Donor Lymphocyte Infusion in Hematologic Malignancies—Good to be Fresh?

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Abstract

Since its initial application in chronic myelogenous leukemia (CML), donor lymphocyte infusion (DLI) has been applied to various hematologic malignancies with varied success. A recent trend has been the shift from using fresh cells to cryopreserved cells. In a retrospective analysis of 63 patients, we found that there was no difference in outcomes based on the type of cells used for DLI. However, in a subset of 32 patients with acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), the use of cryopreserved cells appears to have resulted in improved event-free survival (EFS) in patients who underwent myeloablative transplantation.

Background: Donor lymphocyte infusion (DLI) has been used with variable success in a variety of hematologic malignancies. **Patients and Methods:** We conducted a retrospective analysis of all patients who were treated with DLI for persistent or relapsed disease at the Temple University Bone Marrow Transplant Unit from July 1, 1993 to December 31, 2013 to evaluate the effect of the type of DLI (fresh vs. cryopreserved) on event-free survival (EFS) and overall survival (OS). Median follow-up was 64.8 months (range, 0.3-142.6 months). **Results:** We found that EFS and OS were similar between patients receiving cryopreserved cells and those receiving fresh DLI (median OS for cryopreserved cells, 0.39 years; median OS for fresh cells, 0.32 years; $P = .793$; median EFS for cryopreserved cells, 0.410 years; median EFS for fresh cells, 0.420 years; $P = .4264$). In the setting of relapsed disease, treatment with any chemotherapy regimen before receiving DLI did not significantly impact OS (n = 63; $P = .2203$) or EFS (n = 40; $P = .542$). A subgroup analysis limited to patients with acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) (32 patients) showed that differences in OS and EFS between cryopreserved and fresh DLI approached significance (median OS for cryopreserved cells, 0.34 years; median OS for fresh cells, 0.17 years; $P = .16$; median EFS for cryopreserved cells, 0.37 years; median EFS for fresh cells, 0.094 years; $P = 0.11$). **Conclusion:** We conclude that the use of fresh cells versus cryopreserved cells does not have an impact on outcomes, and selected patients can achieve long-term survival with DLI for treatment of relapse after transplantation, although the overall outcomes remain dismal.

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Introduction

Over the past few decades, donor lymphocyte infusion (DLI) has emerged as an alternative treatment option for individuals with relapsed hematologic malignancies after allogeneic stem cell transplantation.[1] Since first being used successfully in chronic myelogenous leukemia (CML),[2,3] DLI has been applied to a multitude of other hematologic (and nonhematologic) malignancies with varying degrees of success.[1] DLIs are often used after stem cell transplantation, with response rates ranging from 5% to 50% for multiple myeloma, chronic lymphocytic leukemia, and myelodysplastic syndrome (MDS) to 15% to 50% response rates in acute myeloid leukemia (AML) and acute lymphoblastic leukemia.[4] Furthermore, there is no standardized approach to DLI, although 1 recent trend has been the increased use of granulocyte colony–stimulating factor (G-CSF)–mobilized cryopreserved cells versus fresh cells for DLI.[5] This shift has occurred in part because of work by several groups that suggests improved outcomes when transplantation is performed

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using G-CSF–mobilized stem cells.[6,7] There are a lack of data on whether this impacts the outcomes from DLI after stem cell transplantation. We attempted to determine whether the type of cells used for DLI impacted outcomes for patients with relapsed disease after stem cell transplantation treated at our institution.

Patients and Methods

Patient Population

On querying our central bone marrow transplantation (BMT) database, we identified 74 patients who had undergone a total of 113 DLIs between 1993 and 2013 at our institution. To be included in this study, the patients had to have undergone DLI at our institution for either persistent or relapsed disease after stem cell transplantation. This requirement excluded patients who received DLI for other reasons, such as incomplete chimerism after transplantation (11 patients), which reduced our sample size to 63 patients. This included 32 patients with AML/MDS who were also studied separately as part of a subgroup analysis. The study was carried out with institutional review board approval by the Temple/Fox Chase Institutional Review Board committee.

End Points

The primary end point was to determine the event-free survival (EFS; defined as time without disease progression, relapse, or death from any cause) and the overall survival (OS; defined as time from DLI to death from any cause) for the patients who underwent G-CSF–mobilized cryopreserved DLI for persistent or relapsed disease during the period from July 1, 1993 to December 31, 2013 and compare them to a control group who had undergone fresh-cell DLI at our institution. Our secondary end points were to analyze a number of additional variables to determine if any had a significant impact on EFS and OS. These included myeloablative versus nonmyeloablative pretransplantation conditioning, the presence or absence of graft-versus-host disease (GVHD) after DLI, a dose of $CD3^+$ cells infused for DLI, the interval between original transplantation and DLI administration, and whether patients were treated with chemotherapy immediately before their DLIs. The analysis was carried out for the entire cohort of patients and separately for the subgroup of patients with AML/MDS.

Data Analysis

EFS and OS were analyzed as a standard right-censored time-to-event variable, and univariate analysis of these end points was conducted with the log-rank test. Multivariate modeling, controlling for the effects of the other parameters not directly analyzed as part of the study, was conducted with Cox proportional hazards analysis. Based on the assumption that the internal data consisted of approximately 30 patients in each group, and based on the baseline median EFS of approximately 72 days as reported in the literature (Abbi et al.), we determined that our analysis would have approximately 86% power to detect a 3-month difference in median EFS.[5] The power analysis was conducted using the SAS software suite (SAS Institute, Cary NC). The secondary end points as detailed previously were evaluated with the log-rank test, and descriptive statistics were evaluated with the Wilcoxon rank-sum test or the χ^2 test as appropriate. The quality of data used in the study was ensured by running SAS PROC FREQ and PROC UNIVARIATE analyses on all dependent and independent variables.

Methods

Initially, the BMT database at our institution was queried to identify any patient who received a DLI between July 1, 1993 and December 31, 2013. Once these patients were identified, a second query was run to further limit the group to patients who received DLI for persistent or relapsed disease after stem cell transplantation. All extracted data were stored on the secure central server for the BMT department, with all patient identifiers removed in the central database and each patient given a unique study identification that cross-talked with their respective medical record identifications through a secure Word (Microsoft Corp, Redmond, WA) document. Furthermore, data not available in the BMT database were supplemented with data manually extracted from each patient's paper chart. In addition, for the AML/MDS subgroup, the disease burden at time of DLI was collected, and the donor source for DLI was tabulated. The disease burden was evaluated based on querying our records to determine if the patients had bone marrow biopsies within 60 days of DLI.

Results

Patient Population

For the 63 patients we focused on for our analysis, the median follow-up from time of DLI was 5.4 years (range, 0.03-11.88 years). Patients were organized based on the type of DLI they received; 40 patients received cryopreserved DLIs and 23 received fresh DLIs. The median time to DLI from time of transplantation for the study group was 179 days. For the AML/MDS subgroup, the median follow-up from time of DLI was 0.29 years (range, 0.005-5.36 years); 5 of these patients received fresh DLIs and 27 received cryopreserved DLIs. The median time to DLI from transplantation for this group was 184 days. Within the AML/MDS subgroup, 28.1% had $\geq$ 10% blasts in their marrow at the time of DLI, 50% had $<$ 10% blasts in their marrow at the time of DLI, and accurate information was not available for 21.9% of the patients. Furthermore, 13 patients in this subgroup had a matched unrelated donor and 19 patients had a matched related donor as the source of the cells for their DLIs; there were no mismatched donors in any of these cases. Additional demographic characteristics for the entire study group and the AML/MDS subgroup are listed in Tables 1 and 2, respectively.

Analysis of OS and EFS

Overall survival (OS) from the date of DLI was similar between patients receiving cryopreserved cells and those receiving fresh cells (median OS for cryopreserved cells, 0.39 years; median OS for fresh cells, 0.32 years; $P = .793$) (Figure 1A). When analyzed based on myeloablative versus nonmyeloablative pretransplantation conditioning, there was no significant difference in OS (median OS for myeloablative conditioning, 0.263 years; $P = .5226$; median OS for nonmyeloablative conditioning, 0.890 years; $P = .1159$). EFS from date of DLI was also similar between the 2 groups (median EFS for cryopreserved cells, 0.410 years; median EFS for fresh cells, 0.420 years; $P = .4264$) (Figure 1B). When analyzed separately based on pretransplantation conditioning, EFS rates were similar (median EFS for myeloablative conditioning, 0.197; $P = .9803$; median EFS for nonmyeloablative conditioning, 1.16 years; $P = .1419$).