ALL-1 Gene Rearrangements in DNA Topoisomerase II Inhibitor-Related Leukemia in Children  
By Carolyn A. Felix, Matthew R. Hosler, Naomi J. Winick, Margaret Masterson, Albert E. Wilson, and Beverly J. Lange

We examined clinical, morphologic, and cytogenetic features and ALL-1 (MLL, Htrx1, HRX) gene rearrangements in 17 cases of secondary leukemia that occurred 11 months to 9 years from diagnoses of primary cancers in children who received topoisomerase II inhibitors or developed secondary leukemias typical of those associated with this therapy. Primary diagnoses included nine solid tumors and eight leukemias. Ten secondary leukemias were acute myeloid leukemia (AML), one was of mixed lineage, two were acute lymphoblastic leukemia (ALL), and four presented as myelodysplasia. Of 15 cases with 11q23 involvement, 11 (73%) were cytogenetically identifiable; four cases had molecular rearrangement only. By Southern blot, rearrangements within the ALL-1 gene were similar to sporadic cases. The results of this analysis suggest the following: (1) In most pediatric cases of topoisomerase II inhibitor-associated leukemia, there is disruption of the breakpoint cluster region of the ALL-1 gene at chromosome band 11q23. (2) Exposure histories vary in secondary 11q23 leukemia, as the only topoisomerase II inhibitor was administered. (3) There is clinical, morphologic, cytogenetic, and molecular heterogeneity in pediatric secondary 11q23 leukemia. (4) There are some survivors of pediatric secondary 11q23 leukemia, but the outcome is most often fatal. © 1995 by The American Society of Hematology.

THE EPIPODOPHYLLOTOXIN anticancer drugs etoposide and teniposide are intercalating inhibitors of the nuclear enzyme DNA topoisomerase II.1-4 The anthracyclines and daunomycin are intercalating inhibitors that form a complex with DNA and topoisomerase II.5,6 In addition to causing chromosomal deletions and DNA recombinations that are cytotoxic to cancer cells, topoisomerase II inhibitor chemotherapy in humans has been implicated in leukemogenic translocations.9

Translocations of chromosome band 11q23, most commonly with band 9p21, are present in half the cases of secondary leukemia associated with DNA topoisomerase II inhibitors.9 Variant reciprocal partners of 11q23 include chromosomes 1, 2, 3, 16, 17, and 19.10-12 The t(8;21) is present as a recurring chromosomal abnormality in several other cases.13-17 Cases of t(15;17) acute promyelocytic leukemia (APL) and acute myeloid leukemia (AML) with inv(16) related to DNA topoisomerase II interactive drugs have also been described.15,17

Chromosome band 11q23 is involved in reciprocal translocations in most sporadic acute lymphoblastic leukemias (ALLs) and AMLs of infants and young children. The same breakpoint cluster region within the ALL-1 (MLL, Htrx1, HRX) oncogene at band 11q23 for sporadic cases is disrupted in most reported cases of epipodophyllotoxin-related 11q23 leukemia.12,18-26 However, in one case of pediatric etoposide-related AML with t(11;19)(q23;p13), we reported an 11q23 translocation breakpoint outside the ALL-1 genomic breakpoint cluster.18 Although a limited number of children have been examined, most molecular analyses of 11q23 chromosomal breakpoints in secondary AML have involved adults.12,19,27 The present study explores the molecular diversity and provides further clinical definition to DNA topoisomerase II inhibitor-related leukemia in a pediatric population.

MATERIALS AND METHODS

Leukemic specimens from children previously treated for a primary cancer and diagnosed with secondary leukemia were obtained from the Children's Hospital of Philadelphia (Philadelphia, PA), Dallas (Dallas, TX) and Cook-Fort Worth (Fort Worth, TX) Children's Hospitals, Children's Hospital of Cincinnati (Cincinnati, OH), Memorial Sloan Kettering Cancer Center (New York, NY), University of Connecticut Health Center (Farmington), Kaiser Permanente (Los Angeles, CA), and Indiana Oncology-Hematology Consultants (Indianapolis). Molecular studies were approved by the Institutional Review Board at the Children's Hospital of Philadelphia, and individual institutions had provisions either through consent for reference laboratory specimens or for the use of extra diagnostic materials for research. The diagnoses of secondary leukemia were made by morphologic and immunohistochemical examination of the marrow and by fluorescence-activated cell sorter analysis with standard monoclonal antibodies.11 Cytogenetic analyses were performed by individual Children's Cancer Group- or Pediatric Oncology Group-approved laboratories. Molecular analyses were also performed on the cell line B1, which was derived from t(4;11)(q21;q23) secondary ALL cells.28

Eukemic marrow cells were examined by Southern blot analysis using standard methodology. Genomic DNA was isolated from cryopreserved or fresh marrow mononuclear cells using 4 mol/L guanidine isothiocyanate-5.7 mol/L CsCl gradients as described.29,30 First, BamHII- and, in some cases, HindIII-digested genomic DNAs were analyzed with the B859 probe, an 859-bp BamHII fragment of ALL-I cDNA that spans exons 5 through 11, the region of the ALL-I genomic breakpoint cluster.12,17,22 To potentially identify 11q23 breakpoints not located within the ALL-I genomic breakpoint cluster, select cases were assessed for involvement of a more 5' site in ALL-I. The 5' region of ALL-I was studied in HindIII- or BglII-digested
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Fig 1. (A) Genomic Southern blot of BamHI-digested DNA hybridized with B859 human ALL-1 cDNA probe spanning exons 5 through 11, the region of the breakpoint cluster. Several cases of secondary 11q23 leukemia with one or two rearrangements of the ALL-1 gene within the breakpoint cluster as well as unrearranged cases are shown. Sporadic ALL cell line RS411 is positive control. Human placental DNA and human peripheral blood lymphocyte (PEL) DNA show the germline pattern. Numbers above the lanes correspond to patient (Pt) numbers in Tables 1 and 2, and karyotypes are indicated. (B) Germline pattern of the region of the ALL-1 gene 5' to the breakpoint cluster in karyotype-positive leukemic marrow DNA. (C) Schematic of the genomic regions recognized by ALL-1 cDNA probe B859 and the 5' cDNA probe, SKV3.

RESULTS

Clinical, demographic, and morphologic features. Demographic features, primary diagnoses, treatment regimens, and French-American-British (FAB) morphologies and outcomes are summarized in Table 1. Each child had received a DNA topoisomerase II inhibitor or developed secondary leukemia typical of that associated with this therapy. Patients represented a diverse population of children and both sexes. Overrepresentation of any one ethnic background was not apparent. There were nine males and eight females aged from 5 to 14.7 years at onset of the secondary leukemia. Intervals between diagnoses of primary cancer and secondary leukemia ranged from 11 months to 9 years. Primary
Table 1. Demographic and Clinical Features of Pediatric Secondary Leukemias

<table>
<thead>
<tr>
<th>PRIMARY CANCER</th>
<th>SECONDARY LEUKEMIA</th>
<th>Therapy</th>
<th>Status</th>
<th>PRIMARY CANCER</th>
<th>SECONDARY LEUKEMIA</th>
<th>Therapy</th>
<th>Status</th>
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<tr>
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<td>Race</td>
<td>Sex</td>
<td>Therapy</td>
<td>Dx/ FAB</td>
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<td>DOD</td>
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<td>W/F</td>
<td>Age</td>
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<td>AML/M4</td>
<td>NED</td>
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<td>Age</td>
<td>42</td>
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<td>DOD</td>
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<td>Age</td>
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<td>HD</td>
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<td>Age</td>
<td>16</td>
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<td>DOC</td>
</tr>
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<td>Age</td>
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<td>DOD</td>
</tr>
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<td>3.8</td>
<td>H/F</td>
<td>Age</td>
<td>14</td>
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<td>NED</td>
</tr>
<tr>
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<td>9.2</td>
<td>H/F</td>
<td>Age</td>
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<td>TALL/L1</td>
<td>DOC</td>
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<tr>
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<td>PNET</td>
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<td>W/M</td>
<td>Age</td>
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<td>AML/M5</td>
<td>NED</td>
</tr>
<tr>
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<td>OS</td>
<td>14.0</td>
<td>W/M</td>
<td>Age</td>
<td>16</td>
<td>ALL/L1</td>
<td>DOD</td>
</tr>
<tr>
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<td>ALL</td>
<td>12.2</td>
<td>H/F</td>
<td>Age</td>
<td>34</td>
<td>MDS/M7</td>
<td>DOC</td>
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<td>Age</td>
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<td>DOD</td>
</tr>
<tr>
<td>13</td>
<td>RMS</td>
<td>5.0</td>
<td>W/F</td>
<td>Age</td>
<td>60</td>
<td>AML/M4</td>
<td>DOD</td>
</tr>
<tr>
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<td>RMS</td>
<td>4.2</td>
<td>W/F</td>
<td>Age</td>
<td>16</td>
<td>MDS/RAEB-1 108</td>
<td>NED</td>
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<tr>
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<td>ALL</td>
<td>2.4</td>
<td>W/M</td>
<td>Age</td>
<td>8</td>
<td>AML/M5a</td>
<td>DOC</td>
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<td>Age</td>
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<td>AML/M2</td>
<td>NED</td>
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<td>RMS</td>
<td>1.8</td>
<td>W/M</td>
<td>Age</td>
<td>82</td>
<td>MDS/RAEB-1</td>
<td>DOD</td>
</tr>
</tbody>
</table>

Some clinical features in cases 1, 3, 6, 10, 13, 15, and 17 have been described. Case 1 in the present study was case 8 in Winick et al.15 Cases 1 and 15 were cases 1 and 2, respectively, in Felix et al.16 Cases 3 and 6 were cases 13 and 16, respectively, in Rubin et al.17 Cases 13 and 17 were cases 4 and 6, respectively, in Heyn et al.31 The clinical history in case 10 was reported in a case report.18 Cytoreduction for BMT in case 6 was with melphalan and total body irradiation.

Abbreviations: Pt, patient; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; MLL, mixed lineage leukemia; MDS, myelodysplastic syndrome; Dx, diagnosis; OS, osteosarcoma; HD, Hodgkin’s disease; NBL, neuroblastoma; PNET, peripheral neuroectodermal tumor; NHL, non-Hodgkin’s lymphoma; RMS, rhabdomyosarcoma; W, white; B, black; H, Hispanic; A-ase, L-asparaginase; ADR, Adriamycin (doxorubicin); AMD, dactinomycin; Ara-C, cytosine arabinoside; BCNU, carmustine; BMT*, bone marrow transplant; CBDCA, carboplatin; Cort**, corticosteroids {dexamethasone, prednisone, methylprednisolone, or intrathecal hydrocortisone); CPPD, cisplatin; CPM, cyclophosphamide; DNM, daunorubicin; EPO, erythropoietin; 5-AZA, 5-azacytidine; HU, hydroxyurea; IFOS, ifosfamide; MIT, mitoxantrone; MTX, methotrexate; PCZ, procarbazine; 6MP, 6-mercaptopurine; 6TG, 6-thioguanine; VCR, vincristine; VLB, vinblastine; VM26, teniposide; VP16, etoposide; XRT, radiation therapy; FAB, French-American-British; DOD, dead of disease; DOC, dead of complications; NED, no evidence of disease.

Cytoreduction regimen not listed.

Diagnoses included nine solid tumors and eight leukemias. Nine secondary leukemias were monoblastic variants of AML or mixed lineage leukemia (MLL), one was FAB M1 AML, one was FAB M2, four presented as myelodysplasia (MDS), and two were ALL. In 13 cases, there was previous DNA topoisoasemase II inhibitor exposure to epipodophyllotoxin in combination with an anthracycline. In two cases, prior treatment was with an anthracycline without epipodophyllotoxin. The only previous DNA topoisoasemase II inhibitor in one case was dactinomycin and, in another case, no DNA topoisoasemase II inhibitor was administered.

Karyotypic abnormalities in secondary leukemias. Complete karyotypes of the 17 secondary leukemias are listed in Table 2. Eleven cases had translocation of chromosome band 11q23 with bands 1p32, 3q25, 4p21, 9p21-22, or 19p13. One case showed del(11)(q23). In five other cases, the karyotypes were normal or suggested unrelated structural abnormalities or only a numerical abnormality. In one case with multiple cytogenetic abnormalities not involving chromosome band 11q23, there were monosomies of chromosomes 5 and 7, more typical of the alkylator-induced myelodysplasias and leukemias (Table 2).3,32

Localization of genomic breakpoints in secondary 11q23 leukemia by Southern blot analysis. Results of Southern blot analysis of 17 cases of pediatric secondary leukemias are shown in Table 2. Grouped according to whether cytogenetics showed an 11q23 translocation and whether there was ALL 1 gene rearrangement on Southern blot analysis, cases 1 through 10 were karyotype +/molecular +; cases 1 through 11 were karyotype 1/molecular 1; case 15, karyotype +/molecular 1; and cases 16 and 17, karyotype 1/molecular 1. In 8 of 15 cases with cytogenetic and/or molecular rearrangement of chromosome band 11q23, Southern blot analysis of BamHI-digested genomic DNA with the B859 probe showed the normal allele and two additional bands consistent with both derivative chromosomes that resulted from the translocation (Fig 1). In six cases, only one derivative chromosome was detected by the probe. In a previously reported case of etoposide-related AML with a t(11;19)(q23;p13), the 11q23 translocation breakpoint was
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Table 2. Karyotypes and ALL-1 Gene Status in Pediatric Secondary Leukemias

<table>
<thead>
<tr>
<th>Case</th>
<th>Karyotype</th>
<th>ALL-1 Bcr/Abl</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>46,XY,t(9;11)(p22;q23) [15 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>2</td>
<td>46,XX,t(11;19)(q23;p13.3) [10 cells]/46,XX [10 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>3</td>
<td>47,XX,+8,t(11;19)(q23;p13) [19 cells]/46,XX,+8,t(11;19)(q23;p13) [6 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>4</td>
<td>46,XX,t(11;22)(p23;q13) [27 cells]</td>
<td>R1</td>
</tr>
<tr>
<td>5</td>
<td>46,XY,t(11q-;19p+) [25 cells]</td>
<td>R1</td>
</tr>
<tr>
<td>6</td>
<td>46,XY,t(11;23)(p11;q11)inv(2)q21;q37)del(5)(q13);(7;7)(q22;?) [29 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>7</td>
<td>46,XX,t(11;23) [21 cells]/46,XX [14 cells]</td>
<td>R1</td>
</tr>
<tr>
<td>8</td>
<td>47,XX,+del(6)(q27)/47,XX,+8,del(6)(q27),del(11)(q23) [30 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>9</td>
<td>46,XY,t(11;19)(p22;q23) [20 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>10</td>
<td>46,XY,t(4;11)(q21;q23) [7 cells]/46,XY [18 cells]</td>
<td>R1</td>
</tr>
<tr>
<td>11</td>
<td>47,XX,add(1)(p32)+mar [2 cells]/46,XX [38 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>12</td>
<td>46,XX,del(11)(q14),add(14)(p11.2) [16 cells]/46,XX [4 cells]</td>
<td>R2</td>
</tr>
<tr>
<td>13</td>
<td>46,XY [18 cells]</td>
<td>R1</td>
</tr>
<tr>
<td>14</td>
<td>46,XX,t(11;20)(p15;q11.23) [15 cells]/46XX [5 cells]</td>
<td>R1</td>
</tr>
<tr>
<td>16</td>
<td>85-94(4n),XXYY [19 cells]/n=66 [1 cell]</td>
<td>G</td>
</tr>
<tr>
<td>17</td>
<td>45,XY,har(2)(q22),−5,der(7)(q11.23)del(7)(q11.23),del(12)t(12;19)(p11.12;q12),del(17)(t6;17)(p12;11.2),−19,+mar1 (19 cells)/germline [1 cell]/46,XY [2 cells]</td>
<td>G</td>
</tr>
</tbody>
</table>

The status of the ALL-1 gene in the breakpoint cluster region and partial karyotypes in cases 1 and 15 were reported previously. Additional molecular analyses of the ALL-1 genomic breakpoint cluster region and the 5' region of ALL-1 in case 15 were performed herein. Case 1 in the present study was case 8 in Winick et al. Cases 1 and 15 were cases 1 and 2, respectively, in Felix et al. Cases 3 and 6 were cases 13 and 18, respectively, in Rubini et al. Cases 13 and 17 were cases 4 and 6, respectively, in Hehn et al. Molecular analyses on case 10 were performed on the cell line B1 derived from the secondary leukemia in a previous report.

Abbreviations: R1, one rearrangement; R2, two rearrangements; G, germline.

not located within the ALL-1 genomic breakpoint cluster (case 15). In the present study, this leukemia was further analyzed by hybridization of HindIII-digested DNA with the B859 fragment of ALL-1 cDNA, confirming that the translocation breakpoint was not within the region of the breakpoint cluster. Involvement of the 5' region of ALL-1 was also excluded.

Of 11 cases with cytogenetically detectable abnormalities of chromosome band 11q23, 10 had rearrangements within the ALL-1 genomic breakpoint cluster. Included was a case of secondary t(11;19) MLL, where the previous Hodgkin's disease therapy included alkylating agents and irradiation, but not a DNA topoisomerase II inhibitor (case 5, Tables 1 and 2).

Four cases of secondary 11q23 leukemia with molecular ALL-1 gene rearrangements within the breakpoint cluster did not show 11q23 abnormalities by karyotype (Table 2). Included was a case of secondary MDS examined after evolution to secondary AML (case 14). This leukemia showed ALL-1 gene rearrangement and a clonal t(11;20)(p15;q11) without cytogenetic evidence of involvement of band 11q23 (Table 2). Similarly, another secondary AML with molecular ALL-1 gene rearrangement showed del(11)(q14) by karyotype (case 12). In the child previously treated for embryonal rhabdomyosarcoma with cyclophosphamide, ionizing radiation, and dactinomycin as the only DNA topoisomerase I inhibitor, whose clinical course was recently reported, there was molecular but not cytogenetic evidence of involvement of the ALL-1 gene at band 11q23 (case 13, Tables 1 and 2).

DISCUSSION

Secondary leukemia is a complication of effective cancer chemotherapy with epipodophyllotoxins and other DNA topoisomerase II inhibitors. ALL and non-Hodgkin's lymphoma are the most common primary cancers among affected pediatric patients. Epipodophyllotoxin-related leukemia also occurs in children after treatment of germ cell tumors, sarcomas, neuroblastoma, and histiocytosis X. The frequency of topoisomerase II inhibitor-related leukemia appears to be increasing.

We examined the clinical, cytogenetic, and molecular diversity in 17 cases of secondary leukemia in children who received topoisomerase II inhibitors or developed secondary leukemias typical of those associated with this therapy. Although a period of myelodysplasia often precedes the form of secondary AML associated with alkylating agents and irradiation, leukemias associated with epipodophyllotoxins more commonly present as overt AML. However, four patients in this series presented with myelodysplasia rather than overt leukemia.

Of 17 cases, 15 had cytogenetic and/or molecular involvement of chromosome band 11q23. Molecular rearrangement of the AML-1 oncogene at chromosome band 21q22 was not excluded in case 16, which was FAB M2 morphology and negative for involvement of chromosome band 11q23 by both karyotype and Southern blot analysis. Cases with the t(15;17) or inv(16) were not observed. The Southern blot results suggest that the clustering of 11q23 breakpoints within the ALL-1 gene is significant for some pediatric secondary leukemia. The detection of only one derivative chromosome in 6 of 14 cases with molecular rearrangement may be consistent with interstitial deletion of the telomeric region of ALL-1 during translocation. Four of 14 cases showed occult molecular rearrangement, a somewhat higher incidence than in karyotype negative sporadic AML.
Most but not all (11;19)(q23;p13) molecular breakpoints in sporadic infant leukemia are within the ALL-I genomic breakpoint cluster. In this series, three of four (11;19) secondary leukemia breakpoints localized to the ALL-I genomic breakpoint cluster. In case 15, the breakpoint was not identified within the ALL-I genomic breakpoint cluster or 5' of this region. In four cases of sporadic (11;19)(q23;p13) leukemia, fluorescence in situ hybridization showed 11q23 breakpoints distal to (t4;11), (t9;11), and (t6;11) cases, but involvement of the more telomeric locus, rck, has been excluded. These observations suggest an additional leukemia-associated gene at chromosome band 11q23. PLZF, which also maps to band 11q23, is involved in a variant translocation with the retinoic acid receptor-α locus in APL, but case 15 did not have features of APL.

Novel cytogenetic features also suggest diversity in the pediatric DNA topoisomerase II inhibitor-related leukemias. The (9;11)(p21;q23) commonly identified in cases of epipodophyllotoxin-related AML occurred in only three cases in this series. The (3;11)(q25;q23) is a variant translocation previously described in case 6. We determined that the 11q23 chromosomal breakage in this case was within the ALL-I genomic breakpoint cluster. The EVII and EAP genes are fused with AML-I at chromosome band 21q22 in variant t(3;21)(q26;q23) translocations in therapy-related AML and chronic myelogenous leukemia. Whether a common region on chromosome 3q is involved in translocations with both the ALL-I and AML-I genes remains to be explored. Another variant translocation was the (1;11)(p32;q23) in therapy-related MDS (case 7).

Epipodophyllotoxin-induced secondary ALL is uncommon in both children and adults. The secondary ALLs are of B- or T-cell lineage and demonstrate (t4;11) or (t11;16) chromosomal translocations. The del(11)(q23) that we identified in case 8 and mapped molecularly has not been reported in secondary ALL.

Cases 12 and 14 showing the del(11)(q14) or (t11;20) (p15;q11) by karyotype had molecular rearrangements of the ALL-I gene at band 11q23. There may have been complex translocations or inversions involving chromosome 11, or molecular rearrangement of ALL-I independent of the cytogenetically detectable abnormalities. Alternatively, the 11q23 translocations may have appeared falsely in the karyotype as more proximal abnormalities of 11q or of 11p. In sporadic leukemias with the (t9;11) involving bands 11p13 or 11q13, and in leukemias with the (t11;20)(p15;q11), the breakpoints were not explored molecularly.

The association of epipodophyllotoxins and anthracyclines with secondary leukemia is well-established. Dactinomycin without other DNA topoisomerase II inhibitors has not previously been associated with secondary 11q23 leukemia. In this study, a case of secondary AML, where the only prior DNA topoisomerase II inhibitor exposure was dactinomycin, was shown to have ALL-I gene rearrangement (case 13). Also included in the sarcoma treatment were local irradiation, vincristine, and cyclophosphamide. This case suggests that some risk of 11q23 leukemia may be associated with dactinomycin. The agent is probably less leukemogenic than the other DNA topoisomerase II inhibitors, as this complication has not occurred in survivors of Wilms' tumor. It has also been proposed that the development of 11q23 leukemia may be potentiated by alkylating agents in conjunction with DNA topoisomerase II inhibitors.

Case 5 of (11;19) secondary AML occurred 15 months after the diagnosis of Hodgkin's disease that was treated with carmustine, cyclophosphamide, vinblastine, procarbazine, and irradiation, a regimen that did not include a DNA topoisomerase II inhibitor. Cases 5 and 13 suggest heterogeneity in the agents associated with secondary 11q23 leukemia and the mechanism of leukemogenesis.

When used in conjunction with alkylating agents, epipodophyllotoxins may result in secondary AML with characteristic monosomies of chromosomes 5 or 7 as well as 11q23 chromosomal translocations. Case 17 of secondary AML after embryonal rhabdomyosarcoma treated with vincristine, doxorubicin, cyclophosphamide, cis-platinum, etoposide, dactinomycin, and irradiation, showed monosomies of chromosomes 5 and 7. There were two translocations, but chromosomal band 11q23 was uninvolved. Molecular ALL-I gene rearrangement was not present.

Among 15 patients in this series with karyotypic and/or molecular secondary 11q23 leukemia, there was clinical, phenotypic, morphologic, molecular, and cytogenetic heterogeneity. There are some survivors, but the outcome was most often fatal. The clinical efficacy of DNA topoisomerase II interactive agents mandates a better understanding of why these drugs are associated with leukemogenic translocations. By genomic cloning and sequencing, potential DNA topoisomerase II sites were identified in the ALL-I and AF-9 genes at a t(9;11) breakpoint in sporadic AML. This Southern blot analysis provides the framework for further study of the mechanism whereby drug-topoisomerase II-DNA interactions result in translocations.

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ALL-1 gene rearrangements in DNA topoisomerase II inhibitor-related leukemia in children

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