LYMPHOID NEOPLASIA

SET-NUP214 is a recurrent γδ lineage-specific fusion transcript associated with corticosteroid/chemotherapy resistance in adult T-ALL

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Key Points

- *SET-NUP214* is a recurrent (6%) γδ lineage-specific fusion transcript in adult T-ALL.
- *SET-NUP214* is strongly associated with corticosteroid and chemotherapy resistance but does not negatively influence clinical outcome.

The *SET-NUP214* (*TAF1/CAN*) fusion gene is a rare genetic event in T-cell acute lymphoblastic leukemia (T-ALL). Eleven (6%) of 196 T-ALL patients enrolled in the French Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) 2003 and 2005 trials harbored a *SET-NUP214* transcript. *SET-NUP214*–positive patients were predominantly (10 [91%] of 11) T-cell receptor (TCR)–negative and strikingly associated with TCRγδ lineage T-ALLs, as defined by expression of TCRγδ, TCRδ and/or TCRγ rearrangements but no complete *TCRβ* variable diversity joining rearrangement in surface CD3/TCR-negative cases. When compared with *SET-NUP214*–negative patients, *SET-NUP214*–positive patients showed a significantly higher rate of corticosteroid resistance (91% vs 44%; *P* = .003) and chemotherapy resistance (100% vs 44%; *P* = .0001). All *SET-NUP214*–positive patients but one achieved complete remission, and 9 were allografted. Despite the poor early-treatment sensitivity, the outcome of *SET-NUP214*–positive patients was similar to that of *SET-NUP214*-negative patients. (*Blood*. 2014;123(12):1860-1863)

Introduction

T-cell acute lymphoblastic leukemia (T-ALL) accounts for 25% of adult and 10% of pediatric ALL.[1,2] Over the last decade, great progress has been made toward the identification of molecular genetic abnormalities in T-ALL.[3] Proto-oncogene activation by promoter/enhancer substitution (*TLX1/3*, *TAL1/2, LMO1/2, MYB,* and *CCND2*) or gene mutations (*NOTCH1, FBXW7, WT1,* and *RAS*) are frequent events in T-ALL,[3] whereas chromosomal translocations leading to fusion genes are relatively rare.[4] *PICALM-MLLT10* (also known as *CALM-AF10*) and *MLL* rearrangements are the most frequent fusion proteins in T-ALL, in which they are specific to the T-cell receptor γδ (TCRγδ) lineage and lead to overexpression of *HOXA* genes.[5-7] The *SET-NUP214* (*TAF1/CAN*) fusion gene resulting from either cryptic t(9;9)(q34;q34) or del(9)(q34.11q34.13) was first described in a patient with acute undifferentiated leukemia,[8] then in 1 patient with acute myeloid leukemia (AML),[9] and also in a very limited number of pediatric[10-12] and adult T-ALLs.[10,13-16] *SET-NUP214,* similar to *MLL* and *CALM-AF10* rearrangements, contributes to T-ALL pathogenesis, at least in part by transcriptional activation of *HOXA* genes.[12,14] However, since few *SET-NUP214*–positive T-ALL patients have been reported to date, their clinicobiologic features have not been fully determined. These patients were suggested to have a poor prognosis, but this is based on sporadic reports and has not been evaluated within the context of prospective clinical trials. We therefore undertook to evaluate the frequency, clinical, and biologic characteristics of patients with *SET-NUP214*–positive T-ALL and the prognostic significance of *SET-NUP214*–positive T-ALL in a consecutive series of 196 adult patients with T-ALL enrolled in the Group for Research

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Table 1. Characteristics of *SET-NUP214*–positive and *SET-NUP214*–negative adult T-ALL patients enrolled in the GRAALL 2003 and 2005 trials

	Total			*SET-NUP214*–positive			*SET-NUP214*–negative			
	No.	%	95% CI	No.	%	95% CI	No.	%	95% CI	*P*
Total	196			11	6		185	94		
TCR subsets analyzed										
IM0	10			0			10			N/S
IMδ or IMγ	37			9			28			<.0001*
IMβ or pre-αβ	89			1			88			.004*
TCRαβ-positive	18			0			18			N/S
TCRγδ-positive	23			1			22			N/S
N/A	19			0			19			
ETP phenotype										
Yes	38			5			33			.053
No	144			6			138			
N/A	14			0			14			
Genotype subsets analyzed										
CALM-AF10	8			0			8			N/S
SIL-TAL1	16			0			16			N/S
TLX1	41			0			41			N/S
TLX3	25			0			25			N/S
None of the above	106			11			95			.001*
NOTCH1 and/or *FBXW7* mutation	133			4			129			.04*
Clinical subsets analyzed										
Male sex	151			10			141			N/S
Median age, y	30			32			30			N/S
Age ≥35 y	81			5			76			N/S
Median WBC × 10^9/L	35.5			30.4			36.8			N/S
WBC >100 × 10^9/L	53			2			51			N/S
CNS involvement	20			2			18			N/S
Response to treatment and clinical outcome										
Cs	105			1			104			.003*
CHs	104			0			104			.0001*
CR	183			10			173		N/S	
EFS at 3 y		58	51-65		45	16-70		59	55-66	N/S
OS at 3 y		68	61-74		73	45-90		68	65-74	N/S
SCT	75			9			66			.003*
EFS at 2 y posttransplantation		64	55-74		63	23-87		64	54-75	N/S
OS at 2 y posttransplantation		73	63-82		76	43-93		73	60-82	N/S

CHs, chemotherapy sensitive; CI, confidence interval; CNS, central nervous system; Cs, corticosteroid sensitive; N/A, not available; N/S, not significant; SCT, stem cell transplantation; WBC, white blood cell count.

*$P < .05$.

on Adult Acute Lymphoblastic Leukemia (GRAALL) 2003 and 2005 trials.

Study design

Between November 2003 and May 2010, 264 adult T-ALL patients were randomized in the consecutive GRAALL 2003 and 2005 (NCT00327678) trials.[1,17] This study concerns 196 (74%) of these patients, for whom diagnostic complementary DNA was available for *SET-NUP214* screening by reverse-transcriptase polymerase chain reaction (RT-PCR), as described.[12] These 196 patients were representative of the overall GRAALL T-ALL population, with a 3-year overall survival (OS) of 66% vs 68% ($P = .84$; supplemental Table 1). This study was approved by local and multicenter research ethical committees and by the institutional review board of the French Regulatory Agency. This study was conducted in accordance with the Declaration of Helsinki.

Within GRAALL studies, corticosteroid-resistant patients (Cr) are defined by an absolute number of circulating blasts >10^9/L after 7 days of prednisone. Chemotherapy-resistant patients (CHr) are those with circulating blasts or >5% of bone marrow blasts after 1 week of chemotherapy. Patients who demonstrated either corticosteroid or chemotherapy resistance (Cr/CHr) were allografted in first complete remission (CR). Complete methods and GRAALL protocols are described in the supplemental Data.

Results and discussion

Incidence, baseline clinical characteristics, and genetic features of *SET-NUP214*–positive adult T-ALL patients

SET-NUP214 was detected by RT-PCR analysis in 11 patients (6%), 5 of whom had available single nucleotide polymorphism 6.0 array data (supplemental Figure 1) showing del(9)(q34.11q34.13). This incidence (6%) is relatively similar to that previously reported.[13,14] Baseline characteristics of *SET-NUP214*–positive and *SET-NUP214*–negative T-ALL patients were not significantly different (Table1). *SET-NUP214* was mutually exclusive with *CALM-AF10*, *SIL-TAL*, *TLX1,* or *TLX3* overexpression (Table 1). *NOTCH1* and/or *FBXW7* mutations were seen in 36% of *SET-NUP214*–positive compared with 70% of *SET-NUP214*–negative T-ALL patients ($P = .04$). As expected,[12] all *SET-NUP214*–positive T-ALL samples overexpressed

Table 2. Characteristics, response to treatment, and clinical course of *SET-NUP214*–positive T-ALL patients

UPN	Sex	Age, y	WBC × 10^9/L	CNS involvement	ETP-ALL	Cs	CHs	Clinical course
7468	M	34	30.4	No	Yes	No	No	CR, relapse, CR, SCT, died 49 m
8352	F	37	8.6	No	Yes	No	No	CR, SCT, alive 64 m
9322	M	29	10.1	No	Yes	No	No	CR, relapse, CR, SCT, alive 44 m
9766	M	41	18.4	No	Yes	No	No	CR, SCT, alive 46 m
9848	M	23	604.4	Yes	No	Yes	No	Non-CR, died 5 m
10020	M	30	24.9	No	No	No	No	CR, SCT, relapse, CR, alive 66 m
10643	M	36	181.8	Yes	No	No	No	CR, SCT, alive 24 m
10806	M	45	50.8	No	No	No	No	CR, alive 33 m
10884	M	38	2.8	No	Yes	No	No	CR, SCT, died 9 m
11031	M	28	41.8	No	No	No	No	CR, SCT, alive 30 m
11126	M	20	30.9	No	No	No	No	CR, SCT, alive 28 m

F, female; M, male; m, minutes; SCT, stem-cell transplantation; UPN, unique patient number.

HOXA9 transcripts (*HOXA9/ABL1*: median, 227%; range, 65% to 1800%).

Conventional cytogenetic data of *SET-NUP214*–positive T-ALL patients showed 9 abnormal karyotypes, 5 of which were complex (supplemental Table 2). Strikingly, we observed del(12p) and 5q aberrations in 4 patients, including 3 with both abnormalities. Likewise, 2 patients had concomitant del(6q), del(11q), and del(12p).

Immunophenotype and TCR genotype

All *SET-NUP214*–positive T-ALLs but 1 had an immature (IM) immunophenotypic profile with no cytoplasmic TCRβ (cTCRβ) or surface CD3/TCR (sCD3/TCR) expression (supplemental Table 3). They showed TCRδ only (IMδ; n = 2) and/or TCRγ (IMγ; n = 7) rearrangements but no complete variable diversity joining (VDJ) TCRβ by genomic PCR. One patient harbored a VDJ TCRβ rearrangement and thus was classified as IMβ. When compared with *SET-NUP214*–negative T-ALL patients, *SET-NUP214*–positive patients were strikingly associated with an IMδ or IMγ (IMδ/γ) genotype (82% vs 17%; $P < .0001$; Table 1). All 10 patients without TCR rearrangements (IM0) were *SET-NUP214*–negative. The single mature $sCD3^+$ *SET-NUP214*–positive T-ALL expressed TCRγδ, whereas none of the TCRαβ-positive or pre-αβ T-ALL patients were *SET-NUP214*–positive. We therefore undertook to determine whether IMδ/γ *SET-NUP214*–positive could represent TCRγδ precursor T-ALLs. We previously showed that a $CD5^+CD2^-$ phenotype is particularly common in TCRγδ-positive T-ALL patients (53%) compared with only 7% of TCRαβ-lineage T-ALL patients.[5] We also showed that *CALM-AF10* in T-ALL is specific to the TCRγδ lineage and that the $CD5^+CD2^-$ phenotype was much more frequent in IMδ/γ *CALM-AF10*–positive compared with IMδ/γ *CALM-AF10*–negative patients, suggesting that this phenotype may identify TCRγδ precursors.[5] Interestingly, 7 of 9 IMδ/γ *SET-NUP214*–positive patients in this series were $CD5^+CD2^-$. Secondly, TCRδ rearrangements in IMδ/γ *SET-NUP214*–positive patients, like IMδ/γ *CALM-AF10*–positive patients, were predominantly Dδ2-Jδ1, indicative of T-lymphoid lineage restriction.[18,19] In addition, TCRγ rearrangements involved the functional Vγfl/Vγ9 segments in the majority of IMδ/γ *SET-NUP214*–positive patients. These TCR profiles reinforce the immunophenotypic evidence of a TCRγδ lineage origin for immature *SET-NUP*–positive T-ALLs.

Seven (78%) of our 9 IMδ/γ *SET-NUP214*–positive T-ALL patients expressed stem cell and myeloid markers (supplemental Table 3). In keeping with our data, all 6 previously reported adult *SET-NUP214*–positive T-ALL patients with an available phenotype were $CD34^+$, $CD13^+$, and/or $CD33^+$.[10,13,15] Coustan-Smith et al[20] defined a very high-risk subgroup of pediatric T-ALLs as early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) on the basis of its associated distinctive immunophenotype ($CD1a^-$, $CD8^-$, $CD5^{weak}$ with stem cell and/or myeloid markers). Five of 11 of our *SET-NUP214*–positive T-ALLs met these ETP-ALL criteria[20] (Table 1 and supplemental Table 3), and *SET-NUP214*–positive T-ALLs were more often ETP-ALL (45%) than *SET-NUP214*–negative T-ALLs (19%; Table1). The poor prognosis of ETP phenotype, however, is increasingly contested in adult[21] and even pediatric T-ALL.[22]

We performed *SET-NUP214* RT-PCR screening in 22 AML overexpressing *HOXA* genes, including 5 minimally differentiated AML (French-American-British AML-M0) patients. One AML-M0 patient was *SET-NUP214*–positive. Importantly, this patient was $CD7^+$ (but $cCD3^-$) and showed TCRδ and TCRγ rearrangements (supplemental Figure 2). Taken together, these data demonstrate that *SET-NUP214* is permissive of a certain degree of TCRγδ lineage differentiation while maintaining myeloid features.

Treatment response and outcome of *SET-NUP214*–positive T-ALL patients

When compared with *SET-NUP214*–negative patients, *SET-NUP214*–positive patients showed a significantly higher rate of Cr (91% vs 44%; $P = .003$) and CHr (100% vs 44%; $P = .0001$; Table 1). This strong association of *SET-NUP214* with Cr/CHr remained statistically significant (odds ratio, 2.287; 95% confidence interval, 1.37 to 6.85; $P = .003$) after adjusting for white blood cell count ($>100 \times 10^9$/L) and age (≥ 35 years).

All *SET-NUP214*–positive patients but 1 achieved CR, and 9 were allografted (Table 2). Despite their very poor initial sensitivity to induction treatment, the event-free survival (EFS) and OS at 3 years of *SET-NUP214*–positive patients were not significantly different from those of *SET-NUP214*–negative patients (45% vs 59%; $P = .52$ for EFS and 73% vs 68%; $P = .86$ for OS) (Table 1 and supplemental Figure 3). Similarly, EFS and OS following transplantation were comparable for *SET-NUP214*–positive and *SET-NUP214*–negative patients (Table 1). Furthermore, the survival of allografted *SET-NUP214*–positive T-ALL patients was similar to that of allografted *SET-NUP214*–negative Cr/CHr patients and of *SET-NUP214*–negative chemotherapy- and corticosteroid-sensitive patients, while nonallografted *SET-NUP214*–negative Cr/CHr patients had a significantly inferior outcome (supplemental Figure 4). In keeping with this, we considered the fact that *SET-NUP214*–positive and *SET-NUP214*–negative T-ALL patients had a similar outcome is most likely due to the benefit of allografting Cr/CHr patients. This is particularly pertinent in the light of evolving evidence suggesting that appropriately targeted allografting in first CR is the best available option

for cure in younger adult high-risk ALL patients.[23] Emerging data also suggest that allogeneic transplantation can be effective in ETP-ALL.[24,25]

In conclusion, our results demonstrate that *SET-NUP214* is a recurrent oncogenic fusion transcript in adult patients with T-ALL and is specific to the TCRγδ lineage. *SET-NUP214* is strongly associated with corticosteroid and chemotherapy resistance but does not negatively influence clinical outcome after allogeneic transplantation.

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Authorship

Contribution: R.B.A., A. Roggy, E.M., and V.A. wrote the manuscript; R.B.A., A. Roggy, A.C., A.T., H.M., and V.A. performed and/or analyzed molecular and cellular data; T.L., A. Renneville, A.B., E.R., D.C., B.L., A.D., C.P., N.I., and H.D. contributed to the sample collection or provided patient data; and V.A. designed and oversaw conceptual development of the project.

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