

Myeloid Leukemia after Hematotoxins

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Abstract

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)

Key words: cancer therapy, secondary cancers, leukemia, chromosome rearrangement, MLL gene, AML1 gene

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Abbreviations used: ALL, acute lymphoblastic leukemia; t-AML, therapy-related acute myeloid leukemia; t-MDS, therapy-related myelodysplastic syndrome.

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. Koeffler 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 blasts 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.

Table 1 Rior therapy, latency period, and clinical features of therapy-relatedmyeloid leukemia.

Rior treatment, n			Latency, months		Median age, range	No. of patients		Progression of t-MDS to t-AML	Median survi months
RT	CT	RT + CT	Median	Range		t-MOS	t-AML		
8	25	22	48	12–131	62 (22–75)	44	11	84% (median, 5 months)	7
15	17	24	60	1–204	58 (18–90)	0	56	—	5
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%	8
10	29	37	6 years	1–21 years	58 (18–89)	29	47	57% (median, 6 months)	7

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

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 on 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 reticulin fibrosis may be present. The degree of dysgranulopoiesis and dysmegakaryocytopoiesis 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.

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

	Erythroid series	Granulocytic series	Megakaryocyte
Peripheral blood	Anemia, anisopoikilocytosis including teardrops, spherocytes and spiculated RBCs, nucleated RBCs, basophilic	Hypogranular neutrophils, hypolobulated or hyperlobulated nuclei, nuclear excrescences, pseudo Pelger-Huet	Giant platelets, degree of thrombocytopenia, circulating megakaryocytes
oblasts,	stippling, circulating erythroblasts, macrocytosis, polychromasia	nuclei, basophilia, neutropenia, monocytosis, immature myeloid cells with blasts appearing eventually, rarely Auer rods	and megakaryocyte fragments
Bone marrow	Erythroblasts, periodic acid-Schiff-positive normoblasts, dyserythropoiesis, erythroid hyperplasia with megaloblastoid features, ringed sideroblasts, nuclear budding, karyorrhexis, binuclearity, nuclear bridging	Nuclear hyposegmentation, cytoplasmic hypogranulation Widely spaced nuclear lobes, mononuclear forms, giant compound granules, hypogranular cytoplasm	Megakaryocytic hyperplasia, atypical forms, immature or abnormal nuclear contour

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 nonspecific 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.

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

No. of patients	240
No. with clonal abnormalities	218 (91%)
Abnormalities of chromosomes 5 and/or 7	163 (69%)
Chromosome 5 only	38 (16%)
Chromosome 7 only	71 (30%)
Chromosomes 5 and 7	54 (23%)
t(11;23)	7 (3%)
t(3;21)	3 (1%)
t(8;21)	2 (1%)
t(15;17)	3 (1%)
+8	10 (4%)
Other abnormalities	30 (13%)

Data from MML Beau (unpublished data).

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

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

	Chromosome abnormality	Preleukemia phase	FAB morphology	Latency	Response to induction chemotherapy	Long-term survival	Chemotherapy
Alkylating agents	de(5q) -5 de(7q) -7	Myelodysplastic syndrome	Not classifiable by current criteria	5-7 years	Poor	Poor	Melphalan, mechlorambucil, cyclophosphamide, procarbazine, and mitolactol
Topoisomerase II inhibitor	11q23 translocations, 21 q22 translocations	None	Usually M4, M5; some M1, M2 and ALL-L1	6 months-5 years	Good	Poor	Etoposide, teniposide, actinomycin D, 4-epi-doxorubicin
Various agents	t(15;17) inv(16)	None None	M3 M4Eo	2-3 years <3 years	Good Good	Good Good	Bimolane

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).

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 monocytoid 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 exclusively involved the myeloid lineage. The initial case reports of therapy-related leukemia with 11q23 translocations, predominantly with the t(9;11), were also myeloid leukemias, albeit usually of a monoblastic phenotype (17). However, given the involvement of 11q23 in both myeloid and lymphoblastic acute leukemias that occur de novo, it should not be surprising that therapy-related lymphoblastic leukemias have also been described. In 1985 Secker-Walker et al. (22) reported on a child with neuroblastoma who was treated with a multi-drug regimen that included doxorubicin and teniposide; ALL with a t(4;11) developed 12 months after completion of therapy (22). In 1988 Archimbaud et al. (23) reported on the development of ALL with a t(4;11) in two breast cancer patients treated with doxorubicin-containing regimens. Several other cases of therapy-related ALL have been described since that time. In an interesting recent report by Jonveaux et al. (24), a patient initially treated for an acute monoblastic leukemia de novo with a t(6;11)(q27;q23), subsequently developed ALL with a t(4;11) (24). Different MLL gene rearrangements were present in the leukemia cells at each presentation. Whereas the incidence of ALL de novo with 11q23 translocations exceeds that of AML de novo with 11q23 translocations, the ratios are clearly reversed in the therapy-related setting. This may reflect the increased cycling of myeloid precursor cells following chemotherapy. Nevertheless, therapy-related leukemia should not be considered an exclusively myeloid malignancy.

The role of other cofactors besides cytotoxic agents in the formation of therapy-related leukemia is unknown. An interim analysis of data from a recent National Surgical Adjuvant Breast Project trial (NSABP-B25) of intensive adjuvant chemotherapy for breast cancer revealed five cases of t-AML out of

2548 patients treated. All cases were either FAB M4 or M5 and had short latency periods. Two cases were found to have 11q23 abnormalities. There were three arms to this trial; all patients received four monthly courses with doxorubicin plus cyclophosphamide at one of three higher-than-standard doses. All groups received filgrastim (G-CSF) to ameliorate neutropenic toxicities. The rapid appearance of five cases of t-AML in this trial prompted a clinical alert from the National Cancer Institute. Earlier descriptions of t-AML with 11q23 abnormalities 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 had 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(1;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 AML1 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 AML1 gene and either EAP, MDS1, or EVI1 within chromosome band 3q26 in the t(3;21). AML1 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.

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