RAPID COMMUNICATION

Predictability of the t(1;19)(q23;p13) From Surface Antigen Phenotype: Implications for Screening Cases of Childhood Acute Lymphoblastic Leukemia for Molecular Analysis: A Pediatric Oncology Group Study


The t(1;19)(q23;p13) translocation occurs in approximately 5% of B-precursor acute lymphoblastic leukemias (ALLs) occurring in children. Its presence has been associated with a poor prognosis, which may be overcome with more intensive therapy. Although leukemic cells from cases of t(1;19)-ALL frequently express cytoplasmic mu heavy chains, their complete antigenic profile remains undefined. Among 697 consecutive cases of B-precursor ALL with complete phenotypic studies using a panel of monoclonal antibodies, 22 cases were found to carry the t(1;19). Twenty of 22 cases had an identical, complex phenotype, but was lacking data for CD9. The other case differed by virtue of expression of CD34 and was also hyperdiploid with 55 chromosomes. Molecular studies showed E2A-PBX1 abnormalities in all examined cases (12 of 12) with the t(1;19), including the case lacking CD9 data. In contrast, no E2A-PBX1 abnormalities were detected in the sole t(1;19)-ALL with CD34 expression. Seventeen cases with the characteristic phenotype and uninformative cytogenetics were also molecularly analyzed and 5 of 17 (including 4 of 8 with unsatisfactory cytogenetics and 1 of 9 with a normal karyotype) contained E2A gene rearrangements and E2A-PBX1 fusion mRNAs. Our results show that all cases of t(1;19)-ALL with concomitant E2A-PBX1 fusion invariably express a characteristic but uncommon profile of surface antigens. These observations suggest that selective molecular analysis of a small subset of patients (those with uninformative cytogenetics and the characteristic phenotype) can identify a significant number of additional cases of ALL with E2A-PBX1 fusion that might benefit from more intensive therapy. © 1993 by The American Society of Hematology.

The t(1;19)(q23;p13), the most common recurring translocation in childhood leukemia is present in about 5% of all B-precursor acute lymphoblastic leukemia (ALL) cases.1 It has previously been shown to be highly associated with the pre-B (ie, cytoplasmic Ig [clg]-positive) immunophenotype.2 The t(1;19) structurally interrupts the E2A gene located at 19p13, which codes for the helix-loop-helix transcription factors E12 and E47, and fuses it to the chromosome 1 gene PBX1, which encodes a novel homeodomain protein.3,5 The t(1;19) in pre-B-ALL consistently results in fusion of the amino terminal transactivation domain of E12/E47 to the homeodomain of Pbx1, leading to production of proteins with structural features of chimeric transcription factors.7,8 A cytogenetically indistinguishable t(1;19) is also seen rarely in clg-ALL; however, these cases do not have evidence for involvement of either E2A or PBX1.8 The E2a-Pbx1 fusion protein is capable of transforming NIH 3T3 cells,9 but the mechanisms are poorly understood as the binding properties and target genes of Pbx1 have yet to be defined.

The Pediatric Oncology Group (POG) has previously shown that children with the t(1;19) fare poorly, and that the poor outcome of children with pre-B-ALL noted in previous studies is entirely due to its high degree of association with the t(1;19).10 On current therapeutic studies, children with the t(1;19) are being assigned to a high-risk group irrespective of their clinical risk factors. With the advent of molecular methods for detecting the E2A-PBX1 translocation, it has become technically feasible to screen newly diagnosed ALL patients for the presence of this translocation. However, it is probably impractical to screen all patients for an abnormality found in only 5% of cases. Because of the known high level of association of this translocation with a particular immunophenotype, we thought it possible that a more detailed immunophenotypic description of t(1;19) cases, using monoclonal antibodies against B-cell differentiation antigens, might improve our ability to identify these cases. In this report, we describe a complex immunophenotype that is found on only about 8% of cases of B-precursor ALL, which, although not completely specific, allows recognition of all cases of the t(1;19)(q23;p13) that involve E2A and PBX1. By applying molecular analysis to a small subset of patients with this phenotype and uninformative cytogenetics, we were able to detect 25% more cases of ALL with this molecular translocation than were picked up by conventional cytogenetics.

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IMMUNOPHENOTYPE OF THE T(1;19) ALL

MATERIALS AND METHODS

From January 1991 to April 30, 1992, 990 patients were entered onto the POG 9000 classification protocol for newly diagnosed children with acute lymphoid leukemia. Of these, 738 had B-precursor ALL. Blasts from all patients with newly diagnosed lymphoid leukemia were sent to the cytogentic reference laboratory at the University of Alabama at Birmingham and to the cell bank at St Jude Children’s Research Hospital for cryopreservation in liquid nitrogen. Preliminary phenotypic screening was performed at the local institution, as previously described, and cases of suspected B-precursor ALL were sent to the Duke reference laboratory for additional immunophenotypic studies. There, Ficoll-hypaque-enriched blasts were stained by two-color direct immunofluorescence using the following panel of antibodies: CD10-fluorescein isothiocyanate (FITC)/CD19-phycocerythrin (PE); CD7-FITC/HLA-DR-PE; CD34-FITC/CD20-PE; CD45-FITC/CD22-PE. In addition, indirect staining was performed with CD24 and CD9 antibodies, and, in some cases, with a CD34 antibody as well. Isotype-specific FITC- and PE-conjugated reagents were used as negative controls. In cases that were not straightforward B-precursor ALL, additional staining was performed with a more extensive panel of T- and myeloid-associated antibodies. All antibodies were obtained from Becton Dickinson (San Jose, CA), except for CD19-PE (Gentrax, Plymouth Meeting, PA); CD34-FITC (AMAC, Westbrook, ME); CD24 (Boeringer Mannheim, Indianapolis, IN); CD9 (clone DU-ALL-1, kindly provided by Dr Richard Metzgar, Duke University, Durham, NC), and CD34 (clone My10, kindly provided by Dr Curt Civen, Johns Hopkins Medical Institutions, Baltimore, MD). A total of 697 cases of B-precursor ALL had sufficiently complete satisfactory studies at the Duke reference laboratory to be used as the basis for this report.

Samples were analyzed on a FACSscan flow cytometer (Becton Dickinson). After using displays of forward and right angle light scatter to set a gate on the mononuclear cell population, data were displayed as correlated log FITC versus PE fluorescence. With the particular pairs of reagents chosen, it was possible to distinguish leukemic cells from normal T or B lymphocytes, or normal nucleated red blood cells in nearly every case by examining the FITC versus PE scatter display. Several different parameters of information were recorded for each marker analyzed. First, the level of “percent positive” cells was determined in the usual fashion by first setting a threshold with a control antibody. However, no arbitrary criterion was used to determine if a marker was “positive” or “negative.” Rather, the dual-parameter displays of the various antibody pairs (“test” samples) were individually evaluated and the shape of the test histogram for the neoplastic cells was compared with that of the control. For cases in which the shapes of the two curves were the same, a test sample was considered positive provided that the peak was shifted at least 20 log channels on a 256 channel scale. For cases in which examination of the test histogram showed a mixture of positive and negative events, the antibody was recorded as positive provided that reactivity due to contaminating normal cells could be excluded. For positive cases, a coded value of histogram shape was provided that reactivity due to contaminating normal cells could be excluded. For positive cases, a coded value of histogram shape was determined depending on whether the antigen expression on the leukemia was homogeneous or heterogeneous: if heterogeneous, whether the population consisted of a mixture of positive and negative cells, or of cells with two populations of differing intensities; and, if heterogeneous, which population was predominant. Finally, fluorescence intensity was standardized by using calibrated beads (Flow Cytometry Standards Corp, Research Triangle Park, NC) and converting arbitrary channel values to so-called mean equivalent soluble fluorescent (MESF) units.

Cytogenetic studies were performed as previously described on samples sent to the reference laboratory at the University of Alabama at Birmingham.

Samples of leukemic cells, cryopreserved in liquid nitrogen at the time of initial diagnosis, were obtained from the POG cell bank from patients who had the immunophenotype defined below, either with or without a cytogenetically defined t(1;19)(q23;p13). Ten micrograms of high molecular weight DNA from the patient samples were analyzed by Southern blot using an E24-specific probe (pE47M), as described previously. Various restriction enzymes were used, but, in accordance with a previous report, the enzymes Bgl II and Xba I were found to be most informative and these two enzymes were used to analyze all patients reported in this study.

For polymerase chain reaction (PCR) assays, total RNA was isolated from patient samples by the guanidinium-acid phenol chloroform method. E24-PBX1 chimeric transcripts were amplified using the primers JN23 and JN4, and the identity of the product was confirmed with the internal oligonucleotide JN26, as described previously; a portion of the ubiquitously expressed c-Ab1 mRNA was amplified in parallel to ensure that amplifiable RNA had been isolated.

RESULTS

Immunophenotype of cases associated with the t(1;19). Three hundred ninety-one of 697 patients (56%) with newly diagnosed B-precursor ALL and satisfactory phenotyping studies had a clonal cytogenetic abnormality. Of these, 22 (5.6%) had the t(1;19)(q23;p13). Review of the immunophenotype in these cases showed that all had CD10+CD19+CD9+, as described previously. In all 22 cases, the immunophenotype showed that there was homogeneous expression of these antigens (ie, essentially 100% blast positivity), with no cells failing to express these markers. By contrast, CD20 was expressed in 17 of 22 cases; in all 17 cases considered CD20+, only a fraction of the identifiable blasts were positive, and a significant number of CD20− blasts were present as well.

Thus, the composite immunophenotype seen in 20 of 22 cases of ALL with the t(1;19) was CD10+CD19+CD9+ CD34− and CD20−, or only focally positive (Fig 1). Although most of the cases of B-precursor ALL in our series were CD10+CD19+, when expression of all the antigens (and their specific patterns of expression) was considered, this composite phenotype was relatively uncommon, accounting for only 56 of 697 cases (8.0%). Among the 56 "phenotype-positive" cases were 32 with clonal cytogenetic abnormalities; thus, 20 of 32 (62.5%) patients with the phenotype and clonal cytogenetic abnormalities had the t(1;19)(q23;p13), and the false-positive rate was 12 of 369 (3%). There was no consistent pattern seen among the 12 patients with the phenotype and other cytogenetic abnormalities: 2 were hyperdiploid with simple gains of chromosomes, 1 had the Philadelphia chromosome, and the remainder had various translocations with or without numerical abnormalities.
Because the algorithm for defining the unusual phenotype was derived from a set of cases in which both the cytogenetic and immunophenotypic results were known, we subsequently investigated the phenotype of 14 additional cases of t(1;19)(q23;p13) that were detected after the cut-off date for this study. Twelve of the 14 cases had the identical phenotype described above; 1 of the 2 cases that did not agree was hyperdiploid (see below).

E2A gene rearrangements. A subset of the cases of t(1;19)(q23;p13)-ALL with the defined immunophenotype were analyzed by Southern blot for E2A gene rearrangements and by PCR for E2A-PBX1 fusion mRNA (Table 1 and Figure 2). Eleven of 11 cases had E2A gene rearrangements detected after digestion of genomic DNA with either Bgl II or Xba I. Six of these 11 cases were analyzed by PCR, and in each case E2A-PBX1 fusion transcripts of the identical size were amplified. The 1 case of t(1;19)-ALL that conformed to the phenotype but was raising data for CD9 expression also showed E2A gene rearrangements. We also molecularly analyzed the sole case of t(1;19)-ALL that did not conform to the phenotype by virtue of expression of CD34. In this case, E2A gene rearrangements were not observed using the enzymes Bgl II, EcoRI, or Xba I, and PCR analysis was negative for E2A-PBX1 chimeric mRNA. Interestingly, this case was unusual cytogenetically in that it was hyperdiploid, with 55 chromosomes, in addition to having the t(1;19)(q23;p13). The original group of 22 cases included 1 additional case of hyperdiploid t(1;19)(q23;p13) with 54 chromosomes. This case had the characteristic phenotype, E2A rearrangement, and expression of E2A-PBX1 fusion mRNA.

To further investigate the predictive value of this phenotype, we studied samples that were available from 17 of 24 patients with the phenotype in whom cytogenetics were either unsatisfactory or yielded only a normal karyotype. Five of these 17 patients had E2A rearrangements detected with the pE47M probe. These 17 patients included 4 of 8 patients with unsatisfactory cytogenetic studies, but only 1 of 9 patients with a normal karyotype. This rate of 5 of 17 was significantly higher than the rate of 22 of 39 among cytogenetically abnormal cases (P = .005, two-sided exact unconditional Z-test). PCR analysis was also performed on samples from these 17 patients, and E2A-PBX1 fusion transcripts were amplified in each of the 5 cases in which E2A rearrangements were detected. Each case in which E2A was germline was also PCR-negative. A summary of the results of the molecular studies on the various phenotypically and cytogenetically defined groups is provided in Table 1 and selected Southern blot results are shown in Fig 2.

**DISCUSSION**

The t(1;19)(q23;p13) translocation in ALL has previously been shown to be highly associated with cIg expression. Of all t(1;19)s seen in childhood ALL, 90% to 95% are cIg+ and are associated with E2A-PBX1 fusion. A rare subset of cases of t(1;19)-ALL are distinguishable in that they do not have evidence of E2A-PBX1 fusion, and may not have as poor a prognosis. Our data delineate an even tighter association between t(1;19) and an uncommon monoclonal antibody-defined phenotype characterized by homogeneous expression of CD19, CD10, and CD9; lack of CD34; and complete or partial absence of CD20. Of 22 patients with a cytogenetically detected t(1;19), 20 had the complete phenotype; I conformed to the phenotype but was missing data for CD9, whereas the other was phenotypically distinct and expressed CD34. Molecular analyses for E2A gene rearrangements and E2A-PBX1 chimeric mRNAs indicated that E2A was fused to PBX1 in every phenotype-positive case that was examined. The sole case that was different at the molecular level was the phenotype-negative, CD34+ case. It is interesting to note that this discrepant case was one of two hyperdiploid t(1;19)-ALLs in this series. In the study by Privitera et al, 5 of the 6 cIg- t(1;19) cases that did not have E2A-PBX1 fusion were hyperdiploid. Although E2A-PBX1 fusion is rarely seen in hyperdiploid t(1;19)-ALL, our 1 case with hyperdiploid t(1;19) and the characteristic phenotype was positive for the E2A rearrangement, suggesting that the phenotype is a more specific marker than ploidy for the presence of the rearrangement in

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**Table 1. Correlation of Immunophenotype and E2A Rearrangement in t(1;19) (q23;p13) ALL**

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>Immunophenotype</th>
<th>E2A Gene Rearrangement</th>
<th>PCR for E2A-PBX1</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(1;19)(q23;p13)</td>
<td>CD19+10’34’20+9+</td>
<td>20 1/11</td>
<td>6/6</td>
</tr>
<tr>
<td>CD19+10’34’20’9+</td>
<td>1/1</td>
<td>NT</td>
<td></td>
</tr>
<tr>
<td>CD19+10’34’20’9+</td>
<td>0/1</td>
<td>0/1</td>
<td></td>
</tr>
<tr>
<td>CD19+10’34’20’9+</td>
<td>1/9</td>
<td>1/9</td>
<td></td>
</tr>
<tr>
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<td>CD19+10’34’20’9+</td>
<td>4/8</td>
<td>4/8</td>
</tr>
</tbody>
</table>

Abbreviation: NT, not tested.

* For detailed explanation of this characteristic phenotype, see text.

† This case had 55 chromosomes in addition to the t(1;19).

‡ The same samples were positive for rearranged E2A genes and E2A-PBX1 chimeric mRNA.

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**Fig 1. Composite flow cytometric histogram showing the characteristic phenotype seen in cases of t(1;19) ALL containing E2A-PBX1 fusion. CD10, CD19, and CD9 (open histograms) are homogeneously brightly positive, whereas CD34 (shaded) is invariably negative. Histograms of CD20 expression (shaded) from two different cases are shown. In one, CD20 is negative, while in the other there is a negative population and a "tail" of variably intense CD20+ cells.**
Fig 2. E2A gene rearrangements. Southern blot autoradiograms of restriction endonuclease-digested genomic DNA are shown for selected cases. The karyotype, immunophenotype, and E2A status of each leukemia is listed above the lanes. For karyotype, 1;19 indicates that a t(1;19)(q23;p13) was detected cytogenetically. NL, a normal (46,XX or 46,XY) karyotype; and UN, an unsuccessful karyotype (no analyzable metaphases or specimen not received). Cases that have the immunophenotype defined in this report are classified as phenotype+, and those which lack this phenotype are listed as phenotype−. For E2A gene status R denotes rearranged and G denotes germline. The restriction endonucleases used are listed below the blots, and the migration of the marker DNA of standard sizes (in kilobases) is indicated along the sides.

cases of t(1;19)-ALL. Our results, combined with those of earlier studies,7,8 indicate that there are two distinct classes of t(1;19)-ALL. The vast majority (90% to 95%) have E2A-PBX1 fusion, and can be recognized by a distinct and uncommon immunophenotype. A minority of cases do not have this phenotype and have no evidence of involvement of E2A or PBX1.

Although a very large number of reports have appeared describing immunophenotypic variability among cases of ALL,14-19 relatively few have discussed specific criteria for grouping cases of leukemia based on reactivity with combinations of antibodies. Traditionally, arbitrary cut-off figures, most commonly 20%, have been used to determine if a leukemic blast is “positive” or “negative” for a particular antibody. Our approach differs in that we first use multiparameter analysis to best isolate blasts from any contaminating normal cells, and then record the shape of the resulting histogram compared with the control. Rather than using arbitrary criteria for discriminating between groups, we used a biologic endpoint, in this case, the t(1;19). With this endpoint, it became apparent that criteria for inclusion in the phenotypic group differed for different antibodies. Thus, for CD19, CD10, and CD9, essentially 100% positivity if a leukemic blast is “positive” or “negative” for a particular antibody. Our approach differs in that we first use multiparameter analysis to best isolate blasts from any contaminating normal cells, and then record the shape of the resulting histogram compared with the control. Rather than using arbitrary criteria for discriminating between groups, we used a biologic endpoint, in this case, the t(1;19). With this endpoint, it became apparent that criteria for inclusion in the phenotypic group differed for different antibodies. Thus, for CD19, CD10, and CD9, essentially 100% positivity was necessary to be included, whereas for CD34, finding virtually any positive cells was enough to exclude it. In the case of CD20, if traditional criteria had been applied, both “positive” and “negative” cases would have been included among the t(1;19) cases. However, the common phenotypic feature found in all cases was the presence of at least a significant subset of CD20− cells irrespective of whether some or no blasts expressed the antigen. We have previously used this type of “biologic endpoint” approach in setting criteria for determining CD34 “positivity”,20 and in determining a correlation between immunophenotype and translocations involving the 11q23 locus in ALL.21 Our results indicate that, in immunophenotypic analysis, simple descriptions of antigen expression as positive or negative, or arbitrary cutoffs such as 20% for positivity may miss important biologic correlations.

By combining several markers, we were able to narrow down the number of cases in the phenotypic group to only 8% of total cases of B-precursor ALL. Each component of the phenotype, by itself, was a relatively common feature of ALL in general, except for lack of CD34, which is relatively unusual. Thus, lack of CD34 had the largest effect in discriminating the t(1;19) cases from the group at large, but each additional marker further narrowed the number of cases included. Attempts to use the pattern of expression of CD45, HLADR, CD22, or CD24 to further refine the phenotypic subgroup were not successful.

The POG has previously reported that patients with pre-B-ALL and a t(1;19) have a significantly higher risk of relapse than other children with B-precursor ALL.5 Others have suggested that this adverse prognosis can be overcome with more intensive therapy.22 Accordingly, on the current POG ALL study, patients with a t(1;19) are assigned to the
more intensive treatment arm. However, for a significant number of cases of ALL, a cytogenetically abnormal clone will not be identified. Although 21 patients with the t(1;19) were detected by cytogenetics, this study found 5 of 17 patients with both the characteristic phenotype and uninformative cytogenetics who also had molecular evidence of E2A-PBX1 fusion. This estimate of about 25% of cases in which cytogenetics fails to identify the t(1;19) may be a lower estimate, because we were unable to study 7 additional cases with the phenotype who had uninformative cytogenetics. It is potentially of some interest that only 1 of 9 cases with a normal karyotype and the phenotype had E2A rearrangement, whereas among those with unsatisfactory results, the proportion was much greater (4 of 8) and similar to that seen among patients with other clonal cytogenetic abnormalities (20 of 32). A normal cytogenetic result is generally not considered definitive because the neoplastic cells may not be represented in the population of dividing cells. However, it may be that, in the case of the t(1;19), there is such a growth advantage to the neoplastic cell that is always provides metaphases if it is present.

The overall predictive value of a positive phenotype for the t(1;19) associated with E2A-PBX1 rearrangement was about 50% (26 of 51), including cases with both informative and uninformative cytogenetics. However, the sensitivity of the phenotype for the molecular t(1;19) was essentially 100%. This finding suggests that immunophenotyping can be used along with cytogenetics to select a relatively small number of cases to be further studied by molecular analysis. Because the phenotype is found in only 8% of cases of B-precursor ALL, only about 3% of cases of ALL would have to be screened, assuming an informative cytogenetics rate of about 60%. Such a procedure could be readily used to assign patients to a therapeutic regimen appropriate for high-risk ALL. In addition, the small subset of patients with t(1;19)-ALL who lack involvement of E2A or PBX1 can be identified by the fact that they do not conform to the characteristic phenotype that we have defined. As they do not have the biologic high-risk feature conveyed by the E2A-PBX1 fusion and there is no clinical evidence that they fare poorly with standard therapy, there appears to be no need to treat them more intensively, particularly because the majority are hyperdiploid.

The tight correlation between the E2A-PBX1 fusion and the specific immunophenotype that we have defined may have implications for our understanding of the chimera's role in leukemogenesis. Lymphoblasts of these patients are phenotypically homogeneous, and appear to be arrested at a precise stage of differentiation, ie, at a time when CD34 expression has shut off, CD20 is beginning to be expressed, and both CD19 and CD10 persist. This corresponds to a relatively late stage of B-precursor development before surface Ig expression, and is consistent with the known expression of cIg in these leukemias. Cell surface proteins corresponding to these antigens include a neutral endopeptidase (CD10), a phosphorylated protein that functions as a calcium channel (CD20), and a B-lineage-restricted glycoprotein that is part of signal transduction complex (CD19). However, relatively little is known about the biochemical roles that these proteins play in normal or neoplastic lymphoid differentiation. Even less is known about the factors that regulate their sequential expression and downregulation. Our studies raise the possibility that a primary effect of E2a-Pbx1 could be blockage of the transition, whereby developing B cells downregulate CD10 and turn off expression of CD20 and surface Ig. The E2a-Pbx1 oncprotein has structural features that suggest that it may function as a chimeric transcription factor affecting transcription (positively or negatively) by binding to promoters that are cognate targets of Pbx1 and/or its close relatives Pbx2 and Pbx3. Our studies suggest that target genes to be considered should include those of certain cell differentiation-associated surface glycoproteins, or factors that control their sequential expression and disappearance.

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Predictability of the t(1;19)(q23;p13) from surface antigen phenotype: implications for screening cases of childhood acute lymphoblastic leukemia for molecular analysis: a Pediatric Oncology Group study

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