Integrating molecular profiling to predict immunophenotypic MRD clearance in acute myeloid leukemia

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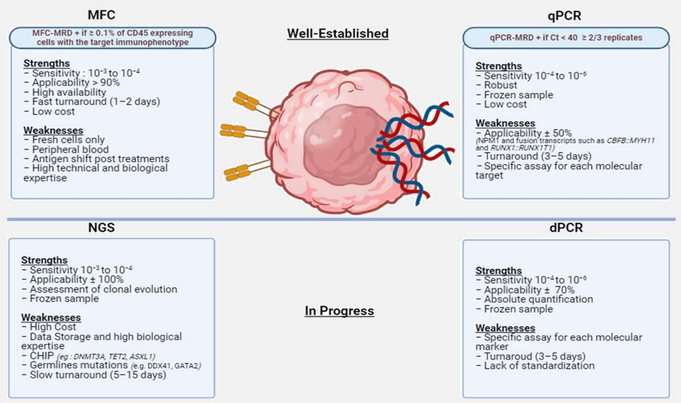
INTRODUCTION

While aggressive induction chemotherapy regimens for acute myeloid leukemia (AML) successfully induce complete remission in the bulk of cases, recurrence frequencies continue to be substantial in the absence of following consolidation cycles or allogeneic hematopoietic stem cell transplantation (allo-HSCT). Disease recurrence following the attainment of a cytomorphological response is fundamentally driven by an inability to completely eliminate persistent malignant cell populations. Measurable residual disease (MRD) refers to the persistence of these trace leukemic clones that remain undetectable through standard microscopic evaluation techniques.

Monitoring MRD status utilizing multiparametric flow cytometry or advanced molecular genetic assays has been established as a highly influential prognostic indicator in AML management, playing a critical role in forecasting both relapse susceptibility and overall survival timelines after allo-SCT. Even though to date, there is a lack of comprehensive research investigating how baseline molecular mutations influence the presence of post-therapy MRD. The discovery and validation of reliable predictive biomarkers associated with MRD eradication would facilitate more personalized clinical decision-making regarding therapy selection.



AIM

To determine associations of genetic aberrations at disease onset with complete remission and the presence of minimal residual disease using next-generation sequencing (NGS).

METHOD

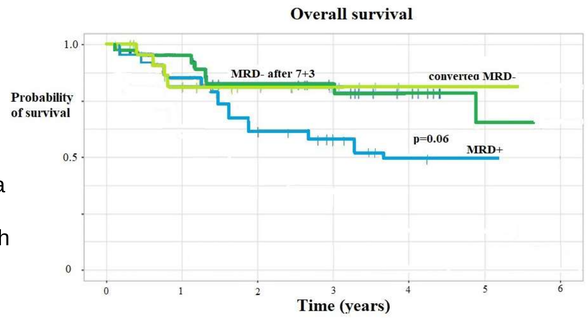
We analyzed 205 patients with AML using NGS on a targeted panel consisting of 118 genes who received induction chemotherapy and whose MRD was assessed by immunophenotypic monitoring after induction therapy.

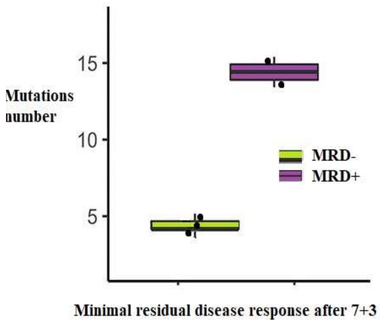
RESULTS

Induction chemotherapy resulted in MRD-negative remission in 144 (70%) patients and MRD-positive remission in 61 (30%) patients. Compared with patients with MRD+ remission, patients who achieved MRD− remission with induction chemotherapy using the 7+3 regimen were more likely to be younger than 60 years (p=0.003), had de novo acute myeloid leukemia (p=0.04), and had a favorable prognosis according to the ELN score (p=0.001).
When assigning patients to prognostic groups according to the ELN2022 classification, we found that MRD status after induction chemotherapy was prognostically significant only for the favorable ELN risk group (p=0.005). A trend toward improved overall survival was also observed in patients with unfavorable ELN risk who achieved MRD− after induction chemotherapy (p=0.28). In patients with intermediate ELN risk, achieving MRD− after induction chemotherapy did not improve survival (p=0.83). We analyzed which cytogenetic and molecular genetic characteristics before treatment predict MRD− remission after 7+3.
Among cytogenetic abnormalities, we observed that all patients with AML and a favorable t(8;21)(q22;q22) rearrangement achieved remission with MRD-. In contrast, none of the patients with monosomy 7/del(7q) achieved remission with MRD-.
Furthermore, mutations in the *NPM1* (p=0.019), *NRAS* (p=0.029), and *KRAS* (p=0.047) genes predicted high MRD-remission rates after 7+3. In contrast, mutations in the *SF3B1* (p=0.035), *ASXL1* (p=0.042), and *DNMT3A* (p=0.015) genes predicted low minimal residual disease clearance rates after 7+3.
Patients who achieved MRD− remission had fewer mutations (mean 5.7) compared with patients in MRD+ remission (mean 7.1; p = 0.031).

Custom gene NGS panel

ABL1, AKT3, ALK, APC, ARID1A, ATM, ATRX, ASXL1, B2M, BCL2, BCOR, BCORL1, BCR, BIRC3, BRCA1, BRCA2, BRAF, BTK, CALR, CARD11, CBL, CCND1, CD79B, CD58, CDKN2A, CDX2, CEBPA, CIITA, CREBBP, CSF3R, CUX1, DDX3X, DEK, DIS3, DNMT3A, EP300, ETV6, EZH2, FAM46C, FAT1, FLT3, GATA1, GATA2, GNA13, GNAS, FBXW7, HIST1H1A, HRAS, ID3, IDH1, IDH2, IRF4, IKZF1, IKZF3, ITPKB, JAK2, JAK3, KDM6A, KDR, KIT, KLF2, KMT2A, KMT2C, KMT2D, KRAS, MAP2K1, MEF2B, MGA, MPL, MSN, MYC, MYD88, NF1, NOTCH1, NOTCH2, NPM1, NRAS, PDGFRA, PHF6, PIK3CB, PIM1, PLCG2, POT1, PRDM1, PTCH1, PTEN, PTPN11, PTPRD, RAD21, RB1, RHOA, RPS15, RUNX1, RYR1, SAMHD1, SETBP1, SF3B1, SH2B3, SMARCA4, SMC1A, SMC3, SOCS1, SRSF2, STAG2, STAT3, STAT6, SUZ12, SYK, TET2, TNFAIP3, TP53, U2AF1, WHSC1, WT1, XPO1, ZRSR2





Genetic predictors of MRD− response after 7+3:
t(8;21)(q22;q22) // 7/del(7q)
NPM1*, *NRAS*, *KRAS* // *ASXL1*, *DNMT3A

CONCLUSIONS

We found that specific molecular characteristics, including cytogenetic abnormalities, genetic mutations, and the number of aberrations detected before induction chemotherapy, are powerful predictors of MRD clearance in AML.

CONTACT INFORMATION

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