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Treatment of Acute Myeloid Leukemia or Myelodysplastic Syndrome Relapse after Allogeneic Stem Cell Transplantation with Azacitidine and Donor Lymphocyte Infusions—A Retrospective Multicenter Analysis from the German Cooperative Transplant Study Group

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A B S T R A C T

To expand the current knowledge about azacitidine (Aza) and donor lymphocyte infusions (DLI) as salvage therapy for relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) and to identify predictors for response and survival, we retrospectively analyzed data of 154 patients with acute myeloid leukemia (AML, n = 124), myelodysplastic (MDS, n = 28), or myeloproliferative syndrome (n = 2). All patients received a median number of 4 courses of Aza (range, 4 to 14) and DLI were administered to 105 patients (68%; median number of DLI, 2; range, 1 to 7). Complete and partial remission rates were 27% and 6%, respectively, resulting in an overall response rate of 33%. Multivariate analysis identified molecular-only relapse (hazard ratio [HR], 9.4; 95% confidence interval [CI], 2.0 to 43.5; $P = .004$) and diagnosis of MDS (HR, 4.1; 95% CI, 1.4 to 12.2; $P = .011$) as predictors for complete remission. Overall survival (OS) at 2 years was 29% ± 4%. Molecular-only relapse (HR, .14; 95% CI, .03 to .59; $P = .007$), diagnosis of MDS (HR, .33; 95% CI, .16 to .67; $P = .002$), and bone marrow blasts <13% (HR, .54; 95% CI, .32 to .91; $P = .021$) were associated with better OS. Accordingly, 2-year OS rate was higher in MDS patients (66% ± 10%, $P = .001$) and correlated with disease burden in patients with AML. In summary, Aza and DLI is an effective and well-tolerated treatment option for patients with relapse after allo-HSCT, in particular those with MDS or AML and low disease burden. The latter finding emphasizes the importance of stringent disease monitoring and early intervention.

INTRODUCTION

In patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT), relapse represents the most common reason for treatment failure [1]. In this situation, no standard therapy is defined, but treatment options generally aim to reduce disease burden and to enforce

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a graft-versus-leukemia (GVL) effect. Commonly employed options are chemotherapy as well as cellular-based approaches, such as donor lymphocyte infusions (DLI) or second transplantation [2,3]. Still, long-term survival is scarcely observed, as indicated by 2-year survival rates hardly exceeding 20%. In addition, because of accompanying toxicities, the use of intensive chemotherapy and second transplantation are limited to medically fit patients [2,3].

Considering its efficacy and moderate toxicity profile in older patients with AML and MDS not eligible for allo-HSCT [4,5], the DNA methyltransferase inhibitor azacitidine (Aza) has also been tested for treatment of relapse after allo-HSCT. So far, 2 prospective studies and some small retrospective series covering a total of 152 patients demonstrated feasibility and clinical efficacy of Aza as salvage therapy for relapse after allo-HSCT [6-15]. As a consequence, Aza has become a viable treatment alternative in this setting. Still, because of the heterogeneity and limited number of patients reported so far, predictive factors for response and long-term survival are unknown. This prompted us to perform a retrospective analysis of 154 patients with relapse of AML or MDS after allo-HSCT who were treated with Aza and were scheduled for DLI at 12 German transplantation centers.

METHODS

Study Design

Between 2005 and 2013, 66 patients were treated with Aza and envisaged DLI for relapse of AML or MDS after allo-HSCT at the University Hospital Duesseldorf. Their data were analyzed together with an additional 88 patients treated with Aza and planned DLI at 11 transplantation centers participating in the German Cooperative Transplant Study Group. Data from the latter patients were obtained by a retrospective survey aiming to collect all patients treated at the participating centers within this interval. In addition, demographic data and basic transplantation information were retrieved from European Society for Blood and Marrow Transplantation Med-A form, and a specific questionnaire asking for further details regarding relapse and treatment was sent to participating centers. Physicians' review of data and personal requests at respective centers helped to improve data quality. Thirty patients were treated within a prospective phase II trial (NCT-00795548) [14]. Their results and results of an additional set of 22 patients had been published previously but were updated for this analysis [8-9-14]. The study was approved by the ethics committee of the Heinrich-Heine-University, Duesseldorf (approval number 4138) and written informed consent was obtained from patients who were alive at the time of data collection.

Definitions and Response Criteria

Hematologic relapse was defined as bone marrow (BM) [16] blasts ≥5%, appearance of blasts in peripheral blood [17,18], reappearance of dysplastic features fulfilling the diagnosis criteria for MDS and/or extramedullary disease manifestation. *Molecular relapse* was defined as decrease of donor chimerism (DC) ≤95% assessed by the individual method of the respective center and/or reoccurrence of patient-specific disease markers, eg, chromosomal aberrations or molecular alterations, without evidence of hematologic relapse.

Graft-versus-host disease (GVHD), cytogenetics, remission status before allo-HSCT, and conditioning intensity were defined as previously described [17-21]. In contrast, for evaluation after relapse, no complete hematologic reconstitution was required for definition of complete remission (CR), as factors other than the underlying disease and treatment for GVHD or viral infections might contribute to cytopenias. Still, for diagnosis of CR, restoration of complete DC and, if available, negativity of disease-specific markers were required. Outside the prospective trial, there was no planned response monitoring consisting of marrow evaluation, molecular testing, and chimerism analysis, but they were performed according to the individual center policy. *Overall survival* (OS) was defined as interval from start of Aza treatment until death or last follow-up. Patients who received a second allo-HSCT were censored at that date. Time to response was calculated from start of Aza treatment until detection of best response, whereas *duration of response* was defined as time from best response until loss of response and death. Patients who were alive with ongoing remission were censored at last follow-up.

Statistics

Continuous variables were summarized using median (range), whereas frequency tables were used for categorical variables. Time-to-event curves were calculated using the Kaplan-Meier method, and log-rank test was employed for univariate comparisons. For univariate comparison cross tabulation, Fisher's exact test and Mann-Whitney test were used. Factors influencing outcome or response in univariate analysis with a P value $<.10$ were included into multivariate analysis. For OS, a Cox regression model was used with a step-wise backward procedure deleting factors in the final model above the cut-off significance level of .05. For variables associated with achievement of CR, a multinominal logistic regression analysis was performed. Statistical analyses were performed using SPSS for Windows (SPSS Inc. Chicago, IL).

RESULTS

Patients and Treatment

We analyzed data of 154 patients (median age, 55 years; range, 21 to 72 years) with AML (n = 124, 81%), MDS (n = 28, 18%), or myeloproliferative syndromes (n = 2, 1%), who had relapsed after a median of 185 days (range, 19 to 3349 days) after allo-HSCT. The majority of patients suffered from hematologic relapse (n = 135, 88%), whereas 19 patients (12%) had molecular relapse. In 14 patients, diagnosis of molecular relapse was based on the detection of a disease-specific marker, such as karyotype abnormality or mutation associated with loss of complete DC. In the other 5 patients with high-risk AML without a disease-specific marker, loss of DC to a median of 91% (range, 90% to 95%) was accompanied with cytopenia and, therefore, judged by the treating physicians as indicative for relapse (Table S1). Six patients (3%) suffered from extramedullary relapse (2 patients skin infiltrations, 1 patient lung chloroma, 1 patient retroperitoneal chloroma, 1 patient with meningeosis leukemica, and 1 patient with meningeosis leukemica and chloroma of femur), which was associated with systemic relapse in 5 of them. Details on patients, transplantation, and relapse characteristics are given in Tables 1 and 2.

In 143 patients (93%), Aza with plans to administer DLI was the first therapy for relapse, reflected by a median time between diagnosis of relapse and onset of treatment of 7.5 days (range, 0 to 214 days). Eleven patients (7%) had received antileukemic treatment before Aza therapy, including 5 patients treated with intensive chemotherapy (3 high-dose cytarabine and mitoxantrone [HAM], 2 fludarabine, cytarabine and idarubicine [FLAG-Ida]), 4 patients with the multikinase inhibitor sorafenib, 1 patient with low-dose cytarabine, and 1 patient with gemtuzumab-ozogamicin. In addition, 6 patients had already received 1 to 3 DLI. All of these patients had failed first-line therapies and were, therefore, switched to Aza treatment.

Patients received a median of 4 courses Aza (range, 4 to 14). Three different dosing regimens were chosen, according to the local policy of the individual transplantation centers: in 70 patients (45%) Aza was administered at a dose of 100 mg/m^2 for 5 days every 28 days. This dosing scheme, which consisted of 6 to 8 cycles Aza and DLI envisaged after every second Aza cycle, was initially chosen in our prospective trial (NCT-00795548) to facilitate an outpatient setting while still delivering a dose almost equal to the approved dosage of Aza. During that time, we and other centers also used this dosing schedule in patients not participating in this trial. Afterwards, we and other centers switched to the approved Aza dose of 75 mg/m^2 for 7 days within a 28-day schedule, which was used in 79 patients (51%). The remaining 5 patients (4%) received 50 mg/m^2 Aza per day for 5 days every 28 days, based on an individual decision of the treating physicians [10].