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A new prognostic score for patients with acute myeloid leukemia based on cytogenetics and early blast clearance in trials of the German AML Cooperative Group

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A B S T R A C T

Background and Objectives. To refine cytogenetically based risk-stratification in acute myeloid leukemia (AML).

Design and Methods. Stratification was improved by combining cytogenetics and day 16 bone marrow blasts and by subdividing unfavorable cytogenetics. The new score identifying five prognostically different groups was developed in 321 patients (AMLCG 1992 trial) and subsequently validated in 680 patients (AMLCG 1999 trial).

Results. Subgroups defined were: 1) favorable cytogenetics (t(8;21), inv(16)); 2) intermediate cytogenetics (normal karyotype, other abnormalities not rated favorable or unfavorable) and day 16 blasts <10%; 3) intermediate cytogenetics and day 16 blasts ≥10%; 4) unfavorable cytogenetics (-5/5q-, -7/7q-, 3q21q26 aberrations, 11q23 aberrations, 12p-, 17p-) excluding complex aberrations; 5) complex aberrant karyotypes (≥3 aberrations). In AMLCG 1992 patients significant differences were observed with regard to complete remission (CR) rate (82%, 83%, 58%, 76%, 53%), persistent leukemia (PL) rate (7%, 8%, 33%, 14%, 31%), median event-free survival (EFS; 25, 14, 5, 6, 2 months), median overall survival (OS; not reached, 26, 12, 14, 6 months), and median relapse-free survival (RFS; 26, 19, 13, 8, 4 months). The prospective validation of the score proved its significant power (AMLCG 1999 cohort) with regard to CR (63%, 65%, 51%, 45%, 35%), PL (17%, 18%, 40%, 35%, 48%), median EFS (14, 7, 3, 2, 2 months), median OS (25, 15, 12, 6, 4 months), and median RFS (not reached, 15, 10, 8, 5 months).

Interpretation and Conclusions. This new prognostic score provides a highly valuable tool for future clinical trials in AML focusing on distinct and subgroup-specific treatment effects.

Key words: acute myeloid leukemia, cytogenetics, prognostic factors.

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Acute myeloid leukemia (AML) is a heterogenous disease as reflected by differences in the morphology of the leukemic blasts,[1-5] by variations in the clinical picture,[6-10] and by the therapeutic outcome.[11-13] Cytogenetic and molecular techniques have, on the one hand provided deeper insights into the biology of AML[14-18] and, on the other hand, have a major impact on the prognosis of patients with AML which can be estimated based on several patient-specific and disease-related factors.[19-21] Thus, three main cytogenetic subgroups with highly different prognoses have been defined:[22,23] (i) CBF-leukemias (AML associated with t(8;21) and with inv(16)/t(16;16)) and acute promyelocytic leukemia with t(15;17). Patients with these AML subtypes achieve long-lasting remissions and many of them can be cured; (ii) AML with normal karyotype or with rare aberrations which is associated with an intermediate prognosis; and (iii) AML with abnormalities of chromosomes 5 and 7 and/or with complex aberrant karyotypes (i.e. ≥3 chromosomes involved) in which the median survival amounts to less than six months. Within the cases with unfavorable cytogenetics, those with complex aberrations have a particularly dismal prognosis with only a few long-term survivors.[24]

Despite the application of additional prognostic factors such as age and history of preceding hematologic diseases, the prognosis of patients within the respective cytogenetically defined subgroups still remains quite heterogeneous.

Several trials have tried to improve the individual risk assignment by the quantification of minimal residual disease (MRD) using molecular markers. However, this approach is limited to cases in which AML is associa-

ted with specific genetic changes such as the fusion gene PML/RARα in acute promyelocytic leukemia.[25] In these cases a persisting or recurring positivity for the transcript during remission and its quantification above a distinct limit following consolidation therapy, respectively, are associated with an increased risk of relapse.[25-32] Similar approaches are being evaluated for other subgroups of AML with molecular markers, all of which focus on the quantification of the level of disease after patients have achieved a remission.[33-41]

Another approach for individual prediction of outcome has been to evaluate early response parameters. As a paradigm, a rapid decline of leukemic blasts was identified as the most important prognostic factor in childhood acute lymphoblastic leukemia.[42] In AML, assessments of early response were mainly restricted to the speed of achievement of remission[43-44] or the achievement of remission by one course of treatment only.[45] Early response to therapy, as assessed by residual leukemic bone marrow blasts during aplasia was shown to have a major prognostic impact in a preliminary report.[46,47] In early studies we demonstrated an association between cell killing kinetics during induction therapy and the achievement of complete remission.[48] We recently demonstrated that early quantification of therapy-induced cytoreduction in leukemic bone marrow correlated strongly not only with response to induction therapy but also with long-term outcome in a cohort of 449 adult patients with newly diagnosed AML.[21;47]

The present analysis is the first step aimed at improving the prognostic model based on the cytogenetic risk stratification: a) by including the level of bone marrow blasts one week after the end of the first course of induction therapy, and b) by defining AML with complex aberrant karyotypes as a distinct group. We defined this model based on 321 patients with *de novo* AML treated within the AMLCG 1992 trial. In the second step we validated the new risk score prospectively in 680 patients treated within the AMLCG 1999 trial. We were able to clearly separate five prognostic subgroups for both studies using the pre-therapeutic parameter cytogenetics and therapy-dependent early blast clearance.

Design and Methods

Patients

Patients older than 16 years with newly diagnosed *de novo* AML were eligible for this trial. Patients with acute promyelocytic leukemia were treated in a separate trial.[49] Patients who had had prior antileukemic treatment, who had AML secondary to prior chemotherapy, and AML developing from an antecedent hematologic malignancy were included in the AMLCG 1999 trial only but were excluded from the AMLCG 1992 trial. Patients with severe co-morbidity precluding the initiation of intensive induction chemotherapy (i.e., severe uncontrolled infections, coronary heart disease WHO grade III/IV, congestive heart failure WHO grade III/IV, severe hyperbilirubinemia WHO grade III/IV or severe creatinine elevation WHO grade III/IV unless due to leukemia) were excluded from both trials. Only patients with both central cytomorphologic diagnosis and cytogenetic results as well as assessment of residual bone marrow blast cells on day 16 were included in this analysis.

Antileukemic therapy

Therapy in the AMLCG 1992 trial

Induction. For remission induction patients were treated according to the previously published double induction strategy with the second course starting on day 21 irrespective of response of the disease to the first course.[47] The first course consisted of the TAD combination with standard-dose cytosine arabinoside 100 mg/m^2/day c.i. on days 1 and 2, 100 mg/m^2 12 hours i.v. as a one-hour-infusion on days 3 to 8, daunorubicin 60 mg/m^2 i.v. as a one-hour-infusion on days 3 to 5, and oral thioguanine 100 mg/m^2 q 12 hours on days 3 to 9.[50] The second course was HAM with high-dose AraC 3 g/m^2 (1 g/m^2 in patients of ≥ 60 years old) q 12 hours i.v. as a three-hour-infusion on days 1 to 3 and mitoxantrone 10 mg/m^2 i.v. as a one-hour-infusion on days 3 to 5.[51] The HAM course was scheduled to start on day 21 unless patients had severe life-threatening non-hematologic toxicity in which case chemotherapy was postponed until resolution of the toxicity. The second course of the double induction therapy was applied to patients older than 60 years only if they had residual leukemic blasts in the bone marrow on day 16, i.e. one week after completion of the first course.

Consolidation. Consolidation therapy consisted of one course of TAD which was applied two to four weeks after achievement of complete remission. Patients under the age of 60 with HLA-identical sibling donors subsequently underwent allogeneic bone marrow or peripheral blood stem cell transplantation.

All other patients received further treatment according to the randomization performed at study entry. Patients were randomized upfront to three years of myelosuppressive maintenance therapy or to a second course of intensive consolidation therapy following TAD-consolidation.

Maintenance. Maintenance therapy was applied every four weeks and consisted of AraC 100 mg/m^2 q 12 hours s.c. on days 1 to 5 in combination with either daunorubicin 45 mg/m^2 on days 2 and 3 (courses one, five, nine, etc.), thioguanine 100 mg/m^2 q 12 hours on days 1 to 5 (courses two, four, six, etc.), or cyclophosphamide 1

g/m^2 on day 3 (courses three, seven, eleven, etc.).[44,52] Treatment was delayed and doses were reduced for hematologic toxicity according to pre-defined criteria. Upon achievement of a cumulative dose of daunorubicin of 540 mg/m^2, the daunorubicin was replaced by thioguanine.

Second course of consolidation. The second course of consolidation therapy consisted of the sequential high-dose AraC and mitoxantrone (S-HAM) combination[53] and was applied four to six weeks after recovery from hematologic toxicity following TAD-consolidation. S-HAM consisted of high-dose AraC as a three-hour infusion every 12 hours on days 1, 2, 8, and 9. The dose per application of high-dose AraC was 1 g/m^2 in patients younger than 60 years and 500 mg/m^2 in older patients. Mitoxantrone was given at a dose of 10 mg/m^2 in a one-hour infusion on days 3, 4, 10, and 11.

Therapy in the AMLCG 1999 trial

Treatment in the 1999 trial was identical to that in the 1992 trial with regard to induction and post-remission therapy with the following exceptions: patients were randomized 1) to receive TAD/HAM or HAM/HAM as double induction therapy and 2) to receive autologous stem cell transplantation or three years of maintenance after consolidation therapy (patients under the age of 60 only; all patients ≥60 years received maintenance treatment). In addition, patients from 25 of the 52 participating study centers were randomized to receive or not priming with granulocyte colony-stimulating factor two days before and during chemotherapy.

Diagnostics

Cytomorphology

Cytomorphologic assessment was based on May-Grünwald-Giemsa stains, myeloperoxidase reaction, and non-specific esterase using α-naphthyl-acetate. All staining was performed centrally according to standard procedures.[54] AML was diagnosed cytomorphologically according to the criteria of the FAB classification.[2,5,55] The percentage of residual leukemic blasts in the bone marrow was assessed cytomorphologically on day 16 at the respective local institutions, i.e. one week after completion of the first course of induction therapy.

Cytogenetics

Cytogenetic analyses were performed centrally according to standard protocols. Cytogenetic data were classified according to the ISCN nomenclature.[24] Patients were classified into three subgroups based on cytogenetics: the group associated with a favorable prognosis included AML with t(8;21), inv(16), or t(16;16); the unfavorable-prognosis group contained AML with aberrations of chromosomes 5 or 7, aberrations of 11q23, 12p, or 17p, inv(3), t(3;3), or with a complex aberrant karyotype (i.e. 3 chromosomes involved); the group associated with an intermediate prognosis included AML with other karyotype aberrations as well as AML with a normal karyotype.

Study parameters

Bone marrow examinations were carried out on day 16 following TAD induction and on day 12 following HAM induction, i.e. one week after the end of chemotherapy (=day 16 blasts), and upon full recovery of peripheral blood counts. Response to therapy was assessed according to CALGB criteria.[47,56] Complete remission (CR) was defined by a bone marrow with normal hematopoiesis of all cell lines, less than 5% blast cells, and peripheral blood with at least 1,500/μL neutrophils and 100,000/μL platelets. Therapeutic failures were classified as persistent leukemia, death less than seven days after completion of the first induction therapy course (early death) and death during treatment-induced bone marrow hypoplasia, irrespective of the time after chemotherapy (hypoplastic death). Cases with early death, i.e. death before day 16 and day 12, respectively, were excluded from the present analyses (group with intermediate cytogenetics only). Relapse was defined as reinfiltration of the bone marrow by 5% or more leukemic blasts or a proven leukemic infiltration at any other site.

Survival was measured by the time from inclusion into the study to death and event-free survival (EFS) was measured by the time from inclusion into the study to death, documentation of persistent leukemia, or relapse, respectively. Relapse-free survival (RFS) was measured by the time from achievement of CR to relapse or death during CR. Freedom from relapse was measured by the time from achievement of CR to relapse. Life-table analyses were calculated by the Kaplan Meier method.[57]

Definition of the new prognostic score for AML

The new prognostic score was defined by introducing the residual bone marrow blasts seven days after the end of the first induction course (day 16 blasts) and AML with complex aberrant karyotype as a distinct group into the cytogenetically based prognostic score (Table 1). Thus, five categories were defined: 1) AML with favorable karyotype; 2) AML with intermediate karyotype and day 16 blasts <10% in bone marrow; 3) AML with intermediate karyotype and day 16 blasts ≥10% in bone marrow; 4) AML with unfavorable karyotype excluding complex aberrations; and 5) AML with complex aberrant karyotype.

Statistics

Dichotomous variables were compared between different groups using the χ^2-test. The time-to-event variables of overall survival, EFS, and DFS were estimated by the Kaplan and Meier method and differences

Table 1. New prognostic score in AML discriminating five subgroups.

- Favorable karyotype, i.e. t(8;21) or inv(16)/t(16;16)
- Intermediate karyotype and day 16 blasts <10% in bone marrow
- Intermediate karyotype and day 16 blasts ≥10% in bone marrow
- Unfavorable karyotype excluding complex aberrant karyotypes
- Complex aberrant karyotype

between the respective groups were calculated using the log rank test. All calculations were performed using SAS 8.2.[58] All *p* values reported are two-sided.

Study conduct

Prior to randomization all patients gave their informed consent to participation in the current study after having been advised about the purpose and investigational nature of the trial as well as of its potential risks. The study design adhered to the declaration of Helsinki and was approved by the ethics committees of the participating institutions prior to its initiation.

Results

Patients

Data on 321 patients with *de novo* AML who were entered into the German AML Cooperative Group 1992 trial between December 1992 and May 1999 were used to develop a new prognostic score (Table 1). Cytogenetics and evaluations of day 16 blasts were available in all of these patients.

The patients' ages ranged from 17 to 76 years (median, 53 years). Cytogenetics were classified as favorable in 45 (14.0%), intermediate in 217 (67.6%), and unfavorable in 59 (18.4%) cases. Patients with unfavorable cytogenetics were further subdivided into those with complex aberrant karyotypes (n=38, 11.8%) and other unfavorable karyotypes (n=21, 6.5%). The day 16 blasts in these 321 patients ranged from 0% to 100% (median, 5%; mean±SD, 18.3±28.2%).

To validate this score prospectively data were used on 680 patients who were entered into the German AML Cooperative Group 1999 trial between June 1999 and June 2002 (median follow-up, 474 days). Four hundred and forty-two (65.0%) patients had *de novo* AML and 238 (35%) had secondary AML or high risk myelodysplastic syndrome (MDS). Their ages ranged from 16 to 81 years (median, 58 years). In all of these patients cytogenetics and evaluations of day 16 blasts were available. Cytogenetics were favorable in 70 patients (10.3%), intermediate in 426 patients (62.6%), other unfavorable in 85 patients (12.5%), and complex aberrant in 99 patients (14.6%). The day 16 blasts ranged from 0% to 100% (median, 5%; mean±SD, 16.7±24.8%). AML subtypes according to the FAB classification are listed in Table 2 for both cohorts.

Table 2. Patients' characteristics (number of cases and median/range are given where applicable).

Parameter	Test cohort	Validation cohort
Number of patients	321	680
Trial	AMLCG 1992	AMLCG 1999
Period of recruitment	Dec. 1992	June 1999
	May 1999	June 2002
Sex (male/female)	166/155	353/327
Age (years, median/range)	53/17-76	58/16-81
De novo	321 (100%)	442 (65%)
secondary AML		238 (35%)
Cytogenetics		
favorable	45 (14.0%)	70 (10.3%)
intermediate	217 (67.6%)	426 (62.6%)
other unfavorable	21 (6.5%)	85 (12.5%)
complex aberrant	38 (11.8%)	99 (14.6%)
FAB subtype		
M0	6	21
M1	72	111
M2	112	267
M4	47	118
M4Eo	26	36
M5a	17	25
M5b	26	28
M6	12	29
M7	1	3
n.a.	2	42
LDH (U/L, median/range)	426/98-5220	373/84-11150
Day 16 blasts (%, median/range)	5/0-100	5/0-100

n.a.: not available.

Treatment outcome

Of all 321 patients in the test cohort, 233 (72.6%) achieved a complete remission, 56 (17.4%) had persistent leukemia and 32 (10.0%) succumbed to hypoplastic death. The median overall survival was 17 months (22.9% at five years), the median event-free survival was 8 months (20.6% at five years), and the median relapse-free survival was 14 months (28.6% at five years). Of all 680 patients in the second cohort, 374 (55.0%) achieved a complete remission, 197 (29.0%) had persistent leukemia and 109 (16.0%) succumbed to hypoplastic death. The median overall sur-

Table 3. Prognostic impact of cytogenetic score.

Test cohort (AMLCG 1992)	*n*	*CR*	*PL*	*ED/HD*	*OS (months) (median)*	*EFS (months) (median)*	*RFS (months) (median)*
Favorable karyotype	45	82%	7%	11%	n.r.	25	26
Intermediate karyotype	217	74%	17%	9%	18	10	15
Unfavorable karyotype	59	61%	26%	13%	8	4	6
Validation cohort (AMLCG 1999)	*n*	*CR*	*PL*	*ED/HD*	*OS (median)*	*EFS (median)*	*RFS (median)*
Favorable karyotype	70	63%	17%	20%	25	14	n.r.
Intermediate karyotype	426	60%	26%	14%	12	5	14
Unfavorable karyotype	184	40%	42%	18%	6	2	7

Ordinal χ^2-test: p = 0.0918 for response rates in test cohort and p <0.0001 for response rates in validation cohort; log-rank test: p <0.0001 for all end-points in both cohorts. CR: complete remission; PL: persistent leukemia; ED: early death; HD: hypoplastic death; OS: overall survival; EFS: event-free survival; RFS: relapse-free survival; n.r.: not reached.

vival was 11 months (17.9% at 2.5 years), the median event-free survival was 4 months (14.2% at 2.5 years), and the median relapse-free survival was 12 months (24.5% at 2.5 years).

Prognostic impact of the standard cytogenetic score

Separation of patients according to favorable, intermediate, and unfavorable cytogenetics resulted in marginally significant differences in response rates and in significant differences in the course after achievement of CR in the test cohort (Table 3). Median overall survival for these three groups was not reached vs. 18 months vs. 8 months (p<0.0001). The same was true for the separation of the validation cohort according to the cytogenetic score (Table 3; Figures 1, 3, and 5), which also showed significant differences in overall survival (median, 25 months vs. 12 months vs. 6 months, p<0.0001).

Prognostic impact of the new score

The application of the newly developed score defining five subgroups resulted in an improvement of the cytogenetic score. Thus, patients with intermediate cytogenetics were further separated into two groups based on day 16 blasts (<10% and ≥10% of blasts in the bone marrow), and patients with unfavorable cytogenetics were further separated into those with other unfavorable cytogenetics and complex aberrant karyotypes. Applying this score to the test cohort both response rates and course after achievement of CR differed very significantly between the five groups (Table 4). In fact, the group identified by intermediate cytogenetics and day 16 blasts <10% had a CR rate comparable to that of cases with favorable cytogenetics, however, OS and RFS were better in the latter cases (Table 4). In addition, patients with AML and complex aberrant karyotypes were identified as having a very dismal prognosis with a median event-free survival of only 2 months and a median overall survival of only 6 months (Table 4).

These data were reproduced prospectively when the new score was applied to the validation cohort. Thus, both response rates as well as RFS and OS differed clearly between the five new groups. In particular, in patients with intermediate cytogenetics the subgroup with day 16 blasts less than 10% was again identified as having CR rates comparable to patients with favorable cytogenetics (65% vs. 63%) although they had an inferior event-free and overall survival (median, 7 months vs. 14 months and 15 months vs. 25 months, respectively; Figures 2, 4, and 6). Also in this validation cohort patients with complex aberrant karyotypes were proven to have the worst prognosis which was even worse than the prognosis of patients with other unfavorable cytogenetics (Table 4, Figure 2; CR rate 35% vs. 45%, median overall survival 4 months vs. 6 months).

Multivariate analyses

In order to prove the relevance of the newly introduced prognostic subgroups of AML, i.e. AML with complex aberrant karyotype and AML with prognostically intermediate karyotype and day 16 bone marrow blasts ≥10%, multivariate analyses were performed.

In the first analysis favorable karyotype, complex aberrant karyotype, and other unfavorable karyotype were included as co-variates. The results are shown in Table 5 and impressively demonstrate that the presence of a complex aberrant karyotype has a very strong prognostic impact, independently of the other parameters, which affects all of the analyzed end points (CR rate, OS, EFS, and RFS). In addition, it is noteworthy that the remaining cases with *other unfavorable karyotype* still have a poor prognosis, independently of the other parameters.

In the second analysis favorable karyotype, unfavor-

Table 4. Prognostic impact of the new score.

Test cohort (AMLCG 1992)	*n*	*CR*	*PL*	*ED/HD*	*OS (months) (median)*	*EFS (months) (median)*	*RFS (months) (median)*
Favorable karyotype	45	82%	7%	11%	n.r.	25	26
Intermediate karyotype + day 16 blasts <10%	136	83%	8%	9%	26	14	19
Intermediate karyotype + day 16 blasts ≥10%	81	58%	33%	9%	12	5	13
Other unfavorable karyotype	21	76%	14%	10%	14	6	8
Complex aberrant karyotype	38	53%	31%	16%	6	2	4
Validation cohort (AMLCG 1999)	*n*	*CR*	*PL*	*ED/HD*	*OS (months) (median)*	*EFS (months) (median)*	*RFS (months) (median)*
Favorable karyotype	70	63%	17%	20%	25	14	n.r.
Intermediate karyotype + day 16 blasts <10%	276	65%	18%	17%	15	7	15
Intermediate karyotype + day 16 blasts ≥10%	150	51%	40%	9%	12	3	10
Other unfavorable karyotype	85	45%	35%	20%	6	2	8
Complex aberrant karyotype	99	35%	48%	17%	4	2	5

Ordinal χ^2-test: p<0.0001 for response rates in both cohorts; log-rank test: p<0.0001 for all end-points in both cohorts. CR=complete remission; PL: persistent leukemia; ED: early death; HD: hypoplastic death; OS: overall survival; EFS: event-free survival; RFS: relapse-free survival; n.r.: not reached.

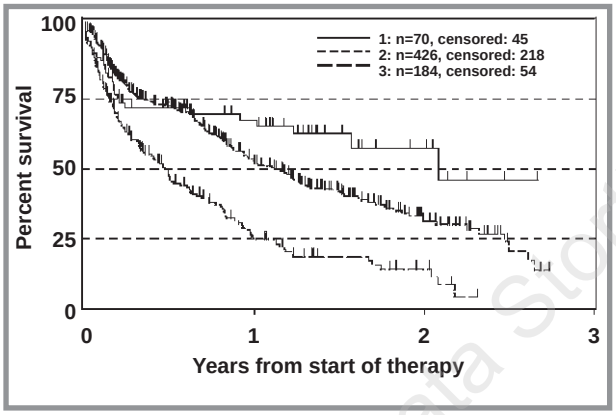

Figure 1. Overall survival in validation cohort (AMLCG 1999) according to cytogenetic score. 1=favorable karyotype, i.e. t(8;21) or inv(16)/t(16;16); 2=intermediate karyotype; 3=unfavorable karyotype.

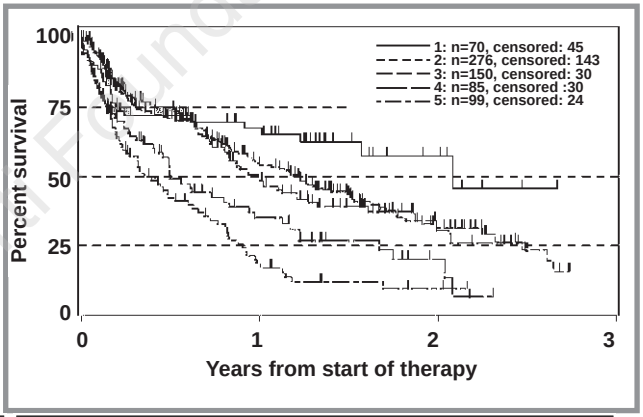

Figure 2. Overall survival in validation cohort (AMLCG 1999) according to new score. 1=favorable karyotype, i.e. t(8;21) or inv(16)/t(16;16); 2=intermediate karyotype and day 16 blasts <10% in bone marrow; 3=intermediate karyotype and day 16 blasts ≥10% in bone marrow; 4=unfavorable karyotype excluding complex aberrant karyotypes; 5=complex aberrant karyotype.

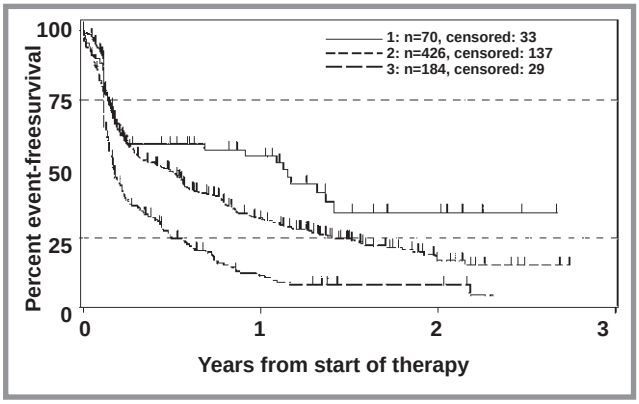

Figure 3. Event-free survival in validation cohort (AMLCG 1999) according to cytogenetic score. (see legend to Figure 1)

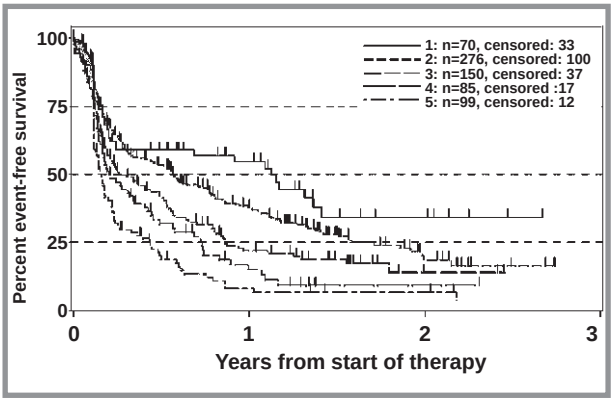

Figure 4. Event-free survival in validation cohort (AMLCG 1999) according to new score. (see legend to Figure 2)

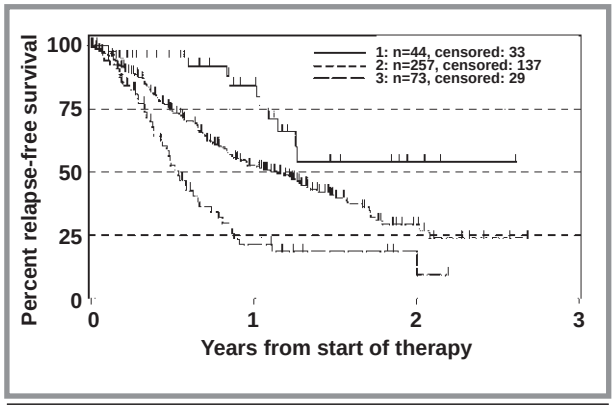

Figure 5. Relapse-free survival in validation cohort (AML-CG 1999) according to cytogenetic score (see legend to Figure 1).

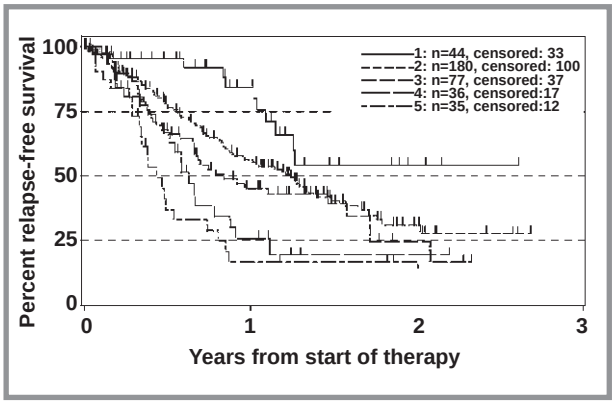

Figure 6. Relapse-free survival in validation cohort (AML-CG 1999) according to new score (see legend to Figure 2).

able karyotype, and intermediate karyotype + day 16 blasts 10% were included as co-variates. The results are shown in Table 6 and clearly indicate that the persistence of ≥10% bone marrow blasts at day 16 defines a subgroup of AML cases with a poor prognosis, the impact of which is independent of that of the other analyzed parameters with regard to CR rate, OS, and EFS.

Discussion

The diagnosis of AML depends on cytomorphology, immunophenotyping, and on cytogenetics.[59] Stratification models for treatment are mainly based on these pre-therapeutic parameters in combination with age. However, the prognosis of patients within the respective subgroups remains heterogeneous. Several other pre-therapeutic parameters such as white cell count,[60-62] lactate dehydrogenase,[47,63] and the history of the disease[60,64-67] were tested for their prognostic importance. However, the cytogenetically based definition of three subgroups as an independent parameter was shown to separate most accurately patients according to their prognosis.[19,22,23] These three subgroups are: i) patients with CBF-leukemias including AML associated with t(8;21) and with inv(16)/t(16;16), and patients with acute promyelocytic leukemia and t(15;17), have a favorable prognosis; ii) patients with normal karyotype or with rare aberrations, who have an intermediate prognosis; iii) cases with abnormalities of chromosomes 5, 7, 12p, 17p, 3q, and/or with complex aberrant karyotypes (i.e. ≥3 chromosomes involved), whose median survival is less than six months.

Several cytomorphologic parameters were tested in detail for classification and risk stratification in AML. However, the FAB classification has only minor prognostic impact. The new category in the WHO classification of AML, defined by dysplastic features, may also has only limited value.[20] In contrast, we were able to

Table 5. Multivariate analysis: prognostic impact of complex aberrant karyotype (AMLCG 1992).

	CR	*OS*	*EFS*	*RFS*
Favorable karyotype	n.s.	0.0344	0.0382	n.s.
Other unfavorable karyotype	n.s.	0.00073	0.0273	0.0002
Complex aberrant karyotype	0.0100	<0.0001	<0.0001	<0.0001

CR: complete remission; OS: overall survival; EFS: event-free survival; RFS: relapse-free survival.

Table 6. Multivariate analysis: prognostic impact of day 16 blasts in patients with prognostically intermediate karyotypes (AMLCG 1992).

	CR	*OS*	*EFS*	*RFS*
Favorable karyotype	n.s.	n.s.	n.s.	n.s.
Unfavorable karyotype	0.0009	<0.0001	<0.0001	<0.0001
Intermediate karyotype + day 16 blasts ≥10%	<0.0001	0.0008	<0.0001	n.s.

CR: complete remission; OS: overall survival; EFS: event-free survival; RFS: relapse-free survival.

demonstrate that the early assessment of response to therapy, as measured by the morphologic parameter early blast clearance in the bone marrow represents an *in vivo* assessment of chemosensitivity and that this parameter is a powerful tool for delineating the prognosis in individual patients.[21] As a consequence, it may be implemented in future treatment decision strategies.

Accordingly, to improve the stratification models used in AML the present study aimed to define a new risk score by combining a pre-therapeutic parameter, cytogenetics, with a therapy-dependent parameter, early blast clearance seven days after the end of the first course of induction therapy. These two prognostic parameters were the most important ones for overall survival in a prior analysis while the impact of age and LDH level was less prominent.[21]

As a further step to the refinement of the risk stratification, AML with complex cytogenetics is defined as a distinct group in the present analysis. These two parameters were incorporated into a stratification model in 321 *de novo* AML patients, all of whom were treated within the AMLCG 1992 trial. The results showed a clear separation of five prognostically highly different subgroups. In order to validate the stratification model we prospectively applied it to an independent cohort of 680 patients with *de novo* AML, AML after MDS, and therapy-related AML, all of whom were treated within the AMLCG 1999 trial.

The validation proved the power of this model by the resulting significant differences in response to treatment as well as in RFS and OS between the five groups. Interestingly, the score was shown to be highly valid even after inclusion of patients with se-condary AML and with MDS, these cases comprising one third of the cohort treated within the AMLCG 1999 trial. In addition, multivariate analyses were performed which confirmed the independent prognostic impact of the newly introduced subgroups, i.e. AML with complex aberrant karyotype and AML with prognostically intermediate karyotype and day 16 bone marrow blasts ≥10%.

In detail, the validation analysis confirms that patients with AML and inv(16) or t(8;21) have a favorable prognosis and in most cases achieve a complete remission after the first course of induction therapy. Since day 16 blasts have no impact on the outcome in these patients this parameter has not been used here. Overall, the CR rates as well as the relapse-free and overall survival in these patients are in the range of those in previously published series.[19,22,23]

A major improvement with regard to the stratification of patients currently assigned as being in a prognostically intermediate group based on cytogenetics has been achieved by inclusion of the therapy-dependent parameter, day 16 blasts, into the new model. This group of patients is defined by normal cytogenetics and infrequent karyotype abnormalities in most series and is characterized by a highly heterogeneous prognosis as reflected by CR rates of 63% to 88%, an overall survival of 21% to 48% at five years, and a relapse-free survival of 47% to 56% at five years.[19,22,23] Thus, even after achievement of a CR a risk assignment cannot be accomplished for individual patients in this group since in half of them long-term control of the disease is achieved and in half of them it is not. Overcoming this dilemma the implementation of day 16 blasts as a stratification parameter has been demonstrated to further separate the former group with intermediate cytogenetics into two prognostically highly different groups (CR rates: 65% vs. 51%). Thus, the application of day 16 blasts in the cytogenetically intermediate group leads to the defintion of a subgroup in which the prognosis is relatively close to that in the group of patients with favorable cytogenetics. With respect to the risk-based intensification of treatment strategies, i.e. allogeneic stem cell transplantations, which are associated with a significant treatment-related mortality, these patients may be candidates for conventional treatment approaches. In contrast, patients with intermediate karyotypes and day 16 blasts ≥10% are defined as a new subgroup in which the prognosis is equivalent to that in patients with unfavorable cytogenetics. In these patients more aggressive treatment approaches, such as early intensification directly following the first course of induction therapy, may be evaluated.

In addition to the improvement in the prognostic score by including the therapy-dependent parameter, day 16 blasts, the pre-therapeutic parameter, cytogenetics, was further refined to yield an additional subgroup with a distinct prognosis. Thus, two subgroups were identified within the former group of AML with unfavorable cytogenetics, i.e. those with and those without complex aberrations. Patients with AML and complex aberrant karyotypes are prone to a particularly dismal outcome with a CR rate of only 35% and a median overall survival of only four months which is even worse than the outcome in patients with AML and other unfavorable karyotypes (CR rate, 45%; median overall survival, six months). Thus, while the remission rates are quite reasonable in patients with intermediate cytogenetics and ≥10% day 16 blasts and in those with other unfavorable cytogenetics, the low remission rates in AML with complex karyotypes highlight the need not only for more effective therapies to prolong the duration of remission but also for alternative strategies for induction treatment. As a consequence, considering the significant toxicity of "3+7" and comparable regimens and their limited efficacy in AML with complex karyotypes it must be stressed that at present it is not possible to define a therapeutic standard in this group. In patients who do not qualify for allogene-

ic transplantation due to advanced age or co-morbidity this may imply that exclusively supportive therapy may be considered the first therapeutic choice and may serve as a control arm in studies evaluating novel drugs.[69] In addition, also in the setting of allogeneic stem cell transplantation, a refinement of the graft-versus-leukemia effect needs to be developed since the majority of patients suffer from relapses even following this treatment strategy.[70]

A concept similar to the present one has been approached on the basis of 1711 patients (range of age, 0 to 55 years) treated within the British MRC AML10 trial.[45] A combination of cytogenetics and response assessment following course 1 of induction treatment as defined by a limit of 15% blasts in a bone marrow with normal maturation yielded three groups with highly different prognoses (overall survival at 8 years, 69% vs. 44% vs. 14%; relapse risk at 8 years, 22% vs. 51% vs. 78%).

However, besides the inclusion of children and the upper age limit this model may not be optimized for the separation of different homogeneous groups which can be used for stratification purposes in clinical trials. Thus, patients with both CBF leukemias and acute promyelocytic leukemias are included in the good prognosis group. The unfavorable group, on the other hand, comprises three groups, i.e. a) patients with prognostically intermediate cytogenetics and a poor response, b) patients with other unfavorable karyotypes, and c) patients with complex aberrant karyotypes.

Since it is anticipated that novel treatment strategies will prove effective only in distinct subgroups of AML, an optimal stratification model would yield subgroups with a high grade of homogeneity with regard to both the biologic background and the clinical behavior in order to detect subgroup-specific treatment effects. The present stratification model fulfills these criteria in a very effective way and therefore may be an important basis for the design of future clinical trials in AML. In particular, this concept is anticipated to be useful in patients with prognostically intermediate karyotypes in whom prognostication is currently difficult to achieve. In addition, the new classification is expected to improve the validity of clinical trials by identifying patients with complex aberrant karyotypes who are refractory to each of the presently available therapeutic approaches and who may, if not separated, lead to an underestimation of treatment efficacies in other patients.

TH: principal investigator; WK: principal investigator; CS: contribution to conducting the work and interpreting the results with specific focus on cytogenetics; SS: contribution to conducting the work and interpreting the results with specific focus on molecular genetics; MCS: contribution to conducting the work; AH: contribution to conducting the work; TB: contribution to interpreting the results; WH: contribution to interpreting the results. All authors contributed to the design of the study and the revision of the manuscript.

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