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To the editor:

Does increased red blood cell deformability raise the risk for osteonecrosis in sickle cell anemia?

The pathogenesis of osteonecrosis in sickle cell anemia (SCA) remains unknown. Blood hyperviscosity has been suggested as a factor involved in the genesis of osteonecrosis,[1] but has not been studied until now. We hypothesized that abnormal hemorheology could play a role in this complication. Hematologic and hemorheologic parameters were assessed in SCA patients with (OST+; n = 30) or without (OST−; n = 67) osteonecrosis. Osteonecrosis was diagnosed as previously described.[2] The study was conducted according to the Declaration of Helsinki guidelines and was approved by the Regional Ethics Committee. The results are reported in Table 1. OST+ patients were older than OST− patients ($P < .05$) and more had a history of vaso-occlusive crises (VOC) within the previous year ($P < .05$) and a higher frequency of α-thalassemia ($P < .05$), confirming previous studies.[3-5] Although the OST+ group exhibited higher hemoglobin (Hb) and hematocrit and a lower hemolytic component than the OST−

group ($P < .01$), blood viscosity was not significantly different between the 2 groups ($P < .20$). In contrast, red blood cell (RBC) deformability ($P < .001$) and aggregation ($P < .05$) were increased in the OST+ group. The hydroxyurea (HU) treatment frequency was not significantly different between the 2 groups ($P < .20$). As HU is known to modulate RBC deformability,[6] we analyzed the data as a function of HU therapy independently of osteonecrosis and found that HU-treated patients had lower blood viscosity and greater RBC deformability (data not shown). Excluding HU-treated patients from the cohort did not change the results (Table 1).

A binary (OST−/OST+) multivariate logistic model was used to identify factors associated with osteonecrosis in SCA patients and included age, Hb, RBC aggregation and deformability, hemolytic component, α-thalassemia status, and previous history of VOC as covariates. The overall model was significant

Table 1. General characteristics and hematologic and hemorheologic parameters in patients with (OST+) and without (OST−) osteonecrosis

	With patients undergoing HU treatment		Without patients undergoing HU treatment	
	OST− (n = 67)	OST+ (n = 30)	OST− (n = 57)	OST+ (n = 22)
Age (y)	32.5 ± 12.2	39.3 ± 13.1*	32.0 ± 12.4	38.8 ± 11.9*
Gender (male/female)	32/35	11/19	27/30	9/13
HU (%)	15.9	27.6	—	—
α-Thalassemia (%)	37.3	56.7*	40.4	59.1
Positive history of VOC (%)	9.0	26.7*	8.8	27.3*
HbF (%)	7.9 ± 5.7	9.6 ± 6.2	7.5 ± 5.6	9.1 ± 6.1
WBC (10^9/L)	9.5 ± 2.0	8.7 ± 2.1	10.0 ± 2.7	9.0 ± 1.7
RBC (10^{12}/L)	2.8 ± 0.6	2.9 ± 0.5	2.8 ± 0.6	3.1 ± 0.4
PLT (10^9/L)	404 ± 126	381 ± 136	414 ± 125	373 ± 144
MCV (fL)	83.5 ± 9.8	86.6 ± 10.1	81.4 ± 8.2	83.5 ± 7.4
MCHC (g/dL)	35.9 ± 1.1	35.6 ± 1.2	35.8 ± 1.1	35.5 ± 1.3
Hb (g/dL)	8.2 ± 1.3	9.0 ± 1.1**	8.1 ± 1.2	9.1 ± 1.1***
Hct (%)	22.9 ± 3.7	25.2 ± 3.0**	22.7 ± 3.4	25.6 ± 3.1***
RET (%)	8.5 ± 3.3	7.7 ± 2.7	8.6 ± 3.3	7.7 ± 2.3
BIL (μmol/L)	61.9 ± 44.1	52.6 ± 37.4	62.8 ± 46.1	54.7 ± 43.0
AST (IU/L)	39.4 ± 14.8	37.0 ± 10.1	39.8 ± 14.3	37.1 ± 11.2
LDH (IU/L)	522 ± 166	433 ± 96**	537 ± 161	442 ± 100**
Hemolytic component (relative unit)	0.16 ± 1.10	−0.35 ± 0.61**	0.23 ± 1.08	−0.33 ± 0.61**
ηb (mPa/s)	7.64 ± 1.79	8.24 ± 2.01	7.80 ± 1.75	8.40 ± 2.16
RBC deformability at 3 Pa (a.u. × 100)	15 ± 6	20 ± 5***	15 ± 5	19 ± 5***
RBC aggregation (%)	52 ± 9	57 ± 8*	52 ± 10	55 ± 7
RBC disaggregation threshold (s^{-1})	306 ± 148	262 ± 108	309 ± 152	265 ± 116

Values are means ± SD. All patients were at steady state at the time of the study, ie, no blood transfusions in the previous 3 months and absence of acute episodes at least two months before inclusion into the study. Measurements of 4 hemolytic markers (BIL, bilirubin; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; RET, reticulocytes) were performed using standard methods, and a principal component analysis was used to derive a hemolytic component value from these markers.[9] This standard statistical data reduction approach uses conventional clinical measurements to explain the maximum-shared variance among these indirect measures of hemolysis. The hemolytic component has recently been demonstrated to reflect intravascular hemolysis,[9] had a mean of 0 (standard deviation = 1.0), and predicted 49.2% of the variation among all 4 measured variables (eigenvalue = 1.97). Blood viscosity, RBC deformability, and aggregation properties were determined as previously described.[10] Polymerase chain reaction (Gap-PCR) was used to detect the 6 common α-thalassemia deletions, including $-\alpha^{3.7}$ and $-\alpha^{4.2}$ alleles, and triplication defects of the α-globin genes.

HbF, fetal Hb; Hct, hematocrit; MCHC, mean corpuscular hemoglobin concentration; MCV, mean cell volume; PLT, platelets; VOC, vaso-occlusive crisis; WBC, white blood cell; ηb, blood viscosity.

Significant difference between the 2 groups: *$P < .05$; **$P < .01$; ***$P < .001$.

($\chi^2 = 30.192$; df = 7; $P < .0001$) and retained age (odds ratio [OR]: 1.06; 95% confidence interval [CI]: 1.01-1.12; $P < .05$), Hb (OR: 2.24; 95% CI: 1.19-4.18; $P < .05$), and RBC deformability (OR: 1.15; 95% CI: 1.01-1.33; $P < .05$) as independent factors statistically associated with osteonecrosis. Two other binary multivariate logistic models were tested: one included the previous parameters plus blood viscosity and HU therapy and the other excluded all HU patients. The results were similar to those in the first model (data not shown).

Our study demonstrates that increased RBC deformability is associated with osteonecrosis in SCA. Irregularly shaped, deformable sickle RBCs were previously shown to be more adherent than rigid, irreversibly sickle RBCs,[7] hence triggering vascular occlusion.[8] The greater RBC deformability found in the OST+ group is probably caused by the greater frequency of patients with α-thalassemia in this group because patients with α-thalassemia had greater RBC deformability (0.18 ± 0.05) than patients without RBC deformability (0.15 ± 0.06, $P < .05$). Although higher Hb levels were observed in patients with osteonecrosis, the data do not support a significant role for blood viscosity in the pathogenesis of this complication, even after excluding data from patients under HU therapy. Further studies will be required to delineate the mechanisms by which RBC deformability raises the risk for osteonecrosis.

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To the editor:

The impact of abn(17p) and monosomy −5/del(5q) on the prognostic value of the monosomal karyotype in acute myeloid leukemia

Acute myeloid leukemia (AML) with monosomal karyotype (MK) at diagnosis has been established as a subset of AML patients with very poor prognosis. After the initial publication by the Dutch-Belgian Hemato-Oncology Cooperative Group and Swiss Group for Clinical Cancer Research (HOVON/SAKK),[1] several studies confirmed the very unfavorable prognostic significance of AML-MK.[2,3] Recently, Middeke et al[4] reported that MK and complex karyotypes in AML lost their excessively poor prognostic value after allogeneic stem cell transplantation (SCT) when AML with abn(17p) or −5/del(5q) were excluded from the AML-MK or AML-complex karyotypes subcategories. Although the impact of abn(17p) or −5/del(5q) among MK was also studied in our original publication,[1] the prognostic distinction that was proposed by Middeke et al was not apparent in our analysis. We set out to examine whether we could confirm the observations of Middeke et al in an expanded cohort of 2898 newly diagnosed AML patients 15 to 60 years of age entered into 5 successive HOVON/SAKK trials between 1987 and 2008.[5-9]

From those 2898 patients, patients with normal karyotype, core binding factor abnormalities, or sole –X or –Y were not considered in this regard so that 1109 patients with ≥1 other chromosomal abnormalities were included in the analysis. Among this latter group, 305 patients had AML-MK. We estimated overall survival (OS) and event-free survival (EFS) of patients with AML-MK and MK subgroups with or without abn(17p) or −5/del(5q) (Table 1). Patients with AML-MK with −5/del(5q) showed an extremely unfavorable 3-year OS from diagnosis (2%), whereas AML-MK patients without −5/del(5q) showed statistically significant better but still very poor 3-year OS (12%), which is much less than the OS of non-MK patients. The same trend was seen in the subgroup of patients with AML-MK after allogeneic SCT in first complete remission, although with reduced statistical significance. The presence or absence of abn(17p) among AML-MK patients showed no relation whatsoever with OS and EFS after diagnosis or after allogeneic SCT and thus did not add prognostic value. Because the various studies spanned a time period that was >20 years and the 5-year OS and EFS improved from 29% and 22% for patients diagnosed between 1987 and 1993 to 43% and 35% for patients diagnosed after 2003, a multivariate regression analysis adjusted for the year of diagnosis was performed. The *P* values from this

Table 1. Overall survival and event-free survival of AML-MK at 3 years after diagnosis and after allogeneic stem cell transplantation in AML-MK in relation to the specific cytogenetic abnormalities abn(17p) or −5/del(5q)

	After diagnosis			After allogeneic stem cell transplantation		
Chromosomal abnormality	**No.**	**OS (SE) at 3 y**	**EFS (SE) at 3 y**	**No.**	**OS (SE) at 3 y**	**EFS (SE) at 3 y**
MK total	305	7 (1)	5 (1)	49	28 (6)	26 (6)
With abn(17p)	38	5 (4)	5 (4)	7	29 (17)	29 (17)
Without abn(17p)	267	7 (2) *P* = .90	6 (1) *P* = .79	42	28 (7) *P* = .93	25 (7) *P* = .81
With −5/del(5q)	172	2 (1)	2 (1)	25	16 (7)	11 (7)
Without −5/del(5q)	133	12 (2) *P* < .01	10 (3) *P* = .02	24	41 (10) *P* = .06	41 (10) *P* = .03
Non-MK abnormalities	804	35 (2)	25 (2)	223	54 (3)	51 (3)

AML patients with normal karyotypes, core binding factor abnormalities, or sole –X of –Y were excluded. Non-MK abnormalities refers to AML not meeting the definition MK but with other non–core binding factor cytogenetic abnormalities as previously described.[1]

SE, standard error.