Journal of Health Study and Medicine
2016, nr 1
ss. 41-59

Review article
Venous thromboembolism in cancer patients

Marta A. Fidyk[1], Grzegorz Piotrowski[23]

[1] Department of Cardiology, Nicolaus Copernicus Memorial Hospital
[2] Department of Cardiology, Nicolaus Copernicus Memorial Hospital, Lodz, Poland
[3] Institiute of Health Science, University of Social Science, Lodz, Poland

Summary
Cancer and its treatment are well-recognized risk factors for venous thromboembolism (VTE). The pathogenic mechanisms for the association include hypercoagulability due to activation of clotting by tumor cells, vessel-wall injury and stasis. Evidence suggests that the absolute risk depends on the tumor type, the stage or extent of the cancer, and treatment with antineoplastic agents. The symptoms of thrombosis are the same in cancer and non-cancer patients. About 10% of patients with idiopathic VTE have an underlying malignant disorder that can be detected by extensive diagnostic investigation. Long-term central venous catheters (CVT) have considerably improved the management of cancer patients because they facilitate chemotherapy, transfusions and parenteral nutrition. However, the use of long-term CVT, especially for chemotherapy, has been associated with venous thrombosis. Low-molecular-weight heparins are the cornerstone of prophylaxis and treatment of VTE in patients with cancer. The review includes a discussion of the epidemiology, pathophysiology, diagnosis and treatment.

Key words
cancer, thrombosis, venous thromboembolism, antithrombotic prevention

Introduction

Venous thrombosis is common clinical problem in patients with cancer. Armand Trousseau was the first who described the connection between thrombosis and cancer. Rudolf Virchow had described, connected three factors now known as the "Virchow's Triade", which are thought to contribute to thrombosis. The risk factors of thrombosis differ across the natural history of the cancer, its treatment and patient's characeteristics. The symptoms of thrombosis are the same in cancer and non-cancer patients. Hospitalized patients with cancer should be considered as candidates for VTE (Venous Thromboemoblism) prophylaxis with anticoagulants. All patients undergoing surgical intervention suffering from malignant disease should receive thromboprophylaxis for 4 weeks after the surgical procedure. Routine prophylaxis with an antithrombic agent is not recommended for ambulatory patients with cancer, unless they are receiving thalidomide or lenalidomide with chemotherapy or dexamethazone. The mechanical methods of thromboprophylaxis should be used together with pharmacological methods. Data from prospective studies indicate that cancer patients, who develop deep vein thrombosis, have an increased risk of recurrence of the disease, as well as shorter survival overall.

The overall risk of venous thromboembolism in cancer patients is four times as great as in the general population. Although the largest absolute numbers of VTE episodes occur in patients with lung, colon, and prostate cancer, the relative risk for VTE is highest in multiple myeloma, brain, and pancreatic cancer 46-, 20-, and 16-fold increased vs. healthy controls, respectively). In the metastatic stage; stomach, bladder, uterine, renal, and lung cancer are also associated with a high incidence of VTE. Patients receiving chemotherapy have a six-fold increase in the adjusted risk ratio for VTE compared with a healthy population [1].

The risk of VTE, comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), increases several times in patients with cancer [2]. Patients who are in hospital or are currently undergoing antitumor treatment seem to be most at risk of VTE. Among all patients who develop VTE, patients with cancer are a total of 20%, and patients undergoing chemotherapy – 13% [3,4]. It appears that the incidence of 4 to 20% VTE presented in clinical studies in patients with cancer, is underreported, because autopsies find VTE even in 50% of cases [5-7]. Currently,

for unknown reasons, the incidence of VTE in patients with cancer seems to be increasing. A recent analysis involving data from more than 66 000 cancer patients hospitalized in 120 academic hospitals in the US, showed that the incidence of VTE was 5.4% based on the number of hospitalizations and increased by 36% from 1995 to 2002 [8]. Toxic damage to the vessel walls is a side effects of anti-angiogenic drugs, often manifesting as drug specific thromboembolic complications. A high incidence of VTE has been described, in patients undergoing treatment with the use of new antitumor chemotherapy regimens, including thalidomide, lenalidomide or bevacizumab [9-12].

Venous thromboembolism (VTE) is one of the most dangerous complications in cancer patients. It is the second most common cause of death in this group of patients and implementation of effective thromboprophylaxis is one of the most important tasks of modern oncology. Guidelines for anticoagulation treatment in patients with cancer have been developed by various national and international oncology societies. Regardless of minor differences between the recommendations there is a general agreement on the need to take preventive actions on patients with the highest risk of thrombosis. It concerns cancer patients hospitalized for acute diseases and treated surgically. In these clinical situations the use of prophylactic doses of low molecular weight heparin (LMWH), unfractionated heparin (UFH) or of fondaparinux is recommened. For patients with a very high risk of thrombotic complications, undergoing surgery, it is recommended to administer anticoagulants in association with mechanical methods. Routine prophylaxis is not recommended in outpatients (exception – patients with multiple myeloma receiving the combination treatment involving anti-angiogenic drugs: thalidomide or lenalidomide) and for the maintenance of central venous catheter [13].

Deviations of coagulation laboratory tests are observed in 50-90% of patients with cancer and 95% of patients with metastatic disease [14]. Clinical signs of venous thrombosis are observed in approx. 15% of all patients with cancer [15-17].

Pathogenesis

The dependancy between cancer and thromboembolic disease (VTE) had been first described by Armand Trousseau (1801-1867). In 1865 he had found that patients, who suffered from thrombophlebitis, were

often diagnosed with cancer. In 1856 Rudolf Virchow described the three broad categories of factors that were thought to contribute to thrombosis [18-23]:

- Hypercoagulability
- Hemodynamic changes (stasis, turbulence)
- Endothelial injury/dysfunction
- Virchow's triad in cancer:
- Abnormal blood flow: increased plasma viscosity, increased stasis due to immobility (e.g., being bed-bound, in a wheelchair) [24-25].
- Abnormal blood constituents: increased platelet activation and aggregability – for example, increased soluble P selectin or beta thromboglobulin; loss of haemostasis with increase in procoagulants – for example, increased fibrinogen, cancer procoagulant, PAI-1.
- Abnormal blood vessel wall: damaged or dysfunctional endothelium (e.g., increased soluble E selectin, increased soluble thrombomodulin, possibly also related to chemotherapy) [26-28]; loss of anticoagulant nature and therefore acquisition of a procoagulant nature (e.g., increased von Willebrand factor, tissue factor, reduced tPA, possibly also related to chemotherapy); angiogenesis (altered release of, and response to, growth factors) [30-33].

There are several factors predisposing to thrombosis in cancer patients, depending on:

- tumor typ
- cancer treatment
- patient

Cancer-related factors: the place of cancer provenance: cancer of reproductive organs, pancreas, lungs, gastrointestinal; factors associated with histopathological type (more common among mucus producing cancers); the severity of the cancer; platelets above 350 g /l; leukocytes above 11 G /l

Many of therapeutic procedures in oncology remarkably increase the likelihood of VTE: Treatment-related factors: systemic therapy- chemotherapy is associated with a two- to six-fold increased risk of VTE compared with the general population. Thalidomide has been associated with high rates of VTE, ranging from 12% to 28%, when given in combination with dexamethasone or other types of chemotherapy [34-

35]. Chemotherapy and hormonotherapy can cause VTE i ATE [arterial thromboembolism) as well. The natural course of cancer per se and some comorbid conditions conducte to thrombosis, which makes it difficult to precisely determine the patomechanisms responsible for VTE. Particularly thrombosis often occurs in patients with advanced stages of malignancies treated chemically. An example might be the results of studies in patients with breast cancer, indicating that the risk of DVT (deep vein thrombosis) in the early stage of the disease is low and is about 0.2-0.8 while in patients undergoing chemotherapy in the second period of the disease DVT risk increases to 2-10%, and for patients in the IV stage of a cancer, treated with cytostatics is as high as 17.6% [36]. It is remarkable that almost in all patients with breast cancer affected by this complication thrombosis occurs during active treatment, which confirms the role of chemotherapy as the causative agent of thrombosis. The risk of VTE in the course of chemotherapy in other cancers is calculated at the level: ovarian cancer – about 11%, germ cell tumors – about 9%, colorectal cancer and NHL – about 7%. An even greater threat by thrombosis is associated with prostate cancer hormonal therapy [12-15]. Venous thrombosis was observed in as many as 16 of 25 patients (65%) of this diagnosis treated with estramustine [37]. Arterial thrombosis in the form of heart attacks, strokes, visceral arterial thrombosis and peripheral arterial thrombotic events, have been reported after chemotherapy and / or hormonal therapy, as well as during the use of granulocyte colony stimulating factor. In breast cancer the risk of this complication is about 1% [38]. The use of different chemotherapeutic agents leads to various clinical presentations of VTE and ATE. After administration of ARA-C (cytarabine) an onset hepatic vein occlusion disease (VOD) has been observed, after using DTIC (dacarbazine) to treat Buddha Chiari syndrome, and in patients undergoing bone marrow transplant, sterile thrombotic endocarditis has been reported [39,40]. In turn, during cisplatin-based treatment programs, high levels of von Willebrand factor and arterial thrombosis have been noticed. The use of adriamycin, Vinca alkaloids, cytosine arabinoside, bleomycin, busulfan, cisplatin, CCNU (lomustine), chlorozotocyny, cyclosporin A, daunorubicin, gemcitabine, mitomycin, semustyny, stimalamer and high-dose chemotherapy (cyclophosphamide, cisplatin, and carmustine) was associated with the onset of symptoms of thrombotic microangiopathy. However, it is the most common

complication that occurs after application of mitomycin C, especially beyond a cumulative dose of 40 mg / m^2 [41]. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS) were also found in patients treated with tamoxifen and in nearly 10% of combined chemo- and hormone therapy subjects (tamoxifen and 3M program). There are reports of thrombosis compliceated by myocardial infarcts and severe blood clottings in cerebral arteries after using ATRA (all-transretinoic acid) in the treatment of acute promyelocytic leukemia. This type of pathology is more common in patients diagnosed with ATRA syndrome. This syndrome is characterized by a high body temperature, respiratory failure, leukocyte infiltration in the lungs, pleural and pericardial effusion in patients diagnosed with high white blood cell count or in the case of a sudden increase in the number of white blood cells. Cytokines released during the treatment with ATRA may be responsible for the activation of insant blood coagulation [42].

Surgery – surgery and the extended postoperative period are historically well-known high-risk settings for VTE. In a recent study of cancer surgical patients, following risk factors for postoperative VTE have been named: age more than 60 years, previous VTE, advanced cancer, anesthesia lasting more than 2 hours, and bed rest longer than 3 days. Of note, 40% of VTE events occurred more than 21 days after surgery [43]. It is understood that the surgical treatment increases the VTE risk in a of 3-5-fold manner, in patients undergoing a surgery for cancer, compared with patients operated on because of other indications.

Table 1. The risk of thromboembolism (VTE) in cancer patients undergoing various surgical procedures (by Bick)

Type of surgical	risk of VTE
General surgery	29%
Gynecological surgery	20%
Urological surgery	41%
Orthopedic surgery	60%
Neurosurgery	28%

Supportive Therapy. A recent retrospective analysis of hospitalized patients with cancer found blood transfusions were independently associated with an increased risk of VTE, arterial events and in-hospital mortality. Central Venous Catheters (CVC)– The incidence of symptomatic catheter-related deep venous thrombosis (DVT) in adult patients ranges from 0.3% to 28% [44]. Radiation. Radiation therapy does not seem to be associated with a risk for VTE, although this has only been evaluated in a small number of studies [45].

Patient-related factors: older age, female sex, race, higher in African Americans, lower in Asians/Pacific Islanders, comorbidities: infection, renal disease, pulmonary disease, obesity, arterial thromboembolism, inherited prothrombotic mutations: Factor V Leiden, prothrombin gene mutation, prior history of VTE, performance status, candidate biomarkers: blood counts (prechemotherapy platelet count ≥ 350,000/μL, prechemotherapy leukocyte count >11,000/μL), TF: (high grade of TF expression by tumor cells, elevated systemic TF (antigen or activity)), D-dimer, soluble P-selectin, C-reactive protein [46].

The characteristic symptoms and physical signs of thromboembolism, both in cancer and non-cancer patients, are: swelling in the place of thrombosis, eg. limbs, increased tension and rigidity of the muscles supplied by the solidified vessel, pain at rest or after pressure administration, increased warming, extension of the superficial vessels of the skin, sine red coloration of the skin, fever – possible occurence, in the case of pulmonary embolism: dry cough, shortness of breath, especially at rest, pain located in the chest, tachycardia, tachypnea, general anxiety. Thrombosis can also be asymptomatic.

For diagnostic purposes, following techniques are used: doppler ultrasound, angiography, angio-CT in case of suspected pulmonary embolism, D-dimer [47].

The pathophysiology of VTE in cancer

The major role of the coagulation cascade is the production of fibrin – the meshwork that holds together the clot – which is produced through a cleavage of fibrinogen by thrombin. Coagulation is initiated by tissue damage, exposing the transmembrane glycoprotein tissue factor (TF). Tissue factor is expressed on the subendothelial surface of blood vessels and is normally exposed only when normal vasculature is disrupted.

Factor VII binds TF, and the TF–factor VII complex directly activates factor X to factor Xa and some factor IX to factor IXa. In the presence of factor Xa, tissue factor pathway inhibitor (TFPI) inhibits further generation of factor Xa and factor IXa. After inhibition by TFPI, the amount of factor Xa produced is insufficient to maintain coagulation. Additional factor Xa (which allows haemostasis to progress to completion) can only be generated by the factor IX– factor VIII pathway. Enough thrombin exists at this point to activate factor VIII, and together with factor IXa (generated by TF–factor VIIa) to further activate factor X. Factor IX activation is also augmented by thrombin activation of the factor XI pathway. Without the amplification and consolidating action of factor VIII/factor IX, there is insufficient generation of factor Xa to produce sufficient thrombin. When sufficient thrombin is generated, this endolytic serine protease selectively cleaves the Arg–Gly bonds of fibrinogen to form fibrin, releasing fibrinopeptides A and B and so forms the meshwork of the clot [48].

Thromboembolic complications

In cancer patients requiring intravenous administration of cytostatics or palliative treatment often a catheter inserted central venous is being used for a long time. Thrombosis associated with the presence of such a catheter leads to the PE in 10-15% of patients and 10% loss of access to the central veins. Major long-term problem of catheter use in cancer patients are thromboembolic complications. Thrombosis may lead to significant morbidity and impairment of patients quality of life. Cancer patients are in general at increased risk of venous thrombosis, and placement of a catheter or venous port system further increases this risk [49]. Increased venous stasis, endothelial injury, prothrombotic effects of malignancy and chemotherapy itself are among the factors implicated as causes of thrombosis in cancer patients. Catheter-associated thrombosis manifests itself either as thrombosis of the vein in which the catheter is situated or as an occlusion of the catheter lumen. Venous thrombosis may be asymptomatic or present with ipsilateral arm or neck pain and swelling. Thrombotic occlusion of the catheter lumen may be partial or complete; it may cause restrictions of the catheter's utility and be a starting point for infections or vice versa [50]. The incidence of catheter-associated thrombosis in cancer patients varies considerably between studies and

patient or cancer type. Four prospective studies of catheter-associated thrombosis in patients with solid tumours and haematological malignancies report rates of thromboembolic events between 37% and 66%. The incidence of catheter-associated thrombosis in retrospective studies varies even more widely (12% to 64%) [51-55]. A literature search on prophylactic treatment in tumour patients with central venous catheters or receiving chemotherapy did not present evidence to support the use of routine prophylactic anticoagulation for these patients [56].

All of recent studies fail to support the routine use of prophylactic anticoagulation in cancer patients with venous catheters to prevent catheter-induced thrombosis. Institutions should assess their rates of catheter-associated thrombosis and the indication for prophylaxis should be individualized for each patient accordingly. Central catheters and venous port systems are a mainstay of chemotherapy administration, and thousands of catheters are inserted annually. When symptomatic thrombosis occurs in association with a catheter, it definitely complicates further clinical care of the patient because of the need for anticoagulant therapy and potential catheter-removal. So far, routine prophylactic anticoagulation cannot be recommended based on the available evidence. Large-scale trials like that of Chew et al. using symptomatic thrombosis as an outcome measure are still urgently needed [57]. In addition, there are no data in the literature concerning frequency and management of mere catheter tip thrombosis, where the port system is flushable but no aspiration of blood is possible due to a small thrombus occluding the catheter tip. It seems to be right administer 5000 IU heparin over 24 hours into the port system via a perfusor system, after which treatment the port system often becomes patent again. However, no further evidence from clinical trials exists to validate this protocol. Moreover, it remains unclear whether catheter tip thrombosis needs to be treated at all since any therapeutic approach is of a merely empirical nature given the lack of any published evidence so far.

Anticoagulation Therapy

No proper prophylaxis of VTE is an important issue in routine clinical practice and in patients with cancer it is used even more seldom. Below are the current guidelines for the treatment and prophylaxis of venous thromboembolism in cancer patients

Initial treatment of established VTE

1. LMWH is recommended for the initial treatment of established VTE in cancer patients [Grade 1B].
2. (LMWHs are easier to use than UFH).
3. Fondaparinux and UFH can be also used for the initial treatment of established VTE in cancer patients [Grade 2D].
4. Thrombolysis in cancer patients with established VTE may only be considered on a case-by-case basis, with specific attention paid to contraindications, especially bleeding risk (brain metastasis)
5. In the initial treatment of VTE, vena cava filters may be considered in the case of contraindication for anticoagulation or in the case of PE recurrence under optimal anticoagulation. Periodic reassessment of contraindications for anticoagulation is recommended and anticoagulation should be resumed when safe. Vena cava filters are not recommended for primary VTE prophylaxis in cancer patients [58].

Early maintenance and long-term treatment of established VTE

1. LMWHs are preferred over VKA for the early maintenance treatment (10 days to 3 months) and long-term treatment (beyond 3 months) of VTE in cancer patients [Grade 1A].
2. Idraparinux is not recommended for the early maintenance treatment (10 days to 3 months) and the long-term treatment (beyond 3 months) of VTE in cancer patients; idraparinux is currently not available on the market [Grade 2C].
3. LMWH should be used for a minimum of 3 months to treat established VTE in cancer patients; however, patients were treated for 6 months in the largest study in this setting [Grade 1A].
4. After 3–6 months, termination or continuation of anticoagulation (LMWH or VKA) should be based on individual evaluation of the benefit-risk ratio, tolerability, patients preference and cancer activity [58].

Prophylaxis of VTE in medical cancer patients:

1. Recommended prophylaxis goes with LMWH, UFH or fondaparinux in hospitalized medical patients with cancer and reduced mobility [Grade 1B]. In some countries price differences between LMWH, UFH or fondaparinux may influence the choice.

2. For children with ALL (acute lymphoblastic leukemia) treated with L-asparaginase, depending on local policy and individual patient characteristics (platelet count, kidney function, fibrinogen and antithrombin III levels, etc.), prophylaxis may be considered in some patients; the same therapeutic option can be considered for adults [Best clinical practice, based on evidence of very low quality and a balance between desirable and undesirable effect depending on individual patient characteristics].
3. In patients receiving chemotherapy, prophylaxis is not recommended routinely [Grade 1B].
4. Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic pancreatic cancer treated with chemotherapy and having a low bleeding risk [Grade 1B].
5. Primary pharmacological prophylaxis of VTE may be indicated in patients with locally advanced or metastatic lung cancer treated with chemotherapy and having a low bleeding risk [Grade 2B].
6. In patients treated with IMiDs (immune-modulating drugs) combined with steroids and/or chemotherapy (doxorubicin), VTE prophylaxis is recommended; in this setting, VKA at low or therapeutic doses, LMWH at prophylactic doses and low-dose aspirin have shown similar effects with regard to preventing VTE; however, the efficacy of these regimens remains unclear [Grade 2C] [58].

Prophylaxis of VTE in surgical cancer patients:

1. Use of LMWH once a day or a low dose of UFH three times a day is recommended to prevent postoperative VTE in cancer patients; pharmacological prophylaxis should be started 12–2 h preoperatively and continued for at least 7–10 days; there are no data allowing conclusions regarding the superiority of one type of LMWH over another [Grade 1A].
2. There is no evidence to support fondaparinux as an alternative to LMWH for the prophylaxis of postoperative VTE in cancer patients [Grade 2C].
3. Use of the highest prophylactic dose of LMWH to prevent postoperative VTE in cancer patients is recommended [Grade 1A].

4. Extended prophylaxis (4 weeks) to prevent postoperative VTE after major laparotomy in cancer patients may be indicated in patients with a high VTE risk and low bleeding risk [Grade 2B]. [58].

Special situations:

1. A braintumor per se is not a contraindication for anticoagulation for established VTE [Grade 2C].
2. For the treatment of established VTE in cancer patients with a brain tumor we prefer LMWH [Best clinical practice, based on evidence of very low quality and a balance between desirable and undesirable effects to be assessed individually (high bleeding risk)].
3. It is recommended to use LMWH or UFH commenced postoperatively for the prevention of VTE in cancer patients undergoing neurosurgery [Grade 1A].
4. In the presence of severe renal failure (creatinine clear- ance- <30mLmin) suggest using UFH followed by early VKA (possible from day 1) or LMWH adjusted to anti- Xa level for the treatment of established VTE
5. In cancer patients with thrombocytopenia, full doses of anticoagulant can be used for the treatment of established VTE if the platelet count is > 50 G/ L and there is no evidence of bleeding; for patients with a platelet count below 50 G L , decisions on treatment and dosage should be made on a case-by-case basis with the utmost caution
6. In cancer patients with mild thrombocytopenia, platelet count > 80 G L , pharmacological prophylaxis may be used; if the platelet count is below 80 G L, pharmacological prophylaxis may only be considered on a case-by-case basis and careful monitoring is recommended [59].

International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters (CVC) in patients with cancer:

1. Use of anticoagulation for routine prophylaxis of CVC is not recommended [Grade 1A]. Values and preferences: bleeding risk with anticoagulants.

2. 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 1A].
3. For the treatment of symptomatic CVC in cancer patients, anticoagulant treatment is recommended for a minimum of 3 months; in this setting, LMWHs are suggested. Oral VKA can also be used, in the absence of direct comparisons of these two types of anticoagulants in this setting
4. The CVC can be kept in place if it is functional, well-positioned and non-infected with good resolution of symptoms under close surveillance; whether the CVC is kept or removed, no standard approach in terms of duration of anticoagulation is established [59].

Identifying patients with cancer, who are most at risk for VTE, is essential to better target thromboprophylaxis, with the eventual goal of reducing the burden as well as the consequences of VTE for patients with cancer.

References

1. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism 3067–3068.

2. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. Arch Intern Med 2000; 160: 809–815.

3. Caine GJ, Stonelake PS, Lip GY, et al. The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia 2002; 4: 465–473.

4. Heit JA, O'Fallon WM, Petterson TM et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med 2002; 162: 1245–1248.

5. Gomes MP, Deitcher SR. Diagnosis of venous thromboembolic disease in cancer patients. Oncology (Huntingt). 2003; 17: 126–135.

6. Baron JA, Gridley G, Weiderpass E et al. Venous thromboembolism and cancer. Lancet 1998; 351: 1077–1080.

7. Ottinger H, Belka C, Kozole G et al. Deep venous thrombosis and pulmonary artery embolism in high-grade non Hodgkin's lymphoma: Incidence, causes and prognostic relevance. Eur J Haematol 1995; 4: 186–194.

8. Khorana AA, Francis CW, Culakova E. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007; 5: 632–634.

9. Cavo M, Zamagni E, Cellini C et al. Deepvein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. Blood 2002; 100: 2272–2273.

10. Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21: 60–65.

11. Kuenen BC, Levi M, Meijers JC et al. Potential role of platelets in endothelial damage observed during treatment with cisplatin, gemcitabine, and the angiogenesis inhibitor SU5416. J Clin Oncol 2003; 1: 2192–2198.

12. Shah MA, Ilson D, Kelsen DP. Thromboembolic events in gastric cancer: high incidence in patients receiving irinotecan- and bevacizumabbased therapy. J Clin Oncol 2005; 23: 2574–2576.

13. Chojnowski K, Treliński J. Prophylaxis of venous thromboembolism in patients with cancer. Oncol Clin Pract 2012; 8(3): 105–112.

14. Stanisławiak J, Markowska J. Powikłania zakrzepowo-zatorowe w przebiegu choroby nowotworowej. Współcz Onkol 2008; 12: 56–60.

15. Prandoni P, Lensing AW, Büller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet 1992; 339: 441–5.

16. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. Lancet Oncol 2002; 3: 27–34.

17. Fotopoulou C, duBois A, Karavas AN et al. Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel – containing first-line chemotherapy: an explorary analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. J Clin Oncol 2008; 26: 2683–9.

18. Wojtukiewicz MZ, Rucińska M. Aktywacja krzepnięcia krwi u chorych na nowotwory: implikacje kliniczne. Nowotwory 1999; 49: 381–91.

19. Falanga A, Levine MN, Consonni R et al. The effect of very-low-dose warfarin on markers of hypercoagulation in metastatic breast cancer: results from a randomized trial. Thromb Haemost 1998; 79: 23–7.

20. Stanisławiak J, Markowska J. Powikłania zakrzepowo-zatorowe w przebiegu choroby nowotworowej. Współcz Onkol 2008; 12: 56–60.

21. Lip GY, Chin BS, Blann AD. Cancer and the prothrombotic state. Lancet Oncol 2002; 3: 27–34.

22. Fotopoulou C, duBois A, Karavas AN et al. Incidence of venous thromboembolism in patients with ovarian cancer undergoing platinum/paclitaxel – containing first-line chemotherapy: an explorary analysis by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. J Clin Oncol 2008; 26: 2683–9.

23. Wojtukiewicz MZ, Rybałtowski M. Powikłania zakrzepowo-zatorowe w chorobie nowotworowej. Leczenie Wspomagające 2003; 4: 3–10.

24. Von Tempelhoff GF, Heilmann L, Hommel G, Pollow K. Impact of rheological variables in cancer. Seminars in Thrombosis and Hemostasis 2003; 29(5): 499–513.

25. Humphreys WV, Walker A, Charlesworth D. Altered viscosity and yield stress in patients with abdominal malignancy: relationship to deep vein thrombosis. BJS 1976; 63(7): 559–561.

26. Lindahl AK, Boffa MC, Abildgaard U. Increased plasma thrombomodulin in cancer patients. Thromb Haemost 1993; 69(2):112–114.

27. Liu P-L, Tsai J-R, Chiu C-C et al. Decreased expression of thrombomodulin is correlated with tumor cell invasiveness and poor prognosis in nonsmall cell lung cancer. Molecular Carcinogenesis. 2010; 49(10): 874–881.

28. Banks RE, Gearing AJH, Hemingway IK, Norfolk DR, Perren TJ, Selby PJ. Circulating intercellular adhesion molecule-1 (ICAM-1), E-selectin and vascular cell adhesion molecule-1 (VCAM-1) in human malignancies. BJC. 1993; 68(1):122–124.

29. Van Wersch JWJ, Tjwa MKT. Coagulation/fibrinolysis balance and lung cancer. Haemostasis 1991; 21(2):117–123.

30. Ross R, Vogel A. The platelet-derived growth factor. Cell 1978;14(2):203–210.

31. Ohi M, Miki C. Tissue concentration of platelet-derived endothelial cell growth factor in colorectal cancer. Scand J Gastroenterol 2000; 35(4): 413–418.

32. Contrino J, Hair G, Kreutzer DL, Rickles FR. In situ detection of tissue factor in vascular endothelial cells: correlation with the malignant phenotype of human breast disease. Nat Med 1996; 2(2): 209–215.

33. Koomägi R, Volm M. Tissue-factor expression in human non-small--cell lung carcinoma measured by immunohistochemistry: correlation between tissue factor and angiogenesis. Int J Cancer 1998; 79(1): 19–22.

34. Cavo M, Zamagni E, Tosi P et al. First-line therapy with thalidomide and dexamethasone in preparation for autologous stem cell transplantation for multiple myeloma. Haematologica. 2004; 89: 826–831.

35. Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: A population-based case-control study. Arch Intern Med 2000; 160: 809–815.

36. Lee AYY, Levine MN. The thrombophilic state induced by therapeutic agents in the cancer patient. Semin Thromb Hemost 1999; 25: 137.

37. Leickman CG, Leichman L, Spears CP, Rosen PJ, Jeffers S, Groshen S. Prolonged continuous infusion of fluorouracil with weekly bolus leucovorin: a phase I study in patients with disseminated colorectal cancer. J Natl Cancer Inst 1993; 85(1): 41–44.

38. Ottinger H, Belka C, Kozole G. Deep venous thrombosis and pulmonary artery embolism in high-grade non Hodgkin's lymphoma.: Incidence, causes and prognostic relevance. Eur J Haematol 1995; 54(3): 186–194.

39. Van de Voorde WM, Elgamal AA, Van Poppel HP, Verbeken EK, Baert LV, Lauweryns JM. Morphologic and immunohistochemical changes in prostate cancer after preoperative hormonal therapy. A comparative study of radical prostatectomies. Cancer 1994; 74: 3164–3175.

40. Saphner T, Tormey DC, Gray R. Venous and arterial thrombosis in patients who received adjuvant therapy for breast cancer. J Clin Oncol 1991; 9: 286–294.

41. Luzzatto G, Schafer AI. The prethrombotic state in cancer. Semin Oncol 1990; 17: 147–158.

42. Bauer KA, Levine M. W: Evaluation and management of the cancer patient with thrombosis. [W.] 35th Annual Meeting of the American Society of Clinical Oncology Educational Book Perry M.C.(red.), American Society of Clinical Oncology, Alexandria, VA, 1999, 223–233.

43. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med 2008; 168: 2377–2381.

44. Verso M, Agnelli G. Venous thromboembolism associated with long--term use of central venous catheters in cancer patients. J Clin Oncol 2003; 21: 3665–3675.

45. Blom JW, Vanderschoot JP, Oostindier MJ et al. Incidence of venous thrombosis in a large cohort of 66,329 cancer patients: Results of a record linkage study. J Thromb Haemost 2006; 4: 529–535.

46. Joseph A. Caprini MD. MS, FACS, RVT, FACPh Risk Factors for Venous Thromboembolism, Update on Risk Factors for Venous Thromboembolism (5–7).

47. Stanisławiak J, Markowska J. Thromboembolic complications in oncology. Prz Menopauzalny 2010; 4: 203–206.

48. Br J Cancer. 2010 Apr 13; Epidemiology and pathophysiology of cancer-associated thrombosis 102 (Suppl 1): S2–S9.

49. Sutherland DE, Weitz IC, Liebman HA. Thromboembolic complications of cancer: epidemiology, pathogenesis, diagnosis and treatment. Am J Hematol 2003; 72: 43–52.

50. Mehall JR, Saltzmann DH, Jackson RJ et al. Fibrin sheath enhances central venous catheter infection. Crit Care Med 2002; 30: 908–912.

51. Newman KA, Reed WP, Schimpff SC et al. Hickman catheters in association with intensive cancer chemotherapy. Support Care Cancer 1993; 1: 92–97.

52. Drakos PE, Nagler A, Or R et al. Low molecular weight heparin for Hickman catheter-induced thrombosis in thrombocytopenic patients undergoing bone marrow transplantation. Cancer 1992; 70: 1895–1898.

53. Lokich JJ, Becker B. Subclavian vein thrombosis in patients treated with infusion chemotherapy for advanced malignancy. Cancer 1983; 52: 1586–1589.

54. Koksoy C, Kuzu A, Erden I et al. The risk factors in central venous catheter-related thrombosis. Aust NZ J Surg 1995; 65: 796–798.

55. Cortelezzi A, Moia M, Falanga A, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective, multicenter study. Br J Haematol 2005; 129: 811–817.

56. Voog E, Lazard E, Juhel L. Prophylaxis of thrombosis induced by chemotherapy or central venous catheters. Presse Med 2007; 36(2): 225–234.

57. Chew H, Wun T, Harvey DJ et al. Incidence of venous thromboembolism and the impact on survival on breast cancer patients. J Clin Oncol 2007; 25(1): 70–76.

58. International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. JTH 2013; 11: 56–70.

59. International clinical practice guidelines for the treatment and prophylaxis of thrombosis associated with central venous catheters in patients with cancer. JTH 2013; 11: 71–80.

Adres do korespondencji / Address for correspondence
Marta A. Fidyk
Department of Cardiology, Nicolaus Copernicus Memorial Hospital,
Pabianicka 62, 93-519 Lodz, Poland
phone: +48-42-6895492
e-mail: martaa.6@o2.pl