Anticoagulation treatment and prophylactic edoxaban for cerebral sinus venous thrombosis in an adolescent with acute lymphoblastic leukemia

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Abstract
Pediatric acute lymphoblastic leukemia regimens include large L-asparaginase dosages and steroids, which are associated with an increased risk of venous thromboemboli in adolescents and young adults. Herein, we report the case of an 18-year-old male with acute lymphoblastic leukemia, who was treated with the pediatric regimen, in which edoxaban was employed as a prophylaxis against cerebral sinus venous thrombosis. The event happened on day 20 of induction therapy, when brain magnetic resonance imaging demonstrated a cerebral sinus venous thrombosis in the superior sagittal sinus. Anticoagulation therapy was initiated, and the patient’s symptoms disappeared 3 days later. The induction therapy was restarted after an interruption of 16 days, and the consolidation therapies, which included L-asparaginase and steroids, were completed. Edoxaban was administered as a prophylaxis during the consolidation therapy. There were no further adverse events. Edoxaban could be an effective prophylaxis for coagulation complications in adolescents and young adults with acute lymphoblastic leukemia.

Keywords
Acute lymphoblastic leukemia, adolescent and young adults, cerebral sinus venous thrombosis, edoxaban, L-asparaginase

Case Report
Treatments for acute lymphoblastic leukemia (ALL) that include L-asparaginase (L-ASP) and steroids are associated with a high risk of venous thromboemboli (VTE).1–3 The central nervous system is one of the locations at which VTE most commonly occurs.3 Although cerebral sinus venous thrombosis (CSVT) is a common complication of ALL therapy in pediatric patients, adolescent and young adult (AYA) patients are at greater risk of developing CSVT than pediatric patients.2,4,6,7 The standard treatment for L-ASP-related VTE is unfractionated heparin or low-molecular-weight heparin (LMWH) followed by warfarin.8 However, some severe cases involving thrombosis of the internal cerebral veins require immediate local thrombolytic treatment.9,10 A recent study reported that the direct oral anticoagulant (DOAC) edoxaban was non-inferior to LMWH as a treatment for cancer-associated VTE.11 Herein, we report the case of an 18-year-old male with ALL, who developed CSVT during induction therapy and received edoxaban as a prophylactic anticoagulation therapy during the remaining ALL treatment, which included L-ASP and steroids. This case highlights the potential effectiveness of edoxaban as a prophylaxis for coagulation-related complications in AYA with ALL.

Case
An 18-year-old male, who presented with migrating arthralgia, had taken prednisolone and certolizumab pegol, an anti-tumor necrosis-alpha antibody, for 9 months for rheumatoid arthritis. The patient was transferred to our hospital due to his peripheral blood test results, which showed leukocytosis with blasts and thrombocytopenia. On admission, the patient had...
pain in both knees, hepatomegaly, and a low-grade fever (37.9°C). Bone marrow aspiration revealed a blast frequency of 98%, and the blasts were positive for CD10, CD19, CD34, cy-CD79a, CD99, terminal deoxynucleotidyl transferase, and human leukocyte antigen-DR. Chromosomal analysis of the patient’s bone marrow cells revealed the following karyotype: 46, XY, t(2;11)(p11.2;p11.2). Magnetic resonance imaging (MRI) demonstrated necrosis of the femoral head, which seemed to be associated with prolonged prednisolone treatment. The patient was diagnosed with B-precursor ALL, and induction therapy, including prednisolone (60 mg/m² daily for 4 weeks), vincristine (1.5 mg/m² on days 8, 15, 22, and 29), daunorubicin (40 mg/m² on days 8, 15, 22, and 29), L-ASP (5000 U/m² on days 12, 15, 17, 21, 24, 27, 30, and 33), and triple intrathecal therapy (methotrexate, cytarabine, and hydrocortisone; 12.5, 25, and 25 mg, respectively, on days 1, 12, and 33). On day 20 of the induction therapy (after three courses of L-ASP), the patient developed left-sided paralysis and anarthria. A neurological examination revealed reduced movement in his left upper arm and left lower leg, together with loss of the deep tendon reflex. The Manual Muscle Test results for the left upper arm and left lower leg were both 1/5. Coagulation tests revealed the following: activated partial thromboplastin time, 191.6 s (normal = 26–36 s); prothrombin time, 17.9 s (normal = 10–15 s); prothrombin time-international normalized ratio, 1.46 (normal = 0.9–1.1); fibrinogen level = 50 mg/dL (normal = 175–430 mg/dL); antithrombin III (AT) activity level, 74% (normal = 80%–120%); and protein C activity level, 67% (normal = 79%–140%). The patient was considered to be in a hypercoagulable state, as he exhibited decreased fibrinogen levels, and the repeated administration of AT-III concentrate was required to maintain an AT-III activity level of >70% due to the effects of L-ASP. Although the patient’s brain MRI findings were normal, it was considered that CSVT had probably occurred due to hypercoagulation. The induction therapy was stopped, and anticoagulation therapy with unfractionated heparin was initiated. MRI performed on day 21 after the initiation of ALL treatment showed a CSVT in the superior sagittal sinus (Figure 1(a) and (b)). The patient’s neurological symptoms improved 3 days after the initiation of anticoagulation therapy. A course of L-ASP was skipped, and the remaining residual induction therapy, which included L-ASP, was restarted 16 days after the interruption (the first dose of L-ASP was a half dose, but full doses were administered thereafter). The unfractionated heparin was switched to LMWH 14 days later. The patient achieved complete remission after the completion of the induction therapy, and the follow-up brain MRI performed at the end of the induction therapy showed that the CSVT had been ameliorated (Figure 1(c) and (d)). As a prophylaxis against CSVT, the patient was switched from LMWH to oral edoxaban 2 months later. The edoxaban treatment was continued for about 12 months, and it was stopped about 4 months after the last round of consolidation therapy, which included L-ASP.

Figure 1. (a and b) Brain magnetic resonance imaging showed cerebral sinus venous thrombosis (arrows) in the superior sagittal sinus. (a) Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-DTPA)-enhanced T1-weighted imaging and (b) diffusion-weighted imaging. (c and d) Brain magnetic resonance imaging performed at the end of the induction therapy showed a cerebral sinus venous thrombosis. The arrow indicates a residual lesion. (c) T1-weighted imaging and (d) fluid attenuated inversion recovery (FLAIR) imaging.
and steroids. During this time, there were no coagulation abnormalities associated with L-ASP or steroids. The patient was successfully treated with all of the therapies that were deemed necessary at admission, except the one and a half doses of L-ASP skipped during the induction therapy, and oral maintenance treatment was subsequently started.

**Discussion**

The cure rate of pediatric ALL is better than that of adult ALL. A recent study of AYA ALL patients revealed that patients who were treated with pediatric regimens exhibited better event-free and overall survival rates than those who were treated with adult regimens.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\)\(^,\)\(^4\)\(^,\)\(^5\)\(^,\)\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\) and AYA patients are commonly treated with pediatric regimens. One proposed reason for the above-mentioned finding is differences in the dosages of chemotherapeutics, especially L-ASP. In the Japanese pediatric induction therapy regimen for ALL, the total dose of L-ASP is 90,000 U/m\(^2\), whereas in the adult Japanese pediatric induction therapy regimen for ALL, the dosages of chemotherapeutics, especially L-ASP. Systematic reviews recommend LMWH, vitamin K antagonists, and warfarin for the management of thrombosis and supplementation with antiplatelet therapy for thromboprophylaxis. Treatment and thromboprophylaxis with direct oral thrombin inhibitors and anti-Xa anticoagulants have also been suggested.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) Recently, DOACs—such as apixaban, rivaroxaban, dabigatran etexilate, and edoxaban—have been added as options for CVT prophylaxis and treatment.\(^1\)\(^,\)\(^5\) Although there have not been any previous studies in which DOACs were used for CVT prophylaxis in ALL patients, the American Society of Clinical Oncology (ASCO) recommended thromboprophylaxis with apixaban, rivaroxaban, or LMWH for cancer patients who are at high risk of CVT.\(^1\)\(^,\)\(^2\) In addition, the ASCO also recommends treatment with LMWH, edoxaban, or rivaroxaban for at least 6 months as a prophylaxis against recurrent CVT.\(^1\) The current patient took edoxaban for about 12 months while he was receiving L-ASP treatment, during which he exhibited normal coagulation values and did not experience any coagulopathic events. The development of novel oral anticoagulants has created an opportunity for chemotherapy-related thromboprophylaxis in patients receiving L-ASP.\(^1\) Unlike warfarin, these novel oral anticoagulants do not require monitoring of the patient’s coagulation status, such as the prothrombin time-international normalized ratio, and have few drug–drug interactions. Prophylaxis with edoxaban during chemotherapy might successfully prevent VTE associated with prednisolone and L-ASP. Furthermore, ALL patients who are at a high risk of VTE, such as AYA patients who are treated with pediatric regimens, might benefit from prophylactic edoxaban during induction therapy. Further investigation in prospective studies is necessary to determine the efficacy and safety of this approach.

**Conclusion**

Our experience in the current case suggests that edoxaban may be an effective prophylaxis against chemotherapy-related VTE in AYA ALL patients.

**Declaration of conflicting interests**

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**Ethical approval**

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