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A retrospective analysis of computed tomography findings in patients with pulmonary complications after allogeneic hematopoietic stem cell transplantation

Tomotaka Ugai[a], Kohei Hamamoto[b], Shun-ichi Kimura[a], Yu Akahoshi[a], Hirofumi Nakano[a], Naonori Harada[a], Kazuaki Kameda[a], Hidenori Wada[a], Ryoko Yamasaki[a], Yuko Ishihara[a], Koji Kawamura[a], Kana Sakamoto[a], Masahiro Ashizawa[a], Miki Sato[a], Kiriko Terasako-Saito[a], Hideki Nakasone[a], Misato Kikuchi[a], Rie Yamazaki[a], Tomohisa Okochi[b], Junya Kanda[a], Shinichi Kako[a], Osamu Tanaka[b], Yoshinobu Kanda[a,*]

[a] Division of Hematology, Saitama Medical Center, Jichi Medical University, Omiya, Saitama, Japan
[b] Department of Radiology, Saitama Medical Center, Jichi Medical University, Omiya, Saitama, Japan

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ABSTRACT

Objective: The purpose of this study was to review the high-resolution computed tomography (CT) findings in patients with pulmonary complications after allogeneic hematopoietic stem cell transplantation (HSCT), and to evaluate the relationship between CT findings and clinical outcomes.
Patients and methods: We collected the clinical data in 96 consecutive patients who underwent CT scan for pulmonary complications after allogeneic HSCT and analyzed the relationships among these clinical characteristics, CT findings and clinical responses. Radiologists who were blinded to clinical information evaluated the CT findings.
Results: In multivariate analyses, the presence of chronic graft-versus-host disease (GVHD) and non-segmental multiple consolidations were significantly associated with a poor response to antimicrobial therapies, and the disease risk was significantly associated with a poor corticosteroid response. In addition, the existence of cavity formation and pleural effusion were significantly associated with a fatal prognosis. Twenty-five patients underwent bronchoscopic examination and 4 of them also underwent transbronchial lung biopsy (TBLB), but diagnostic information was not obtained in 15 patients. There was no significant association between specific CT findings and the diagnosis based on bronchoscopic examination.
Conclusions: No specific CT finding was identified as a predictor for either an antimicrobial response or for a corticosteroid response in this study. The presence of cavity formation and pleural effusion may predict a poor prognosis.

1. Introduction

Pulmonary complications are a common cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). The widespread use of prophylactic antibiotics and various techniques to monitor pulmonary complications has helped to decrease infectious pulmonary complications in patients who undergo HSCT. However, clinically significant pulmonary complications still occur in 40–60% of patients who undergo allogeneic HSCT, and these complications cause 10–40% of all transplant-related deaths [1–5]. The early and accurate diagnosis of these complications is important because of the high morbidity and mortality [2,3,5]..

Several authors have emphasized the importance of high-resolution computed tomography (CT) in the diagnosis of pulmonary complications after HSCT [6–10]. High-resolution CT may show pulmonary abnormalities in patients with normal find-

* Corresponding author at: Division of Hematology, Saitama Medical Center, Jichi Medical University, 1-847 Amanuma, Omiya-ku, Saitama-city, Saitama 330-8503, Japan. Fax: +81 48 644 5166.
E-mail address: ycanda-tky@umin.ac.jp (Y. Kanda).

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ings on radiographs and is superior to radiography in depicting the pattern and extent of abnormalities. Although some specific patterns may exist, it remains a challenge to obtain a reasonable differential diagnosis and there appears to be some overlap in CT features between infectious and non-infectious diagnoses. In addition, the relationships between clinical responses and specific CT findings have not been fully elucidated. In this retrospective study, we reviewed the high-resolution CT findings in 96 patients who developed pulmonary complications after allogeneic HSCT and analyzed the relationship between CT findings and clinical outcomes.

2. Patients and methods

2.1. Study design

We retrospectively reviewed the charts of 203 consecutive patients who underwent allogeneic HSCT at Saitama Medical Center, Jichi Medical University, between June 2007 and July 2013, and selected 96 patients who developed pulmonary complications after HSCT, underwent high-resolution chest CT within 24 h of the onset of symptoms, and were shown to have abnormal findings by high-resolution CT. This study was approved by the Institutional Review Board of Saitama Medical Center, Jichi Medical University.

We collected data regarding their clinical characteristics, CT findings at the onset of pulmonary complications, and clinical responses (antimicrobial responses and steroid responses), and analyzed the relationships among clinical characteristics, specific CT findings at the first episode of pulmonary complications in each patient and clinical outcomes including antimicrobial response, corticosteroid response and fatal prognosis due to pulmonary complications.

An antimicrobial response was defined as the improvement of oxygenation and respiratory symptoms within 7 days after the administration of antibacterial or antifungal drugs. In the clinical setting we frequently administer antibiotics and antifungal drugs at the same time for patients with pulmonary complications and it is difficult to differentiate between the responses to antibiotics and antifungal drugs. Therefore, we defined an antimicrobial response so as to include a response to either antibiotics or antifungal therapy. A corticosteroid response was defined as the improvement of oxygenation and respiratory symptoms within 7 days after the administration of more than 0.5 mg/kg/day of (methyl-) prednisolone. A fatal prognosis due to pulmonary complications was defined as death from pulmonary complications within 30 days after development.

Clinical characteristics were evaluated in terms of age, sex, the existence of acute and chronic graft-versus-host disease (GVHD), days from HSCT, donor source, disease risk, decrease of calcineurin inhibitor (CI) doses, and conditioning regimen. With regard to the disease status, we defined acute leukemia and malignant lymphoma in first or second complete remission, low-risk myelodysplastic syndrome, aplastic anemia, myeloproliferative neoplasm, and chronic myeloid leukemia in chronic phase as standard-risk, and other conditions were considered high-risk.

2.2. Transplantation procedures

Myeloablative conditioning (MAC) regimens included a combination of cyclophosphamide (CY) and either total-body irradiation (TBI) or busulfan (BU). Fludarabine-based reduced-intensity conditioning (RIC) regimens, such as fludarabine combined with BU or melphalan, with or without low-dose TBI, were used in elderly or clinically infirm patients. Patients with severe aplastic anemia received fludarabine, CY, and anti-thymoglobulin, with or without low-dose TBI at 2 Gy [11].

Alemtuzumab-containing regimens were used in HSCT from a two or three antigen-mismatched donor. GVHD prophylaxis consisted of a continuous infusion of cyclosporine or tacrolimus combined with short-term methotrexate (10–15 mg/m^2 on day 1 and 7–10 mg/m^2 on days 3, 6, and optionally on day 11). Prophylaxis against bacterial, fungal and *Pneumocystis jiroveci* infection consisted of fluoroquinolones, fluconazole, itraconazole or micafungin, and sulfamethoxazole/trimethoprim or inhalation of pentamidine, respectively. As prophylaxis against herpes simplex virus infection, acyclovir was administered from day 7 to day 35, followed by a long-term low-dose administration for varicella-zoster virus reactivation [12,13]. Pre-emptive therapy with ganciclovir was applied by monitoring cytomegalovirus (CMV) antigenemia by the C10/11 method weekly after engraftment [14–16]

2.3. Acquisition and review of high-resolution CT images

All CT examinations were performed on a multi-slice CT scanner (Aquilion 64, Tohshiba Medical Systems, Otawara, Japan). The images were obtained at end-inspiration using a 64×0.5-mm collimation of 0.83 pitch and reconstructed in transverse orientations at a slice thickness of 0.5 mm with both lung windows (width, 1500 HU; level, −700 HU) and mediastinal windows (width, 400 HU; level, 20 HU). Expiratory CT scan was also obtained as supplement to normal inspiratory CT scan in stable patients.

Two radiologists with 13 and 5 years experiences, who were blinded to the clinical information reviewed the images in consensus for evidence of pulmonary complications. The observers evaluated the presence, extent, and distribution of CT findings suggestive of pulmonary complications. CT findings were evaluated as major and minor findings. We classified major findings as lung parenchymal findings and minor findings as associated findings. Major findings included nodules (small localized, small multiple, centrilobular granular shadow, random granular shadow, large localized, large multiple), ground-glass attenuation (GGA) (localized, patchy, diffuse), consolidation (non-segmental localized, non-segmental multiple, segmental patchy), and reticulation (localized, patchy, diffuse). The size of nodules was classified as large ($\geqq$1 cm in diameter) or small (<1 cm in diameter). Minor findings included bronchodilation, halo sign, cavity formation, air-crescent sign, pleural effusion, crazy paving pattern, air trapping, tree in bud sign, and curvilinear opacity. Air trapping were evaluated by expiratory CT. The criteria for these findings were those defined in the Fleischner Society's glossary of terms [17].

2.4. Statistical considerations

Dichotomous variables were compared using Fisher's exact test. Factors with at least borderline significance ($P < 0.15$) by a univariate analysis were subjected to a multivariate analysis by logistic regression analysis. The cut-off P-value for significance was set at 0.05. Kaplan–Meier curves were used to estimate survival probabilities. The cumulative incidence of death from pulmonary complications was estimated and compared using Gray's method, considering death without pulmonary complications as a competing risk. The associations between mortality from pulmonary complications over time after HSCT and CT features were analyzed using a multivariate Fine-Gray proportional hazards model. All statistical analyses were performed with EZR [18], which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).