**Title**: Long-term outcome of DLI-based treatment strategy in patients with relapsed AML after allogeneic stem cell transplantation

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**Background:** Relapse of acute myeloid leukemia (AML) after allogeneic stem cell transplantation (SCT) is a major clinical challenge, with poor long-term survival. Donor lymphocyte infusion (DLI) can induce an enduring graft-versus-leukemia effect but may also lead to graft-versus-host disease (GvHD) associated morbidity and mortality. In this study we evaluated the 5-year overall survival of a DLI-based treatment strategy as previously described (Eefting, Haematologica, 2014).

**Methods:** We retrospectively analyzed patients with AML who relapsed after first allogeneic SCT between 2005 and 2020 at the Leiden University Medical Center. Patients with a high tumor burden (>10% blasts in bone marrow or ≥5% blasts in peripheral blood) were treated with re-induction therapy prior to DLI, while patients with a smoldering relapse (≤10% blasts in bone marrow and <5% in peripheral blood) received DLI only. Survival probabilities were calculated using the Kaplan Meier method and exploratory analyses were performed using a Cox proportional hazards regression model.

**Results**: A total of 84 patients were assessed. Median age was 53 years (range 18-77), median time from allogeneic SCT to relapse was 182 days (39 – 1779). Overall survival (OS) for the total cohort was 12% (95% CI 4-22) at 5 years after relapse. Sixty-four patients (76%) received re-induction therapy; the majority including high dose cytarabine. Forty-five (70%) patients received DLI thereafter, with a median time between relapse and DLI of 34 days (range 24-178). The 5-year OS for these 45 patients was 12% (95% CI 2-22). Patients with a smoldering relapse (n=7) received DLI only, with a median of 15 days (range 7-60) between relapse and DLI. 5-year OS was 54% (95% CI 34-94). For 7 patients whose relapse was diagnosed at time of prophylactic or pre-emptive DLI (median blast percentage 35%, range 15-91%), it was decided to await the effect of DLI without re-induction therapy. Six patients only received supportive care. From these two groups, no patient survived longer than 18 months.

Thirty-three (56%) out of all patients receiving DLI (n=59) achieved complete remission, of whom 26 (79%) developed GvHD and 13 (39%) died due to GvHD-related complications. The cumulative incidences of relapse and non-relapse mortality were 51% (95% CI 38-65) and 31% (95% CI 18-44) at 5 years after DLI, respectively.

In univariate analysis, both smoldering and late relapse (>1 year after transplantation) were significantly associated with an improved overall survival (hazard ratio [HR] 0.29, 95% CI 0.09-0.92 and HR 0.47, 95% CI 0.22-0.98, respectively).

**Conclusion:** A DLI-based treatment strategy is a potentially curative approach for patients with relapsed AML post-allogeneic SCT, particularly for patients with a lower leukemic burden at relapse. However, long-term survival is hampered by GvHD-associated mortality and relapsing disease.