Novel oral anticoagulants in the treatment of cancer patients

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ABSTRACT

Cancer and its treatment are well-recognized risk factors for venous thromboembolism. The risk of thrombotic complications increases 4–7-fold in cancer patients and coexistence of both pathologies is associated with shorter survival. Incidence of thrombosis depends on the tumour type, antineoplastic and supportive therapy, and patient-related factors such as age, physical activity and comorbidities. Current recommendations of scientific societies indicate a dominant role of low molecular weight heparins in the treatment and prevention of venous thromboembolism in cancer patients. Long duration of the anticoagulant effect, and the subcutaneous administration route of heparins call for a safer therapeutic option, and one that would be more convenient for the patient. New oral anticoagulants: dabigatran, rivaroxaban, and apixaban, are indicated as prevention of venous thromboembolism following an orthopaedic surgery, and as stroke prevention in nonvalvular atrial fibrillation, with rivaroxaban also applied in the treatment of acute deep vein thrombosis and pulmonary embolism. In the trials evaluating the efficacy of novel oral anticoagulants, they have been compared with enoxaparin or vitamin K antagonists. Cancer patients accounted for a small percentage of the trial population, and they were rarely analysed in subgroup analysis. It was only in the phase II ADVOCATE study that the target group were patients receiving chemotherapy. Direct comparison between test drug and low molecular weight heparins was not performed. The currently available study results do not allow us to recommend the new oral anticoagulants for the treatment and prevention of venous thromboembolism associated with cancer.

KEY WORDS: novel anticoagulants, venous thromboembolism, cancer

INTRODUCTION

Venous thromboembolism (VTE) constitutes a significant problem in oncological patients suffering from malignant neoplasms. In that population the risk of thromboembolic complications is very high, and an idiopathic VTE episode frequently precedes cancer diagnosis. So far, an indisputable role of heparins, mainly the low molecular weight ones (LMWH), has been established beyond doubt in the prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in cancer patients. Over the recent years, novel anticoagulants have been included in clinical practice. The scope of their indications for use is continuously growing. The present paper offers an analysis of the published results of studies focusing on the application of new oral anticoagulants, and on the part they play in cancer patients.

VTE EPIDEMIOLOGY

In oncological patients the risk of thrombotic complications is 4–7-fold higher than in the general population [1]. It is estimated that 20–30% of new thrombotic episodes are associated with malignant tumours [2], and patients with idiopathic venous thromboembolism face a 2–4-fold higher risk of cancer diagnosis within the first year from the occurrence of VTE. Coexistence of the two pathologies is linked to three-fold shorter survival in comparison with the patients suffering from cancer alone, without thrombosis [3]. VTE is the second cause of death of oncological patients, following the neoplastic disease itself [4].

The risk of thromboembolic complications in cancer depends on tumour-related, patient-related, and treatment-related factors [5, 6]. The highest-risk cancers are believed to be the following: pancreatic cancer, lung cancer, ovarian cancer, central nervous system cancers, and hematopoietic cancers. It applies in particular to patients with advanced and highly malignant disease [5, 7].

The following factors predispose to venous thromboembolism: age over 65, immobilization, history of VTE, and concomitant diseases such as obesity, infections, anaemia, kidney and lung diseases, congenital thrombophilia, and thrombocythaemia [2, 8]. Moreover, nearly any type of cancer treatment substantially increases the risk of thrombosis. Those operated on for oncological reasons face the risk of twice as many thrombotic episodes within 90 days from surgery than patients with no history of cancer [9]. Treatments with proven prothrombotic effect include as follows: hormonal therapies (tamoxifene), cytostatic drugs (cisplatin, high doses of fluorouracil, mitomycin), anti-angiogenic drugs (talidomide, bevacizumab), and adjunctive treatments (granulocyte growth factors, erythropoiesis stimulating agents in combination with erythrocyte mass transfusion). The presence of central venous catheter is also conducive to thrombosis [10].

CURRENT MANAGEMENT STANDARD IN VTE

Recommendations of the European Society For Medical Oncology, American Society of Clinical Oncology, American College of Chest Physicians, as well as the *Polish Guidelines for the Prevention and Treatment of Venous Thromboembolism – 2012 Update*, all indicate the prevailing role of low molecular weight heparins in VTE treatment offered to patients with concomitant neoplastic diseases. LMW heparins are efficacious as preventive, initial (around 7 days), long-term (3 months), and chronic (beyond 3 months) treatment of VTE, and exhibit a good safety profile [11–14]. However, their subcutaneous route of delivery may lower the patients' quality of life. The drugs should also be administered with due caution in cases of renal insufficiency. The fact that they are long-acting drugs may also be problematic in oncological patients, remaining at a higher risk of bleeding, and often in need of urgent surgical intervention. Still, in case of haemorrhagic complications, an antidote can be administered in the form of protamine sulphate.

In oncological patients, requiring a series of medical procedures, both conservative and invasive alike, and subject to treatment related to their comorbidities, an ideal anticoagulant should be administered orally, at a fixed dose, and with no need for monitoring the anticoagulation effect. It should not interact with other drugs. It should act quickly and for a short time. Finally, it should guarantee efficacy and safety of use, as is the case of LMWH. New oral anticoagulants manifest many of those features.

NOVEL ORAL ANTICOAGULANTS

Dabigatran etexilate (Pradaxa®, Boehringer Ingelheim) [15]

Dabigatran is a direct, competitive, and reversible thrombin inhibitor. It binds with the active locus of the factor, inhibiting the formation of fibrin out of fibrinogen, as well as the fibrin-dependent platelet activation. Due to its low bioavailability, which is around 6.5%, it is administered in the form of a prodrug, etexilate, which is quickly absorbed in the intestine, and then hydrolysed to its active form by non-specific serum and liver esterases. Maximum concentration of dabigatran is observed around 2–3 hours after delivery (6 hours, if it has been administered shortly after a surgery), with its half-life amounting to 12–17 hours. Nearly 80% of it is excreted by the kidneys. Its metabolism is not associated with the P450 cytochrome complex, which prevents drug-to-drug interactions. Etexilate is transported across the intestinal wall with

the involvement of glycoprotein P, with its inhibitors (rifampicin) and activators (ketoconazole, amiodarone, verapamil) affecting the pharmacokinetics. Indications for the use of dabigatran include prevention of venous thromboembolism in patients undergoing knee joint alloplasty, and prevention of stroke in patients suffering from nonvalvular atrial fibrillation.

Rivaroxaban (Xarelto®, Bayer) [15]

Rivaroxaban is a direct inhibitor of factor Xa, catalysing the formation of thrombin. Its bioavailability upon oral administration totals 80–100%, with the peak plasma concentration reached within 2–4 hours, and its half-life fluctuating from 7 hours on average in healthy subjects to around 11 hours in persons over the age of 75. The drug is excreted in urine (66%) and faeces (33%). It is metabolized by the P450 cytochrome, and constitutes a substrate for glycoprotein P, which is why it is not recommended for simultaneous use with the inhibitors (azole antifungal drugs, HIV protease inhibitors, macrolide antibiotics) or activators (rifampicin, phenytoin, carbamazepine) of the two enzymes. As of today, the drug is indicated in VTE prevention following knee or hip joint alloplasty, stroke prevention in patients with nonvalvular atrial fibrillation, treatment of acute deep vein thrombosis and pulmonary embolism, as well as the prevention of thrombotic episodes with post-ACS atherosclerotic aetiology.

Apixaban (Eliquis®, Pfizer) [15]

As a direct inhibitor of factor Xa, apixaban suppresses the transformation of prothrombin into thrombin, blocking both the extrinsic and intrinsic pathways of the coagulation cascade. Its bioavailability is 50%, with the peak plasma concentration reached around 3 hours upon oral administration. Its half-life fluctuates from 8 to 15 hours. The drug's metabolism depends mainly on the P450 cytochrome, but its affinity with glycoprotein P is also of significance. Its activity is modified, when ketoconazole or rifampicin are administered at the same time. Kidneys are responsible for 30% of total apixaban excretion. As of today, indications for use include: VTE prevention in patients subject to knee or hip joint alloplasty, and stroke prevention in patients with nonvalvular atrial fibrillation.

REVIEW OF CLINICAL TRIALS INVOLVING THE USE OF ORAL ANTICOAGULANTS

VTE prevention in hospitalized patients

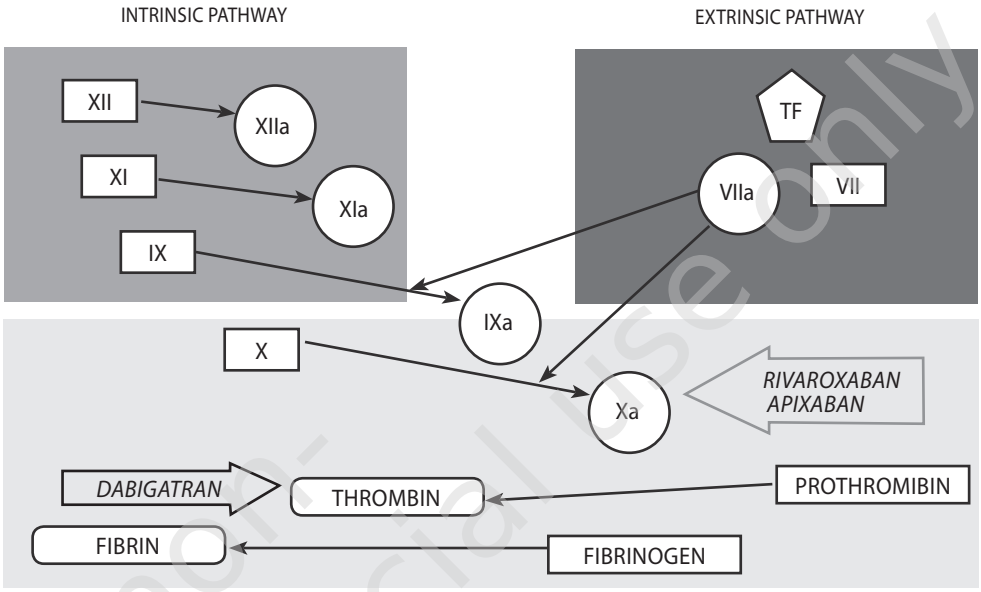
The MAGELLAN study [16] compared the efficacy of rivaroxaban (administered for 35 days) and enoxaparin (10 days) with placebo (continuation of treatment until day 35) in primary VTE prevention in patients hospitalized due to acute internal medicine conditions, requiring immobilization. 8101 subjects were included in the study, suffering from NYHA III–IV heart failure, ischaemic stroke, and infectious diseases, among other conditions. 592 (7.3%) of them had active cancer, and 1378 (17%) of them had a history of neoplastic disease. Short-term prevention with rivaroxaban turned out to be just as good as the one with enoxaparin, while extended prevention with rivaroxaban was better than the combination of enoxaparin and placebo. However, the nonsignificant trend observed in the active cancer subgroup was towards lower efficacy of the extended rivaroxaban-based prevention as compared with the 10-day enoxaparin. VTE was reported to occur in 9.9% and 7.4% of subjects respectively (RR = 1.34; 95% CI: 0.71–2.54), with the risk of bleeding amounting to 5.4% and 1.7% respectively (RR = 3.16; 95% CI: 1.17–8.50) [17].

In the ADOPT study [18] the efficacy of apixaban (administered for 30 days) was assessed in comparison with that of enoxaparin (6–14 days) for the prevention of primary VTE in patients hospitalized due to internal medicine conditions. 6528 subjects were randomized, with 4495 of them included for analysis, including 211 active cancer patients, and 421 study subjects with a history of neoplastic disease. Superiority of the extended prophylaxis with apixaban over short-term prophylaxis with enoxaparin was not demonstrated. Primary endpoint (death related to VTE, pulmonary embolism, symptomatic deep vein thrombosis, or asymptomatic proximal lower-extremity DVT confirmed in ultrasound) was reported in 2.71% versus 3.06% (RR for apixaban was 0.87; 95% CI: 0.62–1.23; p = 0.44). Moreover, there were more bleeding episodes in the study arm (0.47% vs 0.19%; RR = 2.58; 95% CI: 1.02–7.24; p = 0.04). Analysis of the results in the subgroup of cancer patients have not been published.

Initial and long-term VTE treatment

The RE-COVER study [19] assessed the efficacy of dabigatran as compared with warfarin in long-term VTE treatment, following several days of treatment with unfractionated heparin, low molecular weight heparin, or fondaparinux. 2539 patients were enrolled in the study, with 1274 of them in the dabigatran arm, and the remaining 1265 in the control warfarin arm. Recurrence of thrombosis resulting in death 6 months into the treatment was reported in 2.4% of subjects in the study arm, and in 2.1% of those in the warfarin group (HR = 1.10; 95% CI: 0.65–1.84). Pulmonary embolism, not related to death, occurred in 13 cases of patients treated with dabigatran, and in 7 patients on warfarin (HR = 1.85; 95% CI: 0.74–4.64). Major bleedings were reported in both arms with similar incidence (1.6% vs 1.9%; HR = 0.82; 95% CI: 0.45–1.48), but the incidence of any clinically significant haemorrhagic

FIGURE 1.
Sites of action of the new oral anticoagulants in the coagulation cascade.



events was lower in the dabigatran arm (5.6% vs 8.8%; HR = 0.63; 95% CI: 0.47–0.84; p = 0.002). 121 patients included in the study had active cancers. Within that group the relative risk of VTE recurrence was similar in both arms, i.e. both in the dabigatran and warfarin treatment arms (RR = 0.59; 95% CI: 0.10–3.43; p = 0.49). There is no available data on the risk of bleeding in oncological patients.

In a similar design study of RE-COVER II [19] it was proven that long-term treatment with dabigatran is not inferior to the one based on warfarin. The data on subgroup analysis, including oncological patients, have not been published to date.

In the EINSTEIN-DVT trial [20] rivaroxaban monotherapy was compared to standard sequential treatment (enoxaparin, vitamin K antagonist) in months 3, 6 and 12 of acute symptomatic DVT treatment. 3449 patients were randomized to participate in the study, including 207 (6%) subjects with active neoplastic disease. The study demonstrated that the experimental treatment was not inferior to the standard regime in terms of efficacious prevention of recurrent VTE (2.1% vs 3%; HR = 0.68; 95% CI: 0.44–1.04; p < 0.001), as well as its safety. Clinically significant bleeding occurred 8.1% of patients in both arms. The results obtained in the oncological patient group were no different than in the rest of the study population.

4833 subjects were enrolled in a similar study, EINSTEIN-PE [21], devoted to the treatment of acute symptomatic pulmonary embolism. 223 (4.6%) of them had active neoplastic disease at the time. The study demonstrated that the efficacy of rivaroxaban was non-inferior to the therapy with enoxaparin and a vitamin K antagonist, with the risk of major bleeding lower in the experimental arm. In case of oncological patients, a similar incidence of thrombotic episodes was observed in both arms (1.8% vs 2.8%), and a similar percentage of clinically significant bleedings (12.3% vs 9.3%).

The AMPLIFY study [22], involving 5395 subjects, assessed the efficacy of 6-month apixaban monotherapy of acute VTE in comparison with enoxaparin followed by warfarin. Apixaban monotherapy was shown to be non-inferior to standard treatment, and additionally associated with fewer haemorrhagic complications.

Extended VTE treatment

The RE-MEDY study [23] involved 2856 patients whose treatment was continued with dabigatran or warfarin after 3–12 months of standard anticoagulant therapy for acute VTE. It was demonstrated that extended-use dabigatran was non-inferior to warfarin in terms of the number of recurrent thrombotic events. In the dabigatran arm there were fewer clinically significant haemorrhagic episodes, with more acute coronary events at the same time. Patients with active neoplastic disease constituted 4.2% of those included in the study (119 subjects). In that study subgroup,

recurrence of thrombosis was observed in 3.3% of patients treated with dabigatran, and in 1.7% of patients on warfarin.

The EINSTEIN-extension study [20] assessed the efficacy of extended rivaroxaban treatment as compared with placebo in patients who have completed a 6–12-month anticoagulant therapy of VTE. 1197 patients were included in the study, out of which 54 (4.5%) suffered from a concomitant neoplastic disease. Rivaroxaban was shown to be more efficacious than placebo in preventing recurrent VTE events (1.3% vs 7.1%; HR = 0.18; 95% CI: 0.09–0.39; $p < 0.001$), and to cause clinically significant bleedings more frequently (6% vs 1.2%; HR = 5.19; 95% CI: 2.3–11.7). The results obtained in the subgroup of oncological patients have not been published.

The AMPLIFY-EXT trial [24] compared the efficacy of apixaban, at prophylactic and treatment dose, with that of placebo in longer-term treatment of VTE in patients who have completed a 6–12-month anticoagulant therapy. Data pertaining to 2482 study subjects were analysed. Recurrence of symptomatic thrombosis was less frequent in the case of apixaban, at either of the two doses of 5 mg and 2.5 mg, in comparison with placebo (1.7%, 1.7% and 8.8% respectively). The number of haemorrhagic episodes was similar in all of the arms (3.2%, 4.3% and 2.7% respectively). The study group comprised only 42 patients (1.7%) with active cancers. Analysis of the results from that group has not been made available.

In the RE-SONATE study [23], comparing dabigatran with placebo in extended VTE treatment, active neoplastic disease was an exclusion criterion.

Prevention during chemotherapy

The ADVOCATE randomized phase II trial [25] compared the apixaban treatment (at the 5 mg, 10 mg or 20 mg dose) with placebo as VTE prevention in patients undergoing first-line or second-line chemotherapy in an outpatient setting due to an advanced neoplastic disease. The study included 125 patients diagnosed with a solid or haematological tumour. A history of thrombosis as well as high or medium baseline risk of bleeding constituted exclusion criteria. Among the patients treated with apixaban (n = 93) no episode of VTE was observed, and there was no bleeding episode resulting in death. On the other hand, 6 cases of major or clinically significant bleedings were reported (6.4%). In the placebo group (n = 29), there were 3 VTE events (10.3%) and one major bleeding (3.4%) which did not lead to the patient's death. The study treatment was shown to be safe and well-tolerated, and the trial itself was to serve the purpose of a pilot study, when designing the phase III trial.

CONCLUSIONS

No data have been published to date which would unequivocally confirm the efficacy and safety of new oral anticoagulants in oncological patients. Apart from the small phase II ADVOCATE study, no clinical trials have been carried out that would directly compare the new drugs with the existing standard therapy (low molecular weight heparins) in that group of patients. The above mentioned results come from trials in which oncological patients constituted only a fraction of the study population, and very often were not analysed as a separate subgroup. On the basis of the ava-

TABLE 1.
Phase III clinical trials involving oncological patients.

Clinical trial	Study drug	Standard	Number of subjects	Active neoplastic disease (%)	Efficacy	Safety
MAGELLAN [16]	rivaroxaban	enoxaparin	8101	592 (7.3)	inferior	inferior
ADOPT [18]	apixaban	enoxaparin	4495	211 (4.7)	no data	no data
RE-COVER [19]	dabigatran	warfarin	2539	121 (4.8)	similar	no data
EINSTEIN-DVT [20]	rivaroxaban	enoxaparin, VKA	3449	207 (6.0)	non-inferior	non-inferior
EINSTEIN-PE [21]	rivaroxaban	enoxaparin, VKA	4833	223 (4.6)	similar	similar
AMPLIFY [22]	apixaban	enoxaparin, VKA	5395	-	-	-
RE-MEDY [23]	dabigatran	warfarin	2856	119 (4.2)	non-inferior	no data
EINSTEIN-extension [20]	rivaroxaban	placebo	1197	54 (4.5)	no data	no data
AMPLIFY-EXT [24]	apixaban	placebo	2482	42 (1.7)	no data	no data

ilable data, it appears that the efficacy and safety profiles of new oral anticoagulants administered in cancer patients is similar to those observed in the general population. Only the MAGELLAN study reported a statistically negligible superiority of enoxaparin over rivaroxaban.

To sum up, the present analysis of the available study results does not allow us to consider new oral anticoagulants, such as dabigatran, rivaroxaban, and apixaban, as recommended in the prophylaxis and treatment of venous thromboembolism associated with cancer. The view is also reflected in the ASCO recommendations, stating that the above mentioned drugs are not recommended in patients with malignant tumours. Further clinical trials with oral anticoagulants, designed specifically for that group of patients, are required in the coming future. As of the end of 2013, standard management of VTE (both treatment and prophylaxis) in oncological patients involves the administration of low molecular weight heparins.

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