Clinical aspects of venous thromboembolism in special patient populations

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Prevention and treatment of venous thromboembolism in cancer patients: focus on drug therapy

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Chapter 6

Abstract

Venous thromboembolism (VTE) is a common complication in patients with cancer. The anticoagulant treatment of cancer-associated VTE is challenging due to the intrinsically high risk of recurrent VTE as well as major bleeding. Low-molecular-weight heparins (LMWH) are the recommended anticoagulants in this vulnerable population because of their stable pharmacokinetics and the absence of important drug interactions. However, LMWH therapy requires daily subcutaneous injections often for an indefinite treatment period. Direct oral anticoagulants are a more attractive option because of their fixed, oral dosing without routine monitoring, but they first have to be evaluated against LMWH in patients with cancer and VTE before being adopted in clinical practice. Routine primary prophylaxis with LMWH in ambulatory cancer patients is currently not recommended given the number needed to treat of 40 to 50 to prevent one venous thromboembolic event. Risk stratification based on tumor type, combination of clinical parameters, or coagulation biomarkers may identify cancer patients at very high risk of VTE. Ongoing trials are evaluating the effectiveness and safety of thromboprophylaxis in these high-risk patients. If a sufficiently large absolute benefit is demonstrated, this may eventually lead to common use of LMWH prophylaxis in ambulatory patients with cancer.
Introduction

Venous thromboembolism (VTE), which comprises lower-extremity deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer. It is estimated that 20% of all VTE cases occur in cancer patients (1), who present a 4- to 7-fold higher risk of developing VTE compared to patients without cancer (2–4). The absolute incidence of cancer-associated VTE varies greatly depending on the tumor type, cancer stage, and anticancer treatment. For example, the incidence of VTE is 10 per 100 person-years in patients with pancreatic or brain cancer, whereas in prostate or breast cancer it is 1 to 2 per 100 person-years, close to the risk in the general population (4–6). Metastatic disease (6,7) and chemotherapeutic treatment also carry a higher risk of developing VTE (1).

While the focus in literature has traditionally been on symptomatic VTE, it is increasingly recognized that about half of all cancer-associated VTE are incidentally diagnosed on imaging tests performed usually for staging purposes (8). In addition to lower extremity DVT and PE, cancer patients frequently experience VTE at unusual sites such as splanchnic vein thrombosis (SVT) and upper extremity DVT (UEDVT) (9,10).

The risk of VTE recurrence in cancer patients is approximately 3-fold higher than in patients without cancer (11,12) with an absolute incidence during the first 6 months of anticoagulant treatment of 8% (13–16) and a case-fatality rate up to 47% (13). In fact, VTE represents one of the leading causes of death in cancer patients (17,18). The all-cause mortality in the 6 months following VTE is around 30% (13,14,16), which is significantly higher than in matched cancer patients without VTE (19). This probably reflects the worse prognosis of biologically more aggressive cancers which are also more likely to cause VTE (20–24).

In this review we focus on the use of anticoagulant drugs for the prevention and treatment of symptomatic or incidental cancer-associated VTE. Finally, we will address recent data regarding the long-term outcome of cancer patients with VTE at unusual sites including SVT and UEDVT.

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 as they have a higher risk of recurrent VTE and a 2- to 6-fold greater risk of anticoagulant-related bleeding compared to the general population (11,12,25). The rate of major bleeding during the first 6 months of treatment is approximately 6 to 10% (12–15), with a case-fatality rate up to 30% (25–27). Bleeding complications may interfere with diagnostic or therapeutic interventions and delay cancer treatment. In addition, anticoagulant treatment is often temporarily stopped following a bleeding event which exposes these patients to an increased risk of recurrent VTE (28).
In addition to the bleeding risk factors common to the general population such as older age and impaired renal or liver function, other cancer-specific elements contribute to the bleeding tendency and include, among others, chemotherapy-induced mucosal lesions, unstable neovascularization in the tumor environment, and thrombocytopenia related to chemotherapy-induced bone marrow suppression or bone marrow invasion by hematological malignancies (29). Metastatic brain lesions are prone to bleeding and are associated with a 19% risk of significant intracranial hemorrhage during the first year of anticoagulant treatment (30).

The treatment of VTE in patients without cancer traditionally consists of an initial course of heparin followed by vitamin K antagonists (VKA) for at least 3 months (31). VKA treatment can be particularly demanding in cancer patients. Chemotherapy-induced oral mucosal lesions, nausea, and vomiting may decrease oral drug intake, and intestinal mucosal lesions or diarrhea may affect the gastrointestinal drug absorption (32). There may be high inter- and intra-individual variability of drug levels 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 as reflected by a lower time in therapeutic range. In two large trials that evaluated VTE treatment in cancer patients, the time in therapeutic range was only 46% to 47% (13,16), compared to 60 to 70% in patients without cancer treated with VKA (33).

Low-molecular-weight heparins (LMWH) offer a more stable pharmacokinetic profile given the virtually absent interactions with food or drugs. However, the requirement of daily subcutaneous injections with frequent injection site reactions and subcutaneous hematomas may be burdensome for long-term treatment.

Recently, direct oral anticoagulants (DOACs) comprising the thrombin inhibitor dabigatran and the factor Xa-inhibitors apixaban, edoxaban, and rivaroxaban have become available for the treatment of VTE. Large phase 3 studies have shown that DOACs are as effective as VKAs in preventing recurrent VTE and cause significantly less bleeding (33). As discussed later, the evidence on the safety of DOACs in cancer patients is scarce. As with VKAs, nausea, vomiting, and intestinal lesions may affect the oral intake and gastrointestinal absorption. 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 (34). In addition, factor Xa inhibitors are partly metabolized by the cytochrome P450 3A4 pathway and caution is warranted when co-administered with inducers or inhibitors of this enzyme.
Prevention and treatment of venous thromboembolism in cancer patients

Prevention of VTE

Surgical cancer patients
Patients with cancer undergoing major surgical procedures have a two-fold higher risk of VTE than patients without cancer (35,36). Perioperative thromboprophylaxis, usually with LMWH (37), is recommended in these patients (38). Thromboprophylaxis should be started preoperatively and continued for at least 7 to 10 days postoperatively (38,39). In patients undergoing abdominal or pelvic surgery for cancer the postoperative risks remain high for over a month following surgery (40–42). In the ENOXACAN II study which compared enoxaparin with placebo for extended VTE prophylaxis in 332 patients undergoing abdominal or pelvic cancer surgery, asymptomatic DVT was observed in 5.5% of enoxaparin treated patients compared to 13.8% in the placebo group (RR 0.40, 95% CI 0.2 to 0.9). No significant difference was observed in the rate of major bleeding. In a meta-analysis by Akl and colleagues, extended thromboprophylaxis up to 4 weeks after surgery was associated with a 80% lower risk of VTE (RR 0.21; 95% CI 0.1 to 0.9) with no significant increase in major bleeding (RR 2.9; 95% CI 0.1 to 72) (43). Based on these data, it is now recommended that cancer patients undergoing major abdominal or pelvic surgery receive extended thromboprophylaxis for 4 weeks postoperatively (38,39). An ongoing trial is evaluating the efficacy and safety of apixaban versus enoxaparin in 400 women undergoing surgery for suspected pelvic malignancy (https://clinicaltrials.gov/ct2/show/NCT02366871).

Hospitalized cancer patients
Cancer patients hospitalized for medical reasons are also at an increased risk of VTE and the presence of active cancer is one of the strongest predictors of in-hospital VTE in validated risk assessment scores (44–46). The rate of in-hospital VTE is 3-fold higher in cancer patients compared to patients without cancer with an absolute risk that ranges from 0.6% to 7.8% (47). Data on the efficacy and safety of thromboprophylaxis in hospitalized medical cancer patients is scant. A recent meta-analysis by Carrier and colleagues identified only three VTE prevention studies that compared either LMWH or fondaparinux with placebo and reported on the subgroup of cancer patients (48). This combined analysis showed that thromboprophylaxis was not associated with a reduction in the risk of VTE (RR 0.91, 95% CI 0.2 to 4). Major bleeding rates were not reported in any of the studies. Nevertheless, 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. 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 (49,50). The use of DOACs in these patients cannot be recommended at this moment.

**Ambulatory cancer patients receiving chemotherapy**

Most of the trials that evaluated LMWH for thromboprophylaxis in ambulatory cancer patients have restricted inclusion to one or more types of advanced stage cancers associated with a high VTE risk. In a recent Cochrane meta-analysis, LMWH was associated with a significant 47% relative reduction in symptomatic VTE compared to no anticoagulation (RR 0.53, 95% CI 0.4 to 0.8) (51). No significant difference in major bleeding (RR 1.3, 95% CI 0.8 to 2.2) or mortality (RR 0.95, 95% CI 0.8 to 1.1) was observed. Despite these results in favor of LMWH, current guidelines recommend against the routine use of pharmacologic thromboprophylaxis in ambulatory cancer patients. With a baseline risk of 5.2%, the relative risk reduction of almost 50% translates into an absolute risk reduction of 2.4% (51), 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 daily subcutaneous injections for at least 3 months in patients with a limited life expectancy.

To increase the absolute benefit of LMWH thromboprophylaxis, some VTE prevention trials focused on a single high-risk tumor type. The FRAGEM trial randomly assigned 123 patients with advanced pancreatic cancer to therapeutic, weight-adjusted dalteparin versus standard of care (without anticoagulants) during 3 months of gemcitabine chemotherapy (52). Overall, 23% of patients in the standard of care arm developed arterial or venous thromboembolic complications that were symptomatic or incidental compared to 3% in the dalteparin arm (RR 0.15, 95% CI 0.04 to 0.6). Major bleeding rates were similar (3.4% vs. 3.2%). 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 enoxaparin versus standard of care (53). In the first 3 months of treatment, 1.3% of the enoxaparin treated patients developed symptomatic VTE compared to 9.9% of patients not receiving thromboprophylaxis (hazard ratio [HR] 0.12, 95% CI 0.03 to 0.5). Major bleeding occurred in 4.4% and 3.2% of patients (HR 1.4, 95% CI 0.4 to 3.7), respectively. Finally, in a third randomized trial dalteparin 5,000 IU daily was compared to no thromboprophylaxis in 75 patients with advanced pancreatic cancer (54). Consistent with earlier observations, 8% of patients in the dalteparin group developed symptomatic or asymptomatic VTE compared to 22% in the standard of care group (P = 0.02). Weighted combined analysis data from studies in pancreatic cancer patients suggest a 78% relative risk reduction in thromboembolic complications during the first months of chemotherapy (RR 0.22, 95% CI 0.1 to 0.4; Figure 6.1). With an overall baseline risk of 13%, this translates into an absolute risk reduction of 10% (95% CI 5 to 15%),
and a number needed to treat of 10 to prevent one thromboembolic complication. The pooled result of the FRAGEM and CONKO-004 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 and efficacy outcome definitions were heterogeneous. Moreover, most studies had an open-label design without blinded outcome adjudication. Nevertheless, this emerging evidence indicates that patients with advanced, high-risk cancer such as pancreatic adenocarcinoma starting chemotherapy may safely benefit from thromboprophylaxis.

Other VTE prevention trials that restricted enrolment to a single tumor type were inconclusive (55–56). Patients with newly diagnosed multiple myeloma treated with chemotherapy regimens that include lenalidomide or thalidomide are at high risk of VTE (57–59). In these patients the American Society of Clinical Oncology recommends thromboprophylaxis with either LMWH or low-dose aspirin (39).

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 mg, 10 mg, or 20 mg once daily, or placebo (60). Symptomatic VTE was diagnosed in 3 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 due to 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

**Figure 6.1.** Low-molecular-weight heparin compared with no thromboprophylaxis in ambulatory patients with advanced pancreatic cancer: arterial or venous thromboembolism. VTE: venous thromboembolism; ATE: arterial thromboembolism; LMWH: low-molecular-weight heparin; M-H: Mantel Haenszel; CI: confidence interval.
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.

What may be a way forward to prevent thromboembolic complications in ambulatory cancer patients? The net-clinical benefit of thromboprophylaxis could be increased by VTE risk stratification according to well-known risk factors. The Khorana score is a well-validated VTE risk assessment score that could be used to identify cancer patients at higher risk of VTE (61). The PHACS study 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 completed and results are expected soon. Some authors have proposed the use of biomarkers for VTE risk stratification in cancer patients although the evidence is not unequivocal (62). The Microtec study was a phase 2 study that randomized patients with advanced cancer and high levels of tissue factor exposing vesicles to either prophylactic dose enoxaparin or observation (63). During the 2-month follow-up, VTE was diagnosed in 4% of patients on enoxaparin compared to 27% in the observation group (HR 6.7, 95% CI 1.0–43), a difference largely driven by incidental DVT diagnosed on screening ultrasound. While these results require 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 (64), although the extended score needs validation.

**Treatment of VTE in patients with cancer**

**Initial treatment**

As for the general population with no cancer, the mainstay of the initial VTE treatment in cancer patients is parenteral anticoagulation. In a recent review of the literature on the initial treatment 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 (65). Data on the use of fondaparinux as initial treatment of cancer-associated VTE are limited to a post-hoc analysis of the Matisse trials (66). No statistically significant differences in recurrent VTE, bleeding, and mortality were observed between fondaparinux and heparin. Based on the available data, LMWH is now recommended for the initial treatment of cancer-associated VTE (39,67). 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.
(68). UFH may, however, be considered in patients with a creatinine clearance less than 30 mL/min since it is largely dependent on hepatic clearance.

**Long-term treatment**

*Type of anticoagulant*

In the seminal CLOT study, nearly 700 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 5 to 10 days of dalteparin followed by VKAs targeted at an INR between 2 and 3 (13). During a 6-month follow-up, 9% of patients treated with dalteparin and 17% of those receiving VKA developed recurrent VTE (hazard ratio [HR] 0.48; 95% CI 0.3 to 0.8). No significant difference was observed in the rate of major bleeding (6% vs. 4%). Subsequently, three other trials reported similar results (Table 6.1) and a meta-analysis of all these studies demonstrated a significant 53% relative risk reduction in recurrent VTE with LMWH compared to VKAs with no difference in major bleeding (RR 1.07; 95%-CI 0.5 to 2.2) and survival (HR 0.96; 95%-CI 0.8 to 1.1) (69). Based on a superior efficacy and a similar safety profile relative to VKAs, LMWH is currently recommended for the treatment of cancer-associated VTE by all major international guidelines (39,67,70).

In the recent CATCH study, an open-label, randomized clinical trial with blinded outcome evaluation, full-dose tinzaparin was compared with VKA for VTE treatment in patients with active cancer (16). During the 6 month follow-up period, the incidence of recurrent VTE was comparable in patients treated with tinzaparin (7%) and warfarin (10%; HR 0.65, 95% CI 0.4 to 1.0) and no difference in major bleeding was observed (2.7% vs. 2.4%). Tinzaparin was, however, associated with a significant 42% relative reduction in clinically relevant non-major bleeding (11% versus 15%; HR 0.58, 95% CI 0.4 to 0.8). Taken together, 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 to VKAs (RR 0.57, 95% CI 0.4 to 0.8; Figure 6.2) and a comparable risk of major bleeding (RR 1.07, 95% CI 0.7–1.8; Figure 6.3).

The 6 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 VKA (RR 0.57, 95% CI 0.4 to 0.9). No difference in major bleeding rate was observed (RR 0.77, 95% CI 0.44 to 1.33) (33). 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,
Table 6.1. Summary of randomized controlled trials evaluating the efficacy and safety of anticoagulant treatment of cancer-associated venous thromboembolism

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Number of cancer patients</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Intended treatment duration</th>
<th>Recurrent VTE</th>
<th>Major bleeding</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopaciuk et al., 1999 (95)</td>
<td>Open-label; unclear whether end-point assessment was blinded</td>
<td>12 (subgroup analysis)</td>
<td>nadroparin (6)</td>
<td>nadroparin à acenocoumarol (6)</td>
<td>3 months</td>
<td>NR</td>
<td>NR</td>
<td>67%</td>
</tr>
<tr>
<td>Lopez-Beret et al., 2001 (96)</td>
<td>Open-label; unclear whether end-point assessment was blinded</td>
<td>35 (subgroup analysis)</td>
<td>nadroparin (17)</td>
<td>nadroparin à acenocoumarol (18)</td>
<td>3 to 6 months</td>
<td>5.9%</td>
<td>22%</td>
<td>41%</td>
</tr>
<tr>
<td>CANTHANOX, 2002 (27)</td>
<td>Open-label with blinded end-point</td>
<td>138</td>
<td>enoxaparin (71)</td>
<td>enoxaparin à warfarin (67)</td>
<td>At least 3 months</td>
<td>Combined: 10.5%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cesarone et al., 2003 (97)</td>
<td>Open-label; unclear whether end-point assessment was blinded</td>
<td>192</td>
<td>enoxaparin (96)</td>
<td>enoxaparin à coumadin (96)</td>
<td>3 months</td>
<td>6.6%</td>
<td>10%</td>
<td>2.1%</td>
</tr>
<tr>
<td>CLOT et al., 2003 (13)</td>
<td>Open-label with blinded end-point</td>
<td>672</td>
<td>Dalteparin (336)</td>
<td>Dalteparin à VKA (336)</td>
<td>6 months</td>
<td>9%</td>
<td>6%</td>
<td>39%</td>
</tr>
<tr>
<td>ONCENOX, 2006 (15)</td>
<td>Open-label; no blinded end-point assessment</td>
<td>102</td>
<td>enoxaparin (68)</td>
<td>enoxaparin à warfarin (34)</td>
<td>6 months</td>
<td>6.6%</td>
<td>9.0%</td>
<td>33%</td>
</tr>
<tr>
<td>Main-LITE, 2006 (26)</td>
<td>Open-label; no blinded end-point assessment</td>
<td>200</td>
<td>tinzaparin (100)</td>
<td>UFH à VKA (100)</td>
<td>3 months</td>
<td>7%</td>
<td>16%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Romera et al., 2009 (98)</td>
<td>Open-label with blinded end-point</td>
<td>69 (subgroup analysis)</td>
<td>tinzaparin (36)</td>
<td>tinzaparin à acenocoumarol (33)</td>
<td>6 months</td>
<td>5.5%</td>
<td>21%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Van Gogh DV T, 2010 (99)</td>
<td>Open-label with blinded end-point</td>
<td>421 (subgroup analysis)</td>
<td>idraparinux (220)</td>
<td>heparin à VKA (201)</td>
<td>3 to 6 months</td>
<td>2.5%</td>
<td>21.5%</td>
<td>23%</td>
</tr>
<tr>
<td>CATCH, 2015 (16)</td>
<td>Open-label with blinded end-point</td>
<td>900</td>
<td>tinzaparin (449)</td>
<td>tinzaparin à warfarin (451)</td>
<td>6 months</td>
<td>6.9%</td>
<td>2.7%</td>
<td>33%</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; UFH: unfractionated heparin; VKA: vitamin K antagonist
Figure 6.2. Low-molecular-weight heparin compared with vitamin K antagonists for treatment of venous thromboembolism in patients with active cancer: recurrent venous thromboembolism. LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist; M-H: Mantel Haenszel; CI: confidence interval.

Figure 6.3. Low-molecular-weight heparin compared with vitamin K antagonists for treatment of venous thromboembolism in patients with active cancer: major bleeding. LMWH: low-molecular-weight heparin; VKA: vitamin K antagonist; M-H: Mantel Haenszel; CI: confidence interval.

since patients for whom LMWH therapy was anticipated were excluded. Cancer was not consistently defined across the trials and cancer-specific information was either not available or not reported. Most importantly, DOACs were compared to VKA and not to LMWH which is currently the recommended treatment option. Several studies have recently been initiated to evaluate DOACs for the treatment of cancer-associated VTE.

The Hokusai VTE-cancer study is an ongoing international, randomized, open-label trial comparing the efficacy and safety of the factor Xa-inhibitor edoxaban with dalteparin monotherapy for the treatment of VTE in patients with cancer (https://clinicaltrials.gov/ct2/show/NCT02073682). This pragmatic study has incorporated various innovative features in its design to optimize the internal and external validity. 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 6 months. The study aims to enroll 1000 patients and has started recruitment in July 2015.
Chapter 6

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 study aims to enroll 530 patients and has started recruitment in 2013. Last, a single arm study in Korea is currently prospectively evaluating the efficacy and safety of rivaroxaban in a cohort of cancer patients with VTE (https://clinicaltrials.gov/ct2/show/NCT01989845).

Treatment duration

All studies evaluating treatment of cancer-associated VTE limited study treatment to a maximum of 6 months (Table 6.1), hence data regarding the optimal treatment duration are lacking. 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 (70). The decision to continue treatment should be weighed against the threat of major bleeding and the risk-benefit ratio should be reassessed periodically. Patient’s preference and quality of life should also be taken into account. Isolated distal DVT, VTE associated with a superimposed reversible risk factor (e.g. surgery), or cancer that has responded to treatment or has not metastasized seem associated with a lower risk of recurrence and physicians could consider a shorter course of anticoagulant treatment in these cases (70).

Which anticoagulant should be used beyond 6 months remains a dilemma. In a survey conducted amongst thrombosis and non-thrombosis specialists, 44% preferred LMWH, 10% would choose VKA, and the remaining 45% would make a choice between LMWH or VKA on an individual patient basis (71). 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 recently published DALTECAN study was a prospective, single-arm cohort study that evaluated the long-term safety of dalteparin in patients with active cancer and VTE (14). During the first month of treatment when patients were receiving full-dose dalteparin, the rates of major bleeding and recurrent VTE were 3.6% and 5.7%, respectively. Thereafter, the dalteparin dose was reduced to 75% and was associated with a higher monthly risk of major bleeding during month 2 to 6 (1.1%) than month 6 to 12 (0.7%). The risk of recurrent VTE per month was consistent during treatment from 2 to 12 months (0.7%). Two important messages emerge from these findings. First, the risk of anticoagulant-related major bleeding in cancer patients remains high, even with a reduced dose of LMWH. Second, the risk of recurrent VTE is still substantial after the initial 6 months of treatment which would support extending VTE treatment beyond 6 months.
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 (72). 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 concentration of 1.6 to 2.0 U/mL in case of once daily dosing and 0.8 to 1.0 U/mL for a twice daily regimen (72). Patients treated with VKA should be switched to LMWH (69). In a recent registry of 212 cancer patients with recurrent VTE, 41% of patients continued with the same anticoagulant regimen, 31% had higher dosage of the same drug and in the remainder the drug was changed. During 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 significantly higher risk of an additional recurrent VTE than patients receiving LMWH (29% vs. 9%; HR 0.28, 95% CI 0.1 to 0.7). Major bleeding occurred in 8% of the patients, all of whom were on LMWH (OR vs. VKA 4.6, 95% CI 0.3 to 80).

Treatment of incidental VTE

Prospective studies evaluating the prognosis of incidental VTE in cancer patients are lacking. Several retrospective studies suggest that the risk of recurrent VTE is similar in patients with incidental VTE compared to those with symptomatic VTE (73–75). The evidence on the management of incidental VTE in cancer patients is limited to relatively small case series and retrospective studies which overall suggest that the risk of recurrent VTE is not negligible if left untreated (76–81). In an interim analysis of an ongoing international registry, Soler and colleagues observed no recurrences in 78 cancer patients with incidental PE while receiving anticoagulant treatment (82). An individual patient data meta-analysis of 926 cancer patients with incidental PE, reported a VTE recurrence rate of 6% in patients treated with LMWH compared with 12% of those left untreated and 6.4% of patients receiving VKAs (83). The risk of major bleeding was significantly higher in patients treated with VKA compared to those treated with LMWH (13% versus 4%, HR 3.2; 95%CI 1.4 to 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 (39,67,70). Whether selected subgroups such as those with isolated subsegmental PE (SSPE) may be treated more conservatively remains unknown. In a combined post-hoc analysis of two large prospective cohort studies, a similar rate of complications such as recurrent VTE, bleeding and mortality was found for symptomatic SSPE as for more proximal symptomatic PE (84). In a study by O’Connell and colleagues, however, cancer patients with incidental SSPE were found to have a better median survival than patients with more proximal incidental PE, and
a similar survival as patients without PE (76). Comparable results were reported by van der Hulle and colleagues, showing a mortality rate after 6 months of 42% in patients with a central or lobar incidental PE versus 30% in segmental or subsegmental PE (HR 1.8, 95% CI 1.4 to 2.3) (83).

An ongoing RCT is evaluating whether anticoagulant treatment can be safely withheld in patients with symptomatic SSPE and no evidence of concomitant DVT (https://clinicaltrials.gov/ct2/show/NCT01455818), but cancer patients are excluded from participation. Furthermore, an ongoing international, multicenter, observational study is recruiting consecutive cancer patients with incidental PE in over 30 centers worldwide, aiming to record current treatment approaches and to prospectively assess the risk of recurrent VTE, bleeding, and mortality during a 12 month follow-up (https://clinicaltrials.gov/ct2/show/NCT01727427). Results of this study are expected in 2017.

**Treatment of splanchnic venous thrombosis (SVT)**

There is scant information on the efficacy and safety of anticoagulant treatment in patients with SVT. The current guidelines recommend anticoagulant therapy for all patients with symptomatic SVT, for at least 3 months, based on observational studies (85–90) and on extrapolations from treatment of DVT of the leg and PE (70). Treatment of SVT may be complicated by an increased risk of bleeding associated with esophageal varices as a consequence of portal hypertension, and thrombocytopenia secondary to hypersplenism. In fact, some studies showed bleeding risks exceeding the risk of recurrent VTE (85–87,89). For incidentally detected SVT, the risks and benefits of anticoagulant treatment should be weighed on an individual basis (39,67,70). Factors that may support anticoagulant treatment are signs of acute thrombosis (i.e. acute abdominal symptoms or specific radiologic features), ongoing chemotherapy, or progression of thrombus during follow-up imaging (70). Therefore, if left untreated, repeated imaging to detect progression of the thrombus seems justifiable. Recently the results of an international registry of patients with SVT were published (91). In total, 604 patients, of which 22% had solid and 9% hematological cancer, were included and followed prospectively for a median duration of 2 years. Two-thirds of the patients with solid cancer received anticoagulant treatment, mostly heparin. In 136 cancer patients, the incidence of major bleeding was 4.4 per 100 patient-years (95% CI 2.1 to 9.3). There were 12 thrombotic events, corresponding to an incidence of 7.6 per 100 patient-years.

**Treatment of catheter-related thrombosis**

No randomized controlled trials specifically evaluated the treatment of central venous catheter (CVC) related thrombosis. International guidelines suggest the same initial and long-term treatment as for patients with DVT of the leg or PE (67,70). If thrombosis occurs in association with a CVC, the catheter should be removed when it is no longer
required or is not functioning (and cannot be made to function even after a period of systemic anticoagulation). Several studies have suggested that CVC-related thrombosis is associated with a low risk of recurrent VTE (92,93). In a prospective cohort of 74 cancer patients with CVC-related symptomatic UEDVT there were no recurrent VTE events and 4% experienced major bleeding events during 3 months of treatment with dalteparin followed by VKAs. In this study, CVC were not removed (93). In a recent retrospective cohort study of 99 consecutive outpatients with cancer with symptomatic CVC-related UEDVT, no recurrent VTE and two bleeding episodes occurred during a total median treatment duration of 110 days (94). In 80 patients who were followed after cessation of anticoagulant treatment, 5 recurrent VTE were observed during a median of 632 days. The catheter had been pulled out in 96% (94).

Based on expert consensus, guidelines suggest 3 months of anticoagulation for CVC-related UEDVT if the CVC is removed, otherwise anticoagulation may be prolonged beyond 3 months, at least as long as the catheter is in place (67,70).

**Conclusion**

VTE is a major cause of morbidity and mortality in patients with cancer, and cancer patients with VTE are at increased risk of recurrent VTE and major bleeding. Anticoagulant treatment is challenging in these patients who often receive multiple antineoplastic drugs, frequently undergo diagnostic or therapeutic interventions, and are susceptible to nausea and vomiting.

The combined evidence from clinical trials demonstrates the superiority of LMWH over VKA in preventing recurrent VTE, while the risk of major bleeding is comparable. Therefore, LMWH is currently the recommended treatment of cancer-associated VTE, including incidental VTE, UEDVT, and splanchnic DVT. Ongoing trials will evaluate the effectiveness and safety of DOACs in patients with cancer and VTE, but results are not expected before 2017. Given the rise in the incidence of cancer-associated VTE over the past two decades, the focus is shifting to VTE prevention and the importance of thromboprophylaxis is increasingly acknowledged. However, primary VTE prophylaxis in ambulatory cancer patients with LMWH is associated with a 2 to 3% absolute risk reduction, which in general is deemed too low to justify its routine use. Identifying cancer patients at high risk of VTE based on the tumor type, biomarkers, or risk assessment scores could increase the absolute benefit of thromboprophylaxis, but the effectiveness of such selection strategies has not yet been established.
Chapter 6

References

Prevention and treatment of venous thromboembolism in cancer patients


Prevention and treatment of venous thromboembolism in cancer patients

Chapter 6


112
