Multivariate analyses of prognostic factors in acute myeloid leukemia: relevance of cytogenetic abnormalities and CD34 expression*

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Identification of additional prognostic factors besides karyotype is important for the improvement of the risk adapted treatment strategies in acute myeloid leukemia (AML). The aim of this study was to investigate whether other factors besides karyotype could be used as a prognostic tool in newly diagnosed AML.

Biological and disease related established and potential prognostic factors were retrospectively analysed in 124 consecutive AML patients treated between 1993 and 2002 at the University hospital Rostock (Germany). One hundred patients received a potential curative intensive chemotherapy (81%), of whom 28 received an allogeneic HSCT at some point of their treatment course, 17 patients (14%) received palliative therapies and 7 patients (5%) received supportive care only. In patients that received potential curative therapies LDH ≥2000 U/l, WBC >50 GPT/l, CD34 surface expression on the AML blasts, secondary AML, unfavorable karyotype and no allogeneic HSCT at some point of treatment course were associated with unfavorable prognosis. However, in the multivariate risk factor analyses only unfavorable karyotype (p=0.012), CD34 positivity of AML blasts (p=0.046), no allogeneic HSCT (p=0.008) and first diagnosis after 1997 (p=0.025) were independent unfavourable prognostic factors.

In conclusion, karyotype and CD34 expression are independent prognostic markers in newly diagnosed AML. Furthermore, receiving an allogeneic HSCT at some point of the treatment course seems to be of benefit for AML patients.

Key words: leukemia, CD34-antigen, prognosis, cytogenetic abnormalities, hematopoietic stem cell transplantation, AML

Acute myeloid leukemia (AML) is a heterogeneous disease with different morphologies, immunophenotypes and cytogenetic alterations [45]. Although the outcome of AML has improved over the last decades, long term results still remain unsatisfactory. Complete remissions (CR) are achieved with standard intensive chemotherapy in 65–70% of younger AML patients [6, 7, 17]. Unfortunately, even patients that receive a CR have a long term relapse free survival probability of only 31–49% [6, 7, 17]. Older AML patients have an even worse prognosis [25, 30].

Treatment modalities that might improve outcome of AML patients include allogeneic hematopoietic stem cell transplantations (HSCT). Allogeneic HSCT can induce long term survival in refractory and relapsed AML patients [47]. Furthermore, preliminary data suggest that allogeneic HSCT might be beneficial when introduced into the first line treatment of AML patients [9, 14, 41]. However, allogeneic HSCTs are associated with significant treatment related morbidities and mortality (TRM) [9]. So especially patients with a good prognosis following conventional chemotherapy might not benefit from this approach.

Therefore, current algorithms in the treatment of AML include risk stratifications. Based on the observation that AML-morphology is in general of low predicitive value in respect of response and survival, several other prognostic factors have been identified. These can be divided into biological factors and disease specific factors. Age as a biological factor has been established as an independent risk factor

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in a series of studies [30, 48]. However, the karyotype as a disease specific risk factor has been shown to have the major impact on the patients' outcome [10, 16, 17, 22]. Several prognostic risk scoring systems that are mainly based on cytogenetics have been developed [10, 16–18, 48]. Other biological and disease specific risk factors have been postulated [1, 7, 32, 33, 42, 48], but for some such as CD34 expression on the AML cells their prognostic significance remain unclear [31, 38].

Here, we investigated whether established as well as discussed biological and disease specific risk factors had a prognostic significance for patient outcome in our institution.

Patients and methods

Patients with AML that were treated at the Division of Hematology and Oncology (University of Rostock) between 01.01.1993–01.02.2002 were included in this retrospective study. For all cases a chart review was performed and defined risk factors were documented. In general, all laboratory analyses were performed by laboratories of the Division of Hematology. Only in exceptional cases laboratory results from outside laboratories were accepted. Endpoint of data survey was 01.10.2003.

Flow cytometry. Flow cytometry was performed according to the guidelines of the European Group for the Immunological Characterization of Leukemias (EGIL) [2]. CD34 staining was done with anti-CD34 antibody clone 8G12 from Becton Dickinson (Heidelberg, Germany). If more than 10% of the AML-blasts expressed CD34, the AML was grouped as CD34 positive AML.

Cytogenetics. Until 1/96 conventional GTG-banding was performed. Thereafter, all karyotyping was done using R-banding [36]. In all cases >15 metaphases were analyzed and classified according to the International System for Human Cytogenetic Nomenclature [27].

Cytogenetic risk groups were defined as done in the Medical Research Council (MRC) AML 10 study [17]: favorable: t(8;21), t(15;17), inv(16); alone or in combination with other cytogenetic changes; intermediate: normale karyotype, +8, +21, +22, del(7q), del(9q), 11q23, all others aberrations; cytogenetic aberrations, that are not classified as favorable or poor; unfavorable: –5, –7, del(5q), abnormalities at 3q, complex karyotype (≥3 aberrations) alone or in combination with intermediate changes or any other changes of the unfavorable risk group.

AML-definitions. AML cases were classified based on morphological criteria according to the FAB-classification [3]. Patients with a history of known risk factors for AML development, such as preceding myelodysplastic syndrome (MDS), any other prior hematological disease, prior treatment with known mutagenic substances such as radiotherapy or prior chemotherapy were classified as secondary AML (sAML). All others were defined as de-novo AML.

Treatment. The therapy of the patients was classified as a) supportive b) palliative and c) curative. Supportive care was defined as best supportive care and no application of any antineoplastic therapy. Palliative therapy was defined as any antineoplastic, cytoreductive therapy with no curative intention and potential. Common palliative therapies included mitoxantron 10 mg/m^2 i.v. d1+2 q 4 weeks or idarubicin 10 mg p.o. and cytarabine 40 mg s.c. d1-5 q 4 weeks. Curative therapy was defined as any therapy with curative intention. This included standard intensive chemotherapy with induction and consolidation chemotherapy usually with a cytarabine and anthracyclin backbone. Most patients (96%) of this group were treated within consecutive protocols of the East Geman study group for Hematology and Oncology (OSHO), i.e. OSHO AML 93, OSHO AML 96, OSHO AML 97, respectively [20, 43], while others were treated with comparable intensive therapies. All FAB M3 AML patients received an ATRA containing treatment. Three patients received autologous HSCT for consolidation. Allogeneic HSCT was classified as curative therapy and was in 27/28 cases (96%) performed after a myeloablative conditioning regimen.

Statistics. All statistical analyses were done using the SPSS-software Version 11.01. To compare characteristics of patient subgroups summary statistics including frequency counts and percentages for categorial variables as well as medians and ranges were calculated. Comparisons from 2x2 tables were made using chi-squared tests or Fisher test if applicable. Survival rates were determined according to KAPLAN and MEIER [21]. Survival was defined as time period from first diagnosis until death or last patient contact. For determination of significant differences between patient subgroups log-rank testing was performed [29]. All p-values were two-tailed. Univariate and multivariate Cox regression models were used to analyze the influence of selected variables on the risks of death. Factors with unadjusted odds-ratios that had a $p<0.20$ were entered into the multivariate analyses. Cox regression analyses were performed for the whole cohort as well as for curative therapy group in order to identify the influence of allogeneic HSCT.

Results

Between 01.01.1993 and 01.02.2002 124 patients with AML were treated in the Division of Hematology and Oncology (University of Rostock). The median follow up for all patients was 11 months (range 4 days to 129 months) and for patients alive 26 months (range 101 days to 129 months). Patients' characteristics at first diagnosis are displayed in Table 1.

Influence of biological and disease specific markers on prognosis.

Age. Patients <60 years of age at diagnosis had a better survival compared to patients ≥60 years (5 yrs-OS 27% vs 8%, p=0.033, Fig. 1A). Median survival of the patients <60 years

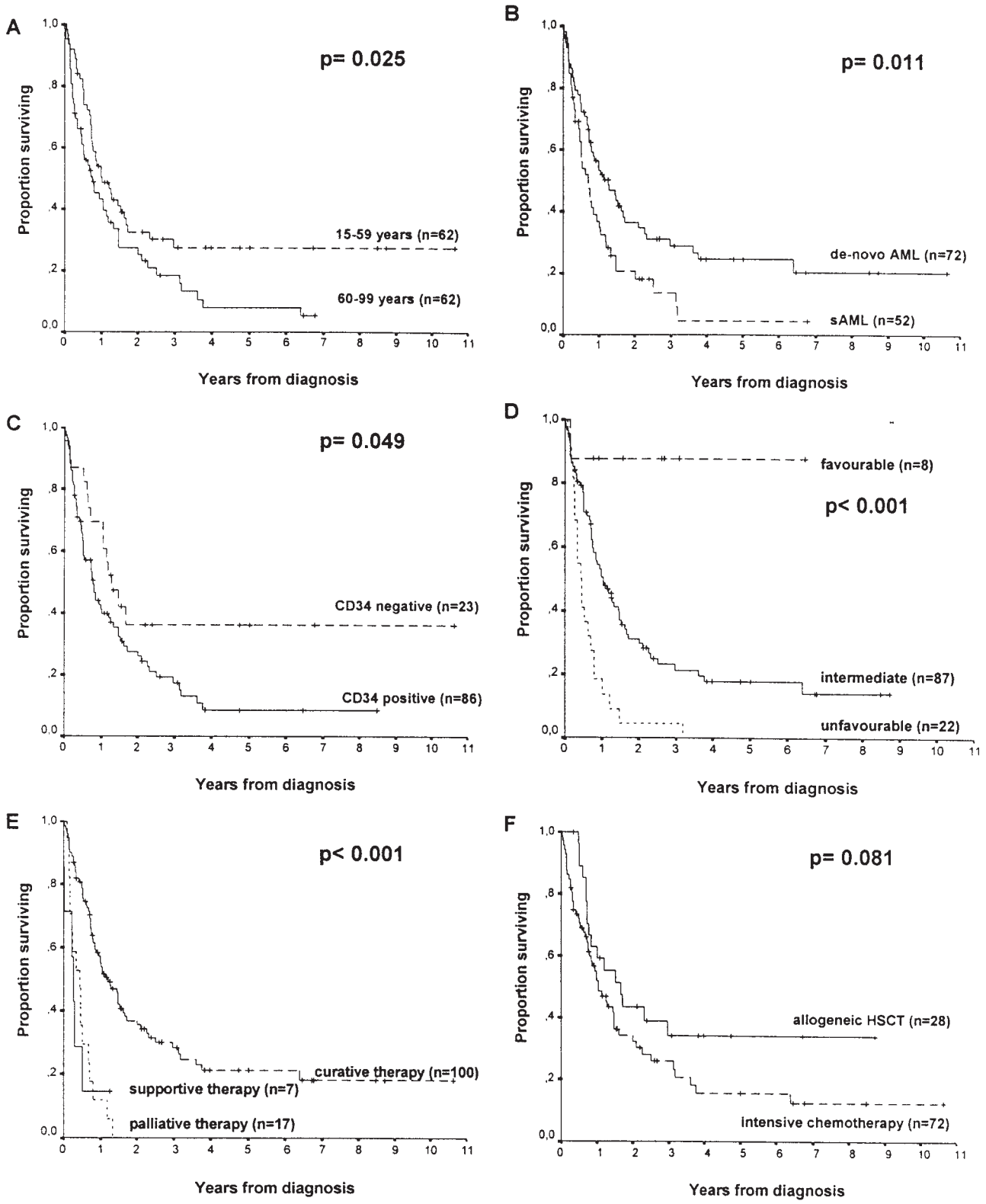

Figure 1. Overall survival of 124 AML patients divided by age (A), type of AML (B), CD34 expression on AML blasts (C), cytogenetic risk group (D) and type of therapy (E) are displayed. Furthermore, OS of the 100 patients that received a potential curative therapy divided by the type of consolidation (F) are presented.

of age was 12 months (range 22 days – 129 months) compared to 9 months (range 4 days – 82 months) in patients ≥60 years (p=0.032). In the ≥60 years old group unfavorable cytogenetics were more common compared to younger patients (18/57 (32%) vs. 4/60 (7%), p=0.002). Whereas in all patients <60 years some potential curative therapy was initiated, older patients were more likely to receive therapies that had only palliative (17/57 (28%)) or supportive (7/57 (11%); p<0.001, both) character.

Type of AML. Patients with de-novo AML at diagnosis had a better survival compared to patients with sAML (5 yrs-OS 24% vs 5%, p=0.010, Fig. 1B). Median survival of the patients with de-novo AML was 15 months (range 4 days – 129 months) compared to 8 months (range 5 days – 82 months) in patients with sAML (p=0.015).

Blood counts and LDH at diagnosis. Laboratory values were available for 119/124 AML patients (96%). Differential counts were available for 117/124 AML patients (94%) from the peripheral blood and 109/124 (88%) from the bone marrow, respectively. Laboratory results are shown in Table 2.

No association between hemoglobin levels or platelet counts at diagnosis and prognosis was found. Median leukocyte count at diagnosis was 8.0 Gpt/l and ranged from 0.5 to 347 Gpt/l (Tab. 2). Patients with WBC >50 Gpt/l had a median survival of 5 months (range 4 days – 37 months) compared to patients with WBC ≤10 Gpt/l (median 15 months (range 5 days – 129 months)) as well as compared to patients with WBC 10 – ≤50 Gpt/l (median 10 months (range 24 days – 103 months)) (p=0.072). Five years OS was 6%, 18% and 22%, respectively (>50 Gpt/l vs. ≤10 Gpt/l: p=0.005; >50 Gpt/l vs. 10 – ≤50 Gpt/l: p=0.034). Overall survival analyses showed significant differences between the WBC >50 Gpt/l and the WBC ≤10 Gpt/l patients (p=0.005) as well as the WBC 10 – ≤50 Gpt/l group (p=0.048). Overall survival analyses showed no significant differences between the WBC ≤10 Gpt/l patients and the WBC >10 – ≤50 Gpt/l group.

Neither the percentages of AML blasts in the bone marrow nor the percentages of AML blasts in the peripheral blood at first diagnosis (Tab. 2) were of prognostic value concerning survival (data not shown).

LDH was elevated in 85/117 patients (73%) at diagnosis (Tab. 2). Survival of patients with LDH values <2000 U/l tended to be better compared to patients with LDH values ≥2000 U/l (5yrs-OS 20% vs 10%, p=0.150).

FAB-type. FAB M2 and M4 were the most common subtypes in our analyses (Tab. 1). Survival analyses of the different groups showed that the 6 patients with AML FAB M3 had a significant better 5yrs-OS (5/6, 83%) compared to all other subtypes (27/118, 15%, p=0.028). This difference remained significant in OS analyses (p=0.028). The median survival time for the FAB-M3 has not been reached (follow up 2–61 months) compared to a median survival of 10 months in all other FAB subgroups (range 4 days – 129 months). Analyses of the other subgroups showed no prognostic influence (data not shown).

Table 1. Clinical characteristics at first diagnosis

Patient characteristics	Total number of patients (n=124)
Age [yrs] (median (range))	61 (17–90)
patients ≥60 yrs [%]	50 (n=62)
patients ≥65 yrs [%]	32 (n=40)
Sex (female) [%]	52 (n=64)
de-novo AML [%]	58 (n=72)
FAB-subtype AML [%]:	
M0	4 (n=5)
M1	10 (n=13)
M2	18 (n=22)
M3	5 (n=6)
M4	27 (n=34)
M5	8 (n=10)
M6	6 (n=7)
M7	1 (n=1)
unclassified	21 (n=26)
Treatment [%]	
supportive therapy	5 (n=7)
palliative therapy	14 (n=17)
curative therapy	81 (n=100)
chemotherapy	58 (n=72)
chemotherapy + allogeneic HSCT	23 (n=28)

Table 2. Laboratory values at the time of first diagnosis

Characteristics	Total number of patients (n=119)
WBC [Gpt/l] (median (range))	8.0 (0.5–347)
pts with ≤10 Gpt/l [%]	52 (n=62)
pts with >10 und ≤ 50 Gpt/l [%]	34 (n=40)
pts with > 50 Gpt/l [%]	14 (n=17)
Hemoglobin [g/dl] (median (range))	8.9 (3.7–16.7)
Plt-count [Gpt/l] (median (range))	50 (2–853)
LDH [U/l] (median (range))*	847 (95–24366)
Blasts in peripheral blood [%] (median (range))	35 (5–97)
Blasts in bone marrow [%] (median (range))	30 (0–99)

*normal LDH range: <200 U/l

CD34-surface expression. Flow cytometry was performed in 109/124 (88%) cases. In most patients (86/109, 79%) the AML blasts expressed CD34 on their surface, in 23/109 patients (21%) the AML blasts were negative for CD34. Patients with CD34 negative AML blasts at diagnosis had a better survival compared to patients with CD34 positive AML blasts (5 yrs-OS 36% vs. 9%, p=0.049, Fig. 1C). Median survival of the patients with CD34 negative AML blasts was 16 months (range 7 days – 129 months) compared to 9 months (range 5 days – 103 months) in patients with CD34 positive AML (p=0.037).

Cytogenetics. Cytogenetics were available for 117/124 (94%) patients. Results of the cytogenetic analyses are displayed in Table 3.

Table 3. Characteristics of the cytogenetic findings

Cytogenetic aberration	Number of patients (%)	as single mutation (%)	with >3 aberrations (%)
normal karyotype	47 (40%)		
+8	20 (17%)	9 (45%)	5 (25%)
inv16 or t(16;16)	2 (2%)	1 (50%)	
–7/del(7q)	19 (16%)	6 (32%)	6 (32%)
–7	9 (8%)	2 (22%)	3 (33%)
del(7q)	10 (8%)	4 (40%)	3 (33%)
–5/del(5q)	17 (14%)	1 (6%)	11 (65%)
–5	4 (3%)		2 (50%)
del(5q)	13 (11%)	1 (8%)	9 (69%)
t(8;21)	1 (1%)	1 (100%)	
–Y	2 (2%)	1 (50%)	1 (50%)
balanced abn. (11q23)	5 (4%)	2 (40%)	2 (40%)
t(9;11)	2 (2%)	1 (50%)	
t(11;21)	3 (3%)	1 (33%)	2 (67%)
del(20q)	4 (3%)		3 (75%)
del/inv(9q)	2 (2%)	2 (100%)	
del(11q)	4 (3%)	1 (25%)	3 (75%)
abn(12p)	2 (2%)	1 (50%)	
del(3q)	2 (2%)	1 (50%)	
inv3/t(3;3)	4 (3%)	2 (50%)	
t(15;17)	4 (3%)	2 (50%)	
t(5;17)	2 (2%)		2 (100%)
other structural aberrations	12 (10%)	7 (58%)	
–18	6 (5%)		6 (100%)
+13	3 (3%)		1 (33%)
+21	2 (2%)		
+(21q)	2 (2%)	1 (50%)	
–X	2 (2%)		1 (50%)
+4	2 (2%)	1 (50%)	
other numerical aberrations	11 (9%)	3 (27%)	5 (45%)

Table 4. Characteristics of the cytogenetic risk groups

Risk Group	Number of patients (%)	Median age (range) [years]	de-novo AML (%)	CD34+ AML (%)	Median survival (range) [months]
favorable	8 (7%)	57 (17–74)	100%	100%	Not reached
intermediate	87 (74%)	58 (17–90)	60%	76%	12 (0–106)
unfavorable	22 (19%)	66 (46–80)	32%	86%	5 (0–38)

Risk grouping according to the risk groups defined in the MRC 10 trial was performed (Tab. 4). Most patients (74%) had an intermediate risk group profile. Patients with poor cytogenetics were older and had more often sAML (Tab. 4) (p=0.002, both).

Median survival of patients with favorable cytogenetic risk has not been reached. One patient of this group (1/8, 13%) died within follow up (at 12 months). Median survival of patients with intermediate cytogenetic risk was 12 months (range 5 days – 106 months). Sixty four patients (74%) of this group died within follow up. Median survival of patients with poor cytogenetic risk was 5 months (range 24 days – 38 months). All 22 patients (100%) of this group died within the follow up. Five year survival as well as OS was significantly different between the 3 risk groups (Fig. 1D). Patients with favorable risk had a better OS compared to the intermediate risk group (p=0.010) as well as compared to the unfavourable risk group (p<0.001). Patients with an intermediate risk had a better OS compared to the unfavorable risk group (p<0.001). The survival at 5 years tended to be better for the favorable risk group (88%) compared to the intermediate risk group (52%, p=0.107) and was significantly better compared to the unfavorable risk group (18%, p=0.005).

Influence of therapy on prognosis. Most patients (81%) received chemotherapy with a curative intention, 14% received a palliative chemotherapy and 5% supportive care only (Tab. 1). Median survival of patients with any curative therapy was 15 months (range 5 days – 129 months). Sixty nine out of 100 (69%) patients of this group died within follow up. Median survival of patients with palliative chemotherapy was 5 months (range 1 month – 16 months). All 17 patients (100%) of this group died within follow up. Median survival of patients with supportive care was 3 months (range 4 days – 15 months). Six out of 7 patients (86%) of this group died within follow up. Overall survival was significantly different between the 3 therapy groups (Fig. 1E). Patients with potential curative therapies had a better survival compared to the palliative therapy group (p<0.001) as well as compared to the supportive care group (p<0.001). Survival of patients with palliative therapy had a similar survival compared to patients with best supportive care (p=0.700).

Twenty eight out of 100 patients (28%) in whom curative therapies were initiated received an allogeneic HSCT at a median of 6 months following first diagnosis. All other patients received conventional chemotherapy ± autologous HSCT. Patients with allogeneic HSCT tended to have a better survival compared to patients with no allogeneic HSCT (5 yrs-OS 34% vs. 15%, p=0.092, Fig. 1F). Median survival of the patients with allogeneic HSCT was 20 months (range 4–106 months) compared to 13 months (range 5 days – 129 months) in patients without allogeneic HSCT (p=0.053).

Of interest, patients in our cohort that were diagnosed before 1.1.1997 (31/124, 25%) had a 5-year survival of 28% compared to patients diagnosed after 1.1.1997, that had a 5 year survival of 14% (p=0.022). The median survival in those two cohorts was 18 months (range 2–129 months) compared to 9 months (range 4 days – 61 months), respectively

Table 5. Risk factor analyses for the event death

Risk factor	univariate RR (95% CI)	p	multivariate RR (95% CI)	p
Therapy				
palliative vs curative	3.8 (2.2–6.9)	<0.001	2.2 (1.0–4.7)	0.040
supportive vs curative	4.3 (1.8–10.2)	0.001	2.5 (0.8–7.5)	0.101
Age				
60 yrs vs <60 yrs	1.1 (0.7–1.7)	0.770		
WBC (Gpt/l)				
>10 and ≤50 vs ≤10	1.1 (0.6–1.8)	0.806	1.0 (0.5–2.0)	0.910
>50 vs ≤10	1.7 (0.8–3.6)	0.148	0.9 (0.4–2.4)	0.871
LDH (U/l)				
LDH ≥2000 vs <2000	1.5 (0.9–2.6)	0.150	1.5 (0.7–3.1)	0.285
Cytogenetic risk group				
Intermediate vs favorable	7.6 (1.1–55.2)	0.044	6.1 (0.7–51.6)	0.094
Unfavorable vs favorable	17.7 (2.3–137)	0.006	16.8 (1.8–154)	0.012
CD34 positivity of blasts				
$CD34^+$ vs $CD34^-$	2.0 (1.0–3.9)	0.047	2.1 (1.0–4.4)	0.046
Type of AML				
sAML vs de-novo AML	1.5 (0.9–2.5)	0.087	0.9 (0.5–1.7)	0.764
FAB-Subtype				
All others vs AML M3	5.7 (0.8–41.2)	0.084	2.7 (0.3–24.9)	0.372
Therapy				
Chemotherapy vs allogeneic HSCT	1.5 (0.9–2.5)	0.156	2.5 (1.3–4.9)	0.008
First diagnosis				
after 97 vs before 97	1.5 (0.9–2.6)	0.129	2.2 (1.1–4.2)	0.025

(p=0.006). Other time intervals did not have a significant influence on prognosis.

Univariate and multivariate analyses. In order to determine independent prognostic factors univariate and multivariate analyses were performed. The prognostic influence of the therapy was calculated based on all patients in the study, whereas all other prognostic factors were calculated for the 100 patients who received any type of curative therapy. Results are displayed in Table 5.

As expected, the type of therapy (palliative as well as supportive vs. curative) had an independent prognostic influence on survival.

Within the curative treatment group favorable cytogenetics and CD34 negativity of AML blasts were significantly associated with a better survival in the univariate analyses. In the multivariate analyses favorable cytogenetics were an independent prognostic factor for better survival compared to intermediate risk cytogenetics (trend, p=0.09) and a significant independent prognostic factor for better survival compared to unfavorable risk cytogenetics (p=0.012). CD 34 positivity of the AML blasts was an independent risk factor for inferior survival (p=0.046). Patients who received no allogeneic HSCT during their treatment had after adjustment for other risk factors an inferior prognosis (p=0.008). The time of first diagnosis, i.e. before 1997 or after, remained a significant risk factor for poor survival (p=0.025) after adjusting for competing risks.

Discussion

Although significant progress has been made in the treatment of AML over the last decades, the majority of patients still die from complications of disease or therapy. In order to improve these results risk adapted treatment strategies have been developed. These are based on the early identification of patients biological and disease specific risk factors, in order to allow influence of treatment decisions. Whereas some prognostic factors such as karyotype are already included in current risk profiling, the prognostic value of others are still unclear. In the current study several proposed risk factors in a cohort of 124 AML patients were retrospectively analyzed to define their influence on prognosis.

Before interpreting our results it has to be considered that some subgroups were small and not all patients received the same treatment. Instead we included all patients treated and diagnosed during the study period leading to an older cohort compared to most studies but also leading to a less biassed cohort. Nevertheless, some results are intriguing, especially results based on immunophenotyping that are not always centralized in large multicentre studies and are therefore open for methodical differences.

The karyotype of AML blasts at diagnosis has been identified as the most important independent determinant of outcome for patients with AML in recent years [7, 10, 16 17, 22, 35, 37]. In our study 60% of the patients had aberrant karyotypes. This is in line with published data that describe cytogenetic alterations in 52–86% of AML and t-AML patients [7, 10, 17, 26 35, 37]. Furthermore, we found in accordance with these studies more unfavorable cytogenetic alterations in the older patients. Based on data from the MRC 10 trial in which 3 different prognostic groups were defined we divided our patients accordingly [17]. The discrimination concerning prognosis was good and the cytogenetic risk group was after adjusting for competing risks the most important prognostic factor. Median survival of our three subgroups confirms data from other studies that defined similar or nearly similar cytogenetic risk groups [10, 17, 354, 37]. In the large British AML MRC 10 trial 5-year overall survival rates for cytogenetic favourable risk patients were in 71%, for intermediate risk patients in 41% and for poor risk patients in 17% range, respectively [17, 48]. While the cytogenetic analysis provides the framework that can distinguish groups of different prognosis, it lacks the ability to distinguish cohorts of patients with differing prognoses within

cytogenetic risk groups [34]. In the future this may be enhanced with discovery of novel rearrangements associated with AML, such as *Flt3* or *CEBPA* mutations [15, 32, 40], or gene expression profiling of AML cells [8, 44].

Easy obtainable prognostic factors such as age, WBC, LDH, and type of AML (secondary vs. de-novo) were able to identify patients with inferior prognosis. However, when adjusted for competing risks their prognostic relevance was substantially reduced. Similar effects were seen for these variables in multivariate analyses of several AML studies [16, 19, 22, 30, 48]. In accordance with published data FAB morphology groups except for AML FAB M3 were of no benefit to determine prognosis [39].

The prognostic value of CD34 expression of AML cells is still unclear. In our study expression of CD34 on the surface of the AML occurred slightly more frequently as described in other studies that describe CD34+AML blasts in 42–77% of all cases [4, 13, 24, 38]. In our study CD34 positivity of AML cells was associated with an inferior survival and was an independent prognostic factor (Fig. 1C). Several studies have investigated the prognostic value of CD34 expression on AML-blasts. Whereas some studies are consistent with our results and found a worse survival of patients with CD34+ blasts [11, 13, 23], other studies could not confirm these data [4, 12, 24, 31]. Instead, LEGRAND et al found that not a single antigen expression on AML cells can be applied for risk stratification in AML patients at diagnosis but expression of two or more of the panmyeloid markers myeloperoxidase, CD13, CD33, CDw65 and CD117 [24]. In fact, this group found CD34 positivity in both, patients with good and poor prognosis. Similarly, the French Groupe d'Etude Immunologique des Leucémies (GEIL) has performed a large multicenter immunophenotyping study and has recently proposed a immunological classification of AML cells using a 7 antigen immunephenotyping approach that could discriminate five AML subsets with different prognosis [11]. In this study CD34 positivity by itself had prognostic significance in some but not all subsets. Therefore, it seems today that the CD34 positive AML patients comprise a heterogenous group with good and poor risk factors and the prognostic significance of CD34 expression remains unclear.

Patients that have received an allogeneic HSCT at some point of their treatment course had a better prognosis compared to patients who received a potentially curative therapy, but no allogeneic HSCT (Fig. 1F). The value of allogeneic HSCT in relapsed AML has been clearly established and preliminary data indicate that allogeneic HSCT as consolidation might be of value in first line treatment depending on karyotype and if appropriate donors are available [9, 14, 37, 41]. Our data support those findings.

Surprisingly, in our analyses patients that were diagnosed before 1997 had a better survival compared to patients that were diagnosed after 1997. An explanation for this finding is lacking. However, one possible reason for this independent prognostic significance might be the incidence of infection related mortality in our patient population. Several reports have described increases of fungal infections after or during reconstruction as has been performed in our wards especially in long term neutropenic patients such as AML [5, 28, 46]. Final analyses of infection rates in our cohort are currently performed.

In conclusion, our study confirms karyotype as an independent prognostic factor for overall survival in patients with newly diagnosed AML. Future studies will likely further modify prognostic categorization of AML patients by subdividing cytogenetic risk groups according to the results of new molecular marker studies and maybe other factors. As shown in this analyses CD34 expression on the surface alone or in combination with other antigens might be one of those and might therefore be considered for further risk stratification models. In addition, this study supports the findings that allogeneic HSCT is beneficial in AML, since receiving an allogeneic HSCT was an independent good prognostic factor.

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