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Clinical Impact of Minimal Residual Disease Monitoring by real time Quantitative PCR in Acute Myeloid Leukemia

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Backgrounds: Despite complete remission (CR) in most acute myeloid leukemia (AML) patients after induction therapy, a substantial proportion of patients eventually relapse. Monitoring of minimal residual disease (MRD) in AML patients is useful in identifying patients with high risk of relapse. Large scale MRD monitoring program of AML patients in Taiwan have not been available in the past. With the support of MOHW, we detected MRD for AML patients in. The purpose of this study was to evaluate the impact of MRD on outcome in AML patients *with PML-RARa, RUNX1-RUNX1T1, CBFB-MYH11, NPM1* mutations and *KMT2A*-PTD from Taiwan AML Consortium. **Materials and Methods:** A total of 304 AML patients were enrolled, in whom 134 AML patients with *PML-RARA* (2002-2017), 72 AML patients with *RUNX1-RUNX1T1* (1999-2016), 21 AML patients with *CBFB-MYH11*
(2006-2016), 48 AML patients with *NPM1* (2012-2017), and 29 AML patients with *KMT2A*-PTD (2000-2015). Follow-up bone marrow samples at different time points were analyzed by RQ-RT-PCR TaqMan assays to measure fusion transcripts or mutations detected at AML diagnosis. The results were expressed as log reduction, except that MRD cutoff by upper normalized copy number (NCN) limit levels of normal marrow in *KMT2A*-PTD AML (e9e3 NCN normal limit < 0.00012; e11e3 NCN normal limit < 0.000012). Relapse-free survival (RFS) and overall survival (OS) were analyzed according to the MRD level. **Results:** The two-year relapse-free survival (RFS) rates of AML patients with *PML-RARa, RUNX1-RUNX1T1, CBFB-MYH11, NPM1* mutation and *KMT2A*-PTD were 94%, 63%, 71%, 53%, and 16%. The two-year overall survival (OS) rates of AML patients with *PML-RARa, RUNX1-RUNX1T1, CBFB-MYH11, NPM1* mutation and *KMT2A*-PTD were 97%, 73%, 91%, 59%, and 26%.
For AML patients with *PML-RARa*, those with post-induction therapy MRD > 3 log reduction (n=60) had a trend of improved OS compared to patients with post-induction therapy MRD < 3 log reduction (n=54) (5-year OS rate 97% vs 88%). During

consolidation chemotherapy, *PML-RARa* AML patients with MRD > 5 log reduction (n=94) had significantly improved RFS (5-year RFS rates 96% vs 73%, P=0.034) and OS (5-year OS rates 97% vs 71%, *P*=0.019) compared to patients with MRD < 5 log reduction (n=9). *PML-RARa* AML patients with off therapy MRD > 5 log reduction (n=107) had significantly improved RFS (5-year RFS rates 95% vs 50%, *P*=0.001) and OS (5-year OS rates 93% vs 50%, *P*=0.007) compared to patients with MRD < 5 log reduction (n=9). For AML patients with *RUNX1-RUNX1T1* patients with post-induction MRD > 1 log reduction was associated with significantly improved RFS and OS compared to patients with post-induction MRD < 1 log reduction. *RUNX1-RUNX1T1* AML patients with post-3rd consolidation therapy MRD > 3 log reduction or with off therapy MRD > 4 log reduction were all associated with significantly improved RFS and OS compared to those with post-3rd consolidation therapy MRD < 3 log reduction or with off therapy MRD < 4 log reduction. *CBFB-MYH11*AML patients who had during consolidation MRD > 3 log reduction had significant better RFS compared to patients with during consolidation MRD < 3 log reduction. *MLL*-PTD AML patients who had during consolidation MRD < NCN upper normal limits had significant better RFS (2-year RFS rates 57% vs 18%, *P*=0.048) and OS (2-year OS rates 100% vs 44%, *P*=0.013) compared to patients with during consolidation MRD > NCN upper normal limits. **Conclusions:** Our data from Taiwan AML Consortium defined the optimal molecular responses at different time points following therapy in t(8;21) and t(15;17) AML patients. MRD monitoring is informative to identify favorable genetic AML patients with higher risk of relapse. MRD-guided therapy is expected to further improve their treatment outcomes.