Treatment and secondary prevention of venous thromboembolism in cancer patients

Current strategies and new therapeutic options

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Summary
Cancer is a major and independent risk factor for venous thromboembolism (VTE). In clinical practice, a high number of VTE events occurs in patients with cancer, and treatment of cancer-associated VTE differs in several aspects from treatment of VTE in the general population. However, treatment in cancer patients remains a major challenge, as the risk of recurrence of VTE as well as the risk of major bleeding during anticoagulation is substantially higher in patients with cancer than in those without cancer. In several clinical trials, different anticoagulants and regimens have been investigated for treatment of acute VTE and secondary prophylaxis in cancer patients to prevent recurrence. Based on the results of these trials, anticoagulant therapy with low-molecular-weight heparins (LMWH) has become the treatment of choice in cancer patients with acute VTE in the initial period and for extended and long-term anticoagulation for 3–6 months. New oral anticoagulants directly inhibiting thrombin or factor Xa, have been developed in the past decade and studied in large phase III clinical trials. Results from currently completed trials are promising and indicate their potential use for treatment of VTE also in cancer patients. However, the role of the new oral thrombin and factor Xa inhibitors for VTE treatment in cancer patients still has to be clarified in further studies specifically focusing on cancer-associated VTE.

This brief review will summarize the current strategies of initial and long-term VTE treatment in patients with cancer and discuss the potential use of the new oral anticoagulants.

Schlüsselwörter
Venöse Thromboembolie, Krebs, Antikoagulation, Therapie, Sekundärprophylaxe

Zusammenfassung

In diesem Übersichtsarticle werden die aktuellen Strategien für die Behandlung der akuten VTE und deren Sekundärprophylaxe bei Patienten mit Krebserkrankung zusammengefasst. Zudem wird der potenzielle Einsatz der neuen oralen Antikoagulanzien diskutiert.

Cancer is a major and independent risk factor for venous thromboembolism (VTE) in the general population. In addition, anticancer treatments including chemotherapy, hormonal therapy, anti-angiogenic or immunomodulatory drugs and major cancer surgery are frequently complicated by deep vein thrombosis (DVT) of the legs or by pulmonary embolism (PE). In some cases the thrombotic event may also occur in other venous sites such as the portal, mesenteric and cerebral venous system.

According to a large population-based cohort study, the risk of VTE compared to persons without cancer (1) is about...
How do we treat VTE?

Standard treatment

Anticoagulation is the cornerstone of treatment of VTE to prevent acute and chronic complications (9) such as

- fatal PE,
- thrombus extension,
- early and late recurrence of VTE,
- pulmonary hypertension and
- post-thrombotic syndrome.

In general, there are parenteral anticoagulants currently available for the initial treatment of an acute VTE, such as

- unfractionated heparin (UFH),
- low-molecular-weight-heparins (LMWH) and
- fondaparinux, a synthetic pentasaccharide that inhibits activated factor X (Xa) via binding to antithrombin III.

LMWH and vitamin K antagonists (VKA) – the latter are administered orally – are the options for extended and long-term therapy of patients with established VTE.

Besides, a number of new oral anticoagulant drugs such as dabigatran, rivaroxaban, apixaban and edoxaban have been developed, which exert their anticoagulant effect through direct inhibition of thrombin or factor Xa (10).

Several large clinical trials with these new agents have been designed for the prevention and treatment of VTE, which are either completed or underway (11).

The treatment of VTE in patients with cancer differs in several aspects from the treatment of VTE in patients without cancer. To understand these differences, the treatment of VTE in the general population, as recommended in the latest version of international guidelines, is outlined here first – currently, the worldwide most-recognized guidelines are those of the American College of Chest Physicians (ACCP) (9). Generally, patients with VTE should be treated with anticoagulants as soon as the diagnosis is confirmed. If the clinical suspicion of VTE, in particular of PE, is high, the treatment should be started without delay, while objective diagnostic evaluation is ongoing and confirmatory results are awaited. In the initial period of the therapy of acute VTE parenteral anticoagulants are administered. LMWHs in a weight-based therapeutic dosage are preferably used in addition to VKA for at least the first 5 days and discontinued once the INR (international normalized ratio, a test for monitoring of therapy with VKA) is within the therapeutic target range of 2.0–3.0 on two subsequent days. VKA therapy could be started within 24 hours or a few days later. Also UFH can be given for initial treatment, either intravenously (i.v.) as a continuous infusion while monitoring the aPTT or subcutaneously (s.c.) in a weight-adjusted dosage. Interestingly, in a recently published meta-analysis a fixed therapeutic dose of LMWH was reported to be more effective and safer than an adjusted dose of UFH for the initial treatment of VTE (12). LMWH was shown to reduce the incidence of thrombotic complications, thrombus size, occurrence of major haemorrhage during the initial period of treatment and overall mortality at follow-up (12). Fondaparinux administered s.c. may represent another option for the initial VTE treatment.

In non-cancer patients, the extended and long-term treatment of VTE is performed with VKA.

The anticoagulant therapy with an INR target range of 2.0–3.0 is continued for a minimum of 3 months in patients with provoked VTE (i.e. events secondary to a transient/reversible risk factor or those with a single episode of an unprovoked isolated distal DVT) and longer in patients with a high risk of VTE recurrence, such as those with unprovoked proximal DVT or PE (9). Long-term (indefinite) anticoagulant therapy for secondary VTE prevention in the latter patient group is indicated, if there are no risk factors for bleeding and if good monitoring of the therapy is possible.

The best method for treatment of VTE in patients with cancer in order to prevent recurrence has been investigated over the last decade in various clinical trials, indicating an advantage of LMWH over VKA in the therapy of cancer-associated VTE.
Initial treatment in patients with cancer

According to the guidelines of the ACCP, American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO), LMWHs are preferred in the initial as well as in the long-term treatment of cancer-associated VTE (9, 13–15). Similarly to non-cancer patients, UFH and fondaparinux are alternatively recommended for the initial treatment of VTE. In comparison to UFH the use of LMWH simplifies the treatment and does not require routine coagulation monitoring. Also the risk of heparin-induced thrombocytopenia (HIT) is lower in patients treated with LMWH than in those receiving UFH. Fondaparinux is in general less frequently used in the cancer population, because presently no studies are available supporting a role of fondaparinux beyond the initial period of VTE treatment for long-term anticoagulation of established VTE.

The standard therapeutic option for the initial treatment of an acute VTE episode in patients with cancer is the administration of LMWH s.c. at a weight-adjusted dose:

- 200 units of anti-Xa activity per kilogram (kg) body weight s.c. once daily, or
- 100 units of anti-Xa activity per kg body weight s.c. twice daily.

For therapies with some particular LMWH, there are also recommendations available for alternative dose regimens (16). As LMWHs are primarily eliminated renally, special attention is paid to patients with severe renal insufficiency, where LMWHs should be used cautiously in order to avoid accumulation. For patients with renal impairment dosing recommendations exist for most LMWHs. Also anti-Xa activity monitoring might be useful to adjust the dose of LMWH in patients with renal insufficiency. General contraindications to anticoagulation should be considered prior to starting any anticoagulation therapy (9, 13). These include most importantly active bleeding or a high risk of bleeding and severe thrombocytopenia.

Thrombolytic therapy in the acute treatment of VTE can be applied in specific subgroups of cancer patients to rapidly reduce the thrombus burden and acute symptoms, when no contraindications due to an increased bleeding risk are present (9, 16). It is, however, associated with a clearly increased risk of major bleeding complications in patients with cancer (17) and should be reserved only for life-threatening PE presenting with evidence for hemodynamic compromise due to a severe right ventricular dysfunction or for limb-threatening massive DVT with risk of limb gangrene, if appropriate expertise and resources are available (9).

Long-term treatment to prevent VTE recurrence in patients with cancer

While the methods and pharmacological options for treatment in the initial phase of acute VTE are clear and well established, the optimal strategy for secondary prophylaxis (long-term treatment) to prevent VTE recurrence has been frequently discussed over the past decades. Oral VKA therapy for anticoagulation in cancer patients in the extended and long-term treatment has been suggested to cause concern because of various drug interactions (which especially might be a problem in cancer patients receiving chemotherapy or other anti-cancer drugs), malnutrition, liver dysfunction etc., leading to significant fluctuations in the anticoagulant effect and in the INR range. This produces higher rates of both recurrent VTE and bleeding complications in cancer patients with VTE than in VTE patients without cancer that are treated with VKA (8, 18).

For long-term treatment of cancer-associated VTE, the standard treatment of VTE with LMWH and VKA therapy that is started in the initial phase and followed by oral anticoagulation with VKA alone in the extended period of 3–6 months has been compared to long-term use of LMWH for 3–6 months in several clinical trials (19–22). Overall, these trials have demonstrated a benefit of LMWH over oral anticoagulation with VKA in the long-term treatment of established VTE; reviewed in (23, 24). The results of the three pivotal studies are outlined in the following.

Up to date, the CLOT (Randomized Comparison of Low-Molecular-Weight-Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer) trial is the largest study of VTE treatment in patients with cancer (19). In this study 673 cancer patients with acute, symptomatic VTE were randomly assigned to receive either the LMWH dalteparin at a dose of 200 IU per kg of body weight s.c. once daily for 5–7 days and a VKA (warfarin or acenocoumarol) for six months (target INR 2.5), or dalteparin alone for six months (200 IU per kg once daily for one month, followed by a daily dose of approximately 150 IU per kilogram for five months). The cumulative probability of recurrent VTE during the 6-month study period was 17% in patients treated with a VKA compared to 9% in patients treated with dalteparin. A statistically significant relative risk reduction of 52% and an absolute risk reduction of 8% were shown in favor of dalteparin. No significant differences between the two groups were observed with regard to the rates of minor and major bleedings. Major bleeding episodes occurred in 6% of patients who received dalteparin and in 4% of those who were in the control group treated with VKA.

In the two other trials that also had an open-label design the long-term VTE treatment of cancer patients with the LMWHs enoxaparin and tinzaparin was investigated over a period of 3 months. The CHANTANOX trial compared enoxaparin s.c. (1.5 mg per kg once daily) with VKA (warfarin, target INR 2.0–3.0) given for 3 months in cancer patients with VTE (20). The combined primary outcome of the study was major bleeding or recurrent VTE within 3 months. During the study period the primary outcome occurred in 10.5% of patients (7 of 67) assigned to the enoxaparin group and in 21.1% (15 of 71) assigned to the VKA group. Major bleeding accounted for most of the primary outcome events. Six deaths due to hemorrhage were reported in the warfarin group compared with none in the enoxaparin group. These results confirm that VTE therapy with VKA is associated with a higher bleeding rate in patients with cancer.

The LMWH tinzaparin (in a fixed dose of 175 units s.c. per kg of body weight once daily) was investigated as an alternative to...
long-term treatment with the VKA warfarin (after an initial treatment with UFH) for the secondary prevention of VTE over 3 months in the LITE (Long-term Inno-
vations in TreatmEnt program) trial (21). This study also confirmed that long-term LMWH treatment is more effective than VKA therapy for preventing recurrent VTE in patients with cancer. Bleeding rates did not differ between the two groups.

The results of these randomized trials, which are supported by a Cochrane sys-
tematic review, have demonstrated that for the extended and long-term treatment (secondary prophylaxis) of established VTE in cancer patients LMWH is more ef-
effective than oral anticoagulation with VKA and reduces the rates of recurrent VTE (25). The risk of bleeding is not increased and treatment of cancer-associated VTE with LMWH appears as safe as with VKA (25). Therefore, international guidelines recommend extended and long-term treat-
ment of VTE in cancer patients preferably with LMWH for a period of at least 3 months up to 6 months for secondary pro-
phylaxis to prevent VTE recurrence and in-
definitely in patients with active malignan-
cy (reviewed in (15)). However, there is no
evidence for the optimal approach (ap-
propriate duration of anticoagulation, optimal dose regimen of LMWH) for secondary pro-
phylaxis beyond the treatment period of 6 months for cancer patients who still have active malignancy. Alternatively, the guidelines of ASCO suggest anticoagula-
tion with VKA at a target INR of 2.0–3.0 in case a long-term therapy with LMWH is not available or not possible for some rea-
sons (13).

**New oral anticoagulants for prevention and treatment of VTE in cancer patients**

Some main disadvantages of currently available anticoagulants, such as the s.c. in-
jection of LMWH or the requirement for regular coagulation monitoring for oral VKA and frequent dose adjustments, have led to the development of new anticoagu-
lant agents. These new drugs are more con-
venient and orally administered at a fixed
dose, have fewer drug interactions and no
need for dose adjustment or routine lab-
oratory monitoring (11, 26). A number of new oral anticoagulant agents have been studied in the recent years and may over
time replace the presently used antithrom-
bolic agents, in particular VKA, for most indica-
tions. They are targeted at the direct
inhibition of either factor Xa (rivaroxaban,
apixaban, edoxaban) or thrombin (dabig-

tran). Currently, some of the new oral anticoagulants are subject to or have com-
pleted phase III trials with promising re-
sults for the use in both the prevention and

treatment of VTE.

Dabigatran, rivaroxaban and apixaban first were extensively investigated in large

trials on thromboprophylaxis after elective hip and knee replacement surgery. Results of these phase III trials indicated that the novel oral anticoagulants were at least as ef-
effective and safe as thromboprophylaxis with enoxaparin (the LMWH that was used in the control group of all of these studies). In Europe and North America some of these drugs have already been approved by the regulatory authorities for thrombopro-
phylaxis and VTE prevention after ortho-
daeic replacement surgeries.

For treatment of VTE, there are pre-

cently two studies completed and published.

In the double-blind double-dummy phase III RE-COVER study patients with acute

VTE who were initially given parenteral anticoagulation therapy with LMWH or UFH for at least 5 days were randomized in a 1:1 ratio to receive long-term treatment with oral dabigatran at a dose of 150 mg twice daily compared to the dose-adjusted VKA therapy with warfarin to achieve an INR of 2.0–3.0 for 6 months (27). The pri-

mary outcome of the study was the 6-month incidence of recurrent sympto-
matic VTE and occurred in 30 of 1274 pa-

ients (2.4%) assigned to treatment with dabigatran and in 27 of 1265 patients (2.1%) assigned to warfarin. The rates of

major bleeding – defined as bleeding that was clinically overt and was associated with a fall in the haemoglobin level of ≥ 2 g per decilitre, resulted in the need for trans-

fusion of red cells, involved critical sites or

was fatal (28) – were 1.6% in the dabigatran
group compared to 1.9% in the warfarin
group, and the rates of major or clinically

relevant non-major bleeding events (5.6% vs. 8.8%) as well as the rates of any bleeding

episodes (16.1% vs. 21.9%) were signifi-
cantly lower in the dabigatran group. In

conclusion, for the treatment of VTE, da-

bigatran was found to be non-inferior to

the VKA warfarin with respect to the risk

of recurrent VTE and to have a safety profile that is similar to that of warfarin. As only a low number of patients with active cancer (about 5% in each group) were included in this trial, conclusions for the treatment of cancer-associated VTE with dabigatran cannot be drawn from these results, al-

though in a subgroup analysis the efficacy

appeared to be similar to the main study results.

In the recently published open-label, randomized phase III EINSTEIN-DVT study, which included 3449 patients with acute symptomatic DVT, the oral factor Xa inhibitor rivaroxaban (in a dose of 15 mg twice daily for 3 weeks, followed by 20 mg once daily) was compared to standard treatment (consisting of enoxaparin s.c., followed by a VKA) for 3, 6 or 12 months (29). A non-inferiority in efficacy of rivar-
oxaban compared to enoxaparin-VKA was


demonstrated. The primary outcome (re-
current non-fatal or fatal VTE) occurred in

2.1% of patients (36 of 1731) treated with

rivaroxaban compared to 3.0% (51 of

1718) among those who received standard
treatment. The principal safety outcome (major bleeding or clinically relevant non-
major bleeding) occurred in 8.1% of pa-

tients in each group. The proportion of pa-

tients with active cancer at the time of study

inclusion was 6.6% in the rivaroxaban arm and 5.2% in the control arm with standard

therapy. Although both, the efficacy and safety of rivaroxaban compared to enox-
aparin-VKA were also similar in the sub-
group analysis of patients with cancer in-
cluded in the EINSTEIN-DVT trial, addi-
tional studies comprising larger numbers of patients with cancer are needed to inves-
tigate the potential of rivaroxaban for the treatment and secondary prophylaxis of
cancer-associated DVT. The efficacy and safety of rivaroxaban compared to standard

therapy for treatment of PE is investigated sepa-

rately in the ongoing EINSTEIN-PE trial.

As even some patients receiving throm-

boprophylaxis or treatment with LMWH
still experience VTE, antithrombotic agents with increased efficacy and safety would be desired also for the prevention and treatment of VTE in cancer patients (30). However, the novel oral anticoagulants have not yet been specifically evaluated for patients with cancer. Future studies are required to investigate their efficacy and safety for thromboprophylaxis and long-term treatment of established VTE for this particular patients group. Moreover, the population of cancer patients is very heterogeneous with respect to the different approaches in the anti-cancer treatment of the various tumor types at different stages (e.g. including chemo- or radiotherapy, angiogenesis inhibitors, immunomodulatory agents, hormonal therapy, cancer surgery; patients receiving palliative care and those who are hospitalized or ambulatory treated, etc.), which might influence the requirements for and the strategy of anticoagulation. Therefore, the advantages of the new oral anticoagulants have to be evaluated and confirmed for those specific settings.

Furthermore, no data on the interaction of factor Xa and thrombin inhibitors with anti-cancer drugs are available up to date. Experimental and clinical studies also have to investigate their effect on cancer progression and survival, as reported for anticoagulation with LMWH.

Conclusion

Anticoagulant therapy with LMWH is the treatment of choice for patients with cancer • in the initial period of acute VTE and • for extended and long-term anticoagulation to prevent VTE recurrence.

According to recommendations by international guidelines, which are based on the results of the main trials performed specifically in cancer patients, the therapy of VTE with LMWH should be administered for three to six months.

It is recommended to continue anticoagulation beyond six months as long as a patient still has active malignancy.

However, there is no clear evidence for the best strategy and appropriate options for prolonged secondary VTE prophylaxis. Other specific problems in the treatment of cancer-associated VTE are the relatively high rates of recurrent VTE while the patients are on LMWH. The optimal approach in this setting is challenging, and dose escalation of LMWH has been shown to be effective in some of these patients (31).

The results of phase III trials with the new oral anticoagulant agents targeted at factor Xa and thrombin inhibition for thromboprophylaxis in orthopaedic knee and hip replacement surgery, and for treatment and secondary prophylaxis of VTE are promising. However, specific studies in cancer patients have to be performed in order to clarify their role as an alternative option to current standard of care in the treatment of cancer-associated VTE.

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Conflicts of interest

The authors declare, that they have no conflicts of interest.

References

22. Deitcher SR, Kessler CM, Merli G et al. Secondary prevention of venous thromboembolic events in