The role of direct oral anticoagulants in the management of cancer-associated thrombosis?

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Conflict of interest:
This publication is based on the Belgian expert consensus meeting logistically organized by Leo Pharma.

Keywords: venous thromboembolism, cancer associated thrombosis, DOAC, LMWH, bleeding

Abstract

Cancer patients are at an increased risk of venous thromboembolism (VTE). The current standard initial treatment of an acute episode of VTE in cancer patients consists of the administration of 3 to 6 months of subcutaneous low molecular weight heparin (LMWH) at a dose adjusted to the body weight. The efficacy- and safety-profile of LMWHs are well-established, but a drawback of these agents is that they require daily subcutaneous administration. In addition, they are mainly cleared through the kidneys, and their use in patients with severe renal insufficiency may be challenging. To address the issues with LMWH, several direct oral anticoagulants (DOAC) have been developed for the treatment of VTE. In contrast to LMWHs and VKA, DOACs directly interfere with thrombin or activated factor X (FXa). DOACs have now become standard treatment options in the general management of VTE, but until recently, there were no results of clinical trials specifically assessing the role of

DOACs in the treatment of cancer associated thrombosis (CAT). Recently, the Hokusai VTE cancer study and preliminary data from the Select-D trial demonstrated that DOACs are non-inferior to LMWH in preventing recurrent VTE. However, both studies also show that this comes at the cost of an increased rate of ~~both major and~~ clinically relevant problem of ~~non-major (CRNM)~~ bleeding. Especially in the subgroup of patients with gastro-intestinal cancer, the benefit in reducing VTE recurrence with the DOAC seems to be outbalanced by a significantly increased bleeding risk. Based on the available results, DOACs might represent an interesting alternative for LMWH in certain subgroups of patients, but with an important list of exceptions. It seems reasonable not to use DOACs in patients with a high bleeding risk (i.e. patients with very active cancer, patients with a bleeding history, etc.) and especially in patients with gastro-intestinal cancer, DOACs should not be the first-line therapy. In summary, LMWHs will currently remain the standard of care in the acute management of CAT in many patients. However, the advent of DOACs is welcomed for patients at low bleeding risk who are in need for long-term anticoagulation.

Introduction

It is well known that cancer patients are at an increased risk of venous thromboembolism (VTE), which includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). The presence of malignancy increases the risk of VTE by a factor of 4.[1,2] Importantly, VTE is strongly associated with short- and long-term mortality. In fact, in cancer patients, thromboembolism represents the second most common cause of death after cancer progression.[2,3] The standard initial treatment of an acute episode of VTE in cancer patients consists of the administration of 3 to 6 months of subcutaneous low molecular weight heparin (LMWH) at a dose adjusted to the body weight. This recommendation is based on the outcome of large randomized controlled trials, indicating that treatment with a LMWH for 6 months is more effective than treatment with a vitamin K antagonist (VKA) and does not cause more bleeding.[4-7,35] Two key studies attributing to this were the CLOT and the CATCH trial.[5,35] CLOT demonstrated that the dalteparin was more effective than a coumarin in reducing the risk of recurrent VTE in patients with cancer, without increasing the risk of bleeding.[5] Similarly, CATCH showed that daily tinzaparin for 6 months was associated with a comparable VTE recurrence rate than 6 months of warfarin, with a lower rate of clinically relevant non-major bleeding among patients with active cancer and acute symptomatic VTE.[35] There are no published studies addressing optimal anticoagulation beyond 6 months in patients with cancer. However, there is consensus that

continuing anticoagulation beyond 6 months should be considered in patients with a persistent high-risk of recurrence in patients with active cancer.[7]

The efficacy- and safety-profile of LMWHs are well-established, but a drawback of these agents is that they require daily subcutaneous administration. In addition, they are mainly cleared through the kidneys, and their use in patients with severe renal insufficiency may be challenging. On the other hand, the narrow therapeutic window and variability in response of VKA imply the need for frequent anticoagulant monitoring to avoid a subtherapeutic anticoagulation associated with an increased risk of thrombosis or an excessive anticoagulation that increases the risk of bleeding. To address the issues with LMWH and VKA, several direct oral anticoagulants (DOAC) have been developed for the treatment of VTE. In contrast to LMWHs and VKA, DOACs directly interfere with thrombin or activated factor X (FXa), an important serine protease in the coagulation cascade.[9,10] Several studies in patients with acute VTE have demonstrated comparable efficacy of DOACs in comparison to VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications.[11-16] Based on these data, DOACs have now become standard treatment options in the general management of VTE. Currently, 4 DOACs are approved for the treatment of VTE in the European Union: the oral direct FXa inhibitors rivaroxaban (Xarelto®, Bayer AG), apixaban (Eliquis®, Bristol-Myers Squibb) and edoxaban (Lixiana®, Daiichi-Sankyo) and the oral direct thrombin inhibitor dabigatran etexilate (Pradaxa®, Boehringer Ingelheim).

Until recently, there were no results of clinical trials specifically assessing the role of DOACs in the treatment of CAT. This changed with the publication of the Hokusai VTE cancer data in the New England Journal of Medicine and with the presentation of the smaller Select-D trial during the 2017 annual meeting of the American Society of Hematology (ASH).[17,18] In this review article, the pharmacokinetic differences between the different DOACs will be discussed as are the potential drug-drug interactions that need to be considered when using DOACs in cancer patients. In addition to this, the clinical data generated with DOACs in CAT patients will be critically reviewed.

Pharmacological and pharmacokinetic properties of DOACs

While DOACs are often referred to as being a uniform group of drugs, there are some important pharmacological and pharmacokinetic differences between these agents (*table 1*).

Pharmacokinetics

First of all, not all DOACs have the same molecular target. In fact, rivaroxaban, apixaban and edoxaban are targeting factor Xa, whereas dabigatran is a direct inhibitor of thrombin. Given their direct mode of action, the factor targeting agents can inhibit both free and prothrombinase-bound FXa as well as fibrin-bound FXa. Similarly, dabigatran is able to inhibit both free and fibrin-bound thrombin. Also important to note is that, in contrast to the three anti FXa agents, dabigatran is administered under the form of a pro-drug (Dabigatran etexilate). This pro-drug is a hydrophilic molecule, with poor intestinal absorption after oral administration and low bioavailability (about 7%). The pro-drug needs to undergo an ester cleavage in order to be transformed into its active form, dabigatran.[19,20]

The direct effect of DOACs on coagulation proteins allow these drugs to reach their peak concentrations after only 2 to 4 hours after intake. Conversely, the half-lives of the DOACs are short, in the order of hours, rather than days as with VKAs (*Table 1*). As such, the anticoagulant effects more quickly dissipate when therapy is stopped.[21] The latter is beneficial when anticoagulation must be reversed for an elective invasive procedure but also makes the DOACs less forgiving drugs in patients who are inconsistently compliant with their therapy.

Renal function is of crucial significance for the plasma concentration and duration of action of DOACs. Pharmacokinetic studies indicate that DOACs are eliminated to a varying extent via the kidneys. The risk of accumulation in the case of renal failure is highest for dabigatran (80% renal elimination), followed in descending order by edoxaban, rivaroxaban, and apixaban.[22-24] This is of particular importance in the context of CAT, given the high incidence of renal impairment in cancer patients.

Routine laboratory monitoring is not required with DOACs due to their wide therapeutic window, which creates a more consistent relationship between dose and pharmacodynamic effect in most patients.

Drug-drug interactions

Although DOACs have significantly fewer drug-drug interactions than VKAs, drugs that strongly affect the CYP3A4 enzyme and/or P-glycoprotein (P-gp) can alter the plasma concentration of the DOACs and lead to clinically significant alterations in their anticoagulant effects. CYP3A4 is a member of the hepatic cytochrome P450 enzyme system and is responsible for the oxidative metabolism of both apixaban and rivaroxaban (only minimal involvement in metabolism of edoxaban). In contrast, the dabigatran pro-drug is metabolized by esterases in the plasma and liver without significant involvement of CYP3A4. As substrates of CYP3A4, rivaroxaban and apixaban are vulnerable to both inducers and inhibitors of this

enzyme when given concomitantly, leading to potential increased toxicity or decreased efficacy.[25]

P-gp is an ATP-dependent efflux transporter belonging to the ATP-binding cassette transporter superfamily. It mediates drug absorption and excretion and is one mechanism of chemotherapy resistance, as its activity decreases uptake of chemotherapeutic agents in some cancer cells.[26] P-gp is present in many normal human tissues, most notably the luminal membrane of enterocytes and the apical membrane of both hepatocytes and renal tubular cells.[27] In the intestines, it causes efflux of absorbed substances and drugs back into the intestinal lumen, decreasing net gut absorption. Inhibitors of P-gp increase plasma levels of its substrates, whereas inducers decrease levels. All DOACs are substrates of P-gp and are therefore susceptible to strong inhibitors or inducers of this transporter.

The clinical impact of the potential drug-drug interactions of DOACs with inducers and inhibitors of P-gp and/or CYP is not clear. Nevertheless, the SMPCs of the different DOACs include some recommendations for their concomitant use with such drugs.[28-31]

Specifically looking at drugs that are used in cancer patients, it becomes clear that many chemotherapy or molecular-targeted drugs induce or inhibit the activity of CYP3A4, P-gp, or both. In fact, some classes of anticancer drugs appear to nearly universally interact with CYP3A4 and/or P-gp. These include the antimitotic microtubule inhibitors (e.g. vinca alkaloids and taxanes), tyrosine kinase inhibitors (with the exception of erlotinib, gefitinib, and sorafenib), and the immune-modulating agents, including glucocorticoids and mammalian target of rapamycin (mTOR) inhibitors (with the exception of everolimus). In contrast, none of the frequently used antimetabolites, platinum-based agents, intercalating agents, or monoclonal antibodies have significant inhibitory or inducing effects on CYP3A4 or P-gp.

Two strong inhibitors of CYP3A4 deserve special attention: enzalutamide, an androgen receptor antagonist used to treat castration-resistant prostate cancer, and dexamethasone, a glucocorticoid used for its antitumor effects in many lymphoid malignancies and for the treatment and palliation of various cancer-related complications, including nausea, vomiting and edema of brain metastases. These agents could potentially increase the plasma concentration of rivaroxaban or apixaban if used in combination with these DOACs. In addition to these strong inhibitors, two other hormonal agents, bicalutamide and abiraterone acetate, were identified as moderate inhibitors of CYP3A4. No strong inducers of CYP3A4 were identified. Four moderate inhibitors of both CYP3A4 and P-gp activity were identified: imatinib, crizotinib, abiraterone acetate, and cyclosporine. The use of these drugs in

combination with any of the DOACs could result in increased plasma concentrations of the DOAC. Drugs that exert moderate induction of CYP3A4 activity without significant influence on the P-gp transporter include paclitaxel, vemurafenib, prednisone, and bexarotene. Use of these agents in combination with rivaroxaban or apixaban could lead to decreased plasma concentration of the anticoagulant. Of note, the vemurafenib SMPC also calls for caution and potential additional monitoring when using it in combination with dabigatran.[32] With respect to supportive care agents, the neurokinin receptor 1 antagonists, aprepitant and fosaprepitant, can both moderately induce and inhibit CYP3A4 activity. However, their effect on DOAC plasma concentrations are not clear. Most other supportive care agents have little drug interaction potential, with the exception of some of the pain palliation agents (e.g. fentanyl, methadone, and acetaminophen).[25]

An extensive table of anti-cancer drugs and their potential to interfere with DOACs is provided in the 2018 European Heart Rhythm Association (EHRA) practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation.[33]

Treating VTE with DOACs

Before discussing the clinical data that were generated with DOACs it is important to underscore that the administration schemes vary between the different DOACs. In fact, with dabigatran and edoxaban, patients are initially treated with a LMWH for 5-7 days. After this initial phase, dabigatran is given twice daily at a dose of 150 mg, while edoxaban needs to be taken once daily at a dose of 60 mg. With rivaroxaban and apixaban, the treatment scheme does not include a LMWH phase, but does include an acute phase in which the DOAC is given at a higher dose. With rivaroxaban, patients first receive 15 mg twice daily for 3 weeks, after which the dose is reduced to 20 mg once daily. Patients on apixaban first receive the drug twice daily at a dose of 10 mg for one week after which the dose is cut in half (5 mg twice daily). After 6 months, the dose of apixaban can be lowered even further to 2.5 mg twice daily. The rationale for the more intensive anti-coagulation during the first week(s) is that patients are at the highest recurrence risk in the first weeks. The higher DOAC dose, or the initial LMWH offers extra protection in this acute, high-risk phase.

DOACs in general VTE management

Several clinical studies in patients with acute VTE have demonstrated comparable efficacy of DOACs in comparison to VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications.[11-15] These findings were confirmed in a meta-analysis grouping the data of the

pivotal trials comparing DOACs to VKA in the treatment of acute VTE. This meta-analysis included data from 24,455 patients and demonstrated that DOACs were as effective as VKA in the prevention of recurrent VTE, or fatal pulmonary embolism. Interestingly, DOACs were associated with a 40% lower risk of experiencing a major bleeding. Also the risk for fatal bleeding, bleedings at critical sites and the risk for intracranial bleeding was significantly lower with DOACs compared to VKA in this meta-analysis.[16]

Cancer patients in pivotal randomized trials with DOACs

The percentage of patients with cancer that were enrolled in the pivotal DOAC trials was limited, ranging from 3 to 9%.[11-16] In a meta-analysis with all cancer patients included in the AMPLIFY (apixaban), Einstein-DVT, Einstein-PE (rivaroxaban), Hokusai (edoxaban) and RECOVER I and II (dabigatran) (N= 1132), similar efficacy results were observed as in the general trial populations. In fact, in this meta-analysis DOACs seemed to be as effective and safe as conventional treatment for the prevention of VTE in patients with cancer. The odds ratio for VTE recurrence with DOACs *vs*. VKA was 0.63 (95%CI: 0.37-1.10), while the odds ratios for major and clinically-relevant non-major (CRNM) bleedings were 0.77 (95%CI: 0.41-1.44) and 0.85 (0.62-1.18), respectively.[34]

However, this meta-analysis has some important drawbacks. First of all, the definition of cancer varied significantly between the different studies included in the analysis. Secondly, the VTE recurrence rate in the cancer patients included in this meta-analysis was only 6%. This recurrence rate is much lower than what was reported in the clinical trials assessing the use of LMWHs in the treatment of CAT (CLOT trial: recurrence rate 17% with VKA and 9% with dalteparin; CATCH trial: 6-month recurrence rate 7.2% with tinzaparin and 10.5% with warfarin).[5,34,35] This indicates that the patient population used in this meta-analysis is not representative for the overall cancer population. Of note, also the bleeding risk was higher in pure cancer VTE trials than in this meta-analysis. This underlines the need for dedicated clinical trials with DOACs in cancer patients.

Clinical trials evaluating DOACs in the treatment of CAT

The first results of a randomized phase III trial specifically evaluating a DOAC in the treatment of CAT came from the Hokusai VTE cancer study. The objective of this study was to evaluate whether initial LMWH followed by edoxaban is non-inferior to dalteparin for the prevention of recurrent VTE or major bleeding in patients with VTE associated with cancer. In the study at hand, patients with active cancer and objectively confirmed VTE were randomized between

treatment with a LMWH for at least 5 days followed by edoxaban (orally 60 mg QD, 2x 30 mg tablets. 30 mg QD for patients requiring dose adjustment), or dalteparin (200 IU/kg for 30 days, from approximately day 31 onwards 150 IU/kg). In *table 2*, an overview of the inclusion and exclusion criteria of the Hokusai VTE study are depicted.[17] The primary endpoint of the Hokusai VTE cancer study consisted of a composite of recurrent VTE and major bleeding. For this endpoint, recurrent VTE was defined as a symptomatic confirmed (new) DVT or (new) PE, an unsuspected (new) proximal DVT of the legs or unsuspected (new) PE located in segmental or more proximal arteries, or a fatal PE (including unexplained death for which PE cannot be ruled out). Major bleeding was defined as overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, leading to a transfusion of ≥2 units of packed red blood cells or whole blood, a bleeding occurring in a critical site (i.e. intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), or a bleeding contributing to death.[17]

The trial enrolled 1,050 individuals from 114 centers in 13 countries. Patients had a wide range of cancer types and were treated with different chemotherapy regimens. About 10% of patients had a hematological malignancy and the rest had solid tumors. At study entry, PE with or without DVT was present in 657 patients (63%) while the remainder had isolated DVT. Of the 1,050 patients, 706 (67%) had symptomatic VTE and the rest was incidental. Active cancer at entry was present in 97% of the patients and 53% had metastatic disease.

The study showed that edoxaban is non-inferior to dalteparin with respect to the composite endpoint of recurrent clots and bleeding, which occurred in 12.8% of patients receiving edoxaban and in 13.5% of patients treated with dalteparin (HR[95%CI]: 0.97[0.70-1.36], p= 0.006). Looking at recurrent VTE or the incidence of major bleeding individually, it becomes clear that edoxaban was associated with a (non significant) lower rate of recurrent VTE compared to dalteparin (7.9% *vs*. 11.3%; HR[95%CI]: 0.71[0.48-1.06]; p= 0.09), but this benefit was balanced by a significantly higher rate of major bleedings under edoxaban (6.9% *vs*. 4.0%; HR[95%CI]: 1.77[1.03-3.04]; p= 0.04). This difference in major bleeding was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban. Of note, the frequency of severe major bleeding events (categories 3 and 4) was similar during treatment with edoxaban and dalteparin (12 patients, corresponding with 2.3% in both treatment arms). The investigators did observe a higher rate of CRNM bleeding with edoxaban compared to dalteparin (14.6% *vs*. 11.1%; HR[95%CI]: 1.38[0.98-1.94]). The incidence of major and CRNM bleedings together was 18.6% with edoxaban, which is significantly higher than the 13.9% seen with dalteparin (HR[95%CI]: 1.40[1.03-1.89]).[17]

The increased risk for major bleeding with edoxaban was particularly pronounced in the subgroup of patients with gastrointestinal cancer. The incidence of major bleeding in this subgroup was 2.4% with dalteparin as compared to 13.2% in patients treated with edoxaban (*vs*. 4.5% and 4.7% in patients with no gastro-intestinal cancer).[17]

On a final note we would like to underline the fact that patients with catheter associated thrombosis were not included in the Hokusai VTE cancer study. This is important for the translation of these data to clinical practice, where this type of VTE is common among cancer patients

A second clinical trial specifically assessing a DOAC in cancer patients was the Select-D trial.[18] This ongoing trial, including 406 patients, compares rivaroxaban (15 mg twice daily for 3 weeks then 20 mg once daily, for 6 months in total) to dalteparin (200 IU/kg daily, month 1 and 150 IU/kg, months 2-6) for the treatment of cancer patients with VTE (symptomatic or incidental PE, or symptomatic lower extremity proximal DVT).[18] The first results of this study, presented during ASH 2017, are very similar to what was seen in the Hokusai VTE cancer study. In fact, rivaroxaban was associated with a lower rate of VTE recurrence (6-months VTE recurrence rate 11% with dalteparin *vs*. 4% with rivaroxaban). Also in this trial, the VTE recurrence benefit came at the cost of an increased incidence of major bleeding: 2.9% with dalteparin vs. 5.4% with rivaroxaban. Also the incidence of CRNM bleeding was significantly higher with rivaroxaban than with dalteparin in Select-D (12% *vs*. 3%). Similar to what was seen in the Hokusai VTE cancer study, most bleedings were gastrointestinal in nature.[18] This is also in line with the higher bleeding rate in gastrointestinal cancer patients in the Hokusai cancer VTE study.

Discussion and conclusions

Several clinical studies in patients with acute VTE have demonstrated comparable efficacy of DOACs and VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications. This comparable efficacy in combination with the oral administration route and the fact that laboratory monitoring is not required, led to the rapid uptake of DOACs in the treatment schemes for acute VTE in the general population. However, there were no data from clinical trial specifically evaluating DOACs in the setting of CAT and, as a result, there was no place for DOACs in the management of VTE in cancer patients. Recently, the Hokusai VTE cancer study and preliminary data from the Select-D trial demonstrated that DOACs are non-inferior to LMWH in preventing recurrent VTE. However, both studies also show that this

comes at the cost of an increased rate of both major and CRNM bleeding. Especially in the subgroup of patients with gastro-intestinal cancer, the benefit in VTE recurrence with the DOAC seems to be outbalanced by a significantly increased bleeding risk. Also among patients with other tumor types, gastrointestinal bleeds account for the majority of bleeding. A possible explanation for this could be that DOACs are oral drugs. Given their oral administration route, it could be that the local concentration of the drug is higher in the gastrointestinal tract, leading to more bleedings at that site, especially in patients with frailty of the mucosal membranes.

In conclusion, more data will be needed to fully elucidate the potential role of DOACs in the treatment of CAT. Based on the results that we have now, DOACs might represent an interesting alternative for LMWH in certain subgroups of patients, but with an important list of exceptions. It seems reasonable not to use DOACs in patients with a high bleeding risk (i.e. patients with very active cancer, patients with a bleeding history, etc.) and especially in patients with gastro-intestinal cancer, DOACs should not be the first-line therapy. It is also important to stress that the patients included in these clinical trials are not fully representative for the typical cancer patients encountered in real-life. In everyday clinical practice, patients often present with comorbidities (i.e. renal impairment) and often have a poorer performance status than patients included in clinical trials. Therefore, it is important to see how these DOACs will perform in a real world setting. In addition to this, DOACs have not yet been evaluated in patients with catheter-associated thrombosis and we also lack data on the use of DOACs in the new era of immunotherapeutics. Finally, physicians also need to take into account the potential drug-drug interactions between DOACs and some anti-cancer drugs. These potential interactions differ between the different DOACs and require proper physician education.

Therefore the current standard anticoagulation therapy consisting of 3-6 months of LMWH may remain the standard of care in the management of CAT for many patients. For other patients, especially these in need for long-term anticoagulation who are at low bleeding risk, the advent of oral DOACs may provide an alternative to continued subcutaneous LMWHs. However, more data on the bleeding risk of DOACs in cancer patients are needed to challenge the current standard.

Key messages for clinical practice

- DOACs are not the same: there are important pharmacokinetic differences and also the dosing schedules are different.
- Drug-drug interactions of DOACs are important and need to be considered. Education will be key.

- DOACs appear to be as effective as LMWHs in protecting CAT patients from recurrent VTE, but seem to be associated with a higher rate of major bleeds
- Clinical trials with DOACs in CAT indicate a particularly high bleeding risk in patients with gastro-intestinal cancer
- Whereas LMWHs will currently remain the standard of care in the acute management of CAT in many patients, the advent of DOACs is welcomed for patients at low bleeding risk who are in need for long-term anticoagulation.

Table 1. Overview of pharmacokinetic properties of the different DOACs approved in the European union (based on SMPCs of the different products).[28-31]

	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Prodrug	Yes	No	No	No
Availability	7%	80%	66%	62%
Time to C_{max}	2-4 hours	2-4 hours	3-4 hours	1-3 hours
Half-life	12-17 hours	7-11 hours	8-15 hours	9-11 hours
Dosing	Twice daily	Once daily	Twice daily	Once daily
Renal elimination	80%	33% (65%)*	27%	35%
CYP metabolism	0%	32% (3A4; 2J2)	15% (3A4)	<4%
Carrier	P-gp	P-gp and BCRP	P-gp and BCRP	P-gp
Protein binding	30%	92%	90%	50%

** Approximately half eliminated unchanged in the urine*

Table 2. inclusion and exclusion criteria of the Hokusai VTE study.[17]

Inclusion criteria	Exclusion criteria
Adult cancer with acute VTE confirmed by imaging: • symptomatic or incidentally detected proximal DVT • symptomatic PE • incidental PE of a segmental or larger pulmonary artery; Cancer other than basal-cell or squamous-cell skin cancer Cancer either active or diagnosed within 2 years Active cancer	More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment to treat the current episode Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban ECOG PS 3-4 at the time of randomization Platelet count < 50,000/mL Calculated creatinine clearance (CrCL) <30 mL/min Acute hepatitis, chronic active hepatitis, liver cirrhosis History of heparin associated thrombocytopenia

• diagnosed or treatment given within last 6 months • recurrent or regionally advanced or metastatic • hematologic cancer not in complete remission Intention for LMWH treatment for at least 6 months	Life expectancy less than 3 months

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