Serial Profile of Vitamins and Trace Elements during the Acute Phase of Allogeneic Stem Cell Transplantation

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A B S T R A C T

Currently, we utilize vitamins and trace elements formulations that are not prepared specifically for patients receiving hematopoietic stem cell transplantation (HSCT), and adequacy of this strategy has not been evaluated. We prospectively measured blood level of vitamins and trace elements in 15 patients once per week at 6 time points around the acute phase of allogeneic HSCT. We provided standard nutrition support, including administration of parenteral nutrition with vitamin and trace elements formulation in case of impairment of oral intake. Most patients had vitamin B1 deficiency from the start of preparative regimens. Vitamin C deficiency was prominent throughout the acute phase of HSCT and this was significantly associated with high inflammatory markers, C-reactive protein and ferritin. Remarkable vitamin K overload associated with administration of parenteral supplementation and ferritin overload caused by repeated transfusions was observed. Moderate deficiency of zinc was at least partially linked to gastrointestinal loss by diarrhea. We revealed several features of vitamin and trace element status in the acute phase of HSCT and provided a basis for attempts to improve the nutritional condition in HSCT recipients.

INTRODUCTION

Nutrition support is one of the most important aspects of supportive care involved in hematopoietic stem cell transplantation (HSCT), and comprehensive recommendations for HSCT procedures have been proposed [1,2]. These recommendations underscore the significance of receiving HSCT in well-nourished conditions and maintaining adequate energy intake during the course of HSCT, even when oral intake is impaired. To achieve this end, optimal nutritional composition and route of administration have been investigated. However, little attention has been paid to fulfillment of vitamin and trace element requirements in the setting of HSCT thus far.

Currently, adult parenteral multivitamin formulation requirements are based on recommendations proposed in a workshop sponsored by the Food and Drug Administration and the American Medical Association in 1985. Similarly, the American Medical Association proposed the recommendation of trace elements in adult parenteral nutrition, and several modifications were made by American Society of Parenteral and Enteral Nutrition [3]. In the field of HSCT, these formulations are widely applied in nutritional management when oral intake is severely impaired. However, appropriateness of these formulations during the highly stressful and hypercatabolic state of HSCT has not been evaluated before. Therefore, we planned this prospective observational study in which we evaluated the blood level of these substances in patients during the acute phase of allogeneic HSCT.

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METHODS AND METHODS

Patients

The subjects were 15 adult patients who received allogeneic HSCT consecutively at The University of Tokyo Hospital, Japan, between October 2010 and July 2012. The basic characteristics of the patients are shown in Table 1. This study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of The University of Tokyo Hospital. We obtained written informed consent from all patients.

Stem Cell Transplantation Procedure

Eight patients received myeloablative conditioning regimens and the other 7 received nonmyeloablative conditioning regimens. Graft-versus-host disease prophylaxis was performed with calcineurin inhibitors with short-term methotrexate. Infection prophylaxis was performed with quinolone, azole, and acyclovir.

We routinely consult with nutrition experts and follow their advice. In most cases, we use a high-calorie total parenteral nutrition solution kit, which contains glucose, electrolytes, amino acids, vitamins, and trace elements. In cases of specific conditions, such as renal damage, we assemble appropriate nutrition components, including multivitamin preparation and trace element supplementation.

Measurements of Vitamins and Trace Elements

Vitamins (vitamin B1, vitamin B6, vitamin C, vitamin E, vitamin K, and folate) and trace elements (iron, zinc, copper, and selenium) were measured before conditioning regimens (before HSCT), at the day of stem cell infusion (day 0), and 4 times weekly post transplantation (day 7, day 14, day 21, and day 28). Alterations of the timing, plus or minus 2 days, were allowed. Peripheral blood was processed adequately for measurement; eg, protein-free blood serum was prepared for vitamin C measurement, whole blood with EDTA-2Na for vitamin B1, and citrate-added plasma for vitamin K series. All the other items were measured with chilled or frozen plasma. These substances were measured at SRL, Inc. Japan.

Measurements of Nutrition Status

Oral and total calorie intake were recorded. Basal energy expenditure (BEE) was calculated with Harris-Benedict equations. Supplementation of parenteral vitamins and trace microelements was also recorded.

Statistical Analysis

Numerical variables were compared with Student *t*-test. Correlation between vitamin C and inflammatory proteins (C-reactive protein and ferritin) were assessed with Spearman's rank correlation test. A *P* value greater than .05 was considered significant. Analyses were computed with R version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1
Characteristics of the Patients and HSCT

Characteristic	n
Sex: male/female	9/6
Age, median (range), yr	48 (34-69)
Disease	
Acute myeloid leukemia	7
Myelodysplastic syndrome	2
Non-Hodgkin lymphoma	2
Myelofibrosis	2
Acute lymphoblastic leukemia	1
Chronic myeloid leukemia	1
Disease status	
Complete remission	4
Chronic phase	1
Refractory	5
Primary	5
Donor source	
uBMT	10
CBT	3
rPBSCT	2
Conditioning	
CY/TBI	7
CY/VP16/TBI	1
Flu/Mel/TBI	5
Flu/Bu/TBI	2
BEE, median (range), Kcal	1410 (1055-1654)

HSCT indicates hematopoietic stem cell transplantation; uBMT, unrelated bone marrow transplantation; CBT, cord blood transplantation; rPBSCT, related peripheral blood stem cell transplantation; CY, cyclophosphamide; VP16, etoposide; TBI, total body irradiation, Flu, fludarabine; Mel, melphalan; Bu, busulfan; BEE, basal energy expenditure.
Data presented are n unless otherwise indicated.

RESULTS

Study Accomplishments

One patient died of severe sepsis on day 11 and another refused to provide blood samples on day 21 and day 28. In the analyses, these 2 patients with incomplete data are included.

Total Calorie Intake and Supplementation Status of Vitamins and Microelements

Oral intake was impaired in all the patients and dipped around day 14, when average oral calorie intake was only 122 Kcal/day (±354 Kcal/day), although this value was 1563 Kcal/day (±654 Kcal/day) before conditioning regimens started. The oral and parenteral energy intake profile is demonstrated in Supplementary Figure 1A and the ratio of total energy intake to BEE is shown in Supplementary Figure 1B. In 92% of the gross examination points, patients had either oral calorie intake more than 500 Kcal/day or parenteral multivitamin preparations (Supplementary Figure 1C). Also, in 82% of the gross examination points, patients had either oral calorie intake more than 500 Kcal/day or parenteral trace elements preparations (Supplementary Figure 1D).

Profiles of Vitamins and Microelements

Vitamin B

The normal range of vitamin B1 is from 20 to 50 ng/mL. Characteristic to the vitamin B1 profile was that average level was around the normal lower limit before the start of conditioning (20 ± 4.9 ng/mL). Then, vitamin B1 level became deficient at day 0 (17.4 ± 4.5 ng/mL) and day 7 (17.8 ± 3.1 ng/mL). Fourteen of 15 samples at day 0 and all 15 samples at day 7 were below the lower normal limit. Although average levels rose to the normal range at day 21 (25 ± 15 ng/mL) and day 28 (28 ± 18 ng/mL), these averages were pulled up by 1 exceptionally high value at each point and many of the samples (10 of 13 samples at day 21, and 9 of 13 samples at day 28) remained below the lower limit level (Figure 1A).

Vitamin B6

Among the 3 components (pyridoxal, pyridoxine, and pyridoxamine) that constitute vitamin B6 compounds, we evaluated pyridoxal value as a representative of vitamin B6. Overdose was not seen at any evaluation point (Figure 1B).

Vitamin C

The vitamin C profile was salient in its deficiency in the acute phase (Figure 1C). Although the pre-HSCT level of vitamin C (6.5 ± 4.2 μg/mL) was within the normal range (5.5 to 16.8 μg/mL), a marked deficiency was seen from day 0 (3.8 ± 2.6 μg/mL) to all the following measurement periods and hit the lowest point at day 14 (2.1 ± 1.4 μg/mL). Vitamin C levels were inversely correlated with C-reactive protein values at day 14 ($P = .020$, $\rho = -.61$), day 21 ($P = .0046$, $\rho = -.73$), and day 28 ($P = .026$, $\rho = -.61$). Similarly, vitamin C levels showed an inverse correlation with ferritin levels at day 7 ($P = .029$, $\rho = -.57$), day 14 ($P = .0046$, $\rho = -.73$), and day 28 ($P = .0011$, $\rho = -.80$) (Supplementary Figure 2).

Vitamin E

The vitamin E level is assumed normal when its value is .75 to 1.41 mg/dL. Contrary to the previous report that suggested vitamin E deficiency in the HSCT setting [4], our patients showed almost normal vitamin E levels throughout the acute phase (Figure 1D). This implies that the current supplementation strategy is well functioning, even under stressful conditions [5]. Although vitamin E is one of the most important antioxidant vitamins, vitamin E levels had no correlation with inflammatory markers at any time points during HSCT (data not shown).

Vitamin K

Before HSCT, all patients except 1 had a normal vitamin K level (.15 to 1.25 ng/mL). However, most patients showed an increase of vitamin K afterwards up to 10 times the normal upper limit at day 14 (13 ± 5.8 ng/mL) and day 21 (16 ± 16 ng/mL) (Figure 1E). This increase was apparently associated with start of parenteral nutrition, because the vitamin levels with and without multivitamin formulation were significantly different (1.5 ± 3.6 ng/mL and 15.6 ± 13.6 ng/mL, $P < .0001$ by *t*-test) (Supplementary Figure 3).

Folate

Average levels of folate were within the normal range (>3.1 ng/mL) at all study points. However, median levels were below the lower normal limit before HSCT (2.9 ng/mL) and on day 0 (2.9 ng/mL), which reflects that more than one half of the patients had insufficient levels (Figure 1F). Paradoxically, folate deficiency ratio dropped to 21% at day14, when parenteral nutrition with adequate folate supplementation was started in most patients.

Ferritin

The ferritin normal range is 3.6 to 340 ng/mL. The serum ferritin profile and its impact on HSCT outcomes have been studied extensively by us and others [6]. Ferritin levels substantially and constantly exceeded the normal range with an increasing trend (Figure 1G).