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Review article

Carcinoma associated pulmonary embolism: summary and treatment challenges

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Abstract Cancer-associated venous thromboembolism (VTE) represents one of the major causes of increased morbidity and mortality in cancer patients. It is very important to determine the risk level in order to adequately treat the patients, but also select the patients for primary and secondary prevention of VTE and assess the risk of early death in case of acute pulmonary embolism. Nowadays the significant development in the VTE treatment in cancer patients is evident. Novel oral anticoagulants (NOACs) simplified the treatment of VTE compared to low-molecular-weight heparin (LMWH) due to their characteristics, way of administration, fixed - dose regimens and lower cost. However, their prescription requires additional caution, especially in patients with gastrointestinal malignancies. The latest available data on reperfusion therapy emphasize the importance of individual approach to each cancer patient with VTE.

Kew words carcinoma, pulmonary thromboembolism, risk stratification, therapy

Cancer-associated venous thromboembolism (VTE), which includes deep vein thrombosis, pulmonary embolism, and central venous catheter-related VTE, is the second leading cause of death in patients with cancer after progression. The prevalence of cancer-associated thrombosis is increasing because of numerous factors, including prolonged patient survival, anticancer therapies, an enhanced detection of incidental VTE during surveillance imaging, and broader use of central venous catheters.[1]
The risk of developing VTE in cancer patients is increased up to seven-fold as compared to the general population.[2] However, VTEs are incidentally detected in about one-half of all cancer patients without any clinical suspicion of VTE at the time of diagnosis.[3] Patients with cancer-associated thrombosis are at high risk of recurrent VTE and anticoagulant-related bleeding, which are associated with high morbidity and resource use.[1] The occurrence of VTE in patients with cancer may interfere with planned chemotherapy regimens, increase the risk of mortality, and result in increased costs compared with patients without cancer.[4] More than 50% of thrombotic events occur within 3 months of the cancer diagnosis, the time when most cancer treatments will be underway.

Risk factors for VTE

VTE risk factors in cancer patients can be grouped into 3 general categories: intrinsic and extrinsic patient-related factors, cancer-related factors and treatment- related factors.[2] The risk for VTE and recurrent VTE is highest among certain hematologic malignancies, such as lymphoma, acute leukemia and multiple myeloma. Patients with high-grade lymphoma and acute promyelocytic leukemia appear to be at higher risk than other forms of lymphoma or leukemia. Lung cancer, gastrointestinal cancer (stomach/colon), pancreatic cancer, kidney cancer, bone cancer, myelodysplastic disorder and patients with distant metastasis are also susceptible.[5]
Several risk factors for developing venous thrombosis usually coexist in cancer patients including surgery, hospital admissions, immobilization; and the presence of the central catheter, older age, platelet count ≥ 350X109 /L, hemoglobin<100 g/L or use of red cell growth factors, and leukocyte count ≥ 11 X 109 /L 35 kg/m^2.[2,6]
The risk of VTE increases with age and is also associated with malignancy. Among cancer patients undergoing surgery, advanced age, disability, prolonged and difficult surgery, and a lengthy and complicated postoperative course add to the risk of DVT.[2,5,6] The extent of cancer impacts the risk of VTE. Chemotherapy and radiation increase the risk of VTE.[4,7]
The risk of VTE in cancer patients is increased by concomitant risk factors such as factor V Leiden mutation or prothrombin 20210A mutation, as well as by the presence of other comorbid features that influence the overall thrombotic complications in non-cancerous patients.[2,8]
Besides antineoplastic therapies, certain supportive care measures used in cancer treatment may also increase the risk of VTE, including red blood cell transfusions, as well as erythropoietin-stimulating agents for managing anemia for patients undergoing cancer treatment.[9]

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Pathophysiological mechanism of cancer induced thromboembolism

Several mechanisms may be involved in the pathogenesis of thromboembolic events in patients with cancer. These include (1) tumor cell procoagulants and/or cytokines, (2) tumor-associated inflammatory cell procoagulants and/or cytokines, and (3) mediators of platelet adhesion or aggregation generated by tumor cells and/or tumor-associated inflammatory cells. Stasis and endothelial damage may also be involved in the pathogenesis of thromboembolic events in patients with cancer.[10] Thromboembolism frequently worsens the course of malignancy and may be the first symptom of cancer.[10,11] The identification of multiple factors, including biomarkers, associated with the risk of cancer-associated VTE has prompted the development of risk scores for predicting VTE and its complications.[12]

Assessment of the thrombotic risk in cancer patients

The Khoranna score is based on five predictive models including cancer sites, platelet counts, hemoglobin level or the use of erythropoiesis-stimulating agents, leukocyte count and body mass index.[12] Risk predictor models involve the Ottawa score which identifies patients at the highest risk of recurrent VTE and who may benefit from prolonged anticoagulation treatment among those with cancer – associated VTE, and the Khoranna score for chemotherapy -associated VTE.[13]

Anticoagulation therapy

Patients with cancer frequently have both an increased thrombotic risk and an increased hemorrhage risk associated with certain cancer locations (e.g. GI, intracranial), thrombocytopaenia, and other coagulation defects (secondary to bone marrow invasion, cancer therapies, or cancer itself) and associated comorbidities (e.g. renal or hepatic dysfunction, GI toxicities). Several anticancer agents are further characterized by drug–drug interactions with anticoagulants. Thromboembolic risk, hemorrhage risk, drug–drug interactions and patient preferences (TBIP acronym) may render anticoagulation in cancer in a quite challenging way.[14]
Since 2019 when ITAC guidelines were published, three randomised clinical trials and 12 meta-analyses have assessed the efficacy and safety of LMWHs or direct oral anticoagulants for the treatment of cancer-associated thrombosis.[1,15] The initial treatment of established VTE (up to 10 days) included LMWHs, unfractionated heparin, or fondaparinux (followed by a vitamin K antagonist) An increased number of patients with cancer-associated thrombosis receiving LMWHs (n=1840) in six randomised clinical trials comparing direct oral anticoagulants with LMWH resulted in an upgrade from 1B to 1A for LMWHs as an initial treatment in the first 5–10 days.[16] Direct oral anticoagulants Rivaroxaban or edoxaban were recommended (grade 1B) in 2019 as the initial treatment options in patients with cancer-associated thrombosis who were not at high risk of gastrointestinal or genitourinary bleeding. Fondaparinux and unfractionated heparin remain acceptable alternative treatment options without new evidence.

Bleeding complications

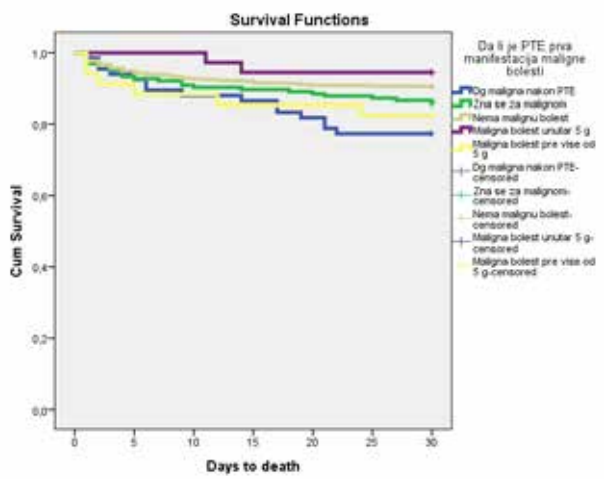
Bleeding complications are more common in patients with cancer than in patients without cancer. This may be directly related to the tumor itself, or indirectly related to chemotherapy- or RT-induced weakening of mucosal barriers.[17] GI and GU cancers in high-risk patients are associated with a significant excess bleeding risk compared with other solid tumors[18]. Thrombocytopaenia and platelet dysfunction due to hematological malignancies or bone marrow suppression may deteriorate bleeding. Other bleeding risk factors include advancing age, renal or hepatic impairment, metastatic disease, low body mass index, and treatment with ibrutinib, VEGFi, cetuximab, or bevacizumab.[17,18] Gastric protection with routine proton pump inhibitor use should be considered in all patients with cancer on DAPT or anticoagulation.[17,19]

REPER registry

In REPER registry that comprised 1814 patients, there were 163 (8.93%) patients with active cancer, 36 (1.98%) patients suffered from cancer within 5 years, 34 (1.87%) before 5 years and 66 (3.64%) patients had pulmonary embolism as a fist sign of cancer. Patients with pulmonary embolism as a first manifestation of cancer had a significantly highest risk of death during 30 days follow-up ($p<0.003$).

Case Processing Summary

Is PTE the first manifestation of malignancy	Total N	N of Events	Censored	
			N	Percent
Dg malignancy after PTE	66	15	51	77,3%
Known malignancy	163	23	140	85,9%
No malignancy	1515	146	1369	90,4%
Malignancy within 5 years	36	2	34	94,4%
Malignnancy more than 5 years	34	6	28	82,4%
Overall	1814	192	1622	89,4%



According to recently published 2022 ITAC guidelines, endorsed by the International Society on Thrombosis and Haemostasis, new evidence on the treatment and prophylaxis of cancer-associated thrombosis, including patients with cancer and with COVID-19 were summarized in the following tables.[1]

Treatment of incidental or symptomatic established venous thromboembolism (VTE) in patients with cancer

Table 1. Initial treatment of established VTE (up to 10 days of anticoagulation) in cancer patients[1]

LMWH once daily (eGFR ≥30 mL/min) (grade 1A). Enoxaparin (1 mg/kg), twice-daily in high risk of bleeding, moderate renal failure, the need for technical intervention surgery or changing regimen.
Rivaroxaban or apixaban (in the first 10 days), or edoxaban (started after at least 5 days of parenteral anticoagulation) for patients who do not have a high risk of gastrointestinal or genitourinary bleeding (eGFR ≥30 mL/min). (grade 1A)
UFH when LMWH or direct oral anticoagulants are contraindicated/not available (grade 2C)
Fondaparinux (grade 2D)
Thrombolysis can only be considered on a case-by-case basis (contraindications – brain metastasis)
Inferior vena cava filters when anticoagulant treatment is contraindicated or, in the case of pulmonary embolism, when recurrence occurs under optimal anticoagulation.

Table 2. Early (up to 6 months) and long-term (beyond 6 months) maintenance[1]

LMWHs are preferred over vitamin K antagonists
Direct oral anticoagulants (edoxaban, rivaroxaban, or apixaban) in the absence of strong drug–drug interactions or gastrointestinal absorption impairment (eGFR ≥30 mL/min) (grade 1A). Caution in patients with gastrointestinal tract malignancies, especially upper gastrointestinal tract malignancies,
LMWH or direct oral anticoagulants should be used for a minimum of 6 months (grade 1A).
Termination or continuation of anticoagulation should be based on individual evaluation of the benefit–risk ratio, tolerability, drug availability, patient preference, and cancer activity.

Table 3. Treatment of VTE recurrence in patients with cancer under anticoagulation[1]

Increase LMWH by 20–25% or switch to direct oral anticoagulants
For direct oral anticoagulants, switch to LMWH
For vitamin K antagonist, switch to LMWH or direct oral anticoagulants

Table 4. Treatment of established catheter-related thrombosis[1]

LMWHs for a minimum of 3 months and as long as the central venous catheter is in place
In patients with cancer and with catheter-related thrombosis, the central venous catheter can be kept in place if it is functional, well positioned, and not infected

Table 5. Prophylaxis of VTE in surgically-treated patients with cancer[1]

LMWH once daily (eGFR ≥30 mL/min) (grade 1A)
Low-dose UFH three times per day
There is insufficient evidence to support fondaparinux (grade 2C) or direct oral anticoagulants (grade 2B) as an alternative to LMWH for the prophylaxis of postoperative VTE in patients with cancer
Highest prophylactic dose of LMWH to prevent postoperative VTE
Extended prophylaxis (4 weeks) with LMWH after major abdominal or pelvic surgery (either laparotomy or laparoscopy) who do not have a high risk of bleeding (grade 1A
Mechanical methods are not recommended as monotherapy except when pharmacological methods are contraindicated (grade 2A)
Inferior vena cava filters are not recommended for routine prophylaxis (grade 1A)

Table 6. Prophylaxis of VTE in medically-treated patients with cancer[1]

LMWH or fondaparinux if eGFR ≥30 mL/min or UFH
LMWH (grade 1A) or DOAC (rivaroxaban or apixaban; grade 1B) in ambulatory patients with locally advanced or metastatic pancreatic cancer treated with systemic anticancer therapy and low risk of bleeding.
LMWH is not recommended for patients with locally advanced or metastatic lung cancer treated with systemic anticancer therapy, and low risk of bleeding
DOAC (rivaroxaban or apixaban) in ambulatory patients who are receiving systemic anticancer therapy and are at intermediateto-high-risk of VTE (Khorana score ≥2), and not actively bleeding or not high risk for bleeding (grade 1B).
In patients with myeloma treated with immunomodulatory drugs combined with steroids or other systemic anticancer therapies, VTE primary pharmacological prophylaxis is recommended (grade 1A); vitamin K antagonists at low or therapeutic doses and apixaban at prophylactic doses), LMWH at prophylactic doses, or low-dose aspirin (100 mg daily) (grade 2B).

Table 7. Prophylaxis of catheter-related thrombosis[1]

Use of anticoagulation for routine prophylaxis of catheter related thrombosis is not recommended (grade 1A).
Catheters should be inserted on the right side, in the jugular vein, and the distal extremity of the central catheter should be located at the junction of the superior vena cava and the right atrium (grade 1B).
In patients requiring central venous catheters, the use of implanted ports are suggested.

Table 8. Treatment of venous thromboembolism (VTE) in unique situations[1]

In patients with a brain tumour, LMWH or DOAC can be used for the treatment (grade 2A).
LMWH or UFH postoperatively for the prevention of VTE in patients with cancer undergoing neurosurgery
Primary pharmacological prophylaxis of VTE in medically treated patients with a brain tumour who are not undergoing neurosurgery is not recommended (grade 1B).
If eGFR <30 mL/min, UFH followed by early VKA (possible from day 1) or LMWH adjusted to anti-Xa concentration for the treatment of established VTE
If eGFR <30 mL/min an external compression device can be applied, pharmacological prophylaxis could be considered on a case-by-case basis; UFH can be used on a case-by-case basis
Full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is >50 × 10^9 per L and there is no evidence of bleeding; for patients with a platelet count <50 × 10^9 per L, decisions on treatment and dose should be made on a case-by-case basis with the utmost caution
If platelet count >80 × 10^9 per L, pharmacological prophylaxis could be used; if the platelet count is <80 × 10^9 per L, pharmacological prophylaxis can only be considered on a case-by-case basis and careful monitoring is recommended
In the CASSINI64 and AVERT65 trials, patients with a platelet count as low as 50 × 10^9 per L were allowed to receive thromboprophylaxis
In patients with cancer who are pregnant, LMWH for treatment of established VTE and for VTE prophylaxis is suggested; avoidance of vitamin K antagonists and direct oral anticoagulants
In obese patients, consideration for a higher dose of LMWH should be given for cancer surgery
For the treatment of symptomatic catheter-related thrombosis in children with cancer, anticoagulant treatment is recommended for a minimum of 3 months and as long as the central venous catheter is in place
In children with acute lymphoblastic leukaemia undergoing induction chemotherapy, we recommend LMWH as thromboprophylaxis
In children requiring central venous catheters, we suggest the use of implanted ports over peripherally inserted central catheter lines

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Sažetak

Plućne embolije kod karcinoma: pregled i izazovi terapije

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Venski tromboembolizam (VTE) je jedan glavnih uzroka povećanog morbiditeta i mortaliteta pacijenata sa malignitetom. Veoma je važno proceniti rizik svakog pojedinačnog pacijenta u cilju adekvatnog lečenja, proceniti potrebu za primarnom i sekundarnom prevencijom VTE, i proceniti rizik od mortaliteta od akutnog plućnog embolizma. Postignut je značajan napredak u terapiji VTE kod bolesnika sa karcinomom. Oralni antikoagulansi nezavisni od vitamina K (NOAC) čine jednostavnijim terapiju VTE u poređenju sa nisko-molekularnim heparinima (LMWH) zahvaljujući njihovim karakteristikama, načinu primene, fiksnom doziranju i nižoj ceni terapije. Ipak, njihova primena zahteva poseban oprez, naročito kod bolesnika sa gastrointestinalnim malignitetima. Dostupni podaci o reperfuzionoj terapiju ističu značaj individualnog pristupa svakom pacijentu sa malignitetom i VTE.

Ključne reči: *karcinom, pulmonalni tromboembolizam, stratifikacija rizika, terapija*