Oncogenetic landscape and clinical impact of IDH1 and IDH2 mutations in T-ALL

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Abstract
IDH1 and IDH2 mutations (IDH1/2Mut) are recognized as recurrent genetic alterations in acute myeloid leukemia (AML) and associated with both clinical impact and therapeutic opportunity due to the recent development of specific IDH1/2Mut inhibitors. In T-cell acute lymphoblastic leukemia (T-ALL), their incidence and prognostic implications remain poorly reported. Our targeted next-generation sequencing approach allowed comprehensive assessment of genotype across the entire IDH1 and IDH2 locus in 1085 consecutive unselected and newly diagnosed patients with T-ALL and identified 4% of, virtually exclusive (47 of 49 patients), IDH1/2Mut. Mutational patterns of IDH1/2Mut in T-ALL present some specific features compared to AML. Whereas IDH2R140Q mutation was frequent in T-ALL (25 of 51 mutations), the IDH2R172 AML hotspot was absent. IDH2 mutations were associated with older age, an immature phenotype, more frequent RAS gain-of-function mutations and epigenetic regulator loss-of-function alterations (DNMT3A and TET2). IDH2 mutations, contrary to IDH1 mutations, appeared to be an independent prognostic factor in multivariate analysis with the NOTCH1/FBXW7/RAS/PTEN classifier. IDH2Mut were significantly associated with a high cumulative incidence of relapse and very dismal outcome, suggesting that IDH2-mutated T-ALL cases should be identified at diagnosis in order to benefit from therapeutic intensification and/or specific IDH2 inhibitors.

Keywords: IDH1, IDH2, T-ALL

Introduction
T-cell acute lymphoblastic leukemia (T-ALL) is aggressive neoplasms resulting from the proliferation of T-lymphoid progenitors blocked at thymic stages of differentiation and account for 15% and 25% of pediatric and adult ALLs, respectively [1]. T-ALL is associated with a wide range of acquired genetic abnormalities that contribute to developmental arrest and abnormal proliferation [2]. Although intensive treatment protocols have markedly improved the outcomes of children with T-ALL, cure rates remain below 60% for adults and 85% for children [3–5]. The prognosis is particularly poor in relapsing patients, justifying the development of novel targeted therapies [6, 7]. For example, alterations affecting epigenetic factors may offer novel targeted therapeutic approaches in high-risk T-ALL [8].

Whole-genome sequencing of AML identified acquired mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) [9]. These paralogous genes encode two enzymes with distinct localizations (cytoplasmic for IDH1 and mitochondrial for IDH2). Both catabolize the conversion of isocitrate to α-ketoglutarate (α-KG). Gain-of-function IDH1/2 mutations (IDH1/2Mut) confer a neomorphic activity on the encoded enzymes, leading to the
conversion of α-KG to 2-hydroxyglutarate (2-HG) in a NAD phosphate-dependent manner [10]. Accumulation of the oncometabolite 2-HG induces multiple cellular alterations, including chromatin methylation and cellular differentiation, by inhibiting α-KG-dependent enzymes related to DNA methylation, such as Tet oncogene family members (TET2, TET3) [11]. IDH1/2Mut have been reported in 10 to 20% of AML cases, when they are predominantly located in the active site of the enzyme (IDH1R132, IDH2R140Q and IDH2R172). IDH1/2Mut in AML are associated with prognostic impact influenced by the genetic context [12, 13]. Importantly, specific drugs targeting mutant IDH1 or IDH2 have recently shown promise in IDH1/2Mut refractory or relapsed AML patients [14, 15].

In T-ALL, IDH1/2Mut have been partially explored and their prognostic impact poorly reported [16, 17]. We now provide the first comprehensive analysis and oncogenic landscape of IDH1/2Mut in a cohort of 1085 T-ALL patients, when the nearly 4% of IDH1/2Mut are associated with extremely poor prognosis, specifically in IDH2-mutated cases.

**Methods**

**Patient’s protocol and clinical trials**

Diagnostic peripheral blood or bone marrow samples from 1085 adults and children with T-ALL were analyzed after informed consent was obtained at diagnosis according to the Declaration of Helsinki. Among the 1085 T-ALL analyzed, 215 adult patients aged from 16–59 years were included in the GRAALL03/05 trials (details provide in supplementary) which were registered at clinicaltrials.gov (GRAALL-2003, #NCT00222027; GRAALL-2005, #NCT00327678). and 261 pediatric patients aged from 1 to 19 years were treated in 10 French pediatric hematology departments, members of the FRALLE study group, according to the FRALLE 2000 T guidelines (Additional file 2: Fig. S5 and Additional file 1: Table S3).

**Gene mutation screening**

A custom capture Nextera XT gene panel (Illumina, San Diego, CA) targeting all coding exons and their adjacent splice junctions of 80 genes was designed, based on available evidence in hematological neoplasms (Additional file 1: Table S1). DNA Libraries were prepared using Nextera Rapid Capture Enrichment protocol and underwent 2 × 150 bp paired-end sequencing on Illumina MiSeq sequencing system with MiSeq Reagent Kit v2 (Illumina). Briefly, sequence reads were filtered and mapped to the human genome (GRCh37/hg19) using in-house software (Polyweb, Institut Imagine, Paris). Annotated variants were selected after filtering out calls according to the following criteria: (1) coverage < 30×, < 10 alternative reads or variant allelic fraction (VAF) < 7%; (2) polymorphisms described in dbSNP, 1000Genomes, EVS, Gnomad and EXAC with a calculated mean population frequency > 0.1%. Non-filtered variants were annotated using somatic database COSMIC (version 78) and ProteinPaint (St Jude Children’s Research Hospital – Pediatric Cancer data portal). Lollipop plots were generated with ProteinPaint (https://pecan.stjude.org/#/proteinpaint).

**Immunophenotypic and molecular characterization of T-ALL samples**

Peripheral blood or bone marrow T-ALL samples were analyzed for immunophenotype, fusion transcripts (SILTALI, CALM-AF10), oncogenic transcripts (HOXA9, TLX1 and TLX3) and T-cell receptor (TCR) recombination and NOTCH1/FBXW7/RAS/PTEN mutations, as previously described [4, 18, 19].

**Minimal residual disease assessment**

Immunoglobulin/T-cell receptor (Ig/TCR) gene rearrangement-based Minimal Residual Disease (MRD) evaluation was centrally assessed for patients who reached complete remission after the first induction cycle, on BM samples after induction (MRD1). MRD was centrally assessed by real-time quantitative allele-specific oligonucleotide PCR and interpreted according to EuroMRD group guidelines [20–22].

**Statistical analysis**

Comparisons for categorical and continuous variables between IDH1Mut or IDH2Mut and IDHW7 subgroups were performed with Fisher’s exact test and Mann–Whitney test, respectively. Overall survival (OS) was calculated from the date of diagnosis to the last follow-up date censoring patients alive. The cumulative incidence of relapse (CIR) was calculated from the complete remission date to the date of relapse censoring patients alive without relapse at the last follow-up date. Relapse and death in complete remission were considered as competitive events. Univariate and multivariate analyses assessing the impact of categorical and continuous variables were performed with a Cox model. Proportional-hazards assumption was checked before conducting multivariate analyses. In univariate and multivariate analyses, age and log10(WBC) were considered as continuous variables. All analyses were stratified on the trial. Variables with a p value less than 0.1 in univariate analysis were included in the multivariable models. Statistical analyses were performed with STATA software (STATA 12.0 Corporation,
Results and discussion

Incidence of IDH1 and IDH2 mutations in 1085 T-ALL

A total of 51 (4%) mutations, mainly clonal, in either IDH1 or IDH2 were apparent in 49 cases (Fig. 1a and Additional file 1: Table S2, Additional file 2: Figs. S2, S3, S4). The red curve represents the IDH2-mutated patients, the green curve the IDH1-mutated patients and the black curve the IDHWT patients.

Fig. 1 IDH1 and IDH2 mutations in the GRAALL03/05 and FRALLE2000 studies. a Lollipop plots indicating the observed mutations for each IDH gene and their consequences. b Oncoplot depicting the genetic anomalies observed in IDH1/2-Mutated or Wild type T-ALL cases of the GRAALL03/05 and FRALLE2000 studies. Genes are classified by functional groups. The right panel indicates the overall frequency of alterations per gene. c The circos plots depict the co-occurrences in genetic lesions observed in IDH1 (left panel) and IDH2 mutated T-ALL (right panel). d Clinical impact of IDH1 and IDH2 mutations in the GRAALL03/05 and FRALLE2000 studies. Overall survival (left panel) and cumulative incidence of relapse (right panel). The red curve represents the IDH2-mutated patients, the green curve the IDH1-mutated patients and the black curve the IDHWT patients.
S3). IDH1 mutations were identified in 19 T-ALL cases (2%) and IDH2 mutations in 32 cases (3%). IDH1/2**Mut** were mutually exclusive except in 2 cases. The IDH2**R140Q** mutation was the most prevalent mutation affecting IDH2 (n = 25, 78%). We identified 7 IDH1 mutations located in the R132 hotspot (37% of IDH1 mutations), 3 cases with IDH1**R132C** mutation, 2 with IDH1**R132S**, 1 with IDH1**R132H** and IDH1**R132G** mutation. The most common IDH2 mutations in AML occur at R140 followed by residue IDH2**R172**. The latter mutation is virtually the only IDH mutation found in angio-immunoblastic T cell lymphoma, reported in about 30% of cases (Additional file 2: Fig. S1) [23]. IDH2**R172** mutation has also been rarely and inconsistently described in peripheral T-cell lymphoma not otherwise specified (NOS) with T- follicular helper (T<sub>FH</sub>) phenotype [24, 25]. In striking contrast, IDH2**R172** was not reported in our series of T-ALL. IDH1**R132** was the most frequent IDH1 mutation reported in our cohort, has recently been recognized to cooperate with NOTCH1 activation in a T-ALL mouse model [26]. These results highlight the specific consequence associated with IDH1/2**Mut** subtype during immature T-cell development.

**Clinico-biological characteristics of IDH1/2**<sup>**Mut**</sup> in GRAALL and FRALLE-treated T-ALLs**

We then investigated the clinical characteristics linked to IDH1/2**Mut** in a subset of 476 patients, including 215 adults enrolled in the GRAALL-2003/2005 trials and 261 children enrolled in the FRALLE-2000 trial (Table 1 and Supplementary Methods). The incidence of IDH1/2**Mut** in this cohort was 3% (15/476). IDH1 mutations were detected in 5 patients (4 adult and 1 pediatric case), and IDH2 mutations were identified in 10 (6 adult and 4 pediatric cases) (Additional file 2: Fig. S2). IDH2**R140Q** was the most frequent mutation (n = 7, 70%) and was most prevalent in adults’ patients (n = 6/7, 86%). Overall, IDH1/2**Mut** were observed in 5% of adults and 2% of children (p = 0.1).

**IDH1 and IDH2 mutations are associated with both specific clinical and mutational profiles**

Patients with IDH2**Mut** were significantly older than IDH<sub>WT</sub> (median 47.6 years vs 15.0, p = 0.01). IDH2**Mut** were associated with an immature immunophenotype (5/7, 71% vs 83/407, 20%, p = 0.006) and ETP-phenotype (3/5, 60% vs 52/298, 17%, p = 0.04). In line with this, IDH2**Mut** correlated positively with abnormalities known to be associated with an immature phenotype, including RAS (50% vs 11%, p = 0.02), ETV6 (40% vs 3%, p < 0.01), DNMT3A (70% vs 3%, p < 0.01), IKZF1 (20% vs 2%, p = 0.02) and TET2 (20% vs 2%, p = 0.04) mutations (Fig. 1b, c). IDH2**Mut** were mutually exclusive with SILTALI<sup>+</sup> cases, associated with a mature TCRαβ lineage. Interestingly, contrary to IDH2-mutated cases, IDH<sub>1</sub><sup>WT</sup> did not statistically differ from IDH<sub>1</sub><sup>Mut</sup> patient regarding age, immunophenotype or mutational co-occurrence.

**IDH2 mutations, but not IDH1, are associated with a poor prognosis in T-ALL**

To investigate the prognostic value of IDH1/2**Mut**, survival analyses were performed on the 476 patient cohort. IDH1/2**Mut** cases did not differ significantly with regard to sex, white blood cell count (WBC) or central nervous system (CNS) involvement (Table 1). Despite an initial good treatment response (IDH2**Mut** cases achieved 90% complete remission rate and IDH2**Mut** did not confer increased poor prednisone response), patients with IDH2**Mut** had an inferior outcome compared to IDH2**Wt** (Table 1, Fig. 1d, Additional file 2: Fig. S4), with an increased cumulative incidence of relapse (CIR) (4y-CIR: 78% vs 29%; specific hazard ratio (SHR) 4.3, 95%CI (2.0–9.2); p < 0.001) and a shorter overall survival (OS) (4y-OS: 30% vs 71%; hazard ratio: 3.6, 95%CI (1.7–7.7); p = 0.001). In multivariate analysis considering variables associated with CIR and OS in univariate analyses as covariates, IDH2**Mut** predicted a trend for lower OS (HR: 1.98, 95%CI (0.86–4.57); p = 0.11) and statistically higher CIR (SHR, 4.06, 95%CI (1.84–8.96), p = 0.001) even after adjustment on the 4-gene NOTCH1/FBXW7/RAS/PTEN (NFRP) classifier which identified poor prognosis patients in both GRAALL and FRALLE trials [3, 4]. Conversely to IDH2**Mut**, IDH1**Mut** was not associated with poor prognostic impact in T-ALL (4y-CIR: 25% vs 29%, p = 0.75 and 4y-OS: 80% vs 71%, p = 0.61).

We provide the largest comprehensive analysis of IDH1 and IDH2 mutations in T-ALL and highlight for the first time both their clinical profile and, most importantly, the extremely poor prognosis impact associated with IDH2**Mut**. We describe the specific oncogenic landscape of IDH1/2**Mut** and interestingly report that IDH2**Mut** T-ALL conversely to IDH1**Mut** were associated with an immature phenotype and alterations such as RAS mutations, transcription factors alterations (ETV6, IKZF1) and epigenetic regulators alterations (TET2, DNMT3A).

Recent studies have shed light on new prognostic factor in T-ALL allowing sharper prediction of the risk of relapse (e.g., NFRP classifier, level of MRD1, IKZF1 alterations) [3, 4, 27]. Despite this, a significant number of T-ALL relapses remain unpredicted, so new predictive markers are needed, given the extremely poor prognosis associated with T-ALL relapse. We therefore consider that IDH2**Mut** T-ALL cases should be identified at diagnosis to benefit from therapeutic intensification and/or specific IDH2**Mut** inhibitors [15].
**Table 1** Clinico-biological and outcome characteristics of adult and pediatric T-ALL (GRAALL and FRALLE protocols) according to IDH1/2 status

| Variable                          | IDH2Mut (n = 10) | p value | Overall (n = 476) | p value | IDH1Mut (n = 5) |
|-----------------------------------|------------------|---------|-------------------|---------|----------------|
| Male                              | 7/10 (70%)       | 0.72    | 357/476 (75%)     | 0.34    | 5/5 (100%)     |
| Age (y)                           | 47.6 (3.6–59.1)  | 0.01    | 15.3 (1.1–59.1)   | 0.26    | 21.6 (5.4–56.5)|
| WBC (G/L)                         | 9 (1–400)        | 0.01    | 64 (0–980)        | 0.60    | 80 (4–110)     |
| CNS involvement                   | 1/10 (10%)       | 0.99    | 51/474 (11%)      | 0.99    | 0/5 (0%)       |
| Immunophenotype                   |                  |         |                   |         |                |
| ETP phenotype                     | 3/5 (60%)        | 0.04    | 56/307 (18%)      | 0.54    | 1/4 (25%)      |
| Immature (IM0/δ/γ)                | 5/7 (71%)        | 0.006   | 89/419 (21%)      | 0.99    | 0/1 (0%)       |
| Cortical (IMB, preαβ)             | 0/7 (0%)         | 0.007   | 211/419 (50%)     | 0.68    | 2/5 (40%)      |
| Mature TCαβ                       | 1/7 (14%)        | 0.99    | 66/419 (16%)      | 0.99    | 0/5 (0%)       |
| Mature TCγδ                       | 1/7 (14%)        | 0.99    | 53/419 (13%)      | 0.12    | 2/5 (40%)      |
| Oncogenetic classification        |                  |         |                   |         |                |
| TLX1                              | 0/8 (0%)         | 0.60    | 54/415 (13%)      | 0.99    | 0/5 (0%)       |
| TLX3                              | 1/8 (12%)        | 0.99    | 72/415 (17%)      | 0.21    | 2/5 (40%)      |
| SII-TAL1                          | 0/8 (0%)         | 0.61    | 57/415 (14%)      | 0.99    | 0/5 (0%)       |
| CALM-AF10                         | 0/8 (0%)         | 0.99    | 13/415 (3%)       | 0.99    | 0/5 (0%)       |
| High-risk classifier              | 8/10 (80%)       | 0.03    | 209/476 (44%)     | 0.99    | 2/5 (40%)      |
| Treatment response                |                  |         |                   |         |                |
| Rapid prednisone response         | 3/10 (30%)       | 0.12    | 259/467 (55%)     | 0.66    | 2/5 (40%)      |
| Complete Remission                | 9/10 (90%)       | 0.54    | 440/476 (92%)     | 0.32    | 4/5 (80%)      |
| MRD1 > 10^{-4}                    | 1/1 (100%)       | 0.36    | 123/340 (36%)     | 0.99    | 0/1 (0%)       |
| Allo-HSCT                         | 2/10 (20%)       | 0.99    | 101/456 (22%)     | 0.99    | 1/1 (100%)     |
| Outcome                           |                  |         |                   |         |                |
| 4-year CIR (95% CI)               | 78% (49;97)      | < 0.001 | 29% (25;33)       | 0.75    | 25% (4;87)     |
| 4-year OS (95% CI)                | 30% (7;58)       | 0.001   | 71% (67;75)       | 0.61    | 80% (20;97)    |

Univariate and multivariate analysis

| CIR     | SHR     | 95% CI | p     | SHR     | 95% CI | p     |
|---------|---------|--------|-------|---------|--------|-------|
| Age     | 1.01    | (0.98; 1.03) | 0.57 | -       | -      | -     |
| CNS     | 1.57    | (0.85; 2.59) | 0.08 | 1.33    | (0.80; 2.20) | 0.28  |
| Log(WBC) | 1.62    | (1.2; 2.18)  | 0.002 | 1.63    | (1.20; 2.22) | 0.002 |
| Prednisone response | 0.67    | (0.47; 0.95) | 0.03 | 1.00    | (0.68; 1.46) | 0.99  |
| High-risk Classifier | 2.78    | (1.94; 3.99) | < 0.001 | 2.62    | (1.81; 3.79) | < 0.001 |
| IDH2Mut | 4.28    | (1.99; 9.23) | < 0.001 | 4.06    | (1.84; 9.86) | 0.001 |
| OS      | HR      | 95% CI | p     | HR      | 95% CI | p     |
| Age     | 1.03    | (1.01; 1.05) | 0.001 | 1.04    | (1.02; 1.07) | < 0.001 |
| CNS     | 2.00    | (1.28; 3.14) | 0.002 | 1.67    | (1.02; 1.07) | 0.03  |
| Log(WBC) | 1.99    | (1.48; 2.67) | < 0.001 | 2.00    | (1.46; 2.76) | < 0.001 |
| Prednisone response | 0.54    | (0.38; 0.76) | < 0.001 | 0.85    | (0.59; 1.24) | 0.41  |
| High-risk Classifier | 2.93    | (2.06; 4.17) | < 0.001 | 2.90    | (2.00; 4.19) | < 0.001 |
| IDH1Mut | 3.56    | (1.66; 7.65) | 0.001 | 1.98    | (0.86; 4.57) | 0.11  |

*p-values < 0.05 are indicated in bold

MRD1 correspond to MRD evaluation after induction and was performed by allele-specific oligonucleotides polymerase chain reaction. T-cell receptor status and oncogenic were performed as described in supplemental methods. IDH1Mut and IDH2Mut were statistically compared to IDH1WT and IDH2WT patients, respectively.

T-ALL: T-cell acute lymphoblastic leukemia; WBC, white blood count; CNS, central nervous system; ETP, early thymic precursor; High Risk classifier, NOTCH1/FBXW7-RAS/PTEN classifier as previously described [3, 4]; CR, complete remission; MRD, minimal residual disease; Allo-HSCT, allogenic hematopoietic stem cell transplantation; CIR, cumulative incidence of relapse; OS, overall survival; HR: hazard ratio; SHR: specific hazard ratio; CI: confidence interval

1 Statistics presented: Median (Minimum–Maximum)

2 Statistical tests performed: Fisher’s exact test; Wilcoxon rank-sum test

3 Univariate and multivariate Cox analyses stratified on protocol
Abbreviations
IDH1/2Mut: IDH1-IDH2 Mutations; AML: Acute myeloid leukemia; T-ALL: T-cell acute lymphoblastic leukemia; NFRP: NOTCH1/FBXW7/RAS/PTEN; CNS: Central nervous system; WBC: White blood cell count; NOS: Not otherwise specified; Tfh: T-Follicular helper; ETP: Early thymic precursor; MRD: Minimal residual disease.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13045-021-01088-4.

Additional file 1. Supplemental Table 1: Custom capture Nextera XT gene panel. Supplemental Table 2: IDH1 and IDH2 mutations identified in 1085 patients with T-ALL. Supplemental Table 3: Chemotherapy in the FRALLE-2000 standard risk group T1 and high risk T2.

Additional file 2. Figure S1: Lollipop plots indicating the observed mutations for IDH1 and IDH2 in the present series confront with Cosmic-reported mutations for AML and AITL. Figure S2: Lollipop plots indicating the observed mutations for IDH1 and IDH2 affecting patients included in FRALLE and GRAALL protocol. Figure S3: Variant Allele Frequency (VAF) of individual IDH1 and IDH2 mutations observed in 1085 T-ALL. Figure S4: OS and CR according to the IDH1 or IDH2 status in the two subgroups (FRALLE and GRALL 03/09). Figure S5: General design of FRALLE 2000 T guidelines.

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Authors’ contributions
N.B, V.A and M.S conceived the study and oversaw the project; M.S, A.S, C.B, V.A, N.B, G.P.A analyzed and interpreted analyses; M.S, A.S, C.B, V.A. collected and assembled data; N.B and M.S performed statistical analysis; M.S, A.S, C.B, VA, N.B, G.PA analyzed and interpreted data; M.S, N.B, A.S, C.B, E.M, V.A wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
Studies were conducted in accordance with the Declaration of Helsinki and approved by local and multicenter research ethical committees.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing financial interests.

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