Major bleeding	1.98% vs 0.99% HR: 1.96, 95% CI: 0.59-6.49 $P = .265$	3.5% vs 1.8% HR: 2.00, 95% CI: 1.01-3.95 $P = .265$	6% vs 4% HR: 1.83, 95% CI: 0.68-4.96 $P =$ NR	6.9% vs 4% HR: 1.77, 95% CI: 1.03-3.04 $P = .04$	0% vs 2.1% $P = .9956$

Abbreviations: CAT, cancer-associated thrombosis; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; NR, non representative; VTE, venous thromboembolism.

An optimal scoring system (for both ischemic/thrombotic and bleeding events) is yet to be developed, consisting in a major issue for VTE overall and for patients with cancer as well.

The duration of anticoagulation for the management of CAT with the LMWHs is recommended for up to 12 to 24 weeks. Extended treatment with LMWH for up to 1 year is found to be

safer. The dose adjustment in extended treatment approaches is recommended depending upon the progress of the patient and the treatment modalities. Several factors need to be considered for the optimal duration of treatment with DOACs. At the same time, it should be recognized that the duration of therapy with each of the different DOACs may be different and require validation. Initial management of CAT with DOAC followed by bridging with LMWHs may be a preferred approach. Extended duration of therapy in patients with cancer with renal impairment must be weighed against their risk of MB to achieve optimal therapeutic outcomes.

Some of the unique clinical issues of anticoagulation in patients with cancer include central venous catheter-associated thrombosis, interruption of treatment, treatment failure, dosing in underweight and overweight patients, and gastrointestinal malignancies. Another challenging area is the management brain malignancies in particular intracranial metastases and its risk of intracerebral bleeding. The DOACs, which are smaller molecular weight compounds, easily pass through the blood–brain barrier posing a major risk of hemorrhagic complications in patients with brain cancer. All of these issues are challenging and require additional studies to validate claims regarding the use of DOACs in patients with cancer.

As the new cancer therapies are continually being introduced offering novel-targeted approaches, the selection of an optimal approach to manage thrombosis and patients with cancer has become more challenging. Despite defined groups of patients with cancer requiring a unified approach, it may be necessary to have a more personalized approach for the prophylaxis and treatment of CAT. Precision oncology will require a more defined approach to treat CAT. The DOACs may be useful in individualizing treatment options; however, several factors need to be considered. At present, warfarin is the drug commonly used in the management of CAT. This is followed by heparins, in particular LMWH. Increased usage of DOACs is occurring in patients with cancer, despite the fact that they are off label.

The DOACs include both anti-Xa and anti-IIa agents. Currently, dabigatran, apixaban, betrixaban, edoxaban, and rivaroxaban are commercially available. There are no data to differentiate the relative safety and efficacy between the anti-IIa and anti-Xa drugs. However, targeting thrombin using such agents, hirudin, has been studied in both experimental and clinical settings, whereas data on anti-Xa agents are still emerging. The anti-Xa drugs exhibit marked differences in their pharmacological profile. Not all of their biologic actions are explainable by considering solely the inhibition of Xa. While clinical trials are ongoing, only safety and efficacy outcomes will be available. Therefore, much more work is needed to differentiate these drugs for the management of CAT. It may be that the therapeutic spectrum of each of the individual DOACs may be different depending upon the type of cancer treated.

A number of guidelines are available which addresses anticoagulation in patients with cancer such agencies as the European Heart Rhythm Association (EHRA 2018), International Initiative on Thrombosis and Cancer (ITAC-CME 2016), American Society of Clinical Oncology (ASCO-2015), American College of Chest Physicians (ACCP 2016), International Society of Thrombosis and Hemostasis (ISTH 2018), and National Comprehensive Cancer Network (NCCN 2018) have become available. Most of these guidelines have focused on the use of heparin and LMWH. However, EHRA, ISTH, and NCCN have recently incorporated some of the DOACs in their recommendations. A more unified approach is required to assist clinicians to choose the appropriate DOACs and the optimal dosage and duration of therapy

Conclusions

Direct oral anticoagulants' use for CAT management is increasing. With emerging new data, including new indications (VTE prophylaxis in high-risk out-of-hospital chemotherapy patients), a personalized approach, weighting VTE/risk of bleeding in individual patients, is preferred. Guidelines tend to incorporate DOACs for the streamlined management of CAT. Unsolved issues, including drug interactions, renal impairment, thrombocytopenia, and difficulty around risk stratification remain a major challenge. Bleeding, particularly from the gastrointestinal CAT require targeted consideration. Future studies, including those evaluating new targets, such as FXIa and FXIIa inhibitors are warranted.

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