HHS Public Access

Author manuscript

J Clin Oncol. Author manuscript; available in PMC 2015 June 29.

Published in final edited form as:

J Clin Oncol. 2008 May 1; 26(13): 2186–2191. doi:10.1200/JCO.2007.14.3552.

Prospective Analysis of *TEL* Gene Rearrangements in Childhood Acute Lymphoblastic Leukemia: a Children's Oncology Group Study

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Abstract

Purpose—To prospectively determine the prognostic significance of the *TEL-AML1* fusion in children with acute lymphoblastic leukemia (ALL).

Patients and Methods—*TEL* gene status was determined for 926 patients with B-precursor ALL enrolled on the Pediatric Oncology Group ALinC 16 trials and patients were followed for a median time of eight years.

Results—Rearrangements of the *TEL* gene were detected in 244 (26%) patients. The estimated 5-year event-free survival rate (± SE) for patients with *TEL* rearrangements was 86% ± 2%, compared with 72% ± 2% for those with germline *TEL* ($p<0.0001$). *TEL* rearrangements were associated with a superior outcome among patients with standard-risk ALL, high-risk ALL, and rapid early responses to therapy. In a multivariate analysis that included risk group, sex, and day 15 marrow status, *TEL* status was an independent predictor of outcome ($p=0.0002$).

Conclusion—We conclude that *TEL* gene status should be incorporated into risk classification schemes and suggest that patients who have the *TEL-AML1* fusion and rapid early responses to therapy should be treated with antimetabolite-based therapy designed to maintain their high cure rates and avoid late effects.

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Introduction

The *TEL-AML1* gene fusion, created by the t(12;21)(p12;q22), is the most common translocation in childhood acute lymphoblastic leukemia (ALL), occurring in about 25% of B-precursor cases.[1-3] Soon after the fusion was cloned in 1995, several retrospective studies suggested that it was associated with an excellent outcome.[4-6] We reported that among patients with ALL treated at St. Jude Children's Research Hospital, *TEL* gene rearrangements, representing the *TEL-AML1* fusion, were associated with a 5-year event-free survival (EFS) rate >90%.[4] In that study, the favorable impact of *TEL* rearrangements was independent of age and leukocyte count. Similarly, we demonstrated that *TEL* rearrangements were associated with an improved survival rate of patients treated on a Pediatric Oncology Group (POG) trial.[5] The *TEL-AML1* fusion was also associated with an outstanding outcome among patients treated on a Dana-Farber Cancer Institute (DFCI) trial.[6] Investigators from St. Jude and from the DFCI also demonstrated a very low frequency of *TEL-AML1* in patients with relapsed ALL, consistent with the excellent outcome of patients with this translocation.[7,8]

Despite the plethora of studies that suggest that *TEL-AML1* is an independent favorable predictor of outcome and should be used in risk classification, questions remain regarding its true impact.[9] For example, some reports demonstrated a high incidence (20% to 24%) of the *TEL-AML1* fusion in relapsed cases of ALL, thereby casting doubt as to the prognostic significance of this genetic alteration.[10,11] The retrospective nature of many of the studies and the short follow-up of others further suggested that a large prospective study should be performed. Hence, in 1996, investigators from the DFCI and from the POG simultaneously undertook prospective studies to determine the prognostic significance of the *TEL-AML1* fusion in childhood ALL. The DFCI recently reported that *TEL-AML1* is associated with an excellent outcome (5-yr EFS=89%), but that *TEL-AML1* status is not an independent predictor of outcome.[12] We report here the results of the POG study.

Patients, materials, and methods

Patients and samples

Bone marrow samples were received for *TEL* testing from 1150 consecutive patients who were eligible for the POG ALinC 16 (9201, 9605, and 9406) treatment protocols for B-precursor ALL from December 29, 1995 to June 16, 1998.[13,14] These patients constituted a subset of all patients who had enrolled on these trials from November 15, 1994 to November 15, 1999. Definitive results regarding *TEL* status were obtained in 926 patients, who are the subject of this report. At the time of diagnosis, patients were assigned to induction treatment based on National Cancer Institute (NCI) risk status:[15] patients with standard-risk ALL received a 3-drug induction regimen (prednisone, vincristine, L-asparaginase), and patients with high-risk ALL received the same 3 drugs plus daunorubicin. At the completion of induction therapy, patients were further stratified into 3 risk groups for postinduction therapy. Patients with low-risk disease (POG 9201) were those with NCI standard-risk features and either simultaneous trisomy of chromosomes 4 and 10, or, in the absence of informative cytogenetics, a DNA index >1.16. Patients with standard-risk disease (POG 9605) included those with NCI standard-risk features who lacked the low-risk characteristics

and those with NCI high-risk features and both trisomies 4 and 10 or a DNA index >1.16. Patients with poor-risk ALL (POG 9406) included any patients with CNS3 status, a t(1;19), t(9;22), or t(4;11) and patients with NCI high-risk features who did not have trisomies 4 and 10 or a DNA index >1.16.

Post induction therapy on POG 9201 consisted of consolidation therapy with intermediate dose methotrexate (1 gm/m^2) given every 3 weeks for 6 doses, and daily mercaptopurine. This was followed by continuation therapy with weekly standard dose methotrexate and daily mercaptopurine. Vincristine/prednisone pulses were given throughout continuation therapy and triple intrathecal therapy was used for central nervous system prophylaxis.[13] Patients with standard-risk ALL (POG 9605) received the same consolidation therapy as the low risk patients, but were randomly assigned, in a 2 × 2 factorial design, to receive divided dose oral methotrexate every other week versus standard weekly dose methotrexate during the first 6 months of continuation therapy and oral mercaptopurine in a single-dose versus divided dose fashion throughout continuation. Patients on 9201 and 9605 received no anthracyclines, epipodophyllotoxins, alkylating agents or cranial irradiation.

Patients with poor risk ALL (POG 9406) received multi-agent intensified consolidation and continuation using rotating agents. The standard arm of 9406 used rotating courses of methotrexate (1 gm/m^2) with intravenous mercaptopurine (1 gm/m^2), followed by teniposide with standard dose cytarabine, followed by daunorubicin, standard dose cytarabine, vincristine, prednisone, and L-asparaginase. On POG 9406, patients were randomly assigned in a 2 × 2 factorial design to determine whether 2.5 gm/m^2 methotrexate was more effective than 1.0 gm/m^2 and to determine whether substitution of high dose cytarabine with PEG asparaginase for the teniposide with standard dose cytarabine would give equally good or better EFS, with less chance of causing second malignancy.

All three studies (POG 9201, 9605, and 9406) used triple intrathecal therapy until July 29, 1999, when the protocols were amended to give only intrathecal methotrexate.

Genomic DNA was extracted, and the *TEL* gene status was analyzed as previously described.[2] Written informed consent was obtained from patients or their legal guardians, and all studies were approved by the institutional review board at each collaborating site.

Study design

At the onset of the ALinC 16 studies, the POG accrued approximately 600 patients with B-precursor ALL each year. The expected proportion of cases with rearranged *TEL* in each group was as follows: low risk, 0% with rearranged *TEL*; standard risk, 40% with rearranged *TEL*; and poor risk, 17% with rearranged *TEL*. None or very few cases with rearranged *TEL* were expected among patients with low-risk ALL because of the lack of overlap between cases with hyperdiploidy (DNA index > 1.16) and cases with *TEL* rearrangements.[4] This prospective study required the submission of diagnostic marrow samples from each patient who agreed to participate. Samples were received for *TEL* testing from 1150 patients enrolled on these studies.

Statistical Methods

The Fisher exact test was used to compare the characteristics between patients who were studied and those who were not on each of the 3 clinical trials. EFS estimates were obtained by using the Kaplan-Meier method,[16] and standard errors of the estimates were calculated by the method of Peto and Peto.[17] Time to event was calculated as the time from study entry to first event (relapse, secondary malignancy, or death) or date of last contact. The log-rank test was used for comparison of survival curves between various groups. Multivariate analysis was conducted by using Cox proportional hazards regression.[18] Categorical data were compared between groups by using the chi-square test. All tests were conducted at a significance level of 5%.

Results

Patient characteristics

A total of 2676 patients were enrolled on the POG ALinC 16 therapeutic trials for B-precursor ALL: 692 patients with low-risk ALL were enrolled on POG 9201; 1077 patients with standard-risk ALL were enrolled on POG 9605; and 907 patients with poor-risk ALL were enrolled on POG 9406. Of these, 926 (152 on POG 9201, 470 on POG 9605, and 304 on POG 9406) had adequate diagnostic bone marrow samples submitted for *TEL* gene analysis. The Fisher exact test revealed only minor differences in characteristics between patients who were and were not studied for *TEL* status on each trial (data not shown). *TEL* gene rearrangements were present in 244 (26%) of 926 cases analyzed, including 7 of 152 (5%) treated on POG 9201, 173 of 470 (37%) treated on POG 9605, and 64 of 304 (21%) treated on POG 9406 (Table 1).

TEL-rearranged cases had a median age of 4.4 years (range, 1.4 to 19.7 years) and a median presenting leukocyte count of 12×10^9/L (range, 1 to 219×10^9/L), whereas those with germline *TEL* had a median age of 5.0 years (range, 1.1 to 21.1 years) and a median presenting leukocyte count of 12×10^9/L (range, 1 to 848×10^9/L). *TEL* rearrangements were detected in 29% of patients in the standard-risk group and in 21% of patients in the high-risk group (Table 1).[15]

Only 27% of patients with *TEL* rearrangements and 36% of patients with germline *TEL* (p=0.0094) had high-risk ALL. Of the 22 patients who had *TEL* rearrangements and were at least 10 years old, 20 (91%) had presenting leukocyte counts $< 50 \times 10^9$/L.

Impact of TEL rearrangements

At a median follow-up of 7.8 years, the estimated 5-year EFS rate (± SE) for patients with *TEL* rearrangements was 86% ± 2%, compared with 72% ± 2% for those with germline *TEL* (Figure 1A, p<0.0001). *TEL* rearrangements were associated with a favorable outcome for patients with standard-risk ALL (5-yr EFS, 88% ± 3% vs. 78% ± 2%; p=0.0011; Figure 1B) and for patients with high-risk ALL (5-yr EFS, 81% ± 5% vs. 62% ± 3%; p=0.0032; Figure 1C). The small group of patients 10 years of age or older with *TEL* rearrangements also appeared to have a good outcome: their 5-year EFS estimate was 85% ± 8%, and 21 of 22 patients are alive. Finally, late events did not appear to constitute a significant problem in

patients with rearrangements of *TEL*. In fact, only 4 (2%) of 198 patients with rearranged *TEL* genes and sufficient follow-up suffered events more than 5 years after the time of diagnosis; in comparison, 19 (4%) of 467 of patients with germline *TEL* genes experienced late events.

Because we previously demonstrated that patients with trisomies 4 and 10 have an excellent outcome,[19] we compared the outcome of cases with rearranged *TEL* with that of cases with trisomies 4 and 10 and cases with neither feature (Figure 2). Patients with *TEL* rearrangements had an outcome similar to that of patients with trisomies 4 and 10 (5-yr EFS, 86% ± 2% vs. 82% ± 3%; p=0.18), and both groups fared significantly better than did the group of patients with neither feature (5-yr EFS, 69% ± 2%; overall p<0.0001).

Impact of early response to therapy

Early response to therapy is one of the best predictors of outcome in childhood ALL.[20,21] We therefore studied the association between day 15 bone marrow status and *TEL* gene rearrangements. Day 15 marrow status was available for 857 of the patients with known *TEL* status. Of the 228 patients with a *TEL* rearrangement, 214 (94%) experienced rapid early responses, defined as M1 marrow at day 15, and 566 (90%) of 629 patients with germline *TEL* genes experienced such responses (p= 0.104). As expected, rapid early responses, compared with slow early responses (M2/M3 marrow at day 15), were associated with significantly improved outcomes for patients with rearranged *TEL* genes (5-yr EFS, 87% ± 2% vs. 71% ± 12%; p=0.043) and for those with germline *TEL* genes (5-yr EFS, 75% ± 2% vs. 56% ± 6%, p<0.0001). In addition, *TEL* rearrangements were associated with a superior outcome in patients with rapid early responses (5-yr EFS, 87% ± 2% vs. 75% ± 2%; p=0.0001; Figure 3A), but the difference in outcome did not attain statistical significance among those with slow early responses (5-yr EFS, 71% ± 12% vs. 56% ± 6%; p=0.16; Figure 3B).

Cox proportional hazards regression was used to determine the effect of *TEL* status on EFS. After adjustment for NCI risk group (standard risk versus high risk), sex, and day 15 marrow status (M1 versus M2/M3), *TEL* status was an independent predictor of outcome (HR=0.51; p=0.0002; Table 2).

Discussion

In this prospective study of more than 900 patients with ALL treated on the POG ALinC 16 study with approximately 8 years of follow-up, we demonstrated that *TEL* status is a highly significant and independent predictor of outcome of patients overall and of patients with standard-risk and high-risk ALL. This finding is in contrast to that in a recent report from the DFCI, which found that NCI risk group, but not *TEL* status, was an independent predictor of outcome. In the DFCI study, *TEL* status was not significantly associated with better EFS within the standard-risk or the high-risk group; however, the power to detect a statistically significant difference was limited by relatively small numbers of patients in each group. In addition, the fact that the outcome of patients with germline *TEL* genes in the DFCI study (5-yr EFS, 80%) was superior to that of patients with germline *TEL* genes in the present study (5-yr EFS, 72%) might have decreased the impact of *TEL* gene

rearrangements. These results also suggest that the ALinC 16 therapy may have been inadequate for patients with high-risk ALL and no *TEL* rearrangements.

In the present study, patients with *TEL* rearrangements who had standard-risk ALL by NCI/Rome criteria had an excellent outcome in response to treatment with antimetabolite-based therapy (POG 9201 or 9605) that did not include anthracyclines, epipodophyllotoxins, alkylating agents, and cranial irradiation. This result suggests that current treatment protocols for this large group of patients should continue to be based on antimetabolites and to avoid agents that are associated with significant long-term sequelae. Patients with *TEL* rearrangements and high-risk ALL as defined by NCI/Rome criteria also had an excellent outcome, which may be attributed to the more intensive therapy that they received on POG 9406. The only subgroup of patients with *TEL* rearrangements and a relatively poor outcome (5-year EFS, 71%) was the approximately 5% of patients with slow early responses to therapy, who probably needed more aggressive or alternative therapies.

What is the optimal therapy for children with ALL and the *TEL-AML1* fusion? The strikingly similar outcomes of patients with *TEL-AML1*–positive ALL treated on the present study, on the DFCI 95-01 trial,[12] and at St. Jude[22] (EFS estimates of 86%, 89%, and 88%, respectively) indicate that different treatment strategies may result in equally good outcomes. Leukemic blasts from patients with *TEL-AML1*–positive ALL are sensitive to steroids, vincristine, and asparaginase in vitro,[23] and it has been suggested that the outstanding outcome of such patients on DFCI trials is related to the intensive use of asparaginase.[12] However, the lack of intensive asparaginase administration in ALinC 16 or in the St. Jude trials suggests that the use of antimetabolite-based therapy or multiagent chemotherapy is also effective. Because of the excellent outcome of patients with *TEL-AML1*–positive ALL, very large randomized clinical trials will be required to determine the best possible therapy for these children.

In summary, our results demonstrate that early response to therapy, sex, NCI risk group, trisomies 4 and 10, and *TEL* status are all independent, significant predictors of outcome and should be used concurrently to determine risk classification in childhood ALL. We suggest that patients who have the *TEL-AML1* fusion and are negative for minimal residual disease as indicated by flow cytometry or polymerase chain reaction at the end of remission induction therapy should be treated with antimetabolite-based therapy designed to maintain their high cure rates and avoid late effects. In contrast, we believe that patients who have the *TEL-AML1* fusion and are positive for minimal residual disease are candidates for more intensive treatment.

Acknowledgments

This work was supported in part by the St. Jude Children's Research Hospital Cancer Center Support (CORE) grant P30 CA-21765; the Pediatric Oncology Group grant CA 30969, Pediatric Oncology Group Statistical Office grant U10 CA-29139, and grant R21 CA-73983 from the National Institutes of Health; by the American Lebanese Syrian Associated Charities (ALSAC) and CA 98543 COG grant . We thank Julia Cay Jones for expert editorial review. A complete listing of grant support for research conducted by CCG and POG before initiation of the COG grant in 2003 is available online at: http://www.childrensoncologygroup.org/admin/grantinfo.htm

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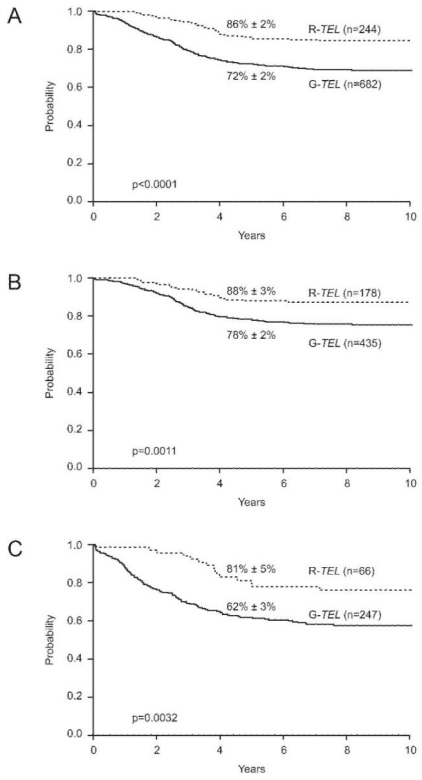

Figure 1. Event-free survival (EFS) estimates of patients treated on ALinC 16 and their relation to *TEL* gene status

(A) EFS estimates of patients with *TEL* rearrangements (R-*TEL*) compared with those of patients with germline *TEL* (G-*TEL*). (B) EFS estimates of patients with NCI standard-risk ALL shown in relation to *TEL* status. (C) EFS estimates of patients with NCI high-risk ALL shown in relation to *TEL* status.

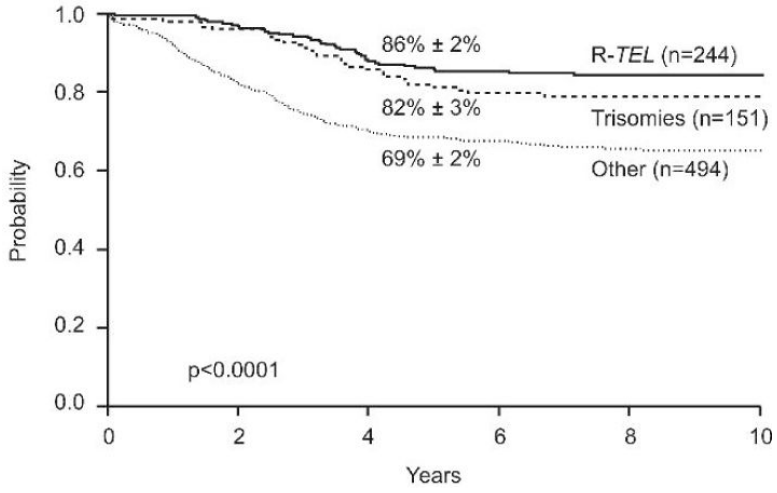

Figure 2.

Event-free survival (EFS) estimates of patients with *TEL* rearrangements compared with those of patients with trisomies 4 and 10 and with those of patients with neither feature (Other).

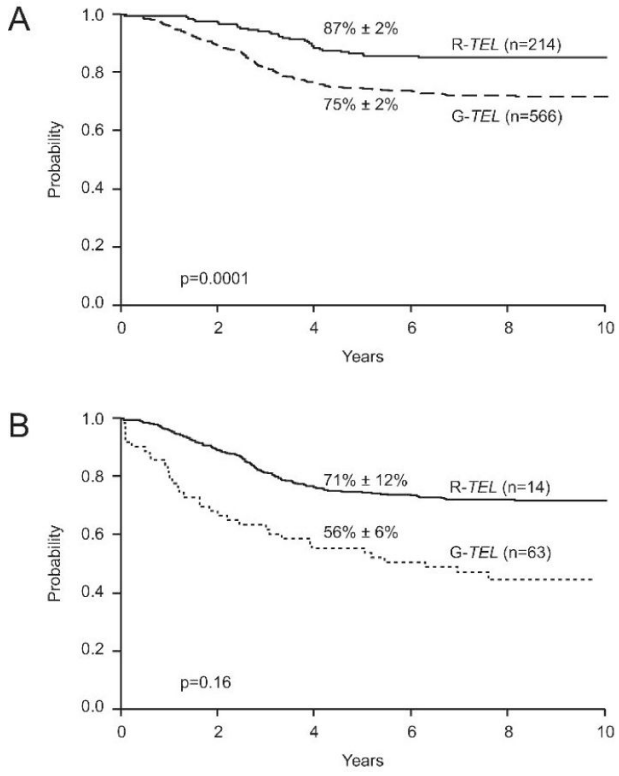

Figure 3.

Event-free survival (EFS) estimates of patients with *TEL* rearrangements compared with those of patients with germline *TEL* and either rapid early responses to therapy (A) or slow early responses (B).

Table 1

Patient Characteristics in Relation to *TEL* Status

Characteristic	Rearranged *TEL*	Germline *TEL*
Median age (years)	4.4 (1.4-19.7)	5.1 (1.1-21.1)
Age group		
< 10 years	222 (29%)	531 (71%)
≥ 10 years	22 (13%)	151 (87%)
Median WBC ($\times 10^9$/L)	12 (1-219)	12 (1-848)
WBC group		
< 50 × 10^9/L	198 (27%)	549 (73%)
≥ 50 × 10^9/L	46 (26%)	133 (74%)
NCI risk group		
Standard	178 (29%)	435 (71%)
High	66 (21%)	247 (79%)
Sex		
Male	123 (24%)	382 (76%)
Female	121 (29%)	300 (71%)
Race		
White	184 (29%)	447 (71%)
Black	12 (16%)	62 (84%)
Hispanic	32 (21%)	124 (79%)
Other	16 (25%)	49 (75%)
CNS Status		
Negative	232 (95.1%)	586 (86.0%)
Positive	12 (4.9%)	96 (14.0%)
Day-15 marrow status		
M1	214 (27%)	566 (73%)
M2/M3	14 (18%)	63 (82%)
Treatment study		
9201	7 (5%)	145 (95%)
9605	173 (37%)	297 (63%)
9406	64 (21%)	240 (79%)
Median follow-up (yrs)	8 (0.0-10.0)	7.7 (0.0-10.0)
Total	244 (26%)	682 (74%)

Table 2

Results of the Multivariate Cox Regression Analysis

Variable	Hazard Ratio	95% CI for Hazard Ratio	P value
M2/M3 marrow on day 15	2.432	(1.722, 3.437)	<0.0001
Male Sex	2.105	(1.582, 2.798)	<0.0001
NCI high-risk ALL	1.954	(1.504, 2.540)	<0.0001
No *TEL* rearrangement	1.972	(1.379, 2.815)	0.0002