Challenging Situations in the Treatment of Cancer-Associated Thrombosis

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Abstract

Cancer-associated thrombosis (CAT) is a common clinical problem in the treatment of cancer patients posing some unique challenges. These include the need to balance between the risk of recurrent thromboembolic events and bleeding complications in the individual cancer patient. A frequently encountered dilemma is the need for long-term anticoagulation in the setting of active malignancy. Until now, optimal duration, intensity, and type of anticoagulation in cancer patients remain an area of ongoing debate. In this case-based review, we present several challenging clinical scenarios and provide guidance on management. For optimal treatment results, CAT generally requires a multidisciplinary approach including specialists for thrombosis and hemostasis as well as hematology and oncology. Individual patient preferences should always be taken into account, especially in clinical situations with weak treatment evidence.

Keywords
- cancer
- thrombosis
- anticoagulation

Zusammenfassung

Die Tumor-assoziierte Thrombose ist ein häufiges klinisches Problem bei Krebspatient*innen und gekennzeichnet durch spezifische Behandlungsherausforderungen. Dazu gehört vor allem die schwierige Abwägung des individuellen Thrombose- und Blutungsrisikos. Ein ständiges Dilemma ist die Notwendigkeit der Langzeitantikoagulation bei aktiver Krebserkrankung. Bis heute sind die optimale Dauer, Intensität und Art der Antikoagulation bei Krebspatient*innen umstritten.

In dieser fallbasierten Übersichtsarbeit gehen wir auf schwierige klinische Situationen ein und präsentieren mögliche Lösungsansätze. Für ein optimales Ergebnis sollte die Behandlung der Tumor-assoziierte Thrombose stets multidisziplinär erfolgen beziehungsweise nach Abstimmung zwischen Hämostaseologen und Hämatoonkologen. Ebenso wichtig ist die Berücksichtigung der individuellen Patientenpräferenz insbesondere in klinischen Situationen mit schlechter Evidenzlage.

Schlüsselwörter
- Krebs
- Thrombose
- Antikoagulation

Introduction

Cancer-associated thrombosis (CAT) poses a clinically relevant complication of malignant disorders.[1] Up to 10% of patients with cancer develop deep-vein thrombosis (DVT), pulmonary embolism (PE), or splanchnic vein thrombosis.[2–4] CAT can have significant consequences and indicate a higher risk of death in patients with malignancies.[5,6]

General recommendations for the treatment of CAT regarding medication and dosing are relatively consistent among guidelines from various societies.[7] Vitamin K antagonists (VKAs), the most frequently prescribed VTE treatment

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in the 20th century, have now been replaced by low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs).[7,8] The choice of a specific drug is mainly based on the patient's individual risk factors for bleeding. These include common comorbidities in cancer patients like renal insufficiency, hepatic impairment, and severe thrombocytopenia. Cancer localization within the gastrointestinal or urinary tract can significantly increase bleeding risk from mucosal lesions. Moreover, pharmacological interactions between anticoagulation and specific anticancer treatments have to be considered with a recommendation to routinely use drug–drug interaction checkers. Historically, LMWHs are often the preferred treatment of choice.[1,7] However, most patients find daily LMWH injections highly inconvenient. Studies have shown that patients with CAT show an improvement in treatment satisfaction after switching from parenteral anticoagulation to DOAC therapy.[9] In the absence of the previously mentioned risk factors for bleeding, DOACs can therefore be a less burdensome CAT treatment. A meta-analysis including almost 3,000 cancer patients showed that DOACs compared to LMWH reduce the incidence of recurrent VTE, without significantly increasing the risk of major bleeding,[10] whereas the risk of clinically relevant non-major bleeding might still be higher in DOACs.[11] The issue of DOAC dosage as secondary prophylaxis remains a matter of debate.[12]

Despite advances in understanding and the treatment of CAT, challenging situations remain common in clinical practice. Here, we present four clinical scenarios, discuss the available evidence, and propose potential treatment strategies.

Case 1: A Palliative Patient with Metastatic Colon Cancer and Incidental Catheter-Associated Thrombosis

A 47-year-old female patient with relapsed colon cancer, ovarian metastasis, and peritoneal carcinomatosis was undergoing palliative chemotherapy (FOLFOXIRI/bevacizumab). After three cycles, her staging computed tomography (CT) showed a partial remission. Incidentally, in the same CT, a catheter-related thrombosis was found (►Fig. 1). The patient was asymptomatic and the portacath was fully functional. The radiologist sent the patient to the emergency department, where anticoagulation with LMWH was started.

Evidence on Clinical Management

Long-term central venous catheters (CVCs) are commonly used in patients with cancer to enable antineoplastic and supportive therapy. CVCs activate all three corners of the Virchow triad. A foreign body in the bloodstream may reduce blood flow, while CVC insertion and cytotoxic infusions can cause injury to the vessel wall and activate inflammatory processes and prothrombotic stimuli. Together with the cancer-related hypercoagulability itself, these CVC-related local mechanisms predispose to the development of catheter-related thrombosis. Catheter

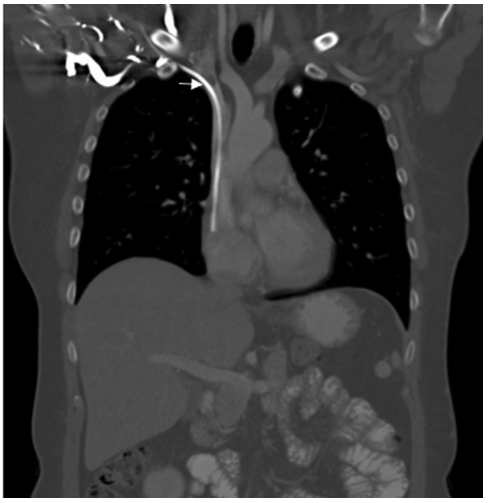

Fig. 1 CT scan with evidence of portacath-associated thrombosis of the *V. brachiocephalica dextra* (arrow).

type (portacath vs. peripherally implanted CVCs),[13] diameter,[14] and catheter position[15] are well-known risk factors for thrombosis development (►Table 1).

The incidence of catheter-related thrombosis varies greatly depending on the diagnostic tool (phlebography vs. Doppler ultrasound) and reaches 20 to 40%,[16] but only a small number of patients present with DVT symptoms.[17] Nevertheless, DVT involving deep veins of the upper extremity can lead to pulmonary embolism or postthrombotic syndrome and therefore requires systemic anticoagulation.[18] Treatment strategies in this case are poorly supported by clinical studies and generally extrapolated from DVT treatment of lower extremities.[19] In most cases, if the portacath remains functional, noninfectious, and correctly positioned, it should not be explanted. However, it requires continuous anticoagulation, as the abovementioned risk factors for thrombus formation persist.[20,21] The choice of anticoagulant should be based on the same principles as for therapy of lower extremities DVT: patient's appearance including body weight, type of cancer, concomitant disorders, blood counts, liver and kidney function, drug–drug interactions, and patient's

Table 1 Catheter-associated risk factors for CVC-related thromboembolism[48–51]

Risk factor	Higher thromboembolic risk	Lower thromboembolic risk
Catheter diameter	Triple-lumen catheter	Single-lumen catheter
Catheter type	PICC	CICC
Catheter length	CICC/portacath inserted from the left	CICC/portacath inserted from the right
Localization	*V. femoralis* (1.4%)	*V. subclavia* (0.5%) *V. jugularis* (0.95%)

Abbreviations: CICC, centrally inserted central venous catheter; CVC, central venous catheter; PICC, peripherally implanted central venous catheter.

preferences.[1] Standard of care in 2024 is parenteral anticoagulation (LMWH, fondaparinux, or unfractionated heparin) or use of DOACs,[9,22] which are now commonly used for catheter-related thrombosis of the upper extremity.[23–26] Anticoagulation should be administered for 3 to 6 months in a therapeutic dose or as long as the central venous line is in place. Patients need to be informed about their individual bleeding risk and behavioral guidance should be given in case of bleeding signs. After the initial treatment phase and if the CVC stays in place, the full therapeutic dosage might be reduced to lower-intensity secondary prophylaxis (e.g., rivaroxaban 10 mg QD, apixaban 2.5 mg BID) depending on the individual risk profile.[27]

Management of Case 1

Anticoagulation was initiated with LMWH (tinzaparin: 175 IE/kg QD), which was well-tolerated without any bleeding complications. The option of replacing LMWH therapy with a DOAC was discussed with the patient, but she initially preferred to continue with LMWH despite a higher risk of osteoporosis due to long-term LMWH treatment. After 1 year of subcutaneous therapy, she requested to switch and, in light of her active cancer and portacath still in place, received full-dose rivaroxaban (20 mg QD). As a consequence, she developed intermittent nose and gum bleeding. Rivaroxaban dose was reduced to 15 mg QD and bleeding symptoms resolved promptly. No further thrombotic events have been observed since then.

This case shows how individualized choice and later adjustments of the anticoagulant drug and dosage in a patient with active cancer can help provide sufficient thrombosis prophylaxis without compromising quality of life.

Case 2: A Patient with Myelodysplastic Syndrome and Pulmonary Embolism

A 72-year-old male patient with recurrent autoinflammatory symptoms and cytopenia was diagnosed with high-risk myelodysplastic neoplasia (MDS). Prior to his MDS diagnosis, he had developed pulmonary embolism and DVT during one of the autoinflammatory episodes. He was treated for CAT with rivaroxaban at a therapeutic dose of 20 mg QD. MDS-specific therapy with a hypomethylating agent (HMA, azacitidine) was initiated. Under HMA, his blood counts were completely normalized, a bone marrow assessment showed complete hematological remission, and the patient's autoinflammatory symptoms resolved. However, a disease-defining cytogenetic aberration (del20q) was still present on repeated bone marrow examination. On a CT scan 6 months after the start of HMA therapy, the pulmonary embolism had resolved, while the DVT appeared stable.

Evidence on Clinical Management

Patients with chronic hematological malignancies (e.g., MDS, indolent lymphomas) are notoriously underrepresented in all large randomized controlled trials on the treatment of CAT. Therefore, evidence-based therapy of this patient population is not feasible. For example, in the Hokusai VTE cancer trial, hematologic patients accounted for only 10% of the whole study population and MDS represents only a small proportion within hematological malignancies.[28]

Ideally, the anticoagulation strategy should depend on the remission status of the hematological cancer. This is not yet adequately addressed in clinical trials and is further complicated by the various levels of remission detection (cytological, cytogenetic, molecular) in modern hematology. Many chronic hematological cancers are considered incurable and therefore categorized as "active cancer," formally requiring life-long full-dose anticoagulation following CAT. However, the life expectancy of patients with chronic hematologic malignancies has significantly improved over the past decades. The bleeding risk associated with life-long anticoagulation might surpass its benefits in patients with CAT and chronic hematologic malignancy in remission. Hence, each patient needs to be consulted individually, and a close cooperation between the hemato-oncologist and hemostasis expert is essential.

A recently published trial on dose reduction of apixaban to 2.5 mg BID in patients with cancer who had completed at least 6 months of anticoagulation with 5 mg BID found no difference in bleeding or thromboembolic rates. The authors concluded that a clear recommendation to apply a dose reduction of apixaban for all cancer patients after 6 months cannot be given currently. Of note, this study included 19% of patients with hematological cancer and did not stratify patients based on remission status.[12]

Management of Case 2

MDS is a chronic hematological malignancy, which often cannot be cured. Therefore, it remains per se an "active cancer," which would require anticoagulation in full therapeutic dose in case of CAT. Although our patient demonstrated a complete hematological remission, he did not achieve cytogenetic remission and MDS-specific therapy with HMA was continued. At the same time, remission status, resolution of all autoinflammatory symptoms, and complete recanalization of the pulmonary embolism on CT scan were reasons for a dose reduction to secondary prophylaxis (apixaban: 2.5 mg BID; ►**Fig. 2**). This treatment was well tolerated and is currently planned as life-long therapy.

Case 2 gives an example of an individualized approach to anticoagulation in a patient suffering from chronic hematological cancer. Here, the decision about extended low-dose anticoagulation was made after a thorough interdisciplinary discussion including available medical data as well as patient's preferences on treatment choice.

Case 3: A Patient with Multiple Myeloma, Recurrent Thrombocytopenia, and DVT during Prothrombotic Myeloma Therapy

A 57-year-old female patient with multiple myeloma (MM) was treated with first-line myeloma-specific therapy

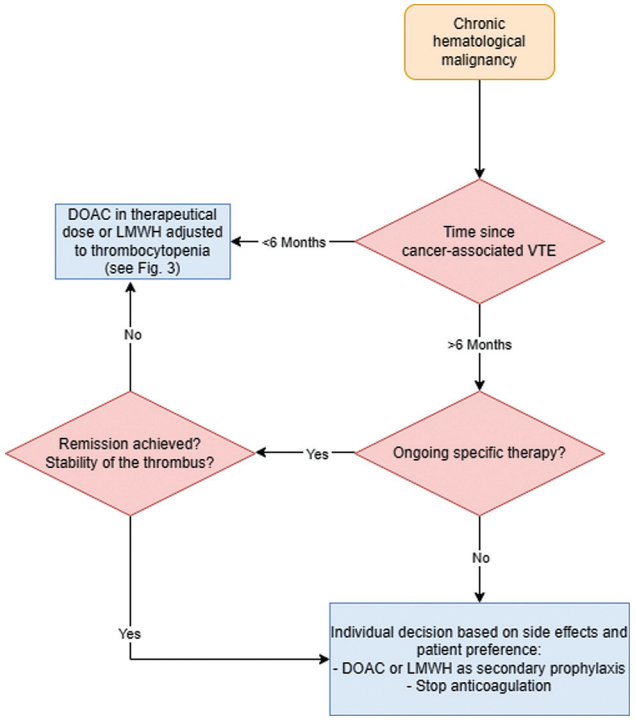

Fig. 2 Management of anticoagulation for VTE in chronic hematological malignancies (e.g., MDS, indolent lymphomas). VTE, venous thromboembolism; DOAC, direct anticoagulant; LMWH, low-molecular-weight heparin.

consisting of a proteasome inhibitor (carfilzomib), an immunomodulatory drug (IMiD, lenalidomide), and dexamethasone. Because of the prothrombotic risk of the IMiD therapy, DVT prophylaxis with LMWH (enoxaparin 40 mg QD) was prescribed according to current myeloma guidelines.[29] After the first cycle, the patient developed hemolytic anemia which was considered a rare side effect of carfilzomib therapy. Upon temporary termination and later, dose reduction of carfilzomib laboratory parameters normalized. However, 2 weeks later, she complained about right leg pain and was diagnosed with popliteal DVT despite LMWH prophylaxis. Moreover, during the course of therapy, the patient presented with recurrent episodes of severe thrombocytopenia (platelets < 50 GPt/L).

Evidence on Clinical Management

Therapeutic options for MM have improved during recent years, leading to substantial prolongation of overall survival rates. However, with longer treatment duration and application of multiple new drugs, there is an increasing incidence of thromboembolic complications in MM patients, with reported rates of thrombosis of up to 10%.[30] When receiving first-line treatment with glucocorticoids and immunomodulatory drugs (IMiDs: lenalidomide, thalidomide, pomalidomide), the incidence of thrombosis may even increase to 30 to 75%.[31,32] Interestingly, the same drugs seem to be less prone to induce thrombosis if used in relapse situations. This is probably due to the lower MM disease burden.[33]

To account for the thrombotic risk of MM patients, guidelines recommend primary prevention strategies, but there is no consensus about the specific type and duration of thromboprophylaxis in parallel to IMiDs. A comprehensive review of the International Myeloma Working Group (IMWG) suggests an individualized approach based on a risk assessment model, whereby patients with no risk factor should receive aspirin 81 to 325 mg QD, and those with two or more risk factors—prophylactic LMWH or VKA with an INR-goal of 2 to 3.[34] This recommendation may be outdated with the availability and increasing use of DOACs in this setting and represent mostly expert opinions from the pre-DOAC era, reflecting a need for interventional trials in this setting.[35,36]

If a patient with MM develops VTE despite prophylactic anticoagulation, the treatment options follow the principles of CAT therapy in other malignancies. Temporary discontinuation of an IMiD in the case of acute thrombosis until full anticoagulation has been established may be discussed with the hematologist.[34]

As with other hematological malignancies, thrombocytopenia is common in patients with MM and may occur as a consequence of therapy, but also as a symptom of uncontrolled disease. Unfortunately, thrombocytopenic patients are usually excluded from clinical trials on anticoagulation. The available evidence originates mostly from cohort studies and case reports. According to current guidelines[37] full-dose anticoagulation is regarded as safe enough when platelets are >50 GPt/L. When platelets drop to 25 to 50 GPt/L, dose reduction of anticoagulation is recommended. Platelets <25 GPt/L usually require interruption or complete discontinuation of any anticoagulation (►Fig. 3), depending on the age and extent of the clot. In the case of acute VTE (defined as within 30 days from diagnosis) with relevant clot burden, dose reduction or interruption of anticoagulation may pose an unacceptable risk. Implantation of an inferior *vena cava* filter may be considered to reduce the risk of fatal PE in case anticoagulation is not feasible. However, patients with inserted filters should be closely monitored to avoid severe filter-related complications and removal must be considered as soon as anticoagulation is possible again.[38] As an alternative, temporary platelet transfusions may be used to enable full-dose anticoagulation, even though this approach is not widely accepted.[39]

Management of Case 3

Our patient developed CAT despite LMWH prophylaxis, presumably triggered by an episode of hemolytic anemia. First, LMWH was escalated to a therapeutic dose (tinzaparin: 175 IE/kg QD), and myeloma therapy was continued, including a full-dose IMiD. Since our patient initially had stable platelet counts > 50 GPt/L, she could be switched to DOAC therapy with edoxaban 60 mg QD. During her following high-dose chemotherapy and autologous stem cell transplantation, she was temporarily switched back to LMWH. During MM maintenance and consolidation therapy, the patient experienced severe thrombocytopenia with platelet counts lower than 25 GPt/L. Therefore, anticoagulation had to be recurrently withheld until platelet regeneration. Despite complete MM remission, thrombocytopenia persisted and anticoagulation was finally stopped. DVT remained stable with partial recanalization. No further

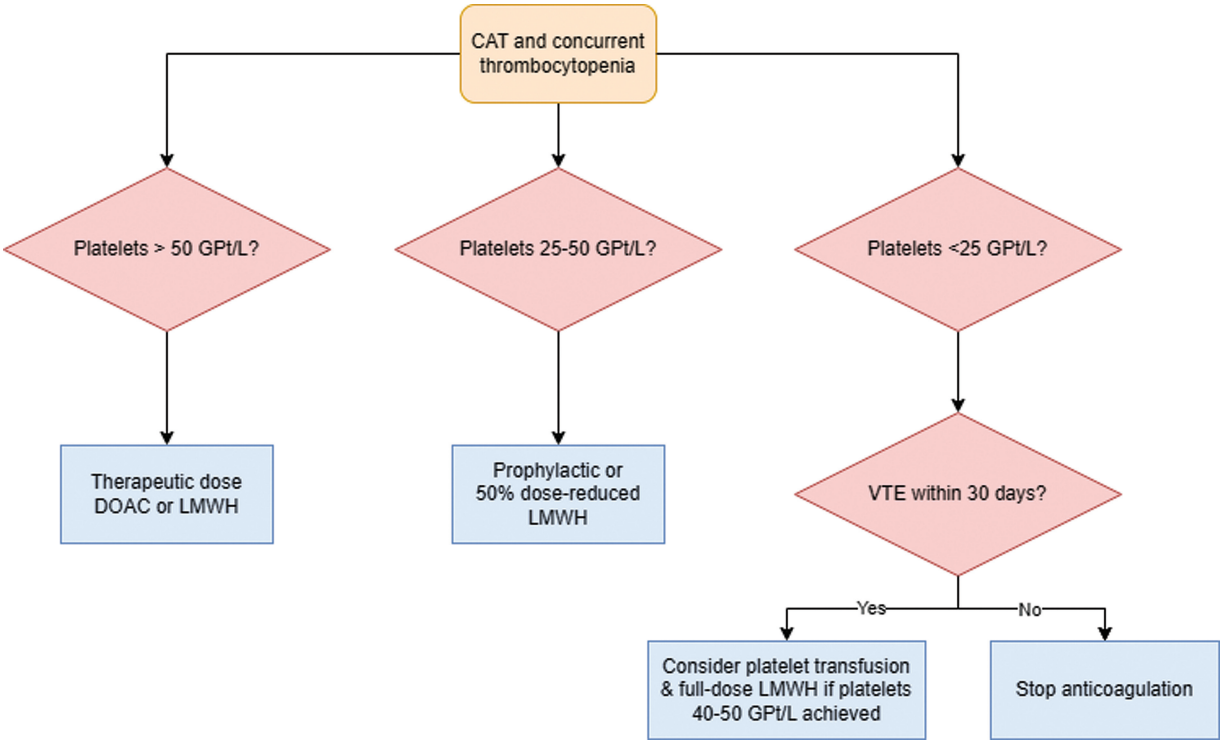

Fig. 3 Management of anticoagulation in patients with CAT and concomitant thrombocytopenia (modified from Falanga et al[37]). CAT, cancer-associated thrombosis; DOAC, direct anticoagulants; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

thrombotic complications occurred during a follow-up period of 4 years.

This case demonstrates that in patients with particularly high VTE risk, clinicians should be aware of the possibility of thrombosis despite prophylactic anticoagulation. Such patients should always be counseled about the signs and symptoms of VTE. Moreover, it shows how CAT treatment needs to be individually adjusted to unstable platelet counts.

Case 4: A Patient with Recurrent Ovarian Cancer, Multiple Thromboembolic Complications, and Paraneoplastic Hyperfibrinolysis

A 45-year-old woman presented to our emergency department with bleeding symptoms (epistaxis, bruises) and neck swelling. Three years earlier, she had received curative treatment for ovarian cancer, including surgery and adjuvant chemotherapy. After admission, ultrasound and CT scans were performed and revealed multiple venous thromboembolic events, including thrombosis of the *V. jugularis sinistra*, portal vein, as well as a central pulmonary embolism. Her laboratory results showed severe coagulopathy without detectable fibrinogen, deranged global assays (prothrombin time and activated partial thromboplastin time not measurable), and profoundly reduced clotting factors VIII and XIII. Factors II, VII, IX, and X were within normal ranges, antiphospholipid antibodies were not detectable, and liver tests and kidney function were normal. CT scan was suspicious for peritoneal carcinomatosis and lymph node metastases. The multiple thromboembolic events were considered CAT due to recurrent ovarian carcinoma and complicated by severe paraneoplastic hyperfibrinolysis.

Evidence on Clinical Management

Hyperfibrinolysis is a rare complication of solid or hematologic malignancies, resulting in severe, life-threatening bleeding[40] as well as systemic prothrombotic states. Pathogenetic mechanisms are still not well understood. They include S100A10- and Annexin II-related profibrinolytic effects (as in acute promyelocytic leukemia[41,42]) and production of urokinase-type plasminogen activator and plasminogen activator inhibitor-1 by cancer cells.[43] Cancer-related hyperfibrinolysis most commonly occurs in patients with prostate cancer, followed by breast cancer, lung carcinoma, and malignant melanoma.[40] If hyperfibrinolysis presents primarily with bleeding, treatment might include the use of antifibrinolytics such as tranexamic acid (TXA), aiming to reduce bleeding events by controlling plasmin activity.[44,45] Of note, patients presenting with cancer-related disseminated intravascular coagulation might be hyperfibrinolytic and prothrombotic at the same time. Therefore, TXA treatment has to be carefully evaluated. As an overall approach, any symptomatic antifibrinolytic or anticoagulation therapy should be combined with causal antitumor therapy. Only controlling the underlying malignancy can stabilize the coagulation system.[46]

No formal recommendation exists regarding anticoagulation during acquired—in this case paraneoplastic—coagulopathy. With only limited retrospective data, therapy of paraneoplastic hyperfibrinolysis, especially concurrent to

CAT, remains a challenging clinical situation with a highly individualized approach.

Management of Case 4

The patient primarily presented with bleeding symptoms and deranged coagulation from hyperfibrinolysis. Initial treatment therefore consisted of TXA (2 g TID) and fibrinogen (up to 4 g QD with the goal to achieve a fibrinogen plasma concentration >1 g/L). Concurrently, close ultrasound monitoring of the DVT and laboratory controls including global coagulation tests, thrombelastography, D-dimers, fibrin monomers, f1 + 2 prothrombin fragments, and fibrinogen concentration were performed to assess clotting time as well as clot stability to balance the concomitant procoagulant and hyperfibrinolytic states. Anticoagulation with prophylactic LMWH was started 3 days later after normalization of global coagulation tests. Hypofibrinogenemia/hyperfibrinolysis persisted and required further fibrinogen substitutions and prolonged treatment with TXA.

After histological verification of recurrent ovarian cancer, palliative chemotherapy was initiated. The patient achieved partial remission. As a result, coagulation parameters normalized and the substitution of clotting factors and treatment with TXA could be stopped. Anticoagulation was gradually intensified to a therapeutic dose (nadroparin 100 IE/kg BID). Ultrasound controls showed a stabilization of thrombosis for over 6 months.

Ultimately the patient developed progressive disease, accompanied again by hyperfibrinolysis and progress of CAT despite full anticoagulation. This required supratherapeutic LMWH dosages (up to 240 IE/kg tinzaparin QD) and fibrinogen substitution, as well as therapy with TXA. Over time, the clinical response of her cancer to multiple antineoplastic therapies repeatedly resulted in the normalization of coagulation parameters.

As this case shows, the therapy of CAT associated with paraneoplastic coagulopathies is extremely challenging and individualized. It requires a coordinated complex approach, involving thrombosis and hemostasis experts and vascular specialists monitoring changes in clot burden. Only by controlling the underlying ovarian cancer stabilization of the coagulation system can be achieved.[47]

Summary and Conclusions

Even though CAT is a common clinical problem, it usually requires individualized decisions around anticoagulation therapy. Especially therapy of CAT in patients with hematological cancer often cannot follow an evidence-based approach, since data from clinical trials for this patient population is lacking. Nowadays, several chronic hematologic malignancies have an excellent prognosis with an almost normal life expectancy. For such patients, bleeding risk due to life-long anticoagulation after CAT might exceed the risk of recurrent thromboembolism. To safely withhold anticoagulation in this setting, a careful interdisciplinary discussion and most importantly active involvement of the patient for shared-decision making is necessary.

Ideally, future studies should explore anticoagulation strategies for CAT in specific hematologic and solid cancer types. Such studies could, for example, clarify which remission level of a chronic hematologic cancer (hematologic vs. cytogenetic vs. molecular) is required to safely withhold anticoagulation.

Novel therapeutic approaches are warranted to decrease the side effects of anticoagulation and improve its effectiveness in cancer patients. Currently, anticoagulants inhibiting factor XI are being studied in randomized clinical trials for the treatment of acute VTE in this patient population (NCT05171049, NCT051710075).

Various challenging situations in the treatment of CAT were not specifically addressed in this review: management of patients with a high risk of bleeding due to luminal gastrointestinal or genitourinary tract tumors or brain metastasis, cancer patients with extremely high or low body weight, or patients with myeloproliferative neoplasia with particularly high VTE risk. Careful consideration and monitoring are essential when managing these complex cases to ensure optimal outcomes and minimize risks. Future research and clinical guidelines should continue to address these challenges to improve the care of patients with CAT.

Authors' Contributions

E.B. was involved in patient treatment and wrote the manuscript; S.M., J.B-W., and K.T-G. were involved in patient treatment, revised the manuscript, and approved the final version for publication.

Competing Interests

E.B. received travel compensation from Novartis. S.M. received honoraria and institutional research support from Bayer AG, Daiichi Sankyo, Pfizer, Swedish Orphan Biovitrum GmbH, Bristol-Myers Squibb, and Biotest AG. J.B-W. received honoraria and institutional research support from Alexion/AstraZeneca, Bayer AG, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, Leo Pharma, Mitsubishi Pharma, Norgine, and Pfizer. K.T-G. received consulting fees from Takeda, Roche, Grifols, and SOBI; honoraria from Amgen, Roche, Sanofi, SOBI, Grifols, Novartis, and Pfizer; and travel support from Grifols and Takeda.

Conflict of Interest

EB received travel compensation from Novartis. SM received honoraria and institutional research support from Bayer AG, Daiichi Sankyo, Pfizer, Swedish Orphan Biovitrum GmbH, Bristol-Myers Squibb, and Biotest AG. JB-W received honoraria and institutional research support from Alexion/AstraZeneca, Bayer AG, Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, Leo Pharma, Mitsubishi Pharma, Norgine, and Pfizer. KT-G received consulting fees from Takeda, Roche, Grifols, and SOBI; honoraria from Amgen, Roche, Sanofi, SOBI, Grifols, Novartis, and Pfizer; and travel support from Grifols and Takeda.

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