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REVIEW ARTICLE

Key Prognostic Biomarkers of Acute Myeloid Leukemia: Genetic Mutations and Measurable Residual Disease

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ABSTRACT: Acute myeloid leukaemia (AML) continues to be one of the most fatal forms of leukaemia, with a high recurring relapse rate (RR) even in patients who have achieved complete remission (CR). Although there is no remedy, certain genetic mutations and measurable residual disease (MRD) play an important role as a prognosticator in monitoring disease progression in AML. This review illustrates some of the most conventional biomarkers that predict patient outcomes in AML, including MRD, fusion genes RUNX-family- transcription-factor-1-RUNX1-partner-transcriptional-co-repressor-1 (RUNX1-RUNX1T1), core binding factor beta subunit-smooth muscle myosin heavy chain 11 (CBFB-MYH11) and promyelocytic leukaemia-retinoic acid receptor (PML-RARA) and genetic mutations such as nucleophosmin 1 (NPM1). Collectively, results have shown that independent mutation factor, $NPM1^{mut}$ and MRD are currently the most accurate indicators for relapse in AML upon CR. Whereas DTA mutations (i.e. mutations in epigenetic regulators DNA methyltransferase 3A (DNMT3A), ten-elevan-translocation-2 (TET2) and additional sex comb-like 1 (ASXL1)) are likely preleukemic clones that persist throughout therapy, and their association with leukemogenesis and older patients leaves their functionality in prognosis uncertain. Studies suggest that genetic mutations isocitrate dehydrogenase (IDH) and fins-like tyrosine kinase 3 (FLT3) as standalone biomarkers are unreliable, but under the condition of concomitant $NPM1^{mut}$, their prognostic validity is enhanced. Outcomes from the increasingly personalised risk-adapted treatments, via patient stratification based on their MRD risk status, have revealed that the previous "one-size-fits-all" approach to AML treatment should be abandoned, whereas a more personalised treatment should be adopted to maximise chances of survival.

KEYWORDS: Biomedical and Health Sciences; Genetics and Molecular Biology of Disease; Hematology; Acute Myeloid Leukemia; Measurable Residual Disease.

Introduction

AML is an aggressive heterogenous group of disorders, characterised by uncontrolled clonal proliferation of myeloid progenitor cells (blasts) and differentiation arrest.[1-3] Making up approximately 25 % of all adult-onset leukaemias in Western countries,[2] with an incidence rate of 4.3 cases per 100,000 adults per year,[4] AML is the most common type of leukaemia with the lowest mortality rate.[5] According to the World Health Organisation (WHO), AML is classified by ≥ 20 % of blasts in the bone marrow (BM) or peripheral blood (PB). In addition, the expression of precursors such as cluster of differentiation (CD) markers CD13, CD33, CD34, CD117 and $HLA\text{-}DR^{pos}$ are used to confirm the immaturity of blasts and myeloid maturation.[4,6] Per the initial stage of induction therapy, chemotherapy (CT) drugs, cytarabine and anthracycline are prescribed, followed by either repeated cycles of high-dose cytarabine and/or haematopoietic stem cell transplant (HSCT),[7] e.g. allogeneic stem cell transplant (AlloSCT) or autologous stem cell transplant (AuSCT). However, despite the increasing understanding of the disease, little improvement has been made in controlling disease progression, particularly in older patients. There is still a 50 % relapse rate (RR) in patients who have achieved morphological complete remission (CR),[8] as the highly varied factors affecting prognostic results, such as age, recurring genetic mutations, cytogenetic and somatic clonal chromosomal abnormalities, remains a challenge to clinicians.[5,9] The common understanding of CR is defined by fulfilling three criteria: 1) less than 5 % myeloblasts present in the bone marrow, 2) peripheral blood absolute neutrophil count of greater than 1,000 cells/μL, and 3) peripheral blood platelet count of over 100,000 platelets/μL.[10] In addition to the existing criteria, a new response category "complete remission without MRD" is added by the 2017 European LeukemiaNet (ELN).[11]

In recent years, clinicians and researchers have been studying the significance of MRD in AML patients, where small numbers of persisting neoplastic cells are detected after treatment.[12] Commonly used biomarkers that account for high relapse rates in AML are as follows:

$NPM1^{mut}$: are amongst the most prevalent genetic aberrations found in AML patients, composing up to 25 % - 35 % of the cases.[13] The presence of NPM1mut results in abnormal expression of the NPM1 protein in the cytoplasm,[1,13] activating myeloid proliferation.

RUNX1-RUNX1T1 fusion gene: is formed from t(8;21)(q22;q22) translocation, where the majority of the coding region of RUNX1T1 gene is fused to the RUNX1 mino terminus containing the DNA-binding runt homology domain generate a RUNX1- RUNX1T1 fusion protein.[14] It is also a

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RUNX1- RUNX1T1 fusion protein.[14] It is also considered one of the most common fusion genes found in AML patients, and represents a favorable prognosis.

CBFB-MYH11 fusion gene: is formed due to the Inv(16) (p13q22) associated AML subtype M4Eo, the chromosomal rearrangement leads to the fusion of the MYH11 gene with Cbfb locus. Other genes may combine with Cbfb-MYH11 to induce leukemia.[15]

PML-RARA fusion gene: is formed by the fusion of PML proteins and RARA. The PML protein is pivotal in several cellular processes and tumor suppression mechanisms. It has a dominant negative action on transcription which inhibits the proliferation of myeloid progenitors and causes maturation arrest at the promyelocytic stage.[16]

MRD: is the term for a small group of leukemic cells that remains in the patient during or after treatment in CR. It is considered an independent prognostic and post-diagnosis indicator with a highly accurate prediction in patient outcome, particularly in AML where relapse occurs recurrently. Many studies have proven that the presence of MRD is associated with higher RR and lower event-free survival (EFS) in acute leukemia.[6,17,18] An empirically distinctive MRD level with a logarithmic scale or a quartile segregation in correlation to the OS is being set up as a threshold to define MRD^{pos} and MRD^{neg}. Currently, the ELN MRD Working Party suggests that MRD denotes the presence of leukemia cells at levels of $1:10^4$ to $1:10^6$ white blood cells, which is compared with 1:20 in morphological examinations.[19] The party also recommends a threshold of 0.1 % to distinguish between MRD^{pos} and MRD^{neg}, in addition to the peripheral blood absolute neutrophil count ≥$1x10^9$/L and platelet count ≥100x109/L, for defining CR.[20] But due to an already lower threshold level, for example, from 0.01 % to 0.1 %, for measuring leukemia associated immunophenotype (LAIP), a 0.1 % may signify MRD positivity in LAIP patients.[21] In later sections, this review will explore the more reliable technologies of MRD detection in facilitating the reflection of MRD's functionality as a biomarker.

Although certain genetic mutations are often detected in AML patients prior and after treatment, it is said that the following mutations when independently evaluated demonstrate a degree of uncertainty in prognostic implications:

$DNMT3A^{mut}$: are epigenetic modifiers that are usually sorted with ten to eleven translocation 2 (TET2) and additional sex comb-like 1 (ASXL1) under the umbrella term - DTA mutations. DNMT3A is a recurrent mutation found in 22 % of AML patients,[13] arising from somatic mutations, they persist throughout therapy and remission.

$FLT3^{mut}$: are identified in one third of AML patients,[2] with two main types: internal tandem duplications (ITD), which mainly occurs in exons 14 and 15 of the juxtamembrane domain; and tyrosine kinase domain (TKD), which are point mutations of D835 and 836.[13] FLT3 activates downstream signalling of the RAS, MAPK and STAT5 pathways, stimulating cellular proliferation.[9]

IDH^{mut}: cause an alteration to the oxidative role of IDH enzymes in the Krebs cycle, such that the original product, α-ketoglutarate (α-KG), is reduced to 2-hydroxyglutarate, a cancer-related metabolite.[2] IDH^{mut} have an occurrence of up to 15 % in AML patients, in which its subtypes IDH1 and IDH2 are mutually exclusive.[13]

This literature review aims to provide insight on the rationale behind selecting the appropriate markers for greater accuracies in prognostic outcomes, as well as guiding the direction of prospective development in treatment strategies for recurring relapse in AML patients.

Results and Discussion

Genetic Mutations as Biomarkers:

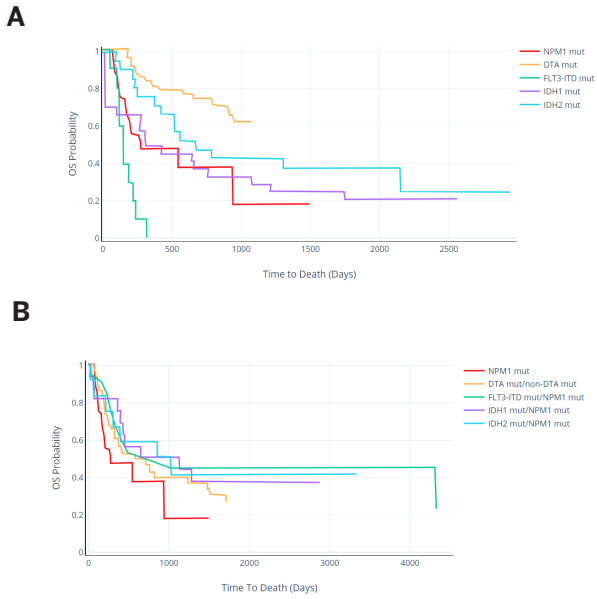

Figure 1: Summarised data from previous research on the OS probability of patients with independent mutations and concomitant mutations with $NPM1^{mut}$.

(A) :

OS probability of patients with the mentioned independent mutations (i.e. $NPM1^{mut}$,[22] DTAmut,23 $FLT3\text{-}ITD^{mut}$,[23] $IDH1^{mut}$,[24] and $IDH2^{mut}$), [24] excluding cohorts with other coexisting mutations;

(B) :

OS probability of patients with concomitant mutations with $NPM1^{mut}$ (i.e. $NPM1^{mut}$,[22] $DTA^{mut}/NPM1^{mut}$,[25] $FLT3\text{-}ITD^{mut}/NPM1^{mut}$,[26] $IDH1^{mut}NPM1^{mut}$,[24] and $IDH2^{mut}/NPM1^{mut}$) [24], excluding combinations with other types of mutations. $NPM1^{mut}$ is the relative point of comparison for the prognostic value of other mutated alleles, the coherence of OS in other mutated alleles with the trend in $NPM1^{mut}$ can only be seen when the supposedly unconclusive gene mutations (e.g. DTA^{mut}, $FLT3\text{-}ITD^{mut}$, $IDH1^{mut}$, and $IDH2^{mut}$) coexist with $NPM1^{mut}$.

In a study by Bertoli *et al.* (2020),[27] 540 patients were documented at diagnosis for $NPM1^{mut}$. 430 of them were in CR1 (67.6 %) and 160 patients relapsed (46.2 %). Among

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the 142 CR1 patients with NPM1^{mut}, 67 relapsed (47.2 %). 58.2 % of the relapses occurred during the first year and 34.3 % occurred after 3 years onwards. Among the 288 NPM1 wild-type (NPM1^{wt}) patients in CR1, there were 160 relapses (55.6 %), 60 % occurred in the first year, and only 11.2 % of relapses were after the 3-year mark. Though the duration of complete remission is seemingly more favorable in patient cohorts of NPM1^{mut} AML, risks of late relapses were significantly higher. Moreover, the notion proposed by Salipante et al. (2014)[12] on NPM1 as a representation of early genetic lesions in AML, an indicator that its mutation serves as one of the few driver mutations in this disease, is refuted in this paper with the reason that NPM1^{mut} cells are responsive to treatment and disappeared in 40 % of the patients with late relapse. Which is why the paper recommends the use of MRD detection in long term complete remissions due to half of the patient's undetectable levels of NPM1^{mut}.

As for whether the NPM1^{wt} is a reflective of potential relapse, insights form another recent investigation by Höllein *et al*. (2018)[28] states that patients with NPM1^{wt} are more susceptible to relapse, suggesting that preleukemic cells with NPM1^{wt} may be a subsequent cause of relapse due to clonal haematopoiesis in AML. Though it is uncertain whether NPM1^{mut} has a higher prognostic value than NPM1^{wt}, it is evident that NPM1^{mut} is a strong indicator of patient outcome, particularly in short-term recovery.

In a study designed by Jongen-Lavrencic *et al*. (2018),[25] DTA mutations are the most common in age-related malignancies. Persistent mutations were detected with targeted NGS, where it was prevalent in 51.4 % of the 430 patient bone marrow samples collected. Within the proportion of persistent mutations, rates of persistent mutation in DNMT3A was at 78.7 %, 54.2 % for TET2 and 51.6 % for ASXL1, all of which are significantly greater than other variant alleles. The distribution of residual mutation-bearing cells could be shown by the large discrepancies in individual variant allele frequencies (VAF), thus existing in virtually negligible volumes to populating most of the cells. It is suggested that morphologic CR is achieved when heterozygous mutations <2.5 %, but levels of DTA in the samples were noticeably above the cut-off during remission. By contrast, non-DTA alleles (e.g. NPM1) only occasionally persisted at >2.5 % levels after induction CT, typically the number of mutations are drastically reduced during CR. The outcome of the research highlights the adverse effects of non-DTA mutations in both training and validation cohorts. The overall survival (OS) and relapse rate (RR), regardless of the presence of persistent DTA mutations, are noticeably lower than patient samples with no detection of non-DTA mutation.

The research by Debarri *et al*. (2015),[29] further supports the notion that DNMT3A mutations are repopulated non-leukemic clones, meaning that they are not associated with increased relapse risk in the short term. Results were obtained from patient samples of BM and PB, in order to compare the makeup of cell subpopulations NPM1, DNMT3A and IDH1/2. The study employed NPM1 as a reference marker for the relative changes in the levels of other indicators, as well as the basis for accuracy in prediction of relapse. The detection limits of 0.07 % and 0.11 % were set for IDH1/2 AND DNMT3A mutation analyses respectively. A trend of decrease in patient's mutated IDH1/2 is visible since diagnosis, although a slight increase after initial post induction (MRD1) period is present in the cohort (n=4) with both IDH1/2 and NPM1 mutations during remission period throughout post consolidation. Compared with the patient cohort with discordant DNMT3A and NPM1 mutations (n=6), the percentage of mutated DNMT3A slightly decreases in MRD1 from the initial levels measured at diagnosis, the numbers continue to rise despite the continual period of post consolidation and complete remission. Another notable feature in this cohort is the long remission period, in which relapse happened in the previously mentioned patients with mutated IDH1/2 significantly early on their post consolidation stages, whereas patients in this cohort remained at remission at an average of 57 months as of the time the investigation has taken place. A major limitation of this study is its small sample size. In patient 5, there was a discrepancy detected in the changes amongst IDH1/2 and NPM1 levels, whereas in patient 2 a correlation is shown. The paper claims that IDH1/2 mutation-based MRD better predicts relapse incidence than NPM1 mutation-based MRD, but observations were made based on the outcome of selected individual samples, where some evidence did not meet the claim.[30] Therefore, the validity of IDH1/2 analyses has yet to be determined by further investigation. However, with prior research on the effects of DTA on complete remission, this paper supports the previously mentioned hypothesis that DNMT3A mutations are insufficient to trigger proliferation of cancer cells. DNMT3A^{mut} patients are significantly older, with an increasing mutation frequency until reaching a plateau in the range of 40 to 60 years.[25,31] Hence, it remains uncertain whether these mutations (IDH1^{mut}, IDH2^{mut} and DNMT3A^{mut}) will play a role in contributing to the driving force of leukemogenesis or relapse in older patients. An opposing finding by Brambati *et al*. (2016),[32] presents the prospective significance of DNMT3A and IDH1/2 mutations in future detection of AML relapse. The study used ddPCR to determine the percentage relapse of patients with molecular alterations, in which 9 out of 17 patients in a longitudinal follow up relapsed and the remaining 8 did not. The results between relapsed to non-relapsed samples are: DNMT3A (77.8 vs 25 %), NPM11 (66.7 vs 25 %), IDH1 (- vs 12.5 %), IDH2 (22.2 vs 87.5 %). However, the outcome only accounts for the number of patients with the said mutated alleles, rather than an evaluation regarding the impact of the genetic abnormalities. Therefore, results that seemingly present significance in DNMT3A, IDH1 and IDH2 are inconclusive. Thus, in reference to the consensus from the ELN MRD Working Party, it is agreed that the prevalence of the aforementioned non-DTA mutations and IDH1/2 alone, without the discordant NPM1^{mut} in view, are inadequate interpretations of prognostic outcome.[19]

FLT3-ITD is often associated with increased RR and poor OS, whereas FLT3-TKD is thought to have a neutral effect on patient outcome in normal karyotype AML (NK-AML). They are discouraged by the ELN to be employed as markers of MRD due to their constantly altering allele ratio of ITD to TKD in various stages of treatment, in which they are occa

sionally undetectable at relapse and often only significant at initial diagnosis.[33] In a study by Santos *et al*. (2011),[34] of the 272 patients with NK-AML, 22 % had isolated FLT3-ITD^{mut}, 7 % had isolated FLT3-TKD^{mut}, and 4 % had both. Patients with FLT3-ITD^{mut} are reported with higher WBC counts and higher BM blast percentages than patients with FLT3^{wt}. There was no significant difference in the CR rate between patients with FLT3-ITD mutations and patients with wt-FLT3, but the results demonstrate patients with FLT3-ITD had inferior EFS, DFS, and OS, in which those with low FLT3-ITD burden had a longer OS. In patients carrying FLT3-TKD^{mut}, there was no significant difference in the CR rate when compared with FLT3^{wt}, and no particular impact on EFS and OS despite varying FLT3-TKD burden.

Another point to note is in the results of patients with FLT3-ITD mutations and concomitant NPM1, OS appears to be higher than cohorts with only FLT3-ITD mutations (Figure 1B). Suggested by some studies, the coexistence of NPM1 and low ratio FLT3-ITD^{wt} is demonstrated in patients with lower relapse rates,[11,35] and can be regarded as a favourable prognostic indicator, along with the co-occurrence of FLT3-TKD and NPM1 mutations.[36] Recently, a novel analysis program, getITD, has been developed to identify and annotate all of the ITDs tested, as well as its insertion sites, length and variant allele frequency, facilitating the investigation on the influence of ITD in MRD.[37] Although the validity of this technology has yet to be reviewed in other lab and clinical settings, the technology offers a prospective vision on the utility of FLT3 in MRD monitoring throughout the patient's recovery. Thus, the prognostic significance and potentials of FLT3 should not be undermined solely because of its minimal utility as an MRD biomarker.

MRD Monitoring:

Multiparametric flow cytometry (MFC)

Diagnostic immunophenotyping is one of the most common applications of MFC.[6,38] A distinctive feature of this technology is the ability to simultaneously characterise mixed cell populations via the detection and combination of cell surface markers present on leukemic blasts. MFC is divided into two major approaches - the leukemia associated immunophenotype (LAIP) and the different from normal (DfN).[6] According to ELN recommendations, both approaches are integrated to define and identify individual specific surface markers that differentiate leukemic cells from healthy cells, in order to track aberrations during and after diagnosis.[19] A major distinction of the MFC technology is its applicability to over 90 % of patients,[6] such that MFC-based MRD is also considered an independent prognostic indicator of AML. However, it has limited standardisation and slightly lower sensitivity than other newly developed methods.

Polymerase chain reaction (PCR)

Quantitative polymerase chain reaction (qPCR):

qPCR uses florescent labelling techniques and identifies targets under three aspects: transcription ratio at diagnoses, reduction kinetics of leukemic clones and early detection of recurring clones.[39] Thus the detection of fusion genes and molecular biomarkers are typically conducted via qPCR. Unlike MFC, it is a standardized technique with notably higher sensitivity, providing high-throughput detection and quantification of target DNA sequences via simultaneous amplification.[6,40] However, functional targets detected are only present in half of the patients, and several mutations do not facilitate MRD monitoring (e.g. FLT3^{mut}).

Digital droplet polymerase chain reaction (ddPCR):

A novel modification of the conventional qPCR assays, encompassing an even higher sensitivity (up to 0.001 % mutated allele frequency) for tracking gene mutations.[32] ddPCR, uses a combination of microfluidics and proprietary surfactant chemistries to emulsify samples,[41] fractioning samples into droplets,[32] in order to distinguish wild-type versus mutant gene copies.[42] But despite its high sensitivity and absolute quantification ability, results produced by ddPCR are often highly variable due to the novelty of the technology, lower accuracy in quantification of larger amplicons, higher risk of contamination due to the open nature of the operating system and high cost in acquiring instrumentation.

Next Generation Sequencing (NGS):

NGS enables a comprehensive and highly sensitive detection of somatic mutations, as well as the identification of hotspots and abnormal blasts.[43,44] It enables simultaneous sequencing in large amounts of DNA or RNA, revealing a broad spectrum of molecular alterations in patient samples. However, due to the novelty of NGS, this technology is not yet widely available, and requires complex interpretation of data, which not all labs can provide.

MRD as a Biomarker:

Considering an investigation carried out by Short *et al.* (2019),[45] 141 adult patients were analysed retrospectively for their MRD levels before and after salvage treatment. 61 % were patients with MRD^{neg} or had undetectable MRD, their results indicate a lower cumulative incidence of relapse and better RFS. Moreover, RR within 1.4 months in second remission were 13 % higher among MRD^{pos} patients without CR, compared with MRD^{neg} patients who have achieved CR. The paper concludes that patients with MRD^{neg} and CR had the best outcomes in 2-year cumulative incidence of relapse, RFS, and OS.[45] In a similar research by Walter *et al*. (2013),[46] 253 patients undergoing first myeloablative HCT were assessed for the presence of MRD after achieving morphological CR. 54 patients were MRD^{pos} and 199 others were MRD^{neg}. After adjustments of factors using multivariate models proposed by the international working group (2003) and the ELN (2010), the hazard ratios of MRD^{pos} to MRD^{neg} were 3.14 for overall mortality, 4.72 for failure of DFS and 6.78 for relapse.[46] The results from both studies and many more conclusively suggest that MRD is a highly accurate and useful measure in disease progression and prognosis at diagnosis, relapse and during CR.[6,17,18]

While it is evident that MRD is an independent biomarker in many cases, molecular MRD monitoring often incorporates the quantification of fusion genes RUNX1-RUNX1T1, CBFB-MYH11 and PML-RARA, as well as NPM1^{mut}, which is the best-validated molecular marker for MRD. Though it is commonly believed that the mentioned fusion genes are

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strong indicators of favourable outcomes, their high copy numbers pose a fatal threat to patient outcome as it signifies the presence of MRD^{pos}, in which case patients with persistent MRD^{pos} seldom survive in the long term.[39] In a research conducted by Kern *et al*. (2007),[39] amongst relapsing patients with core binding factor leukemias (AML with RUNX1-RUNX1T1 or CBFB-MYH11), there is an increase in MRD levels during CR. Another observation was that an increase in patient transcript ratios indicated molecular relapses 1 to 5 months prior hematologic and cytogenetic relapses. This is supported by Ommen *et al*. (2010),[47] in CBFB-MYH11 leukemias where it performed the earliest prediction of relapse in 50 % of the patients tested RQ-PCR positive in BM 8 months prior. By contrast, patients with high copy numbers of RUNX1-RUNX1T1 and PML-RARA showed more rapid relapse kinetics as 50 % of the patients relapsed within 3 to 3.5 months of testing positive. With evidence from Stentoft *et al*. (2005)[48] concluding that virtually all cases of relapse occur with persistent levels of MRD^{pos} in patients with core-binding factor leukemia.

As for high $NPM1^{mut}$ allele burden, it, in various instances, has been shown to be related to MRD positivity in first complete remission. This notion is supported by the findings of Patel *et al*. (2018)[49], where it is suggested that the ability of high-burden NPM1 mutated hematopoiesis to persist after induction chemotherapy reflects the difficulty in full eradication, which correlates to a higher likelihood of MRD. Other results obtained from the University Hospital Leipzig between January 2001 and January 2016 by Bill *et al.* (2018),[22] shows that 33.3 % of the patients were found to be mutated NPM1 MRD^{pos} before HSCT. It was observed that mutated NPM1 MRD^{pos} occurred more frequently during AlloSCT in patients' second complete remission (CR2) after relapse in first complete remission, than during their first complete remission (CR1). Amongst pre-transplant mutated NPM1 MRD^{pos} after AlloSCT, the 2-year cumulative incidence of relapse (64.7 vs 6.0 %) was significantly higher than MRD^{neg} patients, which translates into a lower overall survival rate (38.8 vs 71.7 %). There is a clear correlation between the prevalence of mutated NPM1 that is followed by MRD^{pos}, leading to increased chances of relapse rates and mortality. However, despite the seemingly indicative outcome, cases of false positives and negatives are reported. In the group of mutated NPM1 MRD^{pos} patients, 17 of 51 patients (23.5 %) did not relapse, and 2 cases of MRD^{neg} patients (6 %) relapsed prior HSCT. Further analysis was not possible due to the small sample size. The false negative is suggested to be explained by the limited sensitivity of ddPCR, which despite the presumed accuracy of the technology, may still be at times fallible due to multiple factors (e.g. the equipment available in the clinical setting, and proficiency in employing the technique, etc.), and most importantly the uncertain influence of the $NPM1^{wt}$ subclone.

In conclusion, it is well established that early detection of MRD is indeed crucial for identifying impending relapse, staging intervention as predicted from longitudinal prognosis, assessing objective establishment of remission status and producing accurate prognostic analyses.[50] Although the biomarkers of MRD are distinctive in nature, they are all equally essential in monitoring recovery status during CR.

Defining High and Low Risk Stratification:

The current approach of devising treatment plans for AML patients involves referencing the corresponding risk stratification of the patient. According to the ELN, risk stratifications are generally categorised into three conditions: favourable (FR), intermediate (IR), and poor (PR) (Table 1).[1]

Table 1: 2017 ELN molecular, genetic and cytogenetic mutation risk stratification.[1,31]

Risk category	Genetic abnormality
Favourable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or FLT3-ITD^{low} (normal karyotype) t(9;11)(p22;q23);MLLT3-KMT2A Cytogenetic abnormalities not classified as favourable or poor/adverse
Poor/Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1) −5 or del(5q); −7; −17/abn(17p) Complex karyotype; monosomal karyotype Wild-type NPM1 and FLT3-ITD^{high} Mutated RUNX1/ASXL1/TP53

Genetic Mutation and MRD in Therapeutic Guidance:

The respective conditions provide prognostic value to OS and relapse predictions, in which age >60 is, on its own, an independent risk factor for poor prognosis and therapeutic outcome. Thus low-risk patients, MRD^{neg} with favourable and intermediate conditions, are shown to present significantly higher probability of relapse free survival and lower relapse rates than high-risk patients, MRD^{pos} and FLT3-positive.[13] In the GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed AML,[51] entailing four tiers: favourable-risk (NCCN-FR), intermediate-risk (NCCN-IR), poor-risk (NCCN-PR) and intermediate-risk without LAIP identification (NCCN-IR-no LAIP). NCCN-IR-Neg and NCCN-FR (low risk) patients were submitted to AuSCT, whereas NCCN-IR-Pos and NCCN-PR (high risk) patients received AlloSCT. Combining the results of this study with the investigation of Zhu *et al*. (2013)[52] and Hourigan *et al*. (2020)[23] on risk-adapted treatments (Figure 2), the results reveal that high doses of cytarabine, myeloablative conditioning (MAC) and AlloSCT are the most well received in high risk cohorts, showing an improvement in OS probability. By contrast, the patients in the low risk cohort benefitted the most in CT, with a relatively better OS outcome under reduced-intensity conditioning (RIC) treatment. The effects of CT are significantly more responsive in low risk cohorts, however the lowest probability of OS occurring in high risk patients was from cohorts undergoing CT. Moreover, the effects of the various therapeutic intensities for high and low risk patients are similar in both OS and disease-free survival (DFS) probabilities, conclusively indicating high intensity therapy and AlloSCT are more suitable in high risk patients (Figure 2), whereas low intensity chemotherapy approaches may be more beneficial to low risk patients than transplantation. Therefore, patients should receive transplants based on the treatment plan

devised for their risk stratification, and not because of donor availability.[23]

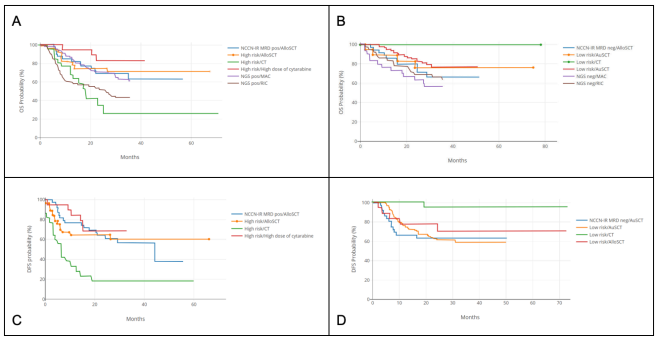

Figure 2: Summarised data from previous research on the OS and DFS probabilities in different treatment methods in high and low risk patient cohorts.
(A) Treatment effects to OS probability in high risk cohorts receiving AlloSCT,[52] CT,[52] high-dose cytarabine,[31] and NCCN-IR MRDpos (which is essentially a subdivision from the high risk cohorts) receiving AlloSCT.[51] Effects of MAC and RIC are contrasted in NGS MRD^{pos} patients;[11]
(B) Treatment effects to OS probability in low risk cohorts receiving AlloSCT,[52] CT,[52] AuSCT,[51] and NCCN-IR MRDneg patients receiving AlloSCT.[31] Effects of MAC and RIC are contrasted in NGS MRD^{neg} patient;[11]
(C) Effects of treatment to DFS probability in high risk cohorts receiving AlloSCT,[52] CT,[52] high-dose cytarabine,[51] and NCCN-IR MRD^{pos} patients receiving AlloSCT;[51]
(D) Effects of treatment to DFS probability in low risk cohorts receiving AlloSCT,[52] CT,[52] AuSCT,[51] and NCCN-IR MRD^{neg} patients receiving AuSCT[51]. Overall, the OS and DFS are most benefitted in low risk cohorts receiving CT and RIC, whereas the OS and DFS are most well received by high risk cohorts undergoing AlloSCT and MAC.

Conclusion

Recent technological advancements have increased the ability to detect and analyze gene mutations as well as MRD in AML patients. Novel instruments have been shown to reduce technical limitations with a heightened sensitivity in monitoring prognostic biomarkers in AML, as well as facilitating the discovery of concomitant and independent mutations associated with poor prognoses, locating an array of leukemic clones and transcription factors for the investigation of potential mutation drivers in hematopoiesis. As reviewed, certain gene mutations not only encompass a high prognostic value, but also provides a valid biomarker to MRD monitoring, an even more sensitive measure of patient recovery. An in-depth review of the potentials and shortcomings of our enhanced understanding of how genetic mutations and MRD affect the actual clinical outcomes is out of scope for this review. Moreover, the question of whether full eradication of $NPM1^{mut}$ or achieving MRD^{neg} is necessary before treatment remains open to further research and discussion. Evidently, monitoring key molecular biomarkers of AML is a quintessential part of standard care and should be continued, but at the same time, the impact of less conventional biomarkers should not be undermined, for they are all possibilities in furthering the progression of AML prognosis and treatment development. Hopefully, costs of standard, as well as less conventional technologies for detection of genetic aberrations will decrease in the future, enabling more advanced discovery in the field of AML prognosis with less financial constraints.

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