The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML

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To study the characteristics and clinical impact of therapy-related acute myeloid leukemia (t-AML). 200 patients (7.0%) had t-AML and 2653 de novo AML (93%). Patients with t-AML were older (P < .0001) and they had lower white blood counts (P = .003) compared with de novo AML patients; t-AML patients had abnormal cytogenetics more frequently, with overrepresentation of 11q23 translocations as well as adverse cytogenetics, including complex and monosomal karyotypes, and with underrepresentation of intermediate-

risk karyotypes (P < .0001); t-AML patients had *NPM1* mutations (P < .0001) and *FLT3* internal tandem duplications (P = .0005) less frequently. Younger age at diagnosis of primary malignancy and treatment with intercalating agents as well as topoisomerase II inhibitors were associated with shorter latency periods to the occurrence of t-AML. In multivariable analyses, t-AML was an adverse prognostic factor for death in complete remission but not relapse in younger intensively treated patients (P < .0001 and P = .39,

respectively), relapse but not death in complete remission in older, less intensively treated patients (P = .02 and P = .22, respectively) and overall survival in younger intensively treated patients (P = .01). In more intensively treated younger adults, treatment-related toxicity had a major negative impact on outcome, possibly reflecting cumulative toxicity of cancer treatment. (*Blood.* 2011;117(7): 2137-2145)

Introduction

Therapy-related acute myeloid leukemia (t-AML) is a recognized clinical syndrome occurring as a complication after cytotoxic and/or radiation therapy.¹⁻³ At present, approximately 10% of all AMLs arise after a patient's exposure to chemotherapy and/or radiation for a primary malignancy or autoimmune disease.^{4,5} Patients with t-AML are considered to have an inferior outcome compared with de novo AML.^{2,3,5} The latency period between diagnosis of the primary disease and occurrence of t-AML ranges between several months to several years and may depend on the cumulative dose, dose intensity, and type of preceding chemotherapy and/or radiation therapy.^{2,3}

With respect to cytogenetics, t-AML more frequently have abnormal cytogenetics; in particular, they have an increased prevalence of adverse-risk karyotypes.⁵⁻⁷ At present, few data exist regarding the frequency of gene mutations.⁷ Chromosomal aberrations in t-AML are thought to be the consequence of mutational events induced by previous therapy.⁸ Hematopoietic progenitor cells, that survive with acquired mutations caused by non- or misrepair, are at risk for leukemic transformation and finally result in overt AML. Some patients may have an inherited susceptibility for the development of t-AML. $^{8\mathchar`-10}$

Depending on the chemotherapeutic agent and/or radiation, 2 subtypes of t-AML can be distinguished. The most common subtype, occurring after exposure to alkylating agents and/or radiation with a latency period of 5-10 years, is frequently accompanied by unbalanced cytogenetic abnormalities, such as loss of all or parts of chromosomes 5 and/or $7^{.5,11-14}$ The second less common subtype, arising after treatment with agents targeting topoisomerase II, has shorter latency period of 1-5 years and frequently exhibits balanced chromosomal rearrangements involving *MLL*, *RUNX1*, and *PML-RARA*.^{5,7,15,16} However, because in recent years most patients have received treatment with both alkylating agents and drugs that target topoisomerase II for previous malignancy, a discrimination according to the type of previous therapy is often not feasible. Therefore, in the current World Health Organization (WHO) classification therapy-related myeloid neoplasms are no longer subcategorized.

Because pretreatment cytogenetic and molecular aberrations are the most powerful prognostic parameters for clinical outcome in de

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Submitted August 12, 2010; accepted November 19, 2010. Prepublished online as *Blood* First Edition paper, December 2, 2010; DOI 10.1182/blood-2010-08-301713.

Presented in part at the 51st Annual Meeting of the American Society of Hematology, New Orleans, LA, December 7, 2009.

The online version of this article contains a data supplement.

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BLOOD, 17 FEBRUARY 2011 • VOLUME 117, NUMBER 7

Table 1. Classification of chemotherapeutic agents by mechanise	m
of action modified according to Smith et al ⁶	

Mechanism of action/	
substance group	Agent
Alkylating agents	
Nitrogen mustard	Chlorambucil, cyclophosphamide, ifosfamide, melphalan
Nitrosourea	Carmustine, lomustine
Platinum-based	Carboplatin, cisplatin, oxaliplatin
Alkylsulfonate	Busulfan, treosulfan
Hydrazine	Procarbazine
Triazene	Dacarbazine
Aziridine	Thiotepa
Antimetabolites	
Folic acid	Methotrexate
Purine antagonist	Cladribine, clofarabine, fludarabine, mercaptopurine
Pyrimidine antagonist	Cytarabine, decitabine, azacitidine, fluorouracil, gemcitabine
Antitubulin	
Taxane	Docetaxel, paclitaxel
Vinca alkaloid	Vinblastine, vincristine, vindesine, vinorelbine
Topoisomerase II inhibitors	
Epipodophyllotoxin	Etoposide, teniposide
Intercalating agents	
Anthracycline ^{29,30}	Daunorubicin, doxorubicin, epirubicin, idarubicin
Anthracenedione ^{31,32}	Mitoxantrone
Streptomyces ³³	Actinomycin, bleomycin, mitomycin

novo AML,^{17,18} the question arises whether the diagnosis of t-AML itself indicates a poor prognosis or whether the inferior outcome results from the association with an adverse genetic risk profile. So far, only a few authors have evaluated the characteristics and clinical impact of t-AML, in particular in the context of other clinical and biologic prognostic markers. The objective of our study was to evaluate the characteristics and clinical impact of t-AML in a large cohort of adult AML patients treated within prospective multicenter treatment trials.

Methods

Patients

Patients were enrolled on 6 prospective multicenter treatment trials of the German-Austrian AML Study Group (AMLSG) between 1993 and September 2008. All patients received age-adapted intensive induction and consolidation therapy as previously described (AML HD9319; APL9520; AML HD98A²¹; AML HD98B²²; AMLSG 06-04, NCT00151255; AMLSG 07-04; NCT00151242). Treatments were significantly less intensive in trials for patients older than 60 years of age. In all trials patients with t-AML were eligible if they had completed therapy for the previous malignancy, had no active disease, and were considered by their physician to be at low risk of relapse. The studies were approved by the institutional review boards of all the participating centers. All patients gave informed consent for treatment and for cytogenetic and molecular genetic analyses according to the Declaration of Helsinki. The diagnosis of AML was based on French-American-British Cooperative Group criteria²³ for the trials AML HD93, AML HD98A, and AML HD98B and after 2004 on WHO 2001 criteria²⁴ for the trials AMLSG 07-04 and AMLSG 06-04.

Cytogenetic and molecular genetic analysis

All leukemia samples were studied centrally in the reference laboratories of the AMLSG at the University of Ulm and at Hannover Medical School.

Chromosome banding was performed by the use of standard techniques, and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.²⁵

Leukemia samples were analyzed for mutations in the *FLT3* (*FLT3* internal tandem duplication [ITD], n = 2355; *FLT3* tyrosine kinase domain mutations at codons D835 and I836, n = 2145), *NPM1* (n = 2300), *MLL* (partial tandem duplication, n = 1804), as well as *CEBPA* (n = 1091; analysis restricted to cytogenetically normal AML), as previously described.²⁶

Statistical analyses

The definition of complete remission (CR) or therapeutic failures followed recommended criteria.²⁷ Overall survival (OS), relapse-free survival (RFS), cumulative incidence of relapse (CIR), and cumulative incidence of death in CR (CID) were defined as recommended.²⁷ Cytogenetic categorization into favorable-, intermediate-, and adverse-risk group followed recommended criteria.²⁸ Pairwise comparisons between patient characteristics (covariates) were performed by Mann-Whitney or Kruskal Wallis test for continuous variables and by Fisher exact test for categorical variables.

A multivariable log-normalized linear regression model was used to identify factors that influenced the duration of the latency period, including the covariates type of primary malignancy (solid vs hematologic), sex, type of chemotherapeutic agent (alkylating agent, antimetabolite, antitubulin, intercalating agent, or topoisomerase II inhibitor; Table 1),²⁹⁻³³ and radiation.

The Kaplan-Meier method was used to estimate the distribution of RFS and OS.³⁴ Confidence interval estimation for the survival curves was determined by the cumulative hazard function with the use of the Greenwood formula for the standard error estimation. A Cox model was used to identify prognostic variables.³⁵ CIR and CID and their standard errors (SEs) were analyzed according to the method described by Gray³⁶ and included only patients attaining CR, with time calculated from the date

Table 2. Comparison of presenting clinical and laboratory findings
between patients with therapy-related (t-AML) and de novo AML

Characteristic	t-AML	de novo AML	Р
Patients, no. (%)	200 (7.0)	2653 (93.0)	
Sex, male/female, no. (%)	64 (32)/136 (68)	1409 (53)/1244 (47)	< .0001
Median age, y (range)	57.8 (18.6-79.4)	53.2 (16.2-85.0)	< .0001
WBC, × 10 ⁹ /L			.003
Median	7.4	12.5	
Range	0.4-258	0.1-527	
Missing	51	58	
Hemoglobin, g/dL			.04
Median	9.4	9.1	
Range	4.2-13.7	2.5-20.6	
Missing	1	60	
Platelet count, × 10 ⁹ /L			.02
Median	50.5	55	
Range	2-595	4-933	
Missing	2	60	
PB blasts, %			.002
Median	22	35	
Range	0-100	0-100	
Missing	20	244	
BM blasts, %			.03
Median	65	75	
Range	2-100	0-100	
Missing	17	246	
LDH value, U/L			.09
Median	372	413	
Range	90-15 098	40-7627	
Missing	8	108	

Percentages may not add to 100 because of rounding.

AML indicates acute myeloid leukemia; BM, bone marrow; LDH, serum lactate dehydrogenase; PB, peripheral blood; and WBC, white blood count.

Table	3. C	comparison o	of cytogenet	ic and mole	cular geneti	c abnorma	lities betwee	en patients w	ith therapy-	related (t-AML) and de novo	AML
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	t-A	t-AML		AML	
Genetic group	No.	%	No.	%	Р
Abnormal	136	75	1207	51	< .0001
Normal	46	25	1174	49	< .0001
Missing	18		272		
Risk category*					
Favorable	28	15	369	16	> .999
Intermediate	83	46	1552	65	< .0001
Adverse	71	39	460	19	< .0001
Cytogenetic abnormalities					
t(15;17)	4	2	99	4	.24
t(8;21)	9	5	128	5	> .999
inv(16) or t(16;16)	15	8	142	6	.20
t(9;11)	20	11	35	1	< .0001
t(v;11)(v;q23)	8	4	52	2	.07
t(6;9)	0	-	19	1	.39
inv(3) or t(3;3)	2	1	39	2	> .999
-5 or 5q-	26	14	187	8	.005
-7	20	11	134	6	.008
7q-	18	10	96	4	.001
abnl(17p)	25	14	117	5	< .0001
trisomy 8†	3	2	109	5	.06
Complex karyotype*	47	26	273	11	< .0001
Monosomal karyotype‡	43	24	246	10	< .0001
Molecular genetic abnormalities					
NPM1 mutation	24	16	654	30	< .0001
Missing	47		467		
FLT3-ITD	17	12	521	24	.0005
Missing	53		444		
FLT3-TKD mutation	12	9	158	8	.62
Missing	69		638		

Percentages may not add to 100 because of rounding.

AML indicates acute myeloid leukemia; ITD, internal tandem duplication; and TKD, tyrosine kinase domain.

*According to Döhner et al.²⁸

†Outside a complex karyotype.

‡According to Breems et al.40

of CR to the occurrence of an event (relapse or death). Prognostic Cox regression models were used for the end points of relapse and death in CR as well as for OS. All models included a variable accounting for different treatment intensities in younger (age 18-60 years) versus older patients (age > 60 years). In all multivariable models no variable selection was performed, and full models were presented. We estimated missing data for covariates by using 50 multiple imputations in chained equations incorporating predictive mean matching.³⁷ There was no difference in clinical outcome (CR, CIR, CID, and OS) between patients with missing data and those with complete datasets (P = .13, P = .12, P = .17, and P = .51, respectively). All statistical analyses were performed with the statistical software environment R Version 2.10.1, by use of the R packages rms Version 2.1-0, and cmprsk Version 2.2-0.³⁸

Results

Patient cohort

In total, 3177 adult AML patients (median age, 54.5 years) were enrolled on 6 prospective treatment trials. In 3026 (95.2%) patients information on type of AML was available: 200 t-AML, 2653 de novo AML, and 173 AML with a history of a myelodysplastic syndrome (MDS) or myeloproliferative neoplasm at least 3 months before diagnosis of AML.³⁹ The subgroup of de novo AML patients included 77 patients with a history of a neoplasm but without previous chemotherapy or radiation. Patients with missing data on type of AML and patients with a history of MDS/myeloproliferative neoplasm without chemotherapy were excluded from this study.

Presenting clinical, cytogenetic, and molecular genetic features

Compared with patients with de novo AML, patients with t-AML were older (57.8 vs 53.2 years; P < .0001), and women were more frequently affected than men (P < .0001), mainly because of the high frequency of t-AML after treatment of breast cancer. t-AML was associated with lower median white blood counts (P = .003), lower platelet counts (P = .02), greater hemoglobin levels (P = .04), and lower percentages of blasts in peripheral blood (P = .002) and bone marrow (P = .03; Table 2).

Compared with de novo AML, t-AML more frequently had abnormal karyotypes (75% vs 51%, P < .0001; Table 3, Figure 1). The distribution among cytogenetic risk categories differed significantly between t-AML and de novo AML. Whereas there was no difference in the frequency of favorable-risk abnormalities, t-AML was underrepresented in intermediate-risk cases but more frequently exhibited adverse-risk karyotypes. t-AML more frequently had -5 or 5q-(P = .005), -7 (P = .008), 7q-(P = .001), t(9;11) (P = .0001), t(v;11)(v;q23) (P = .07, in trend), abnl(17p)(P < .0001), complex karyotypes (P < .0001), and monosomal karyotypes (P < .0001; defined according to Breems et al⁴⁰); in contrast, t-AML less frequently had normal karyotype (P < .0001), and in trend (P = .06) trisomy 8 within a noncomplex karyotype (Table 3). Figure 2 shows the comparison of t-AML and de novo AML patients exhibiting at least one cytogenetic abnormality, with the exclusion of the WHO category "AML with recurrent genetic



51% 33% 42% 15% +8 abnl(12p) 18% abnl(17p) 32% abnl(20q) 13%



Figure 2. Frequency and distribution of cytogenetic abnormalities in patients exhibiting at least one abnormality. Excluding the WHO category "AML with recurrent genetic abnormalities" (A, t-AML n = 78, B, de novo AML, n = 698; definition "complex" according to Döhner et al²⁸ and of "monosomal karyotype" according to Breems et al⁴⁰).

Table 4. Primary diseases in t-AML patients

Primary disease	No. of patients	%
Solid cancers	142	71
Cancers of females		
Breast	74	52
Cervix	4	3
Uterus	2	1
Ovary	1	1
Cancers affecting men		
Prostate	9	6
Testis	9	6
Cerebral cancers		
Glioma	3	2
Head and neck cancers		
Thyroid	12	8
Larynx	1	1
Hypopharynx	1	1
Vocal cord	1	1
Thoracic cancers		
Lung	2	1
Mediastinal	2	1
Abdominal cancers		
Gastrointestinal	10	7
Kidney	3	2
Bladder	1	1
Skin cancers		
Melanoma	4	3
Others	1	1
Bone cancers		
Ewing sarcoma	1	1
Soft-tissue tumors		
Histiocytoma	1	1
Hematologic malignancies	55	27.5
NHL	25	46
Hodgkin lymphoma	20	36
MDS*	6	11
ALL	2	4
AML†	1	1.5
MPN	1	1.5
Autoimmune diseases	3	1.5
Multiple sclerosis	2	67
Rheumatologic	1	33

ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; and NHL, non-Hodgkin lymphoma.

*MDS treated with decitabine, cyclophosphamid, azacitidine, or chemotherapy (unspecified).

†t-AML after 9 years of treatment of de novo AML.

abnormalities."¹ Trisomy 8 in t-AML was frequently associated with a complex karyotype, whereas in de novo AML, trisomy 8 was the most frequent abnormality within a noncomplex karyotype. Regarding molecular aberrations, both *NPM1* mutations and *FLT3*-ITD were significantly less frequent in t-AML (P < .0001 and P = .0005, respectively; Table 3).

Primary diseases, previous therapy, and latency period to the occurrence of t-AML

The median latency period between diagnosis of primary malignancy and the occurrence of t-AML was 4.04 years (range, 0.33-44.14 years). One hundred forty-two (71%) patients with t-AML had a previous solid cancer (Table 4). Breast cancer was the most common neoplasm (n = 74; 52%), followed by thyroid (n = 12; 8%; all patients had received radioiodine therapy), gastrointestinal (n = 10 patients; 7%), prostate (n = 9; 6%), and testicular cancer (n = 9, 6%). Twenty-eight of 142 (20%) patients had various other neoplasms. Fifty-two (27.5%) patients had a primary hematologic malignancy, with non-Hodgkin lymphoma (n = 25; 46%) and Hodgkin lymphoma (n = 20; 36%) being the most common ones. A total of 10 of the 55 (18%) patients had various other hematologic malignancies (Table 4). Three patients had undergone cytotoxic therapy for the treatment of an autoimmune disease, 2 with multiple sclerosis and 1 with a rheumatologic disorder (Table 4).

In 180 (90%) of the 200 t-AML patients, the treatment records were complete with respect to the treatment modality of primary disease; detailed information on type of chemotherapeutic agents and dosages were available in 148 (74%) of the 200 patients. Sixty-nine patients had previous chemotherapy only, 56 radiation only, and 55 patients had both chemotherapy and radiation. Only 7 patients received single-agent chemotherapy.

Chemotherapeutic agents were classified by mechanism of action (Table 1). In a multivariable log-normalized linear regression model, younger age at diagnosis of primary malignancy (P = .006) as well as administration of intercalating agents (P = .01) and topoisomerase II inhibitors (P = .009) were associated with a shorter latency period between diagnosis of primary malignancy and the occurrence of t-AML. In addition, we were interested in the association of latency period and subsequent cytogenetic abnormality categorized into (1) t(15;17); (2) t(8;21); (3) inv(16) or t(16;16); (4) t(9;11); (5) t(v;11)(v;q23); (6) -7; (7) 7q-; (8) -5 or 5q-; (9) abnl(17p); (10) complex karyotype \geq 3 abnormalities, and (11) monosomal karyotype. The log-normalized linear regression model revealed that t(9;11) (P = .0006, median, 1.9 years) was associated with a shorter and -5 or 5q- (P = .009; median, 9.3 years) with a prolonged latency period.

To identify an association between different chemotherapeutic agents and induction of specific cytogenetic abnormalities, we performed a multinomial regression analysis in which the outcome variable was categorized as follows: (1) t(15;17); (2) t(8;21); inv(16) or t(16;16); (3) t(9;11) or t(v;11)(v;q23); (4) *NPMI*; (5) normal karyotype excluding *NPMI*; (6) -5 or 5q-; -7; 7q-; abnl(17p); and (7) all other abnormalities. This model revealed that treatment with intercalating agents was significantly associated with the induction of cytogenetic abnormalities (P = .01), particularly t(9;11) or t(v;11)(v;q23) (P = .02), and the group all other abnormalities (P = .05).

Latency period and cytogenetic abnormalities in patients with de novo AML and previous malignancy without chemotherapy or radiation

Seventy-seven (3%) of the 2653 de novo AML patients had a history of previous neoplasm who did not receive chemotherapy and/or radiation. These patients were significantly older compared with all other patients with de novo AML (60 vs 53 years; P < .0001). All patients had previous solid cancer, commonly prostate cancer (n = 18, 23%), breast cancer (n = 8, 10%), gastro-intestinal cancer (n = 8, 10%), as well as bladder cancer, renal cell carcinoma, and malignant melanoma (n = 7 each, 9%). The latency period to the occurrence of AML was 5.0 years (range, 1 day to 43.9 years). The cytogenetic profile of these cases showed in trend a greater frequency of adverse-risk abnormalities (19/67 [28%] vs 441/2314 [19%]; P = .06), in particular -5 or 5q- abnormalities (10/67 [15%] vs 177/2314 [8%], P = .04). OS of these patients was comparable with that of de novo AML patients (hazard ratio 1.04; P = .87).



Figure 3. Kaplan-Meier estimates. OS (A) and RFS (B) comparing t-AML with de novo AML

Response to induction therapy

Response to induction therapy for t-AML and de novo AML was as follows: CR 63% and 67% (P = .21), refractory disease 25% and 22% (P = .38), and early/hypoplastic death 12% and 9% (P = .20), respectively. In univariate as well as in multivariable analysis, type of AML did not impact the achievement of CR (P = .13, P = .62, respectively).

Survival analysis

The median follow-up for survival in the entire cohort was 4.12 years (95% confidence interval [95%-CI] 3.97-4.28); the estimated 4-year RFS and OS were 38.5% (95%-CI 36.3%-40.9%) and 37.1% (95%-CI 35.2%-39.1%), respectively.

Outcome of patients with t-AML was significantly inferior: the 4-year RFS rates were 24.5% (95%-CI 17.7%-33.9%) and 39.5% (95%-CI 37.2%-42.0%; age-stratified log-rank test P < .0001) and the 4-year OS rates were 25.5% (95%-CI 19.6%-33.1%) and 37.9% (95%-CI 36.0%-40.0%; age-stratified log-rank test P = .001) for t-AML and de novo AML patients, respectively (Figure 3). Both greater CIR (age-stratified test, P = .01) and CID (age-stratified test, P = .002) contributed to the inferior outcome of t-AML patients. In t-AML patients previous therapy (radiation, chemotherapy, or both treatment modalities) and latency period had no impact on outcome.

Allogeneic hematopoietic stem cell transplantation (HSCT) in first CR was performed in 487 of 2064 (24%) patients \leq 60 years and in 30 of 789 (4%) patients > 60 years of age. There was a significant greater proportion of younger patients receiving an allogeneic HSCT in first CR 40/89 (45%) in t-AML compared with de novo AML 410/1445 (28%; P = .002). Because dose intensity in postremission therapy and proportion of patients receiving allogeneic HSCT differed markedly between trials for patients ≤ 60 years versus those > 60 years, we performed subset analyses in these 2 age cohorts. Of note, in patients ≤ 60 years there was no statistically significant difference in CIR between t-AML and de novo AML (4-year CIR, 45.1% vs 46.3%; P = .63), whereas a marked difference was found in CID (4-year CID, 22.9% vs 8.6%; P < .0001; Figure 4A). The significantly greater CID rates were present in this age cohort regardless of the type of postremission therapy but were pronounced in patients who received allogeneic HSCT (Figure 5A-B). The 4-year CID rates in younger patients with t-AML and de novo AML after intensive chemotherapy were 12.3% (SE 5.4%) and 5.3% (SE 0.7%) and after allogeneic HSCT 35.8% (SE 8.3%) and 17.2% (SE 2.0%), respectively. Again no difference was present in CIR (Figure 5C-D). The distribution of causes of deaths in CR was comparable between t-AML and de novo AML and deaths mainly were caused by infections. The



Figure 4. Influence of type of acute myeloid leukemia. CIR and CID in patients 60 years and younger (A) as well as in patients older than 60 years (B).





4-year OS rates in patients, receiving allogeneic HSCT or other intensive consolidation therapy in first CR were 42.6% (95%-CI 29.0%-62.7%) and 37.5% (95%-CI 25.2%-55.8%) for t-AML as well as 58.0% (95%-CI 53.0%-63.6%) and 56.6% (95%-CI 53.5%-59.9%) for de novo AML, respectively. In contrast, t-AML patients > 60 years showed a significantly greater CIR (P < .0001), whereas there was no difference in CID (P = .44; Figure 4B).

Multivariable cause-specific Cox regression analyses on relapse and death in CR showed again a significant adverse impact of t-AML in younger patients for death in CR (P < .0001) but not for relapse (P = .39), whereas the contrary was the case in older patients with a significant adverse impact of t-AML on relapse (P = .02), but not on death in CR (P = .22). The Cox regression model on OS revealed t-AML as a poor prognostic factor in younger intensively treated patients (P = .01), but not in older less intensively treated patients (P = .34; Table 5).

Furthermore, we were interested in the effect of t-AML in specific genetically defined subsets: t(15;17); t(8;21); inv(16) or t(16;16); t(9;11); *NPM1*. In multivariable models adjusted for WBC, in patients exhibiting an inv(16) or t(16;16) t-AML was a significant adverse prognostic factor for OS (hazard ratio 2.35; P = .04).

Discussion

Therapy-related AML is increasing in prevalence with greater life expectancy and improved survival of patients treated with chemotherapy and/or radiation for previous malignancies and other

Table 5. Multivariable ana	yses of relapse,	death in complet	te remission, and	overall survival
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	Relapse		Death in CR		os	
	HR	Р	HR	Р	HR	Р
t-AML						
intensively treated (age 16-60 y)	1.16	.39	2.74	< .0001	1.35	.01
less intensively treated (age $>$ 60 y)	2.13	.02	1.23	.22	1.14	.34
Age (difference of 10 y)	1.11	.003	1.34	.0001	1.34	< .000
Male sex	1.03	.62	1.23	.18	1.10	.06
Cytogenetic favorable-risk*	0.59	< .0001	0.38	< .0001	0.50	< .000
Cytogenetic adverse-risk*	1.55	< .0001	1.49	.07	2.07	< .000
NPM1 mutation	0.69	< .0001	0.67	.04	0.78	< .000
FLT3-ITD	1.42	< .0001	1.61	.01	1.51	< .000
Logarithm of WBC	1.14	< .0001	1.01	.82	1.09	< .000
Logarithm of platelets	0.99	.80	0.93	.37	0.94	.02
BM blasts (difference of 10%)	1.00	.11	1.00	.78	1.00	.51
PB blasts (difference of 10%)	1.00	.17	1.01	.54	1.02	.04

BM indicates bone marrow; CR, complete remission; HR, hazard ratio; ITD, internal tandem duplication; OS, overall survival; PB, peripheral blood; and WBC, white blood count. *According to Döhner et al²⁸; models were stratified for the 6 different treatment trials.

Table 6. Distribution of molecular abnormalities in patients with therapy-related (t-AML) and de novo AML exhibiting a normal karyotype

	t-AML, n (%)	de novo AML, n (%)	Р
NPM1 mutation	16/40(40)	537/1067(50)	.26
FLT3-ITD	10/39(26)	348/1054(33)	.39
CEBPA mutation	2/29 (7)	98/894(11)	.76
FLT3-TKD mutation	3/33 (9)	87/982 (9)	> .999
MLL-PTD	2/27 (7)	57/848 (7)	.70

AML indicates acute myeloid leukemia; ITD, internal tandem duplication; PTD, partial tandem duplication; and TKD, tyrosine kinase domain.

disorders. However, there is a paucity of prospective treatment data because these patients have often been excluded from clinical trials. The frequency of t-AML in our large cohort was 7%, which is comparable with previously reported data.^{4,5}

Consistent with previous studies, 5,6,13 patients with t-AML more frequently had abnormal karyotypes compared with de novo AML (75% vs 51%); in particular, there was a high prevalence of adverse-risk cytogenetics. Among specific abnormalities, t(9;11), -5 or 5q-, -7, 7q-, abnl(17p), complex karyotypes, and the recently described monosomal karyotype category⁴⁰ were significantly overrepresented among t-AML (Table 3; Figures 1-2). For a large proportion of our cases, data on the mutational status of the NPM1 and FLT3 genes were available. Of note, the frequency of both NPM1 mutations and FLT3-ITD was significantly lower in t-AML, indicating that t-AML leukemogenesis in most cases follows mechanisms different from those seen in de novo AML. However, when we focused on patients with cytogenetically normal AML, no difference in the incidence and distribution of mutated NPM1 and FLT3-ITD between t-AML and de novo AML was evident (Table 6), which is consistent with previous reports.^{7,41}

The median latency period between diagnosis of primary malignancy and occurrence of t-AML was 4 years, which is in line with published data.⁴⁻⁶ Beyond the known association between treatment with anthracyclines, as the major compound of intercalating agents (Table 1), or the application of topoisomerase II inhibitors and a short latency period for the development of t-AML, we were able to show that younger age at diagnosis of primary malignancy also was associated with a shorter latency period. With respect to molecular markers, we did not detect an association of previous radiation to *FLT3* mutations, which is in contrast to data from Christiansen et al.⁴²

To evaluate whether the inferior prognosis of t-AML was attributable to an unfavorable genetic profile, or whether the variable "t-AML" itself predicted an inferior outcome, we performed multivariable analyses on the clinical end points response to induction therapy, RFS and OS. In these analyses, t-AML proved to be an adverse prognostic factor for RFS and OS but not for response to induction therapy. Of note, t-AML patients \leq 60 years had a greater CID regardless of the applied therapy, whereas CIR was not different compared with de novo AML patients, likely reflecting cumulative toxicity of primary and secondary cancer therapy.^{43,44} The 4-year transplant-related mortality of 38.5% in our study compares even favorably to the 48% mortality rate at 5 years

reported by the Center for International Bone Marrow Transplant Research.⁴⁴

Intriguingly, results after induction therapy were not different between t-AML and de novo AML patients, pointing to the fact that dosage and modality of treatment during postremission therapy had a marked impact on the cumulative toxicity of cancer therapy. Therefore, intensive induction therapy should not be withheld for t-AML patients, and dose-reduced regimes for allogeneic HSCT should be considered.

In contrast, t-AML patients > 60 years showed a significantly greater CIR and no difference in CID. One reason for the greater CIR in older AML patients might be the lower dosage of applied chemotherapy during postremission therapy compared with younger patients.

In summary, our results add to previous knowledge that t-AML proves to be an adverse prognostic factor for RFS and OS, independent of other clinical and biologic variables. The inferior outcome, especially in intensively treated younger adult patients, was mainly attributable to an increased risk of death in CR, possibly reflecting cumulative toxicity of cancer treatment.

Acknowledgments

We are grateful to all members of the German-Austrian AML Study Group (AMLSG) for providing leukemia specimens and clinical data.

This work was supported in part by grants 01GI9981 (Network of Competence Acute and Chronic Leukemias) and 01KG0605 (IPD-Meta-Analysis: A model-based hierarchical prognostic system for adult patients with acute myeloid leukemia [AML]) from the Bundesministerium für Bildung und Forschung (BMBF), Germany.

Authorship

Contribution: S.K. collected data, designed research, analyzed and interpreted data, and wrote the paper; K.D., J.K., C.-H.K., H.A.H., G.H., M.v.L.T., S.W., A.K., K.G., M.R., D.N., and A.G. provided study materials or patients and collected data; B.S., G.G., D.S., and C.M. collected data; M.Z. analyzed and interpreted data; H.D. and R.F.S. provided study materials or patients, collected data, designed research, analyzed and interpreted data, and wrote the paper; and all authors approved the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

A list of AMLSG institutions and investigators participating in this study appears in the supplemental Appendix (available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

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