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Letter

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Impact of T-cell Receptor Status on Mutational Landscape and Outcome in T-ALL

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T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive and heterogenous hematological cancer representing 15% of pediatric and 25% of adult ALL.¹ Its immunophenotypic classification currently includes early thymic precursor (ETP)-ALLs.² In 2003, we described and have subsequently used a T-cell receptor (TCR)-based classification to divide T-ALLs into mature sTCR $\alpha\beta$ or $\gamma\delta$ expressing cases, IM β /pre $\alpha\beta$ (complete TCR β VDJ/cTCR β expression), and immature IM0/ δ/γ cases (cTCR β negative and no complete TCR β VDJ).³ Two decades on, we describe a cohort of 426 adult and pediatric T-ALLs patients treated on 2 national prospective protocols (see Suppl. Methods for details), aiming to identify specific oncogenetic subtypes, molecular alterations, clinical presentation, and outcome as a function of their TCR status (IM0/ δ/γ ; IM β /pre $\alpha\beta$; TCR $\gamma\delta$; TCR $\alpha\beta$).

Two cohorts were included: 220 children, treated according to the FRALLE2000T recommendations, and 206 adults, treated in the GRAALL03/05 protocol. Overall, the IM β /pre $\alpha\beta$ immunophenotype predominated (51%, n = 215) followed by IM0/ δ/γ (22%, n = 92), TCR $\alpha\beta$ (15%, n = 66), and TCR $\gamma\delta$ (12%, n = 53) (Table 1).

TCR subtype by age (Figure 1A) showed that IM0/ δ/γ and TCR $\gamma\delta$ are relatively common in older patients, whereas $\alpha\beta$ -lineage (IM β /pre $\alpha\beta$ and TCR $\alpha\beta$) T-ALLs predominate in patients <25 years (Suppl. Figure S1). ETP-ALLs were, as expected, most common in IM0/ δ/γ (64%) but were also identified in 11% of

TCR $\gamma\delta$ T-ALLs compared with only 4.9% (10/203) of $\alpha\beta$ -lineage T-ALLs (Table 1).⁴ As such, ETP-ALLs are not synonymous with immunogenetic immaturity, but rarely undergo complete TCR β rearrangement.

Oncogenetic characteristics according to the TCR subtype are described in Table 1 and Suppl. Tables S1 and S2 for adults and children, respectively. The rare *PICALM-MLLT10* predominated in IM0/ δ/γ and TCR $\gamma\delta$ T-ALLs (9/145; 6.2% versus 4/281; 1.4% in $\alpha\beta$ -lineage T-ALLs, $P = 0.01$). *HoxA9* was overexpressed in 24% of T-ALL, predominantly in IM0/ δ/γ (45%) and TCR $\gamma\delta$ (41%).⁵ *TLX1* T-ALLs predominated in the IM β /pre $\alpha\beta$ subgroup (23%) and *TLX3* in TCR $\gamma\delta$ cases (32%). *SIL-TAL1* was most common in TCR $\alpha\beta$ T-ALLs and totally absent in IM0/ δ/γ and TCR $\gamma\delta$ T-ALLs.⁶

RNA sequencing was performed in a subgroup of 112 T-ALL (92 GRAALL03/05 and 20 FRALLE2000T) with available RNA. Uniform manifold approximation and projection for dimension reduction (UMAP) distribution is represented in Suppl. Figure S2. The IM0/ δ/γ subgroup represented a homogeneous cluster, co-segregating with ETP status and *HoxA9* overexpression for some, whereas the IM β /pre $\alpha\beta$ subgroup split into 2 clusters: approximately half cosegregated with the *SIL-TAL1*/TCR $\alpha\beta$ cluster; the other half with *TLX1*/*TLX3* overexpression. The TCR $\alpha\beta$ subgroup was more homogeneous than TCR $\gamma\delta$ cases, which were transcriptionally close to either the IM0/ δ/γ subgroup or within the IM β /pre $\alpha\beta$ /*TLX1*/3 subgroup.

The mutational landscape of the overall cohort is represented in Suppl. Figure S3A and Suppl. Table S3. The overall median number of mutations-deletions/patient was 5 (range, 0–21) and was lower in the TCR $\alpha\beta$ subgroup compared with others, with a median of 4 alterations/patient (range, 1–10), $P < 0.001$ (Suppl. Figure S3B).

In IM0/ δ/γ T-ALLs, more mutations were identified in the *SUZ12* (41%) and *EZH2* (19%) polycomb repressive complex 2 compared with $\alpha\beta$ -lineage T-ALLs. JAK/STAT signaling gene mutations, particularly *JAK3* (44%) and *JAK1* (17%), were also relatively common, whereas *PI3KR1* and *PTEN* alterations were less common than in TCR $\alpha\beta$ T-ALLs, in keeping with the mutual exclusion of these 2 signaling pathways in T-ALLs. More *NRAS* (21%) and *NF1* (24%) mutations (RAS signaling) and *DNMT3A* (16%) and *IDH2* (7%) mutations (epigenetic factors) were identified, whereas *CDKN2A/B* cell cycle alterations were relatively uncommon (26%).

In IM β /pre $\alpha\beta$ T-ALLs, *BCL11B* (31%) and *LEF1* (18%) mutations (transcription factors) and *PTPN2* (12%) mutations were relatively common and almost all had *NOTCH1* (88%) and/or *FBXW7* mutations (38%) and *CDKN2A/B* alterations (84%).

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Table 1

Biological and Clinical Characteristics of GRAALL03/05 and FRALLE2000T-treated Patients According to the TCR Subgroup

All Cohorts	IM0/δ/γ; N = 92 (22%)	IMβ/preαβ; N = 215 (51%)	TCR αβ; N = 66 (15%)	TCR γδ; N = 53 (12%)	Total; N = 426	P-Value
Genotype subsets						
<i>PICALM::MLLT10</i>	5 (5%)	2 (1%)	2 (3%)	4 (8%)	13 (3%)	
<i>SET-NUP214</i>	2 (2%)	1 (0.4%)	0	1 (2%)	4 (1%)	
<i>SIL-TAL1</i>	0	29 (13%)	23 (35%)	0	52 (12%)	
<i>TLX1</i>	2 (2%)	49 (23%)	1	3 (6%)	55 (13%)	
<i>TLX3</i>	3 (3%)	44 (20%)	3 (5%)	17 (32%)	67 (16%)	
<i>HOXA9</i> overexpression	31/69 (45%)	23/163 (14%)	4/44 (10%)	18/44 (41%)	76/320 (24%)	
ETP	42/66 (64%)	9/161 (6%)	1/42 (2%)	4/38 (11%)	56/307 (18%)	
Oncogenetic classifier						
<i>NOTCH1/FBXW7</i> ^{mut}	56/91 (62%)	169 (79%)	31 (47%)	35 (66%)	291/425 (68%)	
<i>RAS</i> ^{mut} / <i>PTEN</i> [#]	20/91 (22%)	44 (20%)	25 (38%)	10 (19%)	99/424 (23%)	
High-risk classifier ^a	46/91 (51%)	73 (34%)	41 (62%)	24 (45%)	184/425 (43%)	
Clinical subsets						
Age, median (range), y	23.7 (1.2–59.1)	16.3 (1.1–57.2)	13.3 (2.4–49.9)	14.8 (1.3–59)	16.2 (1.1–59.1)	<0.001
WBC, median (range), G/L	30.8 (0.3–710)	61 (3.2–965)	119 (2.2–980)	103 (3.8–645)	63.3 (0.3–980)	<0.001
CNS involvement (%)	10/89 (11%)	22/211 (10%)	11/66 (17%)	2/53 (4%)	45/419 (11%)	0.16
Male, n (%)	61 (66%)	160 (74%)	51 (77%)	45 (85%)	317 (74%)	0.09
Treatment response						
Good early prednisone response	38 (41%)	140/211 (66%)	29/63 (46%)	23 (43%)	230/419 (55%)	<0.001
CR	83 (90%)	203 (94%)	63 (95%)	45 (85%)	394 (92%)	0.07
MRD >10 ⁻⁴	35/52 (67%)	36/160 (22%)	17/49 (35%)	20/41 (49%)	108/302 (36%)	<0.001
Allo HSCT	34/86 (39%)	33/205 (16%)	11/64 (17%)	16/49 (33%)	94/404 (23%)	<0.001

^aOncogenetic classifier was performed for 425 patients.

P-values were evaluated by χ^2 test. GPR was defined as <1000 circulating blasts/ μ L on day 8. MRD was evaluated at D35. Notch/FBXW7-RAS/PTEN classifier (oncogenetic classifier) was performed as previously described.⁴

Allo HSCT = allogeneic hematopoietic stem cell transplantation in 1st CR; alt = altered; CNS = central nervous system; CR = complete remission; ETP = early thymic precursor; GPR = good prednisone response; MRD = minimal residual disease; mut = mutated; WBC = white blood cells.

TCR $\alpha\beta$ T-ALLs presented predominantly with *NOTCH1* mutations (63%) and *PTEN* (57%) and *CDKN2A/B* alterations (87%). Relatively few mutations in IL7/JAK/STAT pathway, epigenetic factors, and RAS signaling were found, including compared with IM β /pre $\alpha\beta$ T-ALLs for the latter 2 categories.

TCR $\gamma\delta$ T-ALLs demonstrated a mutational landscape more similar to IM0/δ/γ than to TCR $\alpha\beta$ T-ALLs, with relatively frequent mutations in RAS signaling genes (*NF1* 23%, *NRAS* 9%), epigenetic factors, and *RUNX1* (17%).

The clinico-biological characteristics of GRAALL03/05 and FRALLE2000T treated patients are described in Table 1 and Suppl. Tables S4 and S5. Although clinical presentation (age and white blood cell [WBC] count) and early response to prednisone (EPR) differed between TCR subtypes, this had little impact on complete remission rates, which were >90% in all but TCR $\gamma\delta$ T-ALLs (85%; 87% in children and 83% in adults). Many characteristics were similar in children and adults, with the only major overall differences being WBC at presentation (median 105 G/L and 36.6 G/L, respectively) and use of allogeneic hematopoietic stem cell transplantation (Allo HSCT) (10% versus 37%).

Patients with IM0/δ/γ T-ALL presented with a relatively low WBC (median 30.8G/L). They had a poorer EPR (41%), more frequent minimal residual disease (MRD) positivity at the end of induction (EoI) (67%; 61% in children and 74% in adults) and 51% were high risk with the *NOTCH1/FBXW7/RAS/PTEN* (N/F/R/P) oncogenetic classifier. They underwent Allo HSCT in first complete remission relatively frequently (39%).

In IM β /pre $\alpha\beta$ patients, a good EPR was obtained for 66%, with less frequent EoI MRD positivity, particularly in adults (22%; 29% in children and 12% in adults), and less Allo HSCT (16%) than in the overall cohort. Oncogenetic high-risk status was relatively rare in this category (34%).

Patients with TCR $\alpha\beta$ T-ALL presented with high hyperleukocytosis (median WBC = 119 G/L) and relatively frequent CNS involvement (17%). Despite a poor EPR in most patients from

both the age groups, EoI MRD positivity was only 35% overall and Allo HSCT was not performed more frequently (17%). In keeping with the high incidence of *PTEN* abnormalities, many demonstrated an oncogenetic high-risk classifier (62%).

Patients with TCR $\gamma\delta$ T-ALL presented with high WBC (median WBC = 103 G/L) but rare CNS involvement (4%). There were few good EPR (43%) and frequent EoI MRD positivity (49%). Allo HSCT in first line was undertaken in 33% overall, when it was disproportionately common in children (27%).

Long-term 5-year overall survival (OS) and cumulative incidence of relapse (CIR) are represented in Figure 1B and Suppl. Table S6 for the entire cohort and per protocol (Suppl. Figure S4, Suppl. Figure S5). There was ~9% superiority in 5-year OS and a 5% lower CIR rate in children when compared with adults. Despite different clinical presentations and initial therapeutic response profiles, no significant difference in long-term outcomes could be identified among the different TCR subtypes. Relapses in TCR $\alpha\beta$ T-ALLs occurred earlier, with few occurring after 1.5 years.

When 5-year OS and CIR was compared between protocols (Suppl. Table S6 and Figure 1C–D, Suppl. Figure S4), no significant differences were seen between the 4 TCR subgroups individually, although there was a trend for superior 5-year OS in the FRALLE versus GRAALL-treated IM β /pre $\alpha\beta$ patients ($P = 0.07$, Suppl. Table S6). This trend was also seen for all non-TCR $\alpha\beta$ T-ALLs but was absent in the TCR $\alpha\beta$ subgroup. Comparison of outcome by protocol for TCR $\alpha\beta$ versus non-TCR $\alpha\beta$ showed significantly higher 5-year OS ($P = 0.009$) in children compared with adults (Figure 1C), but not for TCR $\alpha\beta$ T-ALLs ($P = 0.58$), when children did as badly as adults (5-year OS 69% in both groups). No significant differences were seen in the 5-year CIR rates in TCR $\alpha\beta$ or non-TCR $\alpha\beta$ T-ALLs (Figure 1D), suggesting that something in addition to early relapse contributes to the poor outcome of children with TCR $\alpha\beta$ T-ALL treated according to the FRALLE2000T recommendations.

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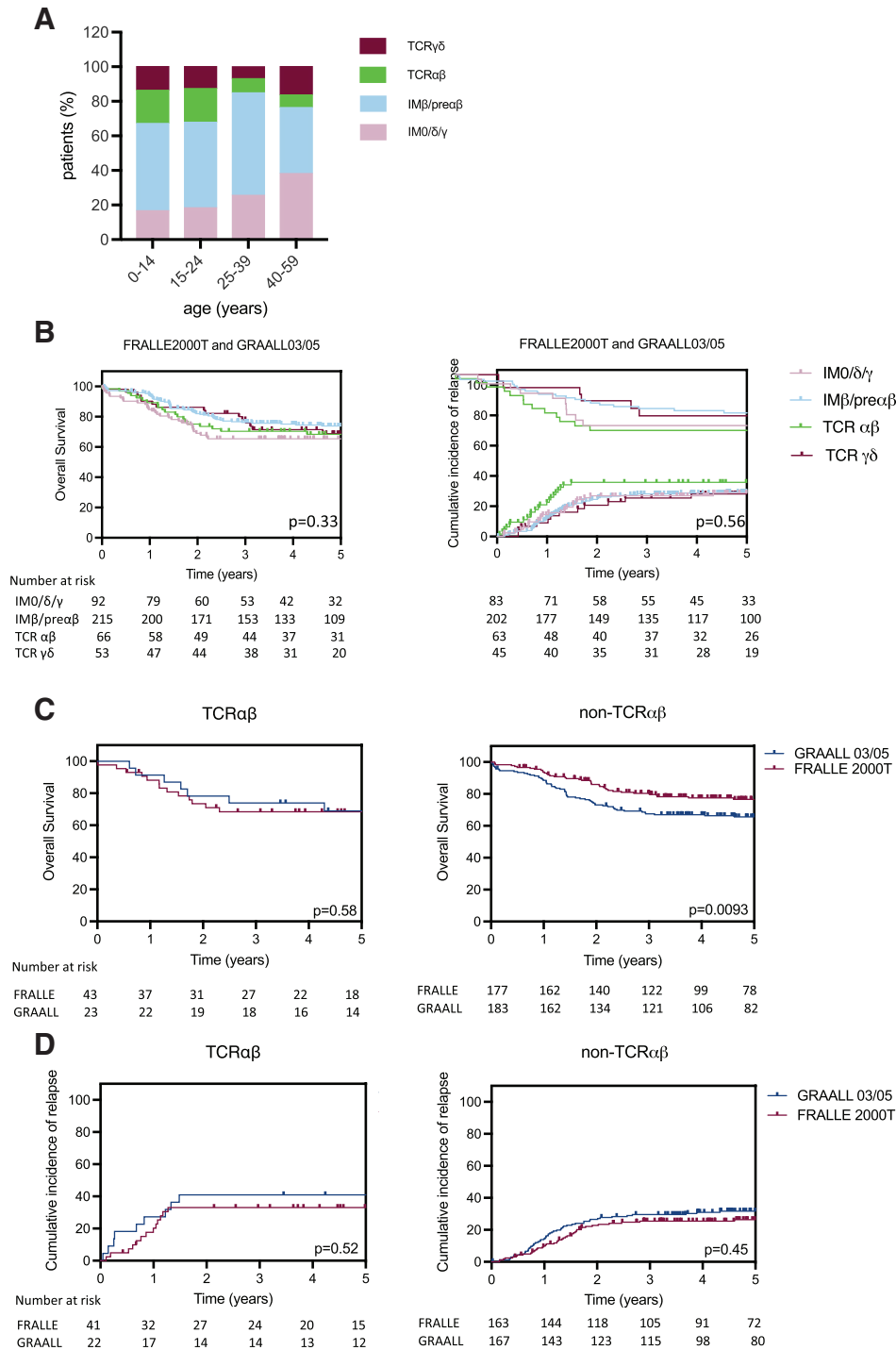


Figure 1. Distribution and outcome of T-ALL according to the TCR subgroup. (A) Proportion of T-ALL with different TCR subgroups according to the age (n = 426 samples). Patients aged from 0 to 14 y: n = 198; from 15 to 24 y: n = 87; from 25 to 39 y: n = 86; from 40 to 59 y: n = 55. (B) Overall survival of patients according to the TCR subgroup (FRALLE + GRAALL) (left). Cumulative incidence of relapse of patients according to the TCR subgroup (FRALLE + GRAALL) (right). (C) Overall survival of patients TCR $\alpha\beta$ (left) and of patients non-TCR $\alpha\beta$ according to the protocol (right). (D) Cumulative incidence of relapse of patients TCR $\alpha\beta$ (left) and of patients non-TCR $\alpha\beta$ according to the protocol (right). T-ALL = T-cell acute lymphoblastic leukemia; TCR = T-cell receptor.

Classification of T-ALL has evolved from immunophenotypic identification of lineage to genetic identification of oncogenic subtypes, which often correlate with both stage of maturation arrest and clinical outcome.⁷⁻¹³ Immunogenetic characterization of TCR (and immunoglobulin) gene rearrangements is rarely required for diagnosis, but is widely used for MRD evaluation.¹⁴⁻¹⁶

TCR $\alpha\beta$ T-ALLs fared particularly badly (5-year OS 68.5%) in FRALLE-treated patients, a protocol that was

shown to be suboptimal for pediatric oncogenetic high-risk patients.¹⁷ In fact, 5-year OS in the present study was virtually identical in pediatric and adult TCR $\alpha\beta$ patients, despite the lower 5-year CIR in children. Possible explanations may include the relatively high incidence of CNS involvement and less frequent use of Allo HSCT. Pediatric TCR $\alpha\beta$ T-ALLs clearly need alternative first-line therapy. Some are intensified on the basis of frequent high leukocytosis, but

inclusion of TCR $\alpha\beta$ expression in stratifying characteristics merits consideration.

Defining oncogenic features of IM0/ δ/γ T-ALLs overlap with those described for ETP-ALLs in children and adults,^{2,5} although only 64% were phenotypically defined as such. Adult IM0/ δ/γ T-ALLs benefit from Allo HSCT, but still trend to inferior survival, despite CIR rates comparable to non-TCR $\alpha\beta$ T-ALLs.⁵ In contrast, although only 12% of FRALLE2000T-treated IM0/ δ/γ T-ALLs underwent Allo HSCT, 5-year OS was comparable to other pediatric TCR subgroups. IM0/ δ/γ T-ALL profiles and response to treatment also overlapped with some TCR $\gamma\delta$ cases. Both commonly overexpressed *HOXA9*, which identifies a poor prognostic group in immature GRAALL-treated T-ALLs.⁵ Further understanding of TCR $\gamma\delta$ T-ALLs requires more in-depth characterization of the 2 clusters identified here.

The lack of overall prognostic significance of this TCR classification limits its use in individual stratification. Our data demonstrate, however, that integration of this parameter alongside oncogenetic annotations adds understanding, encouraging its exploitation in immunogenetic MRD-driven protocols. At a minimum, immunophenotypic diagnostic panels should specify lineage in sTCR positive T-ALLs of all ages.

There were many more similarities than differences between pediatric and adult T-ALLs, arguing for concerted evaluation and common protocols. The data presented here should contribute to selecting subgroups of T-ALL, which may respond differently to specific therapeutic regimens, as recently described for the N/F/R/P oncogenetic classifier in the FRALLE2000T and UKALL2003 pediatric regimens.¹⁷ Such reversed use of discordant responses within oncogenetically or immunogenetically/TCR-defined subgroups will throw light on the fine details of therapeutic practice in ALL.

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AUTHOR CONTRIBUTIONS

MED, EM, and VA conceived the study and oversaw the project. MED, LC, MS, AB, NB, AP, AT, LL, and VA provided study materials or patients. MED and GA performed molecular analyses. MED, LC, VA, and GA collected and assembled data. MED and GA performed statistical analysis. MED, GA, and VA analyzed and interpreted data. MED, EM, and VA wrote the article. All authors approved the article.

DATA AVAILABILITY

This work did not generate new data.

DISCLOSURES

EM reports that she is president of the European Hematology Association. All the other authors have no conflicts of interest to disclose.

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