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Should therapy-related myeloid leukemia be treated like *de novo* acute myeloid leukemia?

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A B S T R A C T

The diagnosis of therapy-related myeloid leukemia (t-MDS/t-AML) identifies a group of high-risk patients with multiple and varied poor prognostic features. Their outcomes have historically been poor compared to people who develop AML *de novo*. The question arises whether a diagnosis of t-AML per se indicates a poor prognosis, or whether their bad outcomes result from certain clinical and biologic characteristics. Because of lingering damage from prior cytotoxic therapy and in some cases the persistence of their primary disorder, t-AML patients are often poor candidate for intensive AML therapy. 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 higher in t-AML. Survival varies according to cytogenetic risk group, with better outcomes observed in t-AML patients with favorable-risk karyotypes. Treatment recommendations should be based on performance status and karyotype. Patients with t-AML should be enrolled on front-line chemotherapy trials, appropriate for *de novo* AML patients with similar disease characteristics. Allogeneic hematopoietic cell transplantation can cure some t-AML patients. Most importantly, the molecular and genetic differences that appear to determine the phenotype and the outcome of these patients need to be investigated further.

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Therapy-related myeloid leukemia (t-MDS/t-AML) is a well recognized clinical syndrome occurring as a late complication following cytotoxic therapy.[1-6] These neoplasms are thought to be the direct consequence of mutational events induced by cytotoxic therapy or via the selection of a myeloid clone with a mutator phenotype that has a markedly elevated risk for a mutational event. Several distinct clinical and cytogenetic subtypes of t-AML are recognized that are closely associated with the nature of the preceding treatment. The latency between primary diagnosis and therapy-related disease ranges between several months to several years, depending in part on the cumulative dose or dose intensity of the preceding cytotoxic therapy, as well as the exposure to specific agents. The majority of patients have clonal chromosome abnormalities in their bone marrow cells at diagnosis. A spectrum of morphologic abnormalities is observed.[6] There is a continuum in the percentage of marrow blasts from a myelodysplastic syndrome (t-MDS) to overt acute myeloid leukemia, and rapid progression from the former to the latter. 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 – perhaps due to a DNA-repair deficiency or a heritable predisposition, such as altered drug metabolism. The identification of such an underlying preexisting condition would help the screening and counseling of patients at the time of treatment for their primary disease.

Factors that influence outcome in t-AML

Therapy-related 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 management is still considered by many to be the standard of care.

A number of potential factors explain the poor outcome of patients with t-AML. The persistence of the pri-

mary malignant disease, particularly metastatic breast cancer or lymphoma, causes morbidity and mortality independent of the bone marrow failure caused by therapy-related 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 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 ideal 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.

Treatment of therapy-related myeloid leukemia

The survival of patients with therapy-related leukemia is often poor despite prompt diagnosis and treatment. 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.[7]

The median age was 61 years old. The median survival was only 9.7 months. 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 7 patients with therapy-related acute promyelocytic leukemia (t-APL). 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.[9] Individual small series report CR rates of 40-50%. This is considerably lower than the 65% to 80% CR rate observed in patients with de novo AML. In addition, remissions are often short even when confirmed cytogenetically and consolidated intensively.[9]

Hematopoietic cell transplantation 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 appears to be about 20-30%.[2,10] However, chronic and cumulative toxicities from prior chemoradiotherapy 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 leukemia.

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 outcome was 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.[11] 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 is a curative therapy, but it is unfortunately not often successful. Nonmyeloablative, reduced intensity allogeneic HCT is under investigation for those who are not eligible for standard HCT.

Similar results have been seen in children who have undergone allogeneic HCT for t-AML developing after therapy for ALL. Hale et al reported the outcomes of 21 children who had received epipodophyllotoxin-containing regimens for ALL and subsequently developed t-AML.[12] Thirteen received induction chemotherapy prior to HCT, whereas 7 underwent HCT immediately after diagnosis. One patient received an autologous HCT in first CR from t-AML, but later relapsed, and was subsequently

Table 1. Survival of 306 patients with therapy-related myeloid leukemia according to clinical and cytogenetic features: the University of Chicago series.[5]

Clinical/cytogenetic subset	*No. of patients*	*Median Survival, months (95% confidence interval)*
Total group	306	8 (7-9)
Presenting as t-MDS	224	8.6 (7.6-9.9)
Presenting as t-AML	82	6.9 (4.0-8.5)
Abnormal chromosome 5	63	7
Abnormal chromosome 7	85	9
Abnormalities of both chromosomes 5 and 7	66	5
Recurring balanced rearrangement	31	11
Other clonal abnormality	39	9
Normal karyotype	24	11

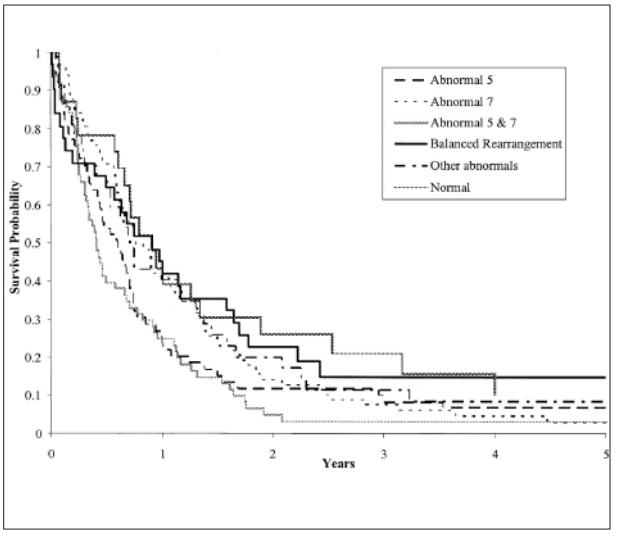

Figure 1. Survival following a diagnosis of therapy-related myeloid leukemia for 306 patients with various cytogenetic abnormalities: the University of Chicago series.[5] Not all patients received intensive remission induction chemotherapy. The median survival time after a diagnosis of t-MDS/t-AML was 8 months. The number of patients alive after one year was 102, after 2 years 41, after 3 years 24, after 5 years 15, and after 9 years 6.

treated at second relapse with an allogeneic HCT. Eleven patients received bone marrow cells from HLA-matched siblings, while 8 received bone marrow cells from matched unrelated donors, and 2 received haploidentical marrow from family members. Three years after HCT, only 4 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.

Cytogenetics impact on outcome of therapy-related myeloid leukemia

The most informative data on the prognostic impact of karyotype on outcome in t-AML were reported by the German AML Cooperative Group (AMLCG).[13] This group compared karyotype analysis and survival between 93 patients with t-AML and 1091 with de novo AML; all received intensive treatment. Favorable, intermediate, and unfavorable karyotypes 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=0.0007). This study confirmed that the survival of patients with t-AML overall was significantly inferior to that of patients with *de novo* AML.

At the University of Chicago, 306 consecutive patients with t-AML were analyzed for clinical outcome according to broad cytogenetic subsets as well as other clinical features, including disease latency.[5] 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 1 and Figure 1. Even patients with a normal karyotype or with a balanced chromosomal rearrangement did poorly overall. Patients were censored only on the date last seen alive. Patients with t-AML who responded to remission induction therapy but subsequently died from their primary malignancy were included in the survival analysis. The incidence of unfavorable karyotypes was greater than 70%. The group with the worst overall survival compared with all other cytogenetic groups were those patients with abnormalities of both chromosomes 5 and 7 (p=0.005).

In an updated analysis of the German AMLCG study, the survival of 121 patients with t-AML was compared to 1511 patients with *de novo* AML according to karyotype.[14] All 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 2). Importantly, about half of the patients with t-AML (58/121)

Table 2. Survival according to cytogenetic risk group for patients with t-AML or de novo AML treated by the German AML Cooperative Group (AMLCG).[14]

Karyotype	*No. of patients*		*Median survival (months)*		
	t-AML (n=121)	*de novo AML (n=1511)*	*t -AML*	*de novo AML*	*p*
Favorable	29	306	27	Not reached	0.02
Intermediate	34	903	12	16	0.19
Unfavorable	58	302	6	7	0.006

had an unfavorable karyotype, whereas only about 20% (302/1511) 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=0.02). Within the large intermediate cytogenetic groups, no significant difference in survival was observed between the t-AML and de novo AML patients. An unfavorable karyotype predicated a very short survival in both groups of AML patients.

Treatment of t-AML with balanced 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 outcomes that are similar to patients with *de novo* AML with the same chromosomal rearrangements. In a report on 106 cases of t-APL identified between 1982-2001 in France, Spain, and Belgium, the characteristics of the t-APL patients were similar to those of de novo APL.[15] 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 7 others died from persistent primary tumor. The actuarial survival was 58% at 8 years, and did not differ between patient groups based on primary treatment (chemotherapy, radiotherapy, or both) or prior exposure to particular drugs (alklyating 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), and 24 of 35 (69%) with t(15;17) achieved a CR.[16] Both subgroups were associated with prior exposure to topoisomerase II inhibitors, but importantly, 21% or 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.

Only 12 of the inv(16) patients relapsed. Five underwent HCT in first CR (4 allogeneic; 1 autologous), and all were alive and leukemia-free at last follow up. The responding patients were significantly younger than the 6 who did not achieve CR (median, 44 years vs 62 years, p=0.012). In the inv(16) subgroup, patients less 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, but was only 12 months for the 13 older patients (p=0.006). A similar tendency was observed in the t(15;17) subgroup, with median survival times of 29 and 20 months in the 21 younger and 15 older patients, respectively (p=0.7).

Seventy-two t-AML patients with t(21q22) were studied at the International Workshop.[17] Their median survival was 14 months, and 18% were alive after 5 years. Patients with t(8;21) had a more favorable outcome than those with other 21q22 rearrangements (p=0.014). The median survivals were 17 months for the 11 t-AML patients with t(8;21) only and 31 months for the 33 patients with t(8;21) plus other abnormalities (p=0.6). Fifty-three patients with t(21q22) received intensive AML therapy; the median survival for the 7 who underwent HCT was 31 months compared to 17 months for those who did not.

Recommendations for treatment of t-AML

Figure 2. Shows a treatment algorithm for the management of patients who develop therapy-related myeloid leukemia. Primary considerations are the patient's performance status which likely reflects age, co-morbidities, 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, these patients should be encouraged to

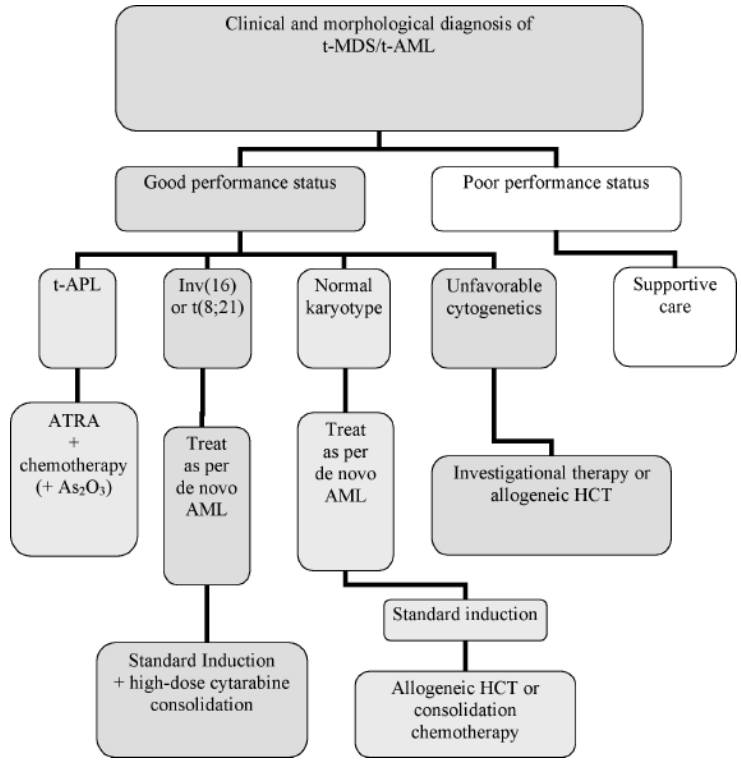

Figure 2. Decision tree for the management of therapy-related myeloid leukemia

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.

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