Original Study

Effectiveness of Single-dose Rasburicase in Patients With Lymphoid Malignancies at a High Risk for Tumor Lysis Syndrome

Young-Woo Jeon,[1,2,3] Dae-Hun Kwak,[1] Sung-Soo Park,[1] Jae-Ho Yoon,[1] Sung-Eun Lee,[1] Ki-Seong Eom,[1] Yoo-Jin Kim,[1] Hee-Je Kim,[1] Seok Lee,[1] Chang-Ki Min,[1] Jong-Wook Lee,[1] Woo-Sung Min,[1] Seok-Goo Cho[1,2,3]

Abstract

Tumor lysis syndrome (TLS) is one of life-threatening disorder in management of hemato-oncologic malignancies. Because of no optimal dose and duration of rasburicase, we evaluated the effectiveness of prophylactic single dose rasburicase in 67 patients with high-risk TLS. The incidence of TLS after single-dose rasburicase was 3.0% without toxicities; it indicated single dose rasburicase effectively prevented progression of TLS.

Background: Tumor lysis syndrome (TLS) is a life-threatening disorder that occurs mainly in patients with high-tumor burden hemato-oncologic malignancies. It results in metabolic derangements, including hyperuricemia and acute renal failure. The powerful management for TLS is a daily dose of rasburicase for up to 5 days before chemotherapy; however, the optimal dose and duration of rasburicase for TLS prophylaxis have not been standardized for patients at high risk for TLS. Therefore, we evaluated the efficacy of single-dose rasburicase for prophylactic purposes in patients with malignant lymphoma at high risk for TLS. **Patients and Materials:** We retrospectively evaluated patients with malignant lymphoma at high risk for TLS treated with a prophylactic single-dose of rasburicase (0.1-0.2 mg/kg) from March 2012 to March 2016. **Results:** A total of 67 patients treated with a single-dose of rasburicase for prophylaxis were analyzed. A relatively large number of patients (n = 23; 34.3%) had the highly proliferative lymphoblastic lymphoma subtype (n = 14) or Burkitt lymphoma (n = 9) and were at the highest risks of tumor lysis. Two patients were newly diagnosed with TLS; the incidence of TLS after single-dose prophylaxis was 3.0%. Multivariate analysis revealed no predictable risk factors for response to prophylactic rasburicase, though increased level of serum creatinine approached statistical significance in reducing the efficacy of single-dose rasburicase to prevent TLS (odds ratio, 3.61; $P = .054$). **Conclusion:** Our data indicated that single-dose rasburicase effectively prevented progression of TLS, and, regardless of any risk factors, including increased creatinine, single-dose rasburicase for TLS prophylaxis was useful in patients with lymphoma at a high risk for TLS.

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Introduction

High-tumor burden malignancies, including high-grade lymphomas, lymphoblastic lymphoma, and bulky solid tumors, are associated with a risk of tumor lysis syndrome (TLS) during aggressive initial treatments.[1,2] TLS is a life-threatening hemato-oncologic emergency characterized by metabolic derangements and the release of large amounts of potassium, phosphate, and uric acid into the peripheral blood stream from the rapid and widespread

[1]Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St Mary's Hospital, College of Medicine
[2]Institute for Translational Research and Molecular Imaging, Catholic Institutes of Medical Science
[3]Laboratory of Immune Regulation, Convergent Research Consortium for Immunologic Disease, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Korea

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Address for correspondence: Seok-Goo Cho, MD, PhD, Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, College of Medicine, Institute for Translational Research and Molecular Imaging, The Catholic University of Korea, #505, Banpo-Dong, Seocho-Ku, Seoul 06591, Republic of Korea
E-mail contact: chosg@catholic.ac.kr

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Table 1 Definitions of TLS

	Laboratory TLS[a]	Clinical TLS[b]
Uric acid	>8.0 mg/dL or 25% increase from baseline	
Potassium	>6.0 mEq/L or 25% increase from baseline	
Phosphorous	>4.5 mg/dL or 25% increase from baseline	
Calcium	Corrected calcium <7.0 mg/dL or 25% decrease from baseline	
		Cardiac arrhythmia or sudden death caused by hyperkalemia or hypocalcemia
		Increase in serum creatinine level of 0.3 mg/dL or single value >1.5 times the upper normal limit
		Seizure: not directly or probably attributable to a therapeutic agent

Abbreviation: TLS = tumor lysis syndrome.
[a]Laboratory TLS requires 2 or more of the following metabolic abnormalities.
[b]Clinical TLS requires the criteria for laboratory TLS as well as one or more of the following factors.

lysis of malignant cells.[2,3] Among these metabolic abnormalities, hyperuricemia plays a crucial role in the pathogenesis of TLS.[2,4] Increased serum uric acid results from the rapid catabolism of purine-containing tumor cell materials, and both crystal-dependent and -independent mechanisms then lead to the development of acute kidney injury (AKI) by obstructive damage to the renal tubules and distal collecting system.[2,4,5] Therefore, a therapeutic goal for TLS is to ameliorate the generated purine-containing substances, and an early preventive approach in high-risk groups is a milestone of therapy.[1,6,7] Recommendations for TLS management by expert consensus include hydration, allopurinol, and early treatment with rasburicase.[6] The preventive approaches for TLS are vigorous intravenous hydration, close monitoring of electrolytes and renal function, and control of uric acid using allopurinol as a xanthine oxidase inhibitor and rasburicase as a recombinant urate oxidase.[2,8,9] However, considering that TLS most commonly occurs within 6 to 48 hours after initial treatment,[10] more rapid and potent dissolutive methods for metabolic by-products are needed for definitive TLS prophylaxis. Allopurinol, a blocker of xanthine-oxidase, prevents the conversion of hypoxanthine and xanthine into uric acid; however, it has a delayed onset of action and lower efficacy than rasburicase.[11] Rasburicase, a recombinant urate oxidase, rapidly catalyzes uric acid to allantoin in a water-soluble form. Several trials have reported that rasburicase is superior to allopurinol for the control of uric acid, rapidly normalizing serum uric acid levels within 24 hours, and is about 5 to 10 times more potent than allopurinol in inhibiting the development of uric acid.[12,13] Although the dose for TLS treatment recommended by the United States Food and Drug Administration (FDA) and manufacturers is 0.2 mg/kg/day for up to 5 days,[12] a major obstacle in the use of TLS-prophylactic rasburicase is its high cost.[8] Whereas treatment strategies for solid cancers and hematologic malignancies have advanced rapidly in the past decade, TLS has not shown the same progress. In lymphoma management in particular, numerous advanced targeted agents and combined chemotherapies have shown strong anti-lymphoma activity. TLS risk may increase with the use of these novel and targeted agents, and it was indirectly reported that the incidence of TLS increased during the initial period of use for several new drugs.[7,14-16]

There are an increasing number of retrospective studies investigating the efficacy of single-dose rasburicase for TLS treatment in patients with solid tumors or limited heterogeneous hematologic malignancies undergoing targeted therapy. However, relatively few studies have examined single-dose rasburicase for prophylactic purposes in lymphoma cases characterized by high tumor burden, high lactate dehydrogenase (LDH) levels, and high cell turnover.[17,18] Moreover, the optimal dose and duration of rasburicase for TLS prophylaxis has not been standardized for lymphoma patients at a high risk for TLS, in particular those with chemosensitive bulky lymphoma. Therefore, we evaluated the efficacy of single-dose rasburicase for prophylactic purposes in patients with lymphoma at high risk for TLS.

Patients and Methods

Stratification of TLS Risk

Different malignancies have been classified into TLS risk groups by expert panel consensus.[6] High-risk diseases for TLS include the followings: chronic lymphocytic leukemia (CLL) with lymph nodes $\geq$ 10 cm (or lymph nodes $\geq$ 5 cm and absolute lymphocyte count $\geq 25 \times 10^9$/L) and increased baseline uric acid; peripheral T-cell lymphomas; Ann Arbor stage III/IV diffuse large B-cell lymphoma; mantle cell lymphomas with bulky disease and/or LDH $\geq$ 2 $\times$ upper normal limit (UNL); Ann Arbor stage III/IV Burkitt lymphoma and/or LDH $\geq$ 2 $\times$ UNL; Ann Arbor stage III/IV lymphoblastic lymphoma and/or LDH $\geq$ 2 $\times$ UNL; renal dysfunction and/or renal involvement.[6,8]

Definition of TLS and Response to Prophylaxis

TLS was classified as laboratory or clinical using the classification system of Cairo and Bishop.[10] Laboratory TLS (L-TLS) was diagnosed when 2 or more serum values of uric acid, potassium, phosphate, and calcium were abnormal within 3 days before or 7 days after the initial cancer treatment (Table 1).[10] Clinical TLS (C-TLS) was diagnosed based on laboratory evidence of a change in serum metabolites and 1 or more symptoms of significant clinical toxicity (increased serum creatinine level, cardiac arrhythmia or sudden death, seizure) in the same period (Table 1).[6,10] Spontaneous TLS was indicated when C-TLS or L-TLS presented before the initiation of chemotherapy. Abnormal serum chemistry defined by definition of TLS (Table 1); abnormal uric acid was > 8.0 mg/dL or 25% increase from baseline, abnormal potassium was > 6.0 mEq/L or 25% increase from baseline, abnormal