RESEARCH LETTER

Reduced-dose apixaban in cancer-associated thrombosis: a single-center experience

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Introduction Venous thromboembolism (VTE) is common in patients with cancer, and it is the most frequent cause of death unrelated to cancer progression.[1] The risk of VTE in cancer patients is 6- to 12-fold higher than in the general population, and increases during chemotherapy or targeted therapy.[2] Malignancy is also associated with elevated baseline risk of major bleeding caused by thrombocytopenia, metastases, kidney and liver failure, anticancer agents, surgery, or radiotherapy.[1] Due to the increased risk of both VTE recurrence and major bleeding, the choice of specific anticoagulant treatment in cancer patients is challenging and determined by several factors, including patient condition and comorbidities, as well as the type, stage, and location of cancer.[1]

According to the current guidelines on cancer-associated thrombosis (CAT),[1] low-molecular-weight heparins (LMWHs) and full-dose non–vitamin K antagonist oral anticoagulants (NOACs), that is, rivaroxaban and apixaban, are recommended in therapy and secondary prevention, with the preference for LMWH in patients at a high bleeding risk, especially those with gastrointestinal and urinary tract cancer.[1]

To date, 2 randomized controlled trials (RCTs) assessed the safety and efficacy of apixaban vs LMWH in CAT.[3,4] The largest of them was the CARAVAGGIO trial (Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer) by Agnelli et al.[4] It included 1155 patients, 576 of whom received apixaban. The authors showed that during a 6-month follow-up, apixaban 5 mg twice daily, as compared with dalteparin, was associated with a lower rate of recurrent thromboembolic events (5.6% vs 7.9%, respectively) and a comparable risk of major bleeding (3.8% vs 4%, respectively).

The use of reduced-dose factor Xa (FXa) inhibitors following 6 months of full-dose therapy in CAT is controversial. In the 2021 European Society for Vascular Surgery[5] or American Society of Hematology guidelines,[6] there is no recommendation for using reduced-dose NOACs in these patients. However, the results of observational studies suggested that such a strategy, based on data from noncancer VTE patients, could be effective in individuals with CAT.[7] A recent small RCT, the EVE trial (Extending Venous Thromboembolism Secondary Prevention with Apixaban in Cancer Patients),[8] conducted in 360 CAT patients, demonstrated that apixaban 2.5 mg twice daily initiated after at least 6 months of the recommended treatment, as compared with the full dose, resulted in similar bleeding rates, without increasing the thrombotic risk.

We evaluated the efficacy and safety of reduced-dose apixaban in real-life CAT patients treated at a Polish tertiary center.

Patients and methods We retrospectively assessed consecutive patients with malignancy who experienced documented symptomatic VTE. They were referred to an outpatient Center for Thromboembolic Disorders at the St. John Paul II Hospital in Kraków, Poland due to persistent unacceptable minor or nonmajor bleeding or other side effects of LMWH (eg, pruritus), in order to optimize further therapy of CAT. We excluded patients with thrombocytopenia below $50 \times 10^3/\mu l$, brain metastases, and poor life expectancy based on oncologic consultations. A diagnosis of deep vein thrombosis (DVT) was established on the basis of a positive finding on color duplex sonography. Pulmonary embolism (PE) was diagnosed based on the presence of typical symptoms and positive results of computed tomography (CT) pulmonary angiography.

All patients were treated with enoxaparin at various daily doses for at least 3 months at the time of consultation. Then, apixaban 2.5 mg twice daily was administered instead of LMWH.

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The decision to administer reduced-dose apixaban was made based on patient preferences.

We recorded symptomatic DVT, PE, and thrombosis at atypical locations. New documented major bleedings and clinically relevant nonmajor bleedings defined according to the International Society on Thrombosis and Haemostasis criteria[9] were also assessed during follow-up visits and phone calls.

We collected data on the type of cancer, metastases, and the type of anticancer treatment, as well as information on noncancer risk factors and comorbidities, along with medications used. Family history was regarded positive if VTE was diagnosed in at least 1 first-degree relative.

Due to a retrospective design, the approval of a bioethical committee was not required.

Statistical analysis Statistical analysis was performed with Statistica 13 software (StatSoft, Tulsa, Oklahoma, United States) and R package v. 3.5.0 (the R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as median (interquartile range [IQR]), whereas qualitative variables are shown as numbers (percentages). Normality of distribution was assessed with the Shapiro–Wilk test.

Results As shown in TABLE 1, the final analysis included 52 CAT patients (26 women [50%]) at a median (IQR) age of 69 (64.8–72) years, mainly following isolated PE (48.1%). The most common type of cancer was colorectal cancer after resection (30.1%), followed by pancreatic (13.5%) and kidney cancer (11.5%). Twenty-eight patients (53.8%) had metastases. Chemotherapy was used in 70.1% of the participants.

Prior to switching to apixaban, 10 patients (19.2%) were on enoxaparin at therapeutic doses, 35 (67.3%) on intermediate doses (1 mg/kg once daily), and 7 (13.5%) on prophylactic doses.

During a median (IQR) follow-up of 18 (11.8–26.3) months, 2 cases of VTE (2.5%/year) were reported on apixaban, including 1 case of DVT with concomitant PE (1.3%/year) and 1 case of isolated PE (1.3%/year). The recurrent VTE episodes were observed in a 70-year-old man with chronic lymphocytic leukemia (CLL), 30 months after initiating apixaban, and in a 71-year-old woman with pancreatic cancer with concomitant diabetes and stage 3 chronic kidney disease, at the ninth month of apixaban treatment. The latter patient had a platelet count below $100 \times 10^3/\mu l$.

Two major gastrointestinal (GI) bleedings (2.5%/year) were recorded, in 65- and 73-year-old men with colorectal cancer after resection and lung cancer, at 15 and 11 months of apixaban use, respectively. The first patient had thrombocytopenia below $100 \times 10^3/\mu l$, while both had concomitant anemia and no prior bleeding. A single episode of hematuria occurred in an 82-year-old woman with CLL, who had anemia and a platelet count below $100 \times 10^3/\mu l$. None of the patients who experienced bleeding received acetylsalicylic acid or clopidogrel, and no potential drug-drug interactions were recorded. Twenty-two patients (28.2%/year) died, in no direct relation to VTE recurrence.

Discussion To our knowledge, the present case series is the first analysis of a Polish group of patients with CAT treated with apixaban 2.5 mg twice daily, and one of few reports published so far.[6-8] Herein, we provide further evidence supporting the view that reduced-dose apixaban is a safe and effective option in the long-term prevention of recurrent VTE in patients with malignancy. The risk of major bleeding observed in our group was similar to that reported in the EVE trial[8] (2.5%/year vs 2.8%/year, respectively), whereas the risk of recurrent VTE was slightly lower in the present series of patients than in the EVE group (2.5%/year vs 5%/year, respectively), despite their similar age. Of note, both cases of clinically relevant bleeding in our series occurred in patients with thrombocytopenia, which confirms an increased risk of such events in this condition, as highlighted in an expert opinion.[10]

Overall, mortality was twice as high in our group as in the EVE trial (28.2%/year vs 13.6%/year, respectively), which most likely corresponds to higher mortality in cancer patients in Poland than in high-income countries.[11]

The differences between the EVE trial and the present study in the rates of thromboembolic events and mortality may result from several reasons, including a different study design, longer follow-up (18 vs 12 months, respectively), a greater number of patients on chemotherapy (71.2% vs 59.7%, respectively), and different distribution of various types of malignancy.[12]

Despite recent advances, implementation of the appropriate dose and type of NOAC is challenging in clinical practice, not only in cancer patients but also in elderly individuals, those with liver cirrhosis, thrombophilia, or COVID-19.[2,6,12-14] It should be highlighted that in patients with CAT, especially those at elevated bleeding risk, the use of reduced-dose FXa inhibitors is more acceptable than LMWH (as reflected by frequent use of lower daily doses than those recommended in the guidelines)[2], and oral FXa inhibitors may improve compliance and possibly outcomes. Nevertheless, anticoagulant therapy in CAT should be regularly reassessed—at least every 3 to 6 months, and more often in the case of any changes in patient management or condition.[2]

The present study has several limitations. Firstly, our case series was small. A different design, for instance, a case-control or cohort study, could provide more robust results; however, our study is preliminary. Secondly, we are aware that asymptomatic thromboembolic events may have gone unnoticed. Recent data suggest that approximately 50% of all cancer-related PEs are incidental, that is, detected in an asymptomatic or symptomatic patient on diagnostic imaging performed for reasons other than suspicion of VTE.[15] Thirdly,

TABLE 1 Baseline characteristics of patients with cancer-associated thrombosis treated with reduced-dose apixaban

Parameter			All patients (n = 52)
Age, y			69 (64.5–72)
Male sex			26 (50)
Body mass index, kg/m^2			28.3 (25.5–30.5)
Current smoker			4 (7.7)
Time since VTE, mo			8 (7–10.5)
Thrombotic manifestation		PE + DVT	14 (26.9)
		Isolated PE	25 (48.1)
		DVT	13 (25)
VTE family history			8 (15.4)
Type of cancer	Colorectal after resection		16 (30.8)
	Lung		7 (13.5)
	Pancreatic		7 (13.5)
	Kidney		6 (11.5)
	Gastric after resection		4 (7.7)
	Ovarian		3 (5.8)
	Breast		3 (5.8)
	Uterine		3 (5.8)
	CLL		3 (5.8)
Metastasis			28 (53.8)
Chemotherapy			37 (71.2)
Platelet count <100 000/µl			21 (40.4)
Comorbidities	Coronary heart disease		19 (36.5)
	Hypertension		14 (26.9)
	Myocardial infarction		11 (21.2)
	Diabetes mellitus		11 (21.2)
	Renal disease		11 (21.2)
	Stroke/TIA		7 (13.5)
	Prior bleeding		4 (7.7)
	Liver injury		4 (7.7)
Medications	Acetylsalicylic acid		10 (19.2)
	Clopidogrel		1 (1.9)
	Statin		31 (59.6)
Follow-up	Duration, mo		18 (11.5–26.5)
	Recurrent VTE		2 (3.8)
	Major bleeding		2 (3.8)
	Death		22 (42.3)

Data are shown as number (percentage) or median (interquartile range).

Abbreviations: CLL, chronic lymphocytic leukemia; DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack; VTE, venous thromboembolism

we have not assessed specific anticancer treatment given the low number of clinical outcomes.

In conclusion, our study indicates that reduced-dose apixaban can be effective and safe as prophylaxis of recurrent VTE in patients with cancer. An ongoing RCT, the API-CAT trial (Extended Anticoagulant Treatment with Full- or Reduced-Dose Apixaban in Patients with Cancer-Associated Venous Thromboembolism),[16] will soon demonstrate whether apixaban 2.5 mg twice daily in CAT patients who completed 6 months of anticoagulant therapy is indeed associated with an acceptable risk of recurrent VTE and a reduced risk of bleeding, as compared with the full-dose regimen. Further real-life studies are needed to optimize anticoagulant therapy with oral anticoagulants in a heterogeneous group of CAT patients.

ARTICLE INFORMATION

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REFERENCES

1 Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood. 2021; 137: 1959-1969.

2 Carrier M, Blais N, Crowther M, et al. Treatment algorithm in cancer-associated thrombosis: updated Canadian expert consensus. Curr Oncol. 2021; 28: 5434-5451.

3 McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost. 2020; 18: 411-421.

4 Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med. 2020; 382: 1599-1607.

5 Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021; 5: 927-974.

6 Kakkos SK, Gohel M, Baekgaard N, et al. Editor's choice – European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis. Eur J Vasc Endovasc Surg. 2021; 61: 9-82.

7 Wumaier K, Li W, Cui J. New oral anticoagulants open new horizons for cancer patients with venous thromboembolism. Drug Des Devel Ther. 2022; 16: 2497-2507.

8 McBane R, Loprinzi CL, Dakhil S, et al. Extending venous thromboembolism secondary prevention with apixaban in cancer patients. The EVE trial. Paper presented at: ISTH 2023 Congress; June 24-28, 2023; Montreal, Canada.

9 Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010; 8: 202-204.

10 Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace. 2021; 23: 1612-1676.

11 OECD. EU Country Cancer Profile: Poland 2023. EU Country Cancer Profiles. OECD Publishing, Paris; 2023.

12 Weronska A, Papuga-Szela E, Broniatowska E, Undas A. Reduced-dose apixaban and dabigatran in patients with advanced liver cirrhosis and venous thromboembolism: a case series. Pol Arch Intern Med. 2021; 131: 762-765.

13 Kolanko E, Senderek T, Prokop-Staszecka A, et al. Thromboprophylaxis in hospitalized COVID-19 patients: the efficacy and safety of the approved hospital protocol. Pol Arch Intern Med. 2021; 131: 16102.

14 Araszkiewicz A, Kurzyna M, Kopeć G, et al. Pulmonary embolism response team: a multidisciplinary approach to pulmonary embolism treatment. Polish PERT Initiative Report. Kardiol Pol. 2021; 79: 1311-1319.

15 Delluc A, Wang TF. How to treat incidental pulmonary embolism in cancer patients? Recent advances. Kardiol Pol. 2021; 79: 1305-1310.

16 Mahé I, Agnelli G, Ay C, et al. Extended anticoagulant treatment with full- or reduced-dose apixaban in patients with cancer-associated venous thromboembolism: rationale and design of the API-CAT study. Thromb Haemost. 2022; 122: 646-656.