Rearrangements of the MLL Gene in Therapy-Related Acute Myeloid Leukemia in Patients Previously Treated With Agents Targeting DNA-Topoisomerase II

By Heidi J. Gill Super, Norah R. McCabe, Michael J. Thirman, Richard A. Larson, Michelle M. Le Beau, Jens Pedersen-Bjergaard, Preben Philip, Manuel O. Diaz, and Janet D. Rowley

Chromosome band 11q23 is frequently involved in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) de novo, as well as in myelodysplastic syndromes (MDS) and lymphoma. Five percent to 15% of patients treated with chemotherapy for a primary neoplasm develop therapy-related AML (t-AML), which may show rearrangements, usually translocations involving band 11q23 or, less often, 21q22. These leukemias develop after a relatively short latent period and often follow the use of drugs that inhibit the activity of DNA-topoisomerase II (topo II). We previously identified a gene, MLL (myeloid-lymphoid leukemia or mixed-lineage leukemia), at 11q23 that is involved in the de novo leukemias. We have studied 17 patients with t-MDS/t-AML, 12 of whom had cytogenetically detectable 11q23 rearrangements. Ten of the 12 t-AML patients had received topo II inhibitors and 9 of these, all with balanced translocations of 11q23, had MLL rearrangements on Southern blot analysis. None of the patients who had not received topo II inhibitors showed an MLL rearrangement. Of the 5 patients lacking 11q23 rearrangements, some of whom had monoblastic features, none had an MLL rearrangement, although 4 had received topo II inhibitors. Our study indicates that the MLL gene rearrangements are similar both in AML that develops de novo and in t-AML. The association of exposure to topo II-reactive chemotherapy with 11q23 rearrangements involving the MLL gene in t-AML suggests that topo II may play a role in the aberrant recombination events that occur in this region both in AML de novo and in t-AML.

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A NUMBER OF DIFFERENT recurring rearrangements of chromosome band 11q23 are observed in human de novo acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL) as well as in lymphoma and myelodysplastic syndromes (MDS). Translocations involving 11q23 with t(4;11), t(6;11), t(9;11), t(11;19), t(11;11)22, 10p11-15, or 17q21-25 are observed primarily in AML.1,2 The t(4;11)(q21;q23) and t(11;19)(q23;p13.3) are associated with ALL as well as with mixed-lineage and biphenotypic leukemias.3 In addition to the 11q23 rearrangements associated with leukemia that arises de novo, balanced translocations involving this band are observed in AML (usually with monoblastic or myelomonocytic characteristics) that occasionally develops after cytotoxic treatment for a primary neoplasm.4,6 The t(9;11)(p22;q23) and the t(11;19) are among the most common 11q23 rearrangements observed in therapy-related AML (t-AML).7,8 These patients develop overt leukemia after a relatively short latent period, most often after treatment with drugs that target DNA-topoisomerase II (topo II). These drugs include, primarily, the epipodophyllotoxins, such as etoposide (VP-16) and teniposide (VM-26), and the anthracyclines, such as daunorubicin, doxorubicin hydrochloride (adriamycin), and 4-epidoxorubicin. The clinical and cytogenetic features of this form of t-AML are distinct from the more common t-AML or t-MDS that follows the anthracyclines, such as daunorubicin, doxorubicin hydrochloride (adriamycin), and alkylating agents, often presenting with losses of whole chromosomes 5 or 7 or deletions of the long arm of these chromosomes.8,9

We have shown that a yeast artificial chromosome (YAC) containing the CD3D and CD3G genes and DNA extending approximately 300 kb distal to these genes, on chromosome 11, was split in leukemia cells from patients with t(4;11), t(6;11), t(9;11), and t(11;19), indicating a clustering of breaks in these common 11q23 rearrangements.9 Genomic probes isolated from a library prepared from this YAC identified a large transcript that spans the breakpoint region. The gene was named MLL for myeloid-lymphoid or mixed-lineage leukemia.10 We cloned a 0.74-kb cDNA Bam HI fragment that detects rearrangements in DNA digested with BamHI on conventional Southern blots in all patients with the most common 11q23 translocations as well as with more rare 11q23 rearrangements.11,12 The 0.7-kb cDNA probe (MLL0.7B) identifies a single 8.3-kb genomic BamHI fragment, indicating that the breakpoints are clustered in this fragment (Fig 1). Others have cloned the same gene and have called it MLL.13,14 Htrx;14 or HRX.15 The gene is transcribed from centromere to telomere.12

Most analyses reported to date have included only patients who developed AML de novo. We report here the molecular analysis of 17 patients diagnosed with t-AML or t-MDS. The majority of the patients received topo II-targeting drugs, often in combination with alkylating agents, for their primary neoplasm. Twelve patients had 11q23 rearrangements detected cytogenetically. Nine of these leukemia samples had DNA rearrangements on Southern blot analysis with the MLL0.7B probe. In addition, we observed a significant association between prior treatment with topo II inhibitors and MLL gene rearrangements in t-AML.

MATERIALS AND METHODS

Patient material. Peripheral blood or bone marrow obtained with informed consent from patients developing AML after cytotoxic treatment for a prior neoplasm was frozen for DNA analysis. All such patients who were studied at the University of Chicago with material stored at the time of diagnosis and who exhibited a

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RESULTS

DNA from 17 patients with t-AML or t-MDS was analyzed for rearrangements of the MLL gene. Clinical information for all patients is presented in Table 1. Included are 12 samples (nos. 1 through 12) that showed cytogenetically detectable 11q23 rearrangements (Table 2). Ten of these 12 patients had received chemotherapy that included topo II inhibitors. On Southern blot analysis, the 0.74-kb BamHI MLL cDNA fragment, MLL0.7B, detected DNA rearrangements in 9 of these 10 patients. All 9 showed balanced translocations of 11q23, cytogenetically. The other patient (no. 12) who showed no rearrangement with the probe had an unbalanced translocation (Tables 2A and 3, Fig 2, and data not shown). Two patients who had unbalanced rearrangements of 11q23 (nos. 10 and 11 with interstitial deletions q13-14q23) had received no topo II inhibitors. No DNA rearrangements were detected in these patients (Tables 2B and 3). A third subset of 5 patients (nos. 13 through 17) presented with t-AML or t-MDS but had no cytogenetically detectable 11q23 rearrangement. Four of the 5 (nos. 13 through 15 and 17) had received topo II inhibitors, whereas 1 (no. 16) had received only other types of chemotherapy. Three (nos. 14, 16, and 17) presented with M4 t-AML. No sample from this group showed any rearrangements with the MLL0.7B probe. Some of the patient samples were flow-sorted into granulocytes and mononuclear cells. In the two cases in which rearrangements were noted in these samples (nos. 7 and 9), both types of cells exhibited the rearrangement.

We reported previously that the MLL0.7B probe detected two rearranged bands, originating from both derivative chromosomes, in approximately 70% of the samples of leukemia de novo, as well as an 8.3-kb BamHI germline fragment.17 Probes made from each end of the MLL0.7B cDNA
the breakpoint were shown to be deleted, whereas the centromeric exons were always retained." We have analyzed that showed rearrangements with the MLL0.7B probe, A. Patients with the other of the two rearranged bands, indicating that each (data not shown).

Cispl. cisplatin; Bleo. bleomycin; Vbl, vinblastine; Etop, etoposide; 5FU. 5-fluorouracil; Hex, hexamethylmelamine; 4-epidox. 4-epidoxorubicin; CCNU, lomustine; ActD. actinomycin D; Ifos, ifosamide; HU, hydroxyurea; MOPP, nitrogen mustard, vincristine, procarbazine, prednisone; ABVD, Dox, Bleo, Vbl. dacarbazine; BCNU. carmustine; Mtx, methotrexate; DTIC, dacarbazine.

only one rearranged band was detected with the MLL0.7B probe, 1 (no. 9) exhibited a deletion of exon sequences telomeric to the breakpoint (Fig 2 and Table 2A). In each case in which two rearranged bands were detected, the centromeric and telomeric probes identified a single rearranged band corresponding to the der(11) and the other derivative chromosome, respectively (data not shown). In the 3 cases in which only one rearranged band was detected with the MLL0.7B probe, 1 (no. 9) exhibited a deletion of exon sequences telomeric to the breakpoint, whereas 2 (nos. 3 and 7) showed a deletion of exon sequences centromeric to the breakpoint (data not shown).

**DISCUSSION**

We recently identified the MLL gene, which is rearranged in both common and rare 11q23 translocations in acute leukemia de novo.\(^{10,11}\) We now have detected molecular rearrangements in the same 8.3-kb region of the MLL gene in 9 of 17 patients who developed t-AML (Table 2A, Fig 2, and data not shown).\(^{11,12}\) Moreover, we have detected MLL rearrangements in 9 of 10 t-AML patients with 11q23 translocations who had received chemotherapy that included topo II-targeting agents (Table 3). All 9 patients had balanced translocations, whereas a single patient (no. 12) who had an unbalanced 11q23 translocation cytogenetically had a germline BamHI fragment with the MLL0.7B probe. We studied this patient by fluorescence in situ hybridization (FISH) with a series of DNA probes from 11p15. We observed that the breakpoint is proximal to the entire MLL locus; thus, the rearrangement in this sample involves another gene or genes, not simply another region of MLL.

The 2 patients who also had leukemia cells with cytogenetic 11q23 rearrangements, but who had not received topo II inhibitors, did not have rearrangements of this gene. We wanted to determine whether any of this group might have a cryptic MLL rearrangement. However, no MLL rearrangement was observed in any of these patients (Tables 1B and 2B).
junction for the development of these leukemias. We have showed no rearrangement in either cell type. Our data suggest that the recombination event involving the MLL gene occurs in a pluripotent stem cell.

In our previous study of MLL rearrangements in AML/ALL de novo, we observed that, in about 30% of the samples, one or more exons 3' (telomeric) of the breakpoint cluster region are deleted, whereas the 5' (centromeric) exons are always retained.17 The preservation of the 5' exons as well as the consistent conservation of the der (11) chromosome in variant translocations (involving a third chromosome) suggests that the der (11) contains the critical junction for the development of these leukemias.19 We have studied 2 t-AML samples that showed deletions of at least some of the centromeric exons of the 8.3-kb breakpoint region. This result may indicate that there is a difference in t-AML/tMDS and acute leukemias that develop de novo with respect to the critical regions of the MLL protein. However, our observations may simply show that exons important for the development of both types of leukemias are further centromeric to the breakpoint cluster region.

Although the MLL gene is rearranged in the majority of 1q23 translocations, a human lymphoma cell line, RC-K8, with a t(11:14)(q23;q32), has been shown to involve another gene, RCK, that is 110 to 400 kb telomeric to the MLL locus.20 Another study showed that a patient with a null-cell acute lymphoblastic leukemia with an (11:14)(q23;q11) translocation had a breakpoint on 11 that is distal to both MLL and RCK, involving an as yet unidentified gene.21 Another gene, PLZF, was identified at the junction of the t(11;17)(q23;q21) translocation in a patient with acute promyelocytic leukemia. The rearrangement resulted in a fusion of this gene with the retinoic acid receptor α gene on chromosome 17.22 Thus, there are a number of other genes involved in the 11q23 rearrangements that are observed in human leukemia cells.

The leukemogenic nature of chemotherapeutic drugs has been recognized for a number of years. The earliest reported cases of t-AML were attributed to prior treatment with alkylating agents. These patients usually present with MDS after a median latent period of approximately 5 years. Cytogenetic features include a loss of chromosomes 5 and/or 7 or the long arm of these chromosomes. The MDS progresses to overt AML that is relatively resistant to chemotherapy; the prognosis is poor and the survival time is short.23,24 Ratain et al25 first reported the association of high doses of the epipodophyllotoxin, etoposide, for treatment of a lung cancer, with the subsequent development of t-AML. This secondary leukemia appeared to be distinct from that induced by alkylating agents, having predominantly monocytic features, involvement of chromosome band 1q23, a short latent period, and a more favorable prognosis.25 We and others have shown that this second subtype of t-AML is often associated with balanced translocations of 1q23, and occasionally with translocations affecting 21q22, after treatment with a number of drugs that, similar to etoposide, target top II.26,27 Our molecular study confirms the previous cytogenetic observations with respect to this type of t-AML/t-MDS. We observed a significant association (P = .01, Fisher's exact test) of MLL rearrangements and prior use of top II-reactive therapy. As expected, all of the patients with

## Table 2. Cytogenetic and Molecular Analysis of Patient Samples

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Karyotypic Abnormality</th>
<th>MLL 78 Hybridizing Fragments</th>
</tr>
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<tbody>
<tr>
<td>A. Patients with MLL rearrangement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>t(9;11)(p22;q23)</td>
<td>G/R1/R2</td>
</tr>
<tr>
<td>2</td>
<td>t(9;11)(p22;q23)</td>
<td>G/R1/R2</td>
</tr>
<tr>
<td>3</td>
<td>t(9;11)(p22;q23)</td>
<td>G/R1</td>
</tr>
<tr>
<td>4</td>
<td>t(9;11)(p22;q23)</td>
<td>G/R1/R2</td>
</tr>
<tr>
<td>5</td>
<td>t(9;11)(p22;q23;12)</td>
<td>G/R1/R2</td>
</tr>
<tr>
<td>6</td>
<td>t(6;11)(q27;q23)</td>
<td>G/R1/R2</td>
</tr>
<tr>
<td>7</td>
<td>t(11;19)(q23;p13)</td>
<td>G/R1 (mono)</td>
</tr>
<tr>
<td>8</td>
<td>t(11;19)(q23;p13)</td>
<td>G/R1 (gran)</td>
</tr>
<tr>
<td>9</td>
<td>t(11;19)(q23;p13)</td>
<td>G/R1 (mono)</td>
</tr>
<tr>
<td>B. Patients with no MLL rearrangement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>del(11)(q13;q23)</td>
<td>G</td>
</tr>
<tr>
<td>11</td>
<td>del(11)(q14;q23)</td>
<td>G (mono)</td>
</tr>
<tr>
<td>12</td>
<td>−5,+der(5)t(5;11)(q13;q23)</td>
<td>G</td>
</tr>
<tr>
<td>13</td>
<td>t(11;17;12)(q24;p13)</td>
<td>G</td>
</tr>
<tr>
<td>14</td>
<td>Complex del(5)(q13q31)</td>
<td>G</td>
</tr>
<tr>
<td>15</td>
<td>−7</td>
<td>G</td>
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<tr>
<td>16</td>
<td>der(11)(p11;11q11)</td>
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<td>17</td>
<td>Normal</td>
<td>G</td>
</tr>
<tr>
<td>18</td>
<td>Normal</td>
<td>G</td>
</tr>
</tbody>
</table>

Abbreviations: mono, mononuclear cells; gran, granulocytes; G, germline fragment; R, rearranged fragment.

Samples from 3 patients were flow sorted into mononuclear cells and granulocytes. In the 2 samples (patients no. 7 and 9, with t-AML, and M4 and M5b, respectively) that showed MLL rearrangements, the same rearranged band was present in both cell types. Patient no. 11 (with MDS) showed no rearrangement in either cell type. Our data suggest that the recombination event involving the MLL gene occurs in both cell types. Patient no. 11 (with MDS) showed no rearrangement in either cell type. Our data suggest that the recombination event involving the MLL gene occurs in a pluripotent stem cell.

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<table>
<thead>
<tr>
<th>MLL rearrangement</th>
<th>Prior Treatment With Topo II Inhibitors</th>
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<tr>
<td>+</td>
<td>9 (nos. 1 through 9) ( \pm ) 0</td>
</tr>
<tr>
<td>−</td>
<td>1 (nos. 12) ( \pm ) 2 (nos. 10 and 11)</td>
</tr>
</tbody>
</table>

Numbers of patients in each category are listed first, with patient numbers in parentheses. All patients listed had cytogenetic 11q23 rearrangements \( P = .01 \), Fisher’s exact test.)
MLL rearrangements had balanced translocations and developed overt t-AML after a relatively short latency period. Those patients who showed no MLL involvement had unbalanced rearrangements, rare translocations, or normal karyotypes and developed t-MDS or t-AML after a much longer latent period (Tables 1 and 2, and Fig 3).

Although the desired effect of treatment with topo II inhibitors is to interfere with the essential functions of topo II...
in dividing neoplastic cells, the actual biologic activities of these drugs vary in vivo. Both the epipodophyllotoxins and the anthracyclines appear to stabilize the DNA-enzyme complex after double-strand cleavage, resulting in the accumulation of DNA double-strand breaks.\textsuperscript{26,27} However, the anthracyclines, such as adriamycin, act by intercalating into the DNA, whereas the epipodophyllotoxins do not intercalate. In addition, in at least one cell line (HL60), the activities of these two types of drugs differ. Treatment with VM-26 results in degradation of DNA in S-phase, whereas doxorubicin causes arrest in S and G2 with no such degradation of the DNA.\textsuperscript{28} In another study, the epipodophyllotoxins have been implicated in the direct or indirect induction of apoptosis in addition to causing DNA double-strand breaks.\textsuperscript{29} Another group of drugs, known as the dioxopiperezines, has recently been associated with t-AML. In one study, the most frequently detected chromosome rearrangements were the t(15;17)(q22;q12) and the t(8;21)(q22;q22). These drugs appear to inhibit the catalytic activity of topo II by competing with DNA for direct binding to the enzyme; thus, they would inhibit, rather than induce, double-strand breaks.\textsuperscript{30}

The association of the use of topo II inhibitors with the development of t-AML may provide insights into the mechanism of aberrant recombination at 11q23 (and 21q22) in both t-AML and t-AML de novo. VP-16 and VM-26 have been observed to induce nonrandom chromosome aberrations, rearrangements of specific genes, and reciprocal exchanges between nonhomologous chromosomes in vitro.\textsuperscript{31-33} It has been proposed that, in the presence of these drugs, topo II molecules become trapped and covalently integrated in the DNA, thus becoming more abundant and available to mediate aberrant recombination. Both prokaryotic and eukaryotic purified topo II proteins have been shown to mediate recombination between nonhomologous DNA molecules in vitro.\textsuperscript{34} Finally, topo II has been implicated in aberrant recombination events as a component of chromatin structure, specifically as a major scaffold attachment region (SAR) protein.\textsuperscript{35} SARs have been localized to translocation breakpoint junctions, some of which have been shown to bind topo II specifically and to act as “hot spots” for double-strand cleavage.\textsuperscript{36}

The genomic $M L L$ breakpoint cluster region (8.3-kb BamHI fragment) has recently been sequenced. Its overall sequence composition is extremely AT-rich and includes several Alu repeats. More importantly, the fragment contains several in vitro and in vivo consensus binding sites for topo II.\textsuperscript{37} At this time, we speculate that the region may contain a number of active topo II binding sites or may be especially prone to cleavage, acting as a “hot spot” for double-strand breakage, which, under the appropriate conditions, leads to aberrant recombination with a number of other chromosomal regions. Certain selected recombination events in hematopoietic cells would provide a proliferative advantage that ultimately results in leukemia. Evidence for translocation breakpoints occurring at or near topo II sites has recently been reported for the t(15;17).\textsuperscript{38}

In summary, rearrangements of the $M L L$ gene are observed in t-AML, especially after treatment for a primary tumor with topo II-reactive drugs. The breakpoint cluster region within the $M L L$ gene is the same as that observed in AML de novo. We are currently investigating the chromatin structure of the breakpoint region and testing for evidence of the ability of topo II to bind and to cut in this region. These studies should lead to an understanding of the possible role of topo II in the frequent illegitimate recombination events that occur both in AML de novo and in t-AML.

ACKNOWLEDGMENT

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REFERENCES

5. Pedersen-Bjergaard J, Philip P: Balanced translocations involving chromosome bands 11q23 and 21q22 are highly characteristic of myelodysplasia and leukemia following therapy with cytokine agents targeting at DNA-topoisomerase II. Blood 78:1147, 1991 (letter)
The t(4;11) chromosome translocation of human acute leukemias fuses the ALL-1 gene, related to Drosophila trithorax, to the AF-4 gene. Cell 71:701, 1992


17. Thirman MJ, Mbangkololo D, Kobayashi H, McCabe NR, Gill HJ, Rowley JD, Diaz MO: Molecular analysis of 3 deletions of the MLL gene in 11q23 translocations reveals that the zinc finger domains of MLL are often deleted. Proc Amer Assoc Cancer Res 34:495, 1993 (abstr)


20. Radice P, Tunnacliffe A: Distinct breakpoints in band 11q23 of the (t;4;11) and (t;11;14) chromosomes associated with leukocyte malignancy. Genes Chromosom Cancer 5:50, 1992


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