
بسم الله الرحمن الرحیم

20th Congress of Iranian Society of Medical Oncology & Hematology

بیستمین کنگره سراسری انجمن پزشکان انکولوژی و هماتولوژی ایران (سال ۱۴۰۰)

IRANIAN SOCIETY OF MEDICAL ONCOLOGY AND HEMATOLOGY
ISMOH

Measurable residual disease in AML

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1400

Background:

❑AML:

- A heterogeneous disease
- Widely variable likelihood of cure with conventional therapies
- Cure rate is only approximately 50% in patients < 60 years

❑Thirty years ago, the term minimal residual disease (MRD) was coined to denote the acute myeloid leukemia (AML) cells that survive seemingly successful remission-induction chemotherapy, hide below the cytomorphological detection limit, and are responsible for relapse.

❑ It was hypothesized that decreasing the detection threshold for leukemic cells would quantify treatment efficacy, establish a new prognostic factor, and help guide decisions regarding treatment continuation (or discontinuation) and assignment to hematopoietic cell transplantation (HCT).

Usefulness of MRD:

Prognostic

Predictive

Monitoring

Efficacy-Response

How should we measure MRD

Karyotyping and FISH:

-Limited

-Relative insensitivity: karyotype 5% and FISH 1%

-Persistent cytogenetic abnormalities have been associated with worse survival in several studies and may also identify patients who could benefit from HSCT in first remission.

-Karyotype only for baseline abnormal karyotype (irrelevant in 50% of patients with normal cytogenetics)

-Insensitivity of karyotyping is exemplifed by observations that despite being in CR with no detectable cytogenetic abnormalities, many patients (up to 50% in some studies) still relapse

-Detection of persistent leukemia associated karyotypes in CR is thus strongly suggestive that residual leukemia cells are present in a background of apparently normal morphology.

Reverse transcription-quantitative polymerase chain reaction (RT-qPCR):

- For detecting and quantifying recurrent genomic alterations.

- Requires that the detected aberration be stable throughout disease while also representing truly residual disease—not merely a preleukemic clone (e.g., a mutation associated with clonal hematopoiesis of indeterminate potential, CHIP) or a differentiated cell retaining the genomic alteration.

- Used primarily to detect fusion transcripts: PML-RARA in acute promyelocytic leukemia (APL), RUNX1-RUNX1T1 and CBF-SMMHC found in corebinding factor (CBF) AML, or recurrent mutations such as those in NPM1, all of which represent founding genomic lesions in AML.

- Other mutations may emerge or disappear at the time of relapse (e.g., mutant FLT3) and are therefore generally unreliable MRD markers for assessing meaningful “MRD negativity, ”although their persistence likely represents residual disease in most cases .

- Outside of these subsets, RT-qPCR is not routinely recommended for MRD monitoring. Unfortunately, this limits the applicability of RT-qPCR for MRD evaluation to less than half of adult AML cases.

- Highly sensitive method of detection, with sensitivities ranging from 10^{-4} to 10^{-5} in most cases (and down to nearly 10^{-6} if adequate genetic material is available)

- In addition, it is a highly standardized platform.

Multiparameter flow cytometry:

- Uses a panel of fluorochrome-labeled monoclonal antibodies to identify aberrantly expressed antigens on leukemic blasts.

- **Leukemia-associated immunophenotypes** consist of the aberrant expression of antigens compared to that on normal myeloid precursors, cross-lineage antigen expression (e.g. expression of lymphoid antigens on myeloblasts), over- or underexpression of antigens normally expressed, and aberrant co-expression of antigens normally found in early or late hematopoietic differentiation.

- **The "difference from normal"** approach is used to detect any differences in the remission immunophenotype compared to the highly stereotypical normal immunophenotype distribution.

Multiparameter flow cytometry:

- Sensitivity of 10^{-4} to 10^{-5}, which is dependent on the number of cells analyzed, gating method, and number of antibody colors used; in most cases, a sensitivity of 10^{-4} is achieved.

- Compared to real-time quantitative RT-qPCR, MFC is significantly faster and less labor-intensive.

- Applicable to more than 90% of patients with AML, unlike other methods that rely on specific genetic or molecular targets.

- Interpretation of MFC MRD is not standardized in most countries, including the USA, and requires significant technical expertise on the part of the interpreting pathologist, which can lead to inter-laboratory discordance.

Next-generation sequencing:

- Targeted next-generation sequencing (NGS) panels are commonly used at the time of diagnosis to identify prognostic gene mutations or mutations that may be therapeutically targeted (e.g. FLT3 or IDH1/2 mutations).

- NGS MRD assessment is relatively expensive, is not standardized, and requires complicated bioinformatics.

- The interpretation of NGS MRD results is further complicated by the presence of preleukemic clones that may not fully clear even in patients who achieve deep, long-term remissions with chemotherapy, such as mutations associated with clonal hematopoiesis of indeterminate potential (CHIP).

- CHIP mutations, particularly DNMT3A, TET2, and ASXL1, commonly persist in patients who do not relapse, suggesting that they should not be routinely used as MRD markers.

- Depending on the NGS platform used and the amount of input DNA, NGS can theoretically achieve a sensitivity of 10^{-6} making it an attractive potential option for very sensitive MRD detection.

Current methods for assessing MRD in AML

Method	Sensitivity	Advantages	Disadvantages
Conventional karyotyping	~5%	• Common in routine clinical practice	• Poor sensitivity • Time-consuming and labor-intensive • Applicable only to patients with baseline abnormal karyotype (~50%)
FISH	Up to 10^{-2}	• Useful for numeric cytogenetic abnormalities (i.e. gains or deletions)	• Worse sensitivity than MFC or PCR • Applicable only to patients with baseline abnormal karyotype (~50%)
MFC for LAIP or DfN	10^{-3} to 10^{-5}	• Sensitive • Fast (results usually available within 24 hours) • Relatively inexpensive • Applicable to >90% of AML cases	• Potential for immunophenotypic shifts (mitigated by using a DfN-based approach) • Requires significant technical expertise to interpret • Limited standardization across laboratories
RT-qPCR	10^{-4} to 10^{-6}	• Sensitive • Well standardized • Can be run in any laboratory with RT-qPCR capabilities	• Appropriate molecular targets present in <50% of cases (<35% in older adults) • Many mutations are not suitable for MRD detection (e.g. *FLT3*) • Time-consuming and labor-intensive • Results may take several days
NGS	Highly variable (1% to 10^{-6})	• Potential for very high sensitivity (depending on technology) • Can test multiple genes at once	• Low sensitivity with most commonly used platforms • May be confounded by persistence of preleukemic mutations (e.g. CHIP) • Results may take several days • Expensive • Not standardized • Requires complex bioinformatics

MRD as a prognostic marker in AML

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Relation of Clinical Response and Minimal Residual Disease and Their Prognostic Impact on Outcome in Acute Myeloid Leukemia

Xueyan Chen, Hu Xie, Brent L. Wood, Roland B. Walter, John M. Pagel, Pamela S. Becker, Vicky K. Sandhu, Janis L. Abkowitz, Frederick R. Appelbaum, and Elihu H. Estey

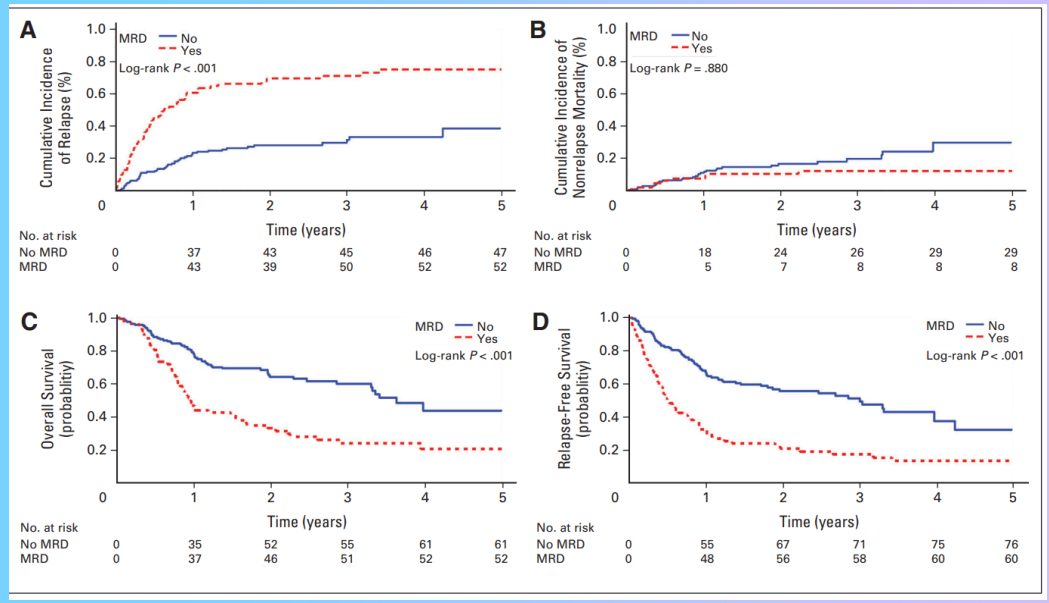


Table 2. Correlation of MRD With Response

	All Patients		CR		CRp		CRi	
MRD Status	No.	%	No.	%	No.	%	No.	%
Total	245	100.0	174	71.0	48	19.6	23	9.4
Positive	73	29.8	33	19.0	26	54.2	14	60.9
Negative	172	70.2	141	81.0	22	45.8	9	39.1
Level, %								
Median	1.0		0.5		1.1		2.7	
Range			0.004 to 3.9		0.1 to 4.0		0.1 to 7.6	

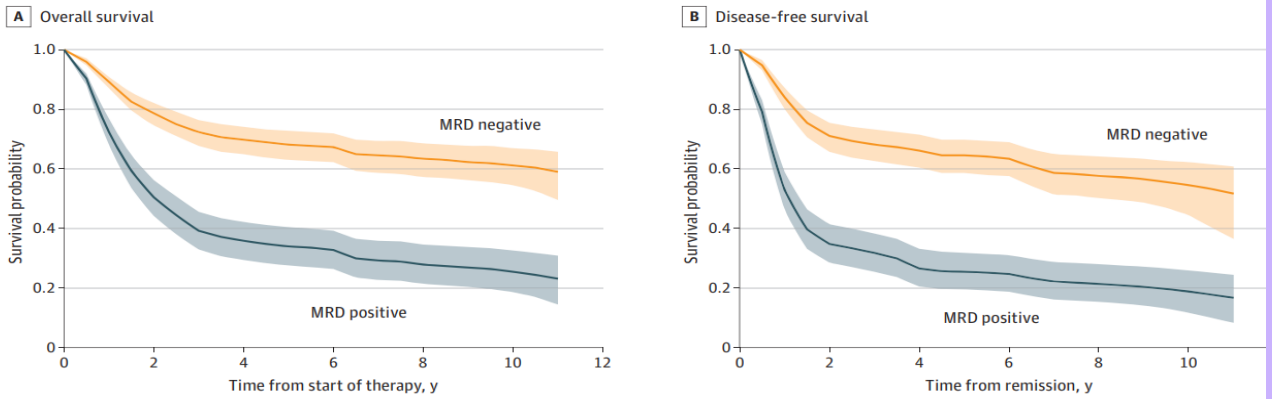
Abbreviations: CR, complete remission; CRi, complete remission with absolute neutrophil count < 1,000/μL; CRp, complete remission with platelet < 100,000/μL; MRD, minimal residual disease.

Research

JAMA Oncology | Original Investigation

Association of Measurable Residual Disease With Survival Outcomes in Patients With Acute Myeloid Leukemia
A Systematic Review and Meta-analysis

Nicholas J. Short, MD; Shouhao Zhou, PhD; Chenqi Fu, MS; Donald A. Berry, PhD; Roland B. Walter, MD, PhD, MS; Sylvie D. Freeman, DPhil, MBChB; Christopher S. Hourigan, DM, DPhil; Xuelin Huang, PhD; Graciela Nogueras Gonzalez, MPH; Hyunsoo Hwang, PhD; Xinyue Qi, PhD; Hagop Kantarjian, MD; Farhad Ravandi, MD



Overall survival (OS) (A) and disease-free survival (DFS) (B). The curves show the posterior means of survival distribution in the bayesian hierarchical analysis. The shadings of each curve show the 95% bayesian credible intervals (CrIs) for the survival proportion at the corresponding point in time of follow-up. The 5-year OS was 68% (95% CrI, 63%-73%) for the MRD-negative group and 34% (95% CrI, 28%-40%) for the MRD-positive group. The average hazard ratio for OS was 0.36 (95% CrI, 0.33-0.39), with a 5-year restricted mean survival time difference of 15.37 months (95% CrI, 13.58-17.19 months). The 5-year DFS was 64% (95% CrI, 59%-70%) for the MRD-negative group and 25% (95% CrI, 20%-32%) for the MRD-positive group. The average hazard ratio for DFS was 0.37 (95% CrI, 0.34-0.40), with a 5-year restricted mean survival time difference of 19.61 months (95% CrI, 17.33-21.92 months).

- While most of the MRD detection methods were able to identify a difference in DFS and OS between groups with MRD negativity vs positivity, the MRD association using cytogenetics/FISH was not significant (average HR, 0.77; 95% CrI, 0.39-1.56 for OS and average HR, 0.65; 95% CrI, 0.34-1.23 for DFS).

- Among studies evaluating MRD by MFC, the impact of MRD was similar between studies using less than 6-color assays vs greater than or equal to 6-color assays (difference in HR, −0.02; 95% CrI, −0.54 to 0.49 for OS and −0.09; 95% CrI, −0.70 to 0.52 for DFS).

- For AML subtypes, the association between MRD and survival outcomes was greater in studies reporting outcomes of CBF AML compared with non-CBF AML.

- Regarding the association of specimen source with survival outcomes, peripheral blood assessment of MRD better distinguished MRD-positive and MRD-negative groups compared with bone marrow assessment of MRD, with a posterior probability of 0.918 for OS and 0.999 for DFS.

MRD as a predictive biomarker in AML

JCO Precision Oncology > List of Issues > Volume 1 >

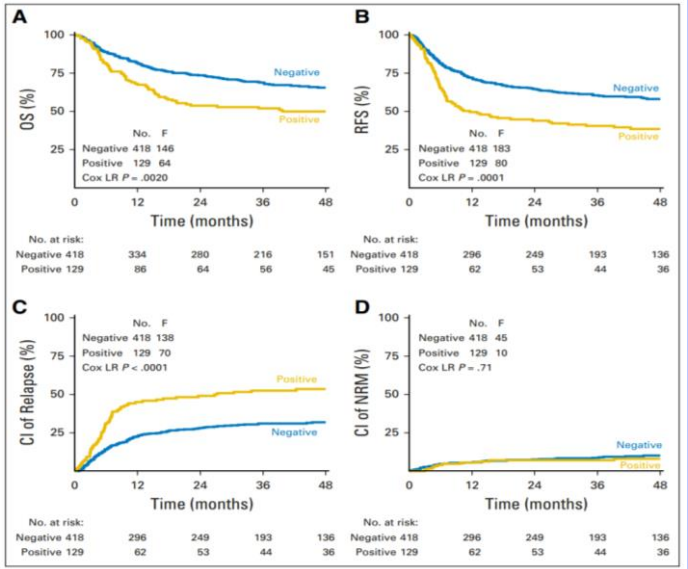
ORIGINAL REPORTS

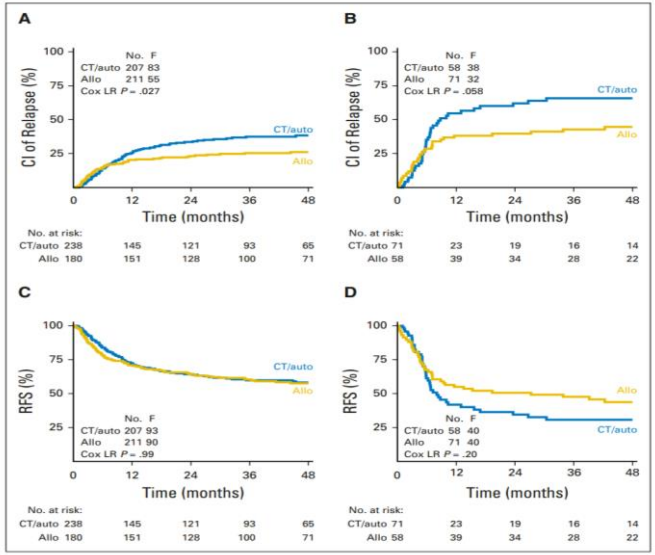
Graft-Versus-Leukemia Effect of Allogeneic Stem-Cell Transplantation and Minimal Residual Disease in Patients With Acute Myeloid Leukemia in First Complete Remission

Jurjen Versluis, Burak Kalin, Wendelien Zeijlemaker, Jakob Passweg, Carlos Graux, Markus G. Manz, ...

study show that the allogeneic GVL effect—as estimated by the relative reduction of relapse— is similar in MRD-positive and MRD-negative patients.

Although alloHSCT is clearly indicated in MRD-positive patients, it is important to study the value of approaches intended to induce MRD negativity by novel agents before alloHSCT.





blood
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia

After induction and consolidation, favorable-risk patients were to receive autologous stem cell transplant and poor-risk patients allogeneic stem cell transplant. Intermediate-risk patients were to receive AuSCT or AlloSCT depending on the postconsolidation levels of MR.

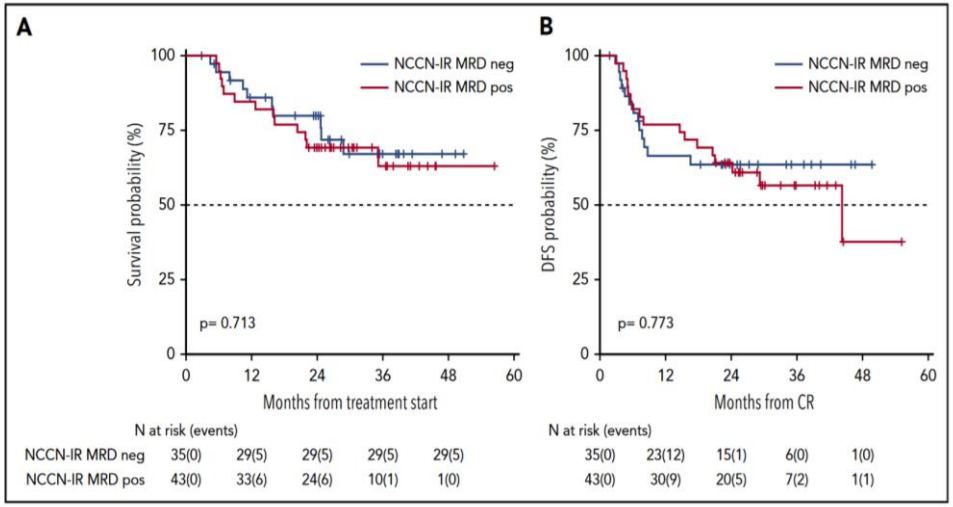


Figure 4. Survival estimates of NCCN-IR category, plotted by the status of MRD after consolidation therapy. (A) Two-year OS of NCCN-IR MRD negative and MRD

Two-year OS and DFS were 74% and 61% in the FR category, 42% and 45% in the PR category, 79% and 61% in the IR MRD-negative category, and 70% and 67% in the IR MRD-positive category. **In conclusion, AuSCT may still have a role in FR and IR MRD-negative categorie**

MRD as an efficacy-response biomarker in AML

- An efficacy-response biomarker is used to show that a response has occurred in an individual who has been exposed to a medical product or an environmental agent

- Even in a disease such as AML where survival is relatively short in many patient subsets, demonstration of improved survival may require long follow-up

- A validated, early post-therapy surrogate endpoint for clinical benefit would address these limitations and could accelerate and simplify drug testing and approval. Such a surrogate endpoint could also lead to shorter clinical trials, reduced costs, and exposure of fewer patients to potentially toxic and/or ineffective treatments.

- Currently, while some data from mostly nonrandomized trials show a treatment effect on both MRD responses and survival, data from randomized trials that may support this requirement are currently extremely limited.

ORIGINAL ARTICLE

Oral Azacitidine Maintenance Therapy for Acute Myeloid Leukemia in First Remission

Showed a significant benefit in OS for oral azacitidine, regardless of whether MRD was detectable or not at baseline.

Almost 20% of patients with detectable MRD at baseline who were assigned to the placebo arm still converted to MRD negativity during follow-up, highlighting the challenge of using MRD as a possible efficacy-response biomarker in AML.

2021 Update Measurable Residual Disease in Acute Myeloid Leukemia: European LeukemiaNet Working Party Consensus Document

❑ Technology:

- For patients with mutant NPM1, CBF AML (RUNX1-RUNX1T1 or CBFB-MYH11), or APL (PML-RARA), we recommend molecular MRD assessment by qPCR or dPCR.

- AML patients outside these molecularly defined subgroups should be monitored for MRD using MFC.

- NGS-MRD monitoring is useful to refine prognosis in addition to MFC but, to date, there are insufficient data to recommend NGS-MRD as a stand-alone technique.

❑ Timing of MRD:

- In NPM1-mutated AML, MRD should be assessed preferentially in PB after 2 cycles of chemotherapy, in BM at the end of consolidation, and in BM every 3 months for 24 months after the end of consolidation. Alternatively, MRD may be assessed from PB every 4-6 weeks during follow up for 24 months.

- In RUNX1-RUNX1T1 and CBFB-MYH11 mutated AML MRD should be assessed preferentially in PB after 2 cycles of chemotherapy, in BM at end of consolidation treatment, and in PB every 4-6 weeks for 24 months after the end of consolidation

- In APL, the most important MRD endpoint is PCR negativity for PML-RARA at the end of consolidation.

- For non-high-risk APL patients, MRD monitoring is only recommended after completion of consolidation and may be discontinued once BM MRD negativity is achieved.

- For high-risk APL, MRD should be assessed by qPCR from BM every 3 months for 24 months, starting at the end of treatment. Alternatively, MRD may be assessed from PB every 4-6 weeks during follow up.

- Based on the relapse kinetics of high-risk APL patients treated with ATRA-based regimens, monitoring for 24 months appears sufficient.

Clinical consequences of MRD assessment:

❖Individualized treatment and/or conditioning regimen strategies should be considered, preferably as part of clinical trials, in an effort to reduce disease relapse in :

(1) MRD positive by MFC after 2 cycles of intensive chemotherapy, after consolidation chemotherapy, prior to stem cell transplantation, and/or after stem cell transplantation

(2) MRD positive by ≥2% NPM1 mutant copies per ABL1 copies measured in BM or transcript levels of NPM1 or CBF fusions failed to reach a 3-4 log reduction in the same tissue after completion of consolidation chemotherapy (ratio of target copies / ABL1 copies between the sample at diagnosis and the sample after completion of consolidation chemotherapy, measured in the same tissue, preferably BM)

Thank you for your attention