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A fresh perspective on anticoagulant therapy in patients with cancer in the era of NOAC

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Abstract

Cancer is a condition associated with hypercoagulability requiring anticoagulant therapy. In recent years, oncological patients have been given heparin and vitamin K antagonists. Nowadays, non-vitamin K antagonist oral anticoagulants (NOAC) are becoming increasingly widely used. Based on the current state of knowledge, NOAC drugs can be used in anticoagulant treatment of cancer patients with caution, *i.e.* after assessing the bleeding risk and a risk-benefit analysis of anticoagulant therapy, as well as of the drug interactions between oncological drugs and the NOAC group.

Key words: cancer, anticoagulant treatment, non-vitamin K antagonist oral anticoagulants

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Introduction

The fact that neoplastic disease is closely related to the hypercoagulable state and the risk of thrombosis was first identified in 1865 by Armand Trousseau [1, 2]. The relationship between the neoplastic process and blood coagulation is in fact mutual — cancer causes a hypercoagulation state, which is itself the main risk factor for venous thromboembolism (VTE). Venous thromboembolism can manifest itself clinically as deep vein thrombosis (DVT) of the lower limbs or as pulmonary embolism (PE). Activated platelets and coagulation factors, as well as fibrinolysis, interfere with the functioning of neoplastic cells, tumour growth, angiogenesis or metastatic processes. They are therefore involved in cancer progression.

According to Shen and Pollak [3], 1/7 hospitalised cancer patients suffers from PE, and 60% of all hospitalised patients who die due to massive PE have local cancer or limited metastases [3]. Recurrent idiopathic VTE is considered to be an early sign of cancer — it can reveal a tumour in 10–25% of cases. The risk of cancer increases ten-fold after a recurrent idiopathic VTE episode [4–7]. Metastases increase by 3.2 times the risk of VTE. The VTE risk increases even more with metastases of aggressive types of cancer (*e.g.* pancreatic cancer). Cancer doubles the risk of postoperative DVT manifestation, and triples the risk of postoperative PE-related mortality [8].

Until now, the standard VTE therapy has included initial treatment with low-molecular weight heparins (LMWH), unfractionated heparin (UFH) or fondaparinux for at least five days, followed by secondary prevention with vitamin K antagonists (VKA) — acenocoumarol or warfarin. Recently, much attention has been paid to non-vitamin K antagonist oral anticoagulants (NOAC). These are homogeneous medications aimed at selected blood coagulation factors. Rivaroxaban, apixaban and edoxaban are targeted against factor Xa, while dabigatran is a direct thrombin inhibitor. The unquestionable advantages of using these preparations include the fact that there is no need for injections and regular dose adjustments to the monitored laboratory result of the international normalised ratio (INR).

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Table 1. Final event concerning effectiveness, 12-month observation (source [9])

Study	Active neoplasm	NOAC		Standard therapy	
		Events [%], (N)	Total, N	Events [%], (N)	Total, N
Recurrent venous thromboembolism					
Einstein DVT [10]	Yes	3.4 (4)	118	5.6 (5)	89
	No	2.0 (32)	1,613	2.8 (46)	1,629
Einstein PE [11]	Yes	1.8 (2)	114	2.8 (3)	109
	No	2.1 (48)	2,305	1.8 (41)	2,304
RE-COVER* [12]	Yes	3.1 (2)	64	5.3 (3)	57
	No	2.3 (28)	1,209	2.0 (24)	1,209
Hokusai-VTE [13]	Yes	3.7 (4)	109	7.1 (7)	99
	No	3.1 (126)	4,009	3.5 (139)	4,023
Summary			9,541		9,619
Clinically relevant bleeding					
Einstein DVT [10]	Yes	14.4 (17)	118	15.9 (14)	88
	No	7.6 (122)	1,600	7.6 (124)	1,623
Einstein PE [11]	Yes	12.3 (14)	114	9.3 (10)	108
	No	10.2 (235)	2,298	11.5 (264)	2,297
RE-COVER* [12]	Yes	NA	NA	NA	NA
	No	NA	NA	NA	NA
Hokusai-VTE [13]	Yes	18.3 (20)	109	25 (25)	99
	No	8.2 (329)	4,009	9.9 (398)	4,023
Summary			8,248		8,338

*Events reported after six months of observation; NA — not applicable

Anticoagulant therapy in patients with neoplastic disease

Bleeding episodes and VTE recurrence in patients with oncological diseases

Numerous clinical trials have confirmed the effectiveness and safety of NOAC application, but few of these trials have involved patients with neoplastic disease. Our aim in writing this paper was to discuss the current state of knowledge regarding anticoagulant therapy in the light of the increasing use of NOAC.

Studies using NOAC and standard therapy in neoplastic disease patients are summarised in Table 1 [9–13]. Since 2013, the number of studies involving people with oncological diseases has been on the rise. A total of 19,160 patients have participated in these studies, 4% of whom (n = 759; 405 and 354 respectively in NOAC- and VKA-treated groups) had active neoplasm at the time of inclusion. The results, based on data obtained from these 759 patients with active neoplasm and VTE, revealed that the risk of VTE and bleeding was reduced in patients receiving NOAC compared to VKA (for VTE: odds ratio [OR] — 0.56, 95% confidence interval [CI] — 0.28–1.13; for bleeding: OR 0.88, 95%, CI 0.57–1.35).

Studies on CAT (cancer-associated thrombosis) using NOAC and LMWH are summarised in Table 2 [10–12, 14–23]. The CLOT (2003) and LITE (2006) studies placed LMWH in first place in terms of the treatment of VTE in neoplastic disease patients [16, 17, 24]. On the other hand, the superiority of NOAC over warfarin was proven in analysis of randomised subgroups. Although there is no evidence concerning the comparison of NOAC to LMWH, the results of the Hokusai-VTE (2017) and SELECT-D (2018) studies suggest that NOACs are no less effective than LMWH [21, 23]. In the Hokusai-VTE randomised clinical trial, the use of NOAC (edoxaban) and LMWH (dalteparin) was compared in patients with VTE. As in previous studies, this one noted a similar or greater efficacy of NOAC compared to LMWH in VTE prevention (7.9% vs. 11.3%, hazard ratio [HR] 0.71; 95% CI 0.48–1.06, p = 0.09). Meanwhile, the percentage of clinically relevant bleeding[1] was higher in the NOAC group (14.6% vs. 11.1%, HR 1.38; 95% CI 0.98–1.94). The

[1]Defined as: bleeding to vital organs: central nervous system (intracranial and subcranial), intraocular, pericardial, extraperitoneal, intra-articular and intramuscular with compartment syndrome; clinical manifestation of bleeding with at least 2 g/dL drop in haemoglobin; requiring surgical intervention; requiring intravenous administration of pressure agents, hospitalisation or increased medical surveillance; immediate medical intervention

Table 2. List of studies on venous thromboembolism (VTE) in patients with oncological disease (modified according to [14])

Study	Year of publication	Recurrence of VTE [%]			Clinically relevant bleeding [%]		
		VKA	LMWH	NOAC	VKA	LMWH	NOAC
CATHENOX [15]	2002	6.7			16		
CLOT [16]	2003	15.8	2.8		3.6	7	
LITE [17]	2006		6.9			6.5	
EINSTEIN (PE + DVT) [10, 11]	2013	3.9		3.7	3.9		2.3
RE-COVER (I, II) [12, 18]	2013	5.3		2.3	5.3		2.1
CATCH [19]	2015	10.5	7.2		2.4	2.1	
Hokusai-VTE 2015 [20]	2015	7.1		3.1	3		7.8
Hokusai-VTE 2017 [21]	2017			7.9			6.9
CASTA-DIVA [22]	2018		11.3			4	
SELECT-D [23]	2018		11	4		4	13

VKA — vitamin K antagonists; LMWH — low-molecular weight heparins; NOAC — non-vitamin K antagonist oral anticoagulants; PE — pulmonary embolism; DVT — deep vein thrombosis

Table 3. Risk factors for bleeding in anticoagulant therapy (based on [27])

Risk factors*	
Age > 75, history of bleeding, malignant neoplasm, malignant neoplasm with distant metastases, kidney failure, liver failure, thrombocytopenia, history of stroke, diabetes mellitus, anaemia, antiplatelet therapy, poor control of anticoagulant therapy, concomitant disease and reduced physical fitness, recent surgery**, frequent falls, alcohol abuse	
Number of risk factors	**Risk class**
0	Low
1	Moderate
≥ 2	High

*The increased risk for bleeding related to risk factors will depend on: 1) severity of the risk factor (*e.g.* location and number of metastases, number of platelets); 2) time since surgery or previous bleeding); and 3) efficacy of treatment for the previous cause of bleeding (*e.g.* from upper gastrointestinal tract); **important for parenteral anticoagulation (*e.g.* first ten days), but less relevant for long-term or prolonged anticoagulant therapy

SELECT-D study compared the use of rivaroxaban and dalteparin. It revealed a higher efficacy of NOAC in VTE (4% vs. 11%, HR 0.43; 95% CI 0.19–0.99). In turn, the percentage of clinically relevant bleeding was also higher in the NOAC group (13% vs. 4%, HR 3.76; 95% CI 1.63–8.69).

In February 2019, Carrier et al. [25] published a study involving 563 patients in which apixaban (2.5 mg 2 ×/d.) and placebo were compared. The risk of VTE when using apixaban has been determined at 4.2%, while in the placebo group at 10.2% (HR 0.41; 95% CI: 0.26–0.65, p < 0.001) [25]. The percentage of clinically significant bleeding was 2.1% in the group treated with apixaban and 1.1% in the group taking a placebo (HR 1.89; 95% CI: 0.39–9.24). In another clinical trial CASSINI (A Study to Evaluate the Efficacy and Safety of Rivaroxaban Venous Thromboembolism (VTE) Prophylaxis in Ambulatory Cancer Participants) Khorana et al. [26], an analysis of anticoagulant therapy in patients with oncological diseases taking NOAC or a placebo was compiled: a group of patients receiving 10 mg rivaroxaban was compared to a placebo group. The risk of VTE recurrence was lower in the NOAC group, and amounted to 5.95% compared to 8.79% (HR 0.66; 95% CI: 0.40–1.09, p = 0.101) in the group treated with rivaroxaban and placebo, respectively. The risk of bleeding, on the other hand, was lower in the placebo group: it amounted to 1.98% compared to 0.99% (HR 1.96; 95% CI: 0.59–6.49, p = 0.265).

In a subanalysis of the RECOVER and RECOVER II studies on patients with cancer and DVT, in the subgroup of patients with DVT and PE with active neoplastic disease treated with dabigatran 150 mg twice a day after an initial heparin administration, it was recorded that the efficacy and the safety in the group of patients receiving dabigatran 150 mg twice a day compared to warfarin were similar in groups of patients with and without active neoplastic disease [12, 18].

On the basis of the studies conducted so far, we believe that NOAC medications can be used in anticoagulant therapy of patients with oncological disease with caution, *i.e.* after analysis of the risk of bleeding and of the risk-benefit ratio of oncological treatment and interaction with antithrombotic medications. When selecting which NOAC, other risk factors for bleeding should also be considered (Table 3) [27].

Table 4. Hazard ratio (HR) and 95% confidence interval (CI) for development of thromboembolic complications and bleeding in first year of use of vitamin K antagonists or non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and neoplastic disease (modified according to [28])

	Thromboembolic complications HR* (95% CI)	Bleeding complications HR* (95% CI)
Time since neoplastic disease diagnosis (years)		
< 2	1.1 (0.99–1.3)	1.2 (1.0–1.4)
2–5	0.92 (0.78–1.1)	1.1 (0.93–1.3)
> 5	0.95 (0.85–1.1)	1.1 (0.95–1.2)
Type of neoplasm		
Gastrointestinal neoplasm	1.2 (0.94–1.4)	1.1 (0.85–1.4)
Lung or pleural cancer	1.5 (1.1–2.2)	2.0 (1.4–2.8)
Breast cancer	0.78 (0.61–0.99)	0.85 (0.63–1.2)
Urological cancer	1.0 (0.83–1.3)	1.7 (1.4–2.0)
Intracranial neoplasm	2.2 (0.31–16)	NA
Haematopoietic neoplasm	0.65 (0.38–1.1)	0.61 (0.33–1.1)
Other types	0.99 (0.89–1.1)	1.0 (0.89–1.2)

*Comparison of patients with and without neoplastic disease according to gender, age group and result in CHA_2DS_2-VASc; HR — hazard ratio; CI — confidence interval; N/A — not applicable

Bleeding complications and recurrence of VTE depending on time of neoplasm detection and its type

In 2017, a major study evaluated the annual follow-up of thromboembolic and bleeding complications during oral antithrombotic treatment in patients with neoplasm and atrial fibrillation (AF) [28]. In this study, patients were characterised by the presence (n = 11,855) or absence (n = 56,264) of neoplastic disease. The risk of thromboembolic complications in patients with AF who received VKA was similar, regardless of the presence of neoplastic disease (6.5% with neoplasm vs. 5.8% without neoplasm; HR 1.0; 95% CI: 0.93–1.1), similarly the risk of bleeding complications (5.4% vs. 4.2%, HR 1.1; 95% CI: 1.0–1.2 respectively). In NOAC patients, the risk of thromboembolic complications (4.9% with neoplasm vs. 5.1% without neoplasm, HR 0.80; 95% CI: 0.61–1.1) and bleeding complications (4.4% vs. 3.1%, HR 1.2; 95% CI: 0.92–1.7 respectively) was also similar regardless of the presence of the neoplastic process.

Patients with lung or pleural cancer (HR 2.0; 95% CI: 1.4–2.8) or urological cancer (HR 1.7; 95% CI: 1.4–2.0) presented an increased risk for bleeding. The results of clinical trials are summarised in Table 4.

All in all, in the presented study, the absolute risk of thromboembolic complications or bleeding was nearly the same for patients with or without neoplastic disease, regardless of antithrombotic therapy.

Coagulation parameters monitoring

Non-vitamin K antagonist oral anticoagulants require neither a determination of plasma concentration nor monitoring of coagulation parameters. During dabigatran treatment, 2–4 h after administration of the medication, in most patients activated partial thromboplastin time (APPT) (up to 50–65 s) and prothrombin time (PT) (which gives values of 1.2–1.5 when calculating INR automatically) are observed. Thrombin time is also greatly extended (often to incalculable values) and changes even with very small doses of medication. If an urgent invasive procedure is required, APTT should be determined. Values over 40 s indicate that the anticoagulant effect is maintained, but a correct result does not exclude the presence of dabigatran at low concentrations.

Specific but poorly accessible methods for laboratory monitoring of dabigatran are the modified diluted thrombin time (Hemoclot®) test and the ecarin clotting time (ETC) test, in which viper venom is the activator of prothrombin. Ecarin clotting time is 2–4 times longer in patients chronically using dabigatran 150 mg every 12 h. Both tests enable quantitative measurement of medication and are recommended for monitoring the extent of dabigatran effect.

In the event of rivaroxaban 2–4 h after administration (poorer effect after administration of apixaban), most patients experience prolongation of APTT (usually up to 50 s) and PT (which may give values > 2 when calculating the INR automatically). However, there is no correlation between

the dose of the administered medication and the degree of APTT or PT prolongation; moreover, the result is so variable that the determination of these parameters is not recommended for monitoring the effect of these drugs. Thrombin time in the group of Factor Xa inhibitors is normal. The effect of rivaroxaban and apixaban may be evaluated based on anti-Xa activity.

NOAC interactions with chemotherapeutic agents and immunosuppressants

However, if NOACs are administered to neoplastic disease patients, they are unlikely to resolve all the problems related to anticoagulant therapy. Interactions between chemotherapeutic agents and immunosuppressants with NOAC are still possible, involving known metabolic pathways. Rivaroxaban, apixaban and edoxaban are all inhibitors of Factor Xa, while dabigatran is a direct thrombin inhibitor. Due to esterase and microsomal carboxylesterase dependent biotransformation, and due to no involvement of CYP450 enzymes, dabigatran shows limited potential for interactions with medications. Medicines that inhibit the transport of P-gp glycoprotein or the CYP3A4 pathway (*e.g.* cyclosporine and tamoxifen) may increase NOAC concentration in the body. In turn, medications inducing P-gp transport or the CYP3A4 pathway may reduce NOAC concentration (*e.g.* dexamethasone, doxorubicin). Another challenge concerns patients with neoplastic disease treated for fungal infection. Azole antifungal medications (*e.g.* ketoconazole, imidazole, fluconazole, itraconazole) may result in an increased NOAC effect (because azoles are strong P-gp transport inhibitors).

Conversion of anticoagulant therapy

In the event of modification of anticoagulant therapy, in patients previously treated with VKA, NOAC medications should be administered only after reaching a specific INR value. Rivaroxaban may be introduced at an INR value of not more than 3.0, edoxaban with an INR not exceeding 2.5, and apixaban and dabigatran with an INR of not more than 2.0. Should it be necessary to replace NOAC with VKA, it is necessary to initially use medications from both groups (VKA and NOAC) for 3–5 days until an INR exceeds 2.0 (measured before the next VKA dose). Each NOAC representative may be administered immediately after the end of the permanent infusion of UFH, or up to two hours after the end of the infusion. This procedure is based on a short (c. 2 h) half-life. If the patient was previously treated with LMWH, the first dose of NOAC should be administered instead of the next predicted dose of heparin. This rule applies also in reverse: when switching between NOAC medications, the first dose of the new medication should be administered within the time limit for the next dose of the previously used medication.

Procedure in the event of bleeding in patient treated with NOAC

One adverse effect of NOAC is bleeding. However, it must be remembered that bleeding (from the nose, gastrointestinal tract, or to the central nervous system) is not necessarily related to the use of medications from this group.

Management in the event of bleeding during the application of NOAC depends largely on the intensity and site of the source of bleeding. Medications from this group should be discontinued and local action taken *i.e.* apply direct pressure or surgically secure the bleeding site in combination with symptomatic treatment. Furthermore, it is advisable to proceed with elimination of the medication. To this end, a patient should be intensively hydrated and diuresis should be maintained or renal replacement therapy implemented in life-threatening conditions. However, of the NOACs, only dabigatran may be removed during haemodialysis. If a patient took the last dose of the medication up to 2 h after the bleeding incident, then — to try to prevent absorption of NOAC from the gastrointestinal tract by limiting exposure to NOAC — the administration of activated carbon should be considered.

In life-threatening situations, the administration of activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rVIIa) should be considered [29, 30]. The recommended doses for dabigatran are: 50–100 IU/kg body weight aPCC, 90 μg/kg body weight rVIIa. If dabigatran has been overdosed, idarucizumab can be administered intravenously in two doses of 2.5 g at an interval of less than 15 minutes [31]. Idarucizumab, being a fragment of a monoclonal antibody, strongly binds to dabigatran, neutralising its anticoagulant properties. For massive bleeding and life-threatening bleeding in patients using rivaroxaban [32], apixaban or edoxaban [33], the application of rVIIa or prothrombin complex concentrate (PCC) should be considered. The recommended doses are 90 μg/kg body weight rVIIa and 50 units/kg body weight PCC. Andexanet alfa was approved by the US Food and Drug Administration (FDA) in May 2018. It is used in life-threatening situations or uncontrolled bleeding to reverse the action of Factor Xa inhibitors (FXa) — apixaban and rivaroxaban [34]. It is worth underlining that the administration of protamine sulphate, vitamin K or fresh frozen plasma during bleeding related to NOAC is ineffective.

Selected medications and their interactions with NOAC are presented in Table 5 [35].

Conclusions

Overall, the risk of VTE in neoplastic disease patients depends on the histological type of tumour, its stage, period since diagnosis, therapeutic interventions, and the co-existence of additional patient-dependent risk factors (*e.g.* obesity, concomitant diseases, other medications

Table 5. Effect of medications on concentrations of non-vitamin K antagonist oral anticoagulants (NOAC) (modified according to [35])

	Dabigatran	Rivaroxaban	Apixaban
Interaction	P-gp	P-gp	P-gp
		CYP3A4	CYP3A4
Increase of NOAC concentration in serum	Cyclosporine	Cyclosporine	Cyclosporine
	Tacrolimus	Tacrolimus	Tacrolimus
	Tamoxifen	Tamoxifen	Tamoxifen
	Lapatinib	Lapatinib	Lapatinib
	Nilotinib	Nilotinib	Nilotinib
	Sunitinib	Sunitinib	Sunitinib
		Imatinib	Imatinib
Decrease of NOAC concentration in serum	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

P-gp — P glycoprotein

increasing the risk of VTE, positive history or family history of VTE). Patients with neoplastic disease are at high risk of recurrent VTE (about 10% per year) and serious bleeding complications (about 6% per year). Although the standard treatment with the currently recommended LMWH is better than VKA, it is not well tolerated by many patients with oncological disease in the long term, and this leads to treatment discontinuation in about 20% of cases within six months. According to the latest data obtained from randomised controlled trials, NOAC seems to be a safe and effective treatment alternative for many patients with neoplastic disease. Meta-analyses indicate that in the group of oncological patients, NOACs are more effective than LMWH [21, 23], although they can cause a greater number of clinically relevant bleedings (13% vs. 4%), especially from the gastrointestinal tract. When choosing NOAC, other risk factors for bleeding should undoubtedly also be considered.

Conflict(s) of interest

The authors declare no conflict of interest.

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