Almost 10% of cancer patients develop venous thromboembolism (VTE), an association known as Trousseau’s syndrome. Treatment of VTE increases survival of cancer patients [1], but recurrent VTE despite therapeutic anticoagulation is common in Trousseau’s syndrome and contributes to increased mortality [2].

We report an individualized treatment approach using dabigatran 150 mg twice daily and fondaparinux 7.5 mg once daily in a patient with therapy-resistant VTE. The patient, a 53-year-old female, was diagnosed with an unprovoked calf deep vein thrombosis (DVT) and treated with vitamin K antagonist (VKA) and 6 days of weight-adjusted doses of enoxaparin (60 mg twice daily), until the VKA therapy reached therapeutic INR levels above 2.0. Ten days later the patient was re-admitted with symptomatic submassive pulmonary embolism (PE) and DVT progression despite adequate anticoagulation (INR value of 2.9). Thorough examination ruled out malignant disease, VKA was stopped and enoxaparin 60 mg twice daily restarted. Four months later VKA was re-initiated (target INR 2.5 to 3.5), which could not prevent disease progression to bilateral recurrent DVT despite an INR of 3.6. Enoxaparin was restarted and the patient transferred to our centre. Heparin-induced thrombocytopenia (HIT), antiphospholipid syndrome and malignant disease were ruled out, but heterozygosity for Factor V-Leiden mutation was found.

On day 157 an acute right subclavian DVT occurred and anticoagulation was changed to fondaparinux 7.5 mg OD. In the following period, unprovoked thrombophlebitis of left cephalic vein, minor bleedings (nose, gingiva) and recurrent PE, complicated by significant haemoptysis, occurred. Coagulation parameters were monitored and treatment repeatedly adapted according to the clinical situation (see Table S1).

On day 307, recurrent subclavian and upper caval DVTs and bulky cervical metastases of a low-differentiated adenocarcinoma were found. Due to recurrent VTE and overwhelming thrombin activation anticoagulant treatment was changed from fondaparinux to argatroban, since direct thrombin inhibition (DTI) is known to be effective in highly coagulable states such as HIT. A short interruption of argatroban during lymph node biopsy for histology led to an acute right iliac DVT. Palliative chemotherapy with carboplatin and paclitaxel was started on day 323. Since DTI with argatroban effectively prevented recurrent VTE, anticoagulant therapy was switched from argatroban to a combination of fondaparinux 7.5 mg once daily and the DTI dabigatran in a prophylactic dose of 75 mg once daily for discharge. However, only 6 days later the patient was re-admitted to our intensive care unit with acute submassive PE with severe right heart strain. The patient consented to fibrinolytic therapy with alteplase together with argatroban, but developed clinically relevant haemoptysis after 50 mg alteplase. Later on, the patient’s condition improved and, to allow discharge, therapy was changed to therapeutic fondaparinux together with escalated dosages of the oral DTI dabigatran (150 mg twice daily) to block the coagulation cascade both at the level of factor Xa and thrombin to control the severe procoagulatory state.

The patient and her husband were informed about the experimental nature of such treatment and the risks of thromboembolic and bleeding complications and written informed consent was obtained. The patient was discharged on day 368. The patient developed slow tumour progression despite five cycles of radio-chemotherapy, but remained free of VTE recurrence for more than 180 days. However, the patient died on day 566 due to final stage cancer and a haemodynamically relevant malignant pericardial effusion.

To our knowledge, this is the first published case of a successful anticoagulant treatment with DTI in combination with fondaparinux in paraneoplastic VTE refractory to conventional anticoagulation. Within 333 days, our patient...
experienced seven thromboembolic events as well as bleeding complications, which are also more common in paraneoplastic VTE [3]. During an individualized treatment with fondaparinux and dabigatran in therapeutic dosages, our patient remained free of VTE recurrence over a period of more than 180 days and survived more than 550 days after the first VTE event despite the progression of malignant disease, demonstrating the beneficial effect of the combined anticoagulant treatment. Clearly, it has to be considered that the stabilization in our patient may partly be attributable to cancer therapy [4]. However, the patient showed progressive malignant disease and died of a terminal complication despite radiation and chemotherapy, indicating that cancer treatment alone does not account for the control of paraneoplastic coagulation activation.

We conclude that patients with recurrent paraneoplastic VTE and massive hypercoagulability untreatable with conventional anticoagulation may benefit from treatment with DTI in combination with selective factor Xa inhibition. DTI seems to be an option in recurrent paraneoplastic VTE, since prothrombotic states are often due to increased thrombin generation. It has to be stressed, however, that dabigatran is currently not approved for treatment of VTE and thorough information of patients as well as close monitoring are required for this off-label use.

Competing Interests
There are no competing interests to declare.

REFERENCES

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Supporting Information
Additional Supporting Information may be found in the online version of this article:

Table S1
Time course of clinical events, anticoagulant treatment and changes in parameters of coagulation activation during therapy in a patient with therapy-resistant Trousseau’s syndrome. D-Dimers (normal value <501 ng ml\(^{-1}\)); PTF = prothrombin fragments F1 + F2 (normal value 0.07–0.23 nmol ml\(^{-1}\)); TAT = thrombin-antithrombin-complexes (normal value 1.0–4.1 ng ml\(^{-1}\))

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