TET2 mutations in secondary acute myeloid leukemias: a French retrospective study

Olivier Kosmider,[1,2,3,4,5] Eric Delabesse,[6] Véronique Mansat-De Mas,[6] Pascale Cornillet-Lefebvre,[7] Odile Blanchet,[8,9] Alain Delmer,[10] Christian Recher,[11] Sophie Raynaud,[12] Didier Bouscary,[1,2,3,4,13] Franck Viguié,[5,14] Catherine Lacombe,[1,2,3,4,5] Olivier A. Bernard,[15] Norbert Ifrah,[9,16] François Dreyfus,[2,3,4,5,13] and Michaëla Fontenay[1,2,3,4,5] on behalf of the GOELAMS

[1]Assistance Publique-Hôpitaux de Paris, Service d'Hématologie Biologique, Hôpital Broca-Cochin-Hôtel-Dieu; [2]Institut Cochin, Département d'Immuno-Hématologie, Paris; [3]Institut National de la Santé et de la Recherche Médicale (INSERM) U1016, Paris; [4]Centre National de la Recherche Scientifique (CNRS) Unité Mixte de Recherche (UMR) 8104, Paris; [5]Faculté de Médecine, Université Paris Descartes, Paris; [6]Laboratoire d'Hématologie, CHU Purpan, Toulouse; [7]Laboratoire d'Hématologie, CHU Reims; [8]Laboratoire d'Hématologie, CHU Angers; [9]Institut National de la Santé et de la Recherche Médicale (INSERM) U892; [10]Service d'Hématologie Clinique, Hôpital Robert Debré, CHU Reims; [11]Service d'Hématologie, CHU Purpan, Toulouse; [12]Laboratoire d'Hématologie et de Cytogénétique, CHU de l'Archet, Nice; [13]Assistance Publique-Hôpitaux de Paris, Unité Fonctionnelle d'Hématologie, Département de Médecine Interne, Hôpital Cochin, Paris; [14]Assistance Publique-Hôpitaux de Paris, Service d'Hématologie Biologique, Hôpital Saint-Antoine; [15]INSERM U985, Institut Gustave Roussy, Villejuif; and [16]Service des Maladies du Sang, CHU Angers, France

ABSTRACT

Ten-eleven translocation 2 (TET2) mutations have been involved in myeloid malignancies. This retrospective study aims at evaluating the frequency and impact of *TET2* mutations in 247 secondary acute myeloid leukemia cases referred to as myelodysplasia-related changes (n=201) or therapy-related (n=46) leukemias. Mutation of at least one copy of the *TET2* gene was detected in 49 of 247 (19.8%) patients who presented with older age, higher hemoglobin level, higher neutrophil and monocyte counts, and lower platelet count. *TET2* mutations were significantly less frequent in therapy-related (8.7%) than myelodysplasia-related changes (22.3%; P=0.035) leukemias and strongly associated with normal karyotype (P<0.001). *TET2* mutations did not significantly associate with *NPM1*, *FLT3-ITD* or *FLT3-D835*, *WT1*, or N- or K-RAS mutations. Complete remission was achieved in 57% of evaluable patients who had received intensive chemotherapy. In this group, *TET2* mutations did not influence the complete remission rate or overall survival.

Key words: secondary AML, *TET2* mutations, characteristics, prognosis.

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Introduction

Mutations of the *ten-eleven translocation 2* (*TET2*) gene, which encodes a 2-oxoglutarate/Fe^{2+} oxygenase that catalyses the conversion of methylcytosine to hydroxymethylcytosine, were recently identified in myeloid malignancies.[1] They involve 19-26% of myelodysplastic syndromes (MDS),[2,3,4] 12-15% of myeloproliferative neoplasms (MPN) or MDS/MPN disorders,[1,5,6,7] and 8-19% of *de novo* adult acute myeloid leukemias (AML).[3,6,8,9] Impact of *TET2* mutation on prognosis in either *de novo* or secondary AML remains controversial.[6,8,9] In addition, the frequency and impact of *TET2* mutations on initial features and response to treatment in secondary AML (sAML) have not yet been fully examined.

In this retrospective study, we analyzed the *TET2* gene coding sequence in a cohort of 247 sAML recorded as myelodysplasia-related changes (MRC) AML and therapy-related (TR) AML based on the WHO 2008 classification.[10] Patients with *TET2* mutations (19.8%) presented with particular characteristics and had the same prognosis as patients with wild-type *TET2*.

Design and Methods

Patients

Between 2000 and 2008, bone marrow (BM) mononuclear cells were collected at diagnosis from 247 patients from 4 French centers of the Groupe Ouest-Est d'étude des Leucémies Aiguës et Autres Maladies du Sang (GOELAMS). Among these, 158 patients received intensive chemotherapy (IC) with

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Correspondence: Michaela Fontenay, Service d'Hématologie Biologique, GH Broca-Cochin-Hôtel-Dieu, and Institut Cochin, 27 rue du Fg St Jacques 75014 Paris, France. Phone: international +33.158412005. Fax: international +33.158411995. Email: michaela.fontenay@inserm.fr

anthracycline-cytarabine. Among 148 of 158 evaluable patients, 85 achieved complete remission (CR). Informed consent was obtained from all patients in accordance with the Declaration of Helsinki. This study was approved by the Paris Centre ethics committee (number 2346). Main patients' characteristics are summarized in Table 1.

Genotyping

Analysis of *TET2* sequence variations was performed by direct sequencing of the PCR products.[2] Germinal DNA or DNA after complete remission were unavailable. Frameshifts or nonsense mutations, mutations in splice site, insertions and missense mutations affecting the conserved regions only were considered. Single nucleotide polymorphisms (SNP) either previously published or recorded in the National Center for Biotechnology Information SNP database (*www.ncbi.nih.gov/projects/SNP*) were excluded. *NPM1*, *FLT3-ITD* or *FLT3-D835*, *N/K-RAS* ex1/2, *CKIT-D816V* and *WT1* ex7/9 mutations were identified as recommended by Dohner *et al.*[11]

Statistical analysis

Complete remission rate was scored according to Cheson *et al.*[12] Continuous and dichotomic variables were compared with the Wilcoxon's and Fisher's exact tests, respectively. Overall survival was estimated using the Kaplan-Meier method and compared with the log rank test. All tests were two-sided and $P<0.05$ was considered significant.

Results and Discussion

The *TET2* gene was sequenced in 247 patients with sAML (MRC-AML n=201, TR-AML n=46). Diagnosis of MRC-AML was based on a past history of MDS, MPN or MPN/MDS in 95, a cytogenetics of MDS in 56, and/or multilineage dysplasia (MD) in 48 patients, respectively. Only 9 patients met the diagnosis of MRC-AML with MD as unique criteria (i.e. no antecedent of MDS, MPN or MPN/MDS and a normal karyotype). Excluding variations corresponding to SNP allowed the identification of 69 abnormalities in 49 (19.8%) patients, including 29 frameshifts inducing a stop codon, 24 nonsense mutations, 2 insertions, 2 mutations at a splice site, and 12 missense mutations in conserved domains. Most of these have been previously reported.[8,9,13] As already shown, mutations spread throughout the coding sequence (*Online Supplementary Figure S1*). Only 5 of 69 mutations (7%) were recurrent, and 20 of 49 (40%) patients had two anomalies (*Online Supplementary Table S1*). The overall frequency of *TET2* mutations was comparable to that reported in smaller cohorts of AML or *de novo* AML.[8,9] However,

Table 1. Clinical and biological characteristics of patients with secondary AML according to *TET2* status.

	All	WT *TET2*	Mutated *TET2*	*P*
Number	247	198	49	
Age [IQR] (year)	66 [57-74]	65 [54-73]	71 [64-80]	<0.001
Sex ratio M/F	1.6	1.4	2.8	0.051
Hemogram median [IQR]				
Hb (g/dL)	9.1 [7.9-10.0]	8.9 [7.9-9.8]	9.6 [8.5-9.8]	0.013
MCV (fl)	95 [88-101]	96 [90-103]	90 [88-95]	<0.001
Leukocytes (10^9/L)	7.8 [3.0-36.5]	6.7 [2.9-23.0]	20.3 [6.0-98.9]	<0.001
Neutrophils (10^9/L)	1.1 [0.6-3.7]	1.0 [0.5-3.0]	2.8 [0.9-8.0]	0.012
Monocytes (10^9/L)	0.4 [0.1- 2.2]	0.2 [0.1-1.3]	2.1 [0.4-4.2]	<0.01
Platelets (10^9/L)	52 [34-113]	64 [36-123]	39 [29-64]	<0.01
Peripheral blood blasts (%)	31 [9-59]	29 [8-53]	40 [17-67]	0.054
Bone marrow blasts (%)	49 [30-69] 50	[33-69]	44 [30-64]	0.568
Multilineage dysplasia (%)	65	65	63	0.861
Karyotype n (%)				
Normal	69 (28)	44 (22)	25 (51)	<0.001
Monosomal	67 (27)	61 (30)	6 (12)	0.012
≥ 3 anomalies	96 (39)	87 (40)	9 (18)	<0.001
Recurrent balanced structural anomalies	25 (10)	23 (12)	2 (4)	0.117
WHO n (%)				
Myelodysplasia-related changes	201(100)	156 (78)	45 (22)	
Therapy-related	46 (100)	42 (91)	4 (9)	0.035
Treatments n (%)	225	180	45	
Best supportive care	51 (23)	38 (21)	13 (29)	0.238
Hypomethylating agents	9 (4)	8 (4)	1 (2)	0.181
Intensive chemotherapy	158 (70)	128 (71)	30 (67)	0.795
AlloSCT	22 (10)	19 (11)	3 (7)	<0.05
Others	7 (3)	6 (3)	1 (2)	-
Complete remission rate (%)*	57 (85/148)	58 (68/118)	56 (17/30)	0.817
Overall survival (median/mos)*	10.9	11.0	9.3	0.461

*All patients had a karyotype. For P values, quantitative and dichotomic variables were compared with Wilcoxon's and Fisher's exact test, respectively. *CRR and overall survival in the group of 148 patients having received intensive chemotherapy +/- alloSCT are indicated. IQR: interquartile range.*

Table 2. Frequencies of classical molecular events according to *TET2* status. (A) MRC or TR-AML. (B) AML with normal karyotype (NK). Mutations or SNP for WT1 exon 7/9. Fisher's exact test for *P* value.

A

MRC or TR-AML	Tested patients (n)	Anomalies n (%)	WT *TET2* n (%)	Mutated *TET2* n (%)	*P*
NPM1	148	16 (11)	8 (7.8)	8 (17.8)	0.070
FLT3-ITD or D835	218	26 (12)	17 (10)	9 (18.7)	0.090
N or K-*RAS*	151	32 (21)	23 (21.5)	9 (20.5)	0.790
CKIT D816	156	2 (1.3)	1 (1.0)	1 (2.2)	-
WT1 exon 7/9	153	44 (29)			
mutation		5 (3)	2 (1.8)	3 (6.8)	0.143
SNP		39 (25)	30 (27)	9 (20)	0.846

B

NK-AML	Tested patients (n)	Anomalies n (%)	WT *TET2* n (%)	Mutated *TET2* n (%)	*P*
NPM1	51	13 (25)	8 (29)	5 (22)	0.749
FLT3-ITD or D835	66	14 (21)	7 (17)	7 (29)	0.348
N or K-*RAS*	50	14 (28)	9 (33)	5 (22)	0.528
CKIT D816	50	0 (0)	0 (0)	0 (0)	-
WT1 exon 7/9	49	12 (24)			
mutation		3 (6)	1 (4)	2 (9)	0.594
SNP		9 (18)	4 (15)	5 (22)	0.716

a recent study including 783 patients with AML aged 16 to 60 years showed a lower frequency (7.6%) than that observed in our cohort in which the median age was 66 years (range 57-74).[14]

Clinical and biological characteristics of patients harboring a *TET2* mutation are described in Table 1. Mutated patients were more frequently male than female (P=0.051) and were significantly older than other patients (71 years *vs.* 65 years; P<0.001) suggesting that *TET2* mutations could be linked to aging. *TET2* mutations were associated with significantly higher Hb level (9.6 *vs.* 8.9 g/dL; P=0.013), higher leukocyte (20.3 *vs.* 6.7×10^9/L; P=0.002), neutrophil (2.8 *vs.* 1.0×10^9/L; P=0.012) and monocyte (2.1 *vs.* 0.2×10^9/L; P<0.01) counts, and a lower MCV (89.7 *vs.* 96 fL; P<0.001) and platelet count (39 *vs.* 64×10^9/L; P=0.003). Percentages of blast cells in blood or bone marrow were the same in the two groups. Older age and high monocyte count have been previously reported in *TET2* mutated MPN, or MDS/MPN.[5,15] We found no difference in FAB subtype, and MD frequency was the same in the two groups. In contrast, the frequency of *TET2* mutations was significantly lower in TR-AML (8%) than MRC-AML (22%; P=0.035). Patients with TR-AML had poor prognostic factors (high leukocyte count, circulating or BM blasts, abnormal karyotype, *FLT3* mutations) and a 5.5-month median overall survival (OS), compared to MRC-AML (median OS 11 months, *Online Supplementary Table S2*).

In the whole cohort (n=247), 69 (28%) patients had a normal karyotype (NK). The percentage of patients with NK was significantly higher in the *TET2* mutated group (25 of 49; 51%) than in the non-mutated group (44 of 198; 22%) (P<0.001). The association with normal karyotype has not been reported in MDS or in *de novo* AML. The presence of a monosomal or a complex (≥ 3 anomalies) karyotype was less frequent in the *TET2* mutated group (P=0.012 and P<0.0001, respectively). Recurrent translocations were uncommon (26 of 247; 10.5%). Strikingly, only 2 *TET2* mutated patients presented a known recurrent chromosome anomaly, both of them involving the 3q26 region. Thus, *TET2* mutations did not associate with cytogenetic abnormalities. In NK patients, *TET2* mutations also associated with older age (68 *vs.* 60 years; P=0.024), higher Hb level (9.9 *vs.* 9.0 g/dL; P=0.018) and leukocyte count (19.9 *vs.* 5.7×10^9/L; P=0.024), and a lower platelet count (44 *vs.* 70×10^9/L; P=0.048). These results suggest that the significant changes in biological parameters of *TET2* mutated patients are independent of cytogenetic abnormalities.

We looked at classical AML mutations in 148 cases for *NPM1*, 218 for *FLT3-ITD* and *FLT3-D835*, 151 for N or K-*RAS*, 156 in *CKIT-D816V* and 153 for *WT1* exon 7/9 at diagnosis (Tables 2A and B). Except for N or K-*RAS* mutations, which were observed at the same frequency in secondary and *de novo* AML, other mutations were less common in sAML than expected from the analysis of *de novo* AML cohorts. Our data are consistent with the frequencies reported in sAML.[16] In the cohort of patients with MRC or TR-AML, we found no difference in the repartition of *FLT3-ITD* or *FLT3-D835* [17 of 170 (10%) *vs.* 9 of 48 (18.7%)], N or K-*RAS* [23 of 107 (21.5%) *vs.* 9 of 44 (20.5%)], or *WT1* [2 of 109 (1.8%) *vs.* 3 of 44 (6.8%)] mutations between *TET2* non-mutated and mutated groups, respectively (Table 2A). Although *NPM1* associated with TET2 mutations in *de novo* AML,[9] this link did not reach statistical significance in our series [8 of 103 (7.8%) *vs.* 8 of 45 (17.8%); P=0.070] or in the mixed *de novo* and sAML cohort reported by others.[8] *CKIT-D816V* mutations are rare in AML. However, they appeared to be more frequent in *TET2* mutated patients as reported in systemic mastocytosis.[17] In NK patients, *TET2* was not associated with *NPM1* or *FLT3-ITD* or *FLT3-D835* mutations (Table 2B). In TR-AML, *TET2* mutations are rare (8%) compared to TP53 mutations which are detected in more than 20% of patients, as previously reported.[18]

Information on treatment was available for 225 (91%) patients. Treatment was best supportive care (n=51), hypomethylating agents (n=9), IC (n=158) followed by alloSCT (n=22), others (n=7). There was no difference in the repartition of treatments between mutated and wild-type patients, except for alloSCT which was less frequent in the *TET2* mutated group, probably because of older age (P<0.05; Table 1).

In the group of 158 patients treated with intensive chemotherapy, mutated patients had the same clinical and biological features as mutated patients in the whole cohort. The rate of complete remission was 57% (85 of 148 evaluable patients). Early death after induction was observed in 4 patients (3 wild-type and one mutated). There was no difference in complete remission rate between *TET2* mutated and wild-type patients (Fisher's exact test P=0.817). When the analysis was restricted to MRC-AML, *TET2* status did not influence the complete remission rate (P=0.319). With a median follow up of 12.4 months, median overall survival from diagnosis was 11 months in wild-type (n=129) and 9.3 months in mutated patients (n=30; P=0.461). Although the median follow up was short, the size of the cohort allowed a Kaplan-Meier analysis to be performed which demonstrated that *TET2* mutations had no predictive value on overall survival in

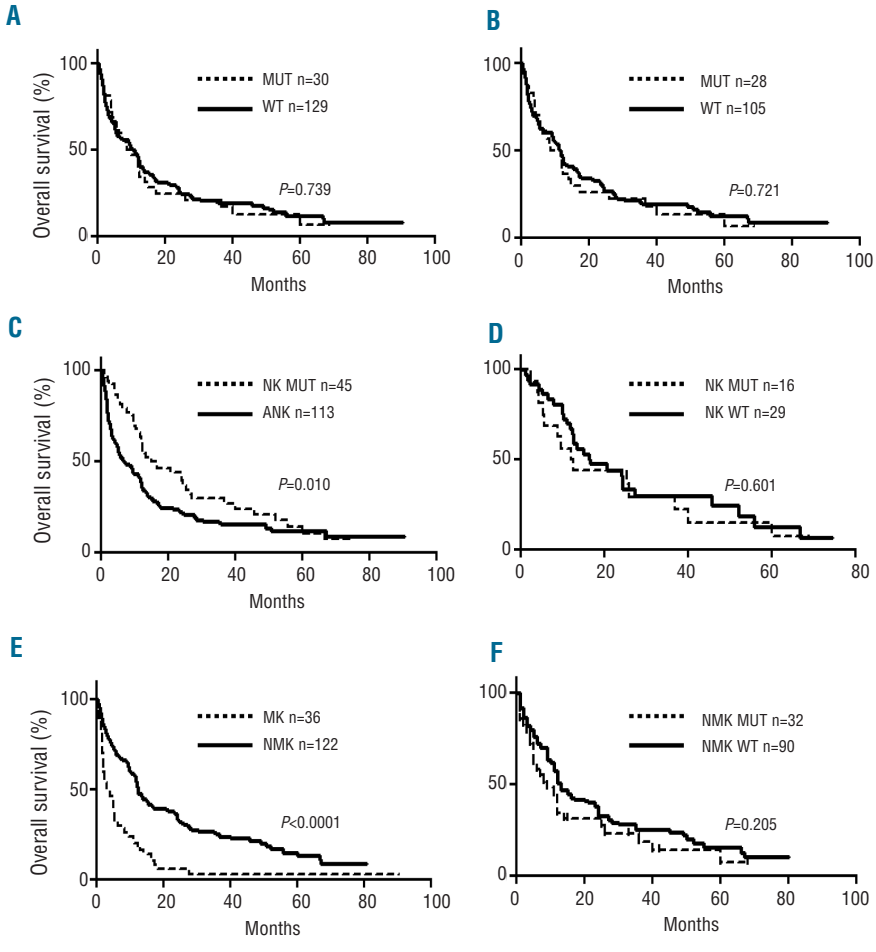

Figure 1. Overall survival. (A) and (B) impact of *TET2* mutation in MRC-AML or TR-AML (A) and MRC-AML (B). (C) Impact of normal karyotype. (D) Impact of *TET2* in AML with normal karyotype. (E) Impact of monosomal karyotype. (F) Impact of *TET2* on non-monosomal karyotype AML. MUT: mutated *TET2*; WT: wild-type *TET2*; NK: normal karyotype; ANK: abnormal karyotype; MK: monosomal karyotype; NMK: non-monosomal karyotype. Log rank test for *P* value.

the group of patients with MRC-AML or TR-AML treated with intensive chemotherapy (log rank test; *P*=0.739; HR 1.04 [95% CI: 0.71–1.52]) (Figure 1A). In addition, *TET2* mutations had no impact on overall survival in the group of MRC-AML (Figure 1B), while their impact in TR-AML could not be analyzed.

Finally, we looked at overall survival in AML treated by intensive chemotherapy depending on the presence of either a normal or a monosomal karyotype (MK) according to Breems *et al.*[19] NK improves overall survival (Figure 1C) and *TET2* had no impact on overall survival in NK AML (Figure 1D). MK was a very poor prognostic factor (Figure 1E). Although the median overall survival was three months in wild-type *TET2* patients (n=46) and 11.4 months in mutated *TET2* patients (n=4) with MK, the trend to better survival of *TET2* mutated patients was not significant (*P*=0.305), possibly because of the small size of the MK subgroup (Figure 1F). These results are consistent with two reports showing that overall survival was independent of *TET2* status[6,9] and differ from the findings of Abdel-Wahab *et al.* which demonstrated an unfavorable impact.[8]

In conclusion, the frequency of *TET2* mutations appears to be higher in sAML than in *de novo* AML and associated with MRC-AML rather than TR-AML. They did not associate with other mutations reported as prognostic factors in AML or modify the poor prognosis of sAML.

Authorship and Disclosures

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