Multicenter experience in hematopoietic stem cell transplantation for serious complications of common variable immunodeficiency

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Background: Common variable immunodeficiency (CVID) is usually well controlled with immunoglobulin substitution and immunomodulatory drugs. A subgroup of patients has a complicated disease course with high mortality. For these patients, investigation of more invasive, potentially curative treatments, such as allogeneic hematopoietic stem cell transplantation (HSCT), is warranted.

Objective: We sought to define the outcomes of HSCT for patients with CVID.

Methods: Retrospective data were collected from 14 centers worldwide on patients with CVID receiving HSCT between 1993 and 2012.

Results: Twenty-five patients with CVID, which was defined according to international criteria, aged 8 to 50 years at the time

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of transplantation were included in the study. The indication for HSCT was immunologic dysregulation in the majority of patients. The overall survival rate was 48%, and the survival rate for patients undergoing transplantation for lymphoma was 83%. The major causes of death were treatment-refractory graft-versus-host disease accompanied by poor immune reconstitution and infectious complications. Immunoglobulin substitution was stopped in 50% of surviving patients. In 92% of surviving patients, the condition constituting the indication for HSCT resolved.

Conclusion: This multicenter study demonstrated that HSCT in patients with CVID was beneficial in most surviving patients; however, there was a high mortality associated with the procedure. Therefore this therapeutic approach should only be considered in carefully selected patients in whom there has been extensive characterization of the immunologic and/or genetic defect underlying the CVID diagnosis. Criteria for patient selection, refinement of the transplantation protocol, and timing are needed for an improved outcome. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Common variable immunodeficiency, hypogammaglobulinemia, hematopoietic stem cell transplantation, immunologic reconstitution, immunoglobulin substitution/replacement, outcome, mortality, survival*

Common variable immunodeficiency (CVID) is an immunologically and genetically heterogeneous condition characterized by hypogammaglobulinemia of at least 2 immunoglobulin isotypes.[1] CVID can be either classified according to immunologic phenotype[2-5] or molecular[6,7] or clinical[8-10] characteristics. Two subtypes can be broadly described on clinical grounds. Patients might have only infections and typically have a normal life expectancy. In contrast, patients with splenomegaly, granuloma, autoimmunity, enteropathy, liver, interstitial lung disease, or neoplasia have a compromised life expectancy.[8,9,11-13] The severity of the clinical phenotype often correlates with aspects of T-cell deficiency.[4,5,14,15] In fact, the French Study Group defined a subgroup of late-onset combined immunodeficiency within the CVID cohort.[16] Hematopoietic stem cell transplantation (HSCT) is often used for patients with T-cell defects.[17] The growing appreciation of the T-cell defect in patients with CVID[16] and greater data suggesting a poor outcome in this subset[13] have led to interest in HSCT for the treatment of CVID. HSCT has been used for individual patients with CVID with malignancy or suspected combined immunodeficiency[18] with variable humoral immune reconstitution. Therefore to understand the indications and outcomes of HSCT in patients with CVID, we performed a retrospective multicenter study of 25 patients with an underlying diagnosis of CVID who underwent HSCT.

Abbreviations used

aGvHD:	Acute graft-versus-host disease
BM:	Bone marrow
cGvHD:	Chronic graft-versus-host disease
CMV:	Cytomegalovirus
CVID:	Common variable immunodeficiency
ESID:	European Society for Immunodeficiencies
GvHD:	Graft-versus-host disease
HCT-CI:	Hematopoietic Cell Transplant-Comorbidity Index
HSCT:	Hematopoietic stem cell transplantation
MAC:	Myeloablative conditioning
PID:	Primary immunodeficiency
RIC:	Reduced-intensity conditioning

METHODS

Inclusion criteria

The study was approved by the Ethics committee of the Freiburg University Medical Center (no. 275/12), and all patients or their parents signed informed consent forms for data collection. Patients with a diagnosis of CVID who underwent transplantation for any indication were recruited through the SCETIDE database of the Inborn Errors Working Party of the European Society for Blood and Marrow Transplantation, European Society for Immunodeficiencies (ESID), and personal communication. Inclusion criteria were HSCT for any indication and a diagnosis of CVID. Currently published definitions of CVID are controversial because they do not specify delineation from predominant T-cell deficiencies. We used a definition elaborated in an expert consensus process for the registration of patients with CVID in the ESID registry (www.esid.org): (1) susceptibility to infection or autoimmune manifestation or granulomatous disease or unexplained polyclonal lymphoproliferation, or affected family member with CVID; (2) reduction in IgG and IgA levels and (3) poor vaccination response or low switched memory B-cell numbers (<70% of age-related normal values) and (4) diagnosis at greater than 4 years of age; and exclusion of both (5) secondary causes and (6) profound T-cell deficiency. The latter is defined as 2 of the following: (1) CD4 cell count at age 4 to 6 years of less than 300/μL, at age 6 to 12 years of less than 250/μL and at age greater than 12 years of less than 200/μL; (2) naive CD4 cells at age 4 to 6 years of less than 25% of CD4, at age 6 to 16 years of less than 20% of CD4, and at age greater than 16 years of less than 10% of CD4; or (3) absent T-cell proliferation (<10% of the lower limit of normal[19]). HSCT was performed in 14 centers from 6 European countries, the United States, and Japan between 1993 and 2012. Follow-up ranged between 10 days to 8 years and 9 months after transplantation (median, 15 months). Data on 4 patients have been previously published.[18]

Patients' characteristics

Of 30 patients with a diagnosis of CVID initially recruited and undergoing transplantation, 5 patients were excluded because the diagnosis was made before the age of 4 years. The remaining 25 patients fulfilled the proposed new CVID registry criteria. Next-generation sequencing was performed in 1 patient, and sequencing of selected primary immunodeficiency (PID)–related genes was performed in 4 patients (see Table E1 in this article's Online Repository at www.jacionline.org).

Statistics

Prism Version 5.01 software (GraphPad Software, La Jolla, Calif) was used for statistical analysis. The Mantel-Cox test was used for comparison of survival curves (Kaplan-Meier estimates). Unpaired 2-tailed *t* tests were used for comparison of 2 continuous variables. For comparison of 2 categorical variables, the 2-tailed Fisher exact test was used, and 1-way ANOVA was used for more than 2 groups.

RESULTS

Indication for transplantation, conditioning, and stem cell source

We examined demographic data and variables related to HSCT to understand the characteristics of this cohort. The indication for HSCT was PID related in 24 (96%) of 25 patients. PID-related indications included lymphoma in 6 (24%) of 25, severe