

Therapy-Related Myeloid Leukemia

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Therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/t-AML) are thought to be the direct consequence of mutational events induced by chemotherapy, radiation therapy, immunosuppressive therapy, or a combination of these modalities, given for a pre-existing condition. The outcomes for these patients have been poor historically compared to people who develop de novo AML. The spectrum of cytogenetic abnormalities in t-AML is similar to de novo AML, but the frequency of unfavorable cytogenetics, such as a complex karyotype or deletion or loss of chromosomes 5 and/or 7, is considerably higher in t-AML. Survival varies according to cytogenetic risk group in t-AML patients, with better outcomes being observed in those with favorable-risk karyotypes. Treatment recommendations should be based on performance status and karyotype. A deeper understanding of the factors that predispose patients to the development of therapy-related myeloid leukemia would help clinicians monitor patients more carefully after treatment for a primary condition. Ultimately, this knowledge could influence initial treatment strategies with the goal of decreasing the incidence of this serious complication.

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Therapy-related myelodysplastic syndrome and acute myeloid leukemia (t-MDS/t-AML) is a well-recognized clinical syndrome occurring as a late complication following cytotoxic therapy.^{1,5} The term “therapy-related” leukemia is descriptive and is based on a patient’s history of exposure to cytotoxic agents. Although a causal relationship is implied, the mechanism remains to be proven. These neoplasms are thought to be the direct consequence of mutational events induced by the prior therapy. Table 1 shows the various primary diagnoses and primary cytotoxic therapies received by 306 patients with therapy-related myeloid leukemia studied at the University of Chicago.⁴

Neither t-MDS nor t-AML is easily categorized according to the French-American-British (FAB) classification schema, but the World Health Organization (WHO) classification recognizes them as a distinct entity.⁶ Morphologically, t-MDS/t-AML most closely resembles acute myeloid leukemia with multilineage dysplasia, also a distinct form of de novo AML within the WHO classification. t-AML is distinguished from t-MDS solely based on the blast count being >20% in either

the peripheral blood or the bone marrow, except for those cases associated with t(8;21) or inv(16) where a blast count less than 20% is sufficient for diagnosis of acute leukemia. Based on clinical, morphological, and genetic features, t-MDS and t-AML are a single disease, each representing different ends of the leukemic spectrum. The specific morphological and cytogenetic features of t-MDS/t-AML are related to the type of prior cytotoxic therapy that the patient received for his/her primary medical condition.

SUBTYPES OF THERAPY-RELATED MYELOID LEUKEMIA

The characteristics of therapy-related leukemia and the timing of its development after a primary diagnosis depend on the exposure to specific agents, as well as the cumulative dose and dose intensity of the preceding cytotoxic therapy.

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 primary MDS, although the degree of dysgranulopoiesis and dysmegakaryocytopenia is typically greater. Fatigue, weakness, and occasionally fever are the most frequent patient complaints. Anemia, often macrocytic, and thrombocytopenia are extremely common, and an increased mean corpuscular volume (MCV) is often the first clue to the diagnosis. Leukopenia also may be present. Dysplastic changes are often observed in all three cell lines (Figure 1). Mild to marked reticulin fibrosis may be present. Auer rods

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Table 1. Primary Diagnoses and Primary Cytotoxic Therapies in 306 Patients Who Developed Therapy-Related Myeloid Leukemia: The University of Chicago Series⁴

Primary Diagnosis	No. of Patients	Chemotherapy Only (%)	Radiotherapy Only (%)	Combined Modality Therapy (%)
No prior malignancy	18	12 (67)*	2 (11)	4 (22)
Hematologic malignancy	171	69 (40)	5 (3)	97 (57)
Hodgkin's lymphoma	77	18 (23)	4 (5)	55 (71)
Non-Hodgkin's lymphoma	70	33 (47)	1 (1)	36 (51)
Myeloma	23	17 (74)	0	6 (26)
Other	1	1 (100)	0	0
Solid tumors	117	40 (35)	36 (32)	38 (33)
Breast	32†	11 (35)	5 (16)	15 (49)
Ovary	15	12 (80)	1 (7)	2 (13)
Prostate	13†	0	11 (100)	0
Lung	9	5 (56)	2 (22)	2 (22)
Cervix	7	0	4 (57)	3 (43)
Other	41	12 (29)	13 (32)	16 (39)
Totals	306†	121 (40)	43 (14)	139 (46)

*Numbers in parentheses are percentages for each row of data according to primary therapy.

†In three patients, the entire chemotherapy regimen used as therapy for the primary tumor was not known.

are rarely seen, and myeloperoxidase and non-specific esterase reactivity are often only weakly expressed.

Clonal chromosome abnormalities, often of a complex nature, are identified in most cases of classical therapy-related leukemia.^{1,3-5,7,8} Loss of part or all of chromosomes 5 and/or 7 are the characteristic findings, and have been reported in more than 90% of cases in some series.⁴ 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 such as benzene. Alkylating agents vary in their likelihood of causing the development of therapy-related disease (melphalan > cyclophosphamide),^{9,10} and there is a dose-response relationship between the amount of alkylating agent received and the risk of disease development.¹ This form of t-MDS/t-AML typically occurs within 5 to 7 years after chemotherapy and/or radiotherapy have been given, and confers a poor prognosis.

Therapy-related leukemia following chemotherapy with topoisomerase II inhibitors is characterized by translocations involving chromosome bands 11q23 or 21q22.¹¹ Balanced translocations may involve the *MLL* gene at chromosome band 11q23, or the *PML/RARA* genes in the case of therapy-related acute promyelocytic leukemia (t-APL). Rearrangements of the core binding factor genes *AML1 (RUNX1/CBFA2)* at chromosome band 21q22 and *CBFB* at chromosome band 16q22, as well as the *NUP98* gene at chromosome

band 11p15.5, also have been described. In contrast to alkylating agent-associated t-AML, these leukemias are rarely preceded by t-MDS. They occur with a shorter latency, often within 2 to 3 years of the first cytotoxic therapy and, in some cases, within 12 months. These t-AMLs often present with rapidly progressive leukemia and high white blood cell counts. Although they also have a poor prognosis overall, they are more responsive to initial remission induction chemotherapy.

Additional studies have indicated that patients treated with the nucleoside analog fludarabine are also at risk for t-AML.¹² Of 521 patients treated for chronic lymphocytic lymphoma (CLL) with fludarabine alone or in combination with chlorambucil, six (1.2%) developed t-AML, many of whom also had characteristic abnormalities of chromosomes 5 and 7.¹³ In another study, eight of 202 CLL patients (4%) treated with fludarabine, mitoxantrone, and dexamethasone developed t-AML, commonly with abnormalities of chromosome 7, between 1 and 5 years after therapy.¹⁴ Another recent report describes a patient with grade 2 follicular lymphoma who was treated with fludarabine, cyclophosphamide, and rituximab who developed t-AML with a chromosomal translocation involving 11q23 40 months after the initial therapy.¹⁵ New compounds for the treatment of CLL include radioimmunotherapeutic agents, such as yttrium-90 ibritumomab tiuxetan, and iodine-131 tositumomab, raising concerns about an increased incidence of t-AML after these agents, which add radiation to chemotherapy and might further damage DNA within bone marrow cells. Reassuringly, however, Czuczman and colleagues reported recently that

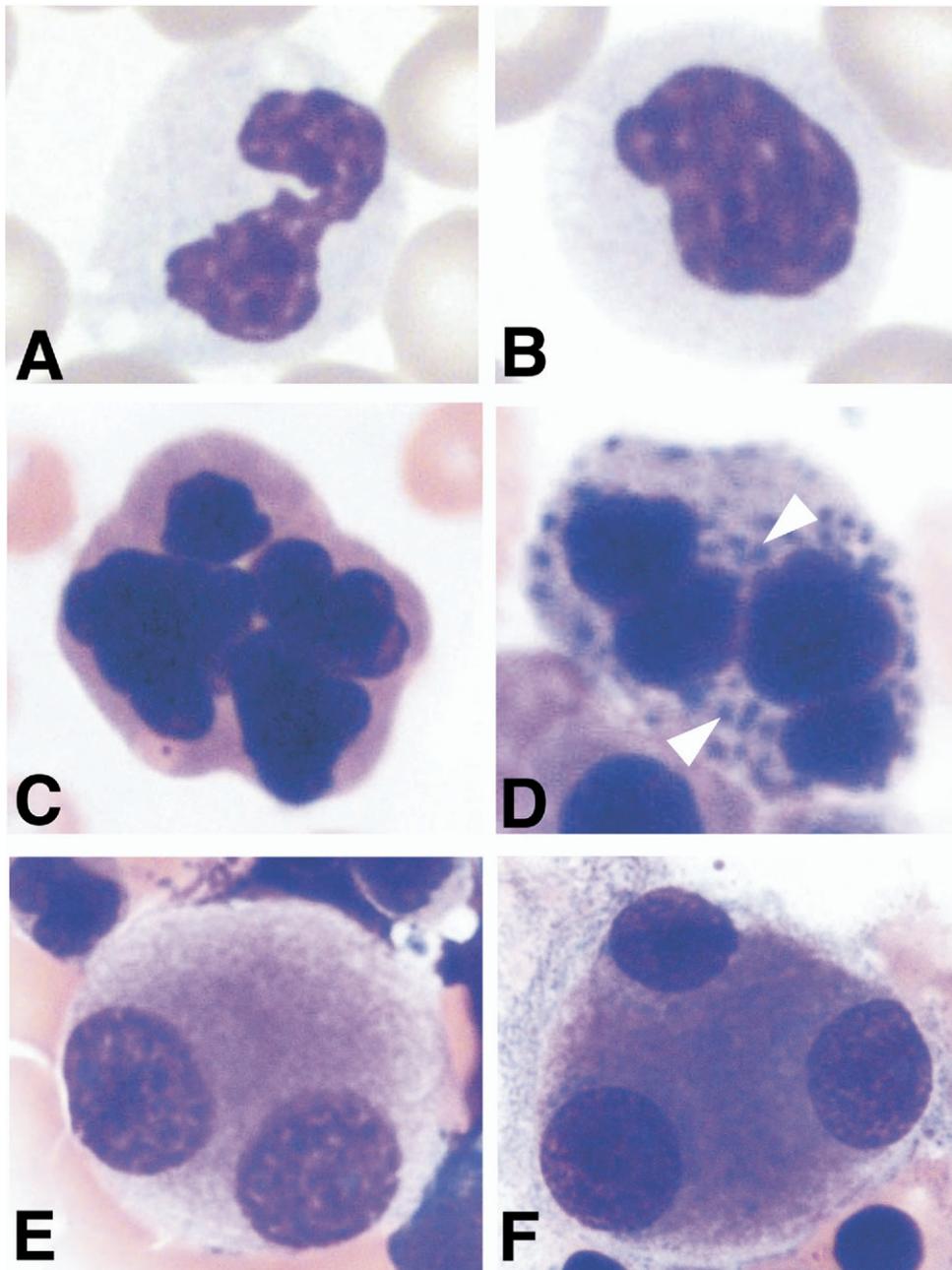


Figure 1. Characteristic but nonspecific cytologic changes are observed in therapy-related myeloid leukemias. Trilineage dysplasia seen in the peripheral blood and bone marrow from a 38-year-old male survivor of Hodgkin's disease, who had been treated with chemotherapy, radiation, and an autologous stem cell transplant. The patient was asymptomatic until presentation with a macrocytic anemia and thrombocytopenia, 5 years after his diagnosis of Hodgkin's lymphoma and 3 years after autologous stem cell transplant. A bone marrow biopsy revealed trilineage dysplasia and fewer than 5% myeloblasts, consistent with a diagnosis of t-MDS. Karyotype analysis revealed a loss of chromosome 7, consistent with alkylating agent-induced disease. (A–C) Dysplasia in the peripheral blood. (A, B) Dysplastic neutrophils have hypolobated, hypercondensed chromatin and hypogranular cytoplasm. The cell shown in (A) has a pseudo-Pelger Huet nucleus. (C) A multinucleated abnormal erythroid precursor in the peripheral blood. (D–G) Dysplasia in the bone marrow. (D) An abnormal multinucleated erythroid cell with basophilic stippling (arrowheads). (E, F) Micromegakaryocytes with abnormal separation of nuclear lobes. Photomicrographs courtesy of Dr. Ozden Ozer, The University of Chicago Department of Pathology.

the incidence of t-AML among non-Hodgkin's lymphoma patients treated with yttrium-90 ibritumomab tiuxetan was 2.5% at 4.4 years, consistent with the expected incidence of t-AML in a patient population heavily pre-treated with chemotherapy.¹⁶

In addition to cancer patients, t-AML has been seen in patients following treatment with immunosuppressive therapies not previously thought to cause DNA damage directly, particularly in patients who have received solid organ transplants.² A mechanism for the development of t-AML has been proposed for azathioprine, an immunosuppressant widely used in recipients of organ transplantation, through selection of a mutator phenotype to allow the emergence of AML with abnormalities of chromosomes 5 and 7.² Thus, a growing body of work suggests that the use of any compound that could damage DNA directly or suppress the immune system's ability to detect malignant cells could lead to an increased risk of t-AML.

RISK FACTORS FOR THE DEVELOPMENT OF THERAPY-RELATED LEUKEMIAS

The etiology and specific factors that predispose to the development of therapy-related leukemia have been difficult to study. It has not yet been possible to determine whether the development of t-MDS/t-AML is a stochastic event, occurring by chance, or whether certain individuals are at higher risk. However, more recent studies have employed newer technology that allows the rapid sequencing of a large number of single nucleotide polymorphisms (SNPs) and suggest that at least a fraction of patients probably have a heritable predisposition to the development of t-AML, such as altered drug metabolism or DNA repair.¹⁷ Widespread identification of underlying preexisting conditions would help inform the choice of initial therapy as well as the screening and counseling of patients at the time of treatment for their primary disease.

We have previously reported that the frequency of the *NQO1-187Ser* SNP, an inactivating polymorphism, in the *NQO1* gene [NAD(P)H:quinone oxidoreductase] is increased among individuals with t-AML.¹⁸ Homozygotes may be particularly vulnerable to leukemogenic changes induced by carcinogens, and heterozygotes are at risk for treatment-induced mutation or loss of the remaining wild-type allele in their hematopoietic stem cells. Other polymorphisms involving detoxifying enzymes also have been reported.¹⁹ A large Japanese study of patients with AML de novo and t-AML found that the *NQO1* polymorphism was more strongly associated with t-AML than polymorphisms in *GST-M1*, *GST-T1*, and *CYP3A4*.²⁰ Furthermore, patients carrying the *NQO1-187Ser* allele and who had been exposed to chemotherapy had significantly shorter telomeres in their neutrophils and lymphocytes and were more

likely to develop clonal hematopoiesis than patients with wild-type *NQO1* alleles.²¹ These findings provide a molecular link between the *NQO1* genotype and an increased risk of developing t-AML. Bolufer et al examined the prevalence of several genetic polymorphisms and found that the *NQO1-187Ser* polymorphism conferred a twofold increased risk of developing t-AML.²² This risk was increased when the *NQO1-187Ser* polymorphism was found in combination with *CYP1A1*2A* and *del[GSTT1]*. However, the risk of developing t-AML was 18-fold lower among patients lacking all three polymorphisms.

Guillem et al identified a haplotype in *MTHFR*, the gene encoding methylene tetrahydrofolate reductase, which conferred an increased risk in particular patient populations.²³ Two SNPs were included in the haplotype: 677C/T and 1298A/C. An increased risk of developing t-AML was associated with the 677T/1298A haplotype in breast cancer patients and the 677C/1298C haplotype in patients with a primary hematopoietic malignancy.

Several groups have examined the genes encoding components of DNA repair pathways. Although about half of t-AML cases show microsatellite instability, promoter hypermethylation, and transcriptional silencing of the *bMSH2* and *bMLH1* genes are not common events.²⁴ Instead, other genetic alterations of these genes seem to predispose to t-AML. Patients with t-AML who have been treated previously with O(6)-guanine alkylating agents, such as cyclophosphamide and procarbazine, have an increased frequency of a variant C SNP that occurs within an intron splice acceptor of the *bMSH2* gene.²⁵ Additionally, two of 13 cases that exhibited microsatellite instability were homozygous for the C allele, a frequency much higher than what was observed in a control population. Furthermore, a variant SNP at position -93 of the *bMLH1* promoter was found in 75% of patients with t-AML who had received methylating chemotherapy as part of prior therapy for Hodgkin's disease.²⁶ In contrast, this variant SNP was found in only 30% of patients with t-AML who had not been treated previously with methylating agents. In patients who had been treated with a methylating agent, the presence of the variant -93 SNP conferred a significantly increased risk of developing t-AML, with an odds ratio of 5.31.

GENETIC PATHWAYS AND COOPERATING MUTATIONS IN THE ETIOLOGY OF THERAPY-RELATED MYELOID LEUKEMIA

Particular mechanisms of DNA damage that lead either to chromosomal deletions or balanced translocations may underlie the differences in latencies between the two main forms of therapy-related leukemia.^{1,27} In the case of chromosomal deletions, one allele of a

putative tumor-suppressor gene may be inactivated. However, before the affected cell would gain a proliferative advantage, the second allele might have to be deleted or mutated also. In some cases, the first allele may be inactivated in the germ-line DNA due to a heritable cause. More recent evidence suggests that haploinsufficiency of individual genes such as *EGR1* on chromosome 5q also may allow for malignant transformation.²⁸ However, even loss 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 fully transform a hematopoietic progenitor cell, relatively fewer genetic events may be required to progress to the leukemic phenotype.

Pedersen-Bjergaard and colleagues have proposed eight different genetic pathways for the multistep development of t-MDS/t-AML (Figure 2).²⁹ There is growing evidence that mutations in a limited number of molecular pathways may cooperate in the genesis of leukemia. Gilliland et al have described AML as a disease arising from the cooperation between two types of alterations.³⁰ Changes in signaling molecules deregulate proliferative and/or anti-apoptotic activities, for example, through mutations that constitutively activate receptor tyrosine kinases like *FLT3*. In addition, fusion proteins encoded by recurring chromosomal translocations, such as *MLL/AF9* that results from the t(9;11), impair normal differentiation pathways with little effect on cellular proliferation. Gene expression array experiments with CD34⁺ t-AML cells have provided evidence to support this hypothesis.³¹ Loss of *TALI*, *GATA1*, and *EKLF* gene expression has been observed. These losses might result in impaired differentiation of hematopoietic cells, whereas overexpression of *FLT3*, *PIK3C2B*, and *BCL2* results in proliferative and survival advantages.

Additional evidence for the notion that t-AML arises from a combination of mutations comes from studies that identify point mutations plus recurring chromosomal rearrangements. One study examined three cases of t-AML with t(8;21), and two of the patients were found to be positive also for the *JAK2*^{V617F} mutation.³² Both patients had received chemotherapy with anthracyclines and topoisomerase inhibitors, one for breast cancer and one for testicular seminoma. Another group examined 140 unselected patients with t-MDS/

t-AML and found that two of the 89 t-MDS patients had the *JAK2*^{V617F} mutation.³³ However, both patients had received radiotherapy, presented with myeloproliferative features including splenomegaly, and had a normal karyotype. Notably, these features are unusual for t-MDS. These investigators went on to look for *PTPN11* mutations in this patient cohort and found four patients with such mutations; three had deletions or loss of chromosome 7q.³⁴ In addition, all four of them had rare balanced chromosomal translocations: two had breakpoints at 3q26 with rearrangement of *EVII*, and two had breakpoints at 21q22 and *RUNX1* rearrangements. Such cases provide additional evidence that t-AML arises through multiple genetic events.

THE THERAPY-RELATED LEUKEMIA AFTER BREAST CANCER

Although long-term survivors of Hodgkin's disease were among the first patients to suffer the development of t-AML, this complication is now increasingly observed in those patients treated for solid tumors. Several large studies have examined the risks for women receiving adjuvant chemoradiotherapy for breast cancer. Several groups have addressed the question as to whether the addition of G-CSF to routine therapy regimens contributes to the risk of developing t-AML out of the concern that G-CSF could promote the proliferation of damaged cells, which might otherwise undergo apoptosis, and drive the development of t-AML. In six trials completed by the National Surgical Adjuvant Breast and Bowel Project, the incidence of therapy-related leukemia was sharply elevated among patients receiving intensified doses of doxorubicin and cyclophosphamide that required G-CSF support; the relative risk (RR) was 6.16 ($P = .0001$).³⁵ Breast radiotherapy alone increased the RR to 2.38 ($P = .006$). In a second study, 5,510 women over 65 years old who received chemotherapy for stage I-III breast cancer were analyzed.³⁶ Sixteen (1.77%) of the 906 patients who also received G-CSF or GM-CSF developed t-AML compared to 1.04% of those who did not receive myeloid growth factors. The incidence of t-MDS was not evaluated. The hazard rate was 2.59 (95% confidence interval, 1.30–5.15) for the development of leukemia within 4 years. Finally, a large case-control study from France compared 182 patients who developed therapy-related leukemia after breast cancer treatment and 534 matched controls.³⁷ The risk of leukemia was markedly increased after chemotherapy that included a topoisomerase-II inhibitor ($P < .0001$), and was higher after mitoxantrone (RR = 15.6) than after anthracyclines. The risk was increased 3.9-fold after breast radiotherapy ($P = .003$). The risk was also increased among those who received G-CSF (RR = 6.3, $P = .0009$), even when controlling for chemotherapy doses.

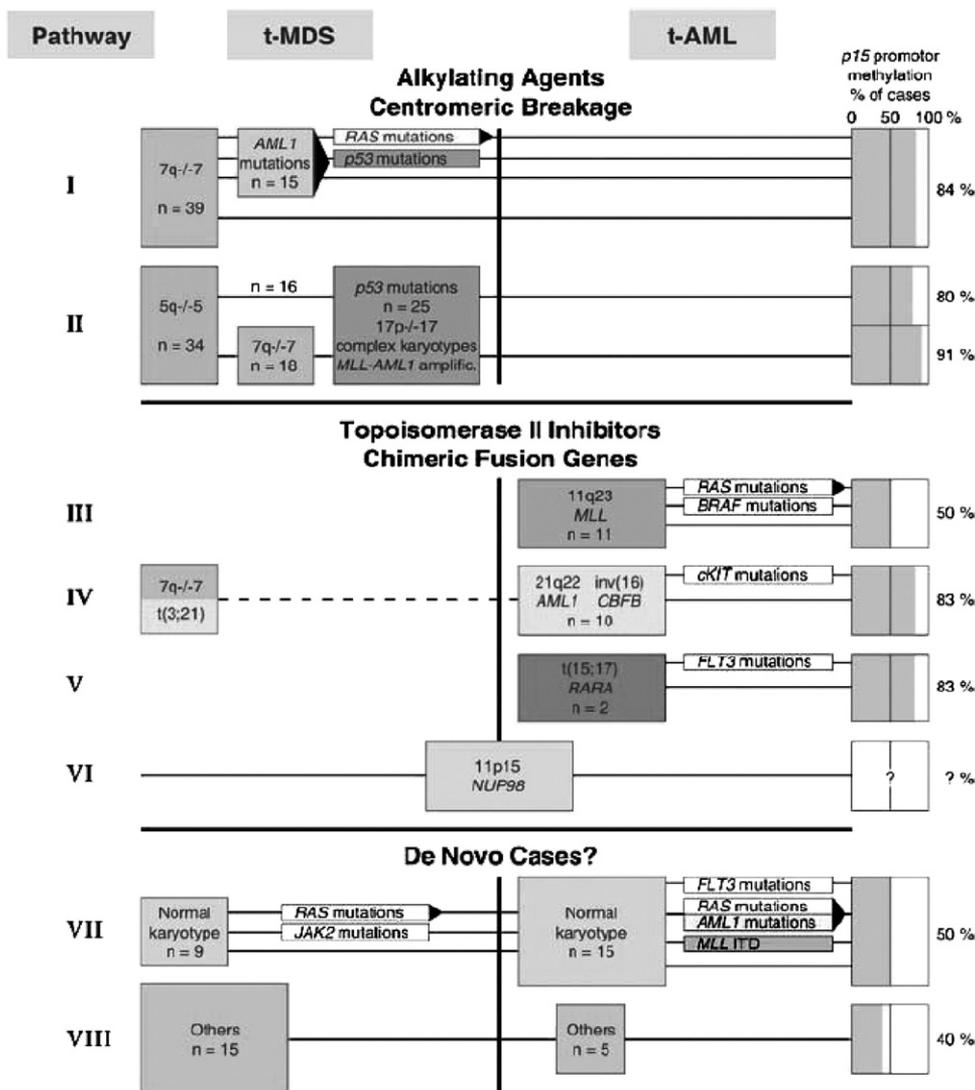


Figure 2. Genetic pathways identified in 140 cases of t-MDS and t-AML by Pedersen-Bjergaard et al.²⁹ At least eight genetic pathways could be distinguished among 140 cases of therapy-related myeloid malignancies. Pathways I and II are characteristic of patients who had been treated previously with alkylating agents. Mutations of *AML1*, *p53*, and *RAS* are common in patients with abnormalities of 7q or -7. Pathways III–VI are often seen in patients who had received topoisomerase-II inhibitors. By definition, any myeloid leukemia arising after prior chemotherapy or radiotherapy is considered therapy-related. However, because there are few characteristic chromosomal changes or genetic mutations seen in leukemias described by pathways VII and VIII, these may actually represent de novo cases, or cases in which the underlying genetic defect has not yet been elucidated. *RAS* mutations are commonly seen in the transition to t-AML within pathway I, in t-AMLs with *MLL* rearrangements (pathway III), and in t-AMLs with a normal karyotype (pathway VII). Reprinted with permission from Macmillan Publishers Ltd: *Leukemia*, © 2006.²⁹

THERAPY-RELATED LEUKEMIA AFTER AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION

Several thousand autotransplants are performed each year for patients with relapsed lymphoma and other diseases. Estimates of the incidence of therapy-related leukemia among these lymphoma and Hodgkin's disease patients range between 1% and 14% at 3 to 15 years.³⁸ The risk appears lower in patients undergoing autologous hematopoietic cell transplanta-

tion (HCT) for breast or germ cell cancers or for myeloma. Important risk factors include age, extent of prior therapy, and exposure to certain agents before and during the transplant procedure. Genotoxic damage and stresses imposed on hematopoietic stem cells during the priming or mobilizing chemotherapy and engraftment are also likely to play a role. As noted above, inherited polymorphisms in genes governing drug metabolism and DNA repair also may contribute to leukemogenesis. Studies of the latency periods be-

tween first cytotoxic exposure, the autologous HCT itself, and the emergence of therapy-related leukemia suggest that the initial malignant event occurs prior to HCT in most cases.^{4,38} However, the cytotoxic therapy delivered during the multi-step HCT procedure is likely additive to previous genomic damage and contributes to the etiology by cooperating mutations and selective pressure.

FACTORS THAT INFLUENCE OUTCOME IN t-AML

Therapy-related myeloid leukemia is generally a fatal disease. The life-threatening complications of this disorder are the result of persistent and profound cytopenias due to the failure of normal hematopoiesis regardless of the fraction of myeloblasts accumulating in the bone marrow or blood. There has been general agreement that patients with t-AML have shorter survivals than patients with *de novo* AML. Supportive care is still considered by many to be the standard management.

A number of potential factors explain the poor outcome of patients with therapy-related leukemia. The persistence of the primary malignant disease, particularly metastatic cancer or lymphoma, causes morbidity and mortality independent of the bone marrow failure caused by leukemia. Injury to organs and their vascular supply from prior treatment may compromise the ability of these patients to receive intensive remission induction chemotherapy or bone marrow transplantation. There may be depletion of normal hematopoietic stem cells as a consequence of previous therapy, so that these patients suffer prolonged cytopenias after induction chemotherapy. The bone marrow stroma may have been damaged, especially by therapeutic radiation to fields that include the pelvis or lumbosacral spine, so that it will not support regeneration of normal hematopoiesis. Patients with t-AML are often chronically immunosuppressed from prior disease or ongoing therapy or may have dysfunctional phagocytes, and thus are often colonized with pathogenic or antibiotic-resistant bacteria and fungi. Following prior supportive care, patients may be refractory to additional transfusion support, and therefore, not good candidates for intensive myelosuppressive chemotherapy. Finally, the high frequency of unfavorable cytogenetic aberrations arising during or after chemoradiotherapy appears to result in the rapid emergence of chemotherapy resistance in t-AML stem cells.

TREATMENT OF THERAPY-RELATED MYELOID LEUKEMIA

The survival of patients with therapy-related leukemia is often poor despite prompt diagnosis and treatment. However, there is a paucity of prospective treatment data since these patients are most often excluded

from frontline clinical trials. There are no randomized studies comparing standard AML therapy to other forms of treatment. In a nationwide Japanese study of 256 patients with t-MDS (41%) or t-AML (59%), a poor prognosis was associated with abnormalities of chromosome 5, hypoproteinemia, high C-reactive protein, thrombocytopenia, and persistence of the primary malignancy.³⁹ The majority of the Japanese patients (72%) received antileukemia chemotherapy, either a standard combination using an anthracycline plus cytarabine, or low-dose cytarabine, or tretinoin (ATRA) in the case of seven patients with t-APL. The median age was 61 years, and the median survival was only 9.7 months. A complete remission (CR) was seen in 85 patients (46%). The median remission duration was 8.2 months.

Poor hematopoietic reserves make the administration of standard AML therapy difficult. Many patients have poor tolerance for the acute toxicity of treatment. Because therapy-related leukemia evolves in the milieu of chemotherapy, the malignant cells are relatively drug-resistant. Expression of the multidrug resistance phenotype is common. In a review of 644 t-AML patients treated with a variety of standard AML chemotherapy regimens, only 182 (28%) achieved a CR.⁴⁰ Individual small series report CR rates of 40% to 50%. This is considerably lower than the 55% to 80% CR rate observed in patients with *de novo* AML. In addition, remissions are often short even when confirmed cytogenetically and consolidated intensively.⁴¹

HCT FOR t-AML

The treatment most likely to cure t-AML is allogeneic HCT. Several small case series have described the outcomes of these patients, and the survival rate appears to be about 20% to 30%.^{1,42} However, chronic and cumulative toxicities from prior chemoradiotherapy have an impact on the ability to perform HCT and adversely affect survival. Early deaths from regimen-related toxicity are more common after HCT for therapy-related leukemia than for primary AML.

In an analysis of 70 patients (31 with t-MDS and 39 with t-AML) who underwent allogeneic HCT between 1980 and 1998 in France, poor outcomes were associated with age greater than 37 years, male sex, positive cytomegalovirus serology in the recipient, absence of CR at the time of HCT, and the use of intensive conditioning chemotherapy.⁴³ The treatments given were heterogeneous, and the donors were varied. The estimated 2-year survival rate was 30%, event-free survival rate 28%, relapse rate 42%, and transplant-related mortality 49%. Thus, for patients who have chemotherapy-responsive t-AML, allogeneic HCT can be curative, but it is unfortunately not often successful. Nonmyeloablative, reduced-intensity allogeneic HCT is under investigation for those patients who are not eligible for standard myeloablative HCT.

Similar results have been seen in children who have undergone allogeneic HCT for t-AML developing after therapy for acute lymphoblastic leukemia (ALL). Hale et al reported the outcomes of 21 children who had received epipodophyllotoxin-containing regimens for ALL and subsequently developed t-AML.⁴⁴ Thirteen received induction chemotherapy prior to HCT, whereas seven underwent HCT immediately after diagnosis. One patient received an autologous HCT in first CR from t-AML, but later relapsed, and was subsequently treated at second relapse with an allogeneic HCT. Eleven patients received bone marrow cells from human leukocyte antigen (HLA)-matched siblings, eight received bone marrow cells from matched unrelated donors, and two received haploidentical marrow from family members. Three years after HCT, only four patients (19%) were alive. Seven patients died from transplant-related causes, and 10 patients died from relapsed t-AML after a median of 5 months.

The European Bone Marrow Transplant registry has reported on 65 t-AML patients who underwent autologous HCT.⁴⁵ The median age was 39 years (range, 3–69). Estimates of overall and disease-free survival at 3 years were 35% and 32%, respectively. The relapse rate was lower for patients transplanted in first CR (48% *v* 89%, *P* = .05). Age over 40 years resulted in higher transplant-related mortality (47% *v* 7%, *P* = .01).

TREATMENT OF t-AML WITH BALANCED CHROMOSOMAL REARRANGEMENTS

In marked contrast to the poor outcome overall for t-AML, those patients who develop t-APL with t(15;17) or those with t(8;21) or inv(16) have response rates that are similar to patients with de novo AML with the same chromosomal rearrangements, although overall survival is less. In a report on 106 cases of t-APL iden-

tified between 1982 and 2001 in France, Spain, and Belgium, the characteristics of the t-APL patients were similar to those of de novo APL patients.⁴⁶ In addition, more than 80% of those treated with anthracycline-based chemotherapy and/or ATRA achieved a CR. Ten of the complete responders relapsed, and seven others died from persistent primary tumor. The actuarial survival was 58% at 8 years, and did not differ between patient groups analyzed by primary treatment (chemotherapy, radiotherapy, or both) or prior exposure to particular drugs (alkylating agents, topoisomerase-II inhibitors, or both).

Among patients analyzed at the International Workshop in Chicago in 2000, 33 of 39 intensively treated patients (85%) with t-AML and inv(16) achieved a CR.⁴⁷ Twelve (36%) subsequently relapsed. Five underwent HCT in first CR (four allogeneic, one autologous), and all of them were alive and leukemia-free at last follow-up. The responding patients were significantly younger than those who did not achieve CR (median, 44 years *v* 62 years; *P* = .012). Patients younger than 55 years of age had improved survival when compared to older patients. The median survival in the young patient group (*n* = 26) was not reached and was longer than 3 years, but it was only 12 months for the 13 older patients (*P* = .006). Similarly, 24 of 35 (69%) patients treated aggressively for t-APL achieved a CR. Development of both inv(16) t-AML and t-APL was associated with prior exposure to topoisomerase-II inhibitors. However, 21% of the inv(16) patients and 29% of the t(15;17) patients had received only radiotherapy previously. The median overall survival for t-AML patients with either inv(16) or t(15;17) was 29 months after receiving intensive AML therapy.

Seventy-two t-AML patients with any t(21q22) also were studied at the International Workshop.⁴⁸ Their median survival was 14 months, and 18% were alive

Table 2. Survival of 306 Patients With Therapy-Related Myeloid Leukemia According to Clinical and Cytogenetic Features: The University of Chicago Series⁴

Clinical/Cytogenetic Subset*	No. of Patients (%)	Median Survival, mo (95% confidence interval)
Total group	306	8 (7-9)
Presenting as t-MDS	224 (73)	8.6 (7.6-9.9)
Presenting as t-AML	82 (27)	6.9 (4.0-8.5)
Abnormal chromosome 5	63 (21)	7
Abnormal chromosome 7	85 (28)	9
Abnormalities of both chromosomes 5 and 7	66 (22)	5
Recurring balanced rearrangement	31 (10)	11
Other clonal abnormality	39 (13)	9
Normal karyotype	24 (8)	11

*One hundred thirty-nine of 306 patients (45%) had complex karyotypes, ie, three or more unrelated chromosomal abnormalities.

Table 3. Survival According to Cytogenetic Risk Group for Patients With t-AML or De Novo AML Treated by the German AML Cooperative Group⁵¹

Karyotype	No. of Patients (%)		Median Survival (mo)		
	t-AML (n = 121)	De Novo AML (n = 1,511)	t-AML	De Novo AML	P
Favorable	29 (24)	306 (20)	27	Not reached	.02
Intermediate	34 (28)	903 (60)	12	16	.19
Unfavorable	58 (48)	302 (20)	6	7	.006

after 5 years. Patients with t(8;21) had a more favorable outcome than those with other 21q22 rearrangements ($P = .014$). Survival was similar in t-AML patients with only t(8;21) ($n = 11$) and those with t(8;21) plus other abnormalities ($n = 3$) ($P = .6$). Fifty-three patients with t(21q22) received intensive AML therapy; the median survival for the seven who underwent HCT was 31 months compared to 17 months for those who did not. Mutations in *C-KIT* were not studied in these patients.

THE IMPORTANCE OF CYTOGENETIC ABNORMALITIES IN PREDICTING PATIENT OUTCOMES

The most informative data on the prognostic impact of karyotype on outcome in t-AML were reported by the German AML Cooperative Group (AMLCG).⁴⁹ This group compared karyotype analysis and survival between 93 patients with t-AML and 1,091 patients with

de novo AML, all of whom received intensive treatment. Favorable, intermediate, and unfavorable karyotypes, respectively, were observed in 26%, 28%, and 46% of t-AML patients, and in 22%, 57%, and 20% of de novo AML patients. Overall, the median survival was 10 months for patients with t-AML compared to 15 months for patients with de novo AML ($P = .0007$).

Armand et al also analyzed the outcomes of 80 patients with therapy-related disease treated at the Dana Farber Cancer Institute.⁵⁰ They found that cytogenetic abnormalities were the strongest predictors for overall survival. When adjusted for patients' cytogenetic changes, the patients with t-AML did as well as the patients with de novo AML, further emphasizing the importance of cytogenetic abnormalities in predicting severity of disease and outcomes.

At the University of Chicago, 306 consecutive patients with t-AML were analyzed for clinical outcome according to cytogenetic subset, as well as other clin-

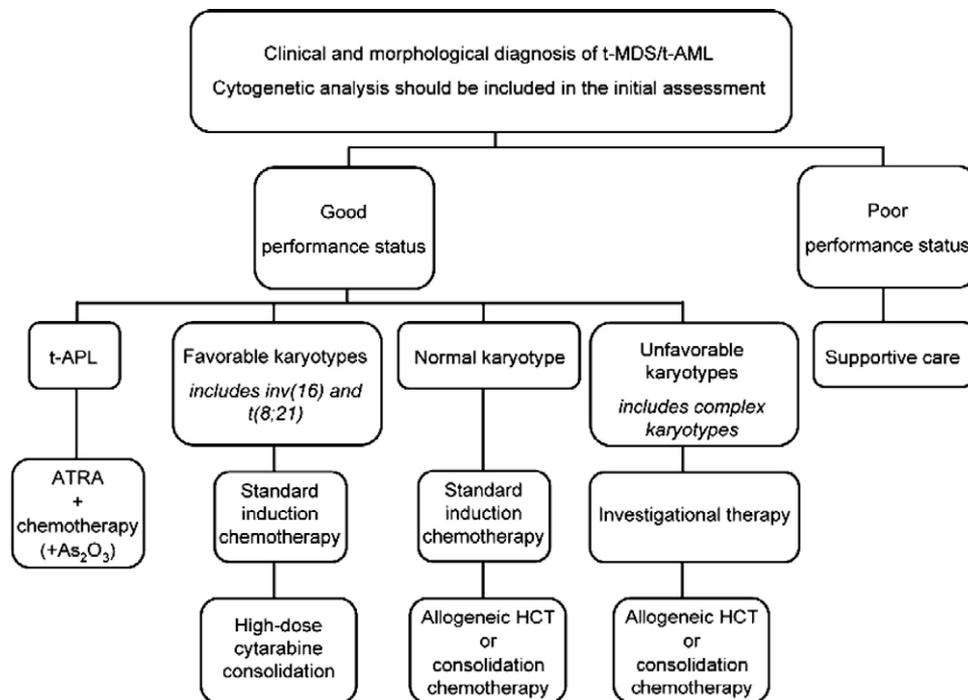


Figure 3. Decision tree for the management of t-AML.

ical features, including disease latency.⁴ In contrast to the German series, not all of our patients underwent intensive remission induction chemotherapy. Many received only supportive care. Survival times are shown in Table 2. Only 24 patients (8%) were alive 3 years after diagnosis. Patients with t-AML who responded to remission induction therapy but subsequently died from their primary malignancy were included in the survival analysis. Even patients with a normal karyotype or with a balanced chromosomal rearrangement did poorly overall. The incidence of unfavorable karyotypes was greater than 70%. The patients who had the worst overall survival were those with abnormalities of both chromosomes 5 and 7 ($P = .005$).

In an updated analysis of the German AMLCG study, the survival of 121 patients with t-AML was compared with that of 1,511 patients with de novo AML according to karyotype.⁵¹ All patients received intensive AML therapy. The median survival for the t-AML patients ranged from 27 months for those with a favorable karyotype to 6 months for those with an unfavorable karyotype (Table 3).⁵¹ Importantly, almost half of the patients with t-AML (58/121) had an unfavorable karyotype, whereas only about 20% (302/1,511) of the de novo AML patients had an unfavorable karyotype. For those with a favorable karyotype, the median survival was not yet reached after 5 years for the 306 de novo AML patients compared to 27 months for the 29 t-AML patients ($P = .02$). Some of these t-AML patients appeared to be cured. Within the large intermediate-risk cytogenetic group, no significant difference in survival was observed between the t-AML and de novo AML patients. An unfavorable karyotype predated a very short survival in both groups of AML patients.

RECOMMENDATIONS FOR TREATMENT OF t-AML

Figure 3 shows a treatment algorithm for the management of patients who develop therapy-related myeloid leukemia. Primary considerations are the patient's performance status, which reflects age, comorbidities, the status of the primary disease, and the presence of complications from primary therapy, as well as the clonal abnormalities detected in the t-AML cells. In general, t-AML patients should be encouraged to participate in prospective clinical trials that are appropriately designed for other AML patients with similar cytogenetic abnormalities. Patients who have an HLA-matched donor should be considered for allogeneic HCT, although patients with favorable karyotypes may do well with conventional intensive chemotherapy.

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