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REVIEW ARTICLE

Prevention and Treatment of Venous Thromboembolism in Patients with Cancer: Focus on Drug Therapy

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Abstract Venous thromboembolism (VTE) is a frequent complication in patients with cancer and is associated with significant morbidity and mortality. The use of anticoagulants for the prevention and treatment of VTE in this population is challenging given the high risk of both recurrent VTE and bleeding complications. Thromboprophylaxis with subcutaneous low-molecular-weight heparin (LMWH) is recommended in cancer patients hospitalized for an acute medical illness and in those undergoing major surgery. In ambulatory cancer patients with or without central venous catheters, routine thromboprophylaxis is not recommended because of the relatively low benefit-to-risk ratio. To identify cancer outpatients at very high risk of VTE who may benefit from thromboprophylaxis, VTE risk stratification tools based on tumour type, clinical parameters, or coagulation biomarkers have been proposed, but their clinical utility needs validation. The mainstay of treatment for cancer-associated VTE is LMWH for at least 6 months or longer in case of active disease. The same initial and long-term treatment for incidental VTE as for symptomatic VTE can be suggested while awaiting additional studies in this area.

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Key Points

Venous thromboembolism (VTE) thromboprophylaxis is currently recommended in cancer patients undergoing major surgery or those hospitalized for an acute medical illness.

The cornerstone of VTE treatment in patients with cancer is represented by low-molecular-weight heparins given for at least 3–6 months or longer periods in case of active disease or ongoing treatment for cancer.

1 Introduction

Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer [1]. It is estimated that 20 % of all VTE cases occur in cancer patients [2–4]. The absolute incidence of cancer-associated VTE varies greatly depending on the tumour type, cancer stage, and anticancer treatment [4–7]. While the focus has traditionally been on symptomatic VTE, it is increasingly recognized that about half of all cancer-associated VTE are incidentally diagnosed [5]. In addition to lower extremity DVT and PE, cancer patients frequently experience VTE at unusual sites such as splanchnic vein thrombosis and upper extremity DVT (UEDVT) [6, 7].

VTE is a major cause of morbidity and mortality in patients with cancer. VTE may delay cancer surgery or treatment with chemotherapy and negatively affect the patients' quality of life. Furthermore, VTE represents one

of the leading causes of death in cancer patients [8, 9]. The risk of VTE recurrence is approximately threefold higher than in patients without cancer [10, 11], with an absolute incidence during the first 6 months of anticoagulant treatment of 8 % [12–15] and a case-fatality rate up to 47 % [12]. In addition, patients with cancer present a two- to sixfold increased risk of anticoagulant-related bleeding compared with the general population [10, 11]. The rate of major bleeding during the first 6 months of treatment is approximately 6–10 % [12–15], with a case-fatality rate up to 30 % [25–27]. Like the occurrence of VTE, bleeding complications may interfere with diagnostic or therapeutic interventions and delay cancer treatment. Moreover, anticoagulants are often temporarily stopped following a bleeding event, which exposes these patients to an increased risk of recurrent VTE [28].

In this review we focus on the use of anticoagulant drugs for the prevention and treatment of cancer-associated VTE.

2 Challenges of Anticoagulant Treatment in Cancer Patients

The goal of anticoagulant treatment is to prevent (recurrent) VTE while minimizing the risk of bleeding. Optimizing this risk–benefit balance in cancer patients is challenging. In addition to risk factors for bleeding common to the general population, such as older age and impaired renal or liver function, other cancer-specific elements may contribute to the bleeding tendency and include unstable neovascularization in the tumour environment and thrombocytopenia related to chemotherapy-induced bone marrow suppression or bone marrow invasion by haematological malignancies [16]. Metastatic brain lesions are prone to bleeding and are associated with a 19 % risk of significant intracranial haemorrhage during the first year of anticoagulant treatment [17].

The use of vitamin K antagonists (VKAs) for cancer-associated VTE can be particularly demanding. Chemotherapy-induced oral mucosal lesions, nausea, and vomiting may decrease oral drug intake, and intestinal mucosal lesions or diarrhoea may affect the gastrointestinal drug absorption [18]. In addition, the inter- and intra-individual variability of drug levels can be substantial owing to interactions with drugs and food, and treatment may be interrupted because of invasive diagnostic or curative procedures resulting in a decreased quality of anticoagulation. For example, in two large trials that evaluated VTE treatment in cancer patients, the time in therapeutic range with VKAs was only 46 % [12, 15], compared with 60–70 % in patients without cancer [19].

Low-molecular-weight heparins (LMWHs) offer a more stable pharmacokinetic profile given the virtually absent interactions with food or drugs. However, the requirement of long-term daily subcutaneous injections that are frequently associated with local site reactions and subcutaneous haematomas may be burdensome.

Recently, direct oral anticoagulants (DOACs) comprising the thrombin inhibitor dabigatran and the factor Xa-inhibitors apixaban, edoxaban, and rivaroxaban have become available for the prevention and treatment of VTE in the general population [19]. As with VKAs, the oral intake and gastrointestinal absorption may be affected by nausea, vomiting, and intestinal lesions. Antineoplastic agents such as tyrosine kinase inhibitors, hormonal therapy, and immunomodulatory agents that inhibit P-glycoprotein may lead to supratherapeutic drug levels, thereby increasing the risk of bleeding [20].

3 Prevention of VTE

3.1 Surgical Cancer Patients

Patients with cancer undergoing major surgical procedures have a twofold higher risk of VTE than patients without cancer [21, 22]. Perioperative thromboprophylaxis, usually with LMWH, is recommended in these patients, starting preoperatively and continuing for at least 7–10 days postoperatively [23–25]. In patients undergoing abdominal or pelvic surgery for cancer, the postoperative risk remains high for a month [26–28]. In a meta-analysis by Akl et al. [29], extended LMWH thromboprophylaxis up to 4 weeks after surgery was associated with an 80 % lower risk of asymptomatic DVT [relative risk (RR) 0.21, 95 % confidence interval (CI) 0.1–0.9] with no significant increase in major bleeding (RR 2.9, 95 % CI 0.1–72). Based on these data and the positive result of a later trial [30], it is now recommended that cancer patients undergoing major abdominal or pelvic surgery receive extended thromboprophylaxis for 4 weeks postoperatively [24, 25]. An ongoing trial is evaluating the efficacy and safety of apixaban versus enoxaparin in women undergoing surgery for suspected pelvic malignancy (https://clinicaltrials.gov/ct2/show/NCT02366871).

3.2 Hospitalized Cancer Patients

Active cancer is one of the strongest predictors of in-hospital VTE in patients with acute medical illness [31–34], but data on the efficacy and safety of thromboprophylaxis in hospitalized medical cancer patients are scarce. A recent meta-analysis by Carrier et al. [35] identified only three VTE prevention studies that compared either LMWH or fondaparinux with placebo and reported on the subgroup of cancer patients. This combined analysis showed that

thromboprophylaxis was not associated with a reduction in VTE (RR 0.91, 95 % CI 0.2–4). Major bleeding rates were not reported in any of the studies. Based on extrapolations from clinical trials in the general population, all international guidelines recommend thromboprophylaxis with heparin or fondaparinux in cancer patients hospitalized for medical reasons, in the absence of bleeding or other contraindications to anticoagulation [25, 36, 37]. An increased prophylactic dose of LMWH may be considered in severely obese patients (body mass index $\geq$40 kg/m^2) [38]. Trials on VTE prophylaxis with DOACs in hospitalized medical patients have led to disappointing results, and data are not available for the subgroups with cancer [39, 40]. Therefore, the use of DOACs in these patients cannot be recommended at this moment.

3.3 Ambulatory Cancer Patients Receiving Chemotherapy

In a recent Cochrane meta-analysis on primary thromboprophylaxis of VTE in ambulatory cancer patients, LMWH was associated with a significant 47 % relative reduction in symptomatic VTE compared with no anticoagulation (RR 0.53, 95 % CI 0.4–0.8) [41] without significant differences in major bleeding (RR 1.3, 95 % CI 0.8–2.2) or mortality (RR 0.95, 95 % CI 0.8–1.1). With a baseline VTE risk of 5.2 %, the absolute risk reduction with LMWH is 2.4 % [41], hence, a number of patients needed to treat of 42 to prevent one thromboembolic event. In general, this absolute risk reduction is deemed too low to justify the risks and burden of daily subcutaneous injections, and international guidelines do not recommend routine LMWH thromboprophylaxis in ambulatory cancer patients [25, 36, 37].

To increase the absolute benefit of LMWH thromboprophylaxis, some VTE prevention trials focused on a single high-risk tumour type. In the recently published CONKO-004 trial, 312 patients with advanced pancreatic cancer receiving gemcitabine were allocated to a half-therapeutic dose of enoxaparin (1 mg/kg/day) for 3 months followed by a once-daily prophylactic dose of enoxaparin or standard of care [42]. In the first 3 months of treatment, 1.3 % of the enoxaparin-treated patients developed symptomatic VTE compared with 9.9 % of patients not receiving thromboprophylaxis [hazard ratio (HR) 0.12, 95 % CI 0.03–0.5]. Major bleeding occurred in 4.4 and 3.2 % of patients (HR 1.4, 95 % CI 0.4–3.7), respectively. Similar findings have previously been reported by others [43, 44]. Taking these VTE prophylaxis studies in pancreatic cancer patients together, the pooled analysis suggests a 78 % RR reduction in thromboembolic complications during the first months of chemotherapy (RR 0.22, 95 % CI 0.1–0.4; Fig. 1). Pooled data of the FRAGEM [43] and CONKO-004 [42] trials suggest that this benefit is not offset by a significant increase in major bleeding (RR 1.25, 95 % CI 0.5–3.3). When interpreting these results, however, it should be acknowledged that different LMWH regimens were used in the trials, efficacy outcome definitions were heterogeneous, and most studies had an open-label design without blinded outcome adjudication.

Other VTE prevention trials that restricted enrolment to a single tumour type were inconclusive [45, 46]. Patients with newly diagnosed multiple myeloma treated with chemotherapy regimens that include lenalidomide or thalidomide are at high risk of VTE [47–49]. In these patients the American Society of Clinical Oncology recommends thromboprophylaxis with either LMWH or low-dose aspirin [25].

The use of DOACs as thromboprophylaxis in ambulatory cancer patients was evaluated in a dose-finding study which randomized 125 patients with advanced cancer to apixaban 5, 10, or 20 mg once daily, or placebo [50]. Symptomatic VTE was diagnosed in three of 29 patients (10 %) in the placebo group and in none of those on apixaban. Major bleeding occurred in 6 % of patients on apixaban 20 mg, and none of those receiving lower doses of the drug. Although conclusions are hampered by the low sample size (the study was stopped prematurely because of the low accrual rate), these results appear promising and have prompted the ongoing AVERT trial (https://clinicaltrials.gov/ct2/show/NCT02048865), which randomly allocates cancer patients with a high VTE risk to either apixaban 2.5 mg twice daily or placebo. The primary outcome is symptomatic or asymptomatic VTE during 7 months of follow-up. The targeted sample size is 574 patients, and enrolment is expected to be complete in 2017.

3.3.1 Risk Stratification of Ambulatory Cancer Patients

The net-clinical benefit of thromboprophylaxis could be increased by VTE risk stratification tools such as the Khorana score [51]. The PHACS trial randomized cancer patients at high risk of VTE according to the Khorana score to prophylactic dose dalteparin for 12 weeks versus no dalteparin (https://clinicaltrials.gov/ct2/show/NCT00876915). Recruitment is complete, and results are expected soon.

Some authors have proposed the use of biomarkers for VTE risk stratification in cancer patients although the evidence for their predictive value is not unequivocal [52]. The Microtec study was a phase II study that randomized patients with advanced cancer and high levels of tissue factor exposing microparticles to either prophylactic dose enoxaparin or observation [53]. During the 2-month follow-up, VTE was diagnosed in 4 % of patients on enoxaparin compared with 27 % in the observation group (HR 6.7, 95 % CI 1.0–43), a difference largely driven by asymptomatic DVT on screening ultrasound. While these results require

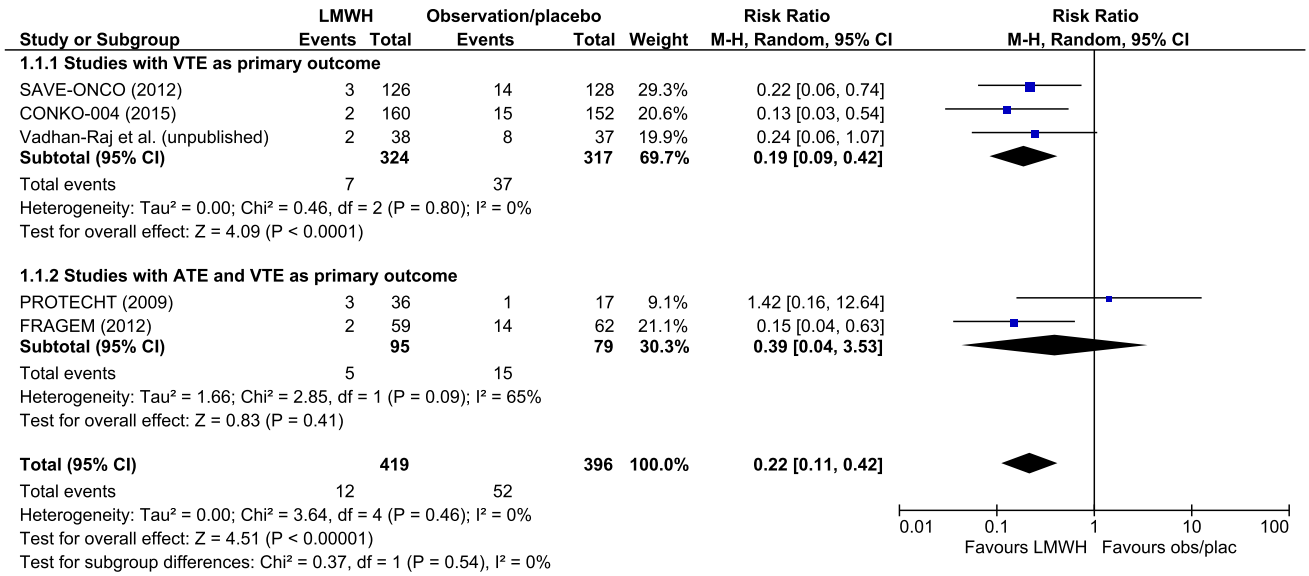

Fig. 1 Low-molecular-weight heparin (LMWH) compared with no thromboprophylaxis in ambulatory patients with advanced pancreatic cancer: arterial thromboembolism (ATE) or venous thromboembolism (VTE) [42–44, 99, 100]. *CI* confidence interval, *M-H* Mantel Haenszel, *obs/plac* observation/placebo

confirmation in larger studies, measurement of coagulant extracellular vesicles for VTE risk stratification in cancer patients may be difficult to implement in routine practice. Finally, the addition of circulating biomarkers to the Khorana score seemed to improve the identification of patients at risk [54], although the extended score needs validation.

3.4 Prevention of Catheter-Related Thrombosis

Central venous catheters (CVCs) are increasingly used in cancer patients to facilitate administration of chemotherapy, blood transfusions, or other parenteral medications. However, catheter-related UEDVT is a frequent complication occurring in 2–6 % of cancer patients [55]. In a meta-analysis by Akl et al. [56], neither heparin [LMWH or unfractionated heparin (UFH)] nor fixed low-dose VKA were associated with a statistically significant reduction in UEDVT or mortality when compared with placebo or no intervention. Routine thromboprophylaxis in cancer patients with a CVC is currently not recommended [37, 57, 58].

4 Treatment of VTE

4.1 Initial Treatment

In a recent review on the initial treatment (e.g. first 5–10 days) of VTE in cancer patients, LMWH and UFH were similarly effective in preventing recurrent VTE, while LMWH was associated with a significant 29 % reduction in mortality at 3 months [59]. Data on the use of fondaparinux are limited to a post hoc analysis of the Matisse trials, which found no statistically significant differences in recurrent VTE, bleeding, and mortality between fondaparinux and heparin [60]. Based on the available data, LMWH is now recommended for the initial treatment of cancer-associated VTE [25, 61, 62]. LMWH offers some advantages over UFH, such as the subcutaneous administration at fixed weight-based doses, lower costs, and lower risk of heparin-induced thrombocytopenia [63]. UFH may be considered in patients with a creatinine clearance less than 30 mL/min given its predominantly hepatic clearance.

4.2 Long-Term Treatment

4.2.1 Type of Anticoagulant

In the seminal CLOT study, 676 patients with active cancer were randomized to receive 6 months of open-label dalteparin monotherapy (full dose in the first month, followed by a 75 % dose for the remaining 5 months) or dalteparin followed by VKAs [12]. During a 6-month follow-up, 9 % of patients treated with dalteparin and 17 % of those receiving VKAs developed recurrent VTE (HR 0.48, 95 % CI 0.3–0.8). No significant difference was observed in major bleeding (6 vs. 4 %). Subsequently, three other trials reported similar results (Table 1), and a meta-analysis demonstrated a significant 53 % RR reduction in recurrent VTE with LMWH compared with VKAs, with no difference in major bleeding (RR 1.07, 95 % CI 0.5–2.2) and survival (HR 0.96, 95 % CI 0.8–1.1) [64]. Based on a superior efficacy and a similar safety profile, all major

Table 1 Summary of randomized controlled trials evaluating the efficacy and safety of anticoagulant treatment of cancer-associated VTE

Trial	Design	Cancer patients (*n*)	Experimental arm (*n*)	Control arm	Intended treatment duration (months)	Recurrent VTE	Major bleeding	All-cause mortality
Lopaciuk et al. [92]	Open-label; unclear whether end-point assessment was blinded	12 (subgroup analysis)	Nadroparin (6)		3	NR	NR	67 %
				Nadroparin → acenocoumarol (6)		NR	NR	50 %
López-Beret et al. [93]	Open-label; unclear whether end-point assessment was blinded	35 (subgroup analysis)	Nadroparin (17)		3–6	5.9 %	12 %	41 %
				Nadroparin → acenocoumarol (18)		22 %	11 %	33 %
CANTHANOX [94]	Open-label with blinded end-point assessment	138	Enoxaparin (71)		At least 3	Combined: 10.5 %		NR
				Enoxaparin → warfarin (67)		Combined: 21.2 %		NR
Cesarone et al. [95]	Open-label; unclear whether end-point assessment was blinded	192	Enoxaparin (96)		3	6.6 %	NR	2.1 %
				Enoxaparin → coumadin (96)		10 %	NR	3.1 %
CLOT et al. [12]	Open-label with blinded end-point assessment	672	Dalteparin (336)		6	9 %	6 %	39 %
				Dalteparin → VKA (336)		17 %	4 %	41 %
ONCENOX [14]	Open-label; no blinded end-point assessment	102	Enoxaparin (68)		6	6.6 %	9.0 %	33 %
				Enoxaparin → warfarin (34)		10 %	2.9 %	32 %
Main-LITE [96]	Open-label; no blinded end-point assessment	200	Tinzaparin (100)		3	7 %	NR	47 %
				UFH → VKA (100)		16 %	NR	47 %
Romera et al. [97]	Open-label with blinded end-point assessment	69 (subgroup analysis)	Tinzaparin (36)		6	5.5 %	2.8 %	5.6 %
				Tinzaparin → acenocoumarol (33)		21 %	9.1 %	6.1 %
Van Gogh DVT [98]	Open-label with blinded end-point assessment	421 (subgroup analysis)	Idraparinux (220)		3–6	2.5 %	2.1 %	23 %
				Heparin → VKA (201)		6.4 %	1.5 %	24 %
CATCH [15]	Open-label with blinded end-point assessment	900	Tinzaparin (449)		6 months	6.9 %	2.7 %	33 %
				Tinzaparin → warfarin (451)		10 %	2.4 %	31 %

DVT deep-vein thrombosis, *UFH* unfractionated heparin, *VKA* vitamin K antagonist, *VTE* venous thromboembolism, *NR* not reported

international guidelines currently recommend LMWH for the treatment of cancer-associated VTE for at least 6 months [25, 36, 57, 61, 65] or 3–6 months [62].

In the recent CATCH study, an open-label, randomized clinical trial with blinded outcome evaluation, 6-month full-dose tinzaparin was compared with VKAs for VTE treatment in patients with active cancer [15]. The incidence of recurrent VTE was comparable in patients treated with tinzaparin and VKAs (7 vs. 10 %; HR 0.65, 95 % CI 0.4–1.0). There was no difference in major bleeding (2.7 vs. 2.4 %), while clinically relevant non-major bleeding was reduced by 42 % by tinzaparin (11 vs. 15 %; HR 0.58, 95 % CI 0.4–0.8). The results of the CATCH study are in line with the earlier trials and support the use of LMWH for the treatment of cancer-associated VTE. The pooled analysis including the CATCH study results shows a 43 % reduction in recurrent VTE with LMWH compared with VKAs (RR 0.57, 95 % CI 0.4–0.8; Fig. 2) and a comparable risk of major bleeding (RR 1.07, 95 % CI 0.7–1.8; Fig. 3).

The six trials evaluating DOACs for VTE treatment in the general population enrolled about 27,000 patients, of whom 5 % had either active cancer or a history of cancer at randomization. In the subgroup analysis of these patients, a significantly lower VTE recurrence rate was found in the DOAC recipients compared with patients receiving VKAs (RR 0.57, 95 % CI 0.4–0.9). No difference in major bleeding rate was observed (RR 0.77, 95 % CI 0.4–1.3) [19]. Although encouraging, these findings should be interpreted with caution. Cancer patients enrolled in the DOAC trials were probably healthier than those in studies specifically designed for patients with acute VTE and active cancer, since patients for whom LMWH therapy was anticipated were excluded. Most importantly, DOACs were compared with VKAs rather than LMWH, which is currently the recommended treatment option.

Three studies have recently been initiated to evaluate DOACs against LMWH for the treatment of cancer-associated VTE. The Hokusai VTE-cancer study is a randomized, open-label trial comparing the efficacy and safety of edoxaban with dalteparin monotherapy in this setting (https://clinicaltrials.gov/ct2/show/NCT02073682). This pragmatic study has incorporated various innovative features in its design to optimize the internal and external validity [66]. The primary outcome is the combination of recurrent VTE and major bleeding, incidental VTE is an inclusion criterion as well as a component of the primary outcome, and the intended treatment duration is 12 months, which is expected to provide valuable information on the anticoagulant treatment in cancer patients beyond

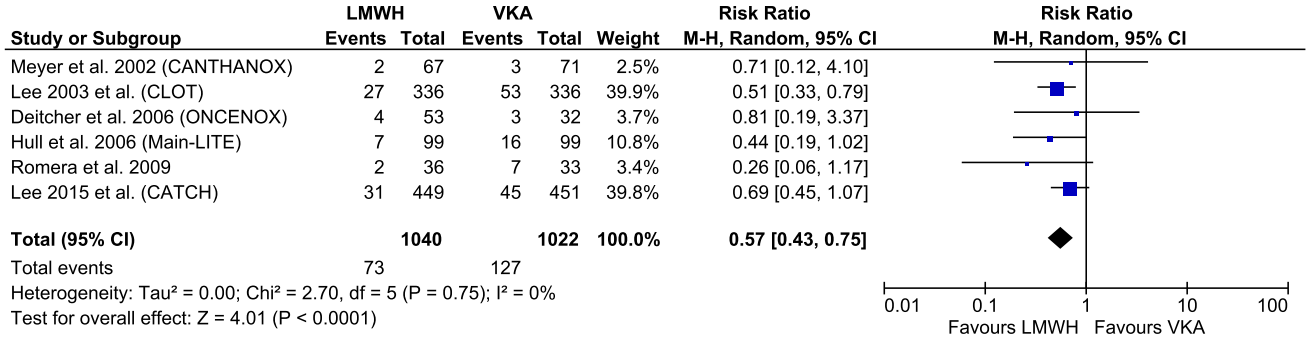

Fig. 2 Low-molecular-weight heparin (LMWH) compared with vitamin K antagonists (VKAs) for treatment of venous thromboembolism in patients with active cancer: recurrent venous thromboembolism [12, 14, 15, 94, 96, 97]. *CI* confidence interval, *M-H* Mantel Haenszel

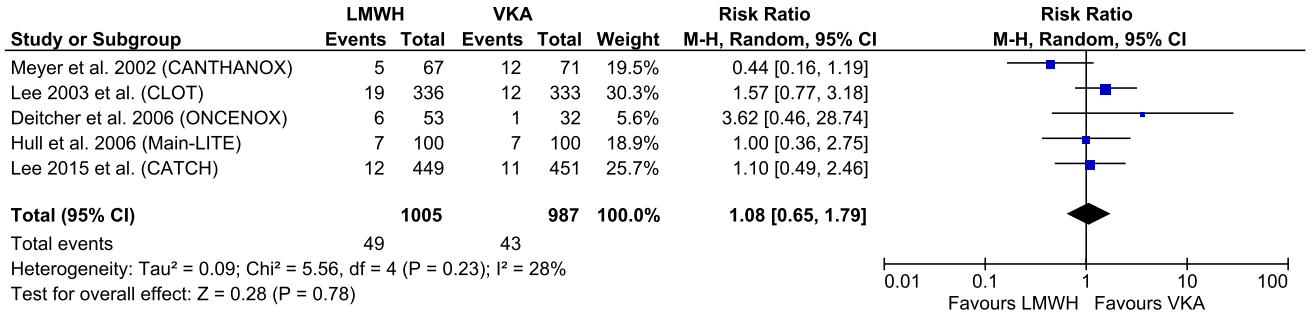

Fig. 3 Low-molecular-weight heparin (LMWH) compared with vitamin K antagonists (VKAs) for treatment of venous thromboembolism in patients with active cancer: major bleeding [12, 14, 15, 94, 96]. *CI* confidence interval, *M-H* Mantel Haenszel

6 months. The study aims to enrol 1000 patients and started recruitment in July 2015.

The Select-d study is a randomized, open-label trial comparing dalteparin with rivaroxaban for the treatment of symptomatic or incidental VTE in patients with active cancer (http://www.isrctn.com/ISRCTN86712308). After 6 months of treatment, patients with residual thrombosis will be randomized again to either placebo or extended rivaroxaban treatment for another 6 months. The targeted sample size is 530 patients.

The CONKO-011 trial will compare 3 months of rivaroxaban with LMWH in cancer patients with VTE (https://www.clinicaltrials.gov/ct2/show/NCT02583191). The primary objective is to evaluate patient satisfaction using the Anti-Clot Treatment Scale. The study aims to enrol 450 patients in the coming 3 years.

Last, apixaban will be compared with dalteparin in a randomized, open-label trial that aims to enrol 315 cancer patients with VTE, including UEDVT, splanchnic vein thrombosis, and cerebral vein thrombosis (https://clinicaltrials.gov/ct2/show/NCT02585713). The primary outcome is major bleeding during 6 months of treatment. Recruitment is expected to end in 2020.

4.2.2 Treatment Duration

All studies on the treatment of cancer-associated VTE have evaluated the use of anticoagulants for up to 6 months (Table 1). Based on the high risk of recurrent VTE, it is generally recommended to extend anticoagulant treatment beyond 6 months when the cancer is active or cancer treatment is ongoing [36]. The decision to continue treatment should be weighed against the risk of major bleeding, taking into account patient preferences and quality of life. Isolated distal DVT or VTE associated with a superimposed reversible risk factor (e.g. surgery) seem associated with a lower risk of recurrence, and physicians could consider a shorter course of anticoagulant treatment in these cases [36].

The type of anticoagulant to use beyond 6 months remains a dilemma. In a survey conducted amongst thrombosis and non-thrombosis specialists, 44 % preferred LMWH, 10 % VKAs, and the remaining 45 % chose between LMWH or VKAs on an individual patient basis [67]. Unfortunately, the only randomized trial which evaluated the treatment of cancer-associated VTE beyond 6 months, the Longheva study, was prematurely terminated due to low accrual rates (https://clinicaltrials.gov/ct2/show/NCT01164046). The DALTECAN study was a prospective, single-arm cohort study that evaluated the long-term safety of dalteparin in patients with active cancer and VTE [13]. During the first month of full-dose dalteparin, the rates of major bleeding and recurrent VTE were 3.6 and 5.7 %, respectively. Despite a subsequent 25 % reduction of the dalteparin dose, the monthly risk of major bleeding remained high during months 2–6 (1.1 %) and months 6–12 (0.7 %). The risk of monthly recurrent VTE was relatively stable from months 2–12 (0.7 %).

4.3 Treatment of Recurrent VTE During Anticoagulant Treatment

Recurrent VTE may develop in cancer patients despite appropriate anticoagulant therapy. Management of these cases is challenging, especially in light of the scant data supporting specific treatment strategies [68]. Once heparin-induced thrombocytopenia is excluded in patients receiving LMWH, the dose could be increased by 25 %, with peak anti-factor Xa levels aimed at a concentration of 1.6–2.0 U/mL in the case of once-daily dosing and 0.8–1.0 U/mL for a twice-daily regimen [68]. Patients treated with VKAs should be switched to LMWH [64]. In a recent registry of 212 cancer patients with recurrent VTE, 41 % of patients continued with the same anticoagulant regimen, 31 % had a higher dosage of the same drug, and in the remainder, the drug was changed. During the 3-month follow-up, 11 % of patients had an additional recurrent VTE which, surprisingly, was not associated with the choice of increasing the dose of anticoagulant treatment. Patients continuing on or switching to VKAs after recurrent VTE were at a significantly higher risk of an additional recurrent VTE than patients receiving LMWH (29 vs. 9 %; HR 0.28, 95 % CI 0.1–0.7). Major bleeding occurred in 8 % of the patients, all of whom were on LMWH (odds ratio vs. VKAs 4.6, 95 % CI 0.3–80).

4.4 Treatment of Incidental VTE

Prospective studies on the prognosis of incidental VTE in cancer patients are lacking. The evidence on the management of incidental VTE in cancer patients is limited to relatively small case series and retrospective studies which suggest that the risk of recurrent VTE is not negligible and similar to symptomatic VTE [69–78]. An individual patient data meta-analysis of 926 cancer patients with incidental PE reported a VTE recurrence rate of 6.2 % in patients treated with LMWH compared with 6.4 % in patients receiving VKAs and 12 % in those left untreated [79]. The risk of major bleeding was significantly higher in patients treated with VKAs compared with those treated with LMWH (13 vs. 4 %; HR 3.2, 95 % CI 1.4–7.4). In the absence of contraindications for anticoagulation, the international guidelines recommend the same initial and long-term treatment for incidental VTE as for symptomatic VTE [25, 36, 61].

Whether selected subgroups such as those with isolated subsegmental PE (SSPE) may be treated more conservatively remains unknown. In the aforementioned individual patient data meta-analysis, the risk of recurrent VTE in cancer patients with isolated SSPE appeared not to be different from that in patients with proximal PE (HR 1.1, 95 % CI 0.5–2.4) [79]. In addition, a post hoc analysis of 3728 cancer and non-cancer patients with clinically suspected PE demonstrated similar rates of recurrent VTE, bleeding, and mortality in patients with symptomatic SSPE as in those with proximal symptomatic PE [80]. Data have not been always concordant [81]. An ongoing international, multicentre, observational study is evaluating the current treatment approaches and long-term clinical outcomes of incidental PE in patients with active cancer (https://clinicaltrials.gov/ct2/show/NCT01727427). Results are expected in 2017.

4.5 Treatment of Splanchnic Venous Thrombosis

There is scant information about the efficacy and safety of anticoagulant treatment in patients with splanchnic vein thrombosis. The current guidelines recommend anticoagulant therapy for at least 3 months on the basis of observational studies [82–87] and extrapolations from treatment of DVT of the leg and PE [36]. Treatment of splanchnic vein thrombosis may be complicated by the frequent concomitant risk factors for bleeding such as the presence of oesophageal varices or thrombocytopenia secondary to hypersplenism. In fact, some studies showed bleeding risks exceeding the risk of recurrent VTE [82–84, 86]. For incidentally detected splanchnic vein thrombosis, the risks and benefits of anticoagulant treatment should be weighed on an individual basis [25, 36, 61]. Factors that may support anticoagulant treatment are signs of acute thrombosis (i.e. acute abdominal symptoms or specific radiological features), ongoing chemotherapy, or progression of the thrombus during follow-up imaging [36]. An international registry prospectively followed 604 patients with splanchnic vein thrombosis, of whom 22 % had solid cancer and 9 % had a haematological malignancy [88]. Two-thirds of the 136 patients with solid cancer received anticoagulant treatment, mostly heparin. The incidence of major bleeding during a median follow-up of 2 years was 4.4 per 100 patient-years (95 % CI 2.1–9.3). There were 12 thrombotic events, corresponding to an incidence of 7.6 per 100 patient-years.

4.6 Treatment of Catheter-Related Thrombosis

No randomized controlled trials specifically evaluated the treatment of CVC-related thrombosis. Several studies have suggested that CVC-related thrombosis is associated with a low risk of recurrent VTE [89, 90]. In a prospective cohort of 74 cancer patients with CVC-related symptomatic UEDVT, there were no recurrent VTEs and 4 % experienced major bleeding events during 3 months of anticoagulant treatment with dalteparin followed by VKAs [90]. In a recent retrospective cohort study of 99 consecutive outpatients with cancer and symptomatic CVC-related UEDVT, no recurrent VTE and two bleeding episodes occurred during a total median treatment duration of 110 days [91]. In 80 patients who were followed after cessation of anticoagulant treatment, five recurrent VTE were observed during a median of 632 days. The catheter had been pulled out in 96 % [91].

International guidelines suggest the same initial and long-term treatment as for patients with DVT of the leg or PE [36, 61]. The catheter should be removed when it is no longer required or is not functioning (even after a period of systemic anticoagulation). If the CVC is removed, anticoagulant therapy may be provided for 3 months. A longer treatment is suggested if the catheter is left in place [36, 61].

5 Conclusion

Anticoagulant treatment in patients with cancer and VTE is challenging. Currently, LMWH is recommended for the prevention and treatment of cancer-associated VTE, including incidental VTE, UEDVT, and splanchnic DVT. Ongoing trials are evaluating the effectiveness and safety of DOACs, but results are not expected before 2017. The risk of VTE in ambulatory cancer patients and the benefit observed with LMWH are deemed too low to justify the routine use of prophylaxis. The identification of cancer patients at higher risk of VTE could increase the absolute benefit of thromboprophylaxis.

Compliance with Ethical Standards

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