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Short communication

Choreito, a formula from Japanese traditional medicine (Kampo medicine), for massive hemorrhagic cystitis and clot retention in a pediatric patient with refractory acute lymphoblastic leukemia

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ABSTRACT

Hemorrhagic cystitis is critical in patients with hemato-oncological disorders. Unlike adult patients, there are limited modalities and invasive procedures are often not well tolerated in children with poor general conditions. We report a pediatric patient with refractory acute lymphoblastic leukemia who developed life-threatening massive gross hematuria. Along with platelet infusion every other day due to suppressed hematopoiesis, his gross hematuria and clot retention in the bladder were successfully treated with choreito, a formula from Japanese traditional medicine (Kampo medicine). He survived free from hematuria for more than four months. Choreito was well tolerated, and no adverse effects were observed throughout the course.

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Introduction

Hemorrhagic cystitis (HC) is one of the critical conditions found in patients with hemato-oncological disorders. Alkylating agents, radiation, viruses and bacteria may lead to the damage of transitional epithelium in the bladder and urethral tract which contribute to the pathogenesis of HC (Hassan 2011). In patients undergoing hematopoietic stem cell transplantation, HC is facilitated by viral infections as a result of impaired immune response and worsened by co-existed thrombocytopenia or coagulopathy (Decker et al. 2009). HC manifests as diffuse vesical bleeding and its management is often challenging due to limited evidence-based medical and surgical treatment approaches (Decker et al. 2009). Some patients present with massive gross hematuria (MGH) that further is complicated by the formation of blood clots. Eventually it progresses to renal failure and rupture of the bladder. MGH requires emergent treatment of the underlying disease and intravenous fluids, as well as manual or continuous bladder irrigation via Foley catheter. However, it is often difficult to perform the continuous irrigation in children due to the limited availability of suitable devices (Hassan 2011; Hicks and Li 2007). Invasive surgical treatments are not often well-tolerated in children with poor general conditions, especially in a palliative case.

We present a pediatric patient with refractory acute lymphoblastic leukemia (ALL) whose course was complicated with HC during palliative therapy. Although MGH progressed, administration of Japanese traditional herbal medicine (Kampo medicine), choreito successfully led to the excretion of clots from the bladder, and eventually microscopic hematuria became negative. Choreito was well tolerated, and no adverse effects were observed throughout the course.

Patient

A 10-year-old Japanese boy presented with prolonged fever, and had a diagnosis of B-cell precursor ALL at age 8 in an outside hospital. He received the standard combination of chemotherapy and was in remission until week 76 of maintenance therapy after induction chemotherapy when he had relapse of ALL. Subsequently, he received re-induction chemotherapy, but had residual blasts in the bone marrow and gradually blasts were seen in the peripheral blood. He was then referred to our hospital for further therapy.

On admission, he had anemia but was otherwise in good general condition. The laboratory data were significant for a peripheral white blood cell count (WBC) 5.0×10^9/l (blast cells 44%), hemoglobin 9.2 g/dl and a platelet count 35×10^9/l. His bone marrow aspirate showed a nucleated cell count 276×10^9/l comprised 90% of blasts.

He received re-induction therapy according to JACLS ALL F-protocol (Suzuki et al. 2010), which succeeded in the reduction of blasts in the peripheral blood. However, his bone marrow aspirate was full of blasts after the therapy. He was administered

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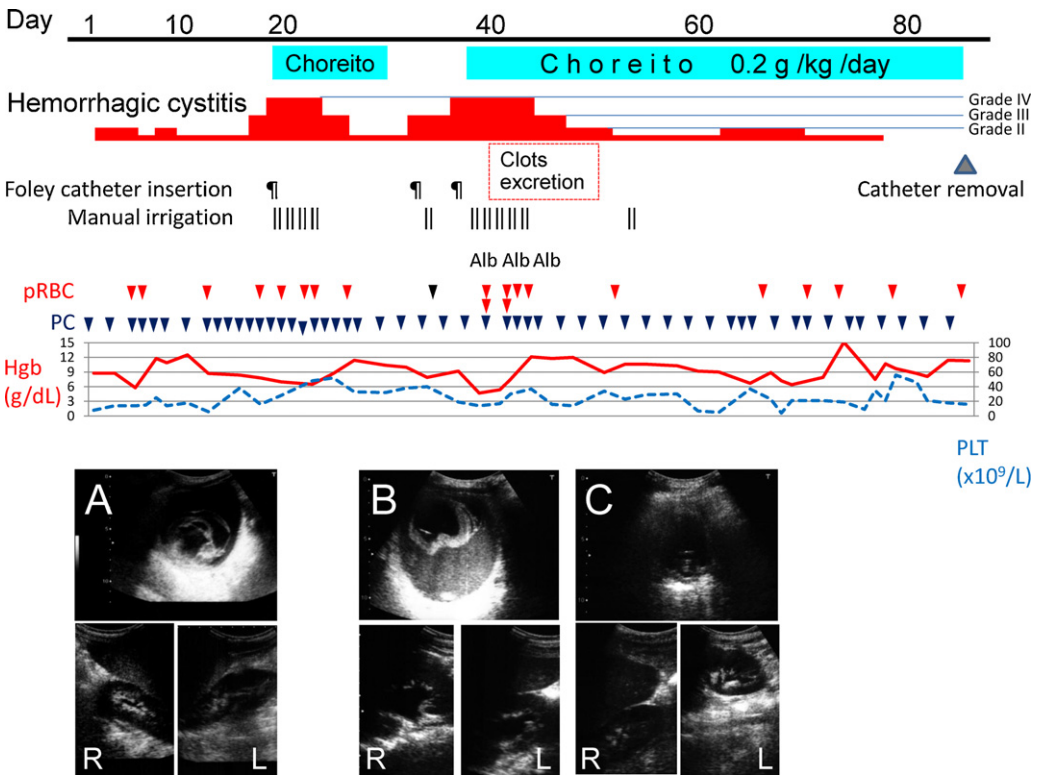

Fig. 1. Clinical course of massive hemorrhagic cystitis and sequential sonograms of the urinary system. The patient had grade II hemorrhagic cystitis (HC) from day 1 and progressed to grade III from day 10, from which he required platelet infusion every day. A Foley catheter 14 Fr was inserted and he received vigorous manual irrigation; however, the catheter was occluded and needed to be exchanged. Choreito was administered from day 20 and succeeded in remission of HC. He stopped taking choreito from day 29, which exacerbated HC, but by restarting choreito from day 38 he recovered from HC again and was finally able to withdraw from catheter insertion. His white blood cell count was less than 0.1×10^9/l throughout the course. Ultrasound images of the urinary system were obtained on day 19 (A), 38 (B) and 43 (C), respectively. Bladder was occupied by clots of 80% of the volume, and bilateral pelvises were enlarged on day 38 (B). After starting choreito, no clots were observed in bladder and renal pelvises were not enlarged on day 43 (C). ¶, exchange of catheters; ▼, number of transfusions; Hgb, hemoglobin; PLT, platelet; pRBC, packed red blood cells; PC, platelet concentrates; Alb, albumin infusion.

additional chemotherapy, but none of them were effective. Thus, he was provided palliative care. Ten days after the chemotherapy, his neutrophil count became less than 0.1×10^9/l and lasted for more than five months. He also had thrombocytopenia that required platelet infusion every other day in order to maintain platelet count more than 20×10^9/l. Although he had febrile neutropenia three weeks after chemotherapy, it was controlled by fourth-generation cephalosporin, as well as voriconazole for fungal prophylaxis and acyclovir for herpes prophylaxis.

He suddenly manifested grade II HC, 5 days after the onset of febrile neutropenia (day 1). His urine cultures were negative, and polymerase-chain reactions for adenovirus, BK virus or JC virus were also negative. He was given G-CSF daily, but he did not recover from neutropenia and HC progressed to grade III from day 10. From the same day, he required a platelet infusion every day. He was infused large-volume crystalloid fluids and diuretics for HC along with danaparoid for prevention of clots in the bladder, but his hematuria progressed to grade IV and MGH from day 17. Ultrasound revealed a large clot in his bladder and an enlarged right pelvis of the kidney (Fig. 1A). A Foley catheter 14 Fr was inserted and vigorous manual irrigations were initiated three times a day in order to maintain urine output. The catheter, however, was occluded by blood clots and needed to be re-inserted frequently. Three-way catheter or cystoscopy was not used due to the unavailability of the appropriate size, and surgical treatment was not undertaken considering the unstable hemostasis. Since he needed less invasive treatment, he was administered Japanese traditional medicine (Kampo medicine), choreito. Choreito is indicated in patients with "dampness-heat" in lower abdomen that causes dysuria, incomplete voiding and thirst. His Kampo pulse examination revealed floating, rapid and slippery pulse, and his abdominal examination was significant for lower abdominal hotness and hardness, which may be attributable to clot retention in the bladder. Those results coincided with the pattern of choreito. He was administered a pharmaceutical grade-medicine, choreito extract granules (Tsumura & Co., Tokyo, Japan) 0.2 g/kg p.o. daily in divided doses from day 20 (HPLC fingerprint of the extract is shown in Fig. 2). On day 23, he became free from lower abdominal discomfort and HC improved to grade I. Ultrasound revealed a normal pelvis of the kidneys, although small amount of clots retained in the bladder. The number of platelet infusion was reduced, and the bladder irrigation was discontinued from day 26.

He stopped taking choreito from day 29, which resulted in the more severe form of MGH. He required intensive albumin, packed red blood cells and daily platelet infusions along with vigorous bladder irrigations to maintain hemodynamics and urine outflow. Ultrasound revealed a large blood clot occupying nearly 80% of the volume of bladder with bilateral enlarged pelvises of the kidneys (Fig. 1B). He was administered choreito again from day 38. From day 39, he started to excrete fragmented blood clots from the side of catheter as he had the sensation of "constriction of the bladder". On day 43, his urine became clear again and the clots in bladder were not visible under ultrasound (Fig. 1C). Although his WBC was below 0.1×10^9/l for more than three months, his HC was controlled under grade I by choreito. No adverse effects were seen throughout the course. He was finally able to withdraw from the catheter and choreito was discontinued without exacerbation of HC until his death of multiple organ failure due to ALL two month later.

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