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Early achievement of measurable residual disease (MRD)-negative complete remission as predictor of outcome after myeloablative allogeneic hematopoietic cell transplantation in acute myeloid leukemia

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To the Editor:

Myeloablative allogeneic hematopoietic cell transplantation (HCT) is commonly used for acute myeloid leukemia (AML) in first morphologic remission [1]. Pre-HCT measurable ("minimal") residual disease (MRD) is a major, independent indicator of relapse in this situation [2]. However, not all MRD^{pos} patients relapse, and not all MRD^{neg} patients are cured. Thus, there is interest in additional predictors to inform more accurately on expected outcomes and, possibly, develop risk-stratified therapies. We previously reported the number of induction courses required to enter remission adds prognostic information for post-HCT outcome independent of that provided by pre-HCT MRD testing [3]. Here, we examined whether achievement of an MRD^{neg} complete remission (CR) after one course of chemotherapy ("early MRD^{neg} CR") is associated with better post-HCT outcomes than seen in patients who do not achieve this response ("no early MRD^{neg} CR").

We studied adults ≥ 18 years who received a first myeloablative allogeneic HCT with peripheral blood or bone marrow as a stem cell source while in first MRD^{neg} CR or CR with incomplete hematologic recovery (CRi) and were evaluated for MRD by multiparameter flow cytometry (MFC) performed on bone marrow specimens obtained after the first cycle of induction chemotherapy and before HCT. We included patients regardless of how many cycles of chemotherapy were necessary to obtain morphologic remission and regardless of whether or not postremission chemotherapy was administered before allografting. Any measurable level of MRD was considered positive [4–8]; MRD test results were available to treating physicians. All patients were treated on institutional review board (IRB)-approved protocols or standard treatment protocols. Our retrospective analysis was approved by the Fred Hutchinson Cancer Research Center IRB. Follow-up was current as of April 29, 2019.

For statistical analysis, unadjusted probabilities of overall survival (OS), relapse-free survival (RFS), and graft-versus-host disease (GVHD)-free RFS (using grade 3–4 acute GVHD, chronic GVHD by NIH criteria, relapse, and death from any cause as events) were estimated using the Kaplan–Meier method. Probabilities of non-relapse mortality (NRM) and relapse were summarized using

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cumulative incidence estimates. Landmark analyses were used, with time 0 set at the time of transplant. NRM was defined as death without prior relapse and was considered a competing risk for relapse, while relapse was a competing risk for NRM. Cox regression and subdistribution competing risk regression models were used to assess covariate associations with outcomes. Given the modest number of events in analyses, large multivariable models were not feasible; multiple multivariable models for early vs. late MRD status were done controlling for the following single clinical covariates: cytogenetic risk group at time of AML diagnosis (modified MRC/NCRI criteria [9]; unfavorable vs. favorable/intermediate), type of AML at diagnosis (secondary vs. de novo), age at the time of HCT, disease risk index (DRI) [10], karyotype at time of HCT (normalized vs. not normalized for patients presenting with abnormal karyotypes), and peripheral blood counts at the time of HCT (recovered vs. not recovered). Missing cytogenetic risk and karyotype were accounted for as separate categories. Categorical patient characteristics were compared between individual patient groups using Fisher's exact tests, and continuous characteristics were compared with Wilcoxon rank-sum tests. Statistical analyses were performed using STATA and R.

From April 2006 (when a refined ten-color MFC-based MRD test was introduced at our institution [4–8]) to January 2019, 321 adults with AML in first remission underwent myeloablative allogeneic HCT with blood or marrow as stem cell source. Of these, three did not agree to their data being used for research purposes, and six did not undergo MRD testing at our institution during the pre-HCT work-up. As a transplant center with a large referral base, the majority of patients referred to our institution for transplantation have received induction (and postremission) chemotherapy elsewhere. However, among the 312 patients left for analysis, 98 patients underwent MFC-based MRD testing at our institution after the first cycle of intensive induction chemotherapy (intensive denoting $7+3$ or treatments using higher cytarabine doses). Despite having no evidence of MRD by flow cytometry, 13 of the 98 patients had abnormal findings in pre-HCT cytogenetic studies (a finding taken to indicate presence of MRD [11]), leaving 85 patients for analysis. Forty five of these patients (52.9%) were in MRD^{neg} CR after one cycle of induction chemotherapy ("early MRD^{neg} CR"). Forty patients (47.1%) achieved responses other than MRD^{neg} CR after the first chemotherapy cycle, including MRD^{neg} CRi ($n=8$), MRD^{pos} CR ($n=4$), MRD^{pos} CRi ($n=3$), MRD^{pos} morphologic leukemia-free state ($n=1$), and refractory disease ($n=24$; "no early MRD^{neg} CR"). Patients who achieved an early MRD^{neg} CR more likely received high-dose cytarabine containing chemotherapy during initial induction ($P=0.009$) and more likely had peripheral blood as stem cell source ($P=0.011$). On the other hand, there were no statistically significant differences in age, white blood cell count at diagnosis, cytogenetic disease risk, secondary AML, DRI, median remission duration before HCT, recovery of absolute neutrophil count and/or platelet count at the time of HCT, or donor type between patients with early vs. no early MRD^{neg} CR (Supplementary Table 1).

There were 30 deaths, 19 relapses, 10 grade 3–4 acute GVHD events, 39 chronic GVHD events, and 16 deaths in remission contributing to the probability estimates for relapse, RFS, GVHD-free RFS, OS, and NRM. The median follow-up after HCT among survivors was 4.1 [0.3–12.0] years and 6.1 [0.4–12.0] years for patients with early vs. no early MRD^{neg} CR, respectively, noting that the great majority of post-HCT relapses and deaths would thus have been expected to have occurred during the follow-up time in our patients. The 3-year estimate of relapse among patients with early vs. no early MRD^{neg} CR was 9.4% (1.0–18.3%) and 29.3% (14.3–44.2%) (Fig. 1). For 3-year RFS, the corresponding estimates were 66.4% (53.4–82.6%) and 59.4% (45.3–77.9%) (Supplementary Fig. 1a). Estimates of 3-year GVHD-free RFS for patients with early vs. no early MRD^{neg} CR were 18.0% (9.4–34.7%) and 28.5% (16.9–47.9%) (Supplementary Fig. 1b). The 3-year estimates of OS were 68.2% (55.2–84.3%) and 63.8% (49.7–81.9%) for these two patient groups (Supplementary Fig. 1c). Finally, the 3-year estimates of NRM for these two

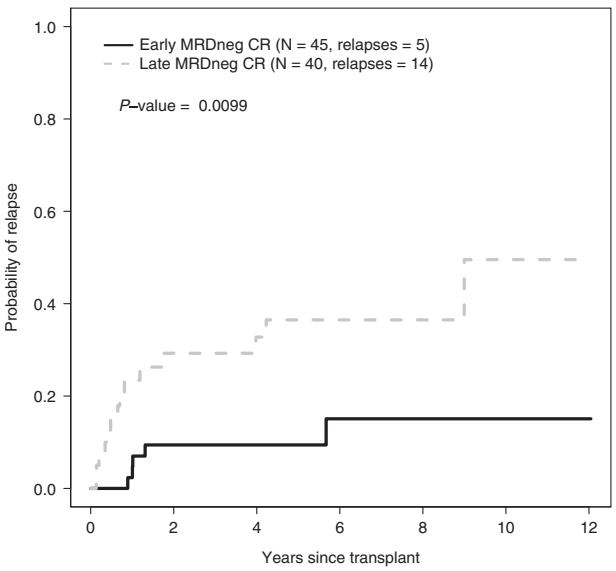

Fig. 1 Association between response to initial cycle of induction and cumulative incidence of post-HCT relapse. Estimates of cumulative incidence of relapse following myeloablative allogeneic HCT for AML in MRD^{neg} morphologic remission, shown individually for patients who achieved an MRD^{neg} CR with the first cycle of induction chemotherapy ($n=45$; black, solid line) and those who did not ($n=40$; gray, dashed line)

patient groups were 24.2% (11.8–37.6%) and 11.2% (0.5–22.1%) (Supplementary Fig. 1d).

Noting the small number of events limited our ability ("power") to detect statistically significant differences, univariate regression models indicated patients who achieved an MRD^{neg} CR early had a lower risk of relapse (hazard ratio [HR] = 0.27 [95% confidence interval: 0.10–0.73], $P = 0.010$) than patients who did not. There were no statistically significant differences in RFS, GVHD-free RFS, and OS for patients with vs. those without early MRD^{neg} CR achievement (for RFS: HR = 0.79 [0.41–1.54], $P = 0.49$; for GVHD-free RFS: HR = 1.08 [0.66–1.78], $P = 0.75$; for OS: HR = 0.99 [0.48–2.03], $P = 0.98$). The lack of significant difference in survival estimates may be partly related to a trend toward higher NRM for patients with early MRD^{neg} CR (HR = 2.97 [0.96–9.26], $P = 0.06$). Finally, we fit multivariable models for relapse, RFS, GVHD-free RFS, OS, and NRM. Due to the small number of events, large multivariable models were not feasible; instead we fit several multivariable models controlling for one additional covariate in addition to response to the first cycle of induction chemotherapy: age at HCT, cytogenetic disease risk at diagnosis, type of AML, pre-HCT karyotype, and pre-HCT peripheral blood count recovery. The HRs and P values for early vs. no early MRD^{neg} CR were similar across these multiple models and similar to the univariate results above: for time to relapse, HRs varied between 0.30 and 0.35 with P values of 0.022–0.047; for RFS, HRs varied between 0.79 and 0.85 with P values between 0.49 and 0.62; for GVHD-free RFS, HRs varied between 1.04 and 1.09 with P values of 0.74–0.84; for OS HRs varied between 0.98 and 1.04 with P values of 0.91–0.98; and for NRM, HRs varied between 0.79 and 0.84 with P values between 0.49 and 0.62.

Together, our findings are consistent with the hypothesis that early achievement of a deep (MRD^{neg}) CR is prognostically informative for relapse for adults with AML in first remission undergoing myeloablative allogeneic HCT and identifies a subset of patients with particularly low risk of post-HCT relapse (~10% at 3–5 years). Several study limitations have to be acknowledged. Given interlaboratory differences in MFC-based MRD testing [2, 12], we only included patients who underwent MRD testing after the initial cycle of induction chemotherapy at our institution, impacting the size of our study cohort. Other limitations include the retrospective nature of our study, the heterogeneous nature of induction and (if given) postremission therapy, and the possibility that some patients considered to not have achieved an early MRD^{neg} CR might have done so had a second course not been started [13]. Moreover, information on molecular and FISH testing was not routinely available. Thus, further studies using larger patient cohorts will be necessary for validation of our observation and to identify whether the beneficial effect of an early MRD^{neg} CR is similar in different prognostic groups, e.g., adverse vs. intermediate cytogenetics. There may be some patient subsets typically considered HCT candidates in whom early achievement of an MRD^{neg} CR conveys such a low risk of relapse even without HCT that the risks of HCT outweigh the benefit of the graft-versus-leukemia effect seen in patients with MRD^{neg} remission undergoing allografting [14].

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Author contributions APH collected and analyzed/interpreted data and drafted the manuscript. ALB and LMM collected data and revised the manuscript. MO analyzed/interpreted data, performed statistical analyses, and revised the manuscript. BLW, MM, EHE, and FRA contributed to the provision of study material and patient recruitment, analyzed/interpreted data, and revised the manuscript. RBW designed the study, collected and analyzed/interpreted data, performed statistical analyses, and drafted the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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