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PROPHYLAXIS WITH RIVAROXABAN OF CATHETER ASSOCIATED THROMBOSIS IN CANCER PATIENTS (CAT-RIVA TRIAL): MAIN DATA AND INTERMEDIATE RESULTS OF PROSPECTIVE MULTICENTER STUDY

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Conflict of interest
The authors declare that they have no conflicts of interest

Keywords:
central venous catheter, CVC, central venous catheter-associated thrombosis, central venous catheter-associated deep vein thrombosis, CAT, catheter-related thrombosis, CRT, culmonary embolism, PE, cancer.

Abstract

Central venous catheters (CVCs), such as the tunneled catheters and the totally implanted ports, play a major role in general medicine and oncology. Thrombosis associated with CVCs is a common complication in cancer patients. Thus, in order to more widely study the problem of catheter-associated thrombosis in cancer patients, we initiated a study for 2022-2023 within one region.

Purpose. *Evaluation of the efficacy and safety of thromboprophylaxis of catheter-associated thrombosis with rivaroxaban in cancer patients.*

Material and methods. *Prospective multicenter study, conducted since 01/05/2022 and planned to be completed by the end of 2022, on the basis of three centers. The subjects are divided into 2 groups to randomize 60 participants in each. The first group: receive DOACs (rivaroxaban) at a dosage of 20 mg per day the day before the inserting of the CVC. Second group: treatment of the underlying disease without the use of DOACs.*

Results. *None of the patients developed submassive or massive pulmonary embolism. There were no cases of CAT in the thromboprophylaxis group compared to the non-thrombotic prophylaxis group (0% vs 15.7%). The relative risk of developing CAT is 0.86, which indicates the effectiveness of thromboprophylaxis with rivaroxaban.*

Conclusion. *Our interim results show the efficacy of rivaroxaban at a dosage of 20 mg per day in cancer patients. The final results are planned to be published at the end of the study.*

Қатерлі ісікпен ауыратын науқастарда катетермен байланысты тромбоздың ривароксабанмен алдын алу (cat-riva сынағы): негізгі деректер және перспективалық көп орталықты зерттеудің алғашқы нәтижелері

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Мүдделер қақтығысы
Авторлар мүдделер қақтығысының жоқтығын мәлімдейді

Түйін сөздер:
орталық веноздық катетер, CVC катетерімен байланысты тромбоз, катетермен байланысты терең вена тромбозы, CAT, өкпе эмболиясы, ПЭ, онкология.

Аңдатпа

Люменді катетер және имплантацияланған хемопорт сияқты орталық венозды катетерлер (ОВК) жалпы медицинада және онкологияда маңызды рөл атқарады. ОВК-мен байланысты тромбоз онкологиялық науқастарда жиі кездесетін асқыну болып табылады. Осылайша, онкологиялық науқастарда катетер-тромбоз ассоциялануы (КТА) мәселесін кеңірек зерттеу үшін біз бір аймақта 2022-2023 жылдарға арналған зерттеуді бастадық.

Мақсаты. *Қатерлі ісікпен ауыратын науқастарда ривароксабанмен катетермен байланысты тромбоздың тромбопрофилактикасының тиімділігі мен қауіпсіздігін бағалау.*

Материал және әдістер. *Үш орталыққа негізделген проспективті көп орталықты зерттеу 01/05/2022 бастап жүргізілуде және оны 2022 жылдың соңына дейін аяқтау жоспарлануда. Науқастар әрқайсысы 60 адамнан 2 топқа бөлінеді. Бірінші топ: ОВК орнатудан бір күн бұрын күніне 20 мг дозада*

ПОАК (ривароксабан) қабылдайтын емделушілер. Екінші топ: ПОАК қолданбай негізгі ауруды емдеу.

Нәтижелер. *Науқастардың ешқайсысында субмассивті немесе массивті өкпе артериясының тромбоэмболиясы болмаған. Тромбопрофилактикасы жоқ топпен салыстырғанда (0% қарсы 15,7%) тромбопрофилактика тобында КТА жағдайлары байқалмады. КТА дамуының салыстырмалы қаупі 0,86 құрайды, бұл ривароксабанмен тромбопрофилактиканың тиімділігін көрсетеді.*

Қорытынды. *Біздің зерттеуіміздің аралық нәтижелері онкологиялық науқастарда тәулігіне 20 мг дозада ривароксабанның тиімділігін көрсетеді. Соңғы нәтижелерді зерттеудің аяғына дейін жариялау жоспарлануда.*

Профилактика ривароксобаном катетер-ассоциированных тромбозов у онкологических больных (исследование cat-riva): основные данные и промежуточные результаты проспективного многоцентрового исследования

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Аннотация

Центральные венозные катетеры (ЦВК), такие как просветные катетеры и имплантированные хемопорты, играют важную роль в общей медицине и онкологии. Тромбоз, ассоциированный с ЦВК, является частым осложнением у онкологических больных. Таким образом, для более широкого изучения проблемы катетер-ассоциированных тромбозов (КАТ) у онкологических больных нами было инициировано исследование на 2022-2023 годы в рамках одного региона.

Цель. *Оценка эффективности и безопасности тромбопрофилактики катетер-ассоциированных тромбозов ривароксабаном у онкологических больных.*

Материалы и методы. *Проспективное многоцентровое исследование на базе трех центров, проводитсяс 05.01.2022 г. и планируется к завершению к концу 2022 года. Испытуемых делят на 2 группы по 60 человек в каждой. Первая группа: пациенты, принимающие ПОАК (ривароксабан) в дозе 20 мг в сутки за день до установки ЦВК. Вторая группа: лечение основного заболевания без применения ПОАК.*

Результаты. *Ни у одного из пациентов не развилась субмассивная или массивная тромбоэмболия легочной артерии. Случаев КАТ в группе тромбопрофилактики не было по сравнению с группой без тромбопрофилактики (0% против 15,7%). Относительный риск развития КАТ составляет 0,86, что свидетельствует об эффективности тромбопрофилактики ривароксабаном.*

Заключение. *Промежуточные результаты нашего исследования показывают эффективность ривароксабана в дозе 20 мг в сутки у онкологических больных. Окончательные результаты планируется публиковать к концу исследования.*

Конфликт интересов
Авторы заявляют об отсутствии конфликта интересов

Ключевые слова:
центральный венозный катетер, ЦВК катетер-ассоциированный тромбоз, катетер-ассоциированный тромбоз глубоких вен, КАТ, тромбоэмболия легочных артерий, ТЭЛА, онкология

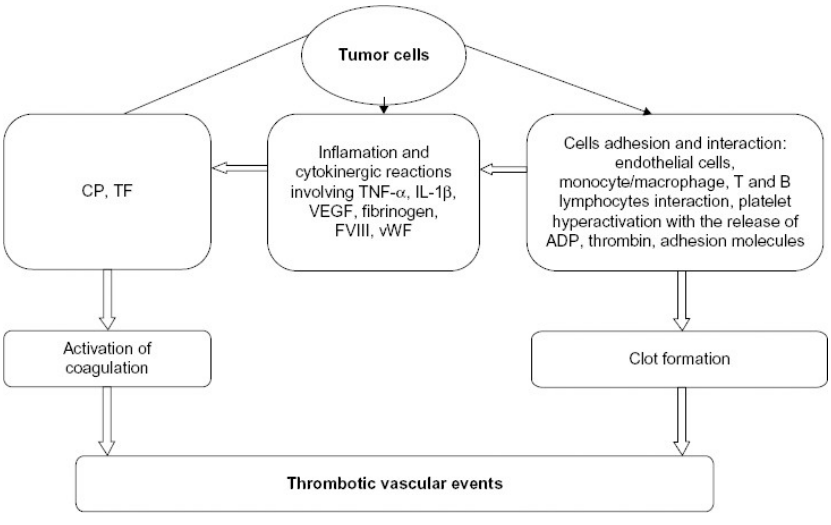
Introduction

Central venous catheters (CVCs), such as the tunneled catheters and the totally implanted ports, play a major role in genera lmedicine and oncology. Aside from the complications (pneumothorax, hemorrhage) associated with their initial insertion, all of these CVCs are associated with the long-term risks of infection and thrombosis [1].

Thrombosis associated with CVCs is a common complication in cancer patients. Most CVC thrombosis will occur within 30 days after placement, with a majority within 8 days. The incidence may depend on the type of CVC and location of the catheter tip. [2].

The pathophysiology of cancer-associated thrombosis is not entirely understood. The hypercoagulable state in cancer involves several complex interdependent mechanisms (Figure 1), including interaction among cancer cells, host cells, and the coagulation system [3]. The presence of tumor cells induces a hypercoagulable state. More recently, novel risk factors, including platelet and leukocyte counts and tissue factor (TF), are associated with high risk of venous thromboembolism (VTE), in cancer patients [12]. Furthermore, cancer-associated thrombosis is linked with poor prognosis, and it is the second leading cause of death in cancer patients [3].

Figure 1. Factors involved in cancer-associated thrombosis



Abbreviations: CP, Cancer procoagulant; TF, Tissue factor; TNF-α, Tumor necrosis factor-α; IL-1β, Interleukin-1β; VEGF, Vascular endothelial growth factor; FVIII, Factor VIII; vWF, Von Willebrand factor; ADP, Adenosine diphosphat.
Source: Karimi M, Cohan N. Cancer-Associated Thrombosis. *The Open Cardiovascular Medicine Journal* 2010;4:78–82.

Typical symptoms associated with catheter-associated thrombosis include swelling, discomfort and erythema of the involved extremity. The presence of both pain and swelling has been shown to be more predictive of a thrombus than either symptom in isolation. However, several studies examining prevalence of catheter-associated thrombosis by screening ultrasound suggest that a high percentage of patients with catheter-associated thrombosis are asymptomatic [5]. Ultrasound imaging has many advantages, including good sensitivity and specificity, low risk due to absence of radiation or contrast exposure, low cost and high accessibility [5]. Catheter-associated thrombosis (CAT) may lead to pulmonary embolism and infection, as well as catheter failure and potential delays in treatment. The vast majority of CAT are asymptomatic, thus a high index of suspicion is required in making the diagnosis. Doppler ultrasound or venography may be employed to identify CAT [6].Cancer patients have a high central venous catheter-related thrombosis risk perioperatively despite prophylactic anticoagulation. Color Doppler sonography is a rapid and noninvasive technique and it is accurate in the diagnosis of venous thrombosis. Early detection of venous thrombosis is important to prevent the systemic and fatal complication of the thrombosis [7].

Recently, the development of direct oral anticoagulants (DOACs) that directly inhibit factor Xa (eg, rivaroxaban, apixaban, or betrixaban) or thrombin (for example, dabigatran etexilate) is a milestone achievement in the prevention and treatment of VTE [8]. Despite recommendations against the use of systemic anticoagulation for prophylaxis against CVC thrombosis, a potential role continues to be explored in selected settings [8]. The risk of venous thromboembolism recurrence in patients whose central venous catheter has been pulled out and cancer is in remission appears low following anticoagulation discontinuation and after a minimum of 3 months of full/intermediate dose [9]. M. Levine et al noted about novel antithrombotic agents that can be administered orally and do not require laboratory monitoring [8].

Rivaroxaban showed promise in treating central venous catheter-related, upper extremity deep venous thrombosis (CVC-UEDVT) in cancer patients, resulting in preserved line function. However, bleeding rates and a fatal pulmonary embolism on treatment are concerning safety outcomes necessitating further study before rivaroxaban can be recommended [10]. Overall the safety and efficacy of rivaroxaban use in patients with active cancer for treatment of central venous catheters associated upper extremity deep venous thrombosis is very favorable in this single institutional cohort. Nevertheless, randomized controlled trials are needed to confirm these results [11].

Thus, in order to more widely study the problem of catheter-associated thrombosis in cancer patients, we initiated a study for 2022-2023 within one region.

Purpose

Evaluation of the efficacy and safety of thromboprophylaxis of catheter-associated thrombosis with rivaroxaban in cancer patients.

Materials and methods

Prospective multicenter study, conducted since 01/05/2022 and planned to be completed by the end of 2022, on the basis of three centers: “Private Clinic Almaty”, JSC “National Scientific Center of Surgery named after A.N. Syzganov”, “Almaty Cancer Center”. The study included patients aged 18-90 years with malignant neoplasms of the breast with inserted central venous catheter (CVC).

The subjects are divided into 2 groups to randomize 60 participants in each (Figure 2).The first group: receive DOACs (rivaroxaban) at a dosage of 20 mg per day the day before the installation of the CVC. Second group: treatment of the underlying disease without the use of DOACs.

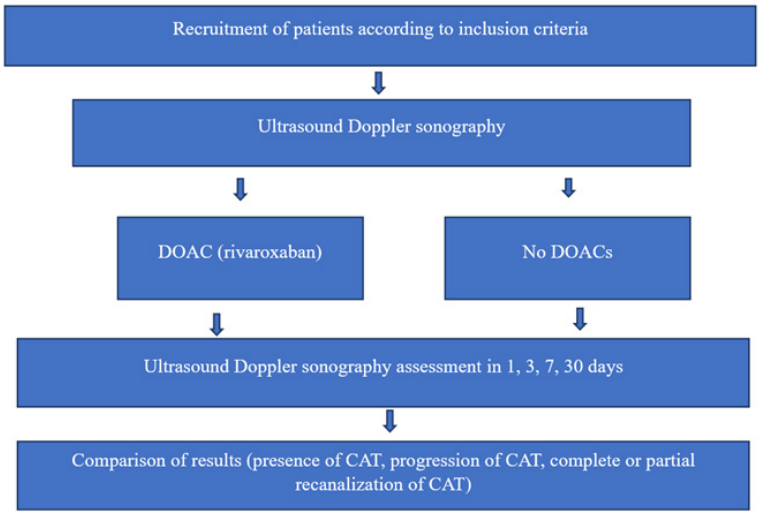


Figure 2.
Design and algorithm of the study

All subjects undergo ultrasound Doppler sonography, D-dimer and routine laboratory tests. The main exclusion criteria are: patients with severe comorbidities, previously receiving of any anticoagulants, patients with GFR<15 ml/min, patients receiving hormonal drugs, patients in the early postoperative period.

Results

During the study period, as of November 1, 2022, 38 patients were randomized, 19 patients in each group, average age 48.3 years. None of the patients developed submassive or massive pulmonary embolism. There were no cases of CAT in the thromboprophylaxis group compared to the non-thrombotic prophylaxis group (0 vs 15.7) (Figure 3, Figure 4A, 4B). The relative risk of developing CAT is 0.86, which indicates the effectiveness of thromboprophylaxis with rivaroxaban.

The risk of venous thromboembolism recurrence in patients whose central venous catheter has been pulled out and cancer is in remission appears low following anticoagulation. From the moment of detection of CAT, patients were prescribed anticoagulants (rivaroxaban) at a therapeutic dosage. In one case, a patient with total occlusion of the internal jugular and subclavian veins had edema of the upper limb for four months, partial recanalization of the thrombus (more than 50%) was recorded on the third month. None of the patients had episodes of “major” bleeding (more than 500 ml) (Table 1).

	Prophylaxis	No Prophylaxis
Number of patients	19	19
Median age	50,1 y	48,9 y
Asymptomatic CVC-associated thrombosis	0	2
Symptomatic CVC-associated thrombosis	0	1
Major bleeding	0	0
Pulmonary embolism	0	0
Posttrombotic syndrome	0	1
Death	0	0

Table 1.
Features of groups with and without thromboprophylaxis

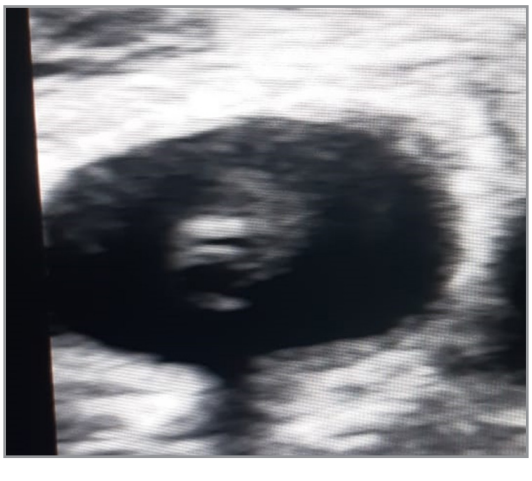
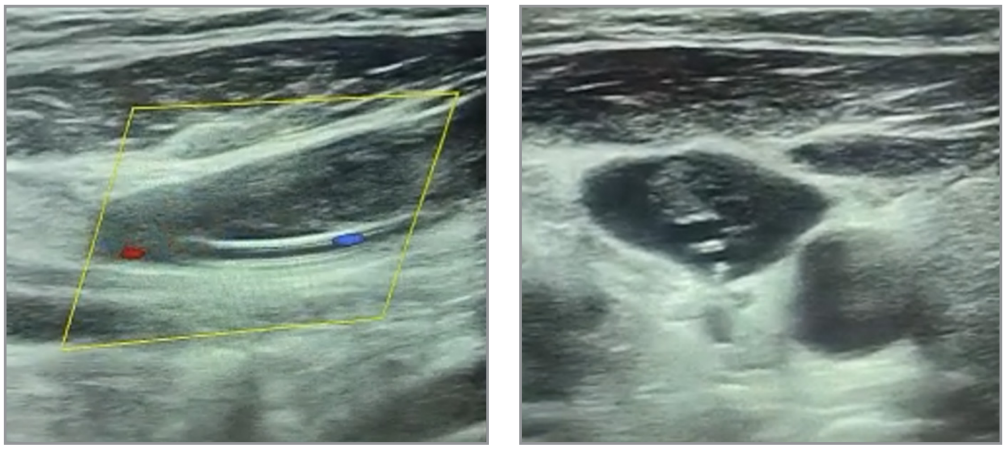


Figure 3.
Thrombosis of CVC in the group without thromboprophylaxis (3rd day)

Figure 4 A,B. Thrombosis in the internal jugular vein in the group without thromboprophylaxis (7th day)



Conclusion

Patients with active cancer are at high risk of central venous catheter-associated thrombosis risk. Our interim results show the efficacy of rivaroxaban at a dosage of 20 mg per day in this category of patients. Ultrasoud doppler sonography is a rapid and noninvasive technique and it is accurate in the diagnosis of venous thrombosis. Currently, the use of DOACs is limited to a rather narrow range of indications, so further randomized controlled trials are needed. The final results are planned to be published at the end of the study.

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