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Late Mortality and Relapse following BuCy2 and HLA-Identical Sibling Marrow Transplantation for Chronic Myelogenous Leukemia

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Allogeneic hematopoietic stem cell transplantation (HSCT) is the only known curative therapy for chronic myelogenous leukemia (CML). Failure, because of relapse or nonrelapse mortality (NRM), generally occurs within 3 years of transplantation, but large studies with long-term follow-up are limited. We present mature results in 335 patients with CML who underwent allogeneic bone marrow transplantation (BMT) from HLA-identical siblings following busulfan and cyclophosphamide (BU/Cy2). Two hundred twenty-nine were in chronic phase (CP) and 106 in accelerated or blastic phase at transplantation. Median follow-up exceeded 14 years. The estimated probability of 18-year leukemia-free survival (LFS) for CP patients was 55.6% and for those beyond CP, 10.5%. Of 182 patients who survived leukemia-free at 3 years, the estimated probability of LFS at 18 years was 61.9%. Late relapse ($P = .039$) and late NRM ($P = .008$) occurred at higher rates in patients beyond CP at transplantation. There was no plateau in LFS.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only proven curative therapy for chronic myelogenous leukemia (CML). Results of allogeneic transplantation in CML have been widely published, but median follow-up in most studies is 3 years or less [1-4]. Few large studies with prolonged follow-up after HSCT have been reported, and these have generally been limited by inclusion of patients with various diagnoses, preparative regimens, and sources and histocompatibility of donor cells. These studies report survival, but not leukemia-free survival (LFS) [5,6], providing the potential for overestimates of cure rates in CML, where patients may attain sustained survival following relapse [7,8]. Further, a single institutional study with prolonged follow-up reported a 15-year estimated cumulative relapse rate of only 8% for CML patients in chronic phase (CP) undergoing transplantation [9], substantially lower than that detected in studies with shorter follow-up [7,8,10].

We present the results of the most extended follow-up of a large cohort of patients with CML who underwent allogeneic bone marrow transplantation (BMT) from human leukocyte antigen (HLA)-identical sibling donors following busulfan and cyclophosphamide (Bu/Cy2), the most commonly used preparative regimen in this malignancy [11]. This report focuses on late relapse and death in patients in whom transplantation is commonly considered to have been successful, those alive, and leukemia-free 3 years following transplantation.

METHODS

Patients

All adults with CML who underwent allogeneic BMT from HLA-identical sibling donors following

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Bu/Cy2 at 4 centers in the United States and 3 in Australia, between March 1984 and December 1995, are included. Informed consent was obtained using forms approved by the institutional review board at each center. Data were analyzed as of January 1, 2008. One hundred fifteen patients were included in a report published in 1992 with a median follow-up of 3 years [2].

Clinical Care

All patients received identical preparation with Bu 1 mg/kg orally 4 times daily for 4 days followed by Cy 60 mg/kg intravenously on each of 2 days (Bu/Cy2) as previously described [2]. Bu doses were not adjusted to target plasma levels. BM from HLA-identical siblings was used as the source of HSC in every patient. Cyclosporine (CsA) or tacrolimus-based regimens were given to prevent graft-versus-host disease (GVHD). Prevention and treatment of infections and other supportive care measures were administered according to institutional guidelines.

Statistical Methods

Kaplan-Meier, cumulative hazard, and hazard rates were used to characterize overall survival (OS), relapse, and LFS. Kaplan-Meier methods were also used to assess the OS, relapse, and LFS for only those 182 subjects who survived 3 years leukemia-free. The log-rank test was used to compare CP, accelerated, and blastic phase patients. Univariate Cox proportional hazard regression was used to estimate the OS, relapse, and LFS hazard ratios for the following covariates: a 10-year increase in age, male versus female, disease phase XP accelerated, and blastic), acute GVHD (aGVHD), chronic GVHD (cGVHD), and interval from diagnosis to transplantation that was log transformed to the appropriate scale.

Smoothed hazard curves were generated by adjustment of the cumulative hazard into a continuous "smoothed" curve and then taking the derivative with respect to time. Multivariable Cox proportional hazard regression was used to estimate OS, relapse, and LFS hazard ratios. These same techniques were also used on the subgroup of patients that survived 3 years without disease. All relapses were hematologic or cytogenetic. Treatment of relapse was heterogeneous and varied over time and by institution. Primary cause of death was defined according to a published scheme [12]. Stata version 10.0 (Stata Corporation, College Station, TX) was used to run all analyses.

RESULTS

Patient Characteristics

A total of 335 consecutive adults with CML who underwent allogeneic HSCT from HLA-identical sibling donors at 7 institutions (Ohio State 88, Hahnemann 64, St. Vincent's 55, Wilford Hall 44, Cleveland Clinic 35, Alfred 33, and Royal Melbourne 16) were included in this analysis. Two hundred twenty-nine individuals were in CP, 62 in accelerated phase, and 44 in blastic phase at the time of transplantation. Table 1 summarizes the clinical characteristics of the study patients. Surviving patients were followed for a median of more than 14 years after transplantation.

OS and LFS from the Time of Transplantation

The 3-year OS from the time of transplantation for the entire group was 57.4% (95% confidence interval [CI]: 51.9 to 62.5%); the estimated probability of 18-year survival was 43.9% (95% CI: 37.9%-49.8%). The estimated 3- and 18-year LFS were 55.6% (95% CI: 50.1%-60.8%) and 34.4% (95% CI: 28.4%-40.5%). For chronic phase patients the OS at 3 years is 70.5% (95% CI: 64.1% - 76.0%) and 58.6% (95% CI 51.4%-65.1%) were estimated to survive at 18 years. LFS for CP patients was 68.8% (95% CI: 62.3%-74.4%) at 3 and 46.0% (95% CI: 38%-53.6%) at 18 years. For accelerated phase patients, 3-year OS and LFS were each 37.9% (95% CI: 25.6%-50%); estimated 18-year OS was 21.0% (95% CI: 10.5%-33.9%) and estimated probability of 18 year LFS was 17.5% (95% CI: 8.2%-29.7%). The 3-year OS for blastic phase patients was 15.9% (95% CI: 7.0%-28.0%), and 3-year LFS 13.6% (95% CI: 5.5%-25.4%); no blastic phase patients were estimated to survive at 18 years. The estimated probability that patients beyond CP at transplantation would be leukemia-free survivors at 18 years is 10.5% (95% CI: 5.2%-18.3%).

Relapse

The hazard rate for relapse fell sharply each year through year 5, and then remained low, but constant from years 6 through 14 (Figure 1). Twenty-seven (42.2%) of the 64 (hematologic or persistent cytogenetic) relapses occurred more than 3 years after transplantation. Thirty-three of the 37 patients (89.2%) who relapsed within 3 years (early) died, compared to 7 of 27 (25.9%) of those who relapsed beyond 3 years (late). (One patient relapsed 20 years following transplantation after data analysis was completed.) Death occurred less frequently ($P < .001$) and the interval

Table 1. Clinical Characteristics of 335 Study Patients

Age, median (range) in years	37	(18-58)
Sex, number (percentage) of females	152	(45.4)
Disease stage at transplant, number (%)		
Chronic phase	229	(68.3)
Accelerated	62	(18.5)
Blastic	44	(13.1)
Interval from diagnosis to transplant		
Median (range) in months	9	(1-210)