


Treatment of pulmonary thromboembolism with edoxaban in a cancer patient with borderline fulfillment of the dose reduction criteria

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Abstract

Venous thromboembolism is the most common cause of death in cancer patients with venous thrombosis. Treatment of venous thrombosis is important in cancer patients, as it can have a major impact on prognosis. We report a case of advanced gastric cancer that was discovered owing to pulmonary thromboembolism and describe the treatment for both conditions. Dose reduction criteria of edoxaban are established. Appropriate dose was based on body weight and creatinine clearance; patients with creatinine clearance values slightly exceeding or below 50 are considered to be on the borderline of the dose reduction criteria. This case had borderline value (body weight: 63 kg, creatinine clearance: 46 mL/min). We observed no response after initiating treatment with 30 mg edoxaban; however, pulmonary thrombus disappeared after increasing the dose to 60 mg edoxaban. When selecting an anticoagulation drug in borderline patients with cancer-associated thrombosis, dose increase should be considered if hemorrhage risk is assessed.

Keywords

Pulmonary thromboembolism, cancer patient, direct oral anticoagulants, edoxaban

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Introduction

Cancer and venous thrombosis are closely related. Therefore, appropriate treatment for each patient should be selected based on background factors and disease state.^{1,2} Venous thromboembolism is the most common cause of death in cancer patients with venous thrombosis.^{3–5} The treatment of venous thrombosis is important in cancer patients, because it can have a major effect on the prognosis. We report a case of advanced gastric cancer discovered owing to the occurrence of pulmonary thromboembolism and describe the treatment for both conditions.

Case

An 84-year-old woman was brought to our hospital by emergency transport due to sudden respiratory discomfort. Her medical history was unremarkable, and she was not on any medication. On arrival, her body weight (BW) was 63 kg, blood pressure was 96/60 mm Hg, pulse rate was 100 beats/min, percutaneous arterial blood oxygen saturation was 89%,

and there was no lower limb edema. Laboratory findings at the time of hospitalization were as follows: white blood cells: 14,180/ μ L (reference value (RV): 3900–9800/ μ L); red blood cells: 344×10^4 / μ L (RV: 427–570 $\times 10^4$ / μ L); hemoglobin: 7.7 (RV: 11.3–15.2) g/dL; hematocrit: 24.4% (RV: 33.4%–44.9%); platelets: 24.9×10^4 / μ L (RV: 13.0×10^4 – 36.9×10^4 / μ L); albumin: 3.0 (RV: 3.8–5.3) g/dL; blood urea nitrogen: 17.4 (RV: 8.0–22) mg/dL; creatinine: 0.91 (RV: 0.4–0.7) mg/dL; estimate glomerular filtration rate: 41.49 (RV: ≥ 90) mL/min; total bilirubin: 0.55 mg/dL (RV: 0.22–1.2 mg/dL); aspartate aminotransferase: 26 IU/L (RV: 13–33 IU/L); alanine aminotransferase: 9 (RV: 6–27) IU/L; lactate dehydrogenase: 300 (RV: 119–229) IU/L; sodium: 138.3

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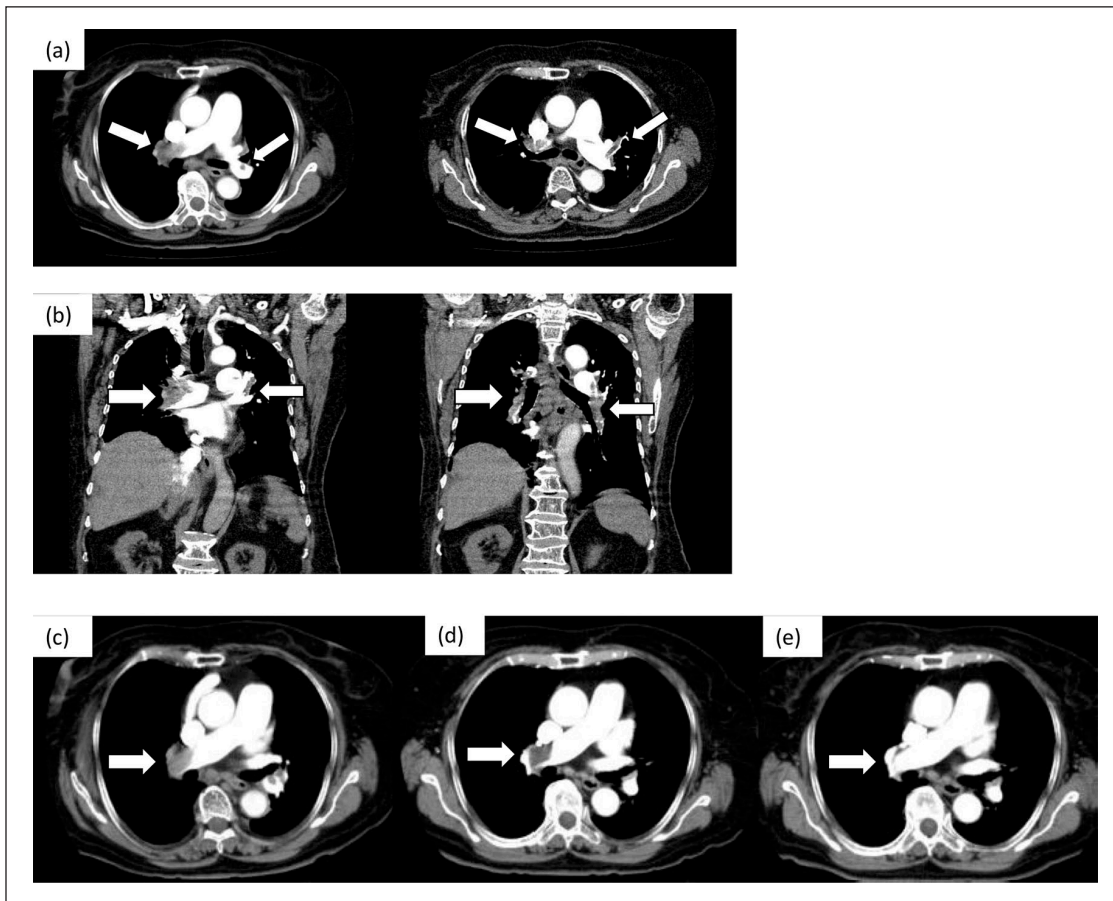


Figure 1. (a) and (b) Contrast-enhanced CT revealing submassive thrombus in both pulmonary arteries (arrows); (c)–(e) contrast-enhanced CT revealing complete disappearance of the thrombus over a period of 3 months (arrows).

(RV: 135–147) mEq/L; potassium: 3.98 (RV: 135–147) mEq/L; chlorine: 103.8 (RV: 98–110) mEq/L; C-reactive protein: 3.34 (RV: 0.01–0.3) mg/dL; creatine phosphokinase: 109 (RV: 47–170) U/L; and D-dimer: 19.1 (RV: 0–1.0) μ . Electrocardiography revealed sinus tachycardia with right bundle branch block, right axis deviation, normal left ventricular systolic performance, right-sided enlargement, tricuspid regurgitation, and findings suggestive of right heart strain. Contrast-enhanced computed tomography (CT) revealed submassive thrombus in both pulmonary arteries (Figure 1(a) and (b)). Thrombi were not found in the deep veins. Acute pulmonary thromboembolism was diagnosed, and she was hospitalized for further treatment.

Her hemodynamic status was stable, and oxygenation was maintained with supplementary oxygen administration. Therefore, she was admitted for oral and intravenous anticoagulant drug therapy. After administration of unfractionated heparin, the anticoagulant drug oral edoxaban was initiated at a dose of 30 mg. Since the thrombus had developed in a healthy patient with no significant medical history, we investigated for congenital abnormalities of coagulation and fibrinolysis factors but found no abnormality. On examination of the digestive tract to determine the cause of anemia,

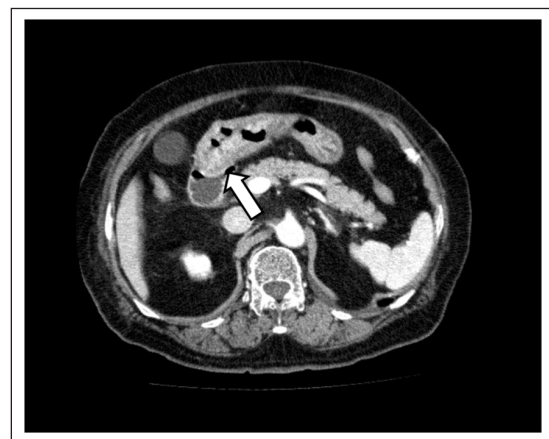


Figure 2. The entire circumference of the wall thickening at antrum to pyloric region of stomach (arrows).

advanced gastric cancer (pT3N1cM0, stage IIB) was detected (Figure 2). However, surgery under general anesthesia was determined to be dangerous due to the pulmonary thromboembolism; therefore, complete removal by laparotomy was planned after thrombus resolution. Contrast-enhanced CT

performed 1 month after starting 30 mg of oral edoxaban did not reveal disappearance of the pulmonary thromboembolism; however, as the patient was stable, oral therapy was continued on an outpatient basis. After one more month, the general condition of the patient and dietary intake were good, respiratory discomfort had abated, and renal function had improved with a creatinine clearance (CCr) of 51 mL/min and D-dimer level reduction to 3.1 μ . After evaluating the risk of hemorrhage at this point, the dose of edoxaban was increased to 60 mg. A re-evaluation of the pulmonary embolism by contrast-enhanced CT performed 2 months after diagnosis revealed complete disappearance of the thrombus, allowing us to perform gastrectomy under general anesthesia (Figure 1(c)–(e)).

Discussion

The established criteria for dose reduction of edoxaban to 30 mg are any of the following: BW \leq 60 kg, CCr: 30–50 mL/min, and concurrent use of a P-glycoprotein blocker. In cancer patients, weight and kidney function may fluctuate depending on physical and medical conditions. Therefore, CCr values may differ in each blood test. Patients with CCr values slightly exceeding or below 50 are considered to be on the borderline of the dose reduction criteria and are therefore eligible to receive 30 or 60 mg of edoxaban. In this case, a few months after the start of treatment, renal function had improved with a CCr of 51 mL/min. There are also borderline cases with patients similar to ours who fulfill the dose reduction criterion during the initial phase of treatment, but who no longer meet the criteria after subsequent improvement of renal function. In borderline cases, the risk of hemorrhage must be evaluated and a dose increase reviewed if the risk is mild or moderate, since this dose increase may lead to thrombus resolution. To the best of our knowledge, this is the first report of successful treatment of acute pulmonary embolism in a cancer patient with borderline fulfillment of the dose reduction criteria.

Pulmonary thromboembolism was treated by administering edoxaban. We observed no response after initiating treatment with 30 mg of edoxaban. Gastrectomy could not be done with the pulmonary thrombus. Then, we evaluated the hemorrhage risk in the present case, which gave the Registro Informatizado de la Enfermedad TromboEmbolica (RIETE) score of 2 points.⁶ This is a moderate risk that encompasses a 1.06% risk of fatal hemorrhage. Therefore, we determined that the risk of hemorrhage was not high in our patient and increased the edoxaban dose to 60 mg. After 1 month, the pulmonary thrombus disappeared after increasing the dose to 60 mg of edoxaban. This was followed by gastrectomy via a laparotomy for treating the gastric cancer. Currently, low-molecular-weight heparin, unfractionated heparin, warfarin, or direct oral anticoagulants (DOACs) are used in the treatment of venous thrombosis. Managing warfarin treatment in patients with cancer is difficult as the coagulation ability is affected substantially by the patient's diet and interaction

with anticancer agents such as 5-fluorouracil derivatives.⁷ Consequently, expectations are rising for the utilization of DOACs as treatment for venous thrombosis in patients with cancer.^{8–13} Among DOACs, edoxaban shows the lowest interaction in chemotherapy using CYP3A4.¹⁴ Hence, we used edoxaban for this patient. Administration of oral edoxaban after parenteral anticoagulant therapy is recommended as a the Japanese Circulation Society 2017 class I/level A anticoagulation therapy for acute pulmonary thromboembolism in patients with stable hemodynamics. The risk of not only thrombosis but also hemorrhage is reportedly higher in patients with cancer than in those without.¹⁵ Both the coagulation system and fibrinolytic system are amplified in patients with cancer; however, the degree of amplification differs between patients and involves a combination of multiple factors that include cancer site, stage, and grade. Therefore, treatment must be reviewed on a patient-by-patient basis.

Pulmonary thromboembolism is also reported to become chronic in 3.8% of cases who survive the acute phase.¹⁶ Thrombi that develop during the acute phase can become organized during the chronic phase, increasing pulmonary vascular resistance and resulting in pulmonary hypertension. This is recognized as a designated intractable disease in Japan, and prognosis for this condition is very poor. In cases of acute pulmonary arterial thromboembolism, thrombus elimination during the acute phase, if possible, is important, and regression and stability must be achieved without allowing the thrombus to become organized. Hence, when selecting an anticoagulation drug in borderline patients, dose increase should be considered if hemorrhage risk is assessed. Further studies are warranted to validate our observations in this report.

Conclusion

When selecting an anticoagulation drug for pulmonary thromboembolism in borderline cancer patients with cancer-associated thrombosis, dose increase should be considered following an assessment of hemorrhage risk.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

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