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Allogeneic Hematopoietic Cell Transplantation for Chronic Myelomonocytic Leukemia

Daniella M. B. Kerbauy,[1] Faith Chyou,[1] Ted Gooley,[1,2] Mohamed L. Sorror,[1,2] Bart Scott,[1,2] John M. Pagel,[1] David Myerson,[1,2] Frederick R. Appelbaum,[1,2] Rainer Storb,[1,2] H. Joachim Deeg[1,2]

[1]Fred Hutchinson Cancer Research Center, Seattle, Washington; [2]University of Washington, Seattle, Washington

Correspondence and reprint requests: H. Joachim Deeg, MD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., D1-100, P.O. Box 19024, Seattle, WA 98109-1024 (e-mail: jdeeg@fhcrc.org).

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ABSTRACT

We evaluated the outcomes of allogeneic hematopoietic cell transplantation (HCT) in 43 patients with chronic myelomonocytic leukemia. Patients were classified according to the French-American-British and World Health Organization classifications, as well as the International Prognostic Scoring System and the M.D. Anderson prognostic score. Comorbidity scores were assessed by using an HCT-specific comorbidity index. Patients were aged 1 to 66 years (median, 48 years). Twenty-one patients received transplants from related donors (18 HLA-identical siblings and 3 HLA-nonidentical family members), and 22 received transplants from unrelated donors (18 HLA matched and 4 HLA nonidentical). Several busulfan or total body irradiation–based conditioning regimens were used. Sustained engraftment was achieved in 41 patients. Eighteen are alive at 1.9 to 14.1 years, for an estimated relapse-free survival of 41% at 4 years. Ten patients have relapsed, thus leading to a cumulative incidence of 23% at 4 years. Risk category by International Prognostic Scoring System, World Health Organization, M.D. Anderson prognostic score, or proliferative/dysplastic status had no statistically significant association with outcomes. However, patients with higher comorbidity scores had worse overall survival than patients with lower scores ($P = .01$). There was a trend for a higher relapse incidence among patients at higher risk by the M.D. Anderson prognostic score. The data suggest that patients with few or no comorbidities and those who undergo transplantation earlier in the disease course have the highest probability of successful outcome after allogeneic HCT.

KEY WORDS

Chronic myelomonocytic leukemia • Allogeneic transplantation • Relapse-free survival • Comorbid conditions

INTRODUCTION

Chronic myelomonocytic leukemia (CMML) is a myeloid disorder, often with features of myelodysplasia and, more prominently, myeloproliferation, classified by the World Health Organization (WHO) as a myelodysplastic/myeloproliferative disorder [1]. To date, no specific cytogenetic or molecular distinction is possible between patients with more dysplastic and those with more proliferative features. According to the WHO, the disorder is subdivided into CMML-1 and CMML-2 according to the proportion of myeloblasts in peripheral blood and marrow and the presence or absence of Auer rods [1]. Investigators at M.D. Anderson have proposed a new prognostic classification that is based on analysis of disease characteristics and survival in 213 patients with CMML [2]. Although the median survival was 12 months, they identified 4 subgroups of patients with median survivals of 24, 15, 8, and 5 months on the basis of hemoglobin levels, the presence of circulating immature myeloid cells, the absolute lymphocyte count, and the marrow myeloblast proportion. Despite the designation as a chronic leukemia, CMML is a progressive disease that often leads to death within months. Various chemotherapy regimens have been used, including hydroxyurea, etoposide, low-dose cytosine arabinoside, or more intensive combinations of cytotoxic agents such as anthracycline and cytosine arabinoside. However, responses to such therapies have generally been short. More recently developed agents, such as farne-

syl transferase inhibitors, have met with limited success [3,4]. The tyrosine kinase inhibitor imatinib mesylate (STI571) may induce remissions, but typically only in patients with mutations or gene rearrangements (for example, involving platelet-derived growth factor receptor β) that generate appropriate targets [5]. The only currently available therapy that offers the potential for cure is hematopoietic cell transplantation (HCT) [6-8]. We previously reported results with allogeneic transplantation in 21 patients with CMML [6]. Here, we update our data and summarize results in 43 patients treated at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, WA.

PATIENTS AND METHODS

Patients

Between June 1990 and January 2004, 43 patients with CMML received transplants from allogeneic donors at the FHCRC. Patient and disease characteristics are summarized in Table 1. The diagnosis of CMML was initially based on the French-American-British classification. For the purpose of this analysis, the disease was also classified according to WHO criteria [1]. In addition, we categorized patients for whom all required parameters were available according to the 4 risk groups recently proposed by Onida et al. [2] (M.D. Anderson Prognostic Score [MDAPS]). All classifications in this analysis were based on findings at the time of transplantation rather than at diagnosis.

Patients were 1 to 66 years (median, 48 years) of age at the time of transplantation. Twenty-five patients were male, and 18 were female. The interval from diagnosis to transplantation was 2 to 156 months (median, 8 months). At the time of transplantation, 16 patients were classified as having proliferative CMML (white blood cell count [WBC] of $>13 \times 10^9$/L), and 27 had nonproliferative CMML (WBC of $\leq 13 \times 10^9$/L) [9]. Lymphocyte counts ranged from 0.04 to 11.86×10^9/L, with a median of 1.8×10^9/L. Five patients had what was considered secondary CMML after therapy for aplastic anemia (n = 2), Hodgkin disease (n = 1), POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; n = 1), and chronic lymphocytic leukemia (n = 1). Three patients had undergone splenectomy. Twelve patients had received either no treatment or transfusion only before transplantation. Fourteen patients had received hydroxyurea, 6 had received steroids or erythropoietin (or both), 2 had received imatinib, and 9 had received various kinds of chemotherapy other than hydroxyurea.

There were 26 patients with nonproliferative CMML who could be scored according to the International Prognostic Scoring System (IPSS). Among these, 4 were low risk, 11 were intermediate 1, 8 were intermediate 2, and were 3 high risk [10]. By IPSS criteria, 23 patients had good-risk cytogenetics (normal karyotype), 9 had poor-risk cytogenetics (monosomy 7 in 5 and complex abnormalities in 4 patients), and 11 had intermediate-risk cytogenetics (3 with trisomy 8, single miscellaneous in 5, and double miscellaneous in 2). Overall, 32 patients had CMML-1 and 11 had CMML-2 by WHO criteria. By the M.D. Anderson criteria, considering hemoglobin <12 g/dL, immature myeloid cells in peripheral blood, marrow blasts >10%, and absolute lymphocyte counts of $>2.5 \times 10^9$/L, 18 patients were in the low-risk category, 9 were intermediate 1, 12 were intermediate 2, and 4 were in the high-risk category.

Table 1. *Patient Characteristics at Transplantation*

Variable	Data
Population studied	43
Age (y)	48 (1-66)
Sex (male/female)	25/18
Disease duration (mo)	8 (2-156)
Diagnosis	
Proliferative	16
Nonproliferative	27
WHO—CMML-1/2	32/11
IPSS risk (26 scored)	
Low	4
Int-1	11
Int-2	8
High	3
MDAPS	
Low	18
Int-1	9
Int-2	12
High	4
CMV serology (+/−)	24/19
Hematologic parameters	
Lymphocytes ($\times 10^9$/L)	1.8 (0.04-11.86)
WBC/ANC ($\times 10^9$/L)	8.8 (0.34-127)/2.913 (0.06-43.46)
Platelets ($\times 10^9$/L)	59 (3-594)
Hemoglobin (g/dL)	10.2 (4.8-16.9)
Cytogenetic findings	
Normal	23
Monosomy 7 (± others)	5
Other abnormalities	15
Pretransplantation therapy	
None	9
Transfusion only	3
Imatinib	2
Hydroxyurea	14
Combination chemotherapy	9
Erythropoietin	2
Prednisolone	4
Splenectomy	3

WHO indicates World Health Organization; IPSS, International Prognostic Scoring System; MDAPS, M.D. Anderson Prognostic Score; CMV, cytomegalovirus; Int, intermediate; ANC, absolute neutrophil count.

Data are n or median (range).