Erken T Hücreli Prekürsör ALL; Kötü Seyri Geri Çevirecek Umut mu Gelişiyor?

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Mersin Üniversitesi Tıp Fakültesi
İç Hastalıkları - Hematoloji BD.

- Çocukluk T-ALL'lerinin %10-13'ü
- Erişkin ALL'Lerin %5-10'u

- CD1a-, CD8-, CD5- (dim), CD7+
- ≥1 kök hücre / miyeloid antijen +

  (CD34, CD117, HLA-DR, CD13, CD33, CD11b, CD65)

- Prognoz oldukça kötü, CR: %90-95,

  1/3 vakada nüks, 10 yıllık OS: %19

- İndüksiyon tedavisi ile MRD (-)'liği diğer T-ALL'lerden daha fazla, ancak prognostik değil

CLINICAL TRIALS AND OBSERVATIONS

Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype

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Key Points

- Adult patients with ETP-ALL/LBL have poor long-term outcomes.
- Novel therapies are urgently needed for adult patients with ETP-ALL/LBL.

Early T-cell precursor (ETP) acute lymphoblastic leukemia/lymphoma (ALL/LBL) is a recently recognized high-risk T lymphoblastic leukemia/lymphoma (T-ALL/LBL) subgroup. The optimal therapeutic approaches to adult patients with ETP-ALL/LBL are poorly characterized. In this study, we compared the outcomes of adults with ETP-ALL/LBL who received treatment on frontline regimens with those of patients with other T-ALL/LBL immunophenotypic subtypes. Patients with newly diagnosed T-ALL/LBL who received frontline chemotherapy between the years 2000 and 2014 at The University of Texas MD Anderson Cancer Center were identified and immunophenotypically categorized into early, thymic, and mature per the World Health Organization (WHO) classification using CD1a and surface CD3 status. Patients with ETP-ALL/LBL were identified on the basis of the following immunophenotypes: $CD1a^-$, $CD8^-$, $CD5^-$ (dim), and positivity for 1 or more stem cell or myeloid antigens. A total of 111 patients with T-ALL/LBL (68% T-ALL; 32% T-LBL) with adequate immunophenotype data were identified. The median age was 30 years (range, 13-79). There was no difference in the outcomes of patients based on the WHO subtypes. Nineteen patients (17%) had ETP-ALL/LBL. The complete remission rate /complete remission with incomplete platelet recovery rate in patients with ETP-ALL/LBL was significantly lower than that of non–ETP-ALL/LBL patients (73% vs 91%; $P = .03$). The median overall survival for patients with ETP-ALL/LBL was 20 months vs not reached for the non–ETP-ALL/LBL patients ($P = .008$). ETP-ALL/LBL represents a high-risk disease subtype of adult ALL. Novel treatment strategies are needed to improve treatment outcomes in this T-ALL/LBL subset. (*Blood.* 2016;127(15):1863-1869)

Table 1. Baseline characteristics of T-ALL/LBL patients stratified by WHO immunophenotypic categories

	WHO categories				
	Total	Early	Thymic	Mature	*P* value
n	111	44	48	19	
Diagnosis					
ALL	76 (68)	34 (78)	27 (56)	15 (79)	
LBL	35 (32)	10 (22)	21 (44)	4 (21)	.05
Age	30 (13-79)	29 (13-75)	31 (17-79)	28 (17-64)	.14
Gender					
Female	29 (26)	9 (20)	15 (31)	5 (26)	
Male	82 (74)	35 (80)	33 (69)	14 (74)	.5
Cytogenetics (n = 105)					
Diploid	71 (68)	24 (57)	34 (74)	13 (76)	.2*
Hyperdiploid	5 (5)	2 (5)	2 (4)	1 (6)	
Hypodiploid	2 (2)	2 (5)			
Miscellaneous	27 (25)	14 (33)	10 (22)	3 (18)	
Presenting laboratory values					
WBC ($\times 10^9$/L)	8.0 (0.4-292.3)	5.5 (0.4-151.2)	8.1 (1.8-292.3)	8.6 (2.7-134.9)	.28
WBC ≥100 ($\times 10^9$/L)	8 (7)	2 (5)	5 (10)	1 (5)	.52
Platelet count ($\times 10^9$/L)	127 (10-488)	82 (10-391)	197 (10-488)	148 (22-402)	.14
Hemoglobin (g/dL)	11.4 (6.8-16.7)	10.3 (6.8-16.7)	11.3 (7.2-15.2)	11.9 (8.8-16.1)	.21
LDH (IU/L)	938 (209-32 029)	879 (209-11 300)	1298 (285-32 029)	834 (284-20 795)	.08
CNS involvement at diagnosis	6 (5)	4 (9)	1 (2)	1 (5)	.33
Treatment received					
Hyper-CVAD	43 (39)	15 (34)	18 (38)	10 (53)	
Hyper-CVAD + nelarabine	44 (40)	19 (43)	19 (39)	6 (31)	
Augmented BFM	24 (21)	10 (23)	11 (23)	3 (16)	

Cytogenetics either not done or insufficient metaphases recovered for 6 patients. Miscellaneous cytogenetics included del(5q), del(6q), del(9p), and others.
*Diploid vs other.

- %88 CR/CRp
- Medyan takip süresi 55 ay
- 8 yıllık EFS: %48, OS: %52
- Tedavi rejimlerinin sonuçları benzer

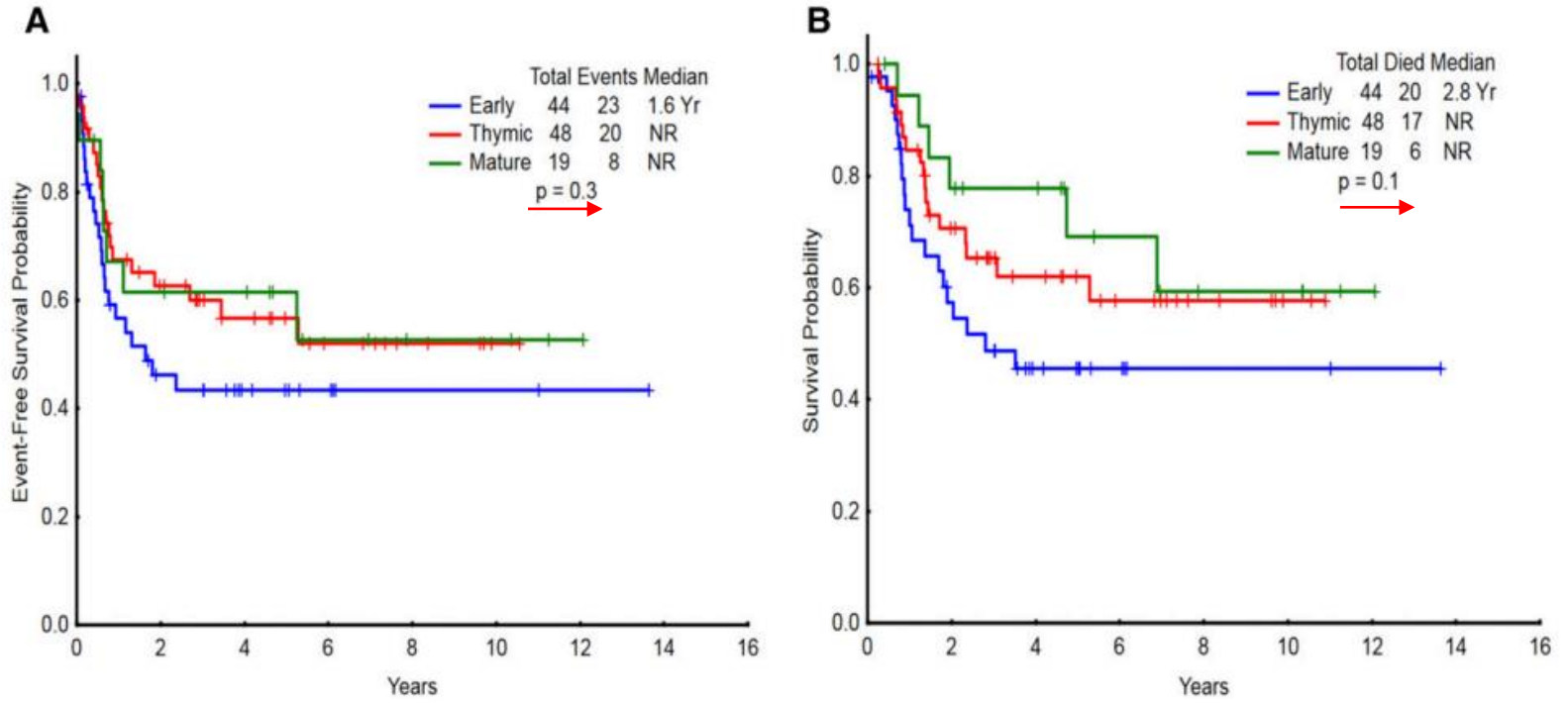

Figure 2. Survival for the entire study population categorized by immunophenotype per WHO classification. (A) Event-free survival and (B) overall survival of patients with T-ALL/LBL (n = 111) categorized as early, thymic, and mature per WHO classification. NR, not reached.

Table 2. Baseline characteristics of ETP-ALL/LBL patients

	Categories			
	Total	ETP ALL	Non-ETP ALL	*P* value
n	111	19	92	
Diagnosis				
ALL	76 (68)	15 (79)	61 (66)	
LBL	35 (32)	4 (21)	31 (34)	.28
Age	30 (13-79)	37 (19-75)	30 (13-79)	.26
Gender				
Female	29 (26)	4 (21)	25 (27)	
Male	82 (74)	15 (79)	67 (73)	.6
Cytogenetics (n = 105)				
Diploid	71 (68)	7 (37)	64 (75)	.002*
Hyperdiploid	5 (5)	2 (11)	3 (3)	
Hypodiploid	2 (2)		2 (2)	
Miscellaneous	27 (25)	10 (52)	17 (20)	
Presenting laboratory values				
WBC ($\times 10^9$/L)	8.0 (0.4-292.3)	13.4 (0.8-87.4)	7.8 (0.4-292.3)	.72
WBC ≥100 ($\times 10^9$/L)	8 (7)	0	8 (9)	.18
Platelet count ($\times 10^9$/L)	127 (10-488)	110 (10-391)	150 (10-488)	.27
Hemoglobin (g/dL)	11.4 (6.8-16.7)	10.3 (6.8-15)	11.4 (7.2-16.7)	.15
LDH (IU/L)	938 (209-32 029)	850 (209-4675)	959 (236-32 029)	.2
CNS involvement at diagnosis	6 (5)	3 (16)	3 (3)	.03
Treatment received				
Hyper-CVAD	43 (39)	6 (31)	37 (40)	
Hyper-CVAD + nelarabine	44 (40)	9 (48)	35 (38)	
Augmented BFM	24 (21)	4 (21)	20 (22)	

Cytogenetics either not done or insufficient metaphases recovered for 6 patients.
*Diploid vs other.

- CR/CRp
  - ETP-ALL: %73, diğerlerinde: %91 (p=0,03)
- Medyan EFS
  - ETP-ALL: 14 ay, OS: %52
- Medyan OS
  - ETP-ALL: 20 ay

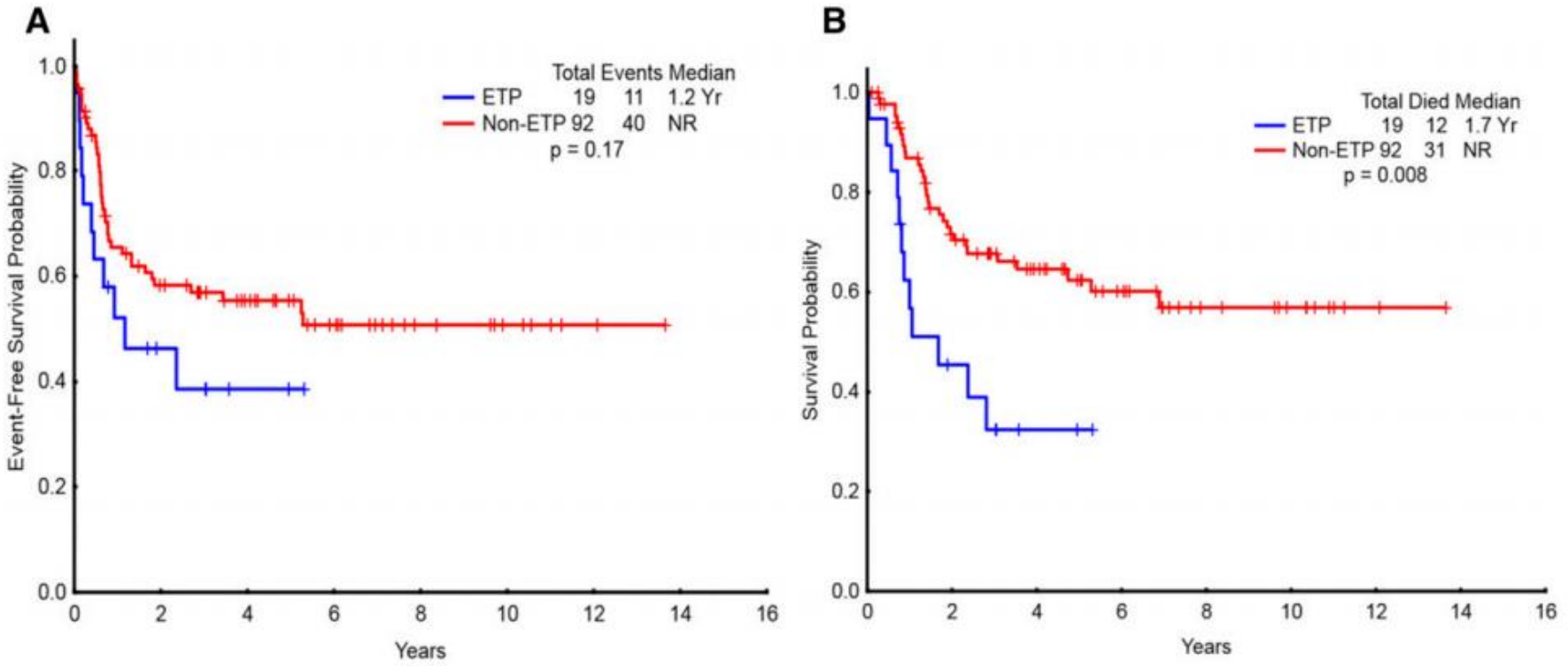

Figure 3. Survival for the entire study population categorized as ETP vs non-ETP. (A) Event-free survival and (B) overall survival of patients with ETP ALL (n = 19) compared with non-ETP ALL (n = 92). NR, not reached.

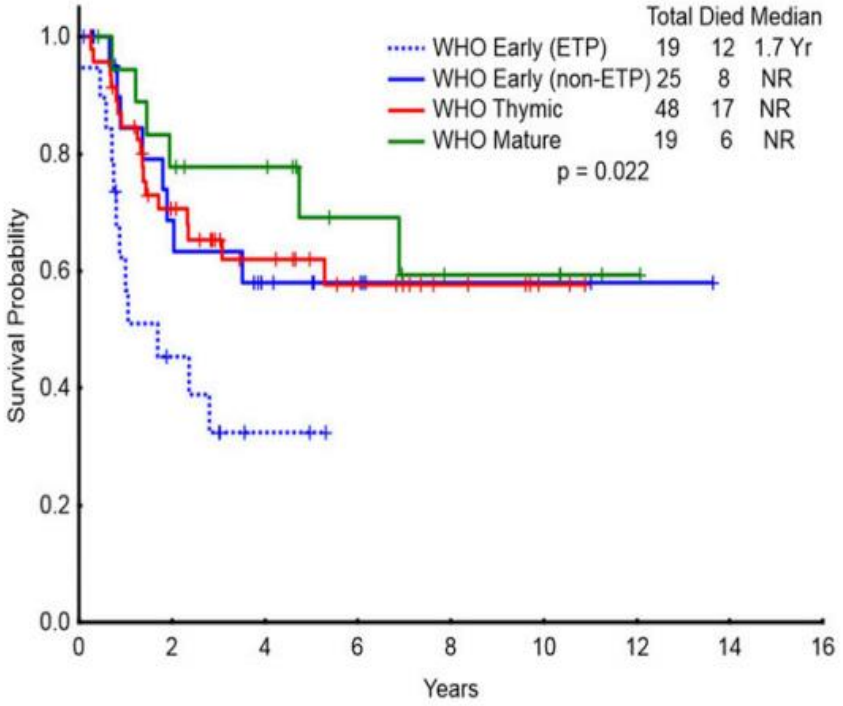

Figure 4. Survival for the entire study population categorized by ETP and WHO classification. Overall survival of patients with the WHO early classification subcategorized as ETP vs non-ETP, WHO thymic, and WHO mature (n = 111). NR, not reached.

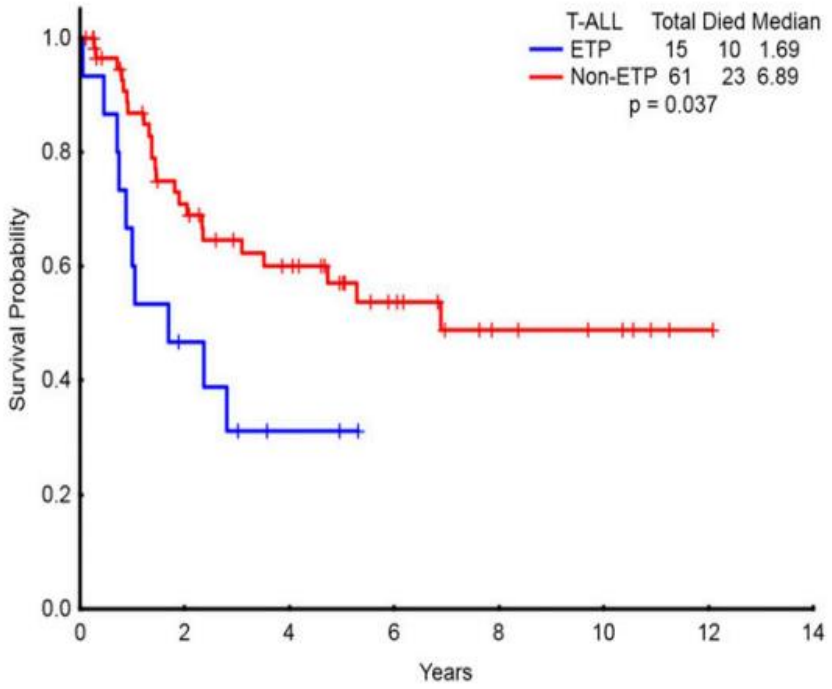

Figure 5. Survival for the patients presenting as ALL categorized as ETP vs non-ETP. Overall survival of ETP subtype (presenting as ALL, n = 15) vs non-ETP subtype (presenting as ALL, n = 61).

Br J Haematol. 2012 Feb;156(3):358-65. doi: 10.1111/j.1365-2141.2011.08955.x. Epub 2011 Nov 30.

Clinical significance of early T-cell precursor acute lymphoblastic leukaemia: results of the Tokyo Children's Cancer Study Group Study L99-15.

Inukai T[1], Kiyokawa N, Campana D, Coustan-Smith E, Kikuchi A, Kobayashi M, Takahashi H, Koh K, Manabe A, Kumagai M, Ikuta K, Hayashi Y, Tsuchida M, Sugita K, Ohara A.

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Abstract

Early T-cell precursor acute lymphoblastic leukaemia (ETP-ALL) is a recently identified subtype of T-ALL with distinctive gene expression and cell marker profiles, poor response to chemotherapy and a very high risk of relapse. We determined the reliability of restricted panel of cell markers to identify EPT-ALL using a previously classified cohort. Then, we applied the cell marker profile that best discriminated ETP-ALL to a cohort of 91 patients with T-ALL enrolled in the Tokyo Children's Cancer Study Group L99-15 study, which included allogeneic stem cell transplantation (allo-SCT) for patients with poor prednisone response. Five of the 91 patients (5·5%) met the ETP-ALL criteria. There were no significant differences in presenting clinical features between these and the remaining 86 patients. Response to early remission induction therapy was inferior in ETP-ALL as compared with T-ALL. The ETP-ALL subgroup showed a significantly poorer event-free survival (4-year rate; 40%) than the T-ALL subgroup (70%, P=0·014). Of note, three of four relapsed ETP-ALL patients survived after allo-SCT, indicating that allo-SCT can be effective for this drug-resistant subtype of T-ALL.

- Allo nakil etkin bir tedavi seçeneği olabilir

Table II. Demographic characteristics of the patients.

		T-ALL	ETP-ALL	χ^2-test
		$N = 86$	$N = 5$	P
Sex	Male	67	2	0·089
	Female	19	3	
WBC	≥100 × 10^9/l	42 (48·8%)	1 (20%)	0·36
Age	≥10 Years old	39 (45·3%)	3 (60%)	0·66
NCI risk group	Standard	14	1	1·0
	High	72	4	
Mediastinal mass	Yes	51 (59·3%)	3 (60%)	1·0
FAB classification	L1	59	2	0·32
	L2	25	3	
CNS involvement	Yes	3 (3·5%)	0 (0%)	1·0
Treatment subgroup	IR	22	1	
	HR	33	0	
	HR-SCT	31	4	
	HR-SCT%	36·0%	80%	0·070
Remission failure	Yes	4/85 (4·7%)	0/5 (0%)	1·0
Relapse	BM	15	4	
	CNS	2	0	
	Thymus	1	0	
	BM + thymus	2	0	
	Unknown	2	0	
SCT	Yes	42/85 (49·4%)	5/5 (100%)	0·057
Status at SCT	CR1	28	2	
	CR2	3	2	
	CR3	1	0	
	Failure	1	0	
	Rel1	3	1	
	Rel2	1	0	
	Unknown	5	0	

Table III. Clinical features of stem-cell transplantation in patients with ETP-ALL.

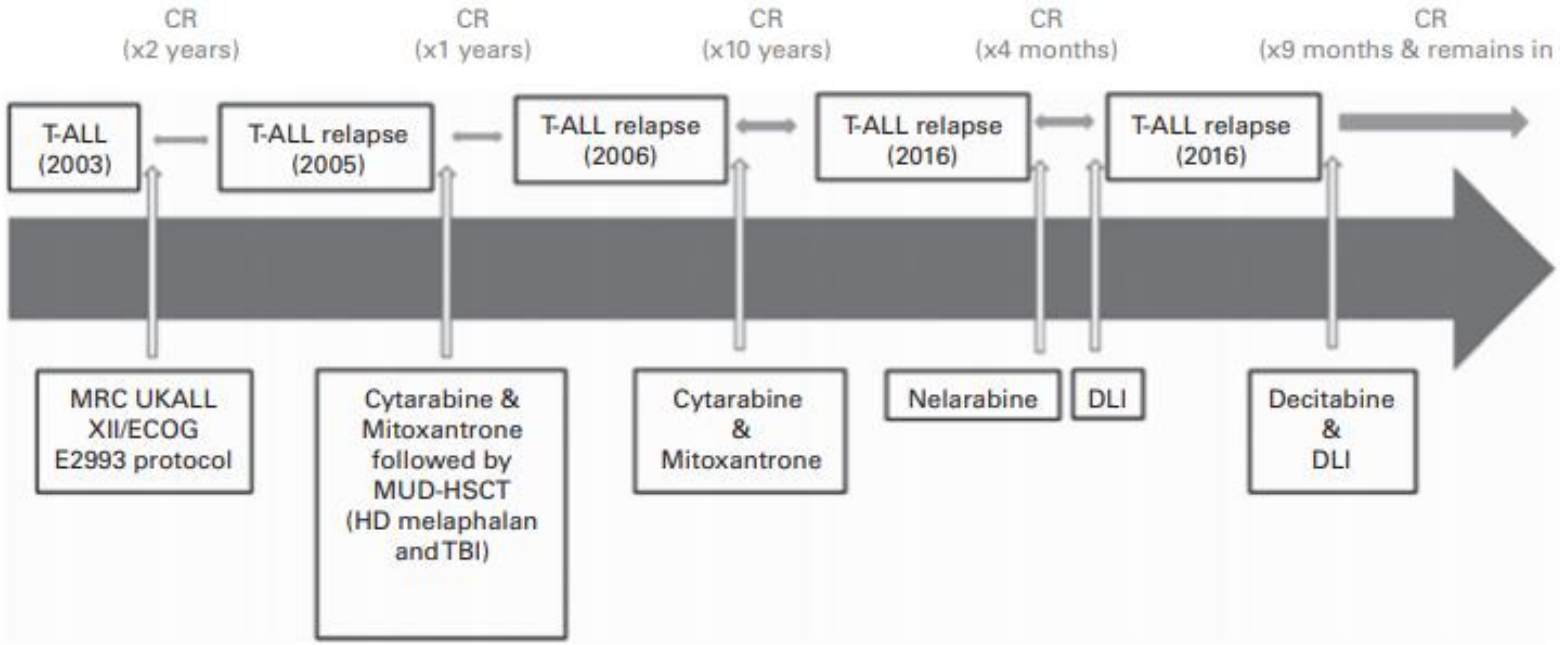
	SCT				Relapse		Final outcome		
Score	Status	Donor	Source	Time from diagnosis (months)	Site	Time from diagnosis (months)	Status	Survival	Time from diagnosis (months)
12	CR2	Unrelated	CB	6	BM	3	CR2	Alive	70
10	CR1	Sibling	BM	8	BM	31	Rel3	Dead	58
8	CR1	Unrelated	BM	8	No		CR1	Alive	31
7	Rel1	Sibling	PBSC	8	BM	7	CR2	Alive	75
7	CR2	Unrelated	BM	53	BM	48	CR2	Alive	61

SCT, allogeneic stem cell transplantation; CB, cord blood cell; BM, bone marrow; PBSC, peripheral blood stem cell; CR1, first remission; CR2, second remission; Rel1, first relapse; Rel3, third relapse.

Bone Marrow Transplant. 2017 Nov;52(11):1583-1584. doi: 10.1038/bmt.2017.191. Epub 2017 Sep 11.

Durable remission with salvage decitabine and donor lymphocyte infusion (DLI) for relapsed early T-cell precursor ALL.

El Chaer F[1,2], Holtzman N[1,2], Binder E[1,2], Porter NC[3], Singh ZN[4], Koka M[4], Rapoport AP[1,2], Emadi A[1,2].



J Exp Med. 2014 Apr 7;211(4):701-13. doi: 10.1084/jem.20122727. Epub 2014 Mar 31.

Interleukin-7 receptor mutants initiate early T cell precursor leukemia in murine thymocyte progenitors with multipotent potential.

Treanor LM[1], Zhou S, Janke L, Churchman ML, Ma Z, Lu T, Chen SC, Mullighan CG, Sorrentino BP.

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1 Department of Hematology and 2 Department of Pathology, Division of Experimental Hematology, St. Jude Children's Research Hospital, Memphis, TN 38105.

Abstract

Early T cell precursor acute lymphoblastic leukemia (ETP-ALL) exhibits lymphoid, myeloid, and stem cell features and is associated with a poor prognosis. Whole genome sequencing of human ETP-ALL cases has identified recurrent mutations in signaling, histone modification, and hematopoietic development genes but it remains to be determined which of these abnormalities are sufficient to initiate leukemia. We show that activating mutations in the interleukin-7 receptor identified in human pediatric ETP-ALL cases are sufficient to generate ETP-ALL in mice transplanted with primitive transduced thymocytes from p19(Arf-/-) mice. The cellular mechanism by which these mutant receptors induce ETP-ALL is the block of thymocyte differentiation at the double negative 2 stage at which myeloid lineage and T lymphocyte developmental potential coexist. Analyses of samples from pediatric ETP-ALL cases and our murine ETP-ALL model show uniformly high levels of LMO2 expression, very low to undetectable levels of BCL11B expression, and a relative lack of activating NOTCH1 mutations. We report that pharmacological blockade of Jak-Stat signaling with ruxolitinib has significant antileukemic activity in this ETP-ALL model. This new murine model recapitulates several important cellular and molecular features of ETP-ALL and should be useful to further define novel therapeutic approaches for this aggressive leukemia.

- IL-7 reseptör mutasyonu ETP-ALL'yi tetikliyor
- Bu hücre dizilerinde STAT4 fosforilasyonu var
  - ruksolitinib bu hücre dizisinin proliferasyonunu inhibe ediyor

Efficacy of JAK/STAT pathway inhibition in murine xenograft models of early T-cell precursor (ETP) acute lymphoblastic leukemia

Shannon L. Maude,[1,2] Sibasish Dolai,[3] Cristina Delgado-Martin,[4] Tiffaney Vincent,[1] Alissa Robbins,[3] Arthavan Selvanathan,[3] Theresa Ryan,[1] Junior Hall,[1] Andrew C. Wood,[5] Sarah K. Tasian,[1,2] Stephen P. Hunger,[1,2] Mignon L. Loh,[4] Charles G. Mullighan,[6] Brent L. Wood,[7] Michelle L. Hermiston,[4] Stephan A. Grupp,[1,2] Richard B. Lock,[3] and David T. Teachey[1,2]

[1]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA; [2]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]Leukaemia Biology, Children's Cancer Institute, Lowy Cancer Research Centre, University of New South Wales, Sydney, Australia; [4]Division of Hematology/Oncology, University of California, San Francisco Benioff Children's Hospital, San Francisco, CA; [5]Molecular Medicine and Pathology, University of Auckland, Auckland, New Zealand; [6]Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN; and [7]Division of Hematopathology, University of Washington and Seattle Cancer Care Alliance, Seattle, WA

Key Points

- ETP-ALL, a high-risk subtype of T-ALL, is characterized by aberrant activation of the JAK/STAT signaling pathway.
- The JAK1/2 inhibitor ruxolitinib demonstrates robust activity in patient-derived xenograft models of ETP-ALL.

Early T-cell precursor (ETP) acute lymphoblastic leukemia (ALL) is a recently described subtype of T-ALL characterized by a unique immunophenotype and genomic profile, as well as a high rate of induction failure. Frequent mutations in cytokine receptor and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways led us to hypothesize that ETP-ALL is dependent on JAK/STAT signaling. Here we demonstrate aberrant activation of the JAK/STAT pathway in ETP-ALL blasts relative to non-ETP T-ALL. Moreover, ETP-ALL showed hyperactivation of STAT5 in response to interleukin-7, an effect that was abrogated by the JAK1/2 inhibitor ruxolitinib. In vivo, ruxolitinib displayed activity in 6 of 6 patient-derived murine xenograft models of ETP-ALL, with profound single-agent efficacy in 5 models. Ruxolitinib treatment decreased peripheral blast counts relative to pretreatment levels and compared with control ($P < .01$) in 5 of 6 ETP-ALL xenografts, with marked reduction in mean splenic blast counts ($P < .01$) in 6 of 6 samples. Surprisingly, both JAK/STAT pathway activation and ruxolitinib efficacy were independent of the presence of JAK/STAT pathway mutations, raising the possibility that the therapeutic potential of ruxolitinib in ETP-ALL extends beyond those cases with JAK mutations. These findings establish the preclinical in vivo efficacy of ruxolitinib in ETP-ALL, a biologically distinct subtype for which novel therapies are needed. (*Blood*. 2015;125(11):1759-1767)

- >%60 vakada *IL7R*, *RAS (NRAS*, *KRAS*, *FLT3)*, *JAK/STAT* (*JAK1*, *JAK3*, *SH2B3*) mutasyonları var
- ETP-ALL'de anormal JAK/STAT aktivasyonu
- IL-7 ile STAT5 hiperaktivasyonu
- Ksenogref 6 fare modelinde ruksolitinib ile yanıt alınmış (*JAK* mutasyonundan bağımsız yanıt)

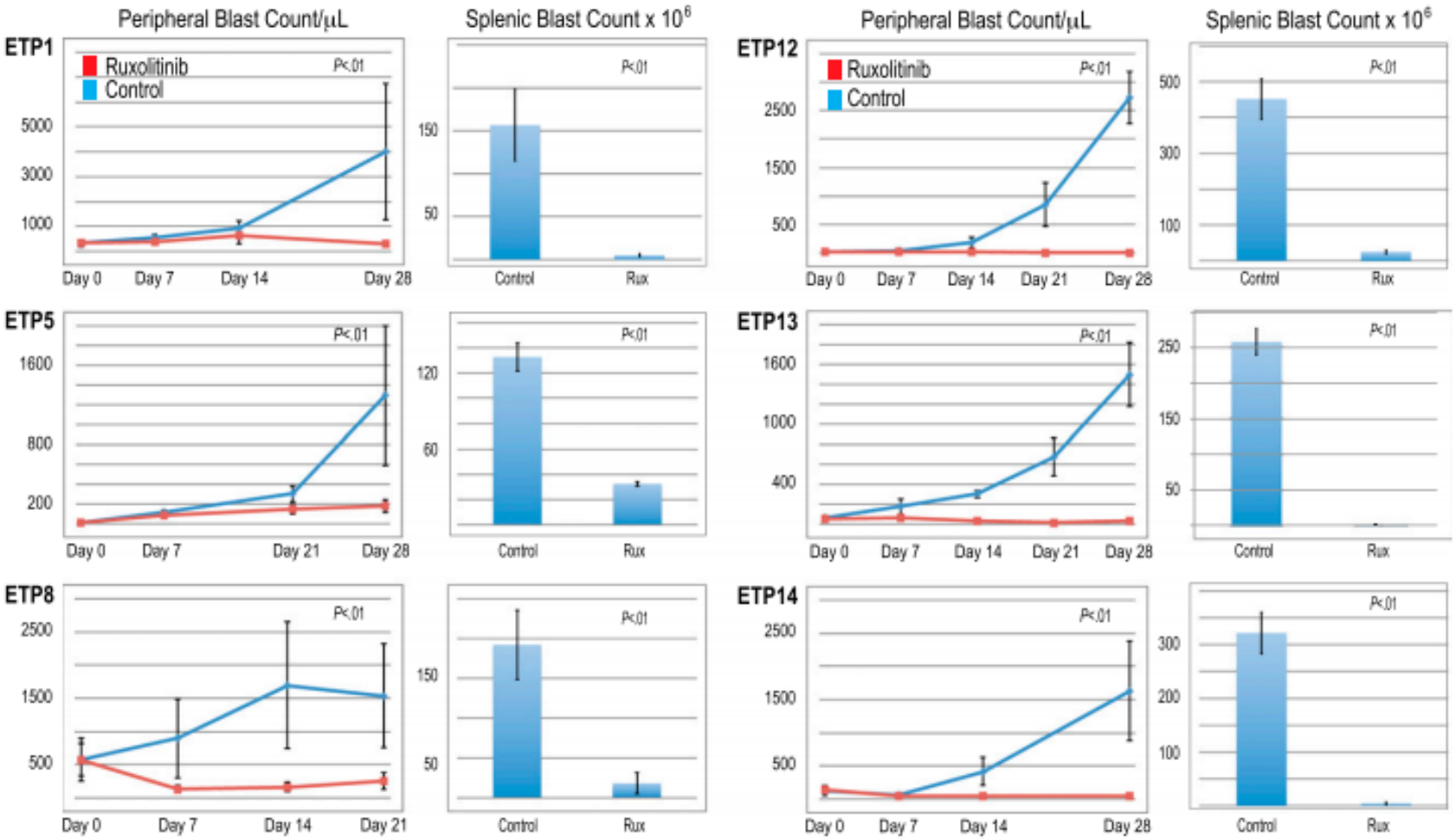


Figure 5. Efficacy of ruxolitinib in xenograft models of ETP-ALL. Peripheral blood blast count over time and splenic blast count at death in ETP-ALL xenografts. Graphed are means and standard deviations with absolute blast count on the vertical axis and days of treatment on the horizontal axis.

Blood. 2014 Dec 11;124(25):3738-47. doi: 10.1182/blood-2014-05-574566. Epub 2014 Oct 9.

ABT-199 mediated inhibition of BCL-2 as a novel therapeutic strategy in T-cell acute lymphoblastic leukemia.

Peirs S[1], Matthijssens F[1], Goossens S[2], Van de Walle I[3], Ruggero K[4], de Bock CE[5], Degryse S[5], Canté-Barrett K[6], Briot D[7], Clappier E[7], Lammens T[8], De Moerloose B[8], Benoit Y[8], Poppe B[1], Meijerink JP[6], Cools J[5], Soulier J[7], Rabbitts TH[4], Taghon T[3], Speleman F[1], Van Vlierberghe P[1].

Author information

Abstract

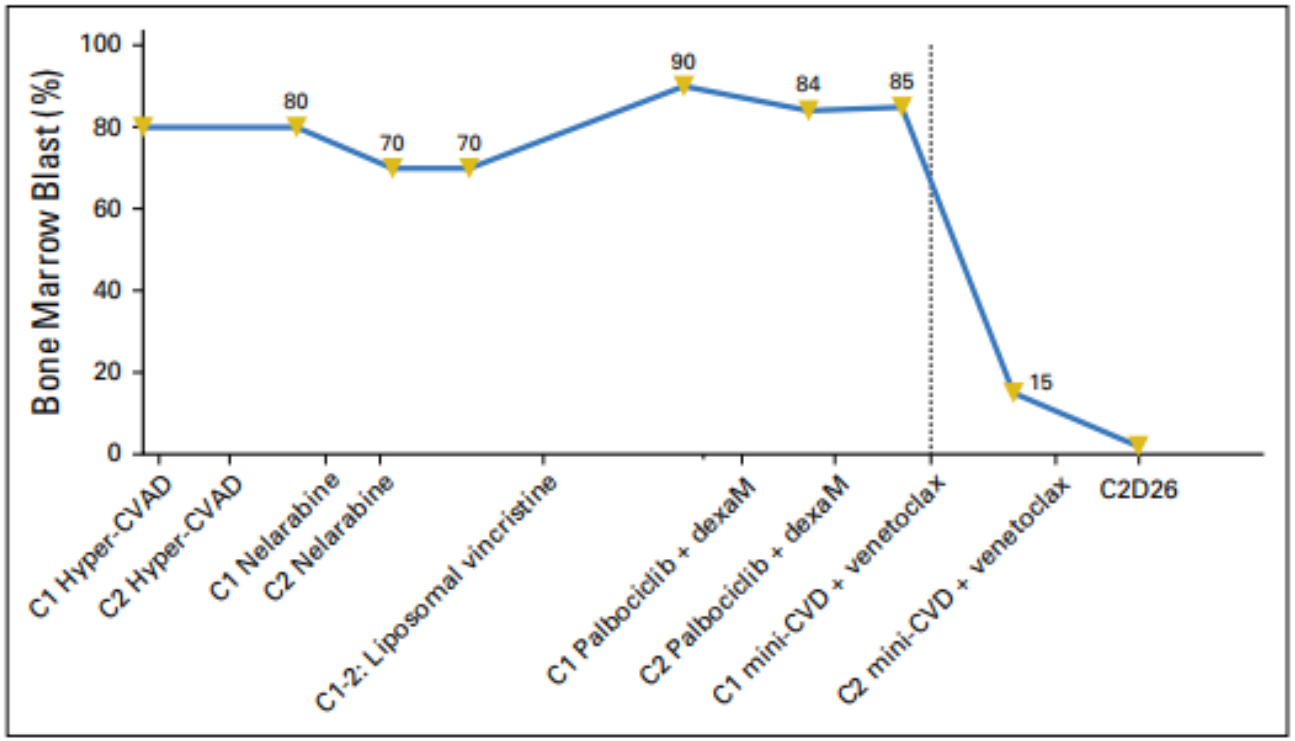
T-cell acute lymphoblastic leukemia (T-ALL) is a high-risk subtype of acute lymphoblastic leukemia (ALL) with gradually improved survival through introduction of intensified chemotherapy. However, therapy-resistant or refractory T-ALL remains a major clinical challenge. Here, we evaluated B-cell lymphoma (BCL)-2 inhibition by the BH3 mimetic ABT-199 as a new therapeutic strategy in human T-ALL. The T-ALL cell line LOUCY, which shows a transcriptional program related to immature T-ALL, exhibited high in vitro and in vivo sensitivity for ABT-199 in correspondence with high levels of BCL-2. In addition, ABT-199 showed synergistic therapeutic effects with different chemotherapeutic agents including doxorubicin, l-asparaginase, and dexamethasone. Furthermore, in vitro analysis of primary patient samples indicated that some immature, TLX3- or HOXA-positive primary T-ALLs are highly sensitive to BCL-2 inhibition, whereas TAL1 driven tumors mostly showed poor ABT-199 responses. Because BCL-2 shows high expression in early T-cell precursors and gradually decreases during normal T-cell differentiation, differences in ABT-199 sensitivity could partially be mediated by distinct stages of differentiation arrest between different molecular genetic subtypes of human T-ALL. In conclusion, our study highlights BCL-2 as an attractive molecular target in specific subtypes of human T-ALL that could be exploited by ABT-199.

- Yüksek düzeyde BCL-2 ekspresyonu
- Venetoklaks ETP-ALL hücre dizisinde apoptozu indükler

JCO Precis Oncol. 2018;2. doi: 10.1200/PO.18.00127. Epub 2018 Aug 22.

First report of clinical response to Venetoclax in Early T-cell Precursor Acute Lymphoblastic Leukemia.

Numan Y[1], Alfayez M[1], Maiti A[2], Alvarado Y[1], Jabbour EJ[1], Ferrajoli A[1], Konoplev SN[3], Kantarjian HM[1], Bose P[1].



- 71 yaş kadın hasta, yüksek BCL-2 ekspresyonu
- Faz Ib çalışma başladı

Özet

- ETP-ALL'de prognoz oldukça kötü
- Uygun hastalarda allo-nakil yapılmalı
- Nelarabin eklenmesi muhtemelen ek katkı sağlamıyor
- Ruksolitinib ve venetoklaks ile başarılı sonuçlar
- Desitabin ± DLI etkili olabilir