Impact of MRD before and after Allogeneic Hematopoietic Cell Transplantation (HCT) of Childhood ALL By FC and RQ-PCR: A Retrospective Study on Behalf of COG, the PBMTTC, the I-BFM the PDWP of the EBMT, and the Westhafen-Intercontinental-Group

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Studies to date of MRD detection pre-/post-HCT in children with ALL include insufficient numbers for multivariate analyses and lack comparison of methodologies (flow cytometry (FC) vs. RQ-PCR). Patients and Methods: Patients (pts) (N=747) were treated in Europe, North America and Australia between 09/99 and 05/16. MRD was assessed prior to HCT and on or near days +30, +60, +100, +180, +365 and beyond after HCT. Pts were in CR1 (n=275), CR2 (n=410), >CR3 (n=53), or non-remission (NR) (n=7). 586 pts had pre-B ALL, 145 had T-cell ALL and 16 had bi-lineage or bi-phenotypic AL. Grafts were sibling (MSD; n=227), unrelated (MUD; n=314), mismatched (MMR, n=75), or cord blood (n=128) Pts were placed in 4 groups for analysis according to MRD level: 1) no detectable MRD (=MRD negative), 2) MRD positive <1E-4 (=MRD low positive), 3) MRD positive ≥1E-4 <1E-3 (=MRD high positive), and 4) MRD positive ≥1E-3 (=MRD very high positive). A further analysis compared those tested by FC (n=272 pre- and 775 post-HCT) with those tested by RQ-PCR (381 pre- and 1532 post-HCT). Results: Pts showed a 4yr-pEFS of 55%, 4yr-pOS of 60%, a CIR of 31%, and a CI-NRM of 13%. MRD: Pre-HCT MRD was available in 648 pts. MRD very high, high, low and negative pts showed a 4yr-pEFS of 28%, 47%, 62%, and 67% (P<0.001). Pts with a very high pre-HCT MRD had a 2.44 fold increased HR for relapse and a 1.96 increased risk of TRM (P<0.001); pts with high MRD had a 1.85 fold increased risk of relapse which was similar in pts with low MRD compared MRD negative pts. Cox Regression analysis showed that pre-HCT MRD and remission status both significantly influenced survival. Post-HCT MRD was analyzed as time-dependent covariates. 4yr-pEFS at day +30 for MRD very high, MRD high, MRD low and MRD negative pts were: 32%, 44%, 59%, and 66%, respectively (P=0.001); at day +60 0%, 40%, 47%, and 64%, respectively (P<0.001); at day +90 29%, 42%, 69% and 65%, respectively (P<0.001); at day +180 10%, 17%, 40% and 79%, respectively (P<0.001); and at day +365 0%, 40%, 36%, and 87%, respectively (P<0.001). Very high and high MRD at all time points post-HCT led to higher relapse. Comparison between FC and PCR MRD: At all pre- and post-HCT time points both FC and RQ-PCR levels ≥10^3 were highly predictive of relapse. At pre- and post-HCT points where adequate numbers were available for comparison, RQ-PCR values ≥ 10^5 ≤ 10^3 better predicted outcomes compared to FC (e.g. pre-HCT FC HR 1.26, RQ-PCR 2.41; d+30 FC HR 1.33, RQ-PCR 2.53; day +365 FC HR 3.54, RQ-PCR 31.84, all points p<0.05). The predictive value of MRD post-transplant could be clearly confirmed.
by the analysis using area under the curve (AUC) survival analysis. Multivariable cox regression analysis confirmed the high association between MRD and outcome. GVHD and outcome: Univariate KM estimates showed that pts with no GVHD, GVHD I, II, III, and IV had a 4y-pEFS of 43%, 67%, 65%, 56%, and 29% (P<0.001), and a CIR of 44%, 24%, 26%, 21%, and 12% (P<0.001). GVHD was significantly correlated to EFS, relapse and TRM. There was a clear interaction between aGVHD and MRD. At all time-points landmark analysis showed that MRD positive pts with GVHD had a superior pEFS compared to MRD positive pts without GVHD. Summary: This large study confirmed that MRD pre- and post-HCT is a powerful predictor for survival. These results suggest MRD measurement pre-/post-HCT could be used to guide post-HCT interventions.

Disclosure of conflict of interest

None