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Outcome of patients with therapy-related acute myeloid leukemia with or without an antecedent history of myelodysplasia

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Abstract

We reviewed 301 patients with newly diagnosed therapy-related acute myeloid leukemia (t-AML) who presented from January 2000 to January 2014 (183, t-AML without antecedent hematologic disorders [AHD]; 118, t-AML with AHD). Overall, median follow-up was 44 months. The primary malignancy was non-Hodgkin lymphoma in 92 (31%); breast cancer in 80 (27%); and prostate cancer in 49 (16%). Median relapse-free survival (RFS) in t-AML without or with AHD was 10 months, and 29 months, respectively (p=0.032): median overall survival (OS) was 8 months, and 8 months, respectively (p=0.53). Multivariate analysis for OS identified older age, poor performance status, thrombocytopenia, non-favorable cytogenetics, and lack of response as adverse factors. The favorable risk cohort had better RFS and OS as compared to the outcomes of patients in the intermediate and adverse risk cohorts; the RFS and OS did not differ between intermediate and adverse cohorts. The presence of AHD did not affect OS.

Keywords

therapy-related acute myeloid leukemia; antecedent myelodysplastic syndrome; relapse-free survival; overall survival

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Authorship contributions

K.S. collected data, designed the study, analyzed the data, and wrote the manuscript. E.J. designed the study, and treated the patients. J.C., G.G.M., G.B., P.J., N.D., S.O., and H.K. treated the patients. S.P. managed the data. F.R. designed the study, and wrote the manuscript. All authors provided significant intellectual input, and reviewed and approved the final version of the manuscript.

Conflicts of interests

E.J. received consultancy for Ariad, BMS, and Pfizer, and research grants from Ariad, BMS, TEVA, and Pfizer. J.C. received research support from Ariad, BMS, Novartis, Pfizer, and Teva, and is a consultant for Ariad, BMS, Novartis and Pfizer. N.D. received research funding from BMS, Novartis, Sunesis, Incyte, and Bioline. H.K. received research grants from Novartis, BMS, Pfizer, and Ariad. Other authors have nothing to disclose. F.R. received research funding from Novartis and BMS.

INTRODUCTION

Therapy-related myeloid neoplasms (t-MN) are well-recognized hematopoietic stem cell malignant neoplasms caused by mutational events provoked by previous exposure to cytotoxic therapy and/or radiation therapy for solid tumors or other hematologic malignancies.[1–4] The incidence of t-MN in patients with previous exposure to cytotoxic agents varies owing to different types of primary cancer, cytotoxic agents, and timing of exposure.[5] Recent reports suggest that t-MN accounts for 5% to 20% of patients with newly diagnosed myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML).[6, 7] Cytotoxic agents implicated in the development of t-MN include alkylating agents (e.g., melphalan, cyclophosphamide, busulfan, carboplatin, and dacarbazine); topoisomerase II inhibitors (e.g., etoposide, doxorubicin, epirubicin, and mitoxantrone); and antimetabolites or antitubulin agents in combination with other cytotoxic agents including alkylating agents, and topoisomerase II inhibitors.[6, 8–11] Compared with patients with de novo MDS/AML, t-MN are more frequently associated with an adverse karyotype, and resistance to conventional cytotoxic therapies.[9, 12, 13] Indeed, patients with t-MN have worse relapse-free survival (RFS) and overall survival (OS) than do those with de novo MDS/AML.[8, 14] The presence of dysplasia at diagnosis of de novo AML does not impact on outcomes when cytogenetic risk is taking into account.[15, 16] However, whether history of an AHD is associated with additional risk in patients with t-AML has not been examined.

The available data on the outcome of patients with t-AML is limited. Patients with therapy-related acute promyelocytic leukemia (t-APL) respond as well as those with de novo APL to all-trans retinoic acid plus chemotherapy, and outcomes of t-APL seem similar to those of de novo APL.[17, 18] On the other hand, patients with therapy-related core-biding factor AML (CBF AML) have worse outcomes than do those with de novo CBF AML.[19] However, data on the differences between the clinical outcomes of patients with t-AML and various cytogenetic abnormalities is limited.

The objective of our study was to evaluate whether t-AML was preceded with prior diagnosed AHD (typically MDS) had an impact on the outcome, and to evaluate the significance of cytogenetic risk on outcome as related to the prior cytotoxic or radiation exposure.

METHODS

Patients

We reviewed records of patients with newly diagnosed AML who presented to our tertiary care center between January 2000 and January 2014. We included all the patients with newly diagnosed AML with available cytogenetic test results at diagnosis, and excluded patients with APL from this study. Patients with de novo AML were excluded, and patients with t-AML with or without AHD were the main focus in this study. AML was defined as the presence of at least 20% blasts in the peripheral blood or bone marrow according to World Health Organization 2008 criteria.[20] T-AML was defined as the diagnosis of AML with a

history of previous cytotoxic chemotherapy or radiation therapy. Patients with prior history of surgery for solid malignancy were not included in this study.

Prior cytotoxic agents were classified by the mechanism of action; this classification was modified according to Smith et al.[12] All the patients received age-adjusted induction chemotherapy, which included idarubicin plus high-dose cytarabine, clofarabine plus low-dose cytarabine, decitabine, azacitidine, sapacitabine, cladribine plus cytarabine, fludarabine plus cytarabine twice daily, and fludarabine plus high-dose cytarabine with growth factor; all patients also received subsequent consolidation chemotherapy after confirmation of complete response (CR). Patients less than 60 years of age with adequate organ function and performance status less than 2 received cytarabine-based induction chemotherapy; patients older than 60 years or patients less than 60 years with other significant medical comorbidities received hypomethylating agent-based regimen or low-intensity chemotherapy. Patients with adequate organ functions and performance status less than 2 were eligible for investigational agents regardless of age. Medically eligible patients were referred for the consideration of allogeneic stem cell transplantation (ASCT) when patients achieved response. All the patients gave informed consent as approved by institutional review board according to the Declaration of Helsinki for participation in various clinical trials.

Cytogenetic and molecular analysis

Chromosomal abnormalities at the time of AML diagnosis were reviewed; chromosome G-banding was performed using standard techniques, and patients' karyotypes were described according to the International System for Human Cytogenetic Nomenclature.[21] We followed the criteria recommended by the European LeukemiaNet to classify patients into favorable, intermediate, and unfavorable risk groups.[22] Monosomal karyotype was as previously characterized, i.e. two or more distinct autosomal chromosome monosomies or one single autosomal monosomy in addition to structural abnormalities.[23] To detect internal tandem duplications (ITD) and D835 point mutations in the *FLT3* gene, *FLT3* analysis was performed with a multiplex polymerase chain reaction (PCR) and the restriction digestion method, followed by capillary electrophoresis. PCR-based DNA sequencing was performed to examine codon 11 of the *NPM1* oncogene.

Statistical analysis

Response criteria, complete remission, OS duration, RFS duration, cumulative incidence of relapse, and cumulative incidence of death in patients with complete remission were defined according to the revised International Working Group criteria.[24] We defined RFS as the time from achieving complete remission to relapse or death. The Kaplan-Meier method was utilized to develop survival curves, and the log-rank test was used for survival analysis by cytogenetic risk factors.[25] We used a Cox model to identify prognostic variables for univariate and multivariate analysis.[26] Cox proportional hazards model with time-dependent covariates was used to assess the impact of allogeneic stem cell transplantation. All statistical analyses were performed with SPSS statistical software (version 22). *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient characteristics

Of the 1677 patients with newly diagnosed AML during the study period, 301 (18%) had t-AML (183 without AHD; 118 with AHD), and 1268 (76%) had AML with no prior cytotoxic or radiation therapy (including 842 with de novo AML and 426 with non t-AML but with AHD). 108 (6%) were excluded due to unavailable karyotype at diagnosis (insufficient metaphases for analysis). Baseline patient characteristics of 301 patients with t-AML with and without AHD are described in Table I. Overall, the median follow-up was 44 months (range, 0.2–130.6 months). The median follow-up in patients with t-AML without AHD was 38 months compared to 62 months in those with t-AML with AHD (p=0.894). Median age at diagnosis of t-AML without AHD was 63 years compared to 69 years in t-AML with AHD (p <0.001). Male gender was less common in t-AML without AHD compared to t-AML with AHD (42% in t-AML without AHD; 66% in t-AML with AHD; p <0.001). Overall, median latency from previous exposure to either chemotherapy or radiation therapy was 76 months (range, 6.0–502.0 months). The median latency in t-AML without AHD was 74 months compared to 77 months in t-AML with AHD (p=0.512).

Primary type of cancer

The original diagnoses of primary cancer in the 301 patients with t-AML are described in Table II. Common types of primary cancer were non-Hodgkin lymphoma in 92 (31%); breast cancer in 80 (27%); and prostate cancer in 49 (16%).

Of these 183 patients with t-AML without AHD, 61 (33%) had a history of non-Hodgkin lymphoma (NHL); 61 (33%) had breast cancer; 11 (6%) had sarcoma; 9 (5%) had colon cancer; 8 (4%) had prostate cancer; and 25 (14%) had other malignancies. Of 118 patients with t-AML with AHD, 41 (35%) had prostate cancer; 31 (26%) had NHL; 19 (16%) had breast cancer; 7 (6%) had Hodgkin lymphoma; 5 (4%) had head and neck cancer; 15 (13%) had other malignancies. The percentages of patients with breast cancer and prostate cancer were significantly different between the t-AML without AHD and the t-AML with AHD cohort (p=0.001; p <0.001).

Of 183 patients with t-AML without AHD, 27 (15%) had a second primary cancer before the diagnosis of t-AML; NHL in 9 (5%); breast cancer in 5 (3%); sarcoma in 3 (2%); thyroid cancer, colon cancer, and non-melanoma skin cancer in 2 each (1%); esophageal cancer, melanoma, prostate cancer, renal cell carcinoma in 1 each (1%). Of 118 patients with t-AML with AHD, 13 (11%) had a second primary cancer before the diagnosis of t-AML; 4 (3%), prostate cancer; 2 (2%), NHL; 1 each (1%), thyroid cancer, sarcoma, renal cell carcinoma, lung cancer, colon, breast, and essential thrombocytosis.

Prior exposure to cytotoxic agents, radiation, and stem cell transplantation

Prior exposure to cytotoxic agents, radiation, and autologous stem cell transplantation are described in Table III. Overall, 240 (80%) patients received cytotoxic agents before the diagnosis of t-AML including alkylating agents in 160 (66%) and topoisomerase inhibitors in 46 (19%). 180 (60%) patients received radiation therapy previously, and 20 (7%)

underwent stem cell transplantation. The percentage of prior cytotoxic exposure was significantly higher in the t-AML without AHD cohort compared to the t-AML with AHD cohort (p<0.001).

Of the 183 patients with t-AML without AHD, 178 (97%) were previously treated with alkylating agents, including cyclophosphamide (97 patients, 55%), ifosfamide (28 patients, 16%), and cisplatin (36 patients, 20%). Thirty-five patients (20%) were previously treated with topoisomerase inhibitors. One hundred nine patients (60%) were previously treated with radiation therapy. Sixteen (9%) had received stem cell transplant: 14 patients with lymphoma (2 had Hodgkin lymphoma; 12 had NHL) had undergone autologous stem cell transplant, and 2 patients with ovarian cancer had undergone autologous stem cell transplant.

Of 118 patients with t-AML with AHD, 39 (53%) were previously treated with alkylating agents, including cyclophosphamide (27 patients, 43%), ifosfamide (5 patients, 8%), and cisplatin 5 patients, 8%). Eleven (18%) were previously treated with topoisomerase inhibitors. Seventy one (60%) patients were previously treated with radiation therapy. Four (3%) had received autologous stem cell transplant: 2, Hodgkin lymphoma; 1, NHL; 1, multiple myeloma.

Cytogenetic and molecular abnormalities

Cytogenetic and molecular abnormalities at diagnosis of t-AML are described in Table IV. Overall, a favorable cytogenetic abnormality was observed in 22 (7%); intermediate, 118 (39%); and adverse, 161 (54%). Favorable cytogenetic risk included t(8;21) in 9 (3%), and inv(16) in 13 (4%); intermediate risk, normal karyotype in 58 (19%), and t(9;11) in 19 (6%); adverse risk, complex in 125 (42%), and monosomal karyotype in 100 (33%). FLT3-ITD and NPM mutations were detected in 31 (12%), and 17 (12%), respectively. T(9;11) was more commonly seen in the t-AML without AHD cohort 16 (9%) than t-AML with AHD, 3 (3%); p=0.031. Normal karyotype was more common in the t-AML with AHD; 28 (15%) in t-AML without AHD, and 30 (25%) in t-AML with AHD; p=0.030. Of 231 patients tested for *RAS* mutations (t-AML with AHD, 92; t-AML without AHD, 139), 25 patients (11%) were found to have *RAS* mutations at diagnosis (t-AML with AHD, 7; t-AML without AHD, 18) (p=0.201); of 70 patients tested for *JAK2* mutation (t-AML with AHD, 35; t-AML without AHD, 35), 8 patients (11%) were found to have *JAK2* mutations at diagnosis (t-AML with AHD, 5; t-AML without AHD, 3) (p=0.452).

Response and survival

Type of induction therapy, response, and RFS and OS are described in Table V. Overall, 121 (40%), 91 (30%), 56 (17%), and 33 (11%) received cytarabine-based, hypomethylating agent (HMA)-based induction therapy, low intensity therapy, and investigational agents, respectively. Of 301 patients with t-AML, 126 (42%), and 33 (11%) achieved CR, and CR with incomplete platelet recovery (CRp), respectively. Thirty-two (11%) patients underwent ASCT. The type of induction therapy was different between cohorts (p<0.001): cytarabine-based, 89 (49%) in the t-AML without AHD cohort, and 32 (27%) in the t-AML with AHD cohort; HMA-based, 41 (22%) in t-AML without AHD, and 50 (42%) in the t-AML with AHD cohort. A higher CR rate was seen in the t-AML without AHD cohort compared to the

t-AML with AHD cohort (p=0.047). Median RFS was 9.7 months, and 29.1 months in the t-AML without AHD, and t-AML with AHD cohort, respectively (p=0.032) (Figure 1); median OS was 7.5 months, and 8.3 months in t-AML without AHD, and t-AML with AHD, respectively (p=0.525) (Figure 2).

Patients with favorable cytogenetic risk had a significantly longer median RFS compared to patients with intermediate and adverse cytogenetic risk (p=0.001; p<0.001) (Figure 3a). Patients with t-AML with intermediate risk had similar median RFS compared to those with adverse risk (intermediate, 12.0 months; adverse, 7.8 months; p=0.496). Median OS in the favorable risk cohort was significantly longer compared to the intermediate and adverse risk cohort (p=0.001; p<0.001) (Figure 4a). Patients with t-AML with intermediate risk had longer median OS compared to those with adverse risk (intermediate, 9.6 months; adverse, 7.7 months; p=0.020).

By European LeukemiaNet risk classification, the favorable risk cohort consistently had longer median RFS and OS (median RFS, not reached; median OS, 58.8 months) compared to the intermediate (median RFS, 12.0 months; median OS, 9.6 months) (p<0.001; p=0.001), and adverse cytogenetic risk cohort (median RFS, 6.2 months; median OS, 7.8 months) (p<0.001; p< 0.001) (Figure 3b; Figure 4b). No significant differences in RFS were observed between the intermediate and adverse risk cohort (p=0.555). Median RFS was similar between the intermediate and adverse risk cohort, and median OS was slightly longer in the intermediate cohort (p=0.013).

Univariate and multivariate analysis for survival

Univariate and multivariate analyses for OS are described in Table VI. On multivariate analysis, age over 60 years (p<0.001; hazard ratio [HR], 2.238; 95% confidence interval [CI], 1.551–3.228), performance status ≥2 (p=0.010; HR, 1.569; 95% CI, 1.115–2.208), thrombocytopenia below $30 \times 10^3/\mu L$ (p<0.001; HR, 1.717; 95% CI, 1.303–2.263), non-favorable cytogenetic abnormalities (p=0.003; HR, 4.558; 95% CI, 1.650–12.589), and the absence of CRp or better (CRp or CR, p<0.001; HR, 2.840; 95% CI, 2.106–3.830: CR, p<0.001; HR, 1.923; 95% CI, 1.431–2.585) were factors that indicated a poor prognosis. There was a tendency for better OS with ASCT (p=0.171; HR, 0.625; 95% CI, 0.319–1.224). The presence of AHD did not result in worse OS by univariate analysis (p=0.525; HR, 0.918; 95% CI, 0.704–1.196).

DISCUSSION

We demonstrated that although overall survival of patients with t-AML without or with a preceding AHD are similar, RFS in patients with t-AML without AHD was shorter compared to those with t-AML with AHD. As regards to therapy, 22% of the t-AML without AHD cohort received HMA-based induction therapy compared to 42% of t-AML with AHD. Prior studies have demonstrated the benefit of azacitidine and decitabine in elderly patients with newly diagnosed AML not fit for intensive cytotoxic chemotherapy. Indeed, in the AZA-001 trial, the median OS in the azacitidine cohort was 24.5 months compared to 15.0 months in the conventional care group (HR, 0.58; 95% CI, 0.43–0.77; p=0.0001) in patients with high-risk myelodysplastic syndromes.[27] Similarly, in the AZA-AML-001 study, the

median OS was 24.5 months in the azacitidine arm compared to 16.0 months for the conventional care regimens (HR, 0.47; 95% CI, 0.28–0.79; p=0.005) in elderly patients with AML.[28] Furthermore, the DACO-016 study showed improved CR plus CRp rate of 17.8% in the decitabine arm versus 7.8% in the treatment of choice arm, and showed a trend for longer median OS with decitabine (median OS, 7.7 months; 95% CI, 6.2–9.2) compared to the treatment of choice (median OS, 5.0 months; 95% CI, 4.3–6.3) (p=0.108; HR, 0.85; 95% CI, 0.69–1.04). In our study, the higher rates of HMA-based therapy in the t-AML with AHD cohort may have contributed to the improved RFS rates compared to those seen in the t-AML without AHD cohort. However, the difference in the rates of HMA-based therapy did not translate to improved OS rates for the cohorts with and without AHD. The multivariate Cox proportional hazards analysis showed the survival benefit was limited to patients with response. Overall, the presence of AHD in the setting of t-AML did not lead to worse outcome (p=0.525; HR, 0.918; 95% CI, 0.704–1.196).

Cytogenetic risk classification used in de novo AML remains applicable in the setting of t-AML. Patients with favorable cytogenetics had significantly better survival compared to those with intermediate and adverse cytogenetics. However, the difference in OS between the intermediate and adverse cytogenetic risk was only by a median of 3.4 months (intermediate, 9.6 months; adverse, 6.2 months; p=0.013). Prior exposure to cytotoxic agents or radiation therapy leads to TP53 mutations which are associated with genetic instability leading to deletion 5q and/or complex karyotype in patients with t-MN.[29] Shih et al. reported 21% of patients with t-MN carried a TP53 mutation, which was the most common mutations in t-MN, and patients with a TP53 mutation or loss of the TP53 locus had a worse OS compared to those who had wild-type TP53 (8.8 months vs. 37.4 months; p=0.0035).[30] Patients with t-AML with normal karyotype may have had TP53 or other molecular mutations leading to a worse prognosis compared to the OS seen in de novo AML with a normal karyotype.

FLT3-ITD and NPM1 mutations were less frequently observed in patients with t-AML (FLT3-ITD, 12%; NPM1 mutations, 12%). These results are consistent with previous publications which have shown the incidence of FLT3-ITD and NPM1 mutations of 12%, and 16%, respectively in patients with t-AML.[8] In that study, the presence of NPM1 and FLT3-ITD mutations impacted the OS (NPM1; p<0.001; HR, 0.78: FLT3-ITD; p<0.001; HR, 1.51). However, in our study and given the relatively small numbers of patients who had NPM1 (17 patients) or FLT3-ITD mutations (31 patients), the presence of NPM1 or FLT3-ITD mutations did not have an impact on the outcomes.

There was a trend for better OS in patents who underwent ASCT (p=0.107; HR, 0.576; 95% CI, 0.294–1.127). Anderson et al. reported the successful treatment with ASCT showing a 5-year actuarial disease-free survival rate of 24.4%.[31] Given only 32 patients received ASCT in our study, early intervention with ASCT should be considered in patients with t-AML if feasible. There are several limitation to our study. First, patients with t-AML without AHD might have had an undiagnosed period of AHD before the diagnosis of t-AML. However, patients were regularly followed by an oncologist after the diagnosis of primary cancer. A common clinical presentation of t-MN is pancytopenia which would facilitate bone marrow study for definitive diagnosis given the patients had prior cytotoxic agent or radiation

exposure. Given the long latency period with median of 75.5 months, patients with t-AML without AHD had a relatively acute presentation of pancytopenia or related symptoms. Second, molecular abnormalities were not comprehensively tested in our study. The true clinical impact of molecular abnormalities remains unclear.

In conclusion, patients with t-AML have a poor prognosis, and the presence of AHD did not affect their survival. The European LeukemiaNet classification appears applicable to patients with t-AML although the intermediate risk cohort had only a slightly better outcome compared to that seen in the adverse risk cohort.

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Clinical practice points

The available data on the outcome of patients with therapy-related acute myeloid leukemia (t-AML) is limited. The common primary malignancies were non-Hodgkin lymphoma, breast cancer, and prostate cancer before the diagnosis of t-AML. The presence of antecedent hematologic disorders at diagnosis of t-AML did not affect overall survival. The European LeukemiaNet classification appears applicable to patients with t-AML although the intermediate risk cohort had only a slightly better outcome compared to that seen in the adverse risk cohort.

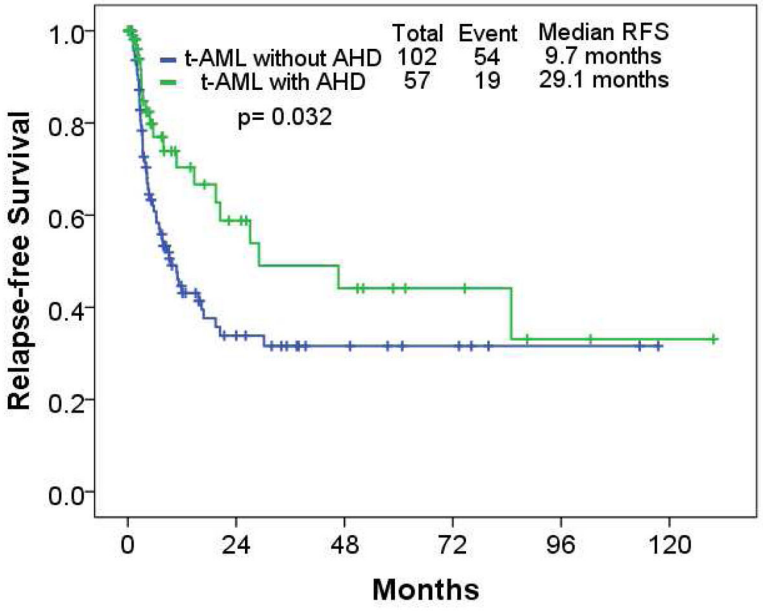

Figure 1.
Relapse-free survival in patients with therapy-related acute myeloid leukemia

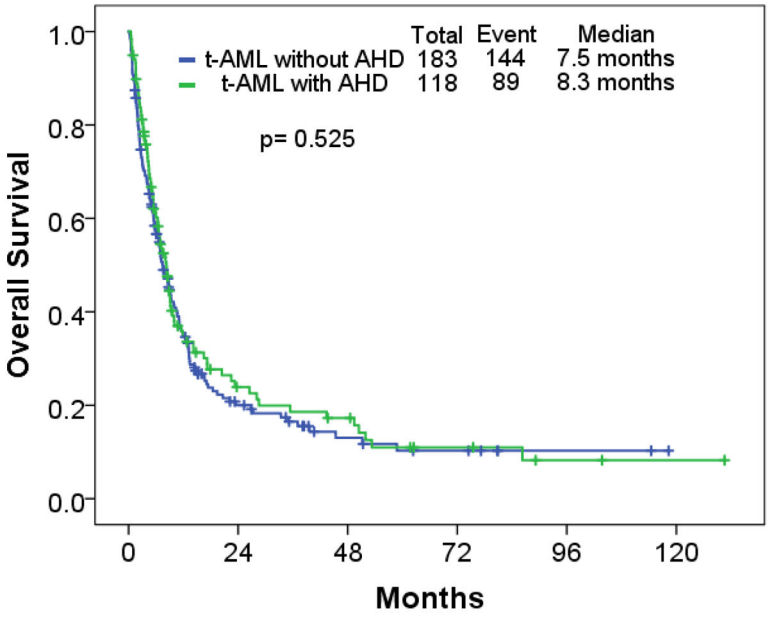

Figure 2.
Overall survival in patients with therapy-related acute myeloid leukemia

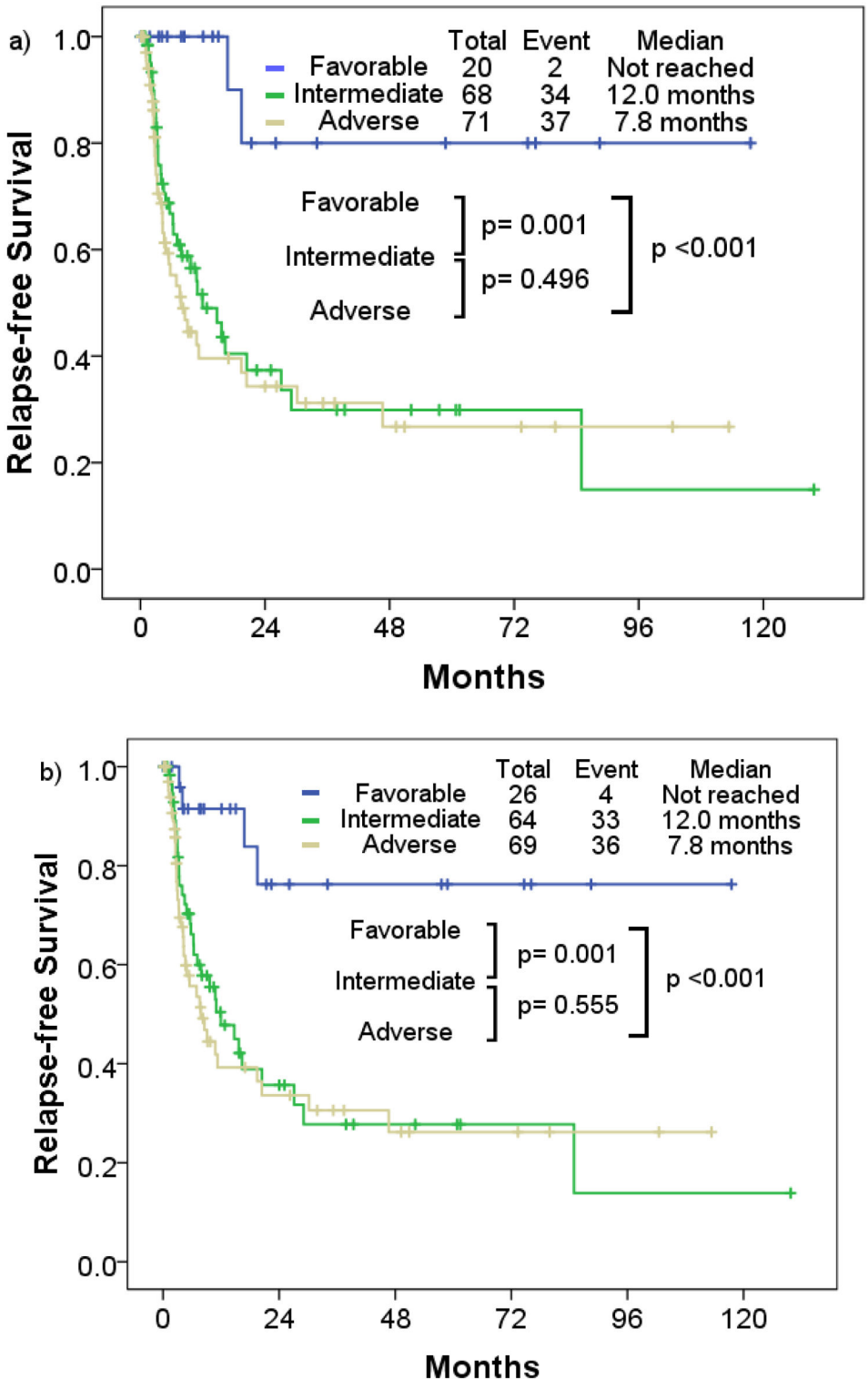

Figure 3.

Relapse-free survival rate of therapy-related acute myeloid leukemia by a) cytogenetic risk, b) European LeukemiaNet risk

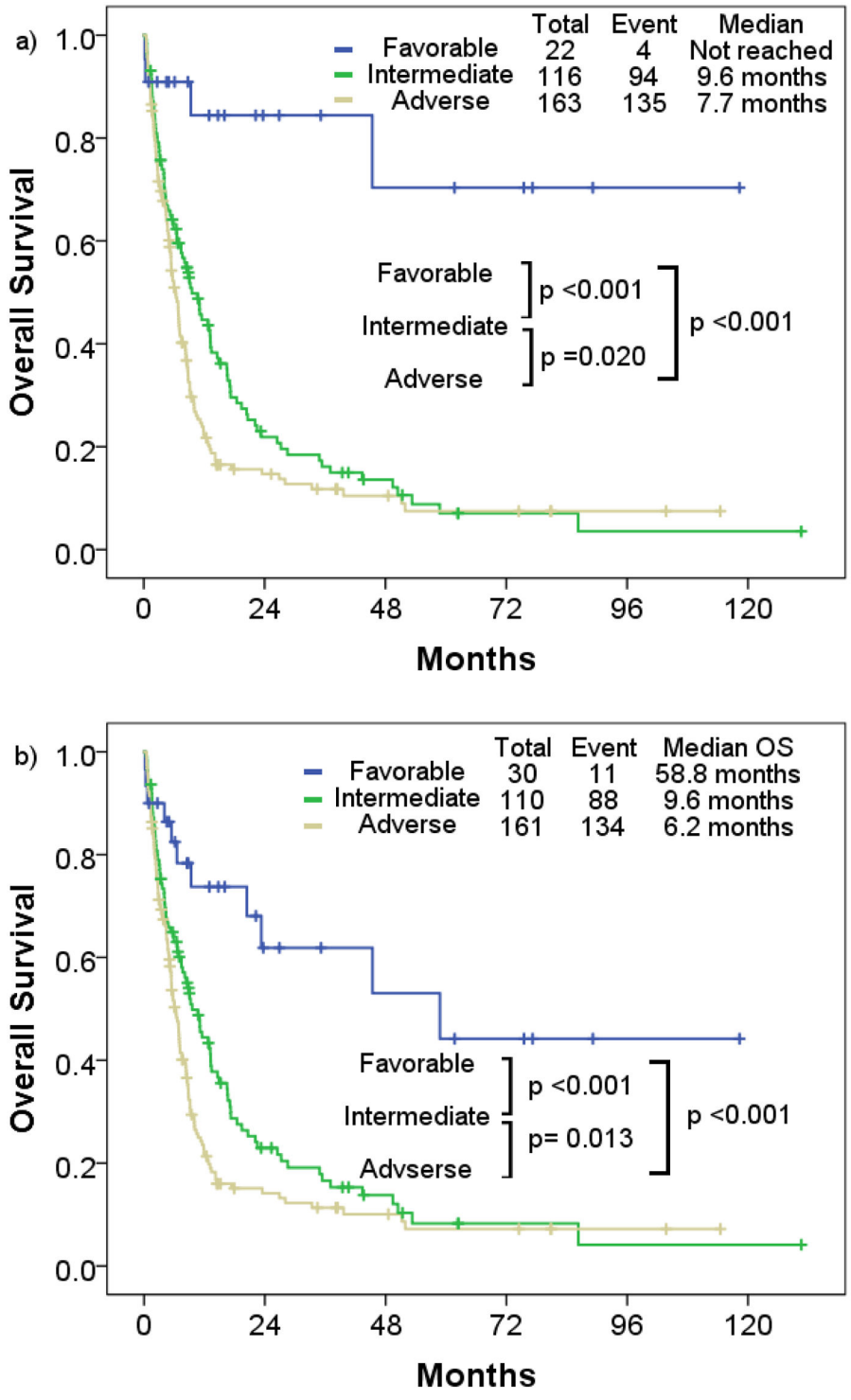

Figure 4.

Overall survival rate of patients with therapy-related acute myeloid leukemia a) by cytogenetic risk, b) European LeukemiaNet risk

Table I

Patient characteristics

	t-AML N=301	t-AML without AHD N= 198	t-AML with AHD N= 103	*P*
Patient demographic at diagnosis, No. (%) / median (range)				
Age (years)	66 (21–89)	63 (21–89)	69 (25–88)	<0.001
Age > 60 years	211 (70%)	116 (63)	95 (81)	0.002
Male	154 (51)	76 (42)	78 (66)	<0.001
Performance Status 0–1	234 (78)	147 (80)	87 (74)	0.286
Diagnosis year				
2000–2007	114 (38)	67 (37)	47 (40)	0.574
2008–2014	187 (62)	116 (63)	71 (60)	
Laboratory data at diagnosis, median (range)				
WBC, ($\times 10^3/\mu L$)	3.3 (0.2–191)	3.3 (0–191)	3.2 (0.2–106.8)	0.866
Hemoglobin, (g/dL)	9.1 (4.5–12.9)	8.9 (4.5–12.9)	9.2 (5.5–12.3)	0.739
Platelet, ($\times 10^3/\mu L$)	34 (2–542)	33 (4–454)	34 (2–542)	0.794
LDH, (IU/L)	658 (210–42000)	645 (210–22090)	681 (301–42000)	0.945
PB blast, (%)	8 (0–99)	8 (0–98)	9 (0–91)	0.913
PB ANC, ($\times 10^3/\mu L$)	0.8 (0.0–81.7)	0.7 (0.0–81.7)	0.8 (0.0–39.5)	0.267
PB AMC, ($\times 10^3/\mu L$)	0.15 (0.0–38.0)	0.14 (0.0–38.0)	0.15 (0–27.8)	0.984
BM blast, (%)	40 (0–96)	40.5 (0–96)	32 (3–95)	0.162
BM monocyte, (%)	2 (0–50)	2 (0–45)	2 (0–50)	0.954
Latency, (months)	75.5 (6.0–502.0)	73.7 (8.6–502.0)	76.5 (6.0–411.8)	0.512

Abbreviations: t-AML, therapy-related acute myeloid leukemia; w/o, without; AHD, antecedent history of myelodysplasia; WBC, white blood cell; ANC, absolute neutrophil count; AMC, absolute monocyte count; BM, bone marrow; LDH, lactate dehydrogenase; PB, peripheral blood.

Table II

Original diagnosis of primary cancer in patients with therapy-related acute myeloid leukemia

Primary Disease, No. (%)	t-AML* N=301	t-AML without AHD* N=183	t-AML with AHD* N=118	P
Solid cancers	204 (68)	121 (66)	83 (70)	0.445
Breast	80 (27)	61 (33)	19 (16)	0.001
Prostate	49 (16)	8 (4)	41 (35)	<0.001
Sarcoma	13 (4)	11 (6)	2 (2)	0.072
Head and Neck	11 (4)	6 (3)	5 (4)	0.665
Colon	11 (4)	9 (5)	2 (2)	0.146
Lung	8 (3)	5 (3)	3 (3)	0.920
Bladder	8 (3)	6 (3)	2 (2)	0.404
Other	24 (8)	18 (10)	6 (5)	0.137
Hematologic malignancies	120 (40)	77 (42)	43 (36)	0.330
Non-Hodgkin lymphoma	92 (31)	61 (33)	31 (26)	0.194
Hodgkin lymphoma	12 (4)	5 (3)	7 (6)	0.166
Multiple myeloma	5 (2)	3 (2)	2 (2)	0.971
Other	8 (3)	4 (2)	4 (3)	0.526

Abbreviations: t-AML, therapy-related acute myeloid leukemia; AHD, antecedent history of dysplasia

*: ≥ 3% of patients with t-AML with or without AHD were described in the table

Table III

Prior exposure to cytotoxic agents, radiation, and stem cell transplantation in patients with therapy-related acute myeloid leukemia

Type of therapy, No. (%)	t-AML N=301*	t-AML without AHD N=183*	t-AML with AHD N=118*	P
Prior chemotherapy	240 (80)	178 (97)	62 (53)	<0.001
Alkylating agents	160 (66)	121 (68)	39 (62)	0.381
Cyclophosphamide	124 (52)	97 (55)	27 (43)	0.112
Ifosfamide	33 (14)	28 (16)	5 (8)	0.122
Cisplatin	41 (17)	36 (20)	5 (8)	0.026
Antiangiogenic agents	12 (5)	11 (6)	1 (2)	0.193
Anthracyclines	138 (57)	113 (64)	25 (40)	0.001
Doxorubicin	126 (52)	102 (57)	24 (38)	0.009
Antimetabolites	75 (31)	56 (32)	19 (30)	0.848
5-fluorouracil	31 (13)	28 (16)	3 (5)	0.025
Cytarabine	34 (14)	29 (16)	5 (8)	0.102
Immunotherapies	66 (27)	44 (25)	22 (35)	0.119
Rituximab	61 (25)	40 (23)	21 (33)	0.088
Taxanes	58 (24)	53 (30)	5 (8)	<0.001
Paclitaxel	36 (15)	35 (20)	1 (2)	0.001
Topoisomerase inhibitors	46 (19)	35 (20)	11 (18)	0.702
Etoposide	44 (18)	33 (19)	11 (18)	0.849
Vinca alkaloids	80 (33)	58 (33)	22 (35)	0.735
Vincristine	73 (30)	54 (30)	19 (30)	0.979
Prior radiation	180 (60)	109 (60)	71 (60)	0.917
Prior stem cell transplant	20 (7)	16 (9)	4 (3)	0.096

Abbreviations: t-AML, therapy-related acute myeloid leukemia; AHD, antecedent history of dysplasia

*Each cytotoxic agent exposure in less than 10% of patients with t-AML was excluded from Table 3. The percentages of cytotoxic agent exposure were derived from patients who received cytotoxic agents.

Table IV

Cytogenetic and molecular abnormalities in therapy-related acute myeloid leukemia

Cytogenetic abnormalities	t-AML N=301	t-AML without AHD N=183	t-AML with AHD N=118	*P*
Favorable	22 (7)	15 (8)	7 (6)	0.461
t(8;21)	9 (3)	5 (3)	4 (3)	0.744
inv(16)	13 (4)	10 (6)	3 (3)	0.223
Intermediate	118 (39)	69 (38)	49 (42)	0.507
t(9;11)	19 (6)	16 (9)	3 (3)	0.031
Normal	58 (19)	28 (15)	30 (25)	0.030
Other	41 (14)	25 (14)	16 (14)	0.980
Adverse	161 (54)	99 (54)	62 (53)	0.792
inv(3) or t(3;3)	7 (2)	6 (3)	1 (1)	0.172
t(6;9)	1 (0)	1 (1)	0	1.000
11q23 rearrangement	18 (6)	13 (7)	5 (4)	0.306
-5 or 5q-	113 (38)	68 (37)	45 (38)	0.864
-7	65 (22)	42 (23)	23 (20)	0.476
abnl(17p)	21 (7)	10 (6)	11 (9)	0.200
Complex	125 (42)	75 (41)	50 (42)	0.811
Monosomal	100 (33)	60 (33)	40 (34)	0.842
FLT3-ITD mutation	31/250 (12)	19/151 (13)	12/99 (12)	0.914
NPM1 mutation	17/147 (12)	8/89 (9)	9/58 (16)	0.455
European LeukemiaNet Risk Classification				
Favorable	30 (10)	17 (9)	13 (11)	0.883
Intermediate	110 (37)	67 (37)	43 (36)	
Adverse	161 (54)	99 (54)	62 (53)	

Table V

Response to therapy and survival of patients with acute myeloid leukemia

	t-AML N=301	t-AML without AHD N= 183	t-AML with AHD N= 118	P
Type of induction chemotherapy, No. (%)				
Cytarabine-based	121 (40)	89 (49)	32 (27)	<0.001
Hypomethylating agent-based	91 (30)	41 (22)	50 (42)	
Investigational agent	33 (11)	17 (9)	16 (14)	
Low intensity chemotherapy	56 (17)	36 (20)	20 (17)	
Response, No. (%)				
CR	126 (42)	86 (47)	40 (34)	0.047
CRp	33 (11)	16 (9)	17 (14)	
PR	3 (1)	3 (2)	0 (0)	
HI	6 (2)	2 (1)	4 (3)	
No response/death	133 (44)	76 (42)	57 (48)	
1-year RFS, (%)	52	43	70	0.032
2-year RFS, (%)	42	34	59	
1-year OS, (%)	35	34	35	0.525
2-year OS, (%)	21	20	24	
ASCT, No. (%)	32 (11)	23 (13)	9 (8)	0.175

Abbreviations: t-AML, therapy-related acute myeloid leukemia; AHD, antecedent history of myelodysplasia; CR, complete response; CRp, complete response without platelet recovery; HI, hematologic improvement; RFS, relapse-free survival; OS, overall survival; ASCT, allogeneic stem cell transplantation.

Table VI

Main results of univariate (UVA) and multivariate analysis (MVA) of overall survival in patients with therapy-related acute myeloid leukemia

	UVA	MVA		
	P	*P*	HR	95% CI
Age at diagnosis: ≤60 vs. >60 years	<0.001	<0.001	2.238	1.551–3.228
Performance status: 0–1 vs. ≥2	<0.001	0.010	1.569	1.115–2.208
Platelet ($\times 10^3/\mu L$): ≥30 vs. <30	0.001	<0.001	1.717	1.303–2.263
Karyotype: favorable vs. non-favorable	<0.001	0.003	4.558	1.650–12.589
FLT3-ITD mutation: pos vs. neg	0.488			
NPM1 mutation: pos vs. neg	0.963			
Response*: CRp or CR vs. non-CRp	<0.001	<0.001	2.840	2.106–3.830
Response*: CR vs. non-CR	<0.001	<0.001	1.923	1.431–2.585
Ara-C-based vs. non-Ara-C-based	<0.001	0.126	1.347	0.920–1.972
HMA-based vs. non-HMA-based	<0.001	0.401	0.863	0.613–1.217
Low intensity chemotherapy vs. other	0.521			
Presence of AHD: pos vs. neg	0.525			
ASCT vs. non-ASCT	<0.001	0.171	0.625	0.319–1.224

Abbreviations: UVA, univariate analysis; MVA, multivariate analysis; HR, hazard ratio; CI, confidence interval; CR, complete response; CRp, complete response with incomplete platelet recovery; HMA, hypomethylating agent; AHD, antecedent history of myelodysplasia; ASCT, allogeneic stem cell transplantation.

*CRp and CR were calculated individually for MVA. CRp was used as a variable to describe other MVA results.