TEL/AML1 Fusion Gene in Childhood Acute Lymphoblastic Leukemia in Southern Taiwan

Pei-Chin Lin,[1] Tai-Tsung Chang,[1,2] Shiu-Ru Lin,[3] Shyh-Shin Chiou,[1,2] Ren-Chin Jang,[1] and Jiunn-Ming Sheen[4]

[1]Division of Hematology/Oncology, Department of Pediatrics, Kaohsiung Medical University Hospital, [2]Department of Pediatrics, School of Medicine, and [3]Graduate Institute of Medical Genetics, Kaohsiung Medical University, and [4]Division of Hematology/Oncology, Department of Pediatrics, Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

Chromosomal abnormalities are found in 80–90% of childhood cases of acute lymphoblastic leukemia (ALL). Leukemia-specific chromosome aberrations not only have prognostic value, but also provide important clues for further investigation into leukogenesis, leukemic cell transformation, and proliferation. This study used reverse transcriptase–polymerase chain reaction techniques to detect transcripts of the leukemia-specific chromosome fusion gene, TEL/AML1, and to monitor the expression levels of the TEL-AML1 fusion transcript in ALL patients at sequential intervals during their treatment course. Twenty-five ALL patients were enrolled, including 20 who were newly diagnosed and five in relapse. The incidence of the TEL/AML1 fusion gene in this study was 32%. The clinical features of our eight TEL/AML1-positive ALL cases were similar to those in other studies. Blotting analysis of the levels of the TEL-AML1 fusion transcript was used to detect minimal residual disease. Reduced levels of TEL/AML1 expression were found in four of the six patients whose bone marrow or peripheral blood samples were obtained after treatment. Further investigation with a larger sample size is warranted.

Key Words: acute lymphoblastic leukemia, polymerase chain reaction, TEL/AML1 fusion gene

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Acute lymphoblastic leukemia (ALL) is the most common type of cancer encountered in pediatric medicine, accounting for 30% of all childhood malignancies [1]. Chemotherapy is the mainstay of treatment and risk-adapted therapy has been developed to improve the event-free survival rate, as well as to reduce therapy-related complications. Important prognostic factors include age at the time of diagnosis and initial white blood cell (WBC) count. Cytogenetic and molecular genetic abnormalities are also important factors [2], while chromosomal karyotype and translocation in cytogenetic studies both have considerable prognostic value [3–5].

Since the discovery of the first fusion gene, BCR-ABL, resulting from a t(9;22) translocation, many fusion transcripts that occur in leukemia, such as t(12;21), t(4;11), and t(1;19), have subsequently been detected [6]. Research has shown that normally-fused translocated genes play a crucial role in the development and function of lymphocytes and bone marrow cells [7]. It has therefore been suggested that the fusion genes may be

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Address correspondence and reprint requests to: Dr Tai-Tsung Chang, Division of Hematology/Oncology, Department of Pediatrics, Kaohsiung Medical University Hospital, 100 Tzyou 1st Road, Kaohsiung 807, Taiwan.
E-mail: tatsch@cc.kmu.edu.tw

closely correlated with the onset of leukemia. Advances in molecular genetics have demonstrated that many fusion genes are difficult to detect with conventional karyotyping and highlight the value of molecular genetics in the diagnosis and treatment of leukemia.

The TEL gene, also known as the ETV6 gene, was first identified in chronic myelomonocytic leukemia as part of a fusion with the PDGFRβ receptor gene [8]. Subsequently, many cases of ALL with TEL gene rearrangement have been reported and a partner gene was found to be the AML gene located on chromosome 21 [9]. Such a fusion gene has been found in approximately 20–25% of ALL cases in children, but less than 0.05% of these can be detected with conventional cytogenetic studies. Most patients are between the ages of 1 and 10 years, white cell count < 50,000/μL, with a B immunophenotype [9–11].

Studies by the Dana Farber Cancer Institute and St Jude's Children Hospital demonstrated that patients with the TEL/AML1 fusion gene had an excellent prognosis (100% 8-year event-free survival and 92% 5-year event-free survival, respectively) [12,13]. However, the British-Frankfurt-Muenster leukemia group later identified the TEL/AML1 fusion gene in 25% of ALL patients who relapsed [14–16], and that better prognostic outcome was probably associated with stronger chemotherapy regimens in the past [17]. Thus, the correlation between the TEL/AML1 fusion gene and disease prognosis requires further investigation.

This study recruited both newly diagnosed and relapsed ALL children. By employing reverse transcriptase–polymerase chain reaction (RT-PCR), the translocation t(12;21) producing the TEL/AML1 fusion gene was detected. Their correlations with the local incidence of disease and other prognostic factors (including age, white cell count, and immunophenotype of disease) were explored and analyzed. Furthermore, the TEL/AML1 fusion gene was used as a marker of the relative changes in residual illness during the course of therapy.

Materials and Methods

Patients and samples

We recruited 25 ALL patients diagnosed between January 2003 and October 2004. Of these, 20 were newly diagnosed and five were in relapse. Following diagnosis, patients began the treatment protocol recommended by the Taiwan Pediatric Oncology Group (TPOG). Information about the subjects, including age, gender, WBC count, and central nervous system (CNS) status, is summarized in Table 1.

After the diagnosis or onset of relapse of ALL and prior to the initiation of treatment, bone marrow and peripheral blood samples were collected. Bone marrow or peripheral blood samples were also collected from 15 subjects 14 days after induction therapy, at the completion of induction or commencement of consolidation therapy, and at commencement of maintenance therapy. A total of 46 bone marrow samples and 37 peripheral blood samples were obtained.

RT-PCR

RNA was extracted from bone marrow and peripheral blood samples and cDNA was synthesized. The target genes were amplified using the cDNA as a template and the synthetic, two-fragment specific primers. The PCR primer sequences were based on those used by van Dongen and colleagues [10], as detailed below: TEL-A, 5′-CCCTCTGATCCTGAAC-3′ (anti-sense), AML1-B, 5′-AACGCCTCGCTCATCTTGC-3′ (sense), TEL-C, 5′-AAGCCCATCAACCTCTCTCATC-3′ (anti-sense), and AML1-D, 5′-TGGAAGGCGGCGTGAAGC-3′ (sense). Primers A and B were used in the first round of a nested PCR; then, primers C and D were used in the second round. Electrophoresis was used to determine the sizes of the final products. The PCR products from the first and second rounds of PCR were 181 and 142 bps, respectively, and the REH-cell line was used as a positive control.

The cDNA prepared from reverse transcription was blotted on a nylon membrane, allowed to dry, and secured with XL-1000 CrossLinker (Spectronics, Westbury, NY, USA). A probe was prepared by PCR amplification of the REH cell cDNA with the primers TEL-C and AML1-D. The PCR products were subsequently verified by electrophoretic analysis, purified, and labeled with DIG by DIG High Prime (Roche Applied Science, Indianapolis, IN, USA) at 37°C for 2 hours. The membrane was then hybridized with DIG-labeled probes for 12–16 hours at 42°C. Following post-hybridization washing and blocking, the anti-DIG AP conjugate was added, and the mixture was washed again. NBT/BCIP solution was then added for staining. The β-actin housekeeping gene was amplified with the primers 5′-GACATCCGCAAAGACCTGTA-3′ and 5′-CAGGAGGAGCAATGATCTTG-3′.

Table 1. Clinical information and gene analysis results for the study subjects

Case	Age (yr)	Sex	WBC	CNS status	Diagnosis	Immunologic markers	TEL/AML1	Protocols	Outcome
1	5.2	M	3.7	I	ALL	Pre-B	–	ALL SRA	CR
2	6.6	M	3.3	I	ALL	B precursor with myeloid	+	ALL SRB	CR
3	5.0	M	3.4	I	ALL	B precursor	+	ALL SRA	CR
4	6.3	F	8.1	I	ALL, relapse	B precursor	+	ALL VHR	CR
5	3.6	F	2.6	I	ALL	Early pre-B	–	ALL SRB	CR
6	16.8	F	115.4	I	ALL	Progenitor B	–	ALL VHR	Died
7	15.0	M	24.1	I	ALL, relapse	Mixed type	–	ALL VHR	3rd relapse
8	5.7	F	35.92	I	ALL	Pre-B	–	ALL SRB	CR
9	8.3	M	288.5	I	ALL	T cell	–	ALL VHR	CR
10	6.9	M	3.3	I	ALL	B precursor	–	ALL SRB	CR
11	0.6	M	37.7	I	ALL	B precursor	+	ALL VHR	CR
12	3.6	M	2.7	I	ALL	Early pre-B	–	ALL SRB	CR
13	0.2	M	93.1	II	ALL	Pre-B	+	ALL VHR	CR
14	13.2	M	9.7	I	ALL, relapse	Early pre-B	–	ALL VHR	Died
15	4.3	M	9.9	I	ALL, relapse	Early pre-B	+	ALL VHR	CR
16	4.3	M	2.1	I	ALL	Early pre-B	+	ALL SRA	CR
17	8.7	M	40.7	I	ALL	Early pre-B	+	ALL HR	Died
18	3.7	F	16.6	I	ALL	B precursor	–	ALL SRB	CR
19	4.42	F	10.6	I	ALL	Pre-B	–	ALL SRB	CR
20	12.2	F	35.1	I	ALL	Early pre-B with myeloid	–	ALL HR	CR
21	3.2	F	31.5	I	ALL	B precursor	–	ALL SRB	CR
22	10.1	M	1.43	I	ALL, relapse	B precursor	–	ALL VHR	Died
23	16.5	M	42.6	I	ALL	Pre-B	–	ALL HR	CR
24	16.5	M	166.3	I	ALL	T cell	–	ALL VHR	CR
25	17.0	M	6.1	I	ALL	Pre-B	–	ALL HR	CR

M = male; F = female; WBC = white blood cell count ($\times 10^3/\mu L$); CNS I = CSF < 5 WBC/μL without blasts; CNS II = CSF < 5 WBC/μL with blasts; ICH = intracranial hemorrhage; ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; ALL SRA = TPOG ALL 2002 SRA; ALL SRB = TPOG ALL 2002 SRB; ALL HR = TPOG ALL 2002 HR; ALL VHR = TPOG ALL 2002 VHR; CR = complete remission; ND = not done.

TEL/AML1 and β-actin blotting analyses were carried out for each sample for comparison of the chromogenic reactions between the two variables. The results are presented as the ratio of TEL/AML1 to β-actin.

Results

The results of the bone marrow and peripheral blood examinations of all 25 study subjects prior to the start of chemotherapy are summarized in Table 2. Eight (32%) of them had detectable TEL-AML1 fusion transcripts, including six (30%) of the 20 newly diagnosed cases and two (40%) of the five relapsed cases.

Relationship between fusion genes and ALL immunophenotypes

Table 3 shows the immunophenotypes of the ALL patients in this study. The pre-B type was the most common in the newly diagnosed patients (six patients), followed by precursor B (five cases), and early pre-B (four cases) types. The other cases included one with progenitor B, two with early pre-B with myeloid coexpression, and two with T cell immunophenotypes. Of the relapsed cases, two were precursor B type, two had early pre-B type, and one was the early pre-B type with myeloid coexpression.

The immunophenotypes of ALL patients with TEL-AML1 fusion transcripts were precursor B, early

Table 2. Gene analyses and associations with age, white blood cell (WBC) count, central nervous system (CNS) status, gender, and chromosome study

	TEL-AML1		Total
	Positive ($n=8$)	Negative ($n=17$)	
Age (yr)			
<1	2	0	2
1–10	6	9	15
>10	0	8	8
WBC count ($\times 10^3/\mu L$)			
<50	7	14	21
50–100	1	0	1
>100	0	3	3
CNS status			
I	7	17	24
II	1	0	1
III	0	0	0
Gender			
Male	7	10	17
Female	1	7	8
Chromosome study			
Normal karyotype	6	15	21
Abnormal	2	2	4

Table 3. Gene analysis and comparison with different immunophenotypes

	Patients, *n*	TEL-AML1 positive, *n* (%)
Fresh cases	20	6 (30)
Progenitor B	1	0
Precursor B	5	3
Early pre-B	4	2
Pre-B	6	1
T cell	2	0
B cell with myeloid	2	0
Relapsed cases	5	2 (40)
Precursor B	2	1
Early pre-B	2	1
B cell with myeloid	1	0
Total	25	8 (32)

pre-B, and pre-B types. No TEL-AML1 fusion transcripts were detected in any T- or B-cell ALL patients with myeloid coexpression. The occurrence of the fusion gene was the highest in the precursor B type patients, with four (57%) of the seven patients expressing the gene. In contrast, the fusion gene was identified in only one (16.6%) of the six pre-B ALL patients.

Relationship between fusion genes and other clinical findings

Age is an important prognostic factor for ALL. Past research has shown that better prognosis is associated with ages between 1 and 10, while those aged younger than 1 or older than 10 years have poorer prognosis. The majority (15) of the study subjects was aged between 1 and 10 years; two were less than 1 year old; and eight were over 10 years old. Most (6/8) of the cases with the TEL/AML1 fusion gene were also between the ages of 1 and 10 years.

The patients were grouped according to their WBC count at the time of diagnosis: the groups were $<50\times10^3/\mu L$ (21 patients), $50–100\times10^3/\mu L$ (one patient), and $>100\times10^3/\mu L$ (three patients). Among the 21 patients with WBC count $<50\times10^3/\mu L$, seven were TEL/AML1 positive. The patient with WBC count between 50 and $100\times10^3/\mu L$ was also TEL/AML1 positive. However, none of the three patients whose WBC counts were greater than $100\times10^3/\mu L$ was TEL/AML1 positive.

Only one subject in this study had CNS II status (cerebrospinal fluid [CSF] cell count <5 WBC/μL with blasts), and this particular patient was TEL/AML1 positive. All of the other subjects had CNS I status (CSF <5 WBC/μL without blasts) and no subject had

Table 4. Quantitative analysis of fusion gene at different stages of illness in six TEL-AML1-positive individuals

Case	Sample	Ratio (TEL-AML1/β-actin)	Sample collection time
2	BM1	1.35	Before C/T
	BM2	0.36	Induction day 14
	BM3	0.02	Induction day 36
3	BM	2.18	Before C/T
4	BM1	0.43	Before C/T
	BM2	0.08	3 mo after C/T
11	PB1	2.73	Before C/T
	PB2	0.10	After 1st phase of induction (2 mo after C/T)
	PB3	0	Before consolidation (5 mo after C/T)
13	PB1	0	Before C/T
	PB2	1.79	Induction day 36
	PB3	0	After consolidation (6 mo later)
15	PB	0.85	Before C/T
16	PB1	0.75	Before C/T
	BM2	0.64	On maintenance (6 mo later)
	PB2	0.58	On maintenance (6 mo later)
17	BM1	0	Before C/T
	BM2	0.95	Relapse (7 mo after initial diagnosis)
	BM3	1.40	8.5 mo after initial diagnosis
	BM4	0.54	9.5 mo after initial diagnosis

BM = bone marrow; PB = peripheral blood; C/T = chemotherapy.

CNS III status (cell count > 5 WBC/μL with blasts) or signs of CNS leukemia at the time of diagnosis.

Seventeen of the 25 subjects (68%) recruited in this study were male. TEL/AML1 was positive in seven of them, but in only one of the eight females in the study.

All of the subjects underwent a chromosome study at the time of diagnosis. Most showed a normal karyotype, but the following abnormalities were found in four subjects: hyperploidy (> 50 chromosomes); 47XY,+8; 45XY,t(5;15)(p15;q13),–17; and the Philadelphia chromosome [46XX,t(9;22)(q34;q11)]. The t(12;21)(p13;q22) abnormality was not detected in any patient.

Treatment response

The 20 newly diagnosed ALL patients underwent treatment with the protocol recommended by the TPOG. The TPOG ALL 2002 (Standard Risk) was started in 11 patients, the TPOG ALL 2002 (High Risk) in four, and the TPOG ALL 2002 (Very High Risk) in five. With one exception (a patient who tested negative for TEL-AML1), all of the patients achieved complete remission by the end of induction therapy. One TEL-AML1 positive patient relapsed during consolidation therapy and subsequently died from advanced disease. To date, all of the other 18 subjects remain in remission, with the longest follow-up period being 2 years.

Of the five relapsed cases, two were TEL-AML1 positive. Following completion of the TPOG ALL 2002 Very High Risk treatment regimen, they both achieved and remained in remission. The other three relapsed patients did not achieve remission. Two died from progressive disease and one continues to receive treatment.

Quantitative analysis of fusion genes at different disease stages

The study of bone marrow and peripheral blood samples commenced after the initiation of treatment in TEL-AML1 positive ALL patients. Of the eight TEL-AML1 positive ALL patients, samples were only available from two at the time of diagnosis, while samples collected after the start of treatment were available from the other six patients. A total of 11 bone marrow samples and nine peripheral blood samples were examined by blotting analysis, the results of which are shown in Table 4. Only one (Case 17) of the eight cases relapsed during consolidation therapy. In the other seven cases, the proportion of lymphoblast cells fell from 95% at diagnosis to less than 2% at the completion of induction therapy, and continued to remain in remission.

It was observed that the expression of TEL-AML1 fusion transcripts dramatically dropped in Cases 2, 4 and 11, and a similar trend (but with a smaller amplitude) was also seen in Case 16. The bone marrow samples of Cases 2 and 4 and the peripheral blood sample of Case 11 showed a similar degree of reduced gene expression. Unfortunately, we were not able to collect both samples at various time points in the same patient. Otherwise, the analysis of peripheral blood could have been more firmly evaluated.

Discussion

The TEL/AML1 fusion gene is thought to be the most common leukemia-specific fusion gene in children with ALL as it is present in 20–25% of patients. Most of these patients are aged between 1 and 10 years, have a WBC count <50,000/μL, and have the B-lineage immunophenotype [10,18]. Our findings are consistent with those reported in previous literature: among the TEL-AML1 fusion gene-positive patients, 88% (7/8) had WBC count <50,000/μL, all (8/8) were of B-lineage immunophenotype, and most (75%, 6/8) were between 1 and 10 years of age.

In four of the six patients with an available series of tissue samples, the expression level of the TEL-AML1 fusion transcript matched the clinical course of the illness. The rationale behind looking for the TEL-AML1 fusion transcript as a means to detect minimal residual disease has been supported by many researchers. However, accurate quantization of the gene has more important clinical implications. For instance, de Haas and colleagues [19] and Pallisgaard and colleagues [20] provided evidence that the quantization of TEL-AML1 by real-time PCR correlated with clinical findings. Although our study did not employ real-time quantitative PCR, our results were similar to the findings of these two studies.

The limitation of this study was its small sample size. Thus, the correlation between TEL-AML1 fusion transcript expression level and disease relapse could not be reliably established from the single relapsed patient in the study. More cases will be required for future research to confirm the efficacy of our quantization method using TEL-AML1 fusion transcripts as the target gene for the estimation of disease progression.

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TEL/AML1 融合基因在南台灣兒童急性淋巴性白血病的表現情形

林佩瑾[1] 張泰琮[1,2] 林綉茹[3] 邱世欣[1,2] 章人欽[1] 沈俊明[4]

[1]高雄醫學大學附設醫院 兒科部 小兒血液腫瘤科

高雄醫學大學 [2]醫學院醫學系 小兒科學 [3]醫學遺傳研究所

[4]高雄長庚兒童醫院 兒童內科部 兒童血液腫瘤科

百分之八十至九十的兒童急性淋巴性白血病個案會出現染色體的異常，這些白血病特異性的染色體變異不僅具有預後的價值，還能提供研究白血病生成、轉型及增生機轉的線索。分子生物學的進步使得這些染色體變化可以經由高敏感度的方法偵測出來。在本研究中我們使用反轉錄酶聚合鍊鎖反應的技術來偵測白血病特異性融合基因 **TEL/AML1**，並且在治療過程中監測它的表現量的變化。共有二十五位急性淋巴性白血病個案納入研究，包括二十位新診斷個案及五位復發的個案。出現 **TEL/AML1** 融合基因的比率是 **32%**，**TEL/AML1** 融合基因陽性的個案臨床表現和其它研究報告相似。其中六位在治療過程中持續監測 **TEL/AML1** 融合基因的表現量，有四位的表現量隨著治療明顯下降。未來需要更大型的研究以進一步證實使用 **TEL/AML1** 融合基因為追蹤治療效果的標記是可行的。

關鍵詞：急性淋巴性白血病，聚合鍊鎖反應，**TEL/AML1** 融合基因

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通訊作者：張泰琮醫師

高雄醫學大學附設醫院兒科部小兒血液腫瘤科

高雄市**807**三民區自由一路**100**號