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Allogeneic Hematopoietic Cell Transplantation for Chronic Myelomonocytic Leukemia: Relapse-Free Survival Is Determined by Karyotype and Comorbidities

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Hematopoietic cell transplantation (HCT) offers potentially curative therapy for chronic myelomonocytic leukemia (CMML). We evaluated HCT outcomes in 85 patients with CMML, 1.0-69.1 (median 51.7) years of age, with follow-up extending to 19 years. CMML was considered de novo in 71 and secondary in 14 patients. Conditioning regimens were of various intensities. Thirty-eight patients had related (34 HLA identical), and 47 (39 HLA matched) unrelated donors. The source of stem cells was marrow in 32 and peripheral blood progenitor cells in 53 patients. Acute graft-versus-host disease (aGVHD) grades II-IV occurred in 72% and chronic GVHD (cGVHD) in 26% of patients. Relapse incidence was 27% at 10 years. Relapse correlated with increasing scores by the MD Anderson prognostic score ($P = .01$). The major causes of death were relapse and infections ±GVHD. Progression-free survival (PFS) was 38% at 10 years. Mortality was negatively correlated with pre-HCT hematocrit ($P = .007$), and increased with high-risk cytogenetics ($P = .02$), higher HCT Comorbidity Index ($P = .0008$), and increased age ($P = .02$). WHO classification did not statistically significantly affect outcome. Thus, a proportion of patients with CMML have lasting remissions following allogeneic HCT and appear to be cured of their disease.

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INTRODUCTION

Chronic myelomonocytic leukemia (CMML), currently characterized as a myelodysplastic/myeloproliferative disorder by World Health Organization (WHO) criteria, is a heterogeneous disease with variable course, generally ending in progression to acute myeloid leukemia (AML). Various classification systems have been described [1]. The WHO distinguishes CMML-1 (<10% marrow blasts) and CMML-2 (10%-20% blasts), for which median survival of 20 and 15 months, respectively, have been reported [2]. The International Prognostic Scoring System (IPSS), recognized dysplastic and proliferative forms of CMML [3], with JAK2 mutations present in approximately 10% of patients with proliferative CMML [4-6]. Investigators at M.D. Anderson Cancer Center proposed a 4-stage classification on the basis of circulating immature cells, hemoglobin levels, lymphocyte counts, and marrow blasts [1]. On the basis of the presence of these risk factors, they divided patients into 4 groups with median life expectancies ranging from 5 to 24 months. Additional studies suggest that younger age at the time of diagnosis, splenomegaly, lymphadenopathy, elevated lactate dehydrogenase (LDH) levels, and clonal cytogenetic abnormalities are associated with a more rapid progression [7,8]. Although occasional patients have prolonged remissions with aggressive chemotherapy, the only current therapy with proven curative potential is hematopoietic cell transplantation (HCT) [9-12].

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We reported previously results in 43 patients transplanted at the Fred Hutchinson Cancer Research Center (FHCRC) [11]. Here, we present results in 42 new patients and provide long-term follow-up extending to 19 years for previously reported patients.

PATIENTS AND METHODS

Patients and Disease Characteristics

Between May 1986 and December 2008, 85 patients with CMML had HCT at the FHCRC, 42 of these since our initial report in 2005 [11]. All provided informed consent for enrollment in investigational protocols and for long-term follow-up as required by the institutional review board of the FHCRC. Patient and disease characteristics are summarized in Table 1. Patients were 1.0 to 69.1 (median 51.7) years old. By WHO criteria [13], 57 patients (67%) had CMML-1 and 26 (31%) had CMML-2; in 2 patients, the staging was inconclusive. In 54 patients (64%), the WBC was <13,000 at HCT, thus qualifying as dysplastic CMML. Among these 54 patients, 8 had low-risk, 23 intermediate-1, 15 intermediate-2, and 7 high-risk disease by IPSS criteria [3] (cytogenetic information was missing for 1 patient). Among 81 patients with cytogenetic data, 45 (53%) were considered good risk, 14 (16%) intermediate risk, and 22 (26%) poor risk according to IPSS criteria. Using the M.D. Anderson prognostic score (MDAPS), 32 patients had low-risk, 23 intermediate-1, 17 intermediate-2, and 8 high-risk disease (data incomplete in 5 patients).

In 14 patients, CMML was thought to be "secondary," following treatment for non-Hodgkin or Hodgkin lymphoma in 4, aplastic anemia in 2, breast cancer in 2, and 1 each for idiopathic thrombocytopenic purpura, chronic lymphocytic leukemia, Wegener's granulomatosis, rhabdomyosarcoma, AML, and liver transplantation.

Treatment before transplantation included transfusions alone in 13 patients; 49 patients received hydroxyurea or cytoreductive chemotherapy or both; 10 received erythropoietin, prednisone, or differentiating agents alone or in combination. Fifteen underwent splenectomy with or without other therapeutic modalities. Nine received other treatment including azacytidine or decitabine in 5, imatinib in 2, thalidomide and lenalidomide in 2.

The HCT comorbidity index (HCT-CI) score was 0 in 19, 1-2 in 23, 3 in 19, and 4-11 in 18 patients; the score could not be calculated in 8 patients because of missing data [14].

Table 1. Patient and Disease Characteristics

Variable		Number of Patients
Number of patients		85
Age (years), range (median)	1–69.1 (51.7)	
Sex (male/female)		52/33
Diagnosis		
FAB		
Proliferative		28
Nonproliferative		54
WHO		
CMML 1		57
CMML 2		26
IPSS risk		
Low		8
Intermediate-1		23
Intermediate-2		15
High		7
MDAPS		
Low		32
Intermediate-1		23
Intermediate-2		17
High		8
Hematology parameters median (range)		
WBC ($\times 10^9$/L)	7.38 (0.08-85.5)	
Lymphocytes ($\times 10^9$/L)	1.55 (0-12.83)	
Platelets ($\times 10^9$/L)	63 (7-882)	
Hemoglobin (g/dL)	10.5 (7.2-15.7)	
Cytogenetics risk (by IPSS)		
Good		45
Intermediate		14
Poor		22
Pretransplantation therapy		
None or transfusion only		13
Cytoreductive with or without HU		49
Differentiating agents		10
Splenectomy with or without other treatment modalities		15
Other modalities		9

HU indicates hydroxyurea; FAB, French-American-British classification; WHO, World Health Organization; IPSS, International Prognostic Scoring System; MDAPS, MD Anderson Prognostic Score; WBC, white blood cell count (see text); CMML, chronic myelomonocytic leukemia.

Donor and Transplant Characteristics

Donor and transplant characteristics are summarized in Table 2.

Donor Selection

HLA typing of related donors involved intermediate-resolution molecular typing for HLA-A, -B, -C, and -DQB1, and high-resolution typing for DRB1 [15]. Unrelated donors were typed for HLA-A, -B, -C, and -DRB1 by high-resolution and for DQB1 by intermediate-resolution typing [15]. Thirty-eight patients (45%) had related donors; 32 were genotypically HLA-identical siblings, 2 were HLA-matched family members other than siblings, 4 were HLA nonidentical family members (parent differing for HLA-A; sibling differing for HLA-A, -B, and -DR; child differing for HLA-A and -DR; in 1 the donor information was incomplete), and 47 (55%) had unrelated donors, 39 were HLA matched, and 8 were HLA nonidentical (4 differing for HLA-A, 3 for HLA-DR, and 1 with an undetermined mismatch).