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Response

NPM1-mutated AML is an entity irrespective of whether or not chromosomal aberrations are present

We thank Micol et al for their critical comments. *NPM1*-mutated AML,[1] a new provisional entity of 2008 World Health Organization (WHO) classification of myeloid neoplasms,[2] usually carries a normal karyotype (NK).[1] The main goal of our paper[3] was to ascertain whether concomitant chromosomal aberrations may influence its features. Our findings clearly supported the view that *NPM1*-mutated AML is a single disease entity, independently of whether it carries a NK or abnormal karyotype (AK). In fact, chromosomal aberrations occurring in *NPM1*-mutated AML emerged as secondary genetic lesions and clinicopathologic features, immunophenotype and gene expression profiles overlapped whether *NPM1*-mutated AML carried a NK or AK.[3] In addition, prognosis of *NPM1*-mutated AML did not appear to be influenced by a concomitant chromosomal aberration.[3] These findings have the potential to impact how we classify and treat AML patients.

Micol et al reported that *NPM1*-mutated AML with NK and AK exhibited the same complete remission rate, overall survival, and event-free survival, thus providing further evidence in support of our view. Unlike our results, however, Micol et al found that event-free survival, but not overall survival, was negatively influenced by the presence of a cytogenetic abnormality in the subset of *NPM1*-mutated/*FLT3*-ITD$^-$ patients. Several explanations may account for these diverging results. Micol et al's conclusions may be biased because of the small number of *NPM1*-mutated/*FLT3*-ITD$^-$ cases they investigated: a total of 95 cases (79 NK, 16 AK) compared with our 355 patients (295 NK; 60 AK). It should be also underlined that our results were confirmed in 2 large independent clinical studies, Munich Leukemia Laboratory and GIMEMA/EORTC.

It may be also possible that differences in event-free survival in the 2 studies may be due to occurrence of a few "unfavorable" chromosomal aberrations in the small cohort of patients analyzed by Micol et al. Unfortunately, the authors provide no information about the type of cytogenetic abnormalities that were identified in their patients. In our paper,[3] we demonstrated that the pattern of chromosome aberrations observed in addition to *NPM1* mutation overlaps with the aberration pattern occurring in addition to t(8;21), t(15;17), inv(16), and 11q23/*MLL* rearrangement, which are regarded as distinct entities irrespective of whether or not additional chromosome aberrations are present.[2] Overall, accompanying chromosome abnormalities had no prognostic impact in AML with t(8;21) and inv(16), respectively, as we showed for *NPM1*-mutated AML, and only in a large meta-analysis by Schlenk et al[4] could distinct aberrations be identified that had an impact on prognosis. We agree with Micol et al that a comparable meta-analysis is necessary to clarify whether single additional aberrations may influence the prognosis in *NPM1*-mutated AML.

In conclusion, a large bulk of evidence,[5-10] including findings from our study,[3] points to *NPM1*-mutated AML as a distinct leukemia entity,

irrespective of whether or not chromosomal observations are present. Accordingly, the impact of secondary genetic alterations, such as *FLT3*-ITD or additional chromosomal aberrations, on survival should be considered in the context of the entity, that is, "*NPM1*-mutated AML," comparable with other genetically defined entities such as AML with t(8;21), inv(16), t(15;17), or 11q23/MLL rearrangement.

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To the editor:

Elevated fibrinogen γ′ ratio is associated with cardiovascular diseases and acute phase reaction but not with clinical outcome

Recently, Nowak-Göttl et al reported on the association between the fibrinogen γ′/total fibrinogen ratio (γ′ ratio) and thromboembolism in children.[1] We and others previously reported on this association in adults.[2-6] However, the underlying mechanism remains unknown. Recently, we reported that the γ′ ratio is higher in the acute phase of ischemic stroke (IS), but not in the convalescent phase.[2] This suggests that the acute phase reaction alters the mRNA processing of fibrinogen γ, thereby increasing the γ′ ratio. Furthermore, the anti- and prothrombotic properties of γ′-fibrinogen suggest that an increased γ′ ratio during the acute phase of cardiovascular disease may influence the secondary thrombotic risk.

Fibrinogen γ′ antigen levels were measured by enzyme-linked immunosorbent assay as described previously.[4] Total fibrinogen levels were measured according to von Clauss, and C-reactive protein (CRP) levels were measured using an in-house high-sensitivity enzyme-linked immunosorbent assay. Statistical analysis was performed using SPSS 16.0 for Windows. All investigations were approved by the Medical Ethics Committee of Erasmus University Medical Center and were performed in accordance with the recommendations of the Declaration of Helsinki.

We confirmed our previous finding of an elevated γ′ ratio in IS and observed significantly higher γ′ ratios in the acute phase of IS (independent cohort of 53 patients), pulmonary embolism (PE, n = 29)[7] and unstable angina pectoris (UAP, n = 202)[8] compared with the γ′ ratios in healthy controls ($P < .001$; Table 1). These observations are in contrast to those of Nowak-Göttl et al, who reported a decreased γ′ ratio in

Table 1. Fibrinogen levels, fibrinogen γ′ levels, and fibrinogen γ′/fibrinogen ratios in healthy controls and patients with various cardiovascular diseases

Group	n	Fibrinogen, g/L	Fibrinogen γ′, g/L	Fibrinogen γ′/ total fibrinogen ratio	*P**	*P*†
Population controls	173	3.30 (0.59)	0.33 (0.10)	0.10 (0.03)		
Patients						
Ischemic stroke (IS)	53	3.87 (1.19)	0.49 (0.18)	0.13 (0.02)	< .001	
Pulmonary embolism (PE)						.54
Nonacute phase	13	2.69 (1.42)	0.53 (0.27)	0.20 (0.06)	< .001	
Acute phase	16	4.39 (2.30)	0.79 (0.33)	0.24 (0.19)	< .001	
Unstable angina pectoris (UAP)						.59
Stabilized	130	3.36 (0.76)	0.46 (0.15)	0.14 (0.04)	< .001	
Refractory	72	3.82 (1.00)	0.53 (0.23)	0.14 (0.04)	< .001	

Data presented are means (SD).
**P* value of fibrinogen γ′/total fibrinogen ratio between patients and healthy controls after adjustment for age and sex.
†*P* value of fibrinogen γ′/total fibrinogen ratio between patient groups after adjustment for age and sex.