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Cancer-associated thromboembolism

Thrombosis management in patients with gastro-intestinal tumors

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Cancer-associated venous thromboembolism represents a significant morbidity and mortality risk for cancer patients. This is particularly true for gastrointestinal (GI) tumors which are also associated with a high risk of bleeding. This article explores approaches for making the most informed and safe decision about personally effective anticoagulation management.

Next to tumor-related mortality arterial and venous thromboembolisms (VTE) are the second most frequent cause of death in cancer patients. The malignant neoplasms themselves as well as cytotoxic or immunomodulatory drugs increase patients' risk of carcinoma-associated VTE by a factor of 4 to 7 [1, 2].

Tumor localization plays a major role in the assessment of the individual risk. According to the prediction model of Khorana et al. patients with GI tumors, especially with gastric or pancreatic cancers, but even patients with lymphoma and multiple myeloma [3] are considered to be at particularly high risk. While patients with pancreatic or gastric cancers have been identified as being at very high risk, patients with lung, colorectal or esophageal cancers have been identified as being at high risk [4]. This increased risk of VTE can be explained by direct paraneoplastic effects, coagulation activation due to inflammatory processes, and the effects associated with therapy. These effects are frequently exacerbated by patients' deteriorated general state of health as a result of weight loss, nutritional problems, and immobility.

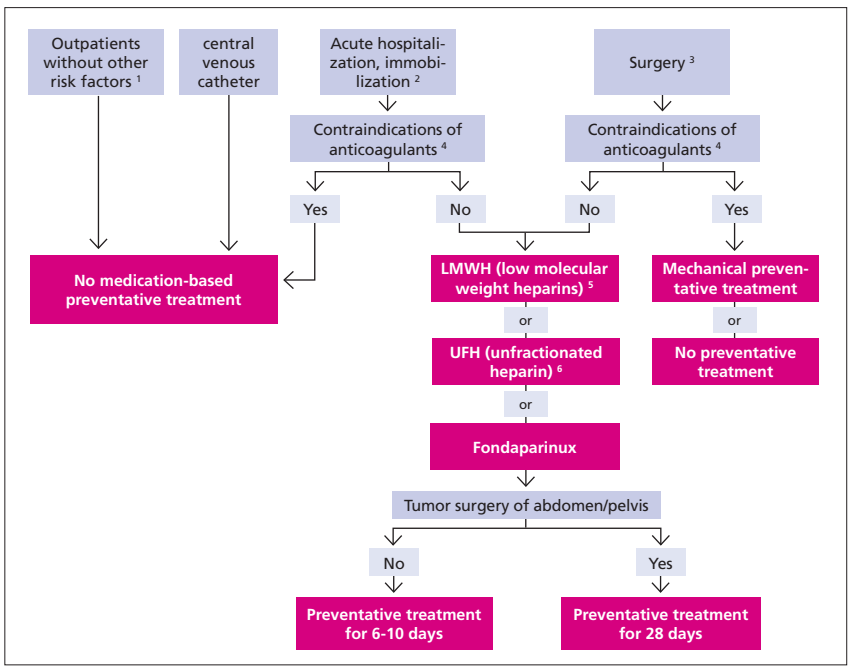

Fig. 1: Primary preventative treatment (modeled after [2]). *[1] RF = risk factors, [2] Acute hospitalization for treatment, [3] Tumor surgery expected to last more than 30 minutes, [4] Contraindications: Bleeding, prolonged thrombocytopenia with a platelet count < 30,000/µl, [5] LMWH = low molecular weight heparins, [6] UFH = unfractionated heparin*

Recommendations for the primary preventative treatment of cancer-associated VTE

The Onkopedia Guideline for the prevention and therapy of venous thromboembolism in cancer patients which is valid for Germany, Austria and Switzerland does not recommend general drug-based VTE prophylaxis for ambulatory patients. However it may be considered for patients with high or very high risk of VTE, i.e. Khorana score ≥3. This score is based on criteria such as tumor type, platelet count prior to chemotherapy, hemoglobin count, etc. [3].

Drug-based VTE prophylaxis is recommended for hospitalized patients expected to remain immobilized for longer periods as well as for prolonged perioperative VTE prophylaxis, e.g. in cases of abdominal or pelvic surgery. Low molecular weight heparins (LMWH) should be used as the prophylactic of choice, thanks to their low potential side effects and their once daily administration. Fondaparinux is indicated for patients with a history of heparin-induced thrombocytopenia (HIT). For perioperative and postoperative preventative treatment drug-based VTE

prophylaxis is recommended for the duration of a patient's hospitalization; in the case of major tumor surgeries of the abdomen or pelvis prolonged prophylaxis is recommended for 28-35 days (Fig. 1) [2].

Since all available direct oral anticoagulants (DOACs) have at most been approved for VTE prophylaxis in elective hip and knee replacement surgery but no other indications, drug-based VTE prophylaxis using LMWH should remain the treatment of choice for outpatient settings. Prophylaxis duration depends on individual, patient- and tumor-specific factors determining the risk of VTE and bleeding [2].

Criterion	Comment
History of (GI) bleeding	• Risk factor for bleeding while on anticoagulants [12, 13, 19].
Known GI disorder	• Indication suggesting preference for LMWH
Patient preference	• Patient information on the advantages and disadvantages of oral and parenteral anticoagulation therapy
Heparin intolerance or history of heparin-induced thrombocytopenia (HIT)	• Therapeutic indication for direct oral anticoagulants (DOACs)
Pregnancy	• LMWH does not pass the placental barrier [20] • DOACs: Reproductive toxicity in animal studies [21-24]*
Severe obesity	• Indication suggesting preference for LMWH

Chart 1: Patient-specific criteria. **no evidence of reproductive toxicity found for Apixaban, although use during pregnancy is discouraged [24], LMWH = low molecular weight heparins, HIT = heparin-induced thrombocytopenia, DOAC = direct oral anticoagulants*

Recommendations for the diagnostics and therapy of cancer-associated VTE

If VTE has occurred in a tumor patient, the diagnostics and therapeutic approaches for that patient differ from those in non-tumor patients. On the one hand this is due to the significantly increased risk of bleeding and VTE recurrence in patients treated with anticoagulants and on the other hand to patient-specific factors such as tumor type, disease stage, and type of cancer therapy. Since there are a number of different oral anticoagulants available, in addition to the parenterally administered anticoagulants, it makes therapeutic decisions in the course of a patient's treatment quite complex. This applies in particular to patients with GI tumors, the focus of this article, who are much more prone to bleeding than other tumor entities while on anticoagulants.

In the long term LMWH is superior to vitamin K antagonists (VKA) in the treatment of patients with cancer-associated VTE. For example the CATCH study found that the LMWH Tinzaparin achieved a 35% risk reduction for recurrent VTE compared to Warfarin [5]. In addition the risk of severe and non-severe bleeding requiring intervention is 36% lower for Tinzaparin than for Warfarin [6]. The CLOT study using Dalteparin vs. VKA yielded similar results [7, 8]. Last but not least, a meta-analysis of long-term anticoagulation therapy using LMWH showed about 40% less recurrent VTE than vitamin K antagonist (VKA) therapy with no increase in the risk of severe bleedings [9]. Tinzaparin and Dalteparin are the only LMWH formally approved in Germany for the treatment and long-term secondary prevention of VTE in cancer patients [10, 11].

Comparisons of LMWH with DOAC also reveal differences with regard to bleeding risks. It is correct that in the HOKUSAI VTE Cancer non-inferiority trial the DOAC Edoxaban did not prove inferior to Dalteparin in its primary combined endpoint. In terms of the individual endpoints, however, Edoxaban showed a certain edge in preventing VTE relapses (p=0.09), but major bleeding occurred more frequently than on LMWH (p=0.04) [12]. The comparison between the DOAC Rivaroxaban with Dalteparin in the SELECT-D pilot study yielded similar results: The lower cumulative VTE recurrence rate on DOAC as compared to LMWH came at the expense of increased cumulative rates of clinically relevant, non-severe, and major bleeding. In most cases, this bleeding affected the GI and urogenital tracts [13].

A systematic review of observational and randomized controlled trials comparing LMWH and DOACs in tumor-associated VTE confirmed that although DOACs revealed a numerical advantage in preventing recurrent VTE compared to LMWH, they are associated with a significantly increased risk of major bleeding and a clear trend towards more clinically relevant, non-major bleeding [14]. This means that VTE patients with GI tumors who are more prone to bleeding, as outlined above, should be advised to use LMWH.

Patient and therapy specific decision criteria

Other aspects of therapy and secondary prophylaxis of tumor-associated VTE concern the patient-specific and therapy-specific factors listed in Charts 1 and 2. Interventional, surgical and systemic therapies have different effects on bleeding risk, bioavailability, and drug interactions. The wide variety of systemic antineoplastic drugs makes matters even more complicated.

Considering the risk of possible renal impairment the different pharmacology of LMWH needs to be taken into account. Due to their high molecular weight Tinzaparin and Dalteparin are less dependent on renal elimination. Tinzaparin will not accumulate up to a creatinine clearance of ≥20 ml/min and can therefore be used in even patients suffering from mild or moderate renal insufficiency.

Thrombocytopenia is a frequent consequence of systemic cancer therapies. According to the Onkopedia Guideline anticoagulant therapy using LMWH is considered acceptable for

thrombocytopenia with a platelet count above 50,000/µl and for high-risk prophylactic to semi-therapeutic anticoagulation for a thrombocyte count above 20,000/µl [2].

The ExAkT expert group (experts on anticoagulation therapy in cancer patients: Prof. Dr. Axel Matzdorff, MD, Schwedt; Burkhard Matthes, Berlin; Prof. Dr. Florian Langer, MD, Hamburg) has developed an algorithm for the treatment of cancer-associated VTE. After VTE has been diagnosed in a patient known to suffer from cancer, a distinction is made between active and inactive cancers. Patients suffering from inactive cancer will receive the standard of care in accordance with the guidelines. In case of active cancer (diagnosed/treated <6 months earlier (with the exception of basal cell or squamous cell carcinoma of the skin); or recurrent, locally advanced or metastatic cancer; or hematologic neoplasia in incomplete remission) we recommend LMWH therapy usually for 3 months plus further therapy with LMWH or DOACs as indicated by the patient-specific, disease-specific and therapy-specific criteria mentioned earlier. In addition we recommend screening of the patient for occult cancers in unprovoked VTE [15, 16], because up to 20% of VTE patients are suffering from an underlying malignancy and up to 10% of patients with unprovoked VTE are diagnosed with cancer within 1-2 years [17, 18].

Criterion	Comment
Prior surgeries	• Risk factor for bleeding while on anticoagulants • ≤2 weeks: Preferably LMWH • >2 weeks: Preferably DOACs
Active systemic therapy systems (anti-angiogenic, complex chemotherapy, tyrosine kinase inhibitors, etc.)	• The use of LMWH is advised due to the potential drug interactions while on oral anticoagulants
Temporarily discontinued systemic therapy (immunotherapy, endocrine therapy)	• Indication suggesting DOACs
Nausea/vomiting Mucositis/diarrhea	• Bioavailability [25, 26] • Risk factor for bleeding while on anticoagulants [12, 13]. • High risk: Preferably LMWH • Low risk: Preferably DOACs
Risk of thrombocytopenia	• The recommendations for dose adjustment should be observed • DOACs studies: Exclusion of patients with a platelet count <50,000/µl [12, 13] • High risk: Preferably LMWH • Low risk: Preferably DOACs
NSAIDs/platelet aggregation inhibitors	• Risk factor for bleeding while on anticoagulants [12, 13]. • HOKUSAI VTE Cancer Study: • Exclusion of patients with chronic NSAID ingestion [12]. • All anticoagulants increase the risk of bleeding; The intake of ASS should be critically checked! [10] • Yes: Preferably LMWH • No: Preferably DOACs
Antimicrobial therapy	• Potential drug interactions [25-31]

Chart 2: Cancer therapy specific criteria. *ASS = acetylsalicylic acid, LMWH = low molecular weight heparins, DOACs = direct oral anticoagulants, NSAIDs = non-steroidal anti-inflammatory drugs*

Conclusion

Active cancers and especially GI tumors are associated with a significantly increased risk of thromboembolism. At the same time patients with GI tumors and VTE who are on anticoagulants are likely to experience increased, clinically relevant bleeding. When weighing efficacy against safety, we should take a systematic look at the disease-specific, patient-specific and therapy-specific criteria to decide on a case-by-case base what type of anticoagulant treatment and drug-based secondary prophylaxis to prescribe. For safety reasons parenteral anticoagulant therapy using LMWH will likely be the regimen of choice, especially for GI tumors. After completion of a patient's initial and early maintenance therapy and during each of his/her routine staging examinations, it should be decided whether to continue long-term relapse prevention using either LMWH or DOAC, taking into account the patient's preferences. Tumor screening is indicated for unprovoked VTE because thromboses may often reveal a previously undetected underlying malignancy.

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Differentiated anticoagulant therapy decision

Interview with Professor Dr. Florian Lordick, MD, Medical and Outpatient Center I, Hematology and Cell Therapy, Internal Oncology, Hemostaseology, Leipzig University Hospital, Leipzig University Cancer Center (UCCL).

Various criteria must be considered when selecting the appropriate anticoagulant for patients with cancer-associated thromboembolism (VTE). This also applies to secondary prophylaxis following thromboembolism.

Professor Lordick, it is well known that cancer patients are particularly at risk of VTE. Which tumor entities are we talking about in particular?

LORDICK: Compared to the population in general, patients with an active tumor disease are between 4 and 7 times more likely to develop thromboses and embolisms. In addition there are distinct differences between the various tumor entities. The highest risk is associated with patients suffering from gastrointestinal (GI) tumors, especially pancreatic and stomach cancer. Equally high-risk patients are those suffering from brain and lung tumor, lymphoma and multiple myeloma.

In cases in which venous thrombosis has occurred under anticoagulant therapy, a particularly increased risk of bleeding from GI tumors has been observed. Which tumor entities pose a particular problem in this respect?

LORDICK: Basically these are the patients suffering from luminal tumors, i.e., esophageal, gastric and colorectal cancers, in cases in which the primary tumor is still present in the lumen. Therapy studies clearly show that these patients are at a particular risk of clinically relevant, severe, and sometimes even life-threatening bleeding.

What does this mean for anticoagulant therapy of VTE?

LORDICK: On the one hand, we have to pay close attention to signs of bleeding while the necessary anticoagulant therapy is being administered. This means monitoring the blood count and clinical signs of bleeding such as hematemesis or tarry stools. When treating these patients, we also pay particular attention to the type of anticoagulant, which now come in quite a range of different types. Patients in whom tumor-associated thromboembolism is associated with a particularly high risk of bleeding are definitely candidates for low molecular weight heparins (LMWH) both for therapy and for the secondary prophylaxis of thrombosis relapses. So far we do not see any indication using direct oral anticoagulants (DOACs) for these patients.

What are your criteria for deciding for or against LMWH or DOACs therapy?

LORDICK: There is any number of individual criteria to consider, the risk of bleeding mentioned earlier certainly being the most significant. This results from direct comparisons of DOACs with LMWH. These studies show that the use of DOACs significantly increases the risk of bleeding in patients treated for thromboembolism compared to those treated with LMWH, especially in patients suffering from intestinal tumors. Another important criterion is to watch out for drug interactions associated with systemic cancer therapy. As an example I would like to mention anthracyclines which can lead to interactions with DOAC although interactions may also occur with other antineoplastic substances such as tyrosine kinase inhibitors or anti-angiogenic substances. In such cases we advise against anticoagulant therapy using DOACs. We also have to take a look at patient compliance during secondary prophylaxis. Is the patient reliable, willing and able to inject him/herself daily or to ingest pills every day for weeks and months at a time? The patient's personal preferences also play an important role. We also need to consider resorption disorders of the gastrointestinal tract for example after major surgery to the gastrointestinal tract which can impair the absorption of active substances from pills, or mucosal pathologies such as gastritis or colitis, and of course the vomiting associated with therapy. All of these factors suggest the use of LMWH both for therapy and secondary prevention of thromboembolism in these patients.

Could you explain this by an example from your medical practice?

LORDICK: We are now treating many cancer patients with neoadjuvant chemotherapy or radiochemotherapy, e.g. patients suffering from esophageal or gastric cancer. Unfortunately some of these patients will develop systemic or port-associated thromboses during this kind of therapy. In this situation we will always opt for LMWH therapy, precisely because the primary tumor is still in situ and is therefore more likely to bleed, or because radiation therapy is inducing mucous membrane changes in cases of esophageal carcinomas. The biggest challenge is to make the best decision in advanced pancreatic cancers: It is true that metastatic situations come with a high risk of thrombosis. In view of the increased risk of bleeding, however, we always debate whether or not to use prophylactic anticoagulants in the first place.

Thank you for granting us this interview!

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