Capsule endoscopy after hematopoietic stem cell transplantation can predict transplant-related mortality

Kazuya Inoki[1,2*], Yasuo Kakugawa[1,3], Hiroyuki Takamaru[1,3], Masau Sekiguchi[1,3], Minori Matsumoto[1,3], Takahisa Matsuda[1,3], Ayumu Ito[4], Takashi Tanaka[4], Yoshihiro Inamoto[4], Shigeo Fuji[4], Saiko Kurosawa[4], Sung-Won Kim[4], Takahiro Fukuda[4], Yuichiro Ohe[2], Yutaka Saito[1]

Institution

1. Endoscopy Division, National Cancer Center Hospital, Tokyo, Japan.

2. Course of Advanced Clinical Research of Cancer, Juntendo University Graduate School of Medicine, Tokyo, Japan

3. Cancer Screening Center, National Cancer Center Hospital, Tokyo, Japan.

4. Department of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan.

Short title: Capsule endoscopy for gastrointestinal GVHD

***Corresponding Author:**

Kazuya Inoki, MD

National Cancer Center Hospital

Endoscopy Division

5-1-1 Tsukiji, Chuo-ku, Tokyo

104-0045, Japan

Tel: +81-3-3542-2511

Fax: +81-3-3542-3815

E-mail: kinoki@med.showa-u.ac.jp

Keywords: Capsule endoscopy, Graft-versus-host disease, Transplant-related mortality

Abstract

Background and Objectives: Allogenic hematopoietic stem cell transplantation (allo-SCT) is a curative therapy for hematological malignancies, but transplant-related mortality (TRM) remains a concern. This study aimed to determine the efficacy of capsule endoscopy (CE) by evaluating the correlation between inflammatory findings on CE and TRM.

Methods: The data of patients after allo-SCT were retrospectively collected. The association between findings on CE and TRM at 100 days from the CE was evaluated.

Results: Of the 94 patients included in the study, 47 showed inflammatory findings on CE. The findings were diagnosed as graft-versus-host disease (GVHD) (n = 17), cytomegalovirus (CMV) infection (n = 14), and GVHD with CMV infection (n = 16). Of the 47 patients, 13 (28%) had TRM. Endoscopic diagnoses of these TRM cases were GVHD (n = 4), CMV infection (n = 0), and GVHD with CMV infection (n = 9). In contrast, in the remaining 47 patients who showed no inflammatory findings on CE, 2 patients (4%) had TRM. The proportion of TRM was higher in patients with inflammatory findings than in those without it (28% vs. 4%, $p < 0.01$).

Conclusions: CE may predict TRM in patients who developed gastrointestinal symptoms after allo-SCT.

Introduction

Allogenic hematopoietic stem cell transplantation (allo-SCT) is widely accepted as a curative therapy for advanced hematological malignancies. Graft-versus-host disease (GVHD) is considered as a major cause of transplant-related mortality (TRM) after allo-SCT. Although the small intestine is the most common site of gastrointestinal GVHD [1 - 4] and only a short segment of the small intestine can be observed by esophagogastroduodenoscopy (EGD) or total colonoscopy (TCS), EGD or TCS with biopsy have been considered as the standard approach for the diagnosis of GVHD. Capsule endoscopy (CE) enables the observation of the entire segment of the small intestine, and it is less invasive than EGD or TCS. The efficacy and safety of CE in patients who exhibited gastrointestinal GVHD after allo-SCT has been reported [5 - 9]. Neumann et al. reported the sensitivity and specificity of CE for the diagnosis of acute gastrointestinal GVHD, which were almost the same as those of EGD or TCS with biopsy [7]. Furthermore, a high negative predictive value of macroscopic findings obtained on CE has been reported for the diagnosis of gastrointestinal GVHD [5, 7]. Although biopsy is currently the gold standard approach for the diagnosis of gastrointestinal GVHD, CE has demonstrated high diagnostic ability for gastrointestinal GVHD. It has been reported that early recognition and treatment of gastrointestinal GVHD immediately after obtaining CE results without waiting for biopsy results can yield good outcomes [10].

Clinical grading defined by the volume of diarrhea is generally used to evaluate the severity of gut GVHD. The grade of gut GVHD is combined with the skin and liver grades to evaluate the overall status of acute GVHD [11, 12]. Although clinical grading is a non-invasive and simple approach to assess the severity of gut GVHD, it is sometimes challenging to measure the precise amount of diarrhea. In contrast, endoscopic findings provide more direct and objective information [13 - 17]. The differential diagnosis of GVHD and cytomegalovirus (CMV) infection is important because the immunosuppressive

treatment of GVHD may worsen CMV infection. Furthermore, the prevention of severe GVHD and the control of infection reportedly associated with bacteria as well as with CMV or fungus are imperative for reducing TRM [16]. Among these, the status of GVHD and CMV infections can be obtained by endoscopy [18 - 21].

Considering that the small intestine is a major target of gastrointestinal GVHD, we hypothesized that the inflammation in the small intestine after allo-SCT may be correlated with TRM, and it is believed that clarifying this correlation may lead to the development of new therapeutic interventions. This study aimed to elucidate the efficacy of CE in patients who underwent allo-SCT and subsequently exhibited gastrointestinal symptoms by evaluating the correlation between TRM and CE findings that indicate GVHD or CMV infection.

Patients and methods

Study design and patients

This was a retrospective single-center observational cohort study that included consecutive patients who underwent allo-SCT at the National Cancer Center Hospital, Tokyo, Japan between March 2009 and February 2017. This study was approved by our Institutional Ethics Committee (2016-245). A total of 683 patients underwent allo-SCT, and 97 patients with digestive symptoms after allo-SCT underwent a total of 156 CEs. Among these CEs, 8 CEs in 7 patients were not evaluated because of the incomplete transit of the capsule during recording, with regional transit abnormality of CE in the stomach or excretion with vomiting. Of the patients who experienced incomplete CE, 4 were evaluated with another CE that was performed on another day. Therefore, 3 patients and 8 CEs were excluded, and 94 patients and 148 CEs were finally included in this study (Figure 1). Endoscopic diagnosis of GVHD and CMV

were made with CE findings by an experienced endoscopist (Y.K.). The clinical data from electronic medical charts and CE reports of the 94 patients were retrospectively collected. We collected data on age, sex, underlying diseases, stem cell source, conditioning regimen for allo-SCT, GVHD prophylaxis, the presence of acute GVHD, number of CE procedures for each patient, adverse events caused by CE, cause of death, and inflammatory findings on CE. The presence of inflammation in the small intestine on CE and the cause of inflammation were evaluated. The reasons for inflammatory findings on CE included GVHD, CMV infection, and GVHD with CMV infection. If a patient underwent CE multiple time, CE that demonstrated the most severe grade with macroscopic classification was adopted to evaluate the relevance between CE findings and TRM. In addition the associations between inflammatory findings observed on CE and TRM at 100 days from the CE was investigated.

CE procedure

CE was performed using PillCam SB® (SB1, SB2, or SB3) (Medtronic, Minneapolis, MN, USA). CE was scheduled when patients developed diarrhea classified as grade 1 or more with clinical gastrointestinal GVHD grading, or when they developed diarrhea classified as less than grade 1, but the wall thickness of the small intestine was confirmed by abdominal echography or computed tomography (CT). CE was performed on the following day. Patients were instructed to fast after taking an evening meal on the day before the procedure. No bowel preparation was performed. On the day of CE, the patients wore a special shirt (Figure 2) with electrical patches outside, which were usually placed directly onto the skin. This approach was adopted because placing adhesive patches directly onto the skin of GVHD patients could harm their vulnerable skin owing to the possibility of skin GVHD. Patients were scheduled to swallow the capsule endoscope with water early in the morning after loading a

recorder. After swallowing the capsule endoscope, 10 mg metoclopramide was administered immediately, followed by 10 mg mosapride citrate hydrate 4 h later to enhance capsule excretion. After swallowing the capsule endoscope, patients were nil per os. Patients were allowed to drink 2 h after and eat a light meal 4 h after swallowing the capsule endoscope. Capsule excretion was confirmed in all patients. The capsule recorder was retrieved after capsule excretion or after confirming battery exhaustion.

Typical CE findings of GVHD and CMV infection

The typical CE findings of GVHD are diffuse inflammatory changes, including edema, erythematous change, and disappearance of mucosa (Figures 3a,3b)[7]. To grade the inflammatory status of GVHD using CE, we developed a macroscopic classification of the small intestine in GVHD patients (Table 1; Figure 4). The grades were as follows: grade 1, redness, edema, and indistinct vascular pattern; grade 2, rough mucosa and mucosal atrophy; grade 3, partial disappearance of the mucosa; and grade 4, total disappearance of the mucosa. Normal mucosa remained in grade 3. In contrast, almost all normal mucosa samples were excluded, and no villi structures were noted in grade 4.

The typical CE findings of CMV infection are scattered inflammatory changes, and they include small erosions or ulcers with a well-demarcated margin in the small intestine (Figures 3c,3d) [18 - 20]. If patients revealed CMV antigenemia or CMV enteritis, they were treated according to the CMV treatment guideline of the Japanese Society for Hematopoietic Cell Transplantation.

Diagnosis of GVHD and CMV

Diagnosis of GVHD was mainly based on histological diagnosis by EGD and TCS [22]. Considering the possibility of false negative results of biopsy, if the patients revealed the typical CE findings of

GVHD by CE, GVHD diagnosis was performed without histological evidence, and treatment for GVHD was initiated. The diagnosis of CMV infection was performed using several diagnostic tools such as histological evidence by EGD and TCS, and CMV antigenemia[18, 20, 23]. We then added CE for the diagnosis of small intestinal CMV infection. If there was at least one positive result for CMV among them, we diagnosed CMV infection, and initiated the treatment for CMV infection.

Definition of inflammation on CE and TRM

The diagnoses on CE were GVHD, CMV infection, GVHD with CMV infection, and no inflammatory findings. Inflammation on CE was considered positive when macroscopic CE findings observed in GVHD or CMV infection were noted. TRM was defined as death from any cause other than disease progression or relapse. The associations between inflammatory findings observed on CE and TRM within 100 days from the day of CE was investigated. The causes of TRM were divided into 3 categories based on the classification proposed by Japanese group for blood and marrow transplantation [24], which were organ toxicity, infectious complication, and GVHD.

Results

During the study period, 94 patients underwent 148 CEs. Table 2 shows the clinical characteristics of the study patients. The median patient age was 55 years (range, 18–70 years), and there were a total of 50 men and 44 women, and. The underlying diseases were acute leukemia (n = 40), chronic myelogenous leukemia (n = 3), myelodysplastic syndrome (n = 8), adult T-cell leukemia/lymphoma (n = 15), lymphoma (n = 27), and plasma cell neoplasms (n = 1). The stem cell sources were related peripheral blood stem cell (PBSC) (n = 27), unrelated bone marrow (n = 30), unrelated PBSC (n = 7),

and unrelated cord blood (n = 30). The conditioning regimen for allo-SCT were myeloablative conditioning (n = 31) and reduced intensity conditioning (n = 63). The medicines used for GVHD prophylaxis were calcineurin inhibitor (CNI) with methotrexate (MTX) (n = 59), CNI with mycophenolate mofetil (MMF) (n = 32), CNI alone (n = 3), anti-human thymocyte immunoglobulin (n = 27), and post-transplant cyclophosphamide (n = 11). The observed target lesion of acute GVHD were skin (n = 63), liver (n = 3), and gut (n = 63). The mean number of CE procedures was 1.5 (range: 1– 5) per patient. No retention after stomach passage was noted in the study period. Furthermore, no strictures including diaphragm-like strictures were noted in the whole intestine for all cases. The median interval from transplantation to CE was 67 days (interquartile range [IQR], 35–104) (Table 2). The median intervals from transplantation to diagnoses of GVHD, CMV infection, GVHD with CMV infection, and no specific findings were 60 (IQR, 30–99), 54 (IQR, 42–149), 60 (IQR, 44–112), and 57 (IQR, 35–101) days, respectively (Figure 5).

The association between diagnosis of GVHD grading by CE (macroscopic grading) and GVHD grading by stool volume revealed (clinical grading) that 8 cases were diagnosed with grade 3 or grade 4 stage by macroscopic grading; however, at the same time they were diagnosed with less than grade 2 gut GVHD by clinical grading (Table 3). In these 8 cases, TRM were noted in 5 cases.

Of the 94 patients, 47 showed inflammatory findings on CE. The findings were endoscopically diagnosed as compatible with GVHD (n = 17), compatible with CMV infection (n = 14), and compatible with GVHD and CMV infection (n = 16). Of these 47 patients, TRM within 100 days from the last CE occurred in 13 patients (28%). The endoscopic diagnoses of these TRM cases were GVHD (n = 4), CMV infection (n = 0), and both GVHD and CMV infection (n = 9). In contrast, in the remaining 47 patients who showed no inflammatory findings on CE, TRM within 100 days occurred in 2 patients (4%). The

proportion of TRM was significantly higher in patients with inflammatory findings than in those without inflammatory findings (28% vs. 4%, $p < 0.01$) (Table 4). The cause of TRM were organ toxicity (multiple organ failure) (n = 8), infectious complication (n = 5), and GVHD (n = 2)

EGD and/or TCS were performed for 79 cases. Of these, 35 cases showed inflammatory CE findings. Of these 35 cases, 3 showed no inflammatory findings with EGD or TCS. EGD or TCS biopsies were obtained from 32 patients of the 47 patients who showed inflammatory findings on CE. Of these 32 patients, 21, 0, 3, and 8 patients were histologically diagnosed with GVHD, CMV infection, GVHD with CMV infection, and no specific findings, respectively. In contrast, EGD or TCS biopsies were obtained from 38 patients of the 47 patients who did not show inflammatory findings on CE. Of these 38 patients, 17, 2, 4, and 15 patients were histologically diagnosed with GVHD, CMV infection, GVHD with CMV infection, and no specific findings, respectively (Figure 6). With regard to the presence of biopsy-proven GVHD (either alone or in combination with CMV histologically), the sensitivity of inflammatory changes on CE for GVHD was 53.3% and specificity was 68%. Further, the negative predictive value was 44.7% and the positive predictive value was 75% (+CE & +GVHD = 24, +CE & −GVHD = 8, −CE & +GVHD = 21, −CE & −GVHD = 17).Table 5 shows the association between macroscopic grading of GVHD and TRM within 100 days from the last CE. No TRM within 100 days from the last CE was noted in grade 1 patients. TRM within 100 days from the last CE was observed in 3 of 10 grade 2 patients (20%) and 2 of 8 grade 3 patients (25%). In contrast, TRM within 100 days from the last CE was observed in 8 of 13 grade 4 patients (62%). A higher proportion of TRM was noted in macroscopic GVHD grade 4 patients than in patients with other grades.

Discussion

This is the first study to investigate the correlation between inflammatory findings on CE and TRM among patients who presented with gastrointestinal symptoms after allo-SCT. This study demonstrated 3 important results. First, a significantly higher proportion of TRM was confirmed in patients with inflammatory findings than in those without inflammatory findings on CE. Second, CE was performed safely in patients with gut GVHD after allo-SCT. Although the inflammatory findings of gut GVHD after allo-SCT are occasionally severe and reduced motility of the gastrointestinal tract is of concern, no CE-related complications such as retention were observed. Third, several cases were diagnosed with severe GVHD by CE, none showed a large amount of diarrhea. In this situation, we may have missed the severe inflammatory status of the small intestine caused by GVHD.

A significantly higher proportion of TRM was noted in patients with inflammatory findings than in those without inflammatory findings on CE. Furthermore, if the patients exhibited a severe macroscopic GVHD grade, the proportion of TRM tended to be higher. The results were appropriate, as GVHD is one of the major causes of TRM [16]. In contrast, it was reported that higher mortality was observed with increasingly severe clinical grading of gut GVHD using the volume of diarrhea [12, 25]. The macroscopic GVHD grade using CE revealed the same tendency with clinical grading about the association between grades and the proportion of TRM.

Macroscopic CE findings of the small intestine in patients with gut GVHD may be an additional predictive factor of TRM after allo-SCT. Survival in patients with systemic steroid-refractory acute GVHD has been shown to be poor despite the use of various immunosuppressive agents [26]. One of the reported risk factors to predict steroid-refractory GVHD is GVHD severity [27, 28]. These patients could be candidates for new treatment strategies other than steroid administration. Although the additional use of anti-thymocyte globulin that induces strong deletion of T cells is one of the treatment options, it can

cause severe infectious complications; therefore, patient selection is important [29]. Early recognition of severe gut GVHD with CE may help select candidate patients for the use of anti-thymocyte globulin.

TRM occurred in 4 of 17 patients (24%) who were diagnosed with GVHD on CE and 9 of 16 patients (56%) who were diagnosed with both GVHD and CMV infection on CE. In contrast, no TRM was observed in patients who were diagnosed with only CMV infection on CE. These findings were obtained because GVHD can be a cause of TRM, and the coexistence of uncontrollable GVHD and CMV infection may result in a worse prognosis, because strong immunosuppressive therapy for GVHD makes appropriate treatment of CMV infection difficult. The standard management for CMV infection involves preemptive therapy, wherein patients receive antiviral agents on developing laboratory-confirmed evidence of infection [30 - 32]. Although a higher sensitivity of real-time polymerase chain reaction in comparison with pp65 antigenemia assay for the diagnosis of CMV gastroenteritis has been reported, the complete detection and prevention of CMV gastroenteritis remains difficult [33, 34]. Macroscopic CE findings can be used as a complementary diagnostic option for CMV gastroenteritis when patients exhibit gastrointestinal symptoms.

Although gastrointestinal dysmotility could occur after allo-SCT [35], and regional transit abnormality of CE or vomiting were observed in several cases in this study, no capsule retention defined as presence of the capsule in the digestive tract for more than 2 weeks was observed. Furthermore, although inflammation of the small intestine with gut GVHD was sometimes severe and large areas of villi were sometimes missing, no apparent stricture or stenosis was observed in this study. The major histological findings of gut GVHD are crypt apoptosis and inflammation, which are limited to the superficial layer [36]. Therefore, stenosis is considered to be unlikely. CE for gut GVHD patients can be performed safely without conducting patency capsule, considering the etiology of gut GVHD.

It is worthy of remark that there was a discrepancy between GVHD grade made by CE (macroscopic grading) and that made by volume of diarrhea (clinical grading). In the present study, 5 TRM were noted in 8 cases who were diagnosed with grade 1 or 2 by clinical grading but were diagnosed with grade 3 or 4 by macroscopic grading. Diarrhea is a result of inflammation and can be influenced by the volume of oral fluid intake; therefore, it often does not reflect the severity of intestinal inflammation. In contrast, visualization of the small intestine with CE provides direct information about the inflammatory status. Therefore, the utilization of macroscopic CE findings in addition to the current clinical grading of gut GVHD using the volume of diarrhea will allow more precise and timely evaluation of the gut GVHD status. Although the sensitivity and specificity of CE findings for biopsy proven GVHD in this study were not so high, the positive predictive value is relatively high, which indicates the usefulness of CE for patients who underwent Allo-SCTs.

The present study has several limitations. First, this was a retrospective study performed at a single institution, and CE diagnosis was made by a single endoscopist. Prospective multicenter studies are warranted to establish evidence about the correlation between CE findings and TRM. Second, the spread of inflammation in the small intestine was not considered in this study. The correlation between the amount of diarrhea and the spread of inflammation in the small intestine caused by gut GVHD should be investigated in the future to further establish the efficacy of CE for gut GVHD. Third, biopsies were not taken from lesions in the small intestine that were detected on CE. Direct comparison between CE findings in the small intestine and biopsy results was difficult. A more direct approach such as double-balloon enteroscopy is necessary to obtain biopsy results from lesions in the small intestine; however, considering the poor general condition of patients after allo-SCT with the clinical suspicion of gastrointestinal GVHD, double-balloon enteroscopy may be extremely invasive. Further investigations,

especially about the diagnosis of CMV infection in the small intestine with CE, are necessary.

In conclusion, this study demonstrated the significant association between inflammatory findings identified on CE and TRM within 100 days in patients with gut GVHD after allo-SCT. It may be beneficial to use CE findings in addition to current clinical grading involving the amount of diarrhea for the evaluation of gut GVHD severity.

Statements

Statement of Ethics

The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding sources

This work was supported in part by The National Cancer Center Research and Development Fund 28-A-4, 29-A-14.

References

1 Jones B, Fishman EK, Kramer SS, Siegelman SS, Saral R, Beschorner WE, Yeager AM, Lake AM, Yolken RH, Tutschka P, et al.: Computed tomography of gastrointestinal inflammation after bone marrow transplantation. AJR American journal of roentgenology 1986;146:691-695.

2 Schimmelpenninck M, Zwaan F: Radiographic features of small intestinal injury in human graft-versus-host disease. Gastrointestinal radiology 1982;7:29-33.

3 Fisk JD, Shulman HM, Greening RR, McDonald GB, Sale GE, Thomas ED: Gastrointestinal radiographic features of human graft-vs.-host disease. AJR American journal of roentgenology 1981;136:329-336.

4 Rosenberg HK, Serota FT, Koch P, Borden St, August CS: Radiographic features of gastrointestinal graft-vs.-host disease. Radiology 1981;138:371-374.

5 Yakoub-Agha I, Maunoury V, Wacrenier A, Couignoux S, Depil S, Desreumaux P, Bauters F, Colombel JF, Jouet JP: Impact of Small Bowel Exploration Using Video-Capsule Endoscopy in the Management of Acute Gastrointestinal Graft-versus-Host Disease. Transplantation 2004;78:1697-1701.

6 Silbermintz A, Sahdev I, Moy L, Vlachos A, Lipton J, Levine J: Capsule endoscopy as a diagnostic tool in the evaluation of graft-vs.-host disease. Pediatric transplantation 2006;10:252-254.

7 Neumann S, Schoppmeyer K, Lange T, Wiedmann M, Golsong J, Tannapfel A, Mossner J, Niederwieser D, Caca K: Wireless capsule endoscopy for diagnosis of acute intestinal graft-versus-host disease. Gastrointest Endosc 2007;65:403-409.

8 Malard F, Mohty M: New insight for the diagnosis of gastrointestinal acute graft-versus-host disease. Mediators of inflammation 2014;2014:701013.

9 Perez-Cuadrado-Robles E, Castilla-Llorente C, Queneherve L, Lopez-Higueras A, Perez-Cuadrado-Martinez E: Short article: Capsule endoscopy in graft-versus-host disease. European journal of gastroenterology & hepatology 2017;29:423-427.

10 Blanco-Velasco G, Cuba-Sasco C, Hernandez-Mondragon OV, Paz-Flores V, Blancas-Valencia JM: Gastrointestinal graft-versus-host disease. What is the role of capsule endoscopy? A case series. Revista de gastroenterologia de Mexico 2017;82:191-192.

11 Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED: Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. Transplantation 1974;18:295-304.

12 Rowlings PA, Przepiorka D, Klein JP, Gale RP, Passweg JR, Henslee-Downey PJ, Cahn JY, Calderwood S, Gratwohl A, Socie G, Abecasis MM, Sobocinski KA, Zhang MJ, Horowitz MM: IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British journal of haematology 1997;97:855-864.

13 Kreisel W, Dahlberg M, Bertz H, Harder J, Potthoff K, Deibert P, Schmitt-Graeff A, Finke J: Endoscopic diagnosis of acute intestinal GVHD following allogeneic hematopoietic SCT: a retrospective analysis in 175 patients. Bone marrow transplantation 2012;47:430-438.

14 Slavin S, Nagler A, Naparstek E, Kapelushnik Y, Aker M, Cividalli G, Varadi G, Kirschbaum M, Ackerstein A, Samuel S, Amar A, Brautbar C, Ben-Tal O, Eldor A, Or R: Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998;91:756-763.

15 Gooley TA, Chien JW, Pergam SA, Hingorani S, Sorror ML, Boeckh M, Martin PJ, Sandmaier BM, Marr KA, Appelbaum FR, Storb R, McDonald GB: Reduced mortality after allogeneic hematopoietic-cell transplantation. The New England journal of medicine 2010;363:2091-2101.

16 Horan JT, Logan BR, Agovi-Johnson MA, Lazarus HM, Bacigalupo AA, Ballen KK, Bredeson CN, Carabasi MH, Gupta V, Hale GA, Khoury HJ, Juckett MB, Litzow MR, Martino R, McCarthy PL, Smith FO, Rizzo JD, Pasquini MC: Reducing the risk for transplantation-related mortality after allogeneic hematopoietic cell transplantation: how much progress has been made? Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2011;29:805-813.

17 Fuji S, Kim SW, Yano S, Hagiwara S, Nakamae H, Hidaka M, Ito T, Ohashi K, Hatanaka K, Takami A, Kurosawa S, Yamashita T, Yamaguchi T, Fukuda T: A prospective multicenter study of unrelated bone marrow transplants using a reduced-intensity conditioning regimen with low-dose ATG-F; Bone marrow transplantation. England, 2016, vol 51, pp 451-453.

18 Kakugawa Y, Kami M, Kozu T, Kobayashi N, Shoda H, Matsuda T, Saito Y, Oda I, Gotoda T, Mori S, Tanosaki R, Murashige N, Hamaki T, Mineishi S, Takaue Y, Shimoda T, Saito D: Endoscopic evaluation for cytomegalovirus enterocolitis after allogeneic haematopoietic stem cell transplantation. Gut 2006;55:895-896.

19 Kakugawa Y, Gotoda T: Necessity of ruling out cytomegalovirus enteritis in cases of erosions and/or ulcerations diagnosed by video capsule endoscopy after allogeneic hematopoietic

stem cell transplantation; Gastrointest Endosc. United States, 2007, vol 66, pp 1068 author reply 1068-1069.

20 Kakugawa Y, Kim SW, Takizawa K, Kikuchi T, Fujieda A, Waki F, Fukuda T, Saito Y, Shimoda T, Takaue Y, Saito D: Small intestinal CMV disease detected by capsule endoscopy after allogeneic hematopoietic SCT; Bone marrow transplantation. England, 2008, vol 42, pp 283-284.

21 Kakugawa Y, Kami M, Matsuda T, Saito Y, Kim SW, Fukuda T, Mori S, Shimoda T, Tanosaki R, Saito D: Endoscopic diagnosis of cytomegalovirus gastritis after allogeneic hematopoietic stem cell transplantation. World J Gastroenterol 2010;16:2907-2912.

22 Dignan FL, Clark A, Amrolia P, Cornish J, Jackson G, Mahendra P, Scarisbrick JJ, Taylor PC, Hadzic N, Shaw BE, Potter MN: Diagnosis and management of acute graft-versus-host disease. British journal of haematology 2012;158:30-45.

23 Boeckh M, Bowden RA, Gooley T, Myerson D, Corey L: Successful modification of a pp65 antigenemia-based early treatment strategy for prevention of cytomegalovirus disease in allogeneic marrow transplant recipients. Blood 1999;93:1781-1782.

24 Yamasaki S, Ohno Y, Taniguchi S, Yoshida T, Hayashi S, Ogawa H, Shimazaki C, Takahashi S, Kasai M, Wake A, Nishimura M, Tokunaga K, Gondo H, Takaue Y, Harada M, Mineishi S: Allogeneic peripheral blood stem cell transplantation from two- or three-loci-mismatched related donors in adult Japanese patients with high-risk hematologic malignancies. Bone marrow transplantation 2004;33:279-289.

25 Cahn JY, Klein JP, Lee SJ, Milpied N, Blaise D, Antin JH, Leblond V, Ifrah N, Jouet JP, Loberiza F, Ringden O, Barrett AJ, Horowitz MM, Socie G: Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. Blood 2005;106:1495-1500.

26 Martin PJ, Schoch G, Fisher L, Byers V, Anasetti C, Appelbaum FR, Beatty PG, Doney K, McDonald GB, Sanders JE, et al.: A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. Blood 1990;76:1464-1472.

27 MacMillan ML, Weisdorf DJ, Wagner JE, DeFor TE, Burns LJ, Ramsay NK, Davies SM, Blazar BR: Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation 2002;8:387-394.

28 Westin JR, Saliba RM, De Lima M, Alousi A, Hosing C, Qazilbash MH, Khouri IF, Shpall EJ, Anderlini P, Rondon G, Andersson BS, Champlin R, Couriel DR: Steroid-Refractory Acute GVHD: Predictors and Outcomes. Advances in hematology 2011;2011:601953.

29 McCaul KG, Nevill TJ, Barnett MJ, Toze CL, Currie CJ, Sutherland HJ, Conneally EA, Shepherd JD, Nantel SH, Hogge DE, Klingemann HG: Treatment of steroid-resistant acute graft-versus-host disease with rabbit antithymocyte globulin. Journal of hematotherapy & stem cell research 2000;9:367-374.

30 Schmidt GM, Horak DA, Niland JC, Duncan SR, Forman SJ, Zaia JA: A randomized, controlled trial of prophylactic ganciclovir for cytomegalovirus pulmonary infection in recipients of allogeneic bone marrow transplants; The City of Hope-Stanford-Syntex CMV Study Group. The New England journal of medicine 1991;324:1005-1011.

31 Ljungman P, Aschan J, Lewensohn-Fuchs I, Carlens S, Larsson K, Lonnqvist B, Mattsson J, Sparrelid E, Winiarski J, Ringden O: Results of different strategies for reducing cytomegalovirus-associated mortality in allogeneic stem cell transplant recipients. Transplantation 1998;66:1330-1334.

32 Yakushiji K, Gondo H, Kamezaki K, Shigematsu K, Hayashi S, Kuroiwa M, Taniguchi S, Ohno Y, Takase K, Numata A, Aoki K, Kato K, Nagafuji K, Shimoda K, Okamura T, Kinukawa N, Kasuga N, Sata M, Harada M: Monitoring of cytomegalovirus reactivation after allogeneic stem cell transplantation: comparison of an antigenemia assay and quantitative real-time polymerase chain reaction. Bone marrow transplantation 2002;29:599-606.

33 Boeckh M, Gooley TA, Myerson D, Cunningham T, Schoch G, Bowden RA: Cytomegalovirus pp65 antigenemia-guided early treatment with ganciclovir versus ganciclovir at engraftment after allogeneic marrow transplantation: a randomized double-blind study. Blood 1996;88:4063-4071.

34 Mori T, Okamoto S, Watanabe R, Yajima T, Iwao Y, Yamazaki R, Nakazato T, Sato N, Iguchi T, Nagayama H, Takayama N, Hibi T, Ikeda Y: Dose-adjusted preemptive therapy for cytomegalovirus disease based on real-time polymerase chain reaction after allogeneic hematopoietic stem cell transplantation. Bone marrow transplantation 2002;29:777-782.

35 Eagle DA, Gian V, Lauwers GY, Manivel JC, Moreb JS, Mastin S, Wingard JR: Gastroparesis following bone marrow transplantation. Bone marrow transplantation 2001;28:59-62.

36 Shidham VB, Chang CC, Shidham G, Ghazala F, Lindholm PF, Kampalath B, George V, Komorowski R: Colon biopsies for evaluation of acute graft-versus-host disease (A-GVHD) in

allogeneic bone marrow transplant patients. BMC gastroenterology 2003;3:5.

Figure legends

Fig. 1. Flow diagram for the study

Fig. 2. A specially designed shirt for capsule endoscopy

The shirt contains electrical patches on the outside to prevent possible skin damage in patients with graft-versus-host disease (GVHD) owing to possible skin GVHD.

Fig. 3. Typical capsule endoscopy findings for the diagnosis of graft-versus-host disease or cytomegalovirus infection

Figures (a) and (b) show the typical capsule endoscopy (CE) findings of graft-versus-host disease that reveal diffuse or circumferential villous atrophy or villous disappearance. Figures (c) and (d) show the typical CE findings of cytomegalovirus infection that revealed scattered erosions or ulcers in the small intestine.

Fig. 4. Macroscopic grading of gastrointestinal graft-versus-host disease

Figure (a) reveals edema, and an indistinct vascular pattern of the small intestine corresponding to macroscopic grade 1. Figure (b) reveals rough mucosa and mucosal atrophy corresponding to macroscopic grade 2. Figures (c) and (d) shows partial disappearance of the mucosa and the total disappearance of the mucosa corresponding to macroscopic grades 3 and 4, respectively.

Fig. 5. Period between the day of transplantation and the day of each diagnosis

The median intervals between the day of transplantation and the day of graft-versus-host disease (GVHD), cytomegalovirus (CMV) infection, GVHD with CMV infection, and no inflammatory findings were 60 (interquartile range [IQR], 30–99), 54 (IQR, 42–149), 60 (IQR, 44–112), and 57 (IQR, 35–101) days, respectively.

Fig. 6. Patient flow regarding capsule endoscopy findings and biopsy results