Myeloid Leukemia after Hematotoxins

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One of the most serious consequences of cancer therapy is the development of a second cancer, especially leukemia. Several distinct subsets of therapy-related leukemia can now be distinguished. Classic therapy-related myeloid leukemia typically occurs 5 to 7 years after exposure to alkylating agents and/or irradiation, has a myelodysplastic phase with trilineage involvement, and is characterized by abnormalities of the long arms of chromosomes 5 and/or 7. Response to treatment is poor, and allogeneic bone marrow transplantation is recommended. Leukemia following treatment with agents that inhibit topoisomerase II, however, has a shorter latency, no preleukemic phase, a monoblastic, myelomonocytic, or myeloblastic phenotype, and balanced translocations, most commonly involving chromosome bands 11q23 or 21q22. The MLL gene at 11q23 or the AML1 gene at 21q22 are almost uniformly rearranged. MLL is involved with many fusion gene partners. Therapy-related acute lymphoblastic leukemia also occurs with 11q23 rearrangements. Therapy-related leukemias with 11q23 or 21q22 rearrangements, inv(16) or t(15;17), have a more favorable response to treatment and a clinical course similar to their de novo counterparts. — Environ Health Perspect 104(Suppl 6):1303–1307 (1996)

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Introduction

Therapy-related leukemia is a neoplastic hematopoietic disorder arising in most cases from a multipotent stem cell and in a few cases from a lineage-committed progenitor. The terms "therapy-related myelodysplastic syndrome" (t-MDS) and "therapy-related acute myeloid leukemia" (t-AML) are used to describe a clinical syndrome that exhibits important differences from AML that arises de novo. The terms "therapy-related or treatment-related" leukemia are descriptive and are based on a patient's history of exposure to cytotoxic agents. They imply a causal relationship, but the mechanism remains to be established. These terms may ultimately be too restrictive, since the leukemia that develops after exposure to benzene or atomic bomb irradiation is similar or identical to the therapy-related leukemia syndrome. The term "secondary leukemia" correctly denotes that the disease did not develop spontaneously or de novo. However, this term is often misunderstood as indicating merely that the leukemia occurred as the second cancer in time or evolving from the primary malignancy, and not necessarily related to the treatment of the first cancer. In the future, as various subtypes of leukemia are distinguished by specific genetic alterations, the terms "de novo" (or primary) and "therapy-related leukemia" will likely be discarded and specific etiologies incorporated into the diagnostic nomenclature.

Mutations and Leukemogenesis

The development of therapy-related secondary neoplasms provides a unique, ethically acceptable environment for studying the effects of mutagens on carcinogenesis in humans. Koelleffler and Rowley (1) have calculated that only 80 days would be theoretically required from neoplastic transformation of a single hematopoietic stem cell to the emergence of leukemia, if a cell doubling time of 60 hr was assumed. Typically, however, 5 to 7 years is required for the emergence of a therapy-related leukemia. Of note, 7 years was the mean latency period for development of leukemia in survivors within 1500 m of the atomic bomb blast at Hiroshima and Nagasaki (2). The long latency period characteristic of therapy-related cancers after initial mutagenic exposure suggests that "two hits" or perhaps multiple intermediate steps are required for full expression of the malignant phenotype. It has not been possible to determine whether the development of a therapy-related neoplasm is a stochastic event or whether certain individuals are at higher risk (perhaps due to a DNA repair deficiency or a heritable predisposition) and thus might be identifiable in advance.

In general, two paths of investigation have been explored. The first involves meticulous clinical-pathologic and cytogenetic analysis of individual cases as they present with therapy-related leukemia (3) (Table 1). The second involves large-scale epidemiological surveys of patients at risk. There are now many such studies of each type in the literature. Patients with Hodgkin's disease were the first large cohort of relatively uniformly treated patients who experienced prolonged survival. After long-term follow-up, hundreds of cases of therapy-related leukemia have now been reported and analyzed (4). It soon became clear that the risk of therapy-related leukemia was shared by patients with other cancers and even nonmalignant disorders if they had received cytotoxic treatment (5). Investigators have sought to answer the following questions: Is the type of chemotherapy used important? Is radiation therapy alone leukemogenic? Does radiotherapy add to the risk from chemotherapy? Is the age of the patient at the time of treatment an important risk factor? Is splenectomy a risk factor? Is the risk of therapy-related leukemia a function of the dose or the duration of chemotherapy administered? Is the excess risk limited to a finite period after treatment?

Classical Therapy-related Leukemia

In the classic form of therapy-related leukemia that follows treatment with alkylating agents and/or radiation therapy, the blood and bone marrow findings resemble
those seen in the primary myelodysplastic syndromes (Table 2). Anemia and thrombocytopenia are extremely common. Leukopenia may also be present. Marked dysplastic changes are observed in all three cell lines. Early in the course of disease, red cell poikilocytosis may be particularly notable in the peripheral blood film (6). The bone marrow may have variable cellularity, but is most often hypercellular. Hypocellular and even aplastic marrows are seen in some cases. Mild to marked reticulocyte fibrosis may be present. The degree of dysgranulopoiesis and dysmegakaryocytopenia is typically greater than that observed in primary MDS. Many cases of therapy-related leukemia are not easily classified by the French–American–British Cooperative Group criteria used for either primary MDS or AML de novo (3,7). When attempts have been made to do so, refractory anemia with excess blasts and refractory anemia with excess blasts in transformation are most common.

About two-thirds of patients present with fewer than 30% blast cells in the marrow and <5% blasts in the blood, and therefore, these patients have been diagnosed as t-MDS. However, unlike primary MDS, which may have a long preleukemic phase, patients with therapy-related leukemia have a more prominent arrest of hematopoietic maturation and more rapidly accumulate >30% marrow blasts. Typically, the t-MDS phase lasts for about 6 months (3,7). As these cases evolve to more overt leukemia, features characteristic of FAB subtypes M1, M2, or M4 are most common. However, there are difficulties in classifying therapy-related leukemia according to the FAB criteria designed for AML de novo because most cases demonstrate trilineage involvement and often overlap several subtypes. Auer rods are rarely seen, and myeloperoxidase and non-specific esterase reactivity are often only weakly expressed.

There is a continuum of clonal expansion and dedifferentiation that occurs in the neoplastic clone and subclones that overlaps the quantitative categories of MDS, AML, and chronic myeloproliferative disorders. Classic t-AML is often not rapidly progressive, but it is relatively refractory to conventional chemotherapy (8). Severe and life-threatening pancytopenia are observed in each stage of the disease. Shortened survival is more a function of failure of normal bone marrow hematopoiesis rather than rapid accumulation of bone marrow blast cells. Allogeneic bone marrow transplantation is recommended when possible.

Clonal chromosomal abnormalities, often of a complex nature, are identified in most cases of classical therapy-related leukemia (3,9–12). Loss of part or all of chromosomes 5 and/or 7 are the characteristic findings, and have been reported in almost 90% of cases in some series (3). Table 3 shows the distribution of cytogenetic abnormalities observed in 240 patients with therapy-related leukemia studied at the University of Chicago. The most common single abnormality is monosomy 7, followed in frequency by deletion of the long arm of chromosome 5 [del(5q)] and by monosomy 5. These same abnormalities are observed in primary MDS and AML de novo, especially in older patients.

### Table 1. Prior therapy, latency period, and clinical features of therapy-related myeloid leukemia.

| Prior treatment, n | Latency, months | Median | Range | Median age, range | No. of patients | Progression of t-MDS to t-AML | Median survival, months | Reference |
|--------------------|----------------|--------|-------|------------------|----------------|-------------------------------|------------------------|-----------|
| RT CT RT + CT      |                |        |       |                  |                |                               |                        |           |
| 8                  | 25             | 22     | 48    | 12-131           | 62 (22-75)     | 44                             | 11                     | 64% (median, 5 months) | 7         |
| 15                 | 17             | 24     | 60    | 1-204            | 58 (18-90)     | 0                              | 56                     | 0         |
| 11                 | 21             | 31     | 56    | 10-192           | 55 (6-76)      | 48                             | 15                     | 60% (median, 5 months) | 8         |
| 14                 | 25             | 26     | 58    | 11-192           | 53 (1-81)      | 39                             | 26                     | 28% (median, 4 months) | 4         |
| 2                  | 7              | 66     | 34    | (from CR)        | ---            | 55                             | 20                     | 73% (median, 7 months) | 4-10     |
| 26                 | 37             | 49     | 71    | 7-331            | 65 (20-82)     | 57                             | 55                     | 55%       |
| 10                 | 29             | 37     | 6     | 1-21 years       | 58 (16-89)     | 29                             | 47                     | 57% (median, 6 months) | 7         |

**Abbreviations:** RT, radiotherapy; CT, chemotherapy; CR, complete remission.

### Table 2. Morphologic features of blood and bone marrow in classic alkylator therapy-related myeloid leukemia.

| Peripheral blood | Granulocytic series | Megakaryocytic series |
|------------------|---------------------|-----------------------|
| Anemia, anisopiketocyrtosis including teardrops, spherocytes, and myeloid blasts in the peripheral blood | Hypogranular neutrophils, hypolobulated or hyperlobulated nuclei, nuclear excrecences, pseudo-Pelger-Huet nuclei, basophilic, neutrophilic, monocytes, immature myeloid cells with blasts appearing eventually, rarely Auer rods | Giant platelets, degranulated platelets, thrombocytopenia, circulating micromegakaryocytes, megakaryoblasts, and megakaryocyte fragments |
| Erythroblasts, periodic acid-Schiff-positive normoblasts, dyserythropoiesis, erythroid hyperplasia with megakaryoblastoid features, ringed sideroblasts, nuclear budding, karyorrhexis, binucleation, nuclear bridging | Nuclear hypossegmentation, cytoplasmic hypogranulation | Megakaryocytic hyperplasia with atypical forms, micromegakaryocytes, abnormal nuclear contours and sizes, |

### Table 3. Cytogenetic abnormalities in therapy-related myeloid leukemia (University of Chicago series).

| No. of patients | No. with clonal abnormalities | Abnormalities of chromosomes 5 and/or 7 |
|----------------|-------------------------------|----------------------------------------|
| 240            | 218 (91%)                     | 163 (69%)                              |
| Chromosome 5    | 38 (16%)                      | Chromosome 7                            |
| 71 (30%)        | Chromosomes 5 and 7           |
| 54 (23%)        | t(11q23)                      | 7 (3%)                                  |
| t(8;21)         | 3 (1%)                        | t(15;17)                                |
| 2 (1%)          | +8                             | t(8;21)                                 |
| 10 (4%)         | Other abnormalities            | 30 (13%)                                |
| Data from MM Le Beau (unpublished data) | | |
The Role of 11q23 Translocations
Chromosome 11q23 translocations occur in both de novo and therapy-related leukemia. These translocations affect 7 to 10% of patients with ALL de novo, with the t(4;11)(q21;q23) and the t(11;19) (q23;p13.3) predominating, and 5–6% of AML de novo with t(6;11)(q27;q23), t(9;11)(p22;q23), and t(11;19)(q23;p13.1) being the most common. The ALL patients are usually FAB L1, but in addition to the usual B-cell markers, they often express myeloid or monocytic markers. The AML patients are typically myelomonocytic (M4) or monoblastic (M5) and often coexpress lymphoid markers. In both AML and ALL with 11q23 translocations, the patients often present with hyperleukocytosis and early central nervous system involvement. The clinical presentation, morphology, and immunophenotype of therapy-related leukemias with 11q23 translocations are indistinguishable from de novo cases.

Therapy-related Acute Lymphoblastic Leukemia
The classic syndrome of therapy-related leukemia with aberrations involving chromosomes 5 and 7 has been observed in therapy-related leukemia. However, subsequent reports have also implicated DNA intercalating agents such as doxorubicin, 4-epi-doxorubicin, mitoxantrone, and actinomycin D (18,21).

Table 4. Contrasting features of therapy-related leukemia secondary to either alkylating agents or topoisomerase II inhibitors.

| Chromosome abnormality | Preleukemia phase | FAB morphology | Response to induction chemotherapy | Long-term survival | Chemotherapy drugs |
|------------------------|-------------------|----------------|-----------------------------------|-------------------|-------------------|
| Alkylating agents      | del(5q), del(7q) | Myelodysplastic syndrome | Not classifiable by current criteria | 5–7 years | Poor | Poor |
|                        |                   |                |                                   |                   | Melphalan, methotrexate, chlorambucil, cyclophosphamide, carmustine, lomustine semustine procarbazine, dacarbazine, mitolactol |
| Topoisomerase II inhibitor | 11q23 translocations, 21q22 translocations | Usually M4, M5, M7, some M1, M2 and ALL-L1 | 6 months–5 years | Good | Poor |
| Various agents         | t(15;17), inv(16) | None | M3, M4Eo | 2–3 years | Good | Good |
|                        |                   | None | <3 years | Good | Good |

and those with occupational exposure to potential carcinogens. Their frequency, however, is clearly higher in therapy-related leukemia. Recent molecular investigation has focused on identifying a putative leukemia suppressor gene in chromosome band 5q31, a critical region that is consistently deleted in leukemia cells with 5q abnormalities (3).

Leukemia Following Topoisomerase II Inhibitors
Whereas classic t-AML is characterized by abnormalities involving the long arms of chromosomes 5 and/or 7, the leukemias secondary to agents that target topoisomerase II result in translocations involving chromosome 11, band q23, and less commonly, chromosome 21, band q22 (11,13–19). In contrast to classic t-AML, these leukemias have a much shorter latency between initiation of chemotherapy for the primary cancer and the development of leukemia (Table 4). In addition, a preceding myelodysplastic syndrome is not associated with these leukemias. The 11q23 cases primarily have monoblastic (M5) or myelomonocytic (M4) phenotypes, but cases of AML-M1 and M2 as well as acute lymphoblastic leukemia (ALL) have been described. The 21q22 cases are typically AML M2 (19,20). The response to chemotherapy in this newer syndrome of therapy-related leukemia also differs from classic t-AML and is more favorable.

A consistent pattern has emerged of prior treatment with inhibitors of topoisomerase II either alone or in combination with alkylating agents. At first, the association was linked only to the epipodophyllotoxins, etoposide, and teniposide (16,17). However, subsequent reports have also implicated DNA intercalating agents such as doxorubicin, 4-epi-doxorubicin, mitoxantrone, and actinomycin D (18,21).
predated the widespread use of hematopoietic growth factors. The unexpected rate of t-AML in this trial has raised the concern that growth factors may be synergistic with chemotherapy in inducing t-AML. However, no data outside of this trial exist yet to examine this issue further.

**Different Genetic Mechanisms for Leukemogenesis**

The particular mechanisms of DNA damage that lead either to chromosomal deletions or to balanced translocations may underlie the differences in latencies between the two forms of therapy-related leukemia (15). In the case of chromosomal deletions, one allele of a putative tumor-suppressor gene may be inactivated. Before the affected cell would gain a proliferative advantage, however, the second allele would also have to be deleted or mutated. Additionally, losses of both alleles of an individual tumor suppressor may not be sufficient to confer a malignant phenotype. As described in the model of colorectal tumorigenesis, multiple tumor-suppressor genes or oncogenes may need to be mutated to ultimately transform a cell. This series of genetic changes may require an extended period of time, thus explaining the long latency of alkylator-induced t-AML. In contrast, balanced chromosome translocations result in the activation of cellular oncogenes in a dominant fashion. These rearrangements, such as those involving the MLL gene at 11q23, may yield a fusion gene that acts as a dominant oncogene. Whereas this fusion gene alone may not be sufficient to transform an hematopoietic progenitor cell, relatively fewer genetic events may be required to proceed to the leukemic phenotype. In line with this hypothesis, 70 to 80% of all acute leukemias de novo in infants, both lymphoid and myeloid, involve the MLL gene. Moreover, these cases have even been reported in the neonatal period. Thus, 11q23 translocations can clearly induce the formation of leukemia over a short interval of time. The striking incidence of MLL gene rearrangements in infant leukemias suggests a potential genetic susceptibility to translocations at this locus. If this were the case, perhaps only certain patients with an as-yet unknown DNA repair deficiency might be susceptible to the mutagenic effect of topoisomerase II inhibitors.

**MLL Gene in Chromosome Band 11q23**

Because of the different phenotypes and the large number of recurring chromosomal aberrations involving 11q23, a major question in the field of cancer molecular genetics has been whether one or several oncogenes at that locus might be implicated in the pathogenesis of these hematologic malignancies. Rowley and co-workers (25) were able to identify a gene that spans the 11q23 breakpoint region and named it MLL for myeloid–lymphoid leukemia or mixed lineage leukemia gene. Several other groups have also cloned the same gene and assigned it names such as *ALL-1*, *HRX*, and *H-trx*. The MLL gene has multiple large transcripts with an open reading frame of 11.7 kb and codes for a predicted protein of 431 kDa. At its amino terminus, MLL contains an AT hook domain that has been shown to bind to cruciform DNA (26). There are two regions with a high homology to the *Drosophila trithorax* gene. The first is a series of zinc fingers immediately 3' to the breakpoint region, and the second region is at the carboxyl terminus and shows an extremely high level of evolutionary conservation. Although the functions of MLL remain unknown, these motifs suggest that it may be acting as a transcription factor.

To address the question of MLL involvement in hematologic malignancies with diverse 11q23 translocations, we studied patients with either AML, ALL, or non-Hodgkin's lymphoma (27). MLL gene rearrangements were detected in 58 of the 61 leukemia patients and in 3 of the 20 lymphoma patients. This included all patients with the five common 11q23 translocations mentioned earlier plus 16 uncommon 11q23 rearrangements that involved the MLL gene, for a total of 21 different chromosomal abnormalities that affect the MLL gene. All of the breaks occurred in an 8.3-kb pair genomic *BamHI* fragment.

Several genes at breakpoints on the partner chromosomes involved in 11q23 translocations have been cloned. These include *AF-4* in the t(4;11)(q21;q23), *ENL* in the t(11;19)(q23;p13.3), *AF-9* in the t(9;11)(p22;q23), *AF-6* in the t(6;11)(q27;q23), *AF-1p* in the t(11;11)(p32;q23), *AF-10* in the t(10;11)(p12;q23), *AF-17* in the t(17;11)(q21;q23), and *AF-X* in the t(X;11)(q13;q23). The functions of these genes have not yet been determined. Thirman et al. (28) recently cloned the gene *ELL* that fuses to MLL in the t(11;19) (q23;p13.1), a recurring abnormality in AML as well as one of the most common breakpoints in topoisomerase II induced t-AML (28). This translocation is distinct from another type of 11;19 translocation with a 19p13.3 breakpoint that results in the fusion of MLL to the ENL gene. *ELL* is not homologous to other MLL partner genes. Because 11q23 translocations always result in the generation of in-frame fusion transcripts, the sequences contributed from these partner genes may be essential to leukemogenesis.

The *AML* gene at chromosome band 21q22 also fuses to genes at multiple chromosomal breakpoint regions, albeit many fewer than MLL (19,20). Nucifora and co-workers (19,20,29) have identified complex intergenic splicing between the *AML* gene and either *EAP*, *MDS1*, or *EVI7* within chromosome band 3q26 in the t(3;21). *AML* also fuses with *ETO* at 8q22 in the t(8;21) in both de novo and therapy-related cases.

**Conclusions**

As the numbers of cancer survivors increase after conventional cytotoxic treatment, the incidence of therapy-related leukemia will undoubtedly rise. It is imperative that the leukemogenic potential of current multiagent treatment regimens for malignant and nonmalignant disorders be considered prospectively in primary treatment planning and be reduced, if possible. As further understanding about mechanisms of mutagenesis accumulates, it is likely that certain individuals who have increased susceptibility to the leukemogenic activity of particular agents can be identified. Prevention of this complication of cancer treatment is a clinical and scientific challenge, but it is clearly the appropriate goal.

**REFERENCES**

1. Koehler HP, Rowley JD. Therapy-related acute nonlymphocytic leukemia. In: Neoplastic Diseases of the Blood (Wiernick PH, Canellos GP, Kyle RA, Schiffer CA, eds). New York: Churchill Livingstone, 1985; 357–381.

2. Ionizing Radiation—Levels and Effects. A Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. New York: United Nations, 1972.

3. Le Beau MM, Albain KS, Larson RA. Clinical and cytogenetic
correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. J Clin Oncol 4:325–345 (1986).

4. Henry-Amar M, Dietrich P-Y. Acute leukemia after the treatment of Hodgkin's disease. Hematol Oncol Clin North Am 7:369–387 (1993).

5. Levine EG, Bloomfield CD. Leukemias and myelodysplastic syndromes secondary to drug, radiation, and environmental exposure. Semin Oncol 19:471 (1992).

6. Butler AE, Vardiman JW, Golomb HM. Ultrastructural characterization of de novo and secondary leukemias. Virchows Arch [B] 39:239–257 (1982).

7. Michels SD, McKenna RW, Arthur DC, Bruning RD. Therapy-related acute myeloid leukemia and myelodysplastic syndrome: a clinical and morphologic study of 65 cases. Blood 65:1364–1372 (1985).

8. Larson RA, Wernli M, Le Beau MM, Daly KM, Pape LH, Rowley JD, Vardiman JW. Short remission durations in therapy-related leukemia despite cytogenetic complete responses to high-dose cytarabine. Blood 72:1333–1339 (1988).

9. Fourth International Workshop on Chromosomes in Leukaemia 1982: Secondary Leukemias Associated with Neoplasia: Treated and Untreated. Cancer Genet Cytofgenet 11:319–321 (1984).

10. Kantarjian HM, Keating MJ, Walters RS, Smith TL, Cork A, McCredie KB, Freireich EJ. Therapy-related leukemia and myelodysplastic syndrome: clinical, cytogenetic, and prognostic features. J Clin Oncol 4(12):1748–1757 (1986).

11. Pedersen-Bjergaard J, Philip P, Larsen SO, et al. Therapy-related myelodysplasia and acute myeloid leukemia: Cytogenetic characteristics of 115 consecutive cases and risk in seven cohorts of patients treated intensively for malignant diseases in the Copenhagen series. Leukemia 7(12):1975–1986 (1993).

12. Rubin CM, Arthur DC, Woods WG. Therapy-related myelodysplastic syndrome and acute myeloid leukemia in children: correlation between chromosomal abnormalities and prior therapy. Blood 78(11):2982–2988 (1991).

13. Larson RA, Le Beau MM, Raiman MJ, Rowley JD. Balanced translocations involving chromosome bands 11q23 and 21q22 in therapy-related leukemia. Blood 79(7):1892–1893 (1992).

14. Pedersen-Bjergaard J, Philip P. Balanced translocations involving chromosome bands 11q23 and 21q22 are highly characteristic of myelodysplasia and leukemia following therapy with cytotoxic agents targeting at DNA-topoisomerase II. Blood 78:1147–1148 (1991).

15. Pedersen-Bjergaard J, Rowley JD. The balanced and the unbalanced chromosome aberrations of acute myeloid leukemia may develop in different ways and may contribute differently to malignant transformation. Blood 83(10):2780–2786 (1994).

16. Pui CH, Risheo R, Hancock ML, Rivera GK, Evans WE, Raimondi SC, Head DR, Behm FG, Mahmoud MH, Sandlund JT, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 325:1682–1687 (1991).

17. Rattai MJ, Kaminer LS, Bitran JD, Larson RA, Le Beau MM, Skosey C, Puri S, Hoffman PC, Wade J, Vardiman JW, et al. Acute nonlymphocytic leukemia following etoposide and cisplatin combination chemotherapy for advanced non-small-cell carcinoma of the lung. Blood 70:1412 (1987).

18. Rattai MJ, Rowley JD. Therapy-related acute myeloid leukemia secondary to inhibitors of topoisomerase II: from the bedside to the target genes. Ann Oncol 3(2):107–111 (1992).

19. Rubin CM, Larson RA, Anastasi J, Winten JN, Thangavelu M, Vardiman JW, Rowley JD, Le Beau MM. t(3;21)(q26;q22): A recurring chromosomal abnormality in therapy-related myelodysplastic syndrome and acute myeloid leukemia. Blood 76:2594–2598 (1990).

20. Nucifora G, Rowley JD. AML1 and the 8;21 and 3;21 translocations in acute and chronic myeloid leukemia. Blood 86:1–14 (1995).

21. Albain KS, Le Beau MM, Ullirsh R, Schumacher H. Implication of prior treatment with drug combinations including inhibitors of topoisomerase II in therapy-related monocytic leukemia with a 9;11 translocation. Genes Chromosomes Cancer 2:53–58 (1990).

22. Secker-Walker LM, Stewart EL, Todd A. Acute lymphoblastic leukemia with t(4;11) follows neuroblastoma: a late effect of treatment? Med Pediat Oncol 13:48 (1985).

23. Archimbaud E, Charrin C, Guyotat D, Magaud JP, Gentilhomme L, Fiere D. Acute leukaemia with t(4;11) in patients previously exposed to carcinogens. Br J Haematol 69(4):467–470 (1988).

24. Jonveaux P, Hillion J, Bernard O, et al. Distinct MLL gene rearrangements associated with successive acute monocyctic and lymphoblastic leukaemias in the same patient. Leukemia 8:2224–2227 (1994).

25. Ziemien-van der Poel S, McCabe NR, Gill HJ, Espinosa R III, Patel Y, Harden A, Rubinelli P, Smith SD, LeBeau MM, Rowley JD, et al. Identification of a gene (MLL) which spans the breakpoint in 1q23 translocations associated with human leukemias. Proc Natl Acad Sci USA 88(23):10735–10739 (1991).

26. Zeleznik-Le NJ, Harden AM, Rowley JD. 11q23 Translocations split the "AT-hook" cruciform DNA-binding region and the transcriptional repression domain from the activation domain of the mixed-lineage leukemia (MLL) gene. Proc Natl Acad Sci USA 91:10610–10614 (1994).

27. Thirman MJ, Gill HJ, Burnett RC, Mbangkollo D, McCabe NR, Kobayashi H, Ziemien-van der Poel S, Kaneko Y, Morgan R, Sandberg AA, et al. Rearrangement of the MLL gene in acute lymphoblastic and acute myeloid leukemias with 11q23 chromosomal translocations. N Engl J Med 329:909–914 (1993).

28. Thirman MJ, Levitan DA, Kobayashi H, Simon MC, Rowley JD. Cloning of ELL, a gene that fuses to MLL in a t(11;19)(q23;p13.1) in acute myeloid leukemia. Proc Natl Acad Sci USA 91:12110–12114 (1994).

29. Nucifora G, Birn MJ, Espinosa R III, Erickson P, LeBeau MM, Roulston D, McKieithan TW, Drabkin H, Rowley JD. Involvement of the AML1 gene in the t(3;21) in therapy-related leukemia and in chronic myeloid leukemia in blast crisis. Blood 81(10):2728–2734 (1993).

30. Pedersen-Bjergaard J, Philip P, Pedersen NT, Hou-Jensen K, Sveiggaard A, Jensen F, Nissen NI. Acute nonlymphocytic leukemia, preleukemia, and acute myeloproliferative syndrome secondary to treatment of other malignant diseases. II: Bone marrow cytology, cytogenetics, results of HLA typing, response to antileukemic chemotherapy, and survival in a total series of 55 patients. Cancer 54:452–462 (1984).

31. Brusamolino E, Papa G, Valagussa P, Mandelli F, Bernasconi C, Marmont A, Bonadonna G, Tura S, Bosi A, Mango G, et al. Treatment-related leukemia in Hodgkin's disease: a multi-institutional study on 75 cases. Hematol Oncol 5:83–98 (1987).

32. Iurlo A, Mecucci C, Van Orshoven A, Michaux JL, Boogaerts M, Noens L, Bosi A, Louwagie A, Van Den Bergh H. Cytogenetic and clinical investigations in 76 cases with therapy-related leukemia and myelodysplastic syndrome. Cancer Genet Cytofgenet 43:227–241 (1989).