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Treatment Strategies of Acute Myeloid Leukemia Relapses after Allogeneic Stem Cell Transplantation: Evidence from the GITMO Nationwide Italian Registry

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INTRODUCTION

Acute myeloid leukemia (AML) is a clonal bone marrow disorder marked by impaired hematopoiesis, leading to cytopenia and transfusion need. Predominantly affecting older adults, its incidence is expected to rise with population aging. Using data from the latest 2021 Global Burden of Disease (GBD) study, the global incidence of AML was 144,645 in 2021 (+82% with respect to 1990) [1]. The age-standardized incidence rate (ASIR) was increasing in Western Europe (from 2.25 (2.17–2.32) in 1990 to 2.79 (2.57–2.93) in 2021) and particularly in Italy (from 2.0 (1.9-2.1) in 1990 to 2.9 (2.7-3.1) in 2021) [2]. Allogeneic stem cell transplantation (Allo-SCT) is considered the only curative treatment for up to 80% of the cases. Unfortunately, 30-40% of the transplanted patients eventually relapse within the first 2 years after allo-SCT, and accordingly, the identification of the most effective and safest therapeutic alternatives after relapse is of paramount importance, especially in high income countries.

The Gruppo Italiano Trapianto di Midollo Osseo (ClinicalTrials.gov NCT06790680) study was designed with the aim to describe the real-life management of AML/MDS post-transplant relapses in Italy and draw some conclusions on the role of the different treatment strategies in the different settings of relapse. It included data of 859 AML/MDS cases from 33 Italian transplant Centers who relapsed after all-SCT between 2015 and 2021, which were extracted from the European PROMISE database (n = 3336).

STATISTICAL METHODS

Descriptive statistics were expressed as Mean (SD), median (range) for continuous variables, and as count and percentages for categorical variables. The probability of the OS was calculated by the Kaplan–Meier method. Cox proportional hazards regression model and the log-rank test were used to compare OS across groups. The Grambsch and Therneau score test (1994) for the time-varying coefficient=0 was used to test the proportionality of the PH Cox regression model. For both Treatment-related Mortality (TRM) and Relapse Mortality (RM), the sub-distribution hazard models were estimated, and the Gray's test was used for comparison across groups.

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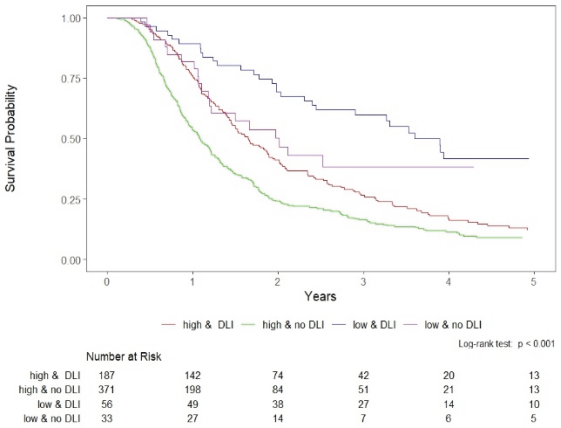
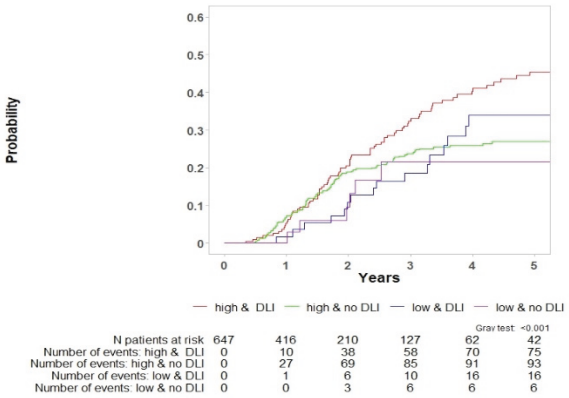
Figure 1. OS and Cumulative incidence of TRM according to disease burden at relapse and DLI-therapy





The association with the independent variables was assessed by the sub-hazard ratios (SHR) with corresponding 95%CIs. Factors that were associated with a two-sided P-value of 0.05 in the univariable analysis were included in a multivariable analysis. In the presence of non-proportional risks in the OS, the interaction of individual covariates with time was modelled as an unrestricted smooth cubic spline function [3]. Conversely, when estimating the Fine and Gray competing risk regression model, we did not test nor correct for non-proportional risks, as suggested in [4-5]. Statistical analysis was performed in the R environment (https://cran.r-project.org/).

RESULTS

Of 859 AML/MDS relapse cases after allo-SCT, 647(75%) received post-relapse treatment, with 86% classified as HIGH disease burden (hematological relapse) and 14% as LOW disease burden (minimal residual disease positivity and/or molecular mixed chimerism). Hypomethylating agents (HMAs) +/- venetoclax were the most frequently used treatment (308/647 (47.6%)), in combination with DLI in 20.4% (132/647) of the cases.

In this series, OS was 55% and 28% at 1 and 2 years, respectively, RM was 39% and 56% at 1 and 2 years, respectively, and TRM was 6% and 15% at 1 and 2 years, respectively.

Among the 647 treated patients, overall survival (OS) was significantly longer in patients with LOW disease burden receiving DLI-based therapy (p<0.001), and the treatment-related mortality (TRM) was influenced by disease burden at relapse (p<0.001) (Figure 1). By multivariate analysis LOW disease burden at relapse (HR 0.4 95%CI=(0.29-0.55)), complete remission status at transplant (HR 0.6 95%CI=(0.49-0.72)) and DLI-based treatment (HR 0.65 95%CI=(0.52-0.8)) were independently associated with improved OS. The use of DLI was independently associated with reduced relapse mortality (HR 0.56 95%CI= (0.43-0.74)) and with increased TRM (HR 1.45 95%CI= (1.06-1.97)). In the subset of 308 patients treated with HMAs +/- venetoclax group, the OS remained significantly longer in patients with LOW disease burden and DLI-based therapy(p<0.001), but TRM was not influenced by disease burden at relapse(p=0.762) (data not in Table).

DISCUSSION

This study confirmed the poor outcome for AML/MDS relapsed patients after allo-SCT, consistently with [6-7]. Interestingly, there was a dramatic unbalance between patients submitted to a post-relapse treatment at the time of hematological relapse (86%) and patients treated in the early phase (14%) that suggests a quite widespread clinical practice of delaying treatment to the most advanced stages of post-transplant relapse. However, our study demonstrates that initiating therapy at an early stage significantly improves survival outcomes, particularly in patients receiving immunotherapy with donor lymphocyte infusion. Notably, also in the subset of patients submitted to hypomethylating agents (HMAs), with or without venetoclax, therapy with DLI seems to improve the survival, especially in patients presenting with a low disease burden at relapse. Furthermore, there is evidence of the relatively safety profile of HMAs +/- venetoclax therapy treatment, as the TRM was not significantly influenced by the disease burden at relapse.

CONCLUSIONS

In relapsed AML/MDS following allo-SCT, disease burden at the time of relapse emerges as the key determinant of long-term treatment outcomes. The early use of molecularly targeted agents and donor lymphocyte infusion (DLI) should be considered in clinical practice as soon as a low disease burden is detected.

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