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ETV6-RUNX1-positive childhood acute lymphoblastic leukemia: improved outcome with contemporary therapy

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Abstract

ETV6-RUNX1 fusion is the most common genetic aberration in childhood acute lymphoblastic leukemia (ALL). To evaluate whether outcomes for this drug-sensitive leukemia are improved by contemporary risk-directed therapy, we studied clinical features, response and adverse events of 168 children with newly diagnosed *ETV6-RUNX1*-positive ALL on St Jude Total Therapy studies XIIIA (N=36), XIIIB (N=38) and XV (N=94). Results were compared to 494 *ETV6-RUNX1*-negative B-precursor ALL patients. *ETV6-RUNX1* was associated with age 1-9 years, pre-treatment classification as low-risk and lower levels of minimal residual disease (MRD) on day 19 of therapy ($p<0.001$). Event-free survival (EFS) or overall survival (OS) did not differ between patients with or without *ETV6-RUNX1* in Total XIIIA or XIIIB. By contrast, in Total XV, patients with *ETV6-RUNX1* had significantly better EFS ($p=0.04$; 5-year estimate, 96.8±2.4% versus 88.3±2.5%) and OS ($p=0.04$; 98.9±1.4% versus 93.7±1.8%) than those without *ETV6-RUNX1*. Within the *ETV6-RUNX1* group, the only significant prognostic factor associated with higher OS was the treatment protocol Total XV (versus XIIIA or XIIIB) ($p=0.01$). Thus, the MRD-guided treatment schema including intensive asparaginase and high-dose methotrexate in the Total XV study produced significantly better outcomes than previous regimens and demonstrated that nearly all children with *ETV6-RUNX1* ALL can be cured.

Keywords

leukemia; *ETV6-RUNX1*; *TEL-AML1*

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Introduction

The t(12;21) (p13.1;q22) translocation causes the fusion of the ETS variant 6 (*ETV6*) and Runt-related transcription factor 1 (*RUNX1*) genes (formerly *TEL* and *AML1* respectively). It is the most common genetic abnormality in childhood acute lymphoblastic leukemia (ALL), occurring in approximately 25% of cases with a precursor-B phenotype.(1) *ETV6-RUNX1*-positive ALL is thought to arise pre-natally and may be preceded by a pre-leukemic phase.(2) The presence of *ETV6-RUNX1* alters differentiation and enhances self renewal of hematopoietic progenitor cells, particularly of B-lineage.(3) The expression of *ETV6-RUNX1* in human cord blood progenitor cells reportedly caused the expansion of a candidate preleukemic population that had a growth advantage in the presence of transforming growth factor-beta.(4) A second hit, commonly a deletion of the non-translocated *ETV6* gene, is often present at leukemic transformation,(5) but additional genomic alterations have been uncovered by high-resolution single nucleotide polymorphism arrays.(6) *ETV6-RUNX1*-positive ALL cells have distinct biologic features and are reported to have an increased *in vitro* sensitivity to anti-leukemic drugs such as L-asparaginase, doxorubicin, etoposide and dexamethasone compared to leukemic cells of other cytogenetic subtypes.(7, 8)

Since its identification in 1995,(9) the presence of *ETV6-RUNX1* has been associated with a relatively low rate of relapse in multiple studies.(10-12) Moreover, relapses tend to occur late and have a better salvage rate than other ALL subtypes.(13) A Children's Oncology Group (COG) study indicated that the presence of *ETV6-RUNX1* was an independent predictor of favorable outcome.(10) However, in a study from the Dana Farber Cancer Institute (DFCI) Consortium, *ETV6-RUNX1* status was not an independent prognostic factor after accounting for age, initial leukocyte count and treatment group.(14) Thus, it is not clear whether the *ETV6-RUNX1* fusion has independent prognostic significance in the context of current risk-adapted therapy and whether the outcome of children with *ETV6-RUNX1*-positive ALL can be further improved by contemporary therapeutic strategies. We addressed these outstanding questions and determined the relation between *ETV6-RUNX1* and presenting clinical and biologic features, early treatment response and clinical outcome among children with B-precursor ALL treated on three successive Total Therapy studies.

Materials and Methods

Patients

From 1991 to 2007, 763 children with B-precursor ALL were enrolled on three institutional protocols for newly diagnosed ALL: Total Therapy studies XIIIA,(15) XIIIB(16) and XV.(17) The Total XIV study (August 1998 to July 1999) terminated early after accrual of 39 patients with B-precursor ALL (including 7 with the *ETV6-RUNX1* fusion). The low accrual in Total XIV precludes meaningful analyses, and patients on this study are not included in this report. *ETV6-RUNX1* status was not evaluated in 101 of the 763 patients (13%) with B-precursor ALL, the majority of whom were treated in the two earlier Total Therapy studies (27 on XIIIA, 55 on XIIIB, and 19 on XV). These patients did not differ with regard to age, race, presenting leukocyte count, risk group allocation, minimal residual disease (MRD) levels after remission induction or outcome from the 662 patients who were evaluated for *ETV6-RUNX1* status (Supplementary table S1, online only). There was a slight female preponderance and a higher number of patients with central nervous system (CNS) disease among patients not evaluated for the fusion.

The treatment protocols were approved by the institutional review board of St Jude Children's Research Hospital, Memphis, TN and Cook Children's Medical Center, Fort

Worth, TX (Total XV). Informed consent was obtained from the parent or guardian and assent obtained from the patient when appropriate.

Diagnostic tests

The diagnosis of ALL and lineage discrimination was made by morphology and immunophenotypic analyses. Genetic subtypes were identified by conventional cytogenetics, fluorescent in situ hybridization and real-time polymerase chain reaction as previously described.(18) MRD was measured by flow cytometric analysis of leukemia-associated markers or polymerase chain reaction of antigen receptor genes at protocol defined time-points as previously described.(17, 19)

Therapy

Details of the therapeutic protocols have been described previously.(15-17) Table S2 (supplement, online only) lists the key differences in risk stratification and treatment in the 3 studies. Briefly, in Total XIIIA (1991-1994), in addition to early intensification of systemic chemotherapy for all patients, intrathecal therapy was intensified for patients with higher risk ALL and those with any blasts in the cerebrospinal fluid.(15) In Total XIIIB (1994-1998), a detailed risk stratification scheme was used, resulting in more patients being treated on the lower-risk arm than in Total XIIIA.(16) Dexamethasone was used instead of prednisone post-remission to improve systemic and CNS disease control.(20) Asparaginase was not given during continuation therapy due to the increased incidence of secondary acute myeloid leukemia noted when it was used in combination with etoposide.(21) In Total XV (2000-2007), risk stratification was further refined by including MRD measurements on day 19 and at the end of remission induction therapy (Day 46).(17) Patients with the *ETV6-RUNX1* fusion or hyperdiploidy without CNS or testicular disease and a satisfactory early MRD decline (<1% on day 19 and <0.01% on day 46) were classified as being low-risk for relapse regardless of age and leukocyte count. The dose and intensity of asparaginase, anthracyclines and high-dose methotrexate differed by risk group. Prophylactic CNS radiation was not used.

Statistical analyses

To compare differences in clinical features between *ETV6-RUNX1*-positive and negative patients, the exact chi-square and Fisher exact test were used. Overall survival (OS) and event free survival (EFS) were estimated by the Kaplan-Meier method and compared by the Mantel-Haenszel test(22). Cox proportional hazard regression models were used to identify independent prognostic factors.

Results

Patient characteristics

The *ETV6-RUNX1* fusion was detected in 168 (25.4%) of 662 evaluable patients with B-precursor ALL. Thirty-six patients were enrolled in Total XIIIA, 38 in Total XIIIB and 94 in Total XV. As shown in Table 1, there was no association between the presence of *ETV6-RUNX1* and gender, race or presenting leukocyte count. However, *ETV6-RUNX1* was significantly related with favorable age (1-9 years; $p<0.001$), CNS1 status (no blasts in cerebrospinal fluid; $p=0.0002$) and low-risk allocation ($p<0.001$). Of all patients assigned to the lower-risk arm, 34.9% were *ETV6-RUNX1*-positive versus 16.6% of those stratified to the standard and high-risk arms. In the most recent study, Total XV, patients with *ETV6-RUNX1*-positive ALL without CNS or testicular involvement who demonstrated a very good early MRD reduction on therapy were treated on the lower-risk arm of the trial regardless of age and presenting leukocyte count. Thus, less intensive therapy was given to

the majority (89.4%) of *ETV6-RUNX1*-positive patients versus 46.8% of *ETV6-RUNX1*-negative patients.

Response and outcome

MRD measurements on day 19 of induction therapy were available for 464 patients (67 from Total XIIIA/B and 397 from Total XV) and on Day 46 for 469 patients (69 from Total XIIIA/B and 400 from Total XV). Patients with the *ETV6-RUNX1* fusion had significantly lower rates of MRD positivity than *ETV6-RUNX1*-negative patients at both time points (Table 1). None of the *ETV6-RUNX1*-positive patients had MRD ≥1% at the end of remission induction (day 46) compared to 16 *ETV6-RUNX1*-negative patients (4.5%). Nine of the 94 patients with the *ETV6-RUNX1* fusion in Total XV switched from the provisional low-risk arm to the standard-risk arm of the trial because of ≥1% MRD on day 19 or ≥0.01% MRD on day 46. Among 310 *ETV6-RUNX1*-negative patients with B-precursor ALL, 27 patients switched from low-risk to standard-risk, 1 from low-risk to high-risk and 10 from standard-risk to high risk (p=0.33).

Figure 1 illustrates the EFS and OS for patients in each study. The EFS and OS did not differ between patients with or without *ETV6-RUNX1* in Total XIIIA or XIIIB. By contrast, patients with *ETV6-RUNX1* had significantly better EFS (p=0.04) and OS (p=0.04) than those without the gene fusion in Total XV: 5-year EFS estimates were 96.8± 2.4% vs. 88.3 ± 2.5%; 5-year OS, 98.9 ± 1.4% vs. 93.7 ± 1.8%.

Treatment failures

A total of 19 patients with *ETV6-RUNX1* had major adverse events. The causes of failure and distribution among three studies are shown in Table 2. There were no induction failures or induction deaths among patients with *ETV6-RUNX1*. Two patients died in complete remission, 1 from pseudomonas sepsis during continuation therapy and 1 from a car accident while off therapy. Six patients developed secondary acute leukemia (4 in Total XIIIA and 2 in Total XIIIB). Eleven patients relapsed, with isolated marrow relapse (n=8), combined marrow and CNS relapse (n=1) and isolated CNS relapse (n=2). Three of these 11 patients (2 with marrow and 1 with isolated CNS relapse) developed a second hematologic relapse 9 months, 2.5 years and 2 years after completing retrieval therapy respectively. Of the 11 relapses, 4 occurred during or within 6 months of completion of therapy while 7 occurred later. The median time to relapse for *ETV6-RUNX1*-positive patients was 38 months (range 6-139 months) as compared to 34 months (range 3-119 months) in *ETV6-RUNX1*-negative patients (p=0.13). In the most recent Total XV study, marrow relapses in four patients were the causes of treatment failure (three are alive in complete remission).

Prognostic features

With the exception of treatment, there were no significant predictors of outcome within the *ETV6-RUNX1* subset (Table 3). Only therapy received on Total XV (vs. Total XIIIA or XIIIB) was independently associated with an improved outcome: EFS (p=0.05) and OS (p=0.01) (Figure 2).

Discussion

Stepwise refinements in risk classification and treatment strategies have led to improved cure rates for children with ALL. In general, over the past 5 decades, the intensity of treatment regimens has continued to increase, albeit with multiple short and long-term adverse events. As insights are gained into host pharmacogenetics and the heterogeneity of response to chemotherapeutic agents in various leukemia subtypes, and therapy is guided by sensitive and specific methods of MRD monitoring, tailoring the type and intensity of

chemotherapeutic agents becomes feasible to improve cure rates and decrease morbidity. The results presented here indicate that the benefits of this approach also extend to a "low-risk" leukemia subtype, *ETV6-RUNX1* ALL as demonstrated in the Total XV study which provided greater benefit to children with *ETV6-RUNX1*-positive ALL than prior treatment protocols. The interpretation of this result should take into consideration the retrospective nature of the study, potential for compounding variables such as improvements in supportive care and the relatively small number of patients in the earlier Total XIII studies that may have introduced a sampling bias. Though the follow-up time is shorter on Total XV and relapses are known to occur later in this particular ALL subtype, the EFS and OS in the first 8 years are significantly better in Total XV compared to those of the previous studies. Modifications that may have contributed to the improved outcome in Total XV include the incorporation of MRD for risk assignment, intensification of asparaginase (compared to Total XIIIB), increased intensity of high-dose methotrexate during the consolidation phase (4 doses of 2.5 to 5 g/m^2 versus 2 doses of 2 g/m^2 in Total XIII studies) and avoidance of agents with high risk of causing secondary leukemia. Total XV therapy provided improvement in outcome for the entire cohort of patients treated on the study,(17) but it was especially advantageous for patients with *ETV6-RUNX1* ALL. With this improved treatment, conventional risk factors such as age and leukocyte count had no prognostic significance among patients with *ETV6-RUNX1* ALL treated in Total XV. Thus, In the *ETV6-RUNX1*-positive subgroup, 5 patients who were 10 years or older, and 17 patients 1-9 years old with leukocyte count 50×10^9/L or greater at presentation received lower-risk therapy in Total XV. Only one of these patients relapsed. She was an 11-year old girl with a presenting leukocyte count of 80×10^9/L who was unable to receive optimal therapy due to invasive fungal infection early during the remission induction phase. She developed an early hematologic relapse and subsequently died with refractory disease.

In Total XV, the 5-year EFS rate of 96.8% for the 94 *ETV6-RUNX1* patients is superior to the EFS rates reported by various ALL study groups in the past 5 years (that included more than 50 patients with this genetic abnormality).(10, 14, 23, 24) Investigators from the AIEOP-BFM 2000 study reported an excellent outcome for the subset of *ETV6-RUNX1*-positive patients (58% of all patients) with negative MRD at days 33 and 78 of therapy (5-year EFS 94.9%), but patients with low level of MRD positivity at either time point (41% of patients) had 5-year EFS of 81.7% and outcome was poorer in the small fraction (1%) of patients with MRD levels ≥ 0.1% on day 78 (5-year EFS, 54.9%). Although the MRD cut-off values and time points of measurement were different in our trials, only a minority of our patients (11.8%) had positive MRD at low levels (≥0.01% to < 1%) on day 46, possibly due to more effective remission induction regimens. MRD did not demonstrate additional prognostic relevance in *ETV6-RUNX1* ALL in our study, but this could be due to the fact that MRD results were used to change risk group allocation in 9 *ETV6-RUNX1* patients (9.6%) on Total XV from low to standard risk, with consequent administration of more intensive therapy (similarly 12.2% of *ETV6-RUNX1*-negative patients were switched to a higher-risk arm). The Children's Oncology Group has recently reported excellent outcomes for NCI standard-risk patients(25). Five-year EFS and OS estimates were 93.2 ± 2.2% and 98.6 ± 1.0 % for *ETV6-RUNX1*-positive patients. Intravenous escalating methotrexate did not provide greater benefit than oral methotrexate for *ETV6-RUNX1* patients in this study. It remains to be seen if NCI high-risk patients (approximately 25% of *ETV6-RUNX1* patients) also have an equally good outcome in the Children's Oncology Group study. In comparison, for the subgroup of *ETV6-RUNX1*-positive patients classified as NCI standard-risk in Total XV (N=71), 5-year EFS and OS estimates were 97.1 ± 2.5% and 100% respectively. EFS and OS estimates for the NCI high-risk patients in Total XV (N=23) were 95.7 ± 2.5%. In the DFCI ALL Consortium study 95-01, 5-year EFS for all *ETV6-RUNX1*-positive patients was 89% compared with 80% for *ETV6-RUNX1*-negative patients.(14)

The 5-year OS was 97%, which is comparable to that of *ETV6-RUNX1*-positive patients in the Total XV study (98.9%).

The Total XV regimen intensified asparaginase (higher cumulative doses compared to Total XIIIB), dexamethasone (post remission) and vincristine, which are known to be preferentially cytotoxic to blasts bearing the *ETV6-RUNX1* fusion.(8, 26) By impairing mesenchymal cell function, vincristine can potentially enhance the efficacy of asparaginase(27, 28), which in turn can increase systemic exposure of dexamethasone(29). In the DFCI study, asparaginase and steroid therapy was intensified as well, but prednisone was used instead of dexamethasone for pre- and post-remission therapy. *ETV6-RUNX1*-positive lymphoblasts are also known to accumulate lower amounts of methotrexate polyglutamates than *ETV6-RUNX1*-negative lymphoblasts,(30) thus patients with *ETV6-RUNX1* ALL on Total XV might have benefitted from the increased intensity of high-dose methotrexate (2.5 g/m^2 for low-risk and 5 g/m^2 for standard and high-risk cases) administered during the consolidation phase. In addition, measures such as avoiding cranial radiotherapy and limiting the use of epipodophyllotoxins and alkylating agents in Total XV decreased the chances of adverse events such as secondary malignancies (none versus 6 in the earlier studies). This reduction in secondary malignancies contributed to the improvement of overall outcome of patients on Total XV. Even though the majority of patients with *ETV6-RUNX1*-positive ALL were treated on the low-risk arm of Total XV, we do not suggest that they receive an overall reduction in therapy. In fact, all patients received two reinduction courses but patients treated in the low-risk arm received lower cumulative doses of cyclophosphamide and anthracyclines, drugs associated with late sequelae. In conclusion, nearly all children with *ETV6-RUNX1* ALL can be cured with risk-directed therapy including intensive asparaginase, vincristine, dexamethasone and high-dose methotrexate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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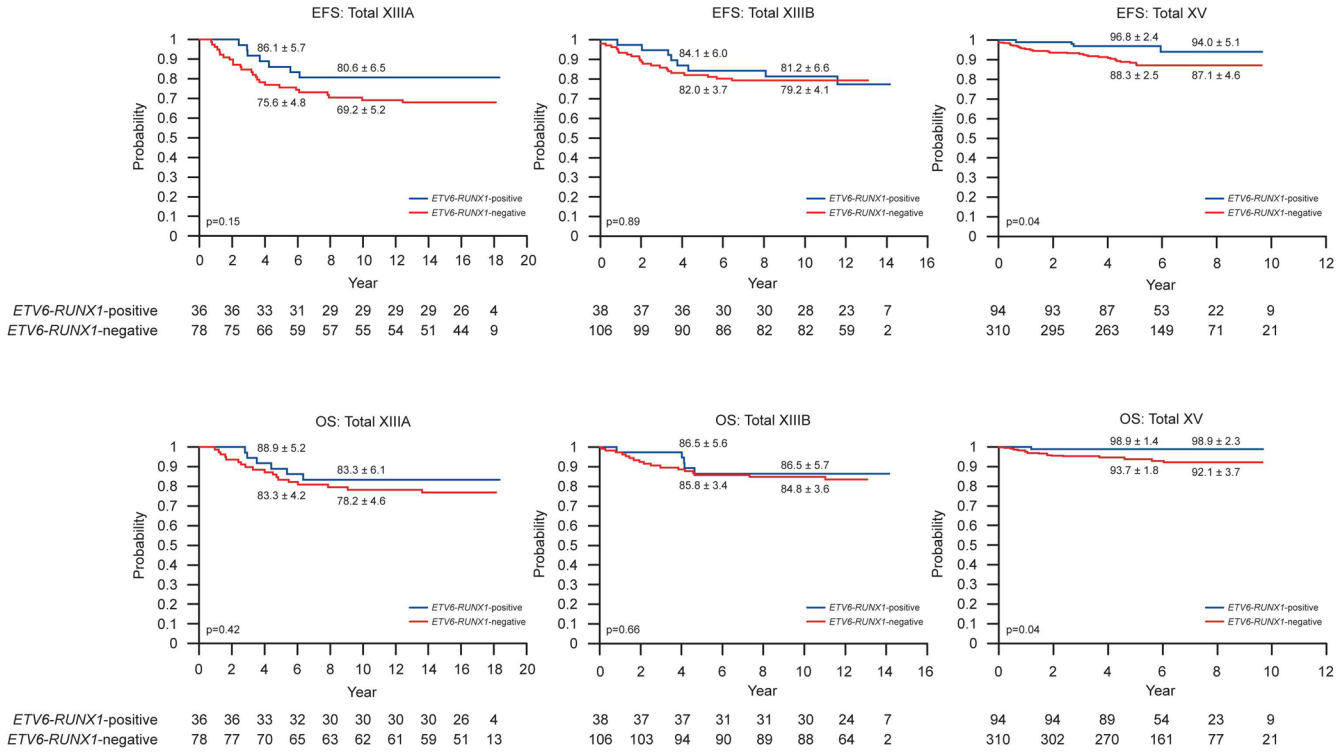

Figure 1.

Kaplan-Meier estimates of EFS and OS in *ETV6-RUNX1*-positive versus negative patients in St Jude Total studies XIIIA, XIIIB and XV. Rates at 5 years, 10 years (for Total XIIIA and Total XIIIB) and 8 years (for Total XV) are reported as means ± standard errors.

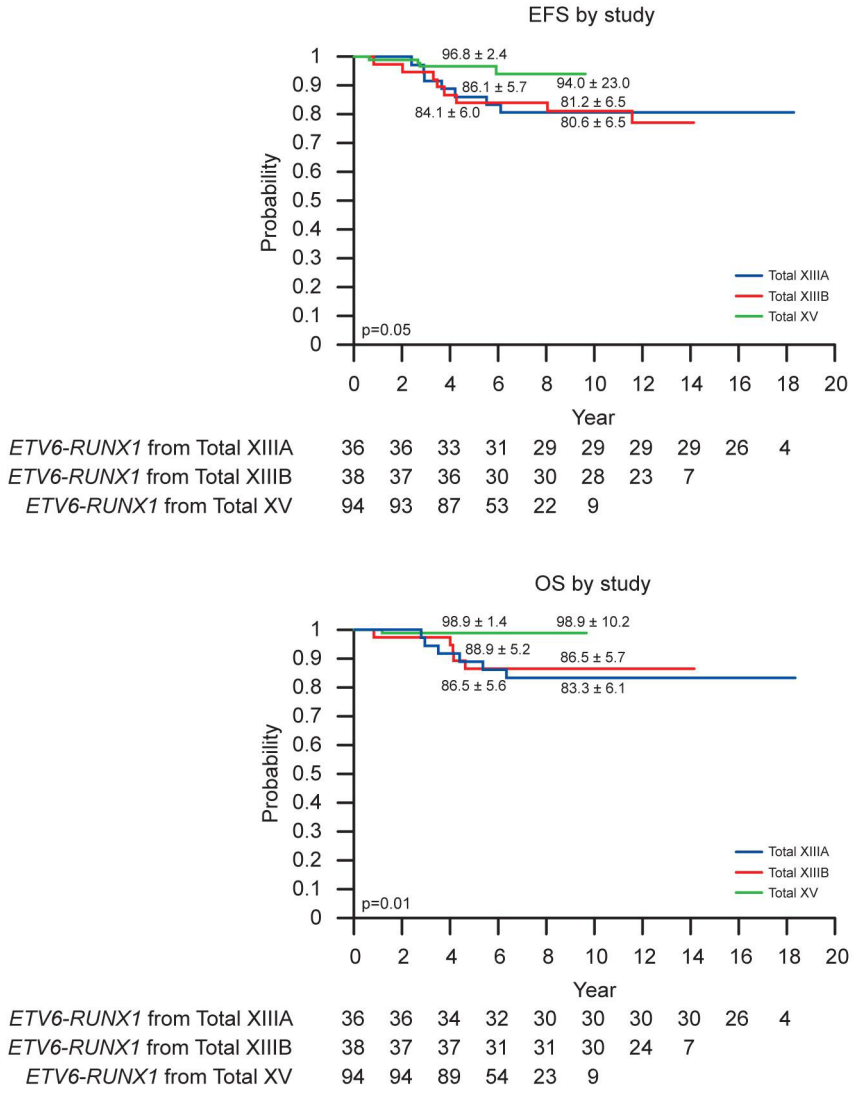

Figure 2.

Kaplan-Meier estimates of EFS and OS in *ETV6-RUNX1*-positive patients by study. Rates at 5 years and 10 years are reported as means ± standard errors

Table 1

Presenting features and early response according to *ETV6-RUNX1* status in patients with B-precursor ALL

Clinical Features		All patients [N (%)] N=662	*ETV6-RUNX1* positive [N (%)] N=168	*ETV6-RUNX1* negative [N (%)] N=494	P-value
Age Groups	< 1 year	12 (1.8)	0 (0.0)	12 (2.4)	<.0001
	1-10 years	498 (75.2)	157 (93.5)	341 (69.0)	
	> 10 years	152 (23.0)	11 (6.5)	141 (28.5)	
Initial WBC	<50 $\times 10^9$/L	527 (79.6)	137 (81.5)	390 (79.0)	0.51
	≥50 $\times 10^9$/L	135 (20.4)	31 (18.5)	104 (21.0)	
Race	White	529 (79.9)	128 (76.2)	401 (81.2)	0.22
	Black	97 (14.7)	27 (16.1)	70 (14.2)	
	Other	36 (5.4)	13 (7.7)	23 (4.7)	
Gender	Male	361 (54.5)	88 (52.4)	273 (54.9)	0.53
	Female	301 (45.5)	80 (47.6)	221 (45.1)	
NCI/Rome Risk group	Standard risk	401 (60.6)	127 (75.6)	274 (55.5)	<.0001
	High risk	261 (39.4)	41 (24.4)	220 (44.5)	
SJ Risk Group	Low risk	318 (48.0)	111 (66.1)	207 (41.9)	<.0001
	Standard/High risk	344 (52.0)	57 (33.9)	287 (58.1)	
CNS status	CNS1	472 (71.3)	141 (83.9)	331 (67.0)	0.0002
	CNS2	141 (21.3)	20 (11.9)	121 (24.5)	
	CNS3	9 (1.4)	0 (0.0)	9 (1.8)	
	Traumatic with blasts	40 (6.0)	7 (4.2)	33 (6.7)	
MRD day 19	<0.01%	199 (42.9)	63 (59.4)	136 (38.0)	<.0001
	≥0.01 to <1%	179 (38.6)	39 (36.8)	140 (39.1)	
	≥1%	86 (18.5)	4 (3.8)	82 (22.9)	
MRD day 46	<0.01%	376 (80.2)	97 (88.2)	279 (77.7)	0.01
	≥0.01 to <1%	77 (16.4)	13 (11.8)	64 (17.8)	
	≥1%	16 (3.4)	0 (0.0)	16 (4.5)	
Treatment protocol	Total XIIIA	114 (17.2)	36 (21.4)	78 (15.8)	0.19
	Total XIIIB	144 (21.8)	38 (22.6)	106 (21.4)	
	Total XV	404 (61.0)	94 (55.9)	310 (62.8)	

WBC: white blood cell; NCI: National Cancer Institute; SJ: St Jude; CNS: central nervous system; MRD: Minimal residual disease

Table 2

Details of events for patients in Total XIIIA, XIIIB and XV according to *ETV6-RUNX1* status

Event	Total XIIIA			Total XIIIB			Total XV			All patients		
	ETV6-RUNX1			*ETV6-RUNX1*			*ETV6-RUNX1*			*ETV6-RUNX1*		
	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total	Positive	Negative	Total
Induction death	0	0	0	0	0	0	0	1	1	0	1	1
No response	0	0	0	0	2	2	0	3	3	0	5	6
Hematologic relapse	1	10	11	3	9	12	4	11	15	8	30	36
Central nervous system relapse	0	1	1	2	2	5	0	5	5	2	9	11
Testicular relapse	0	0	0	0	0	0	0	1	1	0	1	1
Combined relapse	1	4	5	0	0	0	0	4	4	1	8	9
Death in complete remission	1	3	4	1	5	6	0	8	8	2	16	18
Secondary leukemia	4	7	11	2	3	5	0	1	1	6	11	17
Total	7	25	32	8	22	30	4	34	38	19	81	100

Table 3

Potential prognostic variables assessed for relation to outcome in patients with *ETV6-RUNX1* ALL

Features		Total number of patients	5-year EFS ± SE (%)	p-value	5-year OS ± SE (%)	p-value
Age group	1-10 years	157	91.3 ± 2.6	0.10	93.6 ± 2.3	0.14
	> 10 years	11	90.9 ± 9.1		90.9 ± 9.1	
Initial WBC	<50 ×10^9/L	137	90.8 ± 2.8	0.77	92.7± 2.5	0.89
	≥50 ×10^9/L	31	92.9 ± 5.4		96.8 ± 3.7	
Race	Other	40	88.4 ± 5.6	0.71	93.7 ± 4.4	0.57
	White	128	91.9 ± 2.8		93.3 ± 2.5	
Gender	Male	88	90.6 ± 3.5	0.21	93.7 ± 2.9	0.77
	Female	80	92.0 ± 3.6		93.2 ± 3.3	
NCI/Rome Risk Group	Standard risk	127	90.1 ± 3.0	0.88	92.2 ± 2.7	0.96
	High risk	41	94.6 ± 4.1		97.6 ± 2.8	
SJ Risk Group	Low risk	111	92.4 ± 3.1	0.22	94.7 ± 2.6	0.13
	Standard/High risk	57	89.2 ± 4.3		91.0 ± 3.9	
CNS status	CNS1	141	91.1± 2.8	0.47	93.8± 2.3	0.95
	Others	27	92.3 ± 5.9		91.8 ± 6.0	
MRD day 19	Negative (<0.01%)	63	96.3 ± 5.9	0.08	100 ± 0.0	0.09
	Positive * (≥0.01%)	43	93.0 ± 4.7		94.4 ± 4.3	
MRD day 46	Negative (<0.01%)	97	95.6 ± 2.6	0.30	99.0 ± 1.3	0.12
	Positive * (≥0.01%)	13	92.3 ± 8.1		90.9 ± 8.7	
Treatment protocol	Total XIIIA	36	86.1 ± 5.7	0.05	88.9 ± 5.2	0.01
	Total XIIIB	38	84.1 ± 6.0		86.5 ± 5.6	
	Total XV	94	96.8 ± 2.4		98.9 ± 1.4	

* Due to small numbers, data from patients with MRD ≥0.01% to <1% and MRD ≥ 1% were combined. Four of 43 patients had ≥1% MRD on Day 19 and 0/13 on day 46

WBC: white blood cell; NCI: National Cancer Institute; SJ: St Jude; CNS: central nervous system; MRD: Minimal residual disease; EFS: Event-free survival; OS: overall survival