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The Role of Meningioma-1 (Mn1) Gene as Marker for Prognosis and Minimal Residual Disease Monitoring in Acute Myeloid Leukemia: A Concise Review

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Introduction

Molecular markers are necessary for prognostic stratification and monitoring of Minimal Residual Disease (MRD) in Acute Myeloid Leukemia (AML) [1,2]. Cytogenetic aberrations have long been recognized as the most important prognostic variable in AML, and are still the major determinant for post-remission therapy [3]. Unfortunately, only 50-60% of AML patients present an abnormal karyotype at diagnosis, while the remaining cases display a Normal Karyotype (NK). NK AML patients are generally included in an "intermediate risk" prognostic group, that is however characterized by a heterogeneous clinical course. To stratify prognosis of NK AML patients, numerous studies have led, in the last decade, to the introduction of different molecular markers such as FLT3, NPM1, BAALC and CEBPA [4-7]. Still, their use to monitor disease, either defining remission status and detecting relapse as early as possible, is still somehow controversial, due to fluctuations during disease course, low incidence rates in AML and sensitivity of the technologies detecting the single marker [8-10]. These limitations have, to date, precluded a timely and precise quantification of disease in NK AML patients, thus preventing from a complete individualization of post-remission therapy and early treatment in case of impending relapse. In other words, in NK AML it has not been reached the precision achieved in BCR/ABL-positive chronic myeloid leukemia and PML/RAR alpha mutated acute promyelocytic leukemia.

MRD is conventionally defined as the amount of residual AML cells still present in complete remission patients, undetectable at microscope level. The most widely used method for MRD detection is the quantitative Real-Time Polymerase Chain Reaction Assay (RT-PCR). Historically, MRD detection by RT-PCR was limited to those patients characterized by a genetic signature (e.g.: mutations, fusion genes or altered gene expressions) [11]. To overcome this lack, efforts have been made to identify so-called "pan-leukemic" markers validated for MRD detection in NK AML. The Wilms Tumor gene 1 (WT1) has been found to be overexpressed in a large proportion of AML (over 90% of cases, irrespective of karyotype) [12-14]. Although not associated with a specific leukemic clone, WT1 quantification provides information of disease persistence or relapse. However, being WT1 expressed also in normal cells, its determination has limited sensitivity; more, around 10% of AML patients does not express WT1. Therefore, is necessary to associate other possible markers in the characterization of AML.

The *Meningioma 1* (MN1) gene, located on chromosome 22q11, encodes a protein that participates in a gene transcription regulator complex. In cells derived from the bone marrow of healthy donors the MN1 levels are very low [15,16], supporting the hypothesis that high MN1 gene levels are specific for leukemic blasts and not a consequence of differentiation. However, the molecular mechanisms via which MN1 inhibits differentiation and stimulates proliferation of hematopoietic cells remain largely unknown.

MN1 has been found to be over-expressed in AML with inv(16) [17], and high MN1 levels seems to have prognostic impact in NK AML patients (Table 1). In 2006 Heuser et al. [18] found that high MN1 (defined as more than the median expression) was associated with poor response to a double induction therapy of idarubicin + etoposide + cytarabine (71% *vs.* 87%, P = 0.02), and lower Relapse-Free Survival (RFS) (23% *vs.* 51% at 3 years, *P* = 0.002) and Overall Survivals (OS) (38% *vs.* 59% at 3 years, P = 0.03) in 142 adult patients with NK AML. In multivariate analysis, MN1 expression retained its prognostic significance. Few years later, Langer et al. [19] measured MN1 expression by real-time RT-PCR in 119 untreated NK AML patients younger than 60 years to confirm its

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Table 1: Expression and prognostic impact of MN1 in NK AML.

Reference	No. of patients	No. of controls	Cytogenetic	Molecular markers	Incidence of MN1 over expression (%)	Threshold of MN1 over expression	Prognostic impact			Multivariate analysis	
							CRR	RFS/DFS	OS	Variables	Significant parameters
Heuser et al. [18]	142	0	NK	MN1, FLT3, MLL-PTD, NPM1	50	median value	0,02	RFS: 0.002 at 3y	0.03 at 3y	MN1 expression, ECOG performance status, Age above median	OS
Langer et al. [19]	119	0	NK	MN1, NPM1, BAALC, FLT3, WT1¤, MLL-PTD, ERG, CEBPA	25	highest quartile	0,006	DFS: <0.001 at 5y	0.001 at 5y	MN1 and ERG expression, FLT3-ITD, NPM1 and WT1¤, WBCs	CRR, DFS, OS
Aref et al. [20]	100	10	NK	MN1, NPM1, FLT3	48	median value	0,001	DFS: 0.04 at 1y	0.03 at 1y	MN1 expression, Age,WBCs, Blast count,FAB	DFS, OS
Xiang et al. [21]	158	20	not specified, but all FAB except M3	FLT3, NPM1, WT1 expression, miR-20a, miR-181b,	50	median value	fSWOG*: P=0.026 iSWOG§: P=0.04 aSWOG¥: P=0.024	n.s.	fSWOG : P=0.024 at 2yiSWOG: P=0.018 at 2y aSWOG: P=0.033 at 2y	MN1, miR-20a, miR-181b, WT1 expression, FLT3-ITD, NPM1, WBCs	CCR, RFS, OS
Zayed et al. [22]	50	10	NK	MN1, PTEN	50	median value	n.s.	n.s.	n.s.	n.a.	n.a.

CCR: Complete Remission Rate; RFS: Relapse Free Survival; DFS: Disease Free Survival; OS: Overall Survival; NK: Normal Kariotype; ¤: Mutational Status of WT1; y: Years; WBCs: Count of White Blood Cells at Onset, *: Favorable SWOG Group; §: Intermediate SWOG Group; ¥: Adverse SWOG Group

prognostic role in the context of other predictive molecular markers. Their results indicate that higher MN1 expression was associated with NPM1 wild-type and high BAALC expression (P = 0.004); patients over-expressing MN1 had lower Complete Remission (CR) rate (P = 0.005 after adjustment for WBC count), shorter Disease-Free Survival (DFS) (P = 0.01 after adjustment for WT1and FLT3-ITD mutations); and shorter OS (P = 0.04 after adjustment for WT1, NPM1 and FLT3-ITD mutations, and for WBC).

In line with these first experiences, more recently Aref et al. [20] analyzed 100 NK AML patients, treated and followed up for at least 24 months, showing that MN1 overexpression (documented in 48 patients) is a predictor of poor response, as high gene levels at diagnosis were associated with poor CR after induction chemotherapy (8.4% *vs.* 62.5%, P = 0.001), higher risk of relapse (54.1 *vs.* 23%, P = 0.02) and shorter survival (mortality rate 75% *vs.* 46.1, P = 0.03). Multivariable analysis confirmed that MN1 over-expression was an independent risk factor for RFS and OS. Xiang et al. [21] studied MN1 gene and MN1-associated microRNAs expression level in 158 newly diagnosed Chinese AML patients and in 20 healthy donors, finding that MN1 was overexpressed in patients compared with normal controls and that high gene expression was associated with lower CR rates (P = 0.01) and shorter RFS (P = 0.02) and OS (P = 0.02).

If, overall, most of the published experiences identify MN1 overexpression as a marker of a more aggressive disease, a recent paper by Zayed et al. [22] on 50 NK AML patients and 10 controls did not confirm MN1 prognostic role nor suggested its use as a routine diagnostic tool. However, this latter study may suffer from the limited sample size and the consequently low statistical power.

Concerning the potential usefulness of MN1 gene as MRD marker, a recent paper by Carturan et al. [15] showed not only that an increased MN1 expression can be of prognostic significance in predicting relapse of AML patient, but also that MN1 and WT1 gene expression had a good degree of concordance, as an increase above the upper normal limit was documentable four months before hematologic relapse. In our experience, we found an excellent concordance between MN1 and WT1 gene expression and with disease course (i.e. remission achievement and maintenance, relapse) [personal data, unpublished]. In our cohort, WT1 was over-expressed in about 90% of AML patients, while MN1 was high only in 40% of the cases, in line with most published experience [19]. Nonetheless, the concomitant evaluation of the two markers could give clinicians a better tool to early detect a leukemic relapse in AML lacking a specific molecular marker. In their work, Carturan and colleagues analyzed the different cytogenetic prognostic groups according to MN1 expression, finding a lower gene expression in cases with translocation t(8;21) compared to those with inv(16), that have been recognized as unique entities and are usually reported together as Core Binding Factor (CBF) AML [15]. This diversity is in line with an emerging branch of research investigating the clinical and biological heterogeneity of CBF AML [23]. Moreover, they found that MN1 levels in patients with Acute Promyelocytic Leukemia (APL) are very low, comparable to those of healthy controls. This could suggest that MN1 is involved in pathways not activated in APL, contrarily to WT1, whose levels are higher in APL than in other AML [24].

In summary, MN1 gene has peculiar patterns of expression in different AML subtypes, even among the same cytogenetic risk categories, and seems promising to gain further knowledge of leukemogenic mechanisms, particularly in CBF or in NK AML lacking other known mutations (such as FLT3 or NPM1). Even if the published experiences have given discordant results, most of the evidences point towards a prognostic role of MN1 in AML patients; however, further studies on large number of patients are warranted to define the correct weight of MN1 as a factor impacting on outcomes. Last, promising data are emerging on MN1 potential as a marker of MRD, both alone and in combination with other molecular

abnormalities, if present, to allow for a precocious detection of AML relapse and to optimize post-remission therapy. In the last years, various paper focused on therapeutic strategies upon re-emergence of minimal residual disease in AML, mostly after allogeneic stem cell transplant [25,26], but an ultimate consensus on monitoring strategies and on a MDR-driven therapy is still lacking [27].

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