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Long-Term Follow-Up and Impact of Comorbidity before Allogeneic Hematopoietic Stem Cell Transplantation in Patients with Relapsed or Refractory Acute Myeloid Leukemia—Lessons Learned from the Prospective BRIDGE Trial

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A B S T R A C T

In patients with relapsed or refractory (r/r) acute myeloid leukemia (AML), allogeneic hematopoietic stem cell transplantation (HSCT) is considered to be the only treatment providing long-term disease control. The BRIDGE trial studied the safety and efficacy of a clofarabine-based salvage therapy before HSCT in patients with r/r AML. Here, we report the long-term follow-up of this phase II multicenter trial and exploratory analyses on the impact of comorbidity on outcome. Eighty-four patients with a median age of 61 years (range, 40 to 75) were enrolled. Patients were scheduled for at least 1 cycle of salvage therapy with CLARA (clofarabine 30 mg/m^2; cytarabine 1 g/m^2, days 1 to 5). Chemo-responsive patients with a donor received HSCT after first CLARA. The conditioning regimen consisted of clofarabine 30 mg/m^2, day –6 to –3, and melphalan 140 mg/m^2 day –2. The Eastern Cooperative Oncology Group (ECOG) score, the hematopoietic cell transplantation–specific comorbidity index (HCT-CI), and the Cumulative Illness Rating Scale were obtained at study enrollment as well as before HSCT. Sixty-seven percent of the patients received HSCT within the trial. After a median follow up of 40 months, the estimated 3-year overall survival (OS) for all enrolled patients and those with HSCT within the trial was 40% and 55%, respectively. Relapse-free survival for patients who underwent transplantation with a complete remission afterwards (n = 50) was 48%, calculated from the day of transplantation. In multivariate analysis, both the HCT-CI and ECOG score had a statistically significant impact on OS with a hazard ratio of 1.22 (P = .025)

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and 1.72 ($P = .001$), respectively. Using a clofarabine-based salvage therapy combined with early allogeneic HSCT, we were able to achieve good long-term results for patients with r/r AML. In this cohort, both the HCT-CI and the ECOG scores gave prognostic information on OS, showing the feasibility and clinical relevance of comorbidity evaluation at the time of diagnosis of r/r AML patients.

INTRODUCTION

Treatment of patients with relapsed or refractory (r/r) acute myeloid leukemia (AML) remains a challenge. Substantial long-term survival can only be achieved with allogeneic hematopoietic stem cell transplantation (HSCT) [1]. Although there is little doubt about this, the optimal timing and pretreatment is a matter of ongoing debate [2-4]. One reason for limited data on the optimal treatment sequence of r/r AML patients is that prospective clinical trials usually focus on either salvage therapy without a stringent transplantation policy or solely cover allogeneic HSCT without picturing the selection process for transplantation.

Over the last decades, there have been several attempts to improve complete remission (CR) rates in patients with r/r AML. However, despite investigating numerous combination therapies and novel agents, little improvement has been made, with response rates of 30% to 55% [2,5-7] and median overall survival (OS) of around 6 to 7 months [8-10] without allogeneic HSCT. Also, a variety of conditioning regimens including sequential treatments have been studied, with OS rates after allogeneic HSCT between 20% to 55% at 2 years [11-16]. The patient populations in these trials were heterogeneous with respect to the definition of refractory AML, fitness, and age.

Evaluation of the general state of health and comorbidity is essential for treatment allocation. The Eastern Cooperative Oncology Group (ECOG) score [17], representing the general physical performance, and the Cumulative Illness Rating Scale (CIRS) [18], assessing comorbidities, are frequently used for stratification in the context of clinical trials. As the CIRS provides a grading of severity of each organ system involved, we hypothesized that this might increase accuracy of prediction on the impact of comorbidities.

Krug et al. developed an AML score predicting the probability of achieving CR and the risk of early death for older but fit patients with newly diagnosed AML treated with intensive induction therapy [19]. Using a machine learning algorithm, Shouval et al. were able to prognosticate the day 100 mortality after allogeneic HSCT for acute leukemia using 10 variables [20]. Specifically for the context of allogeneic HSCT, Sorror et al. developed the hematopoietic cell transplantation–specific comorbidity index (HCT-CI), which is now widely used for a comparable evaluation of comorbidity before allogeneic HSCT [21]. Recently, consistent guidelines for comorbidity coding have been published clarifying weighting of certain items [22]. Giles et al. were able to predict early death rates and OS in elderly patients with newly diagnosed AML also using the HCT-CI [23]. Comprehensive geriatric assessment has been shown to add further information and to reveal impairments in functional status and disability not captured with widely used assessments such as ECOG or HCT-CI in patients with allogeneic HSCT [24], highlighting the complex interaction of impairments attributed to increasing age and comorbidities.

For patients with r/r AML, the decision on whether to pursue a curative approach with intensive reinduction chemotherapy followed by allogeneic HSCT has to be made before the start of the salvage regimen. Because of the possible complications of reinduction therapy and prolonged neutropenia, evaluation of comorbidity may yield different results, depending on the time of assessment.

Here, we report exploratory analyses on the impact of comorbidity on reaching transplantation and on long-term survival in patients with r/r AML who were treated within the BRIDGE trial. The BRIDGE trial was a multicenter phase II trial studying a clofarabine-based salvage and conditioning therapy followed by allogeneic HSCT. Patients in this trial represented a typical elderly cohort of patients, with a median age of 61 years, ranging from 40 years to 75 years. Treatment *success*, defined as a CR or CR with incomplete recovery (CRi) at final response assessment and 2-year survival outcomes had been reported before [25].

Patients and Methods

Data from all 84 patients treated within the BRIDGE trial were analyzed. The BRIDGE trial was a prospective multicenter phase II trial that evaluated a clofarabine-based salvage therapy in patients with r/r AML before allogeneic HSCT [25]. In brief, all patients received at least 1 cycle of clofarabine 30 mg/m^2 and cytarabine 1 g/m^2, days 1 to 5 (CLARA). All *chemo-responsive patients*, defined as at least a moderate response on day 15 after start of first CLARA, with a HLA-compatible donor received allogeneic HSCT in aplasia after CLARA. Generally, HSCT was performed as soon as possible. The conditioning regimen consisted of clofarabine (30 mg/m^2, days –6 to –3) and melphalan (140 mg/m^2, day –2). Data for calculation of the HCT-CI [21], the CIRS [26], and the ECOG performance status [17] were collected at study enrollment and before the start of the conditioning. The HCT-CI scoring was performed according to current recommendations [22].

The study was conducted in accordance to the Declaration of Helsinki and approved by the responsible ethics committees of all centers. Informed consent was obtained from all patients before enrollment.

Definitions

Refractory disease was defined as ≥5% blasts in the bone marrow (BM) after the second cycle of induction therapy or no reduction in BM blasts at early treatment assessment (day +15) after the first cycle of induction therapy. *Relapsed disease* was defined as an increase in BM blasts ≥5%, reappearance of blasts in the peripheral blood (PB) or extramedullary disease after prior achievement of a CR/CRi. Evaluation of response was performed on day 15 after start of first CLARA, with *good response* defined by <10% leukemic blasts in the BM and absence of blasts in the PB. *Moderate response* was defined as a reduction in the percentage of leukemic blasts in the BM or in BM cellularity together with clearance of blasts in the PB. CR and CRi were defined according to standard criteria [1]. *CR by chimerism* was defined as >95% donor chimerism assessed by short tandem repeat PCR in BM and absence of extramedullary disease together with a neutrophil count >.5 /nL.

The cytogenetic results and complex karyotype were classified according to the current European LeukemiaNet (ELN) categories [1] and the monosomal karyotype were classified as introduced by Breems et al. [27]. All deaths occurring