L-asparaginase 연관 하지 심부 혈전성혈관염의 경구 Rivaroxaban 치료

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Oral Rivaroxaban Treatment for L-asparaginase-induced Deep Thrombophlebitis in Lower Extremity
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We are reporting our experience of oral rivaroxaban (Xarelto®) treatment for L-asparaginase (L-ASP)-induced deep vein thrombophlebitis in the lower extremity developed during childhood acute lymphoblastic leukemia (ALL) chemotherapy, with a brief review of the literature. A 16-year-old boy was admitted to our institution with right lower leg pain and gait difficulties. He was diagnosed with ALL and started chemotherapy protocol. He had been under a chemotherapy course of delayed intensification (DI)-1. We began antibiotics treatment for possible inflammation including cellulitis of the leg and planned an MRI scan. The MRI scan indicated thrombophlebitis of the right posterior calf deep veins. Subsequent DVT CT and coagulation profiles showed other abnormal findings. Coagulation factor assay were noted with decreased levels of multi factors; Factor II 45%, Factor IX 35.3%, Factor X 30%, Factor XI 19%, Factor XII 22%, and anti-coagulants levels were decreased also with variant degrees; Protein C Activity 51%, Protein C Ag 54.5%, Protein S Activity 35%, Protein S Antigen, total 27.1%, Protein S Antigen, free 41.7%. Low molecular heparin (LMWH) treatment was initiated and the patient was switched to oral rivaroxaban (Xarelto®). After 6 weeks treatment, abnormal coagulation profiles and MRI scan showed improvement. Furthermore, the patient had no other symptoms or recurrence of thrombotic events. There was no significant adverse reaction to rivaroxaban in this patient.

Key Words: Chemotherapy, L-asparaginase, Rivaroxaban, Thrombophlebitis

Introduction

Acute lymphoblastic leukemia (ALL) represents a clonal expansion and arrests at a specific stage of normal lymphoid hematopoiesis and accounts for 25-30% of all childhood cancers. Induction treatment of ALL is chemotherapy including vincristine, prednisone or dexamethasone, daunorubicin, L-asparaginase (L-ASP), and intrathecal chemotherapy, depending on the risk classification. Thanks to the effect of these drugs, the remission rate is 95% after induction chemotherapy [1].
However, ALL is the most common malignancy associated with venous thromboembolism (VTE) in children.

The reported prevalence of VTE in children with ALL ranges between 1% and 73%, and the prevalence of symptomatic VTE ranges from 0% to 36%. The mechanism for increased risk of VTE is associated with alteration in the hemostatic system by use of L-ASP alone or in combination with vincristine or steroid, presence of central venous line (CVL) and/or inherited thrombophilia [2].

L-ASP has been a major component of ALL Chemotherapy since 1980s. L-ASP can catalyze the hydrolysis of L-asparagine to L-aspartic acid and ammonia, resulting in selective inhibition of protein synthesis of leukemic cells [1]. However, L-ASP should be used very carefully because of many adverse reactions such as hypersensitivity, hyperglycemia, hyperlipidemia, coagulopathy, acute pancreatitis and hepatotoxicity [3].

Coagulopathy related to L-ASP is caused by reduction of fibrinogen, Factor V, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Antithrombin (AT) and plasminogen. As a result, a few patients experience events of bleeding as well as thrombosis. The frequent sites of event are upper extremity/CVL related, lower extremity, central nervous system (CNS) and lung. The sites distribution of L-ASP-induced thrombotic events is not very different between adults and children, although adults tend to experience more pulmonary embolism while children more CNS events [3].

Pharmacological treatment with heparin or low molecular weight heparin (LMWH) is generally conducted for hospital-acquired thrombosis. Recently, the oral direct factor Xa inhibitor such as rivaroxaban is being attempted as an alternative drug for these patients [4].

We are reporting our experience of oral rivaroxaban (Xarelto®) treatment for L-ASP-induced deep thrombophlebitis in lower extremity during childhood ALL chemotherapy with a brief review of literature.

Case Report

A 16-year-old boy was admitted to our institution with right lower leg pain and gait difficulties. He was diagnosed with ALL and under Children’s Oncology Group (COG)-1961-protocol-based chemotherapy. He had been under a chemotherapy course of delayed intensification (DI)-1. After total 14 doses of L-ASP during chemotherapy (induction to DI-1), his symptoms were developed. His right calf area showed tenderness with mild swelling but there were no signs of heat or linear redness. There were no other specific abnormal findings on physical examination. His laboratory findings were WBC 2,590/mm³, Hb 9.1 g/dL, platelet 220,000/mm³, and CRP 0.02 mg/dL. Coagulation test results showed PT and aPTT within normal range, with mild decrease of antithrombin-III 39.6% and fibrinogen 100.8 mg/dL (reference range: 170-410) and with slight elevation of D-dimer 0.64 mg/L (reference range: 0.0-0.55). There were no remarkable abnormal findings of muscle enzymes including CPK, aldolase, and myoglobin. Nerve conduction velocity study indicated peripheral polyneuropathy with decreased motor conduction amplitude of the right median nerve and sensory conduction amplitude of right ulnar, sural and peroneal nerve.

On the second day, patient complained of worsening pains and swelling with focal erythematous change on right calf with newly developed claudication. Further laboratory evaluation showed worsened leukopenia and mild CRP elevation with coagulopathy (WBC 700/mm³, CRP 1.3 mg/dL, PT 13.5 sec, APTT 45.1 sec). We began antibiotics treatment for suspected inflammatory lesion including cellulitis of the leg and planned MRI scan.

MRI scan on the third day showed slightly dilated right posterior calf deep veins (popliteal vein and peroneal vein) with perivascular enhancement (Fig. 1). Deep vein thrombophlebitis at right distal popliteal vein to tibioperoneal vein was confirmed on subsequent deep vein thrombosis (DVT) CT.

Coagulation factor assay were noted with decreased levels of multi factors; Factor II 45%, Factor IX 35.3 %, Factor X 30%, Factor XI 19%, Factor XII 22%, and anti-coagulants levels were decreased also with variant degrees; Protein C Activity 51%, Protein C Ag 54.5%, Protein S Activity 35%, Protein S Antigen, total 27.1%, Protein S Antigen, free 41.7%. The patient had CVL on his chest but there was no dysfunction or infection evidence of CVL.

We stopped L-ASP administration but continued oral
Fig. 1. Initial MRI showed dilated right posterior calf deep vein (popliteal vein and peroneal vein, white arrow) with perivascular enhancement (A, B). DVT CT confirmed deep vein thrombophlebitis at right distal popliteal vein to tibioperoneal vein (C, black arrow).

Fig. 2. Follow-up MRI scan showed that right posterior calf deep veins dilatation with perivascular enhancement are resolved (A, B).

dexamethasone in chemotherapy. We decided on heparinization with low molecular weight heparin (LMWH, Enoxaparin 1 mg/kg/dose every 12 hours) for a week. The patients’ symptoms were improved 3 days after treatment. However, the patient complained pain at injecting LMWH causing LMWH medication irregular. We changed LMWH to oral rivaroxaban (Xarelto®) 15 mg twice daily. We continued medication for 6 weeks without L-ASP.

After 6 weeks of oral rivaroxaban medication, follow-up coagulation tests were performed. Coagulopathy was improved with PT 11.7 sec, APTT 34.9 sec, fibrinogen 252.9 mg/dl, AT 76.4%, D-dimer 0.3 mg/L. Levels of coagulation and anti-coagulation factors showed progressive recovery with results of Factor II 84%, Factor IX 53.7%, Factor X 63%, Factor XI 38%, Protein C Activity 78%, Protein C Ag 82.6%, Protein S Activity 62%, Protein S Antigen, total 70.5%, Protein S Antigen, free 41.7%. Follow-up MRI scan showed that the thrombophlebitis of right posterior calf deep veins were resolved, as compared to initial MRI scan (Fig. 2). Oral rivaroxaban medication was tolerable without severe adverse events and was done for 3 months totally. Until 3 months after cessation of medication, he has no abnormal thrombophlebitis signs.

Discussion

The majority of thrombotic events are of venous origin in children with ALL. Symptomatic thrombosis was diagnosed in the central nervous system (CNS) in 50% of cases and majority of asymptomatic cases were diagnosed in the
upper venous system. In addition, significant rates of CVL-associated thrombosis primarily occurring in the upper venous system have been reported [2]. In this case, the thrombophlebitis occurred in the lower extremity instead of upper extremities or CNS, suggestive of association with L-ASP and the first sign was cellulitis-like symptom.

Drug-related thrombosis during chemotherapy is related with daily dose of asparaginase, types of steroids and concomitant administration of ASP and steroid, with alteration of hemostasis [2,5].

For pharmacological thromboprophylaxis, the use of fresh frozen plasma or cryoprecipitate is considered for management of L-ASP related thrombosis. However, retrospective analysis showed no clear evidence for thromboprophylaxis. Prophylactic antithrombin supplementation also had no demonstrable clinical benefits of efficacy and safety [6,7]. The CAPELAL study reported lower rates of thrombosis in adults who received prophylactic antithrombin concentrate than in those who had not [8].

Enoxaparin, a low molecular weight heparin is the conventional agent for thrombosis showing a prophylactic effect in both, patients with Chemotherapy including L-ASP and with re-exposure with L-ASP following initial thrombosis [7,9].

However, heparins that rely on antithrombin for their mechanism of action may not be the most appropriate option and need to check aPTT for drug monitor.

The new oral direct thrombin inhibitors and anti-Xa anticoagulants are currently being assessed in medical patients for thromboprophylaxis, Oral rivaroxaban (Xarelto®), a direct Factor Xa inhibitor, is a small molecule oxazolidinone derivative with direct binding [4]. It does not require cofactors such as antithrombin. Furthermore, drug monitoring is not required for maintaining a therapeutic level. Known adverse reactions to rivaroxaban include hemorrhage, back pain, limb pain, wound secretion, and pruritis.

Its predictable pharmacokinetic profile, high oral bioavailability and once-daily dosing make rivaroxaban and optimal anticoagulant that warrants investigation in children. But investigation of safety and efficacy in cancer children is still underway. Attaredd et al, reported there are no significant differences in rivaroxaban effect across the age groups in vitro [10].

In this case, oral rivaroxaban (Xarelto®) was used in the treatment of L-ASP-induced deep thrombophlebitis in lower extremity during childhood ALL chemotherapy. The patient had no other symptoms and no recurrence of thrombotic events. There was no significant adverse reaction in this patient.

In our experience, oral rivaroxaban (Xarelto®) is a suitable alternative agent for thromboprophylaxis in patients with thrombosis after LMWH or with risk factors of thrombosis.

References

1. Ueno T, Ohtawa K, Mitsui K, et al, Cell cycle arrest and apoptosis of leukemia cells induced by L-asparaginase, Leukemia 1997;11:1858-61.
2. Nowak-Göttl U, Kenet G, Mitchell LG, Thrombosis in childhood acute lymphoblastic leukaemia: epidemiology, aetiology, diagnosis, prevention and treatment, Best Pract Res Clin Haematol 2009;22:103-14.
3. Truelove E, Fielding AK, Hunt BJ, The coagulopathy and thrombotic risk associated with L-asparaginase treatment in adults with acute lymphoblastic leukaemia, Leukemia 2013; 27:553-9.
4. Roehrig S, Straub A, Pohlmann J, et al, Discovery of the novel antithrombotic agent 5-chloro-N-((5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl)methyl)thiophene-2-carboxamide (BAY 59-7939): an oral, direct factor Xa inhibitor, J Med Chem 2005;48:5900-8.
5. Caruso V, Iacoviello L, Di Castelnuovo A, et al, Thrombotic complications in childhood acute lymphoblastic leukaemia: a meta-analysis of 17 prospective studies comprising 1752 pediatric patients, Blood 2006;108:2216-22.
6. Abbott LS, Deevska M, Fernandez CV, et al, The impact of prophylactic fresh-frozen plasma and cryoprecipitate on the incidence of central nervous system thrombosis and hemorrhage in children with acute lymphoblastic leukemia receiving asparaginase, Blood 2009;114:5146-51.
7. Qureshi A, Mitchell C, Richards S, Vora A, Goulden N, Asparaginase-related venous thrombosis in UKALL 2003 re-exposure to asparaginase is feasible and safe, Br J Haematol 2010;150:410-3.
8. Hunault-Berger M, Chevalier P, Delain M, et al, Changes in antithrombin and fibrinogen levels during induction chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma, Use of supportive coagulation therapy and clinical outcome: the CAPELAL study, Haematologica 2008;93:1488-94.
9. Elhasid R, Lanir N, Sharon R, et al. Prophylactic therapy with enoxaparin during L-asparaginase treatment in children with acute lymphoblastic leukemia. Blood Coagul Fibrinolysis 2001;12:367-70.

10. Attard C, Monagle P, Kubitza D, Ignjatovic V. The in vitro anticoagulant effect of rivaroxaban in children. Thromb Res 2012;130:804-7.