Regular Article

TRANSPLANTATION

# Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission

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## Key Points

- The negative impact of pre-HCT flow cytometrically determined MRD is similar for AML in CR1 and CR2.
- Even minute levels of MRD (≤0.1%) are associated with adverse outcome.

**Minimal residual disease (MRD) before myeloablative hematopoietic cell transplantation (HCT) is associated with adverse outcome in acute myeloid leukemia (AML) in first complete remission (CR1). To compare this association with that for patients in second complete remission (CR2) and to examine the quantitative impact of MRD, we studied 253 consecutive patients receiving myeloablative HCT for AML in CR1 (n = 183) or CR2 (n = 70) who had pre-HCT marrow aspirates analyzed by 10-color flow cytometry. Three-year estimates of overall survival were 73% (64%-79%) and 32% (17%-48%) for $MRD^{neg}$ and $MRD^{pos}$ CR1 patients, respectively, and 73% (57%-83%) and 44% (21%-65%) for $MRD^{neg}$ and $MRD^{pos}$ CR2 patients, respectively. Similar estimates of relapse were 21% (14%-28%) and 58% (41%-72%) for $MRD^{neg}$ and $MRD^{pos}$ CR1 patients, respectively, and 19% (9%-31%) and 68% (41%-85%) for $MRD^{neg}$ and $MRD^{pos}$ CR2 patients, respectively. Among the $MRD^{pos}$ patients, there was no statistically significant evidence that increasing levels of MRD were associated with increasing risks of relapse and death. After multivariable adjustment, risks of death and relapse were 2.61 times and 4.90 times higher for $MRD^{pos}$ patients ($P < .001$). Together, our findings indicate that the negative impact of pre-HCT MRD is similar for AML in CR1 and CR2 with even minute levels (≤0.1%) as being associated with adverse outcome. (*Blood*. 2013;122(10):1813-1821)**

## Introduction

Allogeneic hematopoietic cell transplantation (HCT) is an effective therapy for many patients with acute myeloid leukemia (AML) in first or subsequent complete remission (CR).[1,2] However, even in the absence of morphologically detectable disease at the time of transplantation, relapse remains a major cause of treatment failure post-HCT,[2] demonstrating that microscopy-based evaluations are incapable of detecting clinically relevant amounts of tumor cells. Over the last 2 decades, several techniques were developed that enable the sensitive quantification of minimal residual disease (MRD) amounts in patients with AML in morphological remission.[3-6] The most widely exploited method in AML other than acute promyelocytic leukemia is multiparameter flow cytometry (MFC)-based because AML cells feature immunophenotypic abnormalities ("leukemia-associated immunophenotypes" [LAIP]) that can be used to distinguish them from normal hematopoietic cells in the vast majority (>90%) of cases with high sensitivity.[3-6]

Previous studies from our group[7] and others[8-13] have demonstrated that MFC-detectable MRD at the time of autologous or myeloablative allogeneic HCT is a powerful, independent predictor of subsequent relapse and shorter survival for AML patients in CR. These studies have exclusively or primarily focused on patients undergoing HCT in first CR (CR1). The relationship between MRD and outcome is much less studied for patients in second CR (CR2). Furthermore, although several studies in patients with acute lymphoblastic leukemia suggest that the association between MRD and risk of post-HCT relapse is dose-dependent,[6] the quantitative impact of MRD levels on outcome in AML has not been well studied. To address these uncertainties, we investigated the quantitative significance of MRD in 253 consecutive patients who underwent allogeneic myeloablative HCT for AML in CR1 or CR2 at our institution.

## Patients and methods

### Study cohort

Patients of all ages, identified from our computerized database, were included in this study if they had AML in CR1 or CR2 with or without incomplete peripheral blood count recovery based on morphologic criteria[14,15] (ie, regardless of the presence of MRD) at the time of HCT, underwent myeloablative conditioning, had either a matched sibling or unrelated donor,

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**Table 1. Pretransplantation demographic and clinical characteristics of study cohort, stratified by CR status**

| | All (n = 253) | CR1 (n = 183) | CR2 (n =70) | P* |
|---|---|---|---|---|
| Median age at HCT (range), y | 43.1 (0.6-72.6) | 44.7 (0.6-69.5) | 42.3 (2.1-72.6) | NS |
| Male gender, n (%) | 131 (51.8%) | 92 (50.3%) | 39 (55.7%) | NS |
| Median WBC at diagnosis, $\times 10^3/\mu L$ | 9.6 (0.2-326) | 8.6 (0.2-280) | 14.9 (1.2-326) | NS |
| **Cytogenetics, n (%)** | | | | <.001 |
| Favorable | 22 (8.7%) | 6 (3.3%) | 16 (22.9%) | |
| Intermediate | 168 (66.4%) | 124 (67.8%) | 44 (62.9%) | |
| Adverse | 56 (22.1%) | 48 (26.2%) | 8 (11.4%) | |
| Missing | 7 (2.8%) | 5 (2.7%) | 2 (2.9%) | |
| Secondary AML, n (%) | 69 (27.3%) | 63 (34.4%) | 6 (8.6%) | <.001 |
| **No. of induction courses, n (%)** | | | | .014 |
| 1 | 167 (66.0%) | 109 (59.6%) | 58 (82.9%) | |
| 2 | 75 (29.6%) | 64 (35.0%) | 11 (15.7%) | |
| ≥3 | 11 (4.3%) | 10 (5.5%) | 1 (1.4%) | |
| **Consolidation after initial induction, n (%)** | | | | .006 |
| No | 40 (15.8%) | 36 (19.7%) | 4 (5.7%) | |
| Yes | 213 (84.2%) | 147 (80.3%) | 66 (94.3%) | |
| No. of consolidation courses | | | | <.001 |
| 1 | 111 (43.9%) | 93 (50.8%) | 18 (25.7%) | |
| ≥2 | 102 (40.3%) | 54 (29.5%) | 48 (68.6%) | |
| **No. of re-induction courses, n (%)** | | | | NA |
| 1 | — | NA | 57 (81.4%) | |
| 2 | — | NA | 10 (14.3%) | |
| ≥3 | — | NA | 3 (4.3%) | |
| **Consolidation after re-induction, n (%)** | | | | NA |
| No | — | NA | 46 (65.7%) | |
| Yes | — | NA | 24 (34.3%) | |
| No. of consolidation courses | | | | |
| 1 | — | NA | 22 (31.4%) | |
| ≥2 | — | NA | 2 (2.9%) | |
| Median remission duration before HCT (range), days | | 121 (16-465) | 59.5 (17-231) | <.001 |
| **Peripheral blood counts before HCT** | | | | .001 |
| ANC ≥1 000/μL and platelets ≥100 000/μL | 216 (85.4%) | 164 (89.6%) | 52 (74.3%) | |
| ANC <1 000/μL and/or platelets <100 000/μL | 36 (14.2%) | 18 (9.8%) | 18 (25.7%) | |
| Missing | 1 (0.4%) | 1 (0.6%) | 0 (0%) | |
| **Routine cytogenetics before HCT** | | | | NS |
| Normal karyotype | 222 (87.8%) | 159 (86.9%) | 63 (90.0%) | |
| Abnormal karyotype | 24 (9.5%) | 20 (10.9%) | 4 (5.7%) | |
| Missing/inadequate data | 7 (2.8%) | 4 (2.2%) | 3 (4.3%) | |
| **MRD status at HCT** | | | | NS |
| Positive, n (%) | 54 (21.3%) | 36 (19.7%) | 18 (25.7%) | |
| <0.1% | 14 (5.5%) | 12 (6.6%) | 2 (2.9%) | |
| 0.1%-1% | 24 (9.5%) | 14 (7.7%) | 10 (14.3%) | |
| >1% | 16 (6.3%) | 10 (5.5%) | 6 (8.6%) | |
| Median % abnormal blasts, range | 0.30 (0.007-7.8) | 0.29 (0.007-7.8) | 0.41 (0.05-3.5) | |
| Negative, n (%) | 199 (78.7%) | 147 (80.3%) | 52 (74.3%) | |

ANC, absolute neutrophil count; NA, not applicable; NS, not significant; WBC, white blood cell count.
*For the comparison CR1 vs CR2.

and received the first transplant. We included all consecutive patients meeting these criteria if they underwent pre-HCT workup from late April 2006 (the time a refined MFC-based MRD detection method was introduced at our institution and was used routinely during the pre-HCT work-up in all patients) until November 2011. Results on the first 99 CR1 patients have been previously reported.[7] We used the 2008 World Health Organization criteria to define AML[16] and the refined United Kingdom Medical Research Council criteria to assign cytogenetic risk.[17] Cytogenetic analysis was performed with the G-banding method. Treatment response criteria were used as proposed by international working groups.[14,15] Because many patients were referred from outside institutions, molecular testing for nucleophosmin, fms-related tyrosine kinase 3, and CCAAT/enhancer binding protein alpha mutations was not uniformly available. Chronic graft-versus-host disease (cGVHD) was diagnosed using the National Institutes of Health consensus criteria.[18] Information on post-transplant outcomes was captured via the Long-Term Follow-Up Program through medical records from our outpatient clinic and local clinics that provided primary care for patients. All patients were treated based on Institutional Review Board-approved protocols and provided consent in accordance with the Declaration of Helsinki. Follow-up was current as of April 1, 2013.

## MFC detection of MRD

Ten-color MFC was performed on bone marrow aspirates obtained as routine baseline assessment before HCT with a panel consisting of 3 tubes as follows[7]: (1) HLA-DR-Pacific Blue, CD15-fluorescein isothiocyanate, CD33-phycoerythrin (PE), CD19-PE-Texas Red (PE-TR), CD117-PE-Cy5,

**Table 2. Donor and transplant recipient demographic and clinical characteristics**

| | All (n = 253) | CR1 (n = 183) | CR2 (n = 70) | P* |
|---|---|---|---|---|
| **Donor type, n (%)** | | | | NS |
| Related | 83 (32.8%) | 62 (33.9%) | 21 (30.0%) | |
| Unrelated | 170 (67.2%) | 121 (66.1%) | 49 (70.0%) | |
| **Median donor age** (range), y | 38.7 (5.7-77.8) | 39.1 (5.7-67.4) | 37.6 (10.6-77.8) | NS |
| **Donor gender, n (%)** | | | | NS |
| Male | 125 (49.4%) | 96 (52.5%) | 29 (41.4%) | |
| Female | 109 (43.1%) | 72 (39.3%) | 37 (52.9%) | |
| Missing | 19 (7.5%) | 15 (8.2%) | 4 (5.7%) | |
| **Patient/donor gender, n (%)** | | | | NS |
| Male/male | 66 (26.1%) | 49 (26.8%) | 17 (24.3%) | |
| Female/female | 56 (22.1%) | 40 (21.9%) | 16 (22.9%) | |
| Male/female | 53 (21.0%) | 32 (17.5%) | 21 (30.0%) | |
| Female/male | 59 (23.3%) | 47 (25.7%) | 12 (17.1%) | |
| Missing | 19 (7.5%) | 15 (8.2%) | 4 (5.7%) | |
| **Conditioning regimen, n (%)** | | | | .001 |
| Bu/Cy ± ATG or CAMP | 65 (25.7%) | 57 (31.2%) | 8 (11.4%) | |
| Bu/Flu ± ATG | 34 (13.4%) | 24 (13.1%) | 10 (14.3%) | |
| H-TBI/Cy or H-TBI/TEPA/Flu | 72 (28.6%) | 48 (26.2%) | 24 (34.3%) | |
| Treo/Flu ± L-TBI | 68 (26.9%) | 49 (26.8%) | 19 (27.1%) | |
| Flu/radiolabeled Ab/L-TBI | 14 (5.5%) | 5 (2.7%) | 9 (12.9%) | |
| **Source of stem cells, n (%)** | | | | NS |
| PBSC | 136 (53.8%) | 99 (54.1%) | 37 (52.9%) | |
| BM | 75 (29.6%) | 56 (30.6%) | 19 (27.1%) | |
| Cord Blood | 42 (16.6%) | 28 (15.3%) | 14 (20.0%) | |
| **GVHD prophylaxis** | | | | NS |
| Calcineurin inhibitor + methotrexate | 170 (67.2%) | 129 (70.5%) | 41 (58.6%) | |
| Calcineurin inhibitor + MMF | 56 (22.1%) | 33 (18.0%) | 23 (32.9%) | |
| Cytoxan | 23 (9.1%) | 17 (9.3%) | 6 (8.6%) | |
| Other | 4 (1.6%) | 4 (2.2%) | 0 (0%) | |

Ab, antibody; ATG, antithymocyte globulin; BM, bone marrow; Bu, busulfan; CAMP, campath; Cy, cytoxan; Flu, fludarabine; H-TBI, high-dose TBI; L-TBI, low-dose TBI; MMF, mycophenolate mofetil; NS, not significant; PBSC, peripheral blood stem cells; TEPA, thiotepa.
*For the comparison CR1 vs CR2.

CD13-PE-Cy7, CD38-Alexa 594 (A594), CD34-allophycocyanin (APC), CD71-APC-A700, and CD45-APC-H7. (2) HLA-DR-Pacific Blue, CD64-fluorescein isothiocyanate, CD123-PE, CD4-PE-TR, CD14-PE-Cy5.5, CD13-PE-Cy7, CD38-A594, CD34-APC, CD16-APC-A700, and CD45-APC-H7. (3) CD56-Alexa 488, CD7-PE, CD5-PE-Cy5, CD33-PE-Cy7, CD38-A594, CD34-APC, and CD45-APC-H7. All antibodies were obtained from Beckman-Coulter (Fullerton, CA) or Becton-Dickinson (San Jose, CA). Up to 1 million events per tube were acquired on a custom-built LSRII and data compensation and analysis were performed using software developed in our laboratory (WoodList). MRD was identified as a population showing deviation from the normal patterns of antigen expression seen on specific cell lineages at specific stages of maturation as compared with either normal or regenerating marrow. Thus, this approach was not restricted to the use of LAIP, as immunophenotypic data from initial disease presentation was only available for a subset of patients; however, if available, such LAIP abnormalities were also assessed in the pre-HCT specimens. The routine sensitivity of this assay was estimated at 0.1%, although a higher level of sensitivity was possible for a subset of leukemias featuring more frankly aberrant immunophenotypes. When identified, the abnormal population was quantified as a percentage of the total $CD45^+$ white cell events. As done previously, and as pre-specified, any level of residual disease was considered MRD-positive ($MRD^{pos}$).[7]

## Statistical analysis

Unadjusted probabilities of overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method, and probabilities of

**Table 3. Comparison of pretransplantation characteristics between $MRD^{neg}$ and $MRD^{pos}$ patients**

| | $MRD^{neg}$ (n = 199) | $MRD^{pos}$ (n = 54) | P* |
|---|---|---|---|
| Median age at HCT (range), y | 42.5 (0.6-71.6) | 47.6 (2.2-72.6) | NS |
| Male gender, n (%) | 95 (47.7%) | 36 (66.7%) | .014 |
| Median WBC at diagnosis, $\times 10^3/\mu L$ | 11.6 (0.2-297) | 5.3 (0.3-326) | NS |
| **Cytogenetics, n (%)*** | | | .040 |
| Favorable | 20 (10.1%) | 2 (3.7%) | |
| Intermediate | 137 (68.8%) | 31 (57.4%) | |
| Adverse | 37 (18.6%) | 19 (35.2%) | |
| Missing | 5 (2.5%) | 2 (3.7%) | |
| Secondary AML, n (%) | 46 (23.1%) | 23 (42.6%) | 0.004 |
| **No. of induction courses, n (%)** | | | NS |
| 1 | 136 (68.3%) | 31 (57.4%) | |
| 2 | 56 (28.1%) | 19 (35.2%) | |
| ≥3 | 7 (3.5%) | 4 (7.4%) | |
| **Consolidation therapy after initial induction, n (%)** | | | <.001 |
| No | 23 (11.6%) | 17 (31.5%) | |
| Yes | 176 (88.4%) | 37 (68.5%) | |
| **No. of consolidation courses** | | | .009 |
| 1 | 92 (46.2%) | 19 (35.2%) | |
| ≥2 | 84 (42.2%) | 18 (33.3%) | |
| **No. of re-induction courses, n (%)** | | | NS |
| 1 | 41 (20.1%) | 16 (29.6%) | |
| 2 | 8 (4.0%) | 2 (3.7%) | |
| ≥3 | 3 (1.5%) | 0 (0%) | |
| **Consolidation therapy after re-induction, n (%)** | | | NS |
| No | 32 (16.1%) | 14 (25.9%) | |
| Yes | 20 (10.1%) | 4 (7.4%) | |
| **No. of consolidation courses** | | | NS |
| 1 | 18 (9.1%) | 4 (7.4%) | |
| ≥2 | 2 (1.0%) | 0 (0%) | |
| **Median remission duration before HCT (range), d** | | | |
| For CR1 patients | 127 (18-465) | 93 (16-383) | .015 |
| For CR2 patients | 59.5 (17-231) | 54 (17-203) | NS |
| **Peripheral blood counts before HCT** | | | .006 |
| ANC ≥1000/μL and platelets ≥100 000/μL | 176 (88.4%) | 40 (74.1%) | |
| ANC <1000/μL and/or platelets <100 000/μL | 22 (11.1%) | 14 (25.9%) | |
| Missing | 1 (0.5%) | 0 (0%) | |
| **Routine cytogenetics before HCT, n (%)** | | | <.001 |
| Normal karyotype | 183 (92.0%) | 39 (72.2%) | |
| Abnormal karyotype | 11 (5.5%) | 13 (24.1%) | |
| Missing/inadequate data | 5 (2.5%) | 2 (3.7%) | |
| **CR status, n (%)** | | | NS |
| CR1 | 147 (73.9%) | 36 (66.7%) | |
| CR2 | 52 (26.1%) | 18 (33.3%) | |

ANC, absolute neutrophil count; NS, not significant; WBC, white blood cell count.
*For the comparison $MRD^{neg}$ vs $MRD^{pos}$.

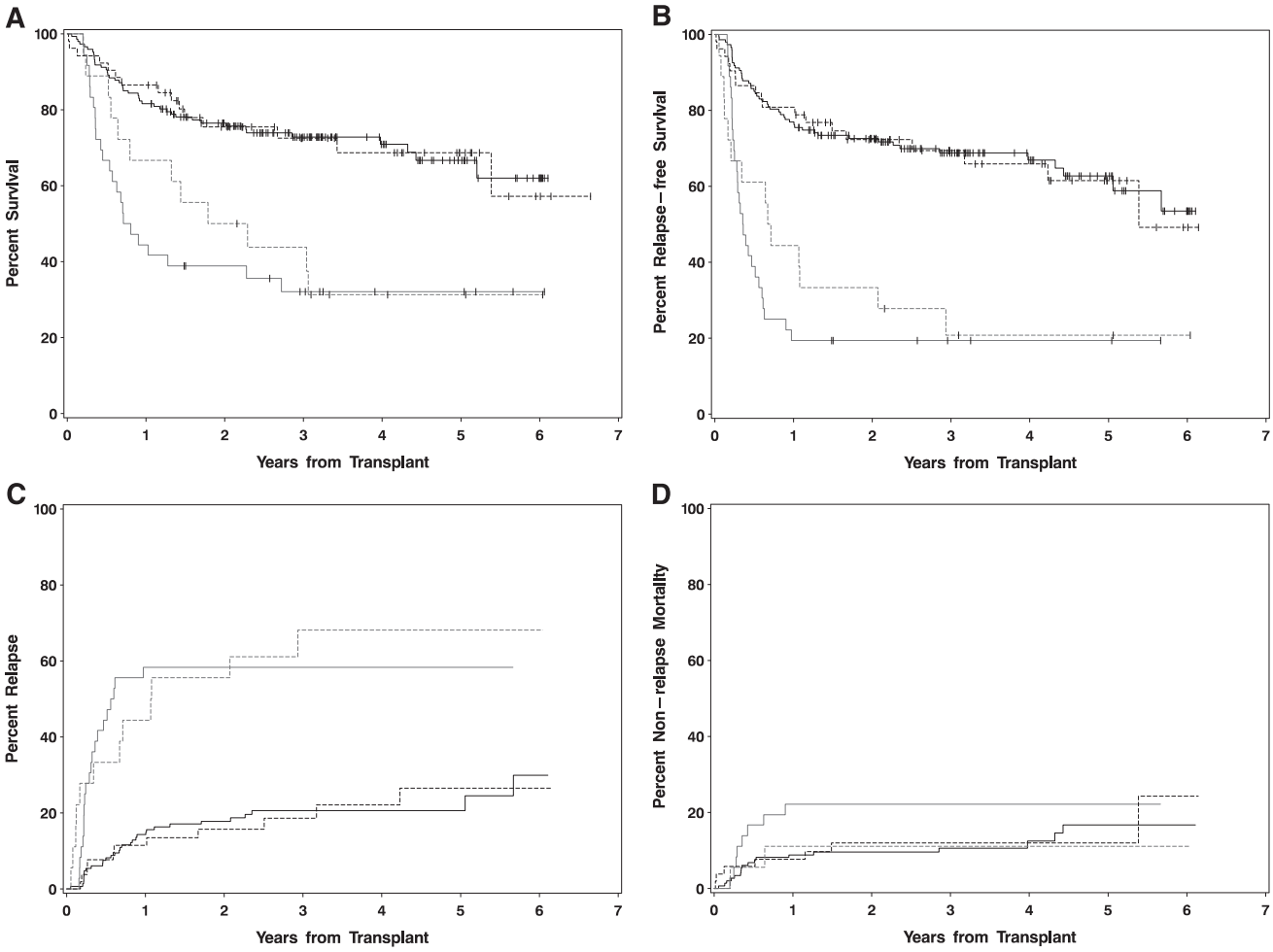


**Figure 1. Association between pre-HCT MRD, as determined by multiparameter flow cytometry, and post-HCT outcome for AML patients in CR1 and CR2.** Estimates of OS (A), DFS (B), cumulative incidence of relapse (C), and cumulative incidence of NRM (D) after myeloablative allogeneic HCT for AML in complete morphologic remission, shown individually for $MRD^{neg}$ (n = 147; black solid line) and $MRD^{pos}$ (n = 36; gray solid line) CR1 patients, as well as $MRD^{neg}$ (n = 52; black dashed line) and $MRD^{pos}$ (n = 18; gray dashed line) CR2 patients.

nonrelapse mortality (NRM) and relapse were summarized using cumulative incidence estimates. NRM was defined as death without prior relapse and was considered a competing risk for relapse, although relapse was a competing risk for NRM. All outcomes were treated as time-to-event end points. Outcomes between $MRD^{pos}$ and MRD-negative ($MRD^{neg}$) groups were compared using Cox regression. Multivariate models included the following additional factors: age at the time of HCT, CR status (CR1 vs CR2), cytogenetic risk group at time of AML diagnosis (unfavorable vs favorable/intermediate), type of AML at diagnosis (secondary vs primary), number of induction chemotherapy cycles before HCT, type of consolidation chemotherapy before HCT (none vs high-dose cytarabine [HIDAC]-containing vs non-HIDAC containing), CR duration before HCT, karyotype at time of HCT (normalized vs not normalized for patients presenting with abnormal karyotypes), peripheral blood counts at the time of HCT (CR vs CR with incomplete peripheral blood count recovery [CRi]), and conditioning regimen (with vs without total body irradiation [TBI]). A graft-versus-leukemia (GVL) effect was evaluated by adding cGVHD as a time-dependent covariate in the analysis of relapse. Missing cytogenetic risk and karyotype were accounted for each as separate categories. Categorical patient characteristics were compared between $MRD^{pos}$ and $MRD^{neg}$ groups using Pearson's $\chi$-square tests, and continuous characteristics were compared with two-sample Student $t$ tests. No adjustments were made for multiple comparisons, and all two-sided $P$ values from the regression models were derived from the Wald test. Statistical analyses were performed using STATA (StataCorp LP, College Station, TX).

## Results

### Patient characteristics

We identified 253 patients undergoing first myeloablative HCT from a matched-related or an unrelated donor for AML in first (n = 183) or second (n = 70) remission between April 2006 and November 2011 who had pre-HCT MFC studies available for retrospective analysis. All patients had <5% bone marrow blasts and thus met the morphologic criterion for CR. Among these, 54 patients had MRD by flow cytometry (ie, were $MRD^{pos}$), whereas 199 others had no evidence of flow cytometric MRD (ie, were $MRD^{neg}$). The characteristics of the study population, induction and consolidation chemotherapies, donors, and transplants are summarized in Table 1 and Table 2. Notably, CR2 patients differed from CR1 patients in that they were more likely to have favorable risk disease by standard cytogenetic criteria (22.9% vs 3.3%); in contrast, they were less likely to have adverse risk (11.4% vs 26.2%) or secondary AML (8.6% vs 34.4%). The CR1 duration before relapse was relatively long for patients transplanted in CR2 (median 337 days, range 9-2000 days).

The median time between MFC study and HCT was similar between $MRD^{pos}$ and $MRD^{neg}$ patients (24 days, range 11-46 vs 25 days, range 9-68 days, respectively; $P = .58$). Consistent with our

**Table 4. Univariate Cox regression models for impact of $MRD^{pos}$ status, entire study cohort (n = 253)**

| | CR1 (n = 183) | CR2 (n = 70) | All (n = 253) |
|---|---|---|---|
| **OS** | | | |
| $MRD^{neg}$ | 1 (reference) | 1 (reference) | 1 (reference) |
| $MRD^{pos}$ | 3.35 (2.02-5.55), $P < .001$ | 2.68 (1.25-5.74), $P = .011$ | 3.13 (2.06-4.76); $P < .001$ |
| MRD <0.1% | | | 2.91 (1.44-5.89);$P = .003$ |
| MRD 0.1%-1% | | | 2.79 (1.58-4.92); $P < .001$ |
| MRD >1% | | | 3.98 (2.13-7.46); $P < .001$ |
| **DFS** | | | |
| $MRD^{neg}$ | 1 (reference) | 1 (reference) | 1 (reference) |
| $MRD^{pos}$ | 4.76 (2.97-7.65); $P < .001$ | 3.34 (1.65-6.77); $P = .001$ | 4.15 (2.81-6.13); $P < .001$ |
| MRD <0.1% | | | 3.93 (2.06-7.48); $P < .001$ |
| MRD 0.1%-1% | | | 3.22 (1.89-5.50); $P < .001$ |
| MRD >1% | | | 6.83 (3.84-12.13); $P < .001$ |
| **Relapse** | | | |
| $MRD^{neg}$ | 1 (reference) | 1 (reference) | 1 (reference) |
| $MRD^{pos}$ | 5.60 (3.16-9.94); $P < .001$ | 4.84 (2.11-11.06); $P < .001$ | 5.19 (3.26-8.27); $P < .001$ |
| MRD <0.1% | | | 5.22 (2.52-10.81); $P < .001$ |
| MRD 0.1%-1% | | | 4.03 (2.16-7.53); $P < .001$ |
| MRD >1% | | | 8.13 (4.11-16.07); $P < .001$ |
| **NRM** | | | |
| $MRD^{neg}$ | 1 (reference) | 1 (reference) | 1 (reference) |
| $MRD^{pos}$ | 3.41 (1.46-7.99); $P = .005$ | 1.14 (0.23-5.53); $P$ = NS | 2.48 (1.18-5.21); $P = .017$ |
| MRD <0.1% | | | 1.85 (0.43-7.86); $P$ = NS |
| MRD 0.1%-1% | | | 1.93 (0.67-5.57), $P$=NS |
| MRD >1% | | | 4.69 (1.59-13.84), $P = .005$ |

Values are given as hazard ratio (95% confidence interval [CI]), *P* value.
NS, not significant.

previous findings,[7] $MRD^{pos}$ patients were of comparable age ($P = .32$), but more likely had AML with unfavorable vs favorable/intermediate cytogenetics ($P = .040$) and also had a higher prevalence of secondary AML ($P = .004$) (Table 3). Among CR1 patients, those with MRD less often received consolidation therapy than those that were $MRD^{neg}$ ($P = .001$), whereas a high proportion of CR2 patients did not receive consolidation chemotherapy before HCT, regardless of MRD status ($P = .21$). The median duration of remission prior to HCT was shorter for $MRD^{pos}$ than $MRD^{neg}$ patients undergoing HCT in CR1 ($P = .015$), whereas no such difference was noted for the subset of CR2 patients ($P = .93$). Similarly consistent with our previous findings,[7] a higher proportion of $MRD^{pos}$ patients had incomplete blood count recovery and was thus classified as having CRi rather than CR relative to $MRD^{neg}$ patients ($P = .006$). Likewise, $MRD^{pos}$ patients were more likely to have abnormal cytogenetic studies than $MRD^{neg}$ patients at the time of HCT ($P < .001$).

### Association between MRD status and post-HCT outcome

There were a total of 93 deaths, 75 relapses, and 35 NRM events contributing to the probability estimates for OS, DFS, relapse, and NRM stratified by MRD status for CR1 and CR2 patients. The median follow-up after HCT among survivors was 1,134 days (range 389-2,230 days) for CR1 patients and 1,217 days (range 376-2,428 days) for CR2 patients, respectively. Among CR1 patients, the 3-year estimates of OS were 73% (95% confidence interval [CI] 64%-79%) and 32% (95% CI 17%-48%) for $MRD^{neg}$ and $MRD^{pos}$ patients, respectively; among CR2 patients, the 3-year OS was estimated to be 73% (95% CI 57%-83%) and 44% (95% CI 21%-65%), respectively (Figure 1A). For DFS, similar estimates were 69% (95% CI 60%-76%) and 19% (95% CI 8%-34%) for $MRD^{neg}$ and $MRD^{pos}$ patients transplanted in CR1, respectively, and 69% (95% CI 54%-80%) and 21% (95% CI 6%-42%) for $MRD^{neg}$ and $MRD^{pos}$ patients transplanted in CR2, respectively (Figure 1B). Three-year estimates of relapse among CR1 patients were 21% (95% CI 14%-28%) and 59% (95% CI 41%-72%), respectively, and 19% (95% CI 9%-31%) and 68% (95% CI 41%-85%), respectively, among CR2 patients (Figure 1C). Finally, among CR1 patients, the 3-year estimates of NRM were 11% (95% CI 6%-16%) and 22% (95% CI 10%-37%) for $MRD^{neg}$ and $MRD^{pos}$ patients, respectively; among CR2 patients, 3-year NRM was estimated to be 12% (95% CI 5%-23%) and 11% (95% CI 2%-30%), respectively (Figure 1D). Among the CR1 patients who underwent HCT without evidence of MRD, post-HCT disease eradication appeared to be somewhat better if consolidation chemotherapy was given before transplantation. Specifically, in this patient subset, having received any consolidation chemotherapy before transplantation was associated with a trend toward lower risk of relapse (hazard ratio [HR] = 0.48; 95% CI 0.21-1.07; $P = .07$) and better DFS (HR = 0.60; 95% CI 0.30-1.17; $P = .13$).

### Pre-HCT MRD status as independent prognostic factor

Univariate regression models for OS, DFS, relapse, and NRM were fit to assess the relevance of MRD as a prognostic factor. As summarized in Table 4, being $MRD^{pos}$ at the time of HCT was significantly associated with shorter OS ($P < .001$) and DFS ($P < .001$), as well as with an increased risk of relapse ($P < .001$) and NRM ($P = .017$). The association of MRD with outcome among patients in CR1 was similar to that among patients in CR2 (e.g., $P = .63$ and $P = .77$ for tests of interaction for mortality and relapse, respectively). Among patients with MRD, there was no statistically significant evidence that increasing levels of MRD were associated with increasing risk of any outcome. This was true when MRD was evaluated as a continuous variable (on a log scale) or as a test for a trend across the 3 groups: ≤0.1% (n = 14), >0.1% to 1% (n = 24), and >1% (n = 16) (Figure 2).

Multivariate models were fit for OS, DFS, relapse, and NRM using MRD status ($MRD^{pos}$ vs $MRD^{neg}$), age at HCT, CR status (CR1 vs CR2), cytogenetic disease risk at diagnosis (adverse vs

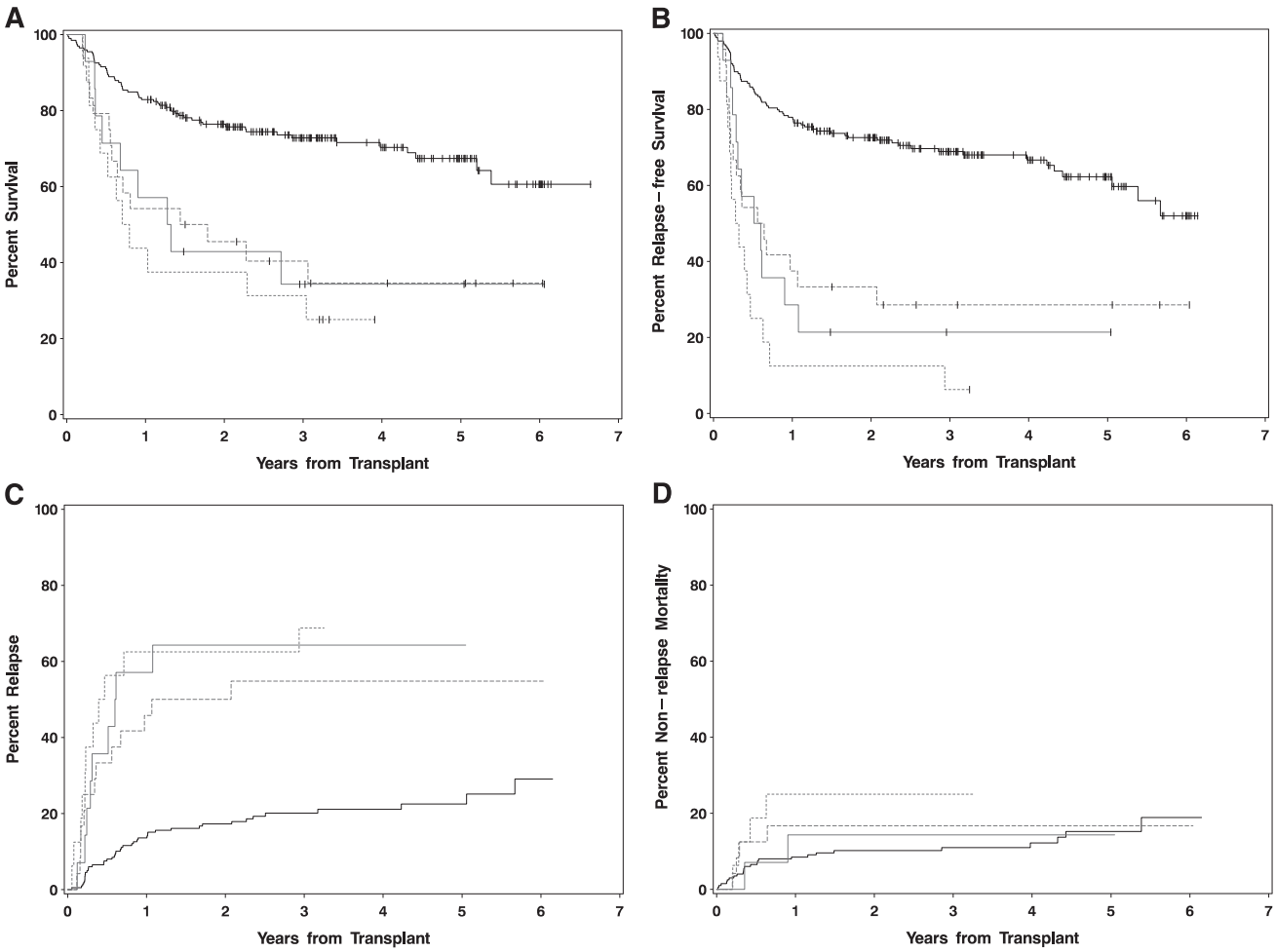


**Figure 2. Relationship between pre-HCT MRD levels, as determined by multiparameter flow cytometry, and post-HCT outcome for AML patients in morphologic remission.** Estimates of OS (A), DFS (B), cumulative incidence of relapse (C), and cumulative incidence of NRM (D) after myeloablative allogeneic HCT for AML in complete morphologic remission, shown individually for patients without flow cytometric evidence of MRD ($MRD^{neg}$; n = 199; black solid line), low-level MRD (≤0.1%; n = 14; gray solid line), intermediate-level MRD (>0.1%-1%; n = 24; gray long-dashed line), or high-level MRD (>1%; n = 16; gray short-dashed line).

intermediate/favorable), type of AML (secondary vs primary), number of induction chemotherapy cycles before HCT, type of consolidation chemotherapy before HCT (none vs HIDAC-containing vs non-HIDAC containing), CR duration before HCT, pre-HCT karyotype (not normalized vs normalized for patients initially presenting with abnormal karyotype), pre-HCT peripheral blood count recovery (CRi vs CR), and conditioning regimen (with vs without TBI) as covariates. After adjustment for these factors, the hazard ratios of $MRD^{pos}$ vs $MRD^{neg}$ were 2.61 (95% CI 1.62-4.20; $P < .001$) for overall mortality, 3.74 (95% CI 2.38-5.87; $P < .001$) for failure for DFS, 4.90 (95% CI 2.87-8.37; $P < .001$) for relapse, and 1.88 (95% CI 0.78-4.53; $P = .16$) for NRM, respectively (Table 5). Then we performed similar multivariate models restricting the study cohort to those 216 patients who met peripheral blood criteria for CR as proposed by international working groups.[14,15] We found very similar hazard ratios of $MRD^{pos}$ vs $MRD^{neg}$ after adjustment for the same covariates: overall mortality 3.14 (95% CI 1.82-5.43; $P < .001$); failure for DFS 4.72 (95% CI 2.83-7.86; $P < .001$); relapse 6.78 (95% CI 3.70-12.40; $P < .001$); and NRM 1.80 (95% CI 0.65-5.02; $P = .26$).

### Effect of cGVHD on relapse in $MRD^{pos}$ and $MRD^{neg}$ patients

Thus far, our analyses have focused on the relationship between pre-HCT characteristics (including conditioning regimen) and post-HCT outcome in $MRD^{pos}$ and $MRD^{neg}$ patients. However, as GVHD has been linked to anti-leukemic (GVL) effects of allogeneic HCT and relapse risk for AML patients,[19,20] and it is conceivable that such an effect might be different for $MRD^{pos}$ and $MRD^{neg}$ patients, we assessed the impact of cGVHD on post-HCT relapse and its relationship to MRD status in our cohort. Using cGVHD as a time-dependent variable, the GVL effect of cGVHD on relapse was found to have a HR = 0.46 (95% CI 0.24-0.88; $P = .02$). However, the magnitude of the GVL effect of cGHVD was similar between patients with and without MRD (for $MRD^{pos,}$ HR = 0.39, 95% CI 0.15-1.03 [$P = .06$] and for $MRD^{neg}$, HR = 0.52, 95% CI 0.24-1.11 [$P = .09$]). The difference in effect between $MRD^{pos}$ and $MRD^{neg}$ was not statistically significant ($P = .63$).

## Discussion

For many patients diagnosed with AML, myeloablative allogeneic HCT is an option once a first morphologic CR is obtained with chemotherapy. Consistent with previous studies,[6] the data presented in this retrospective analysis demonstrate that such patients have a very favorable long-term outcome with a 3-year OS that approximates

**Table 5. Multivariate Cox regression models, entire study cohort (n = 253)**

| | Overall mortality | Failure for DFS | Relapse |
|---|---|---|---|
| **MRD status** | | | |
| Negative (n = 199) | 1 (reference) | 1 (reference) | 1 (Reference) |
| Positive (n = 54) | 2.61 (1.62-4.20); $P < .001$ | 3.74 (2.38-5.87); $P < .001$ | 4.90 (2.87-8.37); $P < .001$ |
| Age (per 10 y) | 1.05 (0.90-1.22); $P$ = NS | 1.07 (0.94-1.23); $P$ = NS | 1.02 (0.87-1.21); $P$ = NS |
| **CR status** | | | |
| CR1 (n = 183) | 1 (reference) | 1 (reference) | 1 (reference) |
| CR2 (n = 70) | 1.01 (0.54-1.92); $P$ = NS | 1.22 (0.69-2.17); $P$ = NS | 1.15 (0.58-2.31); $P$ = NS |
| **Cytogenetic risk group** | | | |
| Intermediate/favorable (n = 190) | 1 (reference) | 1 (reference) | 1 (reference) |
| Adverse (n = 56) | 1.41 (0.78-2.54); $P$ = NS | 1.50 (0.88-2.57); $P$ = NS | 1.61 (0.83-3.13); $P$ = NS |
| **Type of AML** | | | |
| Primary AML (n = 184) | 1 (reference) | 1 (reference) | 1 (reference) |
| Secondary AML (n = 69) | 1.24 (0.74-2.09); $P$ = NS | 1.29 (0.80-2.07); $P$ = NS | 1.06 (0.59-1.92); $P$ = NS |
| Number of induction/re-induction courses before HCT* | 1.21 (0.83-1.77); $P$ = NS | 1.45 (1.04-2.01); $P$ = .03 | 1.53 (1.03-2.27); $P$ = .04 |
| **Consolidation before HCT** | | | |
| No (n = 82) | 1 (reference) | 1 (reference) | 1 (reference) |
| Yes, with HiDAC (n = 132) | 0.74 (0.40-1.37); $P$ = NS | 0.89 (0.49-1.61); $P$ = NS | 0.89 (0.43-1.86); $P$ = NS |
| Yes, without HiDAC (n = 39) | 0.96 (0.48-1.91); $P$ = NS | 1.08 (0.56-2.07),;$P$ = NS | 0.97 (0.43-2.16); $P$ = NS |
| CR Duration before HCT (per mo) | 1.00 (0.96-1.04); $P$ = NS | 1.01 (0.97-1.05); $P$ = NS | 1.00 (0.95-1.05); $P$ = NS |
| **Pre-HCT karyotype** | | | |
| Normalized (n = 120) | 1 (reference) | 1 (reference) | 1 (reference) |
| Not normalized (n = 24) | 1.52 (0.75-3.08); $P$ = NS | 1.25 (0.65-2.40) $P$ = NS | 1.07 (0.47-2.42); $P$ = NS |
| **Pre-HCT blood counts†** | | | |
| Recovered (n = 216) | 1 (reference) | 1 (reference) | 1 (reference) |
| Not recovered (n = 36) | 0.69 (0.37-1.30); $P$ = NS | 0.77 (0.43-1.36); $P$ = NS | 0.71 (0.36-1.42); $P$ = NS |
| **Conditioning regimen** | | | |
| Without high-dose TBI (n = 181) | 1 (reference) | 1 (reference) | 1 (reference) |
| With high-dose TBI (n = 72) | 0.79 (0.42-1.48); $P$ = NS | 0.81 (0.46-1.43); $P$ = NS | 0.77 (0.38-1.54); $P$ = NS |

Values are given as hazard ratio (95% CI), $P$ value.
NS, not significant.
*Number of induction courses for CR1 patients and number of re-induction courses for CR2 patients.
†Recovered: absolute neutrophil count (ANC) ≥1000/μL and platelets ≥100 000/μL; not recovered: ANC <1000/μL and/or platelets <100 000/μL.

70% to 75%, and a 3-year cumulative incidence of relapse of approximately 20% to 25% if they have no flow cytometric evidence of MRD at the time of transplantation. Conversely, relative to $MRD^{neg}$ patients, $MRD^{pos}$ CR1 patients had a significantly worse outcome with a 3-year cumulative incidence of relapse that approximates 60%, resulting in an estimated survival of approximately 30%. The current study extends these findings to AML patients transplanted in morphologic CR2. Specifically, in our cohort, the outcomes of $MRD^{neg}$ patients were similar for CR1 and CR2 patients. Likewise, the outcomes of $MRD^{pos}$ patients were similar for CR1 and CR2 patients. At first glance, the relatively similar outcome for CR1 and CR2 patients may be surprising. However, our data suggest that, rather than the number of remission, MRD status (and, therefore, the susceptibility to preceding chemotherapy) is the dominating pre-HCT factor associated with post-HCT relapse risk and outcome.

$MRD^{neg}$ and $MRD^{pos}$ patients differed in many factors that predict outcome in AML, including cytogenetic disease risk and type of AML (secondary vs primary). There were also notable differences among these patient subsets regarding several pre-HCT factors, such as pre-HCT blood count recovery or abnormal pre-HCT karyotype, previously shown by us to be associated with increased risk of post-HCT outcome in univariate analyses for AML patients undergoing transplantation in CR1.[7] However, our multivariate models indicate that pre-HCT MRD is an adverse risk factor for HCT outcome for both CR1 and CR2 patients even after adjusting for these other factors. With the caveat that we did not have full molecular characterization of all cases, these multivariable Cox regression models suggest that MRD is the decisive pre-HCT factor for post-HCT outcome and the only one independently associated with increased relapse risk and shorter OS and DFS (Table 5).

Our data confirm the previous studies showing that the development of cGVHD is associated with a reduced risk of relapse in AML patients undergoing myeloablative HCT.[19,20] At least in our cohort, we were unable to discern any statistically significant difference in the magnitude of this GVL effect between $MRD^{pos}$ and $MRD^{neg}$ patients. This finding suggests that the high relapse risk after allogeneic transplant for $MRD^{pos}$ patients is not due to less strong GVL effects in this patient subset. This observation is somewhat reminiscent of recent data indicating that the allogeneic HCT-associated reduction of relapse and improvement of survival in patients with monosomal karyotype AML is relatively similar to that of patients with less unfavorable AML subtypes.[21]

The threshold below or above which patients should be considered $MRD^{neg}$ or $MRD^{pos}$ based on flow cytometric assessment of residual tumor amounts has been controversial, and several groups have proposed the use of different thresholds above the minimal detection limit as optimal cutoffs for the best segregation of patients into categories of post-HCT relapse risk rather than using the technical detection limit of the MRD assay as threshold.[5,6] Our findings from the current study lead us to question the usefulness of this approach. Specifically, in our cohort, the risk of relapse among $MRD^{pos}$ patients with a level ≤0.1% (a level considered "negative" in recent series[12,13]) was significantly higher than that among patients in which we were unable to detect any MRD. On the other hand,

among patients with MRD, there was no statistically significant evidence that increasing levels of MRD were associated with increasing risk of any outcome. Of course, despite the size of our study cohort, the number of $MRD^{pos}$ patients was still relatively modest, and such an association cannot be ruled out with certainty. In fact, our HR estimates for patients with MRD >1% were consistently (but statistically nonsignificantly) higher than those with MRD ≤0.1%, and the study of larger numbers of patients may indeed yield a statistically significant quantitative between these patient subsets. Nonetheless, these data suggest that $MRD^{pos}$ patients (regardless of the level of MRD) are more similar to each other than $MRD^{neg}$ patients are to $MRD^{pos}$ patients with the lowest detectable levels of MRD, an observation that would support the approach of using the MRD assay detection limit as a threshold to distinguish $MRD^{neg}$ from $MRD^{pos}$, as is currently the approach at our institution. As stated, we a priori defined $MRD^{pos}$ as any level of residual disease. Although the number of $MRD^{pos}$ patients in the different residual disease categories was not sufficient to evaluate the full range of association, it is noteworthy that when assessing each possible cutoff within the ≤0.1% category, we found the 0 vs >0 split to be the most statistically significant.

In our previous study, we observed that, in addition to higher risk of relapse and inferior OS and DFS, $MRD^{pos}$ patients with AML transplanted in CR1 also had a higher risk of NRM relative to $MRD^{neg}$ patients.[7] Our present analysis on the expanded CR1 and CR2 AML patient cohort confirms this initial finding, indicating an approximately twofold increased risk of NRM for $MRD^{pos}$ patients that did not, however, remain statistically significant after multivariate adjustment. We speculate that differences in the type and timing of pre-HCT therapy may account for this increase in NRM, but further studies will be required to better understand this relationship.

In summary, our findings suggest that the negative impact of MRD on outcome among AML patients in CR2 is similar to the negative impact seen in patients in CR1, whereas the outcomes of $MRD^{neg}$ AML patients are excellent after myeloablative HCT in either CR1 or CR2. An important question to address in future well-controlled studies is whether less intensive consolidation strategies (eg, chemotherapy, autologous HCT, or reduced-intensity allogeneic HCT) could provide a similar level of disease control with lower risks for treatment-related toxicities and mortality for these low-risk (ie, $MRD^{neg}$) patients. On the other hand, even patients with minute amounts of MRD (≤0.1%) have significantly worse outcomes than $MRD^{neg}$ patients. Observations by others have suggested that the outcomes of AML patients with pre-HCT MRD may be better when they undergo allogeneic rather than autologous HCT,[6] consistent with the demonstration of a GVL effect in $MRD^{pos}$ patients in our cohort. However, no well-controlled studies have analyzed the outcomes of $MRD^{pos}$ patients after different transplantation strategies and assessed the differential impact, if any, of such immunologic anti-leukemia effects. Clearly, the poor outcome of $MRD^{pos}$ patients provides the rationale for interventional studies investigating whether cure rates could be improved by MRD-directed therapy before, during, or after HCT.

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## Authorship

Contribution: R.B.W. and F.R.A. contributed to conception and design of the study; J.M.P., B.L.W., B.M.S., M.F., B.G., C.D., J.P.R., and F.R.A. contributed to provision of study material, patient recruitment, and acquisition of data; R.B.W., S.A.B., and J.M.P. participated in collection and assembly of data; R.B.W., S.A.B., B.E.S., E.H.E., and F.R.A. participated in data analysis and interpretation; R.B.W. and F.R.A. participated in drafting the manuscript; and R.B.W., S.A.B., J.M.P., B.L.W., B.E.S., B.M.S., M.F., B.G., C.D., J.P.R., E.H.E., and F.R.A. critically revised the manuscript and gave final approval to submit for publication.

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# Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission

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