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Therapy-related acute lymphoblastic leukemia has distinct clinical and cytogenetic features compared to *de novo* acute lymphoblastic leukemia, but outcomes are comparable in transplanted patients

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ABSTRACT

Therapy-related acute lymphoblastic leukemia remains poorly defined due to a lack of large data sets recognizing the defining characteristics of this entity. We reviewed all consecutive cases of adult acute lymphoblastic leukemia treated at our institution between 2000 and 2017 and identified therapy-related cases - defined as acute lymphoblastic leukemia preceded by prior exposure to cytotoxic chemotherapy and/or radiation. Of 1022 patients with acute lymphoblastic leukemia, 93 (9.1%) were classified as therapy-related. The median latency for therapy-related acute lymphoblastic leukemia onset was 6.8 years from original diagnosis, and this was shorter for patients carrying the *MLL* gene rearrangement compared to those with other cytogenetics. When compared to *de novo* acute lymphoblastic leukemia, therapy-related patients were older (P<0.01), more often female (P<0.01), and had more *MLL* gene rearrangement (P<0.0001) and chromosomes 5/7 aberrations (P=0.02). Although therapy-related acute lymphoblastic leukemia was associated with inferior 2-year overall survival compared to *de novo* cases (46.0% *vs.* 68.1%, P=0.001), prior exposure to cytotoxic therapy (therapy-related) did not independently impact survival in multivariate analysis (HR=1.32; 95% CI: 0.97-1.80, P=0.08). There was no survival difference (2-year = 53.4% *vs.* 58.9%, P=0.68) between the two groups in patients who received allogenic hematopoietic cell transplantation. In conclusion, therapy-related acute lymphoblastic leukemia represents a significant proportion of adult acute lymphoblastic leukemia diagnoses, and a subset of cases carry clinical and cytogenetic abnormalities similar to therapy-related myeloid neoplasms. Although survival of therapy-related acute lymphoblastic leukemia was inferior to *de novo* cases, allogeneic hematopoietic cell transplantation outcomes were comparable for the two entities.

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Introduction

Therapy-related leukemia has increasingly emerged as a long-term complication of cytotoxic therapy (i.e., chemotherapy and radiation) for patients who have undergone treatment for preceding malignancies.[1] Therapy-related myeloid neoplasms (t-MNs) are widely recognized and comprise an established category in the WHO classification of MNs, which include therapy-related acute myeloid

leukemia (t-AML) and therapy-related myelodysplastic syndrome (t-MDS).[2] T-MNs, in general, carry poor cytogenetic and molecular features at the time of diagnosis compared to de novo MNs, and are characterized by poor responsiveness to conventional treatment and inferior rates of overall outcome, such as complete remission (CR), death in remission, relapse and survival.[1,3,4]

Similar to t-MN, acute lymphoblastic leukemia (ALL) may also develop after prior exposure to cytotoxic therapies and is often referred to as therapy-related ALL (t-ALL).[5-11] Similar to t-MNs, the pathogenesis of t-ALL is likely attributed to the genotoxic effect of cytotoxic therapies on hematopoietic progenitor cells. However, to date, this entity has not been fully recognized and only a few relatively small series have been reported.[5-11] Unfortunately, several of these studies also include "secondary ALL," i.e., cases with a history of prior malignancies (including non-lymphoid cancers), but no cytotoxic therapy exposure, making the accurate identification of t-ALL- specific clinical and genetic features somewhat challenging. Few large registry series of secondary ALL have been reported and have highlighted the inferior survival of this entity.[12,13] However, these registry studies have not drawn a distinction between cases with prior malignancies that did not receive cytotoxic therapies and those that did. Additionally, these studies lack specific details on ALL genetics as well as details on prior cancer-specific therapies due to limitations of registry data.[12,13] Furthermore, the optimal therapy for t-ALL as well as t-ALL patients' ability to tolerate intensive treatment remain poorly defined. This becomes particularly important when a t-ALL patient has high risk features and is being considered for allogeneic hematopoietic cell transplantation (HCT). A particular concern in this regard is higher treatment-related morbidity and mortality given the prior exposure to cytotoxic therapies in t-ALL patients. Therefore, studies that clearly distinguish t-ALL are necessary in order to fill the scientific and clinical knowledge gap in this field.

We report here a large, single institutional, t-ALL cohort defined using strict inclusion criteria that restrict analysis only to cases with documented exposure to cytotoxic therapy prior to developing ALL. In contrast to registry data, we were able to gather details regarding prior malignancies and therapies, clinical and genetic characteristics of the ALL, treatment, and outcomes of t-ALL from our institutional database. Our study aims to estimate the frequency of t-ALL among adult patients, to evaluate unique clinical and genetic features associated with t-ALL that are distinctive from *de novo* ALL, and to evaluate the prognostic impact of prior exposure to cytotoxic therapy (t-ALL) on clinical outcomes, including response to induction therapy, utilization and outcomes of allogeneic HCT and survival.

Methods

Patients

We reviewed all consecutive cases of adult ALL seen at City of Hope between 2000 and 2017 in order to identify cases of t-ALL. For the purposes of this study, t-ALL was defined as ALL occurring after prior exposure to chemotherapy and/or radiation. Any cases of ALL preceded by a malignancy but without exposure to cytotoxic therapy were classified as de novo ALL. t-ALL and *de novo* ALL cases were then compared for distinctive demographic, clinical, and cytogenetic features and for outcomes. The study was approved by the City of Hope Institutional Review Board.

Endpoints

Overall survival (OS) for all patients was defined as the time interval from ALL diagnosis to date of death from any cause or date of last contact. When analyzing patients who underwent allogeneic HCT, OS was defined as the time from transplant to date of death from any cause or date of last contact. Non-relapse mortality (NRM) was measured from time of transplant to death from any cause other than relapse/progression. Relapse/progression was treated as a competing event for NRM.

Statistical analyses

Demographic, disease, and treatment characteristics were summarized using descriptive statistics. Two sample *t*-test, chi-squared test, and fisher's exact test were used to determine differences in demographics and disease characteristics of interest. Survival estimates were calculated using the Kaplan-Meier product-limit method and differences between Kaplan-Meier curves were assessed using the log-rank test.[14] The cumulative incidence of NRM was calculated using competing risk analysis and differences between cumulative incidence curves were tested using the Gray method.[15]

Prognostic variables analyzed include age and white blood cell (WBC) count as continuous variables, cytogenetics (NK, Ph^+, MLL, complex [≥5 abnormalities], or other/unknown), prior therapy (chemotherapy, radiation, or chemotherapy plus radiation), prior disease (solid tumor *vs.* blood cancer), allogeneic HCT treated as a time dependent variable, race/ethnicity (white, Hispanic, other), phenotype (T *vs.* B), sex (female *vs.* male), and use of topoisomerase II inhibitor (no *vs.* yes). The significance of demographic, disease, and treatment features was assessed using logistic regression to determine effect on type of ALL diagnosis and Cox proportional hazards regression analysis to determine effect on survival. All analyses performed using SAS version 9.4 (SAS Institute, Cary, NC). Data were locked for analysis January 17, 2018.

Results

Comparison of clinical and pathologic characteristics t-ALL and *de novo* ALL

Between 2000 and 2017, 1022 cases of adult ALL were evaluated and/or treated at City of Hope; 93 (9.1%) had t-ALL. When compared to *de novo* ALL, t-ALL patients were older (55 years *vs.* 37 years, $P<0.01$), and were more often female (57% *vs.* 42%, $P<0.01$). There was no difference in proportions of leukemia phenotypes (precursor B-cell *versus* T-cell) between t-ALL and *de novo* ALL. t-ALL patients were more often whites (52% *vs.* 34%) and less often Hispanics (29% *vs.* 48%) compared to *de novo* ALL ($P<0.01$). t-ALL cases were associated with different cytogenetic profiles ($P<0.01$) compared to *de novo* ALL. t-ALL cases were enriched with *MLL* gene rearrangement (KMT2A) (17% *vs.* 4%, $P<0.01$) and have less normal karyotype (18% *vs.* 30%, $P=0.017$) when compared to *de novo* ALL. Among patients with available conventional cytogenetics, monosomy and/or long arm deletion of chromosomes 5 and/or 7 were more common in t-ALL compared to *de novo* ALL (16% *vs.* 8%, $P=0.02$) (Table 1).

In multivariate analysis, t-ALL was associated with older age (OR= 1.06; 95% CI:1.04-1.07, $P<0.0001$), female

sex (OR=1.64; 95% CI:1.02-2.65, *P*=0.04), lower WBC at presentation (OR=0.996; 95%CI:0.99-1.00, *P*=0.038), and *MLL* gene rearrangement (OR=6.52; 95%CI:2.66-15.96, *P*<0.0001) (Table 2).

Characteristics of the t-ALL cohort

The original diagnosis prior to t-ALL onset was solid cancer in 52 (56%) patients, hematological cancer in 33 (35%) patients, combined solid and hematological cancers in 2 (2%) patients, and 6 (6%) patients had non-malignant diseases treated with cytotoxic therapies. Breast cancer was the most common prior diagnosis (n=23, 25%) followed by lymphoproliferative neoplasms (non-Hodgkin lymphoma, chronic lymphocytic leukemia, Hodgkin's lymphoma) (n=21, 23%), and multiple myeloma (MM) (n=11, 12%). Thirty-five (38%) patients had chemotherapy alone as prior therapy for the original diagnosis, 26 (28%) had only radiotherapy, 32 (34%) had a combination of chemotherapy and radiation, 17 (18%) received an autologous hematopoietic cell transplant (HCT) as part of prior therapy, and 13 (14%) had immunomodulatory agents in combination with chemotherapy. Interestingly, 2 cases had antecedent MDS before presenting with t-ALL (Table 3).

Eighty-three percent of t-ALL patients with available conventional cytogenetic and/or FISH studies had cytogenetic abnormalities. Philadelphia (Ph) chromosome was the most common finding on cytogenetics for the t-ALL cohort, and followed by normal karyotype and mixed lineage leukemia (MLL) gene rearrangement. Among 78

Table 1. Overall comparison between t-ALL and *de novo* ALL.

	All patients	*De novo* ALL	t-ALL	*P*
Number	1022	929	93	
Age	39 (6-85)	37 (6-85)	55 (23-85)	< 0.01
Sex				
Female	440 (43)	387 (42)	53 (57)	<0.01
Male	582 (57)	542 (58)	40 (43)	
Phenotype				
B	870 (85)	785 (85)	85 (91)	0.09
T	150 (15)	142 (15)	8 (9)	
ETP#	20(19)	19 (19)	1 (17)	
B/T	2 (<1)	2 (<1)	0 (0)	
WBC	16.3 (0.2-778)	17 (0.2-778)	10 (0.9-330)	0.10
Cytogenetic				<0.01
Ph+	270 (26)	241 (26)	29 (31)	0.27
MLL	57 (6)	41 (4)	16 (17)	<0.01
NK	296 (29)	279 (30)	17 (18)	0.017
Complex	46 (5)	4 (4)	5 (5)	0.60
Others	250 (24)	229 (25)	21 (23)	
UK	103 (10)	98 (11)	5 (5)	
Ch 5/7q deletion/ monosomy				0.02
YES	71 (8)	58 (8)	13 (16)	
NO	779 (92)	711 (92)	68 (84)	
Ph+ & available cytogenetics	204	182 (76)	22 (76)	0.07
ACA	107	91 (50)	16 (73)	
Isolated Ph	97	91 (50)	6 (27)	
Race				<0.01
White	368 (36)	320 (34)	48 (52)	
Hispanic	472 (46)	445 (48)	27 (29)	
Asian	86 (9)	76 (8)	10 (11)	
AA	31 (3)	29 (3)	2 (2)	
Others	22 2)	19 (2)	3 (3)	
UK	43 (4)	40 (4)	3 (3)	

ETP: early thymic T cell; WBC: white blood cell count; Ph+: Philadelphia-chromosome positive; MLL: Mixed lineage leukemia; NK: normal karyotype; UK: unknown, Ch: chromosome; ACA: additional cytogenetic abnormalities; AA: African American. # There were 108 cases of T-cell ALL (*de novo* = 102, t-ALL = 6) with available adequate markers upon review to make the diagnosis of ETP.

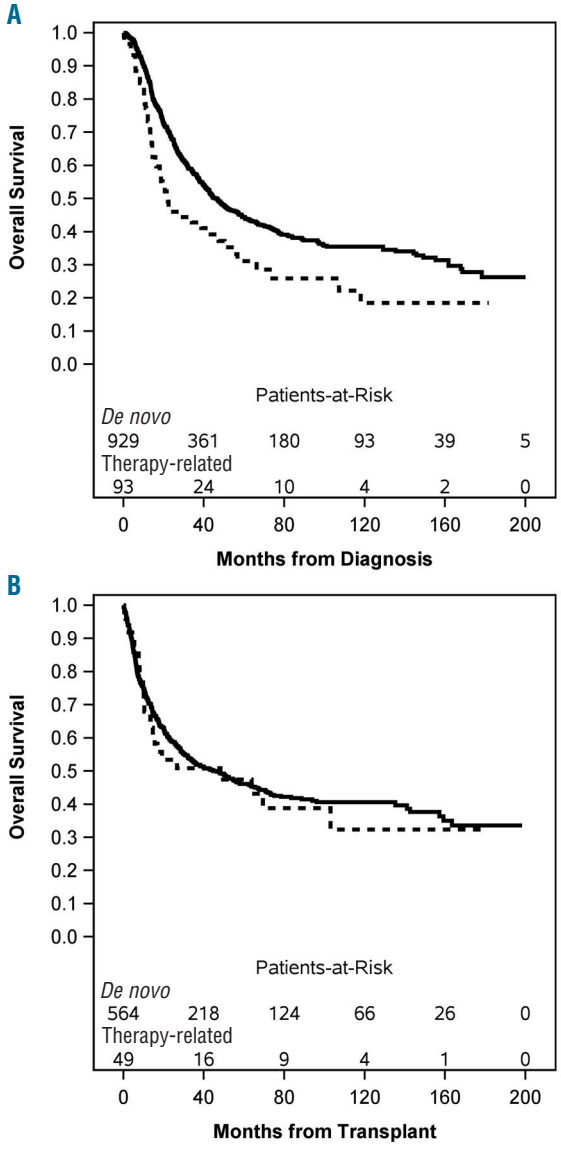

Figure 1. Survival for t-ALL and *de novo* ALL. A. Survival curves for all t-ALL (dashed line) and *de novo* ALL (solid line) and B. Survival curves for t-ALL (dashed line) and *de novo* (solid line) ALL in patients who underwent allogeneic HCT during ALL therapy.

cases with available conventional cytogenetics, 14 (18%) patients met the definition of monosomal karyotype (two or more distinct autosomal chromosome monosomies or one single autosomal monosomy in the presence of structural abnormalities).[16]

The median latency for developing ALL was 6.8 years (0.8-50.7) from the time of original malignancy/disease diagnosis, and it was shorter in patients carrying the MLL gene rearrangement compared to patients carrying the Ph chromosome or other cytogenetic subgroups (2.8 years *vs.* 7.0 years *vs.* 8.0 years, $P<0.01$), respectively. Only cytogenetics was independently associated with the interval duration for developing ALL ($P=0.02$) (Table 4).

Topoisomerase II inhibitors were administered as part of prior therapy in 41% (n=38) of the t-ALL cohort, and were given in combination with alkylators and radiation in the majority of patients. Prior topoisomerase II inhibitor exposure did not influence the latency period between the original disease diagnosis and ALL onset ($P=0.45$) or the cytogenetic profile ($P=0.69$).

All t-ALL patients except for one received induction therapy for ALL. HyperCVAD with or without tyrosine kinase inhibitors was the most commonly used regimen (n=48, 52%) to induce t-ALL patients. Median follow up for all patients and surviving t-ALL patients was 14.4 months (range: 0.2-181.7) and 17 months (range: 0.8-181.7), respectively. Neither age ($P=0.43$), prior therapy ($P=0.44$), cytogenetic subgroup ($P=0.51$), prior diagnosis ($P=0.51$) nor the use allogeneic HCT ($P=0.07$) influenced OS for t-ALL patients in multivariate analysis (*Online Supplementary Table S1*). Nine (9.7%) patients had their original malignancies relapse after ALL diagnosis. However, 2-year OS was not different between patients who had recurrence of their original disease and those who did not (45% *vs.* 50%, $P=0.91$).

Comparison of outcomes of t-ALL and *de novo* ALL

The median follow up for all patients and for surviving patients were 26 months (range: 0.2-255.5) and 43.6 months (range: 0.3-255.5), respectively. The 2-year OS for all patients was 66.2% (95% CI 63.0-69.2). CR rate was similar for both t-ALL and *de novo* ALL patients (85%, $P=0.88$) as was the percentage of patients who underwent allogeneic HCT consolidation (53% *vs.* 61%, $P=0.15$). However, more patients with t-ALL were transplanted in CR1 compared to *de novo* ALL (76% *vs.* 60%, $P=0.05$).

The 2-year OS was inferior for t-ALL compared to de novo ALL (46.0% *vs.* 68.1%, P=0.001) (Figure 1A). In multivariate analysis, age at ALL diagnosis ($P<0.0001$), WBC at diagnosis ($P=0.003$), cytogenetics ($P<0.0001$), sex ($P=0.005$), HCT ($P=0.02$) and leukemia phenotype ($P=0.02$) influenced OS for all patients. Interestingly, prior exposure to cytotoxic therapy before ALL onset (t-ALL) was not an independent predictor of OS [HR=1.32; 95% CI: 0.97-1.80, $P=0.08$] (Table 5).

When analysis was restricted to the 613 patients who underwent allogeneic HCT as part of their ALL therapy (t-ALL=49, *de novo* ALL=564), the median follow up was 25.5 months (range: 0.03-198.3) and 2-year OS was 58.5% (95% CI: 54.4-62.4) for all patients. The 2-year OS was similar for both t-ALL and *de novo* ALL (53.4% *vs.* 58.9%, $P=0.68$) despite more frequent use of reduced-intensity conditioning for t-ALL compared to *de novo* ALL ($P<0.01$) (Figure 1B). No difference was observed in non-relapse mortality (NRM) between t-ALL and *de novo* ALL (28.5% *vs.* 22.7%, $P=0.38$), respectively (*Online Supplemental Figure S1*).

For the 409 patients who did not undergo allogeneic HCT (t-ALL=44, *de novo* ALL=365), the 2-year OS was inferior for t-ALL compared to *de novo* ALL (27.1% *vs.* 52.9%, $P=0.0004$) (*Online Supplemental Figure S2*). Again, prior cytotoxic therapy before ALL onset (t-ALL) was not

Table 2. Multivariable model for factors associated with t-ALL or *de novo* ALL.

	Therapy-related N=88	*De Novo* N=823	Odds Ratio	95% CI	*P*
Age at ALL diagnosis	54.5 (23-85)	38 (18-85)	1.06	1.04-1.07	<0.0001
WBC	9.95 (0.9-330)	17 (0.2-778)	0.996	0.99-1.00	0.038
Cytogenetic Group					0.0009
NK	16 (18)	257 (31)	–	–	
Ph+	28 (32)	223 (27)	1.46	0.74 -2.90	0.28
MLL	15 (17)	39 (5)	6.52	2.66 -15.96	<0.0001
Complex	5 (6)	34 (4)	2.16	0.70-6.64	0.18
Other/Unknown	24 (27)	270 (33)	1.41	0.71-2.80	0.33
Race/Ethnicity					0.19
White	47 (53)	280 (34)	–	–	0.07
Hispanic	25 (29)	399 (48)	0.60	0.34-1.04	0.07
Other	16 (18)	144 (18)	0.79	0.41-1.50	0.46
Phenotype					
T	8 (9)	107 (13)	–	–	
B	80 (91)	716 (87)	1.40	0.61-3.20	0.42
Sex					
Male	38 (43)	469 (57)	–	–	
Female	50 (57)	354 (43)	1.64	1.02-2.65	0.04

WBC: white blood cell count; NK: normal karyotype; Ph+: Philadelphia chromosome positive; MLL: mixed lineage leukemia.

an independent predictor of survival per se when included in multivariate analysis in this cohort (P=0.11).

Discussion

We present here the largest retrospective study of t-ALL with analysis solely restricted to cases with prior exposure to cytotoxic therapies. Unlike some previously published reports, we excluded cases of ALL that were preceded by other malignancies but did not receive cytotoxic chemotherapy or radiation in an attempt to more narrowly define the entity of t-ALL.[7,8] Although t-ALL does not have unique defining pathologic features, we show that certain recurrent cytogenetic abnormalities are more common in t-ALL compared to *de novo* ALL.

The cytogenetic features of t-ALL bear some resemblance to t-AML and may help define t-ALL. Therapy-related leukemia with balanced translocations has been observed in t-AML, especially in patients with prior exposure to topoisomerase II inhibitors.[3,17,18] MLL (11q23) is the prototypic cytogenetic finding among t-AML patients exposed to topoisomerase II inhibitors, and here we have shown that the incidence of MLL is also more common among t-ALL compared to *de novo* cases. However, we could not demonstrate association between prior topoisomerase II exposure and MLL findings, and this is likely due to the frequent administration of radiation and alkylator therapy along with topoisomerase II inhibitors. Consistent with t-AML data, we show that the latency for t-ALL onset was shorter among patients carrying the MLL gene rearrangement compared to other cytogenetic findings. Furthermore, similarly to t-MN, our t-ALL cases were associated with a higher occurrence of long arm deletions or monosomy 5 and 7.[3] These cytogenetic findings support the etiologic role of prior chemotherapy in pathogenesis of attribution of t-ALL in a manner similar to t-MN. Philadelphia (Ph) chromosome is another balanced translocation and was more commonly noted among t-ALL cases, but this was not statistically significant in this cohort. Ph chromosome is rarely observed among T-cell phenotype ALL and AML cases, and prior reports have shown that some of those cases were potentially therapy-related and developed after cytotoxic exposure.[6,19] Nonetheless, we have observed a trend toward higher rates of additional cytogenetic abnormalities among Ph$^+$ t-ALL compared to Ph$^+$ *de novo* ALL (73% *vs.* 50%, P=0.07), and this likely reflects various levels of genomic instability as a result of prior cytotoxic therapy. The incidence of Ph-like ALL would have been an interesting comparison to make between *de novo* and t-ALL, but unfortunately, we did not have the necessary data available in our cohort.

The latency for ALL development from time of prior diagnosis was 6.8 years in our series, which is slightly longer than what is observed in t-MN (4-4.5 years).[1,3] Both B and T-cell ALL phenotypes were observed in a similar proportion compared to *de novo* ALL. Breast cancer was the most common prior malignancy, likely related to the elevated utilization of alkylator and topoisomerase II inhibitor chemotherapy as well as radiation in early stage disease, and excellent long-term survival for breast cancer patients, allowing time for hematopoietic clonal evolution to acute leukemia.

The patient demographics of our cohort also support the existence of t-ALL as a distinct entity. Interestingly, although the overall majority of ALL patients in our series were Hispanics, t-ALL was twice as common in whites compared to Hispanics. In the United States, ALL is more common in Hispanics in general[20,21] and is characterized by unique genetic profiles such as the Ph-like signature,[22] which in turn is associated with inherited genetic polymorphisms in the *GATA3* gene.[23] Although we do not have data on Ph-like ALL in our cohort, it would likely have been higher in our *de novo* ALL cohort given the demographics of our patient population. In contrast, the higher proportion of whites in our t-ALL cohort may be reflective of the ethnic distribution of the antecedent malignancies (e.g., breast cancer) in the t-ALL population.

Given the prior exposure to chemotherapy, side effects

Table 3. Prior diagnoses and characteristics associated with t-ALL.

Number	93
Median latency in years for all patients (range)	6.8 (0.8-50.7)
Prior diagnosis	
Solid cancer	52 (56)
Hematological cancer	33 (35)
Benign	6 (6)
Both solid and hematological cancers	2 (2)
Prior diagnoses	
More than one prior diagnosis	4 (4)
Breast cancer	23 (25)
Lymphoproliferative neoplasms#	21 (23)
Multiple myeloma	11 (12)
Thyroid cancer/disease	8 (8)
Sarcoma	8 (8)
Testicular	4 (4)
Prostate cancer	3 (3)
Gastrointestinal malignancies	3 (3)
Gynecological malignancies	3 (3)
Rheumatological disease	2 (2)
Head and neck malignancies	2 (2)
Others	8 (8)
The type of prior therapy	
Chemotherapy	35 (38)
Radiation	26 (28)
Combination of chemo/radiation	32 (34)
Topoisomerase II inhibitors	
Yes	38 (41)
No	55 (59)
Preceded or concurrent MDS	2 (2)
Original disease relapse during or after ALL diagnosis	9 (10)
Induction regimen +/- TKI	
HyperCVAD	48 (52)
Linker	8 (9)
BFM	8 (9)
CALGB-9511	7 (7)
DVP	6 (6)
Others	15 (16)
No treatment	1 (1)

MDS: myelodysplastic syndrome; TKI: tyrosine kinase inhibitor #includes non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and Hodgkin's lymphoma.

of subsequent ALL therapy is a concern in t-ALL patients. t-ALL patients achieved a high CR rate and had low induction mortality similar to *de novo* ALL, despite prior exposure to cytotoxic therapy. Although OS of t-ALL patients was inferior to *de novo* ALL patients, this was not independent in multivariate analysis. This is likely because t-ALL cases were enriched with poor prognostic factors that have driven the inferior outcomes of t-ALL cohort. Nonetheless, t-ALL patients who were able to receive allogeneic HCT fared better and had comparable OS to those with *de novo* ALL despite the more frequent use of reduced-intensity regimens. There was no increased risk of TRM among t-ALL patients who underwent allogeneic HCT despite prior cytotoxic exposure but this also could be related to earlier use of HCT (CR1) and more frequent use of RIC in this population.

The limitations of our study include the retrospective nature of the data collection and the inclusion of patients

Table 4. Factors associated with latency among t-ALL patients.

	Number of patients	Hazard Ratio	95% CI	*P*
Prior Therapy				0.75
Chemo	31	–	–	
Radiation	23	0.75	0.36-1.59	0.45
Chemo/Radiation	30	0.91	0.49-1.67	0.75
Cytogenetic Group				0.02
NK	15	–	–	
Ph+	27	1.65	0.82 -3.31	0.16
MLL	15	3.06	1.45-6.45	0.003
Complex	5	0.78	0.27-2.30	0.65
Other/Unknown	22	1.17	0.58-2.36	0.67
Prior disease				
Solid Cancer	51	–	–	
Blood Cancer	33	1.01	0.55-1.86	0.97
Topoisomerase II inhibitor				
No	46	–	–	
Yes	38	0.99	0.56-1.73	0.97

NK: normal karyotype; Ph+: Philadelphia chromosome positive; MLL: mixed lineage leukemia.

Table 5. Predictors of overall survival from time of diagnosis–multivariable model.

	Number of patients	Number of events	Hazard Ratio	95% CI	*P*
Age at ALL diagnosis	911	462	1.02	1.01-1.03	<0.0001
ALL Disease Type					
De novo	823	412	–	–	
Therapy-related	88	50	1.32	0.97-1.80	0.08
WBC	911	462	1.001	1.001-1.002	0.003
Cytogenetic Group					<0.0001
NK	273	138	-	–	
Ph+	251	115	0.63	0.48-0.82	0.0006
MLL	54	28	0.83	0.54 -1.29	0.41
Complex	39	25	1.22	0.79-1.87	0.37
Other/Unknown	294	156	1.19	0.94 -1.50	0.14
Sex					
Female	404	188	–	–	
Male	507	274	1.31	1.09-1.59	0.005
Phenotype					
T	115	50	–	–	
B	796	412	1.46	1.08-1.97	0.02
HCT (time dependent)					
No	359	169	–	–	
Yes	552	293	1.29	1.04-1.60	0.02

WBC: white blood cell count; NK: normal karyotype; Ph+: Philadelphia chromosome positive; MLL: mixed lineage leukemia; HCT: hematopoietic cell transplantation

diagnosed over a 15 years period which introduces bias both with regard to changing treatments for the primary malignancies as well as ALL therapy. Examples include decreasing use of anthracyclines for breast cancer therapy as well as improved outcome of HCT over the time period of the study. It is also possible that some cases of t-ALL may be a coincidental occurrence of ALL after the patient has had a previous malignancy particularly in cases with long latency and lacking MLL rearrangement or monosomy karyotype. Moreover, the referral bias to our center may have introduced overestimation of t-ALL frequency. This is likely because t-ALL cases may have been perceived as being high risk, leading to earlier referral as well as earlier application of more intense therapy including allogeneic HCT. Our data suggest a good outcome for t-ALL when allogeneic HCT is used in CR1 and these patients should be considered candidates for HCT if they are in sustained remission from their primary malignancy. What remains unclear is the outcome of these cases, particularly ones treated with an intensive pediatric type ALL regimen in younger patients. The use of such regimens could be problematic in some of these patients due to cumulative toxicity from treatment of their previous malignancy. This high rate of allogeneic HCT use for both *de novo* and t-ALL in our cohort may have minimized the survival difference between the two groups and underestimate the poor prognosis of t-ALL.

In conclusion, we have attempted to define t-ALL more narrowly using stricter criteria than those used by previous reports and show that these cases have cytogenetic abnormalities that confirm a causative role for their prior cytotoxic therapy in many cases. Large molecular studies using next generation sequencing methodology and accurate correlation with clinical data regarding prior cytotoxic therapy will be required to further characterize this entity.

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