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Case Report

Single-drug approach with rivaroxaban: A case of successful anticoagulation against cancer-associated thrombosis

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ABSTRACT

We report a patient with pulmonary embolism and deep vein thrombosis induced by cancer chemotherapy who received successful anticoagulation using a single-drug approach with rivaroxaban. Cancer-associated thrombosis (CAT) is a leading cause of non-cancer death in patients with cancer, which is induced by cancer itself and/or chemotherapy agents including cisplatin and gemcitabine. By contrast, hemorrhagic state is another feature of advanced cancer. In these opposite conditions of cancer patients, CAT have to be controlled by appropriate anticoagulation. This case shows potential for single-drug approach with rivaroxaban and direct oral anticoagulants being effective and safety strategy against CAT.
<**Learning objective:** Single-drug approach of direct oral anticoagulants (DOACs) against CAT induced by cisplatin and gemcitabine showed satisfactory anticoagulation without heparin and warfarin. CAT has been important issue in oncology field, and single-drug approach of DOACs could be an effective and safety strategy for anticoagulation against CAT.>

Introduction

Close relationship between cancer and venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), has been known as Trousseau's syndrome. In the first event of VTE, 20–30% of patients with VTE are estimated to have cancer. Additionally, occurrence of VTE in patients with cancer has increased over the years due to improvement of diagnostic tests and increased awareness. Cancer cells secrete procoagulant factors and activate platelets and vascular endothelial cells to induce thrombosis [1]. On the other hand, chemotherapy is also serious cause of VTE in patients with cancer. Patients with cancer show high relative risk of VTE compared with the general population, and the risk is further increased when chemotherapy is received. Recently, thrombosis induced by cancer itself and/or cancer treatment including chemotherapy has been defined as cancer-associated thrombosis (CAT). As the prognosis of patients with cancer has improved, management of CAT has become an emerging critical issue in the clinical setting.

Low-molecular-weight heparin (LMWH) or oral vitamin K antagonists (VKAs) has been the standard treatment for VTE for more than half a century [2]. However, because patients with cancer are both hypercoagulable and in a hemorrhagic state simultaneously, the safety of anticoagulation has always been discussed. Recently, direct oral anticoagulants (DOACs) have become a new category of anticoagulants that have demonstrated effectiveness in VTE [3]. Furthermore, rivaroxaban has been reported to be safe and effective in patients with CAT following initial parenteral anticoagulation in a prospective cohort study [4], suggesting the beneficial effect of rivaroxaban in patients with CAT. However, it remains unclear whether anticoagulation initiated with rivaroxaban is effective for chemotherapy-induced CAT. Here, we report a patient with CAT induced by neoadjuvant chemotherapy who was successfully treated using a single-drug approach with rivaroxaban.

Patient information

A 76-year-old man was diagnosed as having invasive bladder cancer (pT4+isN0M0) in July 2017, and received neoadjuvant

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Table 1 Timeline.

2017	July	Patient was diagnosed as having invasive bladder cancer.
	August 15	Neoadjuvant chemotherapy (cisplatin + gemcitabine) was initiated every 3 weeks.
	August 28	Contrast-enhanced CT did not detect PE at the end of the first cycle of chemotherapy.
	October 5	Contrast-enhanced CT revealed PE at the end of the third cycle of chemotherapy.
		Ultrasonography revealed DVT in both legs. D-dimer 21.1 mg/mL, TAT 28.1 ng/mL
	October 6	Anticoagulation with rivaroxaban 15 mg twice a day was started.
	October 20	Ultrasonography showed a significant improvement of DVT.
	October 21	Anticoagulation was reduced to rivaroxaban 15 mg once a day.
	October 31	Contrast-enhanced CT showed a disappearance of PE.

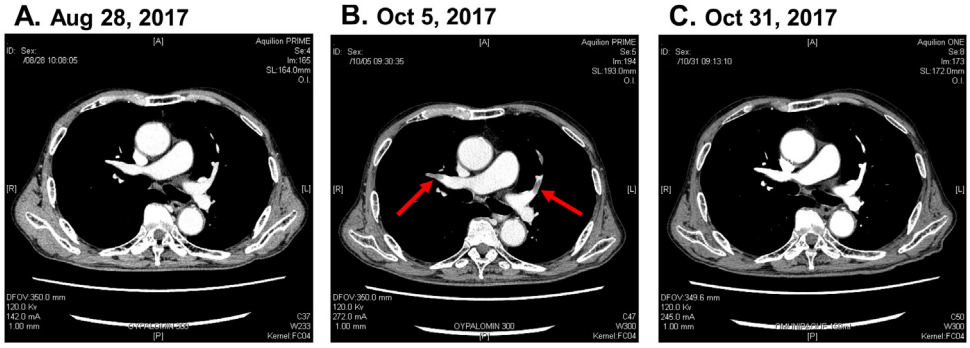

Fig. 1. Timeline of contrast-enhanced thoracic computed tomography (CT). (A) Contrast-enhanced CT on August 28, 2017, showed no evident thrombus in the pulmonary arteries at the end of the first cycle of neoadjuvant chemotherapy. (B) Follow-up contrast-enhanced CT on October 15, 2017, revealed pulmonary embolism (PE; allows) at the end of the third cycle of chemotherapy. (C) Contrast-enhanced CT on October 31, 2017, showed that the PE had completely disappeared from the pulmonary arteries after 16 days of rivaroxaban treatment.

chemotherapy including 1000 mg/m^2 gemcitabine and 70 mg/m^2 cisplatin every 3 weeks (Table 1). The patient had a history of smoking but no other coronary risk factors.

Physical examination and diagnostic assessment

The patient was asymptomatic and his general condition, including vital signs, blood gas analysis, and performance status, was stable. Electrocardiography showed a normal sinus rhythm with inverted T waves in II, III, aVF, and V3-6. Echocardiography showed apical hypertrophic cardiomyopathy which associated electrocardiographic changes. D-dimer and thrombin-antithrombin complex (TAT) levels were elevated at 21.1 μg/mL and 28.1 ng/mL, respectively (Table 1), while protein C/S, anticardiolipin antibody, and lupus anticoagulant were within normal range. At the end of third cycle of neoadjuvant chemotherapy on October 5, 2017, follow-up contrast-enhanced computed tomography (CT) revealed PE unexpectedly (Fig. 1B and Table 1). Ultrasonography of the lower extremities also revealed DVT from the popliteal vein to the soleal vein in both legs. Because contrast-enhanced CT at the end of the first cycle of chemotherapy on August 28, 2017, did not detect PE (Fig. 1A), development of CAT must have occurred after second cycle or later, and was closely related to cisplatin and gemcitabine administration.

Interventions and follow-up

Because the patient's condition was stable, we started anticoagulation against CAT with rivaroxaban 15 mg twice a day for 3 weeks as the initial dose with patient's agreement. We carefully monitored his clinical symptoms, physical signs, and D-dimer levels. After 2 weeks of rivaroxaban treatment, ultrasonography showed significant improvement of DVT. After 3 weeks of initial rivaroxaban treatment, rivaroxaban 15 mg once a day was initiated as a maintenance dose. After 1 month of rivaroxaban treatment, the patient's PE had completely disappeared on contrast-enhanced CT (Fig. 1C and Table 1). After three cycles of neoadjuvant chemotherapy and resolution of CAT, radical cystectomy was performed. Then, we restarted rivaroxaban 15 mg once a day and have observed no recurrence of CAT and no adverse event such as bleeding over 1 year with rivaroxaban.

Discussion

Here, we reported a patient with CAT induced by cisplatin and gemcitabine, which was resolved using a single-drug approach with rivaroxaban. In this report, a series of contrast-enhanced CTs clearly detected progression of chemotherapy-induced CAT and complete anticoagulation by single-drug approach with rivaroxaban against CAT.

CAT remains a major complication and one of the leading causes of non-cancer death in patients with cancer [1]. In the present case, CAT was detected at the end of the third cycle of neoadjuvant chemotherapy including cisplatin and gemcitabine. A retrospective study showed that prevalence of VTE in patients with cancer who received chemotherapy including cisplatin was significantly higher than that in patients who received any other chemotherapy regimen, and that cisplatin has been implicated as an independent risk factor of VTE [5]. Mechanistically, the alkylating agent cisplatin induces coagulation-stimulating platelet activity and von Willebrand factors, and induces vascular endothelial dysfunction [6]. On the other hand, gemcitabine, a fluorinated analogue of the nucleoside cytidine, has cytotoxicity in endothelium, but it does not significantly increase the risk of VTE in patient with cancer compared with non-gemcitabine-based chemotherapy [7]. Both cisplatin and gemcitabine possibly induce with CAT, but we consider that CAT in the present case was closely related to cisplatin administration.

A single-drug approach with rivaroxaban successfully resolved CAT in this case, and the patient sequentially returned to cancer therapy with a standard dose of rivaroxaban without recurrence of CAT or any bleeding event. Guidelines for VTE have stated recommendation of LMWH and oral VKAs over the DOACs in patients with cancer [2]. However, a prospective study revealed a twofold increase in major bleeding events in patients with active cancer receiving conventional anticoagulation compared with patients without cancer [8]. In the present case, we considered the patient's stable hemodynamic condition and balance between safety and effectiveness of anticoagulation, we initiated a single-drug approach with rivaroxaban. The guideline for VTE recommend a minimum duration of 3 months of anticoagulation for patients with active cancer [2]. However, the optimal duration of therapy for CAT has not been determined definitively. In this case, we extended anticoagulation therapy over 1 year. As demonstrated in the EINSTEIN-DVT and -PE clinical trials, rivaroxaban has shown its non-inferiority and reduced major bleeding events when compared with VKAs [3,4]. Moreover, the J-EINSTEIN DVT and PE program demonstrated that a single-drug approach with rivaroxaban has both safety and effectiveness in Japanese patients with DVT and PE [9]. These previous clinical trials of rivaroxaban support our approach. However, in truth, the evidence of rivaroxaban against CAT is very limited. The CASSINI trial of rivaroxaban against primary CAT in high-risk patients with cancer has been launched [10], which will provide further evidence to confirm the benefits of a single-drug approach with rivaroxaban in patients with CAT.

Conclusions

We reported a patient with CAT induced by chemotherapy for treatment of bladder cancer, which were successfully resolved by a single-drug approach with rivaroxaban. Although the evidence of DOACs against CAT is very limited, accumulation of this approach will provide an anticoagulation strategy for CAT other than LMWH and VKAs, and we believe this single-drug approach is a promising strategy against CAT.

Consent

The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest

None declared.

Author contributions

All authors had substantial contribution to this work and they all take full responsibility for the contents of the manuscript, including review and approval of this version.

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