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REVIEW ARTICLE

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Nadroparin in the prophylaxis and treatment of thromboembolic complications in cancer patients

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ABSTRACT

Thromboembolic events are the most frequent complications and second leading cause of death among cancer patients. The most common forms include deep venous thrombosis of lower extremities and pulmonary embolism. The risk of thrombosis is correlated with underlying, patient's clinical characteristic, functions of coagulation system as well as anticancer treatment. There is a well-established evidence for using of antithrombotic prophylaxis in cancer patients undergoing surgery and hospitalised due to different causes. There are some scores, based on laboratory and clinical factors, that facilitate qualification to the prophylaxis (e.g. Caprini score, Padua Prediction Score). The role of low-molecular-weight heparins (LMWH) in prophylaxis of thrombosis in cancer patients was established based on the results of many randomised clinical trials. Currently, the use this group of drugs — both in the treatment and in prophylaxis of venous thromboembolism (VTE) — is a part of standard of care. Nadroparin is one of the LMWHs with well-documented efficacy and safety in cancer patients.

Key words: venous thromboembolism, cancer, nadroparin, thrombosis prophylaxis, thrombosis treatment, pulmonary embolism

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Thromboembolic complications in cancer patients

Thromboembolic events (TE) are the most frequent complication and second leading cause of death in cancer patients [1, 2]. Diagnosis of cancer increases the risk of thrombosis by 4–6-fold and the prevalence is affected by cancer stage, (4–13-fold more prevalent in patients with metastatic disease as compared to local cancer), type (approximately one third of pancreatic and lung cancer patients have thrombotic events vs. approximately 15% of patients with other types of cancer), and histology (incidence of thrombosis differs between different histologic types of lung cancer) [3]. Furthermore, the recurrence of TE events in cancer patients is 3 times more frequent than in non-cancer patients, and the risk of death due to thrombosis is as much as eight times higher [4]. In parallel, occurrence of thrombosis or embolism is an unfavourable prognostic factor, and overall survival time is significantly shorter as compared to the patients without such complications [1, 2].

In the nineteenth century Professor Armand Trousseau noticed that venous thromboembolism (VTE) is much more frequent in cancer patients. Currently, it is very well recognised that cancer development and coagulation disorders are inextricably interlinked. There are different causes of such disorders, including primarily procoagulant activity as well as cytokines, which are produced and released by cancer cells. They influence host monocytes/macrophages, endothelial cells, and platelets inducing prothrombotic activity. Tissue factor (TF) is the most important procoagulant in cancer patients. TF expression was documented in the majority of tumours, like breast, pancreatic, lung, gastric cancer, glioblastoma, and melanoma. Additionally, it was proven that TF expression on the surface of cancer cells could be associated with a decrease in

overall survival (e.g. in breast cancer patients) or higher prevalence of metastatic disease (e.g. in colon cancer patients) [5].

The pathophysiology of thromboembolic complications is described by the still valid classical Virchow's triad, that includes changes of blood flow, endothelial damage, and changes within blood components. Causes of blood flow impairment in cancer patients broadly vary, including patient's immobilisation, external pressure of bulky mass on blood vessels, as well as during congestive heart failure resulting from cancer treatment-related cardiomyopathy. Hypoxia also affects blood flow, very often intensified by anaemia, being a consequence of either cancer itself or its treatment [6]. Of note, correlation between haemostatic disturbances and cancer is mutual, as current clinical trial results show, because cancer-dependent activation of coagulation cascade influences cancer growth, tumour neo-angiogenesis, and formation of distant metastases [7, 8].

Different forms of thromboembolic episodes

The most frequent clinical pictures of VTE in cancer patients are deep venous thrombosis (DVT) of lower extremities and pulmonary embolism (PE). Additionally, the most characteristic form of thrombosis in this group of patients is Trousseau's syndrome, e.g. migratory thrombosis of superficial veins. Below are discussed some clinical forms of thromboembolic complications, a detailed description of which is presented elsewhere [9].

Deep venous thrombosis (DVT) of lower extremities

Suspicion of DVT of lower extremities could be driven by some clinical symptoms from lower leg, like oedema, erythema (or bruising) of skin, and changes of skin warmth. Those signs and symptoms could be accompanied by pain of the lower leg or entire lower extremity. Diagnosis is based on compression ultrasound (US) examination, and more rarely on magnetic resonance angiography (MRA) or phlebography.

Deep venous thrombosis (DVT) of upper extremities

Especially predisposed to this form of thrombosis are patients with mediastinal tumours or lymphomas with axillary lymph node involvement, patients after central venous access device implantation, and patients treated with intravenous chemotherapy. Clinical signs and symptoms of upper extremities DVT are mostly unspecific or are simply lacking. Extremity oedema, erythema and increased skin warmth, and pain are noticeable, which could also involve the shoulder, axillary region, lower jaw, neck or head, as well as collateral circulation on the chest, together with symptoms of Superior Vena Cava Syndrome (SVCS). Upper extremities DVT may be complicated by PE (8–35% of patients) and chronic venous insufficiency (20–50%) [9]. Similarly to lower extremities DVT, diagnosis is established based on Doppler US, MRA, or phlebography.

Pulmonary embolism (PE)

The first clinical symptoms of PE are of sudden onset, most frequently as chest pain, intensifying during cough or attempting a deep breath, and could be accompanied by dizziness and syncope. Sudden ventilation impairment (dyspnoea) leads to suspicion of PE. Apart from computed tomography (CT) angiography diagnostic workout should include total blood count (TBC), APTT (activated partial thromboplastin time), INR (international normalised ratio), renal function, acid-base balance, and assessment of cardiac function and blood pressure (BP) monitoring.

Migratory thrombosis of superficial veins (Trousseau's syndrome)

Trousseau's syndrome presents with recurrent thrombosis in different localisations observed in patients with predisposing factors. It could be placed in different superficial veins, most frequently of unusual localisation. Very typical is spontaneous resolution and resistance to standard management. Migratory superficial phlebitis is mostly observed in patients with pancreatic cancer and other gastrointestinal (GI) malignancies.

Hepatic veins thrombosis (Budd-Chiari syndrome)

Hepatic veins thrombosis (HVT) is most frequently seen in patients with myeloproliferative syndromes. The symptoms include the presence of ascites, hepatomegaly, and abdominal pain.

Thrombosis of portal, splenic, visceral, and renal veins

These changes are primarily observed in patients with myeloproliferative syndromes, and more rarely in patients with primary hepatic, renal, and suprarenal gland cancers. The most frequent symptoms of thrombosis in these localisations are: splenomegaly, oesophageal varicose, abdominal pain, and ascites. Imaging evaluation techniques include US, CT, MR, scintigraphy, and phlebography.

Non-bacterial thrombotic endocarditis (NBTE)

This type of TE is the most commonly diagnosed in patients with mucus-producing GI adenocarcinoma and other cancers in higher stages. Usually, thrombotic foci develop as the first within affected valves, both aortal and mitral. The most frequent symptom of NBTE is newly diagnosed heart murmur, but often the complication of NBTE is the only symptom of the disease, including embolism of arteries: cerebral, coronary, splenic, renal, and extremities. Echocardiographic evaluation (ECHO) enables the appropriate diagnosis to be established.

Thrombosis risk assessment and primary prophylaxis

The risk of development of VTE in cancer patients is connected with patient-related factors, cancer type, as well as therapeutic modalities. Patient-related — most frequent — VTE risk factors include: age, male gender, black race, immobilisation, obesity, concomitant diseases, and previous thrombosis. Cancer-related important factors are: histology, clinical stage and primary location (the highest treatment of VTE is correlated with pancreatic, lung, ovarian, hepatic, and gastric cancer and some haematological malignancies) [10], pressure and damage of blood vessel by bulky mass, and production and release of pro-coagulation factors and cytokines by cancer cells (e.g. it was shown that high expression of tissue factor in cancer cells derived from totally resected tumours is connected with increased VTE risk during the postoperative period) [5]. The use of chemotherapy in anticancer treatment could increase the risk of VTE by six-fold [11]. The pathophysiology of this phenomenon is quite complicated, combining damage of endothelial cells, decreased level of natural coagulation inhibitors (C-protein, S-protein, antithrombin), and platelets activation. The drugs used in systemic therapy in cancer patients, which are related to the highest VTE risk, include: thalidomide, angiogenesis inhibitors, hormones (tamoxifen in particular), and some agents that are used for supportive care, such as granulocyte-colony stimulating factors (G-CFRs), erythropoiesis stimulating factors, and megestrol acetate [12–14]. Additionally, catheterisation of central veins could also be related to increased risk of thromboembolic complications [15]. Surgical procedures significantly increase VTE risk. Especially high risk applies to patients with positive VTE history, those having undergone general anaesthesia longer than two hours, and patients who have stayed in bed for longer than two days after operation [1]. Furthermore, radiotherapy could also increase the risk of thrombosis [16].

Currently the efficacy of antithrombotic prophylaxis in surgically treated cancer patients and in those hospitalised due to surgical treatment or medical causes is quite well documented. In these groups of patients antithrombotic prophylaxis is recommended by oncology societies and experts. Despite comparable efficacy of unfractionated heparin (UFH), low-molecular-weight heparins (LMWH), fondaparinux, and warfarin in VTE prophylaxis, most clinical trials to date have been dedicated to the analysis of LMWH activity and safety. This results from the many benefits of this class of drugs, mainly as directly compared to UFH: possibility of once daily administration of a therapeutic dose, favourable pharmacokinetic (PK) profile, and lower risk of heparin-induced thrombocytopaenia.

Prophylaxis in patients after surgical cancer treatment

Surgical treatment increases by 3–5-fold the VTE risk in cancer patients undergoing surgery due to cancer as compared to patients with other diseases, who have undergone operations. The recommendations in this group of patients assume initiation of VTE prophylaxis with LMWH before operation, and then its continuation once daily in doses according to the labels [17–19].

Antithrombotic prophylaxis should be used in all patients after surgery with high risk of VTE, provided no contraindications exist (mainly connected to high risk of bleeding complications). However, in the group of VTE intermediate-risk patients, the use of antithrombotic prophylaxis is suggested. Evaluation of threatening levels of VTE occurrence in patients during operation could be performed using one of the available scores, e.g. the Caprini score (Tab. 1), whereas the duration of prophylaxis depends on the type of resection. According to the European Society of Medical Oncology (ESMO) [and the American Society of Clinical Oncology (ASCO), American College of Clinical Pharmacy (ACCP), etc.] recommendations, in case of laparoscopic procedures, laparotomy, and thoracoscopy lasting longer than 30 minutes — LMWH should be used for at least 10 days after operation. However, in cancer patients who have undergone abdominal and pelvis minor resections prophylaxis using LMWH should be continued for up to one month after operation [18].

There is a great deal of evidence supporting this approach. Whilst they are different for particular LMWHs, the use of nadroparin is well documented. One of the first clinical trials with a separated subgroup of cancer patients was the prospective, randomised study led by Encke et al. [20]. The researchers compared the efficacy of nadroparin with UFH in prophylaxis of DVT in patients undergoing abdominal surgery.

Table 1. Caprini DVT risk assessment score [32]

1 point	2 points	3 points	5 points
Age 41–60 years	Age 61–74 years	Age ≥ 75 years	Experienced a stroke (< 1 month)
Minor surgery	Arthroscopic surgery	History of deep vein thrombosis or pulmonary embolism	Planned (elective) alloplastic surgery of joint
BMI > 25 kg/m^2	Major open surgery (> 45 min)	Family history of history of deep vein thrombosis or pulmonary embolism	Pelvis, thigh, or shin bone fracture
Swollen legs (peripheral oedema)	Laparoscopic surgery (> 45 min)	V Leiden factor	Severe spinal cord injury (< 1 month)
Varicose veins	Malignant disease	G20210A prothrombin gene mutation	
Pregnancy or post-delivery period	Confined to bed (> 72 hours)	Lupus anticoagulant	
History of unexplained or repeated stillborn	Non-removable plaster cast that has kept from moving	Anticardiolipin antibodies	
Oral contraception or hormonal replacement therapy	Central venous access	Anti-β_2-GPI antibodies	
Sepsis (< 1 month)		Elevated serum level of homocysteine	
Serious lung disease, including pneumonia (< 1 month)		Heparin inducted thrombocytopaenia (HIT)	
Lung dysfunction		Other congenital or acquired thrombophilia	
Acute myocardial infarction			
Exacerbation or diagnosis of heart failure (< 1 month)			
History of inflammatory bowel disease			
Conservative treatment, on bed rest			

0 point — very low risk; 1–2 points — low risk; 3–4 points — intermediate risk; ≥ 5 points — high risk

The prevalence of thrombosis in 694 cancer patients (among a total of 1896 included patients) was lower in the group receiving nadroparin as compared to UFH, and there was no difference in the treatment-related bleeding complications [20]. In turn, in another clinical trial Pezzuoli et al. [21] compared use of nadroparin with placebo in antithrombotic prophylaxis in a group of 4498 surgically treated patients (among which 1507 were operated due to cancer). The risk of death was lower in the group of patients treated with nadroparin, according to general mortality as well as deaths specifically related to thromboembolic complications [21]. Simonneau et al. [22] performed a clinical trial evaluating the influence of antithrombotic prophylaxis on the frequency of thromboembolic complications in cancer patients upon surgical treatment. The efficacy and safety of nadroparin in the dose of 0.3 mL (2850 IU) were analysed comparing to enoxaparin in the dose of 0.4 mL (40 mg) in thrombosis prevention in a group of nearly 1300 patients with colon cancer undergoing surgical treatment with curative intent. Interestingly, the use of nadroparin in this study was correlated with a significantly lower number of bleeding complications. Furthermore, symptomatic VTE was rarer in the group of patients receiving nadroparin [22]. Meta-analysis of 51 clinical trials comparing LMWH (including five with nadroparin) and UFH in operated patients indicated that LMWH as a class are at least as effective as UFH in VTE prophylaxis. However, nadroparin was the only LMWH with higher efficacy in prophylaxis of asymptomatic and overt VTE than

Table 2. Venous thromboembolism (VTE) risk assessment model in hospitalised patients (Padua Prediction Score)

Active malignant neoplasm (patients with metastatic regional lymph nodes or distant metastases receiving chemotherapy or radiotherapy within last 6 months	3 points
History of VTE (despite superficial vein thrombosis)	3 points
Immobilisation (expected need of staying in bed [with possibility of bath/toilet use] due to patient's incapacity or physician recommendation for ≥ 3 days)	3 points
Diagnosis of thrombophilia (antithrombin deficiency, protein C or S deficiency, V Leiden factor, G20210A prothrombin gene mutation, or antiphospholipid syndrome)	3 points
Recent (≤ 1 month) trauma or surgical procedure	2 points
Age ≥ 70 years	1 point
Heart failure or respiratory failure	1 point
Recent myocardial infarction or ischemic stroke	1 point
Severe infection or rheumatologic disease	1 point
Obesity (BMI ≥ 30 kg/m^2)	1 point
Hormonal treatment	1 point

Sum of ≥ 4 points — high risk of venous thromboembolism (VTE); sum of < 4 points — low risk of VTE

UFH [23]. The dose of nadroparin in this indication was precisely established in a study led by Azorin et al. [24], in which surgically treated lung cancer patients were randomly assigned to one of two therapeutic groups. In the first arm antithrombotic prophylaxis was used with nadroparin in the stable dose of 0.3 mL (2850 IU), whilst in the second arm the dose was adjusted to body weight [in patients under 70 kg — 0.4 mL (3800 IU), and in patients over 70 kg — 0.6 mL (5700 IU)]. Based on the results the 0.3 mL dose of nadroparin is characterised by the best benefit:risk ratio according to the complications risk; therefore, this is the recommended dose in antithrombotic prophylaxis in surgically treated cancer patients [24].

Prophylaxis in cancer patients with systemic treatment

According to the ESMO (and the ASCO and ACCP) recommendations in cancer patients hospitalised due to medical causes, especially from emergencies, as well as in patients in general bad health status, staying in bed for the majority of time, primary VTE prophylaxis should be used. To asses VTE risk in hospitalised patients, use of the Padua Prediction Score could be helpful (Tab. 2) [25]. Of note, the majority of cancer patients assessed based on this score would be classified to a high-risk group, which should be a premise for the introduction of prophylaxis in the majority of patients. Additionally, patient immobilisation supports this approach, and some systemically treated patients significantly reduce physical activity due to weakness after chemotherapy, cancer fatigue syndrome, nausea, etc. It should also be remembered that the International Society of Thrombosis and Haemostasis (ISTH) does not recommend VTE prophylaxis in patients hospitalised for a short period just for chemotherapy infusion [25, 26].

The use of antithrombotic prophylaxis in cancer patients with systemic therapy depends on many factors (among them — histology, stage, type, and aim of treatment). Routine prophylaxis in patients during palliative chemotherapy in the outpatient setting is not recommended. It could be considered in some patients with high thrombosis risk, e.g. in patients with pancreatic or non-small cell lung cancer. To assess the risk of thromboembolic complications in this group of patients the validated Khorana model could be used, including clinical and laboratory variables, which is presented in Table 3 [27]. The grading expressed in the number of points in this model reflects the probability of VTE occurrence. This model was supplemented by Austrian researchers with two additional laboratory parameters: D-dimer concentration and P-selectin concentration, which significantly increased sensitivity and specificity of this scale [28].

A clinical study made by Klerk et al. [29] provided some new data regarding the usefulness of nadroparin in cancer patients with conservative treatment. This study assessed the influence of nadroparin on overall survival in systematically (but not surgically) treated cancer patients. Nadroparin was used in the group of 148 patients for a total of six weeks and compared with a control group of 154 patients receiving placebo. Mortality dropped at 12 and 24 months by 12% and 10%, respectively, and median of overall survival was also increased by approximately 1.5 months (6.6 *vs*. 8 months, respectively). The effects of nadroparin use were more enhanced in patients with life expectancy of more than six months (15.4 *vs*. 9.4 months). However, there were no differences regarding others bleeding rates [29].

Table 3. Risk assessment score of VTE occurrence in cancer patients treated with chemotherapy in an outpatient setting

Parameters assessed:
— primary site of cancer (stomach, pancreas, brain — 2 points; lung, lymphoma, reproductive system, bladder, testicle, kidney — 1 point)
— PLT ≥ 350 × 10^9/L — 1 point
— haemoglobin concentration < 100 g/L and/or use of EPO — 1 point
— LEU > 11 × 10^9/L — 1 point
— BMI ≥ 35 kg/m^2 — 1 point
Low-risk category (0 risk factors) — risk of thromboembolic complications < 1%
Intermediate-risk category (1–2) — risk of thromboembolic complications app. 2%
High-risk category (≥ 3) — risk of thromboembolic complications app. 7%

Table 4. Clinical trials assessing nadroparin at the dose of 2850 IU 1 × daily in the prevention of thromboembolic complications in cancer patients (adapted from [43])

Study	Study population	% of cancer patients	Comparator
Azorin et al.	Operated on due to lung cancer (n = 150)	100%	Nadroparin at the dose of 3.800 IU in patients weight ≤ 70 kg or at the dose of 5.700 IU in patients weight > 70 kg
Boncinelli et al.	Underwent urological surgery (n = 50)	100%	UFH 5000 U 3/day
Bounameaux et al.	Underwent abdominal surgery (n = 194)	47.4%	Dalteparin 2500 IU 1/day
European Fraxiparin Study	Underwent abdominal surgery (n = 1.896)	36.6%	UFH 5000 U 3/day
Harenberg et al.	Bedridden patients (n = 1 590)	7.5%	UFH 5000 U 3/day
Marassi et al.	Underwent abdominal surgery (n = 61)	100%	No treatment
Mismetti et al.	Patients with malignant neoplasms and central venous access (n = 59)	100%	Warfarin 1 mg 1/day
Niers et al.	Patients with haematological malignancies and central venous access (n = 113)	100%	Placebo
Nurmohamed et al.*	Underwent neurological surgery (n = 485)	82.5%	Compression stockings
Pezzuoli et al.	Underwent surgery (n = 4 498)	33.5%	Placebo
Simonneau et al.	Operated on due to colorectal cancer(n = 1 288)	100%	Enoxaparin 40 mg 1/day
Weber et al.**	Cancer patients with palliative care (n = 20)	100%	No treatment

*Despite nadroparin compression stockings were used as well; **in patients weighted over 70 kg nadroparin was used at the dose of 3800 IU; UFH — unfractionated heparin

The PROTECHT study [30] also provided very interesting data. This placebo-controlled trial assessed the prophylactic effect of nadroparin 0.4 mL (3800 IU) on thromboembolic complications in cancer patients exposed to chemotherapy. A total of 1166 patients were included — they were exposed to palliative chemotherapy due to lung, GI, breast, ovarian, or head and neck cancer. The PROTECHT study indicated that in this group of patients prophylactically used nadroparin decreased the prevalence of thromboembolic episodes (2% *vs.* 3.9%); additionnally there was no increase in bleeding rate [30]. Furthermore, the results obtained in this study were stratified by VTE risk according to the Khorana model [31]. This analysis showed that introduction of primary prophylaxis with nadroparin in the group of VTE high-risk patients gives a decrease in the number of thromboembolic complications by 62%. It is important to note that appropriate patient selection to nadroparin prophylaxis based on Khorana score allows limitation of the number of needed-to-treat (NNT) patients from 50 to 15 [31].

The presence of a central catheter in central veins or venous access port in cancer patient can be of concern in terms of indications to primary antithrombotic prophylaxis. Different types of catheters, ports, and

Table 5. Studies assessing nadroparin in the treatment of thromboembolic complications in cancer patients (adapted from [43])

Study	Thromboembolic event Number of patients included	% of patients with cancer	Nadroparin dose	Comparator
Charbonnier et al.	Proximal deep vein thrombosis n = 651	14%	Double dose estimated per body weight 1/day	Nadroparin at the dose estimated per body weight 2/day
Koopman et al.	Proximal deep vein thrombosis (outpatient treatment) n = 400	17.5%	Due dose estimated per body weight 2/day	UFH — dose adjusted according to APTT
Lopaciuk et al.	Proximal deep vein thrombosis (extension therapy) n = 193	6.2%	Dose estimated per body weight 1/day	Acenocoumarol — dose adjusted according to INR for 6 months
Lopez-Beret et al.	Proximal deep vein thrombosis (extension therapy) n = 158	22.2%	Dose estimated per body weight 2/day for 3 months ± dose estimated per body weight 1/day	Acenocoumarol — dose adjusted according to INR for 3–6 months
Prandoni et al.	Proximal deep vein thrombosis n = 170	19.4%	Dose estimated per body weight 2/day for 3 subsequent months	Intravenous UFH — dose adjusted according to APTT
Prandoni et al.	Venous thromboembolism n = 720	21.7%	Dose estimated per body weight 2/day	Subcutaneous UFH — dose adjusted according to APTT

APTT — activated partial thromboplastin time; UFH — unfractionated heparin; INR — international normalized ratio

Table 6. Studies assessing influence of nadroparin on OS and TTP in cancer patients in comparison to placebo or no treatment (adapted from [43])

Study	Type of cancer Number of patients included	Nadroparin dose
Icli et al.*, ##	Pancreatic cancer n = 69	0.3 mL (2850 IU) 1/day for 8 days every 3 weeks (average 6 cycles)
INPACT*, ##	Pancreatic, lung or prostate cancer n = 500	Therapeutic doses for 2 weeks, followed by 1/2 dose for 4 weeks After 4 weeks break — 2-weeks of therapeutic doses, 6 cycles
Klerk et al.*, #	Various n = 302	0.4 mL (3800 IU) < 50 kg 0.6 mL (5700 IU) 50–70 kg 0.8 mL (7600 IU) > 70 kg 2/day for 2 weeks, followed by 1/day for 4 weeks
NVALT-8b**, ##	Non-small-cell lung cancer after surgery with high risk of recurrence n = 600	Starting 4–6 weeks after surgery: therapeutic dose for 2 weeks, followed by half of therapeutic dose for 14 weeks

*Assessed OS; **assessed TTP
Comparator: #placebo, ##no treatment

central vein devices are more frequently used during systemic treatment. Despite the fact that such equipment increases the patient's predisposition to thrombosis in upper extremity veins, routine VTE prophylaxis is not recommended [32]. The management should be individualised, depending on additional VTE risk factors. Interestingly, the prevalence of VTE in connected with the localisation of the catheter and is lowest when it is placed in the right jugular vein.

Initial, long-term, and chronic treatment of VTE in cancer patients

Treatment of VTE in cancer patients significantly differs from the management in patients without malignancy. Primarily it should be considered that thrombosis prevalence in cancer patients is 2–5-fold higher, and additionally bleeding complications are 2–6-fold more frequent [4]. Use of LMWH is a method of choice in

cancer patients with normal renal function during the initial phase of thrombosis treatment as well as in prolonged treatment. This approach is recommended by various scientific societies as well as by experts. There were no differences according VTE recurrence rate and bleeding rate in analysis comparing the efficacy and safety of UFH and LMWH during initial treatment of VTE episodes; however, a trend was observed in favour of LMWH according to a decreased mortality [33]. Additionally, LMWH was compared with vitamin K antagonists (VKA) in prolonged treatment and it was revealed that relapse and bleeding rates were lower in patients treated with LMWH, whilst there was no difference in mortality rate between the groups [34–36]. The possibility of using oral anticoagulants in cancer patients also is limited by numerous drug-drug and drug-food interactions in this group of agents. Therapy with VKAs requires invasive monitoring of INR levels (as a standard it should be within the range 2.0–3.0). However, in cancer patients frequent and significant INR fluctuations are observed during therapy with VKAs. As a result, these patients may experience increased risk of bleeding complications (INR over 3.0 — excessive anticoagulation), but increased thrombosis risk may exist (INR below 2.0 — insufficient anticoagulation).

Prandoni et al. [37] compared use of nadroparin and UNF according to aPTT level in the treatment of phlebography-confirmed DVT. Risk of death in cancer patients, comprising nearly 20% of all eligible patients, was significantly reduced at six months (44% *vs*. 7%). Of note, in patients without cancer such differences were not observed [37]. Results of meta-analysis of 13 clinical trials comparing LMWH with UFH used in VTE treatment (Dolovich et al. [38]) confirmed the efficacy of LMWH as a class and additionally indicated the differences in safety profile between LMWH and UFH in favour of the former, and also between particular LMWHs — e.g. major bleeds were the most uncommon in nadroparin-treated patients [38].

According to ESMO recommendations, the use of LMWH administered for four weeks in full therapeutic dose and thereafter in a maintenance dose amounting to approximately 75–90% of starting dose is a standard of care in the treatment of TE in cancer patients [39], but the ASCO and ACCP recommend prolonged treatment without indicating a specific dose of drug.

The first three months is known as active VTE treatment, and its follow-up, aimed at reducing the risk of late thrombosis recurrence, is defined as prolonged therapy. The duration of this treatment phase is individualised, but it should last the entire time during which the risk factors of thrombosis recurrence sustain. It could lead in practice to the need for continuous treatment until cancer cure, and in uncommon cases even until terminal phase of disease. It should be also highlighted that not all LMWHs bring benefits in this indication. A study evaluating the efficacy of enoxaparin in maintenance treatment did not indicate any lowering of thrombosis recurrence risk in cancer patients [40].

Lopez-Beret et al. [41] compared nadroparin with oral anticoagulants (acenocoumarol administered based on INR monitoring) in prolonged VTE treatment (cancer patients comprised 22% of included patients). There were no differences according to the prevalence of thromboembolism episodes, bleeding complications, and deaths. However, an increased rate of recanalisation of blood vessels with thrombosis was noticed, as well as a lower number of late valvular insufficiencies in penetrating veins in patients treated with nadroparin [41].

The requirement of daily subcutaneous injections with concomitant pain could discourage patients from being compliant during treatment with heparins. Billon et al. [42] assessed in healthy volunteers local soreness connected to subcutaneous injections of enoxaparin and nadroparin. Self-assessed soreness was significantly lower in individuals taking nadroparin [42].

It should also be remembered that LMWHs are excreted by kidneys — in patients with severe renal impairment (estimated creatinine clearance below 30 mL/minute) the half-life of LMWH is prolonged and dose verification (based on anti-Xa activity) or the use of UFH is required.

Summary

Thromboembolic complications significantly worsens the prognosis in cancer patients. The treatment of VTE in this group of patients is uncommonly challenging. Antithrombotic prophylaxis is currently being used in a significant proportion of cancer patients, and its introduction depends among others on treatment modality (surgical vs. conservative). LMWHs remain a group of drugs recommended for use in VTE prophylaxis in cancer patients as well as for treatment of thrombotic episodes. Nadroparin has proven efficacy and a favourable safety profile in cancer patients (Tabs. 4–6) [43]. It is included in the recommendations of different scientific societies as the only LMWH recommended for prophylaxis as well as treatment of thromboembolic complications in cancer patients.

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