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Prevention of arterial and venous thrombosis in cancer patients

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ABSTRACT

Patients with cancer have prothrombotic and hypercoagulable state, which leads to higher risk for venous thromboembolism and other clinical manifestations of thromboses. Pathophysiology of thrombosis in cancer patients is influenced by many factors, different from patients without malignancy. Tumor cells express tissue factor and other procoagulant factors and during tumors invasive growth, dissemination and metastasis process tumor cells interact with endothelial cells, leukocytes, monocytes and platelets. Increased platelet activation and aggregability as well as changes in coagulation and fibrinolysis are present in cancer and especially in metastatic disease. Higher risk for venous thromboembolism is well known in patients with cancer during hospitalization, in patients with malignancy before, during and after operation, during ambulatory active chemotherapy, as well as in patients with different kinds of adjunctive therapy. Associated complications such as pulmonary embolism and others are associated with the increase of early mortality in these patients. Prevention of venous thromboembolism in this population is recommended in nearly all patients, especially in patients with prior venous thromboembolism or pulmonary embolism. Drugs of choice are low-molecular weight heparins, unfractionated heparin, vitamin K antagonists and fondaparinux. With the evolution of new anticoagulants which are coming to clinical praxis such as dabigatran, we can expect their further use for prevention in cancer patients in the future.

Klíčová slova:
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SOUHRN

U pacientů s karcinomy vzniká protrombotický a hyperkoagulační stav zvyšující riziko žilní tromboembolie a dalších klinických projevů trombózy. Patofyziologii trombózy u jedinců s karcinomem ovlivňuje řada faktorů, které se liší od faktorů přítomných u osob bez nádorových onemocnění. Nádorové buňky exprimují tkáňový faktor a další koagulační faktory a v průběhu invazivního růstu, diseminace a metastazování karcinomu dochází k interakci mezi nádorovými buňkami a buňkami endotelu, leukocyty, monocyty a krevními destičkami. V přítomnosti karcinomů a zvláště metastazujícího onemocnění lze pozorovat zvýšenou aktivaci a agregabilitu krevních destiček i změny v koagulaci a fibrinolýze. Je známo, že u hospitalizovaných pacientů s karcinomem, u pacientů s nádorovým onemocněním v období kolem i během chirurgického výkonu, během ambulantní aktivní chemoterapie i u nemocných s různými typy přídatné léčby existuje vyšší riziko rozvoje žilní tromboembolie. Přidružené komplikace, jako např. plicní embolie, zvyšují časnou mortalitu těchto pacientů. V této populaci se prevence žilní tromboembolie doporučuje téměř u všech pacientů, zvláště u jedinců se žilní trombózou nebo plicní embolií v anamnéze. Mezi léky první volby patří nízkomolekulární heparin, antagonisté vitaminu K a fondaparinux. S vývojem a zaváděním nových antikoagulancií, např. dabigatranu, do klinické praxe lze očekávat jejich budoucí využití i v prevenci tepenné a žilní trombózy u pacientů s karcinomy.

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Introduction

The association between cancer and thromboembolism was described first in 1865 by Trousseau who noticed association between malignant disease and venous thrombosis [1]. Much later, autopsy rates showed that occurrence of venous thromboembolism (VTE) in cancer patients could be up to 50% [2–4], clinically detectable VTE is found in 4–20% of patients and now it is well known that VTE is one of the leading causes of death in patients with cancer [5]. Some types of cancer are more likely to be prothrombotic, and several studies confirmed changes in clotting factors in following tumors: solid cancers, ductal adenocarcinoma of pancreas, colorectal carcinoma, melanoma, breast cancer, gastrointestinal cancer, gynecological cancers, cervical and endometrial cancer, myeloma and other hematological cancers. Prothrombotic state in these patients is also influenced by many other factors: disease stage, hospitalization, immobilization as well as surgery and chemotherapy. The risk of development of VTE in hospitalized patients with cancer is 4.1 times higher than in patients without cancer; the risk is higher when chemotherapy is used [6,7]. The incidence of VTE with the use of new antiangiogenic drugs and cancer regimens including thalidomide, lenalidomide or bevacizumab is also higher than before [8–11]. Deep vein thrombosis is the most common clinical presentation of prothrombotic state in cancer patients, but also arm vein thrombosis, pulmonary embolism, migratory superficial thrombophlebitis, thrombotic microangiopathy and cerebral sinus thrombosis can occur in cancer sometimes before the detection of cancer. Thromboses may also occur in arterial system and it is estimated that from all thromboses about 25% are arterial ones.

Risk factors for cancer associated VTE

There is evidence, that the risk of deep vein thrombosis (DVT) and VTE depends on tumor type, stage and extent of cancer and treatment used. The role of risk factors such as treatment during hospitalization, immobilization, obesity, varicose veins has been evaluated by Kröger et al. [12]. Several risk factors have been shown to increase risk of VTE in their study, starting from history of prior DVT, or family history of DVT, chemotherapy and fever. The only laboratory parameter which reached statistical significance was C-reactive protein. When the chemotherapy used was looked at, the following drugs influenced the incidence of VTE significantly: anthracyclines, platinum based drugs and nitrogen mustard analogs. Other risk factors such as age, gender, obesity, chronic venous insufficiency, time from first diagnosis of cancer or diarrhea had only a minor role for VTE in patients with malignancy. They concluded that the risk of DVT in cancer patients without additional risk factors is low, but the risk is increasing with the increasing number of risk factors present in individual patient. The risk assessment is therefore very important to identify high risk patients with further application of prophylactic treatment.

Specifics of thrombosis pathophysiology in cancer patients

There are several different aspects of the cause of thrombosis in cancer; the presence of a tumor itself is the factor for development of prothrombotic state. Increased platelet activation and aggregability as well as changes in coagulation and fibrinolysis are present in cancer and especially in metastatic disease [13]. In cancer patients, hypercoagulable state with abnormalities of three basic components of Virchow's triad is common. Abnormal blood flow, abnormal blood constituents and abnormalities of the vessel wall represent three main parts of this triad, and mechanisms leading to prothrombogenicity are multiple and synergistic.

Abnormal blood flow

This component of Virchow's triad is probably less important in cancer patients than in cardiovascular diseases. However, altered blood viscosity and yield stress was found in patients with abdominal malignancy and a relationship of this to deep vein thrombosis was shown already many years ago [14]. Increased stasis plays important role during immobility of patients. Other possibilities in this component of triad represent abnormal blood vessel formation due to cancer based neoangiogenesis [15].

Abnormal blood constituents in cancer patients

Generally, several changes are pronounced in patients with malignancy: increased platelet activation and aggregation, increased procoagulant factors and decreased anticoagulant and fibrinolytic factors.

Platelets

It was shown that in myeloma and in cervical and endometrial cancer there is reduced sensitivity to prostacyclin, resulting in increased platelet aggregability [16]. Also in lung, breast, ovarian and prostate cancers higher levels of platelet products such as beta-thromboglobulin, platelet factor 4, thrombospondin and soluble P-selectin are found [17]. There are several possible explanations for the excess platelet activity: when studied in vitro, cancer cells activate platelets by direct contact, with the release of platelet activators such as thromboxane A_2 and ADP, also increase of von Willebrand factor (vWF), fibrinogen and PAI-1 has been demonstrated in cancer patients [18].

Clotting – fibrinolytic system

Other mechanisms of prothrombotic state are related to coagulation – some degree of altered coagulation can be found in most of the cancer patients. Soluble plasma molecules are involved in both procoagulant and fibrinolytic systems and their balance is shifted to prothrombotic state in cancer patients. Monocytes have important role in these pathological changes. Their ability to express tissue factor as well as delivery of cytokines and procoagulant

activities of monocyte microparticles is important, which have potential role to promote thrombosis in patients with malignancy.

Role of the tissue factor and the cancer procoagulant

Tissue factor is produced by monocytes and endothelial cells; in cancer its production is upregulated due to high circulating concentrations of vascular endothelial growth factor (VEGF). Rickles et al. [19,20] showed that tissue factor can be expressed also by tumor cells, including sarkoma, melanoma, lymphoma, neuroblastoma and acute promyelocytic leukemia cells. It has been suggested that tissue factor is a marker for switching to an angiogenic and prothrombotic phenotype for instance as in breast cancer. Other less known direct activator of coagulation is a cysteine proteinase growth factor – ***cancer procoagulant***, which activates directly factor X. Increased concentrations of cancer procoagulant have been found in patients with malignant melanoma, acute promyelolytic leukemia, and cancer of colon, breast, lung and kidney [21,22].

Coagulation cascade

Changes of proteins within coagulation cascade were found in many studies in cancer patients. For example, increased plasma concentrations of thrombin-antithrombin III complexes, as well as increased fibrinogen and vWF have been observed in patients with breast cancer. Also reduced concentrations of tissue plasminogen activator with concomitant increased plasminogen activator inhibitor-1 and other inhibitory factors in fibrinolytic pathway were found in patients with gastrointestinal cancer which resulted in prothrombotic and hypercoagulable state. In lung cancer thrombosis-inducing activities increase with the stage of the disease of all cell types and are associated with shorter survival time in inoperable non-small-cell lung cancer [23]. Elevated levels of D-dimer were found in numerous studies in patients with VTE and malignancy, and also in patients with cancer who do not have VTE. It has been suggested that high D-dimer levels in malignancy reflect the biology of the tumor itself, higher levels were observed in breast, bowel and prostate cancers [24].

Abnormalities of vessel wall

Endothelial function may be assessed by plasma changes of several molecules such as soluble E-selectin, thrombomodulin and vWF. Endothelial cells are influenced by proinflammatory cytokines as interleukin-1 and tumor necrosis factor, resulting in suppression of endothelial fibrinolytic activity and increase of production of vWF and thrombomodulin, which leads to decrease of anticoagulant thrombomodulin on endothelial surface. The role of vWF in promoting thrombosis in cancer patients is well known – its increase indicates endothelial damage; it can also increase fibrinogen level and contribute to platelet to platelet and platelet to subendothelium adhesion. Similarly, thrombomodulin is increased in cancer and can promote coagulopathy in these patients.

Recommendations for prevention of VTE in cancer patients

American Society of Clinical Oncology summarized recommendation for the use of anticoagulation in the prevention of VTE in patients with malignancy in 2007 [25]. These recommendations are based on several well known facts: tumor cells express tissue factor and other procoagulant factors and during tumor's invasive growth, dissemination and metastasis process tumor cells interact with endothelial cells, leukocytes, monocytes and platelets. Also immobilization and chemotherapy increase risk of changes in hemostasis with subsequent thrombotic complications. Inhibiting of hemostasis by different drugs may change biology of cancer and can modify direct effect of thromboses on patient survival.

Anticoagulation terapy during hospitalization

The frequency of venous thrombosis in hospitalized patients with cancer is reported with incidences ranging between 0.6% and 18% (Lyman Table 2 [25]). Higher incidence of VTE is common in patients with malignancy of the brain, gastrointestinal tract, ovary, kidney, pancreas, bladder, lung and hematologic malignancies [26]. Also older patients and patients on hormonal therapy are at higher risk for VTE, as well as patients with central venous catheters. Therefore, patients with cancer should be considered candidates for VTE prophylaxis with anticoagulants during hospitalization in the absence of bleeding or other contraindications to anticoagulation. Multiple randomized clinical trials focused on medically treated patients with cancer showed results from which prophylaxis with either low-dose heparin or low molecular weight heparin (LMWH) for bedridden patients is strongly recommended [27].

Perioperative VTE prophylaxis

Risk of DVT during surgery in cancer patients is about double when compared with patients without cancer [28]; therefore all patients undergoing major surgical intervention for malignant disease should receive drugs for thrombosis prophylaxis. Up to 25% of symptomatic VTE occurs after discharge from the hospital, the @RISTOS project showed that 40% of VTE events occurred three weeks after surgery and VTE was responsible for 46% of deaths in the first month after the surgery [29]. In patients undergoing surgery VTE ***prophylaxis*** can be ***mechanical*** or pharmacological. Prevention of venous stasis is either passive with graduated compression stockings, or active with intermittent pneumatic calf compression or mechanical foot pumps. The reduction of VTE with these methods reduced frequency of DVT by 66%, but reduction of pulmonary embolism was only 31% when pooled data from three studies were analyzed [30]. For ***pharmacological VTE prophylaxis*** the use of several drugs is common, including unfractionated heparin (UFH), low molecular weight heparins (LMWHs), fondaparinux and vitamin K antagonists. Low-dose UFH has been used for perioperative prevention of DVT and PE in cancer patients for years. The meta-analysis of 10 trials published in 1998 showed that administration of low-dose UFH

decreased rates of incidence of DVT from 30.6% in control group to 13.6% in the active treatment group ($p < 0.001$) [31]. Low molecular weight heparins are currently used more often and their comparison with UFH showed similar efficacy in DVT prevention [32]. Once daily s.c. injection and lower risk of heparin induced thrombocytopenia are main potential advantages of LMWH over UFH. Bergqvist et al. demonstrated that in patients with cancer undergoing laparotomy, an increasing dose of LMWH (2500 U versus 5000 U) can improve prophylactic efficacy without increasing the risk of bleeding [33]. Inhibitor of factor Xa, fondaparinux, was found to be at least as effective as LMWH dalteparin in randomized clinical trial with 2048 patients undergoing abdominal surgery, 68% of them were patients with cancer [29]. The duration of prophylaxis prevention is also a factor of high importance – 4 weeks prophylaxis with enoxaparin was more effective than 1 week duration enoxaparin in randomized trial focused on incidence of DVT after abdominal or pelvic cancer surgery [34].

Anticoagulation therapy during systemic outpatients chemotherapy

In ambulatory patients with cancer, routine prophylaxis of DVT and PE during systemic chemotherapy is not recommended. Available data from clinical trials are conflicting: generally, the risk of VTE is relatively low, but non-randomized clinical trials of thalidomide containing regimens showed risk of VTE in 17% of patients and even in 26% when its combination with dexamethazone was used. Prophylactic anticoagulation with combination of LMWH, warfarin 1.25 mg and antiaggregation with aspirin showed efficacy in prevention of DVT in patients receiving thalidomide for multiple myeloma [35]. But generally, the use of aspirin is not recommended due to higher risk of bleeding in cancer patients [36].

Prevention of recurrent VTE for patients with established VTE

When VTE is diagnosed in cancer patients, the indication for anticoagulant therapy is essentially the same as for patients who do not have cancer. LMWHs are the preferred mode of treatment for initial 5–10 days; for long-term anticoagulant therapy LMWHs are also the treatment of first choice. When LMWHs are not available, vitamin K antagonists with targeted INR 2–3 are usually used. The CLOT study (Randomized Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Reccurent Venous Thromboembolism in Patients with Cancer) randomly compared LMWH (dalteparin 200 IU/kg body weight s.c. once daily 5–7 days) followed by coumarin derivative for next 6 months versus dalteparin alone – first month 200 IU/kg body weight followed by 150 IU/kg body weight for next 5 months – in patients with cancer and VTE [37]. The recurrent symptomatic VTE occurred in 9% of patients in dalteparin-alone group versus 17% in the coumarin group ($p = 0.002$). Major bleeding was present in 6% vs. 4%; any bleeding in 14% vs. 19% in dalteparin coumarin group and this difference was not statistically significant in both comparisons. Other randomized trial compared enoxaparin 1.5 mg/kg once daily s.c. with warfarin in 147 patients with cancer and VTE. The incidence of recurrent VTE or major bleeding was higher in warfarin group – 21.1% vs. 10.5% ($p = 0.09$). Currently LMWHs are approved in the USA for extended treatment of symptomatic VTE in patients with malignancy [38].

Conclusions

Patients with cancer have prothrombotic and hypercoagulable state, which leads to higher risk for venous thromboembolism and other clinical manifestations of thromboses. Associated complications such as pulmonary embolism and others are associated with the increase of early mortality in these patients. Prevention of VTE in this population is recommended especially in several groups of cancer patients who have higher risk of VTE: those are patients with prior VTE or PE, patients during hospitalization, patients with malignancy before, during and after surgical therapy, patients on active chemotherapy on an ambulatory basis as well as patients with different kinds of adjunctive therapy. Drugs of choice are low molecular weight heparins, unfractionated heparin, vitamin K antagonists and fondaparinux. With the evolution of new drugs for VTE prevention we can expect their further use for prevetion in cancer patients in the future as well.

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