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Donor Lymphocyte Infusions for Chronic Myeloid Leukemia Relapsing after Allogeneic Stem Cell Transplantation: May We Predict Graft-versus-Leukemia Without Graft-versus-Host Disease?

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A B S T R A C T

Donor lymphocyte infusions (DLI) are an effective treatment for relapsed chronic myeloid leukemia (CML) after allogeneic stem cell transplantation (alloSCT). Leukemia resistance and secondary graft-versus-host disease (GVHD) are major obstacles to success with DLI. The aim of this study was to identify pre-DLI factors associated with prolonged survival in remission without secondary GVHD. We retrospectively analyzed 500 patients treated with DLI for CML relapse (16% molecular, 30% cytogenetic, and 54% hematological) after alloSCT. The overall probabilities of failure- and secondary GVHD–free survival (FGFS) were 29% and 27% at 5 and 10 years after DLI, respectively. The type of relapse was the major factor influencing FGFS (40% for molecular and/or cytogenetic relapse and 20% for hematological relapse at 5 years, $P < .001$). Chronic GVHD before DLI and an interval <1 year between alloSCT and first DLI were independently associated with inferior FGFS in patients with molecular and/or cytogenetic relapse. Consequently, FGFS was 13%, 35%, to 56% at 5 years in patients with 2, 1, and 0 adverse features, respectively. In patients with hematological relapse, independent adverse prognostic factors for FGFS were initial dose of $CD3^+$ cells $\geq 50 \times 10^6$/kg, donor-recipient sex mismatch, and chronic GVHD before DLI. FGFS was 0%, 17%, 33%, to 37% in patients with 3, 2, 1, and 0 adverse features, respectively. The probability of survival in remission without secondary GVHD was highest (>50% at 5 years) when DLI were given beyond 1 year from alloSCT for molecular and/or cytogenetic CML relapse that was not preceded by chronic GVHD.

INTRODUCTION

Despite the introduction of imatinib and other tyrosine kinase inhibitors (TKI), allogeneic stem cell transplantation (alloSCT) remains an important treatment option for chronic

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myeloid leukemia (CML) patients who do not respond adequately to TKI therapy [1]. Currently, alloSCT is recommended for eligible patients in advanced-phase CML and in instances of failure of and/or intolerance to TKI treatment [2]. Because of advances in supportive care and improvement of conditioning regimens, relapse of the original malignancy has become the most common cause of treatment failure and mortality after alloSCT [3].

Treatment with donor lymphocyte infusions (DLI) represents 1 of the most established therapeutic approaches to post-allograft relapse and has radically changed the prognosis of CML patients relapsing after alloSCT [4,5]. Responses achieved after DLI in relapsed CML are frequently durable, offering potential cure for the majority of patients [6-8]. CML relapse may be diagnosed at the molecular, cytogenetic, and hematological level, resulting in extreme heterogeneity of patient and disease status when treatment with DLI is applied [9-11]. This is even more complex nowadays with the availability of TKI, capable of restoring complete molecular remission (CMR) after relapse [12-14].

Major obstacles to success with DLI are represented by leukemia resistance and by the induction of graft-versus-host disease by the infused lymphocytes (secondary GVHD), the latter representing the most threatening side-effect of DLI treatment [4]. Response to DLI, incidence of secondary GVHD, and outcome of patients developing secondary GVHD have been reported in previous studies by the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation (EBMT) [15-17]. Occurring in up to 40% of patients, secondary GVHD was shown to be associated with a 2.3-fold increased risk of death compared with patients without secondary GVHD [17]. With regard to the availability of TKI, additional treatment modalities are available for preventing and treating relapse after alloSCT. However, since alloSCT is increasingly performed in TKI-resistant patients, DLI is an attractive and important treatment modality, especially if the resistant clone persists. It is evident that the best result is obtained when a patient treated with DLI achieves a durable molecular remission without experiencing secondary GVHD. In fact, CML response to DLI is frequently, but not always, separated from secondary GVHD, suggesting that the graft-versus-leukemia effect (GVL) may be independent of the development of secondary GVHD [6,9,16,18]. However, it remains unclear what the proportion of such patients is and which factors may predict for such a favorable outcome when DLI are administered for CML relapsing after alloSCT. The aim of this study was, therefore, to identify pre-DLI factors associated with probability of survival in remission without secondary GVHD. The information may be used to determine when treatment for CML relapse with DLI can be "optimal" (ie, high chance of achieving a prolonged survival and a durable remission without experiencing secondary GVHD).

PATIENTS AND METHODS

This study was based on the registry of the EBMT and conducted within the Chronic Malignancies Working Party. The study was approved by the review board of the Chronic Malignancies Working Party. EBMT member centers were asked to report and update their experience with patients treated with unmanipulated DLI for recurrent CML after the first alloSCT from an HLA-identical sibling or an HLA-matched volunteer unrelated donor. The reports included adequate information collected on disease response, secondary GVHD, and survival after DLI.

Lymphocytes were collected from the donors by apheresis on 1 or more occasions and administered as single or multiple infusions. Infusions given on multiple days had to be at least 7 days apart to be counted as separate infusions. The phase of CML was classified in accordance with the criteria proposed by the Center for International Blood and Marrow Transplant Research [19]. Relapse was classified as molecular, cytogenetic, or hematological in accordance with previous reports [16,17]. Patients treated with DLI for CML relapse in blast crisis were excluded. Relapse stage at DLI was defined as molecular, cytogenetic, and hematological assessed on the date of first DLI infusion after relapse or closest date before this infusion. Acute and chronic GVHD occurring after DLI was reported according to the standard clinical criteria and in accordance with previous reports [16,17]. A total of 500 patients treated with DLI for CML relapse at 68 EBMT centers between 1988 and 2004 had complete data for analysis. None of the patients had received imatinib before transplantation. All patients received DLI for relapse of CML after alloSCT in absence of GVHD and/or its treatment.

Survival was calculated from the date of the first infusion of donor lymphocytes until death or last follow-up evaluation. Failure-free survival (FFS) was calculated from the date of the first infusion of donor lymphocytes until death, last follow-up evaluation, or occurrence of an event such as unresponsiveness to DLI or relapse after response to DLI. Failure- and secondary GVHD–free survival (FGFS) was calculated from the date of the first infusion of donor lymphocytes until death, last follow-up evaluation, or occurrence of an event, such as unresponsiveness to DLI, relapse after response to DLI, or secondary GVHD.

Survival curves were calculated according to the method of Kaplan and Meier; the log-rank test was used to compare survival curves; a proportional hazard regression model (Cox model) was used for survival probabilities [20]. We studied the following possible risk factors (categorization criteria): patient gender (0 = male, 1 = female), patient age at DLI (0 = <40 years, 1 = ≥40 years), donor type (0 = HLA-identical sibling, 1 = unrelated), donor gender (0 = male, 1 = female), sex mismatch with the donor (0 = matched, 1 = mismatched, ie, female donor/male recipient and male donor/female recipient), phase at alloSCT (0 = first chronic phase [CP1], 1 = beyond CP1), stem cell source (0 = bone marrow, 1 = peripheral blood), total body irradiation in the conditioning regimen (0 = no, 1 = yes), T cell depletion (0 = no, 1 = yes), acute GVHD before DLI (0 = no, 1 = yes), chronic GVHD before DLI (0 = no, 1 = yes), interval from alloSCT to DLI (0 = ≥1 year, 1 = <1 year), type of relapse (0 = molecular and/or cytogenetic, 1 = hematological), initial cell dose (ie, donor CD3 + cells/kg recipient body weight of first transfusion) (0 = <median value, 1 = ≥median value). Factors significantly associated with shorter FGFS in univariate analysis were tested for their predictive value on FGFS in multivariate Cox regression models. Hazard ratios were estimated with 95% confidence interval (95% CI). Values of $P < .05$ were considered statistically significant.

RESULTS

Patient Characteristics

Fifty-nine percent of patients were males and the median patient age at time of DLI was 39 (range, 4 to 64) years with 15% older than 50 years. The donor was an HLA-identical sibling in 73% and unrelated in 27%. The donor was female in 37% of the cases and 44% of patients were sex mismatched with the donor. AlloSCT was performed in CP1 in 410 patients (82%), whereas 89 (18%) underwent transplantation in more advanced phases of the disease. Stem cell source was bone marrow in 408 (86%), peripheral blood in 64 (14%), and information was not available in 28 patients. All patients were conditioned with a standard regimen, including total body irradiation in 77% of the cases. GVHD prophylactic measures included in vivo T cell depletion in 241 patients (51%). A total of 316 patients (69%) had GVHD before relapse: 124 acute GVHD only, 66 chronic GVHD only, 114 acute and chronic GVHD, and 12 GVHD unclassified. Median follow-up time of surviving patients was 56 months (range, 1 to 168).

DLI Characteristics

DLI was started at a median interval of 23 months from alloSCT (range, 1 to 146 months) in 132 patients (26%) within 12 months from alloSCT. Relapse type was molecular in 80 (16%), cytogenetic in 150 (30%), and hematological in 270 (54%) cases. DLI was started with a cell dose of $\leq 20 \times 10^6$ $CD3^+$ cells/kg recipient body weight in 62% of patients; 207 patients (41%) received 2 or more additional infusions of donor cells. Cumulative cell dose ranged from 1×10^5 to 1.4×10^9 $CD3^+$ cells/kg recipient body weight (median, 70×10^6