Rivaroxaban treatment for cancer-associated venous thromboembolism in a patient with heparin-induced thrombocytopenia: a case report

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Abstract: Low molecular weight heparin (LMWH) is the first-line therapy in acute cancer-associated venous thromboembolism (CAT). However, heparin-induced thrombocytopenia (HIT) is a life-threatening adverse drug reaction that occurs in anticoagulation therapy with LMWH. This article reports the case of a 66-year-old Chinese male who received nadroparin 4100IU twice daily for treating CAT. Unfortunately, the epistaxis persisted and the blood count examination revealed serious thrombocytopenia on postoperative day 5. The patient was diagnosed with HIT and thereafter LMWH therapy was replaced with rivaroxaban. During three months follow-up, the patient had a good recovery without recurrent CAT or bleeding.

Keywords: Heparin-induced thrombocytopenia (HIT); cancer-associated venous thromboembolism (CAT); anticoagulant; rivaroxaban

Introduction

Venous thromboembolism (VTE) is a common and potentially life-threatening complication in cancer patients, with a greater risk than non-cancer patients (1). Furthermore, these specific patients may receive chemotherapy, glucocorticoid, or antiangiogenic agents during the course of their diseases, which consequently increase the risk of VTE. At present, anticoagulant therapy with low molecular weight heparin (LMWH) is suggested as the first-line treatment for cancer-associated venous thromboembolism (CAT) while rivaroxaban is considered as an alternative to patients without gastrointestinal cancer (2). Whereas, for certain special clinical scenarios, such as the patient suffered from heparin-induced thrombocytopenia (HIT), the optimal anticoagulant strategy poses a challenging task in these fragile patients. During the past decade, direct oral anticoagulants (DOACs) have been proven to be more effective or at least non-inferior to conventional anticoagulants [vitamin K antagonists (VKAs) and LMWH] in terms of prophylaxis/treatment for VTE, with a lower risk for major bleeding (3). Here, we report a lung adenocarcinoma patient who suffered from a HIT. Finally, an individual DOACs, rivaroxaban, was chosen as an optimal anticoagulant in consideration of up-to-date evidence and patient’s characteristics.

Case presentation

A 66-year-old male (weight: 52 kg) was admitted with a diagnosis of lung adenocarcinoma (T4N0M1, stage IV), with the negative expression of EGFR and ALK gene. The patient was treated with first-line chemotherapy, including cisplatin (75 mg/m²), pemetrexed (500 mg/m²), and bevacizumab (7.5 mg/kg) for every 3 weeks. After the 3rd course of chemotherapy, B-ultrasound revealed the presence of right internal jugular VTE (Figure 1). Laboratory tests showed the increase of serum D-dimer value (3.87, reference range, 0–0.5 μg/mL), meanwhile the
platelet count was normal (266×10^9/L) at this time. Therefore, nadroparin (4,100 IU twice daily, subcutaneous injection) was immediately administrated for the treatment of CAT. Five days later, the patient experienced a persisted epistaxis, and laboratory detection showed the serious thrombocytopenia [(58–98)×10^9/L]. At this juncture, local compression is done for epistaxis. As a high 4Ts score (Table 1) (6 points, 2 points for platelet count fall >50% and platelet nadir ≥20×10^9/L, 2 points for timing of platelet count fall clear onset between days 5 and 10, 0 points for thrombosis or other sequelae, 2 points for no other cause for platelet count fall is evident) as well as the positive value of anti-platelet factor 4 (PF4)/heparin antibodies (0.67 optical density, negative reference range 0–0.399), this patient was diagnosed with HIT and thereafter LMWH therapy was replaced with rivaroxaban (15 mg twice daily at beginning and 20 mg once daily after 21 days) (4). On the 12th day of rivaroxaban therapy, platelet count showed a good recovery (229×10^9/L). During three months follow-up, the patient has been doing well without any evidence of recurrent CAT and bleeding, and the repeat platelet count was stable [(190–266)×10^9/L].

**Discussion**

Cancer patients, due to both disease and corresponding therapy, were considered to have a greater risk of VTE when compared to patients without cancer. For these fragile population, the Khorana risk score, which includes site of cancer, platelet count, total leukocytes, hemoglobin concentration and body mass index (BMI), can help us to identify the high thrombotic risk patients (5). In this case, the Khorana risk score was 1 for the site of cancer, which meant that the rate of CAT was 1.8–2.0% with intermediate-risk.

Bevacizumab, as a humanized monoclonal neutralizing antibody against vascular endothelial growth factor (VEGF), was considerably proved to provide a significant survival advantage in the treatment of non-small cell lung cancer (NSCLC) as an addition to platinum-based chemotherapy (6). Whereas, the mechanism of VEGF-antibody reminds us that the use of bevacizumab may cause serious thrombosis-associated clinical events, such as VTE and stroke. A meta-analysis including 13,185 patients showed an increased risk for venous thromboembolic events associated with bevacizumab use in cancer patients (7). In the present patient, bevacizumab usage also contributes to the development of CAT.

Current guidelines recommended the continued LMWH therapy (at least 6 months) for acute CAT (8). This drug strategy comes mainly from the CLOT study, which demonstrated a statistically significant reduction in recurrent VTE and improvement in survival with LMWH versus oral anticoagulation (OAC) in patients with CAT (9). In this case, patient received standard therapy by nadroparin (LMWH). Unfortunately, serious thrombocytopenia occurred and is considered as HIT according to 4Ts score criterion and PF4 value.

HIT, occurring in anticoagulation therapy with heparin or LMWH, can be categorized as the nonimmunogenic form (type 1) with a benign course and immune-mediated form (type 2) which is a life-threatening adverse drug reaction (10). Clinically, the incidence of HIT type 2 relative to LMWH is rare (0.1–0.2% in different studies) (11,12). HIT is caused by the development of heparin-dependent IgG antibodies directed against a complex of PF4 by exposure to heparin (13,14). Guidelines recommend that patients with HIT should cease heparin or LMWH

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**Table 1 4Ts score in this HIT patient**

| Items                                      | Points |
|--------------------------------------------|--------|
| Thrombocytopenia                           | 2 (>50% fall and platelet nadir ≥20×10^9/L) |
| Timing of platelet count fall or other sequelae | 2 (clear onset between days 5 and 10) |
| Thrombosis or other sequelae               | 0 (none) |
| Other cause for thrombocytopenia not evident | 2 (no other cause for platelet count fall is evident) |

The pretest probability score: 6–8, high probability. HIT, heparin-induced thrombocytopenia.
therapy and prompt initiation of anticoagulation with argatroban, bivalirudin or fondaparinux (15). Nevertheless, these agents are burdensome because they require parenteral administration and frequent laboratory monitoring to adjust dosage, which may limit their long-term adoption. Given above limitations, oral anticoagulants (warfarin or DOACs) may represent an alternative choice for this patient. For cancer patients taking warfarin, time in therapeutic range (TTR) is hard to be well-controlled owing to frequent interactions with chemotherapeutic agents and immunosuppressive agents in anticancer therapy. In addition, warfarin may increase the risk of venous limb gangrene and skin necrosis in the HIT patients in its initiation (16).

Other oral anticoagulants should be considered in such patient. Of late years, DOACs, with a predictable dose response and no need for laboratory monitoring, have been considered non-inferior and probably safer than VKAs in patients with VTE. Whereas, evidence of DOACs on the treatment of CAT was limited, and guidelines’ recommendations of DOACs treatment for CAT was only class IIa level C (2). Encouragingly, several clinical trials of DOACs that specially aimed at patients with cancer have been finished. Hokusai-Cancer study, which included 1050 patients with cancer and VTE, showed that the use of edoxaban (Xa factor inhibitor) for up to 12 months reduced the risk of recurrent VTE but increased risk of major bleeding when compared to dalteparin (17). SELECT-D trial also observed that rivaroxaban (Xa factor inhibitor) was associated with relatively low VTE recurrence but higher clinical relevant nonmajor bleeding (CRNMB) compared with dalteparin in cancer patients with VTE (18). The latest AVERT trial, which aimed at ambulatory patients with cancer who were at intermediate-to-high risk for VTE (Khorana score ≥2) and were initiating chemotherapy, suggested a significantly lower risk of VTE and a higher risk of major bleeding for the use of apixaban when compared to the use of placebo (19). Accordingly, treatment with DOACs in cancer patients may reduce the risk of VTE at the expense of increased risk of bleeding. Thus, the net clinical benefit (NCB) is of concern, which has been growingly used to quantify both thromboembolism and hemorrhage in the field of anticoagulant treatment. Our prior NCB analysis supported that DOACs might represent a better NCB property compared to VKA and LWMHs in patients with cancer (20). On the basis of available evidence, DOACs are likely to be a reasonable alternative for CAT patients who are unable to use LWMHs. Regarding individual DOACs, only rivaroxaban, which was approved for treating VTE by China Food and Drug Administration (CFDA), has been evaluated on the efficacy and safety in patients with HIT in prospective study. In this study, none of the treated patients experienced any major bleeding and platelet recovery was achieved in all patients who completed treatment, which showed rivaroxaban appear to be a treatment option in HIT patients (21). To summarize, rivaroxaban might be an effective and safe agent to treat with CAT patients who suffered from HIT. In our case, the patient was followed by rivaroxaban over 3 months, without recurrent VTE and no episodes of bleeding.

In conclusion, based on current evidence, we believe that rivaroxaban use has numerous advantages in this clinical scenario, including patient compliance, easy to access, and positive NCB property. However, further studies with large sample size on evaluation of DOACs in the treatment of these fragile population are necessary.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.09.55). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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