PROGNOSTIC ROLE OF MINIMAL RESIDUAL DISEASE BEFORE AND AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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BACKGROUND AND OBJECTIVES

Currently, more than 80% of children with acute lymphoblastic leukemia (ALL) can be cured through intensive and risk-oriented chemotherapy protocols. Allogeneic hematopoietic stem cell transplantation (HSCT) is considered beneficial for approximately 10% of the patients who are at very-high risk at frontline therapy and for the majority of patients after relapse. Consequently, it is critically important to identify prognostic factors in this group of patients in order to tailor risk-adapted therapy.

In this retrospective study, we aimed to assess the prognostic role of minimal residual disease (MRD) before HSCT and at different time points after transplantation in children with ALL.

PATIENTS AND METHODS

We analyzed 64 pediatric ALL patients given HSCT: 22/64 were in first complete remission (1CR) and 42/64 in second complete remission (2CR). Genomic DNA was obtained from bone marrow aspirates collected at diagnosis/relapse, before HSCT (pre-HSCT) and at the first and third trimesters after HSCT (post-HSCT1 and post-HSCT3). MRD was measured by quantitative real-time PCR assays based on patient-specific junctional regions and interpreted according to the EuroMRD guidelines (**Fig.1**). The association between MRD and survival was assessed by chi-square test.

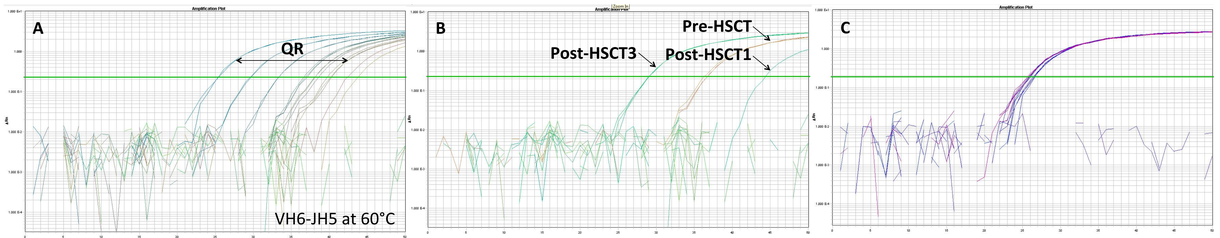

Fig.1 Amplification plots of RQ-PCR assay in patient TMO63 (relapse S4). Panel **A** shows the standard curve e il Quantitative Range (1.0E-04); panel **B** shows the MRD results for pre-HSCT (8.5E-04), post-HSCT1 (<1.0E-04) e post-HSCT3 (1.0E-01); panel **C** represents the albumin housekeeping gene amplification.

RESULTS

All evaluated patients were analyzed for MRD before transplantation (pre-HSCT). MRD was negative in 26/64 patients and positive in 38/64 patients. As for cases with positive MRD, 17/38 showed MRD levels ≥1x10-3 and 21/38 <1x10-3. Any detectable MRD positivity at pre-HSCT was significantly associated with a poor prognosis: 28/38 patients with positive MRD are dead, whereas 22/26 with negative MRD are alive in CR (P < 0.001) (**Fig.2**).

Among the 42 patients in 2CR, 14/42 had negative pre-HSCT MRD and 28/42 were MRD positive. The negativity of MRD before transplantation was found to be significantly associated with a good prognosis: 13/14 patients with negative MRD are alive in CR, while 23/28 with positive MRD are dead (p < 0.001) (**Fig. 3**).

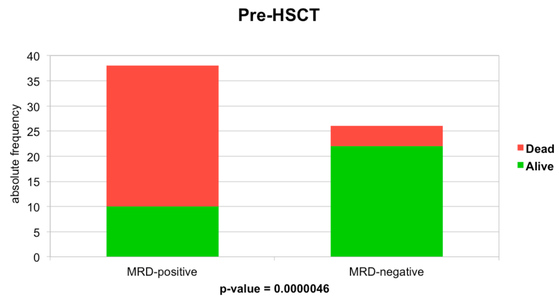

Fig.2 Outcome according to pre-HSCT MRD.

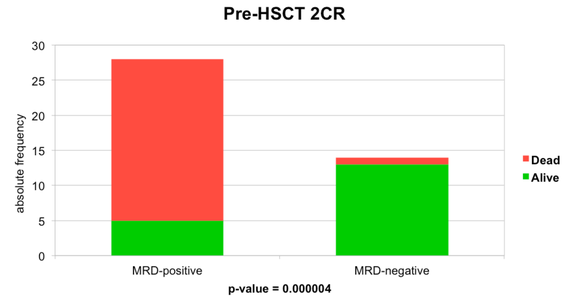

Fig.3 Outcome according to pre-HSCT MRD in 2CR patients.

Post-HSCT1 MRD was analyzed in 53 patients: 17/53 were MRD positive and 36/53 were MRD negative. Based on MRD status, the prognosis was significantly different: 26/36 patients with negative post-HSCT1 MRD are alive in CR, whereas 14/17 of patients with positive MRD are dead (P < 0.001) (**Fig.4**).

Post-HSCT3 MRD was assessed in 41 patients and 19/41 were found positive. Persistence of MRD was associated with a poor prognosis also at this time-point (P = 0.001) (**Fig. 5**).

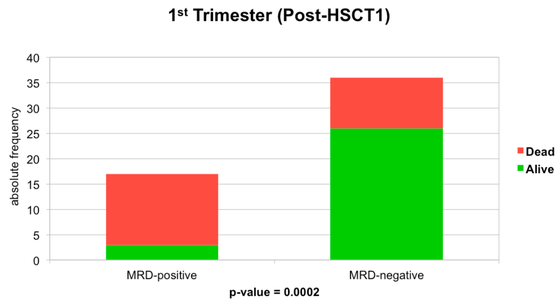

Fig.4 Outcome according to post-HSCT1 MRD.

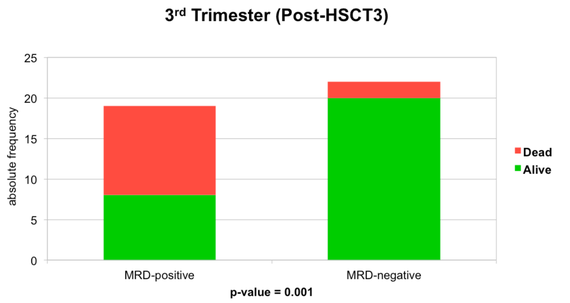

Fig.5 Outcome according to post-HSCT3 MRD.

CONCLUSIONS

These results confirm that MRD assessment has a critical role both before and after transplantation. Negative MRD before transplantation is strongly associated with a good prognosis, particularly in 2CR patients. Since persistence of MRD after HSCT is significantly associated with a worse outcome, these patients could benefit from early discontinuation of immunosuppression, adoptive T-cell therapy and the use of new drugs.

CONFLICT-OF-INTEREST DISCLOSURE

The authors declare no conflict of interest.