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The influence of age on prognosis of *de novo* acute myeloid leukemia differs according to cytogenetic subgroups

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A B S T R A C T

Background and Objectives. In the presented study the effect of age and cytogenetics on clinical outcome in acute myeloid leukemia (AML) was evaluated. The 1225 patients with *de novo* AML were separated according to age as follows: A1: 16 to 49 years (n=442), A2: 50 to 59 years (n=246), A3: 60-69 years (n=333), A4: 70 years and older (n=204).

Design and Methods. Patients were categorized with respect to cytogenetics into 5 groups: C1: t(15;17) (n=107), C2: CBF-AML/inv(16)/t(8;21) (n=171), C3: 11q23/MLL (n=42), C4: complex aberrant karyotype (n=130), C5: *other*: normal, other abnormalities, 5q-/-5, 7q-/-7, inv(3)/t(3;3), other 3q abnormalities (n=746). For each age category univariate cox regression analysis was performed using age as a continuous variable and C1 to C5 as dichotomous variables.

Results. In cohort A1 all parameters were significantly associated with overall survival (OS). However, in multivariate analysis all cytogenetic parameters were independently correlated with OS, while age was not. In cohort A2 only CBF and complex aberrant karyotype were significantly correlated with OS. In A3 t(15;17), complex karyotype and age, and in A4 only complex karyotype and age were significantly associated with OS in univariate and multivariate analyses. Within all cytogenetic subgroups except AML 11q23/MLL there were significant associations between age and OS.

Interpretation and Conclusions. (i) Both age and cytogenetics are independent prognostic parameters in AML;(ii) up to the age of 49 years age has no major impact on prognosis while the karyotype has; (iii) in patients 50 years and older the influence of age on outcome increases, and (iv) cytogenetics show an independent effect on survival also in patients over 60 years old.

Key words: *de novo* AML, cytogenetics, age, prognosis.

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Several prognostic parameters have been identified in acute myeloid leukemia (AML).[1-10] The most important factors with respect to survival are age and cytogenetics. For clinical purposes, AML are subdivided according to the karyotype of the leukemic blasts into three major prognostic groups. A favorable outcome under currently used treatment regimens was observed in several studies in patients with t(8;21) (q22;q22), inv(16) (p13q22) or t(15;17) (q22;q11-12). Chromosome aberrations with an unfavorable clinical course are -5/del(5q), -7/del(7q), inv(3)/t(3;3) and a complex aberrant karyotype. The remaining karytotypes are assigned to an intermediate prognostic group. This group is very heterogeneous because it includes patients with a normal karyotype and so-called *other* chromosome aberrations, most of which have a poorly defined or debated prognostic impact. In this study we tried to subdivide this group further. There are slight differences between clinical study groups with respect to the assignment of cytogenetic categories to prognostic subgroups based on results of clinical outcome.[3-6,9] Furthermore, it must be kept in mind that treatment itself influences the impact of prognostic parameters.

Overall, prognosis worsens with rising age,[11] but the prognostic impact of cytogenetics was demonstrated in children as well as in younger and elderly adults.[2-5,9,12-15] The incidence of distinct karyotype abnormalities does, however, vary with age.[5,16-18] While favorable chromosome abnormalities are more frequent in younger adults, unfavorable cytogenetics, especially complex aberrant karyotypes predominate in elderly patients. Several studies showed an independent impact of age and cytogenetics on clinical outcome, demonstrating that the

poorer outcome in AML of the elderly is not solely due to the more unfavorable pattern of cytogenetic aberrations.[5] So far the impact of age within distinct cytogenetic subgroups as well as the impact of cytogenetics within age groups has not been studied in detail.

Design and Methods

Patients

The basis of this study are 1225 patients with *de novo* AML and available clinical follow-up data and cytogenetics. The median duration of follow-up was 15.7 months. Most of these patients (991/1225; 80.9%) were treated within the AMLCG 1992, AMLCG 1999 and AMLCG APL trials, while the others were treated with comparable intensive therapies. The AMLCG trials incorporated the following age-specific treatment modifications: patients ≥ 60 years old received a 2nd course of induction only if they had ≥5% residual leukemic blasts in the bone marrow on day 16. Patients under 60 years old with an HLA-identical sibling donor underwent allogeneic bone marrow transplant or peripheral blood stem cell transplant (PBSCT), except those with acute promyelocytic leukemia. Autologous PBSCT was performed in patients < 60 years old. The dose of high dose cytarabine was 3 g/m^2 in patients younger than 60 years and 1g/m^2 in older patients.[6,7,19,20] Among patients aged between 16 to 49 years 17.5% received an allogeneic graft and 10.3% an autologous BMT or PBSCT. In the age group of 50 to 59 years the respective data were 9.8% and 7.1%. Among patients aged 60 to 69 years, 88% of cases reaching a complete remission actually received consolidation therapy. Consolidation therapy was administered to 77% of the patients ≥ 70 years old.

Cytogenetics

Cytogenetic analyses were performed as described elsewhere.[21] Fifteen to 30 metaphases were analyzed and classified according to the International System for Human Cytogenetic Nomenclature (ISCN).[22] In all cases with 11q23/MLL abnormalities the MLL rearrangement was confirmed by fluorescence *in situ* hybridization and/or reverse transcription polymerase chain reaction (RT-PCR).

Statistics

Overall survival (OS) was defined as the time from diagnosis of AML until death and was calculated according to the Kaplan-Meier method: the differences between groups were analyzed using log-rank statistics.[23,24] Data on survival refer to an *intention to treat* approach. Univariate and multivariate analyses were performed applying the Cox model. All *p*-values reported are two-sided. All calculations were performed using SPSS 11.0.1 software.

Results

Patients' characteristics

The median age of this series of patients was 57.4 years (range 16 to 87); 634 patients (52%) were male and 591 (48%) were female. The median white blood cell count was 11.2×10^9/L (range 2-563×10^9/L).

Cytogenetics

An aberrant karyotype was detected in 59.4% (728/1225) of cases. In the total cohort 7.1% had a t(8;21), 6.9% had an inv(16)/t(16;16), 8.7% had a t(15;17), 3.4% had an 11q23/MLL-rearrangement, 10.6% had a complex aberrant karyotype, 4.1% had other unfavorable karyotype abnormalities such as 5q-/-5, 7q-/-7, inv(3)/t(3;3), other 3q abnormalities or 17p abnormalities and, finally, in 18.6% abnormalities other than the ones mentioned above were observed. The frequency of the balanced chromosome abnormalities t(8;21), inv(16), t(15;17) and 11q23/MLL-rearrangements decreased with increasing age, while the proportion of AML with normal karyotype and complex aberrant karyotype increased with rising age. The frequencies of the major cytogenetic abnormalities according to age are shown in detail in Table 1 and in Figure 1.

Prognostic impact of age

In a first analysis patients were separated, roughly by decade of age, into 7 groups. D1: 16-19 years, n=21; D2: 20-29 years, n=83; D3: 30-39 years, n=142; D4: 40-49 years, n=196; D5: 50-59 years, n=246; D6: 60-69 years, n=333; D7: 70 years and older, n=204. In pairwise comparisons between successive age groups significant differences in OS were observed only between D5 vs D6 and between D6 vs D7 using the log rank test (p=0.0042 and p=0.0008, respectively). Therefore, for subsequent analyses the cohort was finally grouped according to age as follows: A1: 16 to 49 years (n=442); A2: 50 to 59 years (n=246); A3: 60-69 years (n=333); A4: 70 years and older (n=204). Using log rank-test significant differences in OS were observed in all pairwise comparisons between all of these subgroups (p<0.004 for all). Figure 2 shows a Kaplan-Meier plot for all 1225 patients separated into the 4 age groups. The rates of complete remission for the age groups A1, A2, A3 and A4 were 75.1%, 66.3%, 60.7% and 55.9%, respectively.

Prognostic impact of cytogenetics

Patients were first categorized with respect to cytogenetics into 7 groups: (i) t(15;17), (n=107); (ii) CBF-AML/inv(16)/t(8;21), (n=171)); (iii) normal, (n=497); (iv) other abnormalities, (n= 228); (v) unfavorable/not complex: 5q-/-5, 7q-/-7, inv(3)/t(3;3), other 3q abnormalities, 17p abnormalities, (n=50); (vi) 11q23/MLL, (n=42); (vii) complex aberrant karyotype (3 or more abnormal-

Table 1. Frequencies of karyotypes according to age.

Karyotype	*16-19 yrs n=21*	*20-29 yrs n=83*	*30-39 yrs n=142*	*40-49 yrs n=196*	*50-59 yrs n=246*	*60-69 yrs n=333*	*≥ 70 yrs n=204*
t(8;21), n=87	2 (9.5%)	10 (12.0%)	14 (9.9%)	17 (8.7%)	19 (7.7%)	17 (5.1%)	8 (3.9%)
inv(16), n=84	0 (0%)	14 (16.9%)	21 (14.8%)	12 (6.1%)	14 (5.7%)	18 (5.4%)	5 (2.5%)
t(15;17), n=107	4 (19.0%)	14 (16.9%)	19 (13.4%)	24 (12.2%)	19 (7.7%)	16 (4.8%)	11 (5.4%)
normal, n=497	6 (28.6%)	22 (26.5%)	49 (34.5%)	71 (36.2%)	101 (41.1%)	150 (45.1%)	98 (48.0%)
other abnormalities, n=228	3 (14.3%)	14 (16.9%)	17 (12.0%)	37 (18.9%)	39 (15.8%)	71 (21.3%)	47 (23.0%)
11q23, n=42	2 (9.5%)	3 (3.6%)	10 (7.0%)	15 (7.7%)	9 (3.7%)	3 (0.9%)	0 (0%)
other unfavorable, n=50	1 (4.8%)	3 (3.6%)	7 (4.9%)	7 (3.6%)	14 (5.7%)	14 (4.2%)	4 (2.0%)
complex aberrant, n=130	3 (14.3%)	3 (3.6%)	5 (3.5%)	13 (6.6%)	31 (12.6%)	44 (13.2%)	31 (15.2%)
Total	21 (100%)	83 (100%)	142 (100%)	196 (100%)	246 (100%)	333 (100%)	204 (100%)

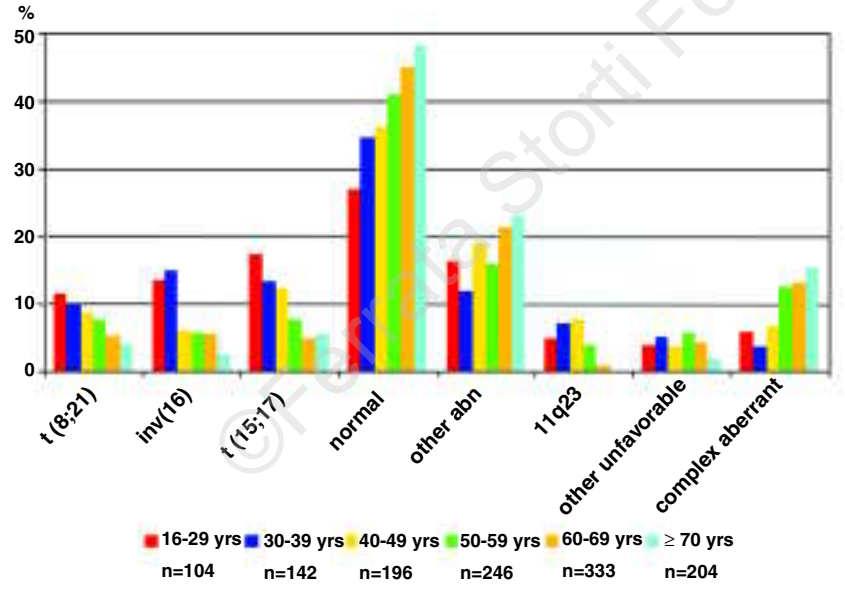

Figure 1. Relative proportion of distinct cytogenetic subgroups within age cohorts.

ities), (n=130). Figure 3A shows the Kaplan-Meier plot with respect to the most commonly used cytogenetic grouping favorable (t(15;17) and CBF), intermediate (normal and other abnormalities) and unfavorable (unfavorable/not complex, 11q23/MLL and complex aberrant). Figure 3B, on the other hand, presents the data with patients separated into the above mentioned 7 cytogenetic groups. The rates of complete remission for the 7 cytogenetic groups were 88.8%, 75.4%, 67.8%, 61.4%, 64.0%, 64.3% and 39.2%. In univariate Cox regression analysis only the following cytogenetic parameters were significantly associated with OS: APL/t(15;17), CBF-AML/inv(16)/t(8;21), 11q23/MLL, and complex aberrant karyotype. Therefore, the cohort was finally grouped according to cytogenetics as follows: C1: t(15;17) (n=107); C2: CBF-AML/inv(16)/ t(8;21) (n=171); C3: 11q23/MLL (n=42); C4: complex aberrant karyotype (n=130); C5: *other*: normal, other abnormalities, 5q/-5, 7q-/-7, inv(3)/t(3;3), other 3q abnormalities, 17p abnormalities, (n=746). The final grouping of

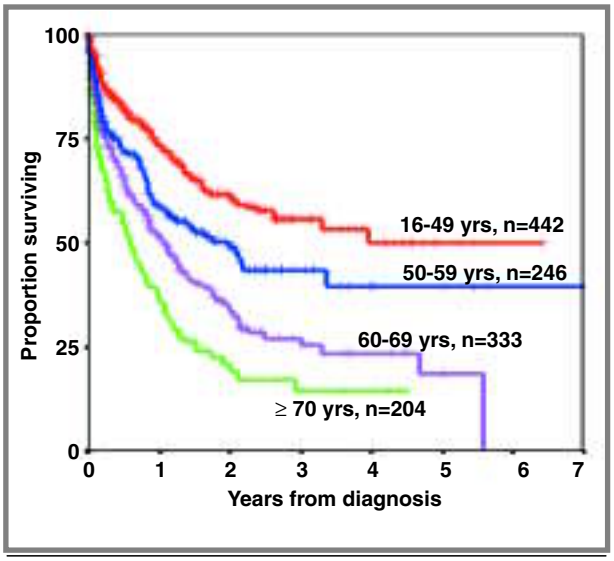

Figure 2. Overall survival of 1225 patients with *de novo* AML divided into four age groups. *p* values according to the log-rank test were *p*=0.0009 for 16-49 years vs. 50-59 years, *p*=0.0042 for 50-59 years vs. 60-69 years and *p*=0.008 for 60-69 years vs. 70 years.

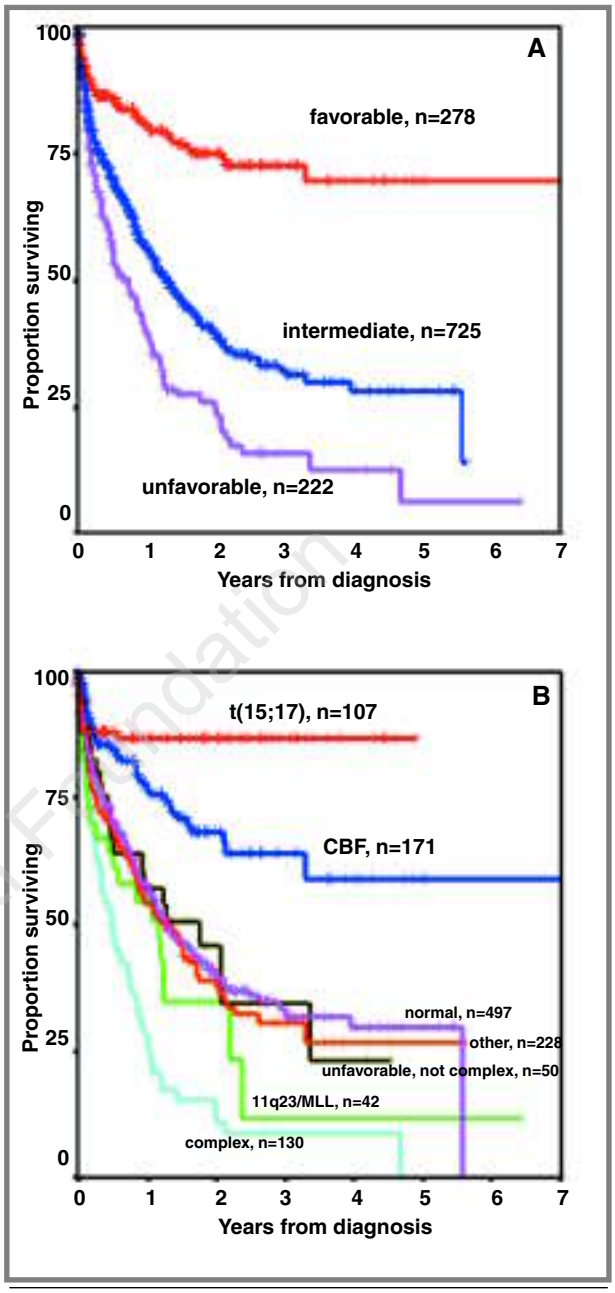

Figure 3. A. Overall survival of 1225 patients with *de novo* AML with respect to the most commonly used cytogenetic grouping (favorable, intermediate and unfavorable). *p* values according to the log-rank test were *p*<0.0001 for all comparisons. B. Overall survival of 1225 patients with *de novo* AML divided into 7 cytogenetic groups. *p* values according to the log-rank test were *p*=0.002 for t(15;17) vs. CBF, *p*<0.0001 for CBF vs. normal, *p*=0.58 for normal vs. other, p=0.89 for normal vs unfavorable/not complex, *p*=0.14 for normal vs MLL, *p*=0.20 for other vs. MLL, *p*=0.16 for unfavorable/not complex vs. MLL, *p*=0.0006 for unfavorable/not complex vs. complex and *p*=0.04 for MLL vs. complex.

patients according to age and cytogenetics is shown in Table 2. A Kaplan-Meier plot for all 1225 patients separated into 5 cytogenetic groups is depicted in Figure 4.

Prognostic impact of cytogenetics within age groups

For each age category univariate Cox regression analysis was performed using age as a continuous variable and the cytogenetic groups: t(15;17)/APL, CBF, MLL, complex aberrant karyotype and *other* karyotype as dichotomous variables. In cohort A1 (16-49 years) all parameters were significantly associated with OS (p=0.021, p=0.002, p=0.005, p=0.0003, p=0.007). However, in multivariate analysis all cytogenetic parameters were independently correlated to OS, while age was not (Table 3). In cohort A2 (50-59 years) only CBF and complex aberrant karyotype were significantly correlated with OS in univariate and multivariate analysis (Table 3). In A3 (60-69 years) APL, complex aberrant karyotype and age, and in A4 (70 years and above) only complex aberrant karyotype and age were significantly associated with OS in univariate and multivariate analyses (Table 3). Overall survival of patients within the age groups A1, A2, A3 and A4 is shown according to cytogenetics in Figure 5.

Prognostic impact of age within cytogenetic subgroups

Within the cytogenetic subgroups C1 to C5 univariate Cox regression analysis showed significant associations between age as a continuous variable and OS in APL, CBF-AML, *other*-AML, and AML with complex aberrant karyotype (Table 4). Age had no influence on OS in MLL AML. Using different age separators for the log-rank test in APL and AML with complex aberrant karyo-

Table 2. Number of patients assigned to 4 age groups and 5 cytogenetic subgroups.

	C1 t(15;17)	*C2 CBF*	*C3 other*	*C4 MLL*	*C5 complex*	*Total*
A1 16-49 yrs	61 (57.0%)	90 (52.6%)	237 (30.6%)	30 (71.4%)	24 (18.5%)	442
A2 50-59 yrs	19 (17.7%)	33 (19.3%)	154 (19.9%)	9 (21.4%)	31 (23.8%)	246
A3 60-69 yrs	16 (15.0%)	35 (20.5%)	235 (30.3%)	3 (7.2%)	44 (33.9%)	333
A4 70+ yrs	11 (10.3%)	13 (7.6%)	149 (19.2%)	0 (0%)	31 (23.8%)	204
Total	107 (100%)	171 (100%)	775 (100%)	42 (100%)	130 (100%)	1225

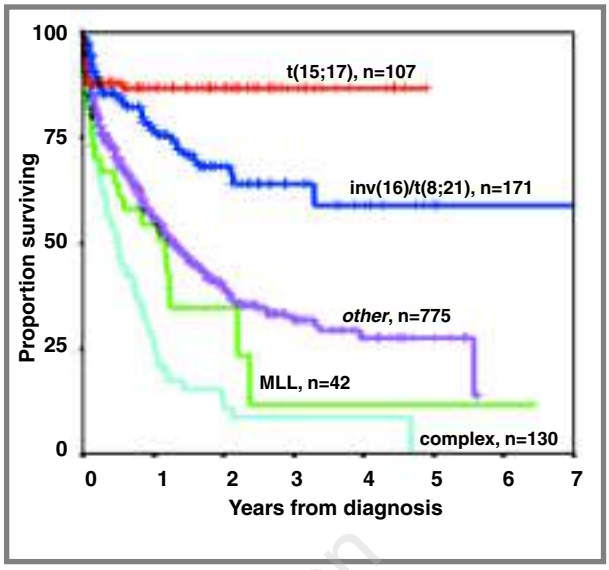

Figure 4. Overall survival of 1225 patients with *de novo* AML divided into 5 cytogenetic subgroups. *p* values according to the log-rank test were *p*=0.002 for t(15;17) vs. CBF, *p*<0.0001 for CBF vs. *other*, *p*=0.14 for *other* vs MLL, and *p*=0.04 for MLL vs. complex.

Table 4. Influence of age as a continuous variable on OS within cytogenetic subgroups (*p*-values, Cox regression analysis).

	t(15;17)	*CBF*	*other*	*MLL*	*complex*
age continuous	0.046	0.006	<0.001	0.444	0.016

Table 3. Influence of cytogenetics on OS within age groups. Parameters without a significant association in univariate analysis were not included in the multivariate analysis (Cox regression analysis).

	A1: 16-49 yrs		*A2: 50-59 yrs*		*A3: 60-69 yrs*		*A4: 70 yrs+*	
	p	*Hazard ratio*	*p*	*Hazard ratio*	*p*	*Hazard ratio*	*p*	*Hazard ratio*
t(15;17)	<0.001	0.11	not included		0.013	0.08	not included	
CBF	0.002	0.43	0.035	0.43	not included		not included	
MLL	0.032	1.80	not included		not included		not included	
Complex	0.050	1.90	<0.001	2.43	0.005	1.77	0.013	1.78
Age continuous	0.060	1.02	not included		0.033	1.06	0.044	1.06

type the best distinction with respect to OS was observed between patients < 50 and ≥ 50 years. In CBF-AML and *other*-AML the separation was clearest between < 60 and ≥ 60 years. In APL the white blood cell count has an impact on prognosis with the most discriminating cut-off value being 10×10^9/L. Therefore, we assigned APL cases into subgroups with white cell counts below and above this cut-point. Overall 73.9% of APL cases showed a WBC count below 10×10^9/L. For the age groups A1, A2, A3 and A4 the respective percentages were 68%, 86%, 81% and 83%. Overall survival of patients within each cytogenetic group is shown according to age group in Figure 5.

Discussion

In AML several pre-therapeutic parameters, such as cytogenetics, age, WBC count, lactate dehydrogenase concentration, and the history of the disease (occurring *de novo* or after an antecedent hematologic disorder or therapy-related) have been shown to be of prognostic importance.[1,3-6,9,25-28] The early assessment of response to therapy as measured by the morphologic parameter of early blast clearance from the bone marrow, represents an *in vivo* assessment of chemosensitivity and is also a powerful tool for delineating the prognosis in individual patients.[7] The impact of the above mentioned parameters

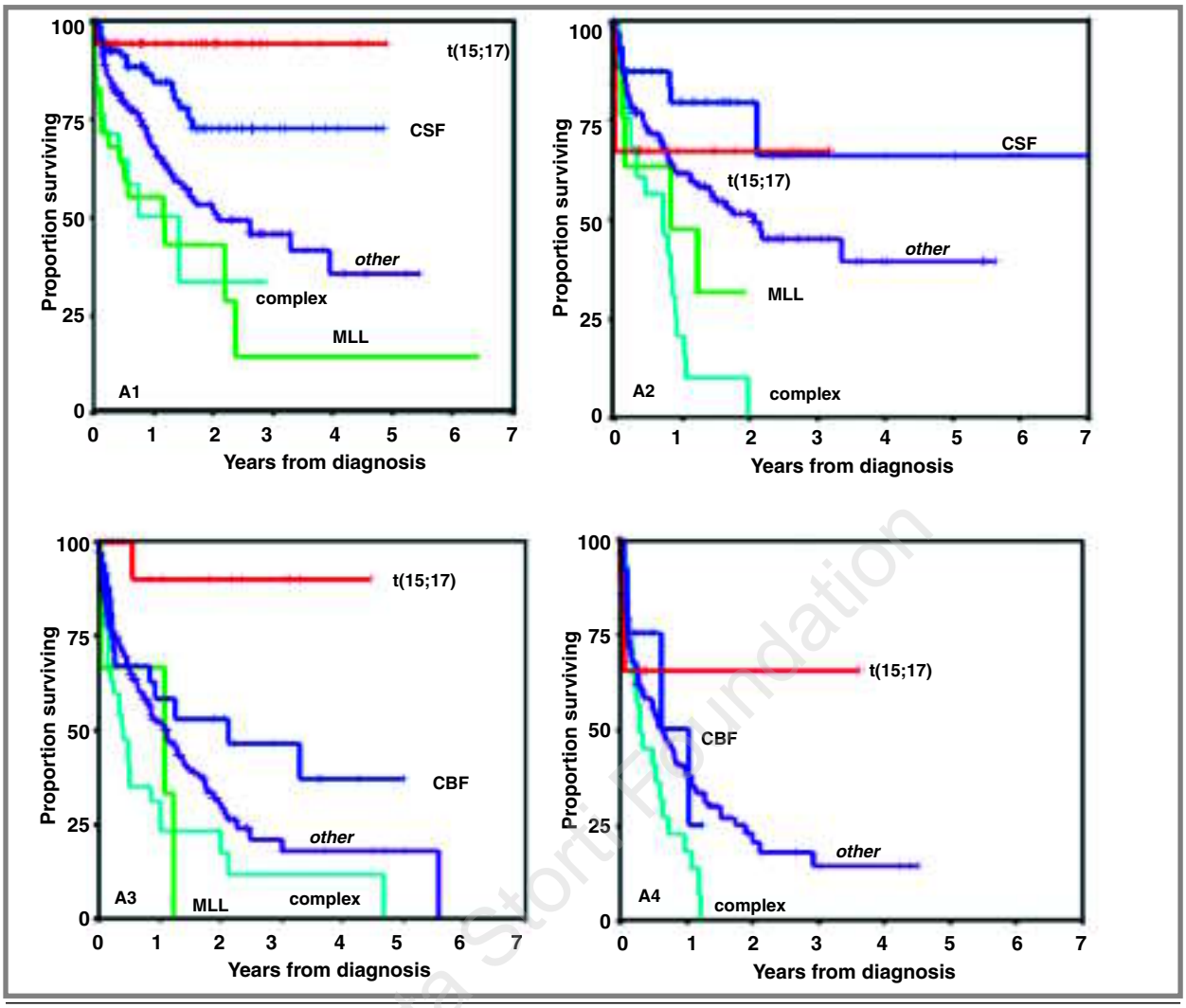

Figure 5. Overall survival of 1225 patients with *de novo* AML divided into 5 cytogenetic subgroups [t(15;17), CBF: inv(16)/t(8;21), *other*: normal karyotype and other abnormalities, 11q23/MLL and complex aberrant karyotype] within each of the age groups: A1 (16-49 years), A2 (50-59 years), A3 (60-69 years) and A4 (≥ 70 years). For the comparisons within A1: t(15;17) vs. CBF, CBF vs. *other*, *other* vs. MLL and *other* vs. complex the respective p-values according to the log-rank test were 0.025, 0.0013, 0.014, and 0.04, respectively. For the comparisons within A2: t(15;17) vs. complex, CBF vs. *other*, and *other* vs. complex the respective *p* values according to the log-rank test were 0.02, 0.04, and 0.0001. For the comparisons within A3: t(15;17) vs. CBF, CBF vs. *other*, CBF vs. complex and *other* vs. complex the respective *p* values according to the log-rank test were 0.015, 0.12, 0.005, and 0.008. For the comparisons within A4: t(15;17) vs. complex, CBF vs. complex, and *other* vs. complex the respective *p* values according to the log-rank test were 0.08, 0.14, and 0.02.

on prognosis has been mainly studied in younger patients. According to a study dealing with the age profile within clinical cancer trials only 27% of patients in leukemia trials were over 65 years of age although patients above 65 years comprise 63% of all leukemia cases.[29] Several large clinical trials specifically in AML included only patients up to the age of 55 or 60 years old, while in others there were no age limit but patients above the age of 60 were usually underrepresented. In this study 537 patients (44%) with *de novo* AML were 60 years or older. Out of these, 204 were over 70 years old. The prognostic impact of cytogenetics and age in AML has been clearly demonstrated in several large clinical trials.[3-6,9,11,12,14,15,25,26,30] For survival analyses patients are usually assigned to three different prognostic subgroups (favorable, intermediate and unfavorable) on the basis of cytogenetics. Drawing on the results of our recent analysis evaluating a new prognostic score in adult AML based on cytogenetics and therapy response[20] we subdivided our cohort of patients into 7 cytogenetic subgroups: 1. t(15;17), 2. inv(16)/t(8;21), 3. normal karyotype, 4. other karyotype abnormalities, 5. unfavorable/not complex karyotype abnormalities: 5q-/-5, 7q-/-7, inv(3)/t(3;3), other 3q abnormalities, 17p abnormalities, 6. 11q23/MLL rearrangements and 7. complex aberrant karyotype (3 or more abnormalities). Univari-

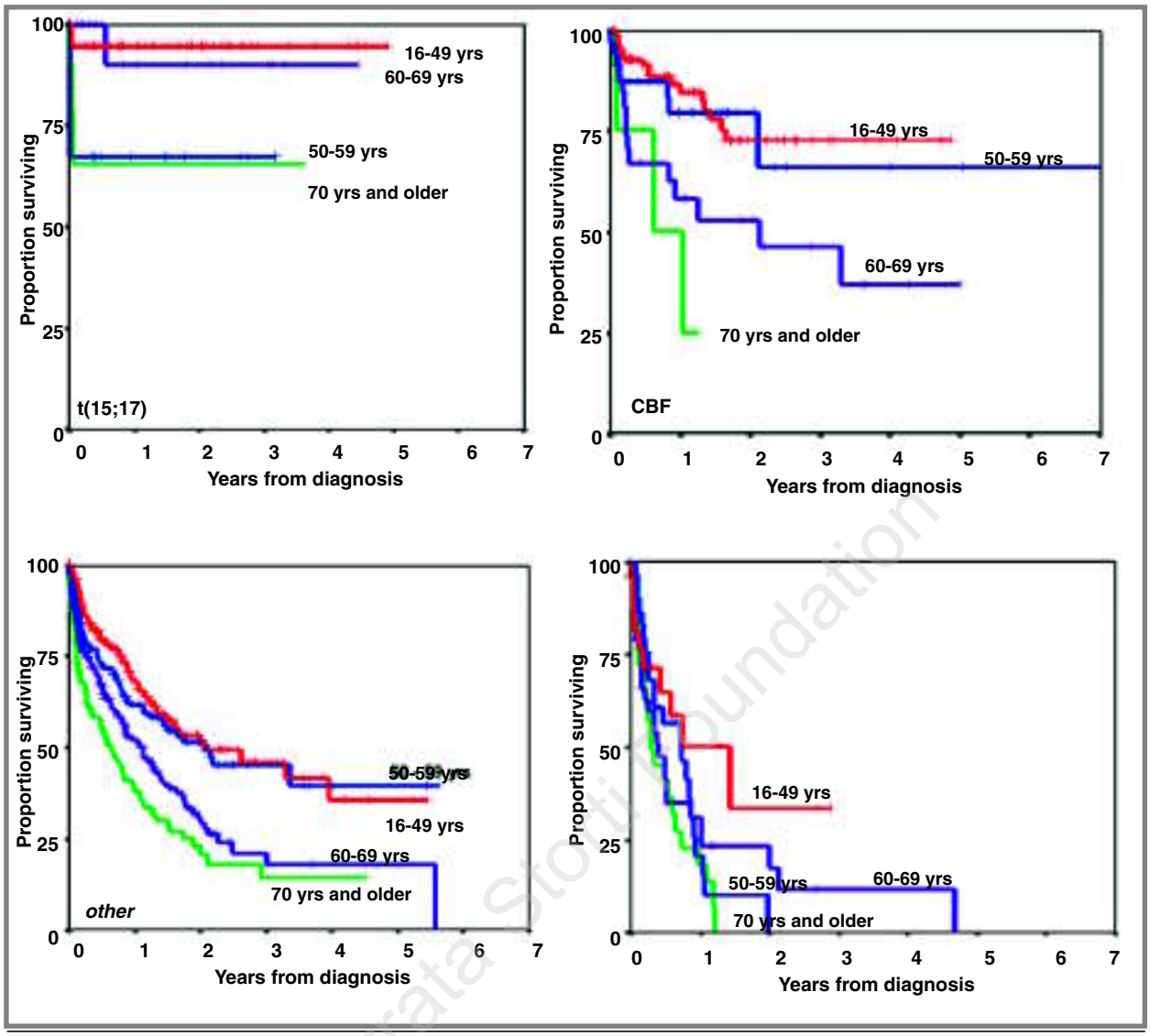

Figure 6. Overall survival of 1225 patients with *de novo* AML divided into 4 age groups (16-49 years, 50-59 years, 60-69 years and ≥ 70 years) within each the cytogenetic subgroup t(15;17), CBF: inv(16)/t(8;21), *other*: normal karyotype and other abnormalities and complex aberrant karyotype. Within t(15;17) the *p* values according to the log-rank test for the comparisons A1 vs. A2, A1 vs. A4, A2 vs. A3 and A2 vs. A4 were 0.0005, 0.006, 0.05, and 0.05, respectively. For the comparisons within CBF: A1 vs. A3, A2 vs. A3, A2 vs. A4 and A3 vs. A4 the respective *p*-values according to the log-rank test were 0.002, 0.07, 0.03, and 0.5. For the comparisons within the *other* cytogenetic group: A1 vs. A3, A2 vs. A3, and A3 vs. A4 the respective *p* values according to the log-rank test were <0.0001, 0.003, and 0.02. For the comparisons within the *complex* cytogenetic group only A1 vs. A4 showed a statistically significant difference (*p*=0.02).

ate Cox regression analysis as well as analyzing overall survival by Kaplan-Meier-plots revealed no differences in outcome between AML with normal karyotype, so-called *other* abnormalities and unfavorable but not complex abnormalities. Therefore, the major subgroups with unequivocally unfavorable cytogenetics are AML with complex aberrant karyotype and AML with 11q23/MLL rearrangement. For all other smaller cytogenetic subgroups that have been assigned into the unfavorable category there are conflicting data or age independence has not been proven because of the small numbers of cases even in large clinical trials. So far only meta-analyses can provide sufficient valid data to determine the prognostic impact of cytogenetic subgroups with an incidence below 3%. Data supporting the practice of assigning unfavorable, non-complex karyotypes into the intermediate prognostic group in adult AML until more conclusive data are available have been published by the MRC group. In the original MRC AML10 hierarchical cytogenetic classification system, which was based on AML patients between 0 and 55 years old (median 35 years), unfavorable non-complex aberrant karyotypes were assigned together with complex aberrant karyotypes, Grimwade *et al.* stated in their paper on the MRC AML11 trial, which included AML patients aged 44-91 years (median 66 years), that a

minor modification of the original MRC 10 classification entailing assignment of non-complex adverse abnormalities to the intermediate risk category was found to provide a more predictive and clinically relevant system.[5] Data from a study performed by ECOG and SWOG examined the role of complex aberrant karyotypes in the presence or absence of -5/5q- and/or -7/7q- within the unfavorable group and observed that patients with aberrations of 5 and /or 7 in a complex aberrant karyotype had a particularly poor outcome, while those with a non-complex karyotype showed a higher rate of complete remission although not resulting in a markedly superior long-term survival than that in cases with complex aberrant karyotypes in cases including -5/5q- and/or -7/7q-. In contrast to our analysis and that of the MRC, patients with 11q23 abnormalities were assigned to the unfavorable subgroup, accounting for 42 of the 121 cases with an unfavorable non-complex karyotype.[9] Clinical study groups recruiting large numbers of patients, for example the CALGB, MRC, and SWOG/ECOG groups, differed with respect to their assignment of several cytogenetic abnormalities to the intermediate or unfavorable category, but there was a consensus in all studies to assign complex aberrant karyotypes to the group with an adverse prognosis.[3-5,9,31] Therefore, this subgroup should be evaluated as a separate, specific group in all further analyses. Meta-analyses are mandatory to clarify the prognostic impact of all other cytogenetic abnormalities with low incidences.

It is well known that the incidence of distinct cytogenetic abnormalities varies with age.[4,5,16-18] Chromosome aberrations associated with a more favorable outcome, such as t(8;21)(q22;q22), inv(16)(p13q22) and t(15;17)(q22;q12), occur more frequently in younger patients while karyotypic changes with an unfavorable prognostic impact, especially complex aberrant karyotypes, occur with a higher incidence in elderly patients[4,5,16,17] This was confirmed in the present study. While 14% of patients between 16 and 49 years had a t(15;17), the incidence decreased to 8%, 5% and 5% in the age groups 50-59, 60-69 and ≥ 70 years, respectively. The respective incidences for the t(8;21) and inv(16) were 20%, 13%, 11% and 6%, and for complex aberrant karyotypes 5%, 13%, 13% and 15%. We also observed a relative increase in the proportion of normal karyotypes with advancing age, as was reported by Grimwade *et al.*[5] The MRC 11 trial reported on 1065 patients with *de novo* AML as well as secondary AML. The recruited patients ranged from 44 to 91 years old (median age 66). A higher incidence of complex aberrant karyotypes and a lower incidence of favorable karyotypes in elderly patients was also noted in this MRC study. The analysis of survival data revealed that age remained a highly significant prognostic factor even when hierarchical cytogenetic risk group was taken into account and *vice versa* cytogenetic risk group retained its prognostic value when age was taken into account. The authors concluded that differences in the distribution of cytogenetic risk groups influence but do not fully explain the more unfavorable outcome with increasing age.

In contrast to the MRC 11 trial, we excluded patients with secondary AML from our analysis as this type of AML is an unfavorable prognostic factor itself and occurs more frequently with increasing age.[32] Our series did, however, include adults of all ages, ranging from 16 to 87 years old. Therefore, we confirmed the independent prognostic impact of age and cytogenetics in adult patients with *de novo* AML. In addition, we determined the prognostic impact of the main cytogenetic subgroups in different age groups. Within the cytogenetic subgroups t(15;17), inv(16)/t(8;21), AML with other abnormalities as well as in AML with complex aberrant karyotype a significant association between age as a continuous variable and overall survival was observed. In contrast in AML with 11q23/MLL rearrangement age had no influence on overall survival. Comparing the different age cohorts in AML with t(15;17) revealed no clear cut-point for a worse prognosis. In AML with inv(16)/t(8;21) as well as in AML with *other* abnormalities no difference in outcome was detected between the cohort of patients aged 19 to 49 years and the cohort aged 50 to 59 years while a substantial decrease in the probability of survival was observed between the cohort aged 50 to 59 years and that aged 60 to 69 years. It must be considered that differences in treatment protocol may be at least partly responsible for the more unfavorable outcome in patients 60 years and older as they received a lower dose of cytosine arabinoside than did the younger patients. The overall prognosis of patients with complex aberrant karyotype is very poor, only patients under 50 years old had a slightly better outcome than patients in the other age groups. This may be due to a higher rate of allogeneic bone marrow transplantation in this cohort.

In conclusion, this study demonstrates an independent prognostic impact of both age and cytogenetics in adult *de novo* AML. Age has no major impact on prognosis up to the age of 49 years. Beyond this threshold the influence of age on outcome increases. In all age groups separating the patients on the basis of karyotype resulted in subgroups with different prognoses. Therefore, cytogenetics is mandatory in all age groups to allow risk-adapted treatment approaches and to predict outcome.

CS: principal investigator, WK: contribution to conducting the work and interpreting the results with special focus on statistics, SS: contribution to conducting the work and interpreting the results, TB: contribution to interpreting the results, WH: contribution to interpreting the results, TH: principal investigator.

The cell samples included in this study were sent for central diagnosis from various hospitals in Germany participating in the AMLCG trials (coordinators: T. Büchner and W. Berdel, Münster; W. Hiddemann, München; B. Wörmann, Braunschweig, Germany; statisticians: A. Heinecke, M.C. Sauerland, Münster, Germany).

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