Southwestern Oncology Group pretreatment risk criteria as predictive or prognostic factors in acute myeloid leukemia

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Abstract. Acute myeloid leukemia (AML) is a clonal hematological malignant condition and the implications of pretreatment risk criteria as predictive or prognostic factors are constantly under evaluation. With this study, the authors' intent was to characterize AML patients and to evaluate the clinical outcome associated with Southwestern Oncology Group (SWOG) coding pretreatment risk criteria/cytogenetic score. Between 2002 and 2010, 225 patients were diagnosed with AML at the Portuguese Institute of Oncology (Porto, Portugal). From this patient group, 128 patients aged <65 years were selected. The patients were treated using a combination of cytarabine and anthracycline, with the addition of cyclosporine when bone marrow dysplasia was observed. A median survival of 24 months was observed in this group. The patients were divided in subgroups according to the SWOG pretreatment risk criteria. We observed a statistically significant association of non-favorable SWOG coding with female gender [P=0.025; risk ratio (RR)=3.632, 95% confidence interval (CI): 1.113-11.852], indication for allogeneic bone marrow transplantation (P=0.023, RR=1.317, 95% CI: 1.184-1.465), complete response achievement (P=0.013, RR=1.385, 95% CI: 11.232-1.556) and relapse (P=0.048, RR=3.181, 95% CI: 10.966-10.478). Furthermore, SWOG pretreatment risk criteria also significantly affected global overall survival (OS; P=0.003) and OS at 5 years (P=0.001). A multivariate Cox regression analysis supported response to induction therapy (3-year OS: P=0.011, RR=0.385, 95% CI: 10.184-0.806; 5-year OS: P=0.012, RR=0.388, 95% CI: 10.597-1.994), consolidation (3-year OS: P=0.005, RR=0.328, 95% CI: 0.150-0.720; 5-year OS: P=0.002, RR=0.308, 95% CI: 0.144-0.657) and the diagnosis of therapy-related AML (3-year OS: P=0.016, RR=2.756, 95% CI: 0.486-1.281; 5-year OS: P=0.031, RR=2.369, 95% CI: 1.081-5.189) as prognostic factors, but this was not confirmed for SWOG pretreatment risk criteria. Therefore, we concluded that the reproducibility of the application of the SWOG pretreatment risk criteria may not be available as a prognostic factor in every acute leukemia population. However, its application as a predictive factor of response has been confirmed in our population.

Introduction

Acute leukemias are clonal malignant disorders arising from the primitive pluripotent hematopoietic cell, characterized by impaired proliferation of leukemic progenitors (1,2). They are characterized by recurring chromosomal aberrations and gene mutations, with contribution of epigenetic modifications (3), which are crucial in differentiation, proliferation and survival pathways.

According to the latest GLOBOCAN data published in 2012, 351,965 individuals worldwide were diagnosed with leukemia (chronic and acute, as well as lymphoid and myeloid) and 265,491 succumbed to this disease. A marginal male predominance was also reported by the World Health Organization (WHO), with a male:female ratio of ~1.4 (http://globocan.iarc.fr/Default.aspx).

The diagnosis is based on bone marrow analysis: A smear morphology with a blast count >20% or the presence of recurring cytogenetic abnormalities [t(8,21), inv16, t(16,16), or t(15,17)] confirms the diagnosis (4).

The classification of acute leukemia, previously based only on morphological and cytochemistry findings, from 2002 onwards it includes phenotypic aspects, as well as cytogenetic

and molecular characteristics, which are of well-known prognostic value (4).

Over the last 30 years, conventional treatment has been based on the combination of anthracyclines with cytarabine (5). The outcome depends on multiple characteristics, including karyotype (6-9), response to the induction regimen (10), age and comorbid conditions (11). AML originating *de novo* vs. therapy-related, was also associated with outcome. As cytogenetics is considered the single most important prognostic marker, predicting remission, relapse and overall survival (OS), several cooperative group trials, including the United Kingdom Medical Research Council, Southwest Oncology Group (SWOG), Eastern Cooperative Oncology Group and Cancer and Leukemia Group B, designed risk scores based on large cohorts of patients (6,8,9,12), dividing patients in four groups, namely favorable, intermediate, unfavorable and unknown, based on the cytogenetic findings.

However, despite these efforts, the cure rates remain disappointing, with complete response rates at first induction of 60-80% (age <60 years), but with cure rates of 30-40% (13).

The aim of the present study was to investigate the Portuguese AML population and assess the effect of cytogenetics.

Patients and methods

Study design. A retrospective observational study was conducted, including AML patients aged <65 years, diagnosed and treated at the Portuguese Institute of Oncology (Porto, Portugal), between January, 2002 and December, 2010.

Patients. Between 2002 and 2010, a total of 225 patients were diagnosed with AML in our department. Following exclusion of patients aged >65 years and cases with acute promyelocytic leukemia, 128 patients were selected for inclusion in this cohort.

Data regarding gender, age, date of diagnosis, WHO classification, cytogenetic abnormalities, SWOG pretreatment risk score (6), first- and further-line treatment, response, consolidation, relapse, date of relapse, bone marrow transplantation (allogeneic or autologous), date of last hospital visit or date and cause of death, were obtained from the medical records of previously selected patients and retrospectively reviewed.

Diagnosis was based on standard criteria (4,14,15). All cases initially classified according to the French American British classification (14) were reviewed and reclassified according to WHO (4). A blast count >20% confirmed the diagnosis of AML.

Specimens were collected for morphological, immunophenotypic and genetic analyses (cytogenetic and molecular biology).

The patients were treated with the classic idarubicin and cytarabine combination (16,17) or with daunorubicin, cytarabine and cyclosporine (18,19) if bone marrow dysplasia was present.

The response criteria used (complete remission, failure or relapse) were defined by international working groups (4,15,20,21).

This investigation was performed in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee.

Cytogenetics. Standard G-banding was performed on patient bone marrow samples using standard techniques; the cytogenetic results were presented according to the International System for Human Cytogenetic Nomenclature (22). The patients were then analysed according to the cytogenetic risk subgroups defined by the SWOG (6).

Statistical analysis. Analysis of data was performed using the SPSS statistical software for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA). Differences in proportions were evaluated by the Chi-square test. The probabilities of survival were calculated, and the means and life tables were computed using the product limit estimate of the Kaplan-Meier method and analysed using the Breslow (generalized Wilcoxon) test, a statistical test for equality of survival distributions. $P<0.05$ was considered to indicate statistically significant differences. Hazard ratio was also accessed using a multivariate Cox regression analysis for 3- and 5-year OS.

Survival duration was defined as the time between diagnosis and death, or the time of the last clinical evaluation.

As defined, prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy; predictive factor is a measurement that is associated with response or lack of response to a particular therapy (23,24).

Results

Patient cohort. Between 2002 and 2010, a total of 225 patients were diagnosed with AML at the Portuguese Institute of Oncology (Porto, Portugal); of those, 128 were aged <65 years. Both genders were equally represented with 64 patients. The median age at diagnosis was 54 years (range, 17-65 years). Therapy-related AML constituted 23.1% of all cases.

Karyotype analysis was performed in all patients; in 2.3% of the cases (n=3), there were insufficient metaphases for karyotype analysis. A normal karyotype was the most frequent result (n=54; 43.2%). Core-binding factor anomalies were detected in 17 karyotypes (13.6%). Anomalies involving chromosomes 5, 7 and 8 were detected in 18 cases (14.4%); a complex karyotype was observed in 9.6% (n=12) of the studied cases. Other less frequent alterations were detected in the remaining 24 cases (19.2%).

Using the SWOG pretreatment risk criteria system, the intermediate group included the majority of the patients (55.5%; n=71), whereas 37 patients (28.9%) had an unfavorable risk and 17 (13,6%) were included in the favorable group.

There was a statistically significant association between cytogenetic groups and age (P=0.031), gender [P=0.025; risk ratio (RR)=3.632; 95% confidence interval (CI): 1.113-11.852], indication for allogeneic stem cell transplantation (P=0.023; RR=1.317; 95% CI: 1.184-1.465), complete response achievement (P=0.013; RR=1.385; 95% CI: 1.232-1.556) and relapse (P=0.048; RR=3.181; 95% CI: 0.966-10.478) (Table I). A significant association was also observed with global OS (P=0.003) and 5-year OS (P=0.001).

Treatment. Complete remission was achieved in 86.7% (n=111) of the cases. Relapse occurred in 52 patients (46.8% of the responders; 46.5% of the total population).

Table I. Characterization of the complete cohort and of the 3 different SWOG pretreatment risk criteria groups.

| Factors | Total, 128 (100.0) | SWOG pretreatment risk criteria, n (%) | | | | P-value[a] | RR[a] (95% CI) |
		Favorable, 17 (13.3)	Intermediate, 71 (55.5)	Unfavorable, 37 (28.9)	Unknown, 3 (2.3)		
Median age (years)	54	44	52	53	54	0.043[b]	-
Female gender	64 (50.0)	13 (76.5)	34 (47.9)	17 (45.9)	0 (0.0)	0.019[b]	3.82 (1.07-14.92)
t-AML	24 (23.1)	2 (11.8)	11 (15.5)	11 (29.7)	0 (0.0)	0.428[b]	1.85 (0.36-12.69)
Treatment ('7+3').	87 (68.0)	15 (88.2)	49 (69.0)	22 (59.5)	1 (33.3)	0.054[b]	4.06 (0.82-27.17)
Consolidation	96 (86.5)	17 (100.0)	57 (86.4)	20 (54.1)	2 (66.6)	0.248[b]	3.23 (0.40-69.84)
Allogeneic stem cell	26 (20.3)	0 (0.0)	16 (22.5)	10 (27.0)	0 (0.0)	0.084[b]	0.10 (0.01-1.49)
Complete response	111 (86.7)	17 (100.0)	66 (93.0)	26 (70.3)	2 (66.6)	0.041[b]	6.59 (0.86-138.32)
Relapse	52 (46.5)	4 (23.5)	33 (50.0)	13 (48.1)	2 (100.0)	0.040[b]	0.30 (0.08-1.09)
OS (months)	24	NR	20	14	2.4	0.006[c]	-
5-year OS (%)	44.5	80.9	31.3	29.4	0.0	0.003[c]	-

[a]Cytogenetic risk score: non favorable vs. favorable. [b]Chi-square test. [c]Log-rank test. SWOG, Southwestern Oncology Group; RR, risk ratio; CI, confidence interval; t-AML, therapy-related acute myeloid leukemia; OS, overall survival; NR, not reached.

Table II. Multivariable analysis for 5-year overall survival.

| Factors | 5-year overall survival | |
	P-value[a]	HR[b] (95% CI)
Female gender	0.293	1.376 (0.759-2.494)
Age	0.627	1.006 (0.981-1.031)
Complete response	0.019	0.421 (0.204-0.866)
Treatment	0.540	1.053 (0.893-1.242)
SWOG pretreatment risk criteria	0.074	1.724 (0.949-3.134)
t-AML	0.019	2.404 (1.152-5.017)
Consolidation therapy	0.005	0.342 (0.161-0.727)

[a]Chi-square test. [b]Risk of death within 5 years. HR, hazard ratio; CI, confidence interval; SWOG, Southwestern Oncology Group; t-AML, therapy-related acute myeloid leukemia.

Consolidation followed induction with at least one chemotherapy course (median of 4 courses; range, 1-5) in 96 patients (86.5%). All patients from the favorable group followed treatment after induction; 86.4% (n=57) and 54.1% (n=20) of the patients from the intermediate and unfavorable groups, respectively, received consolidation therapy with hight dose cytarabine.

Allogeneic stem cell bone marrow transplantation was performed in 26 patients. The majority of the transplants (61.5%) were performed in the intermediate group (n=16).

Outcome. The median survival including all patients was 24 months. The OS at 3 and 5 years was 48.4 and 44.5%, respectively. Different factors were found to statistically significantly affect OS at 3 and 5 years, such as complete response achievement (P<0.001 for both), SWOG pretreatment risk criteria (P=0.001 for both), presence of therapy-related AML (P<0.001 for both) and consolidation therapy (P<0.001 for both). Age (P=0.024) and therapy (P=0.01) only affected 5-year OS (Fig. 1).

A multivariate Cox regression analysis (Table II) demonstrated that OS at 3 and 5 years was affected by the same factors: Achievement of complete response (P=0.011; RR=0.385; 95% CI: 0.184-0.806; and P=0.012; RR=0.388; 95% CI: 0.597-1.994, respectively), therapy-related AML (P=0.016; RR=2.756; 95% CI: 0.486-1.281; and P=0.031; RR=2.369; 95% CI: 1.081-5.189, respectively) and consolidation therapy (P=0.005; RR=0.328; 95% CI: 0.150-0.720; and P=0.002; RR=0.308; 95% CI: 0.144-0.657, respectively). Other studied variables, such as gender, age (<50 or >50 years), therapy and SWOG pretreatment risk criteria did not significantly affect outcome.

Discussion

To the best of our knowledge, this study is the first to investigate and characterize Portuguese patients diagnosed with AML and their outcome.
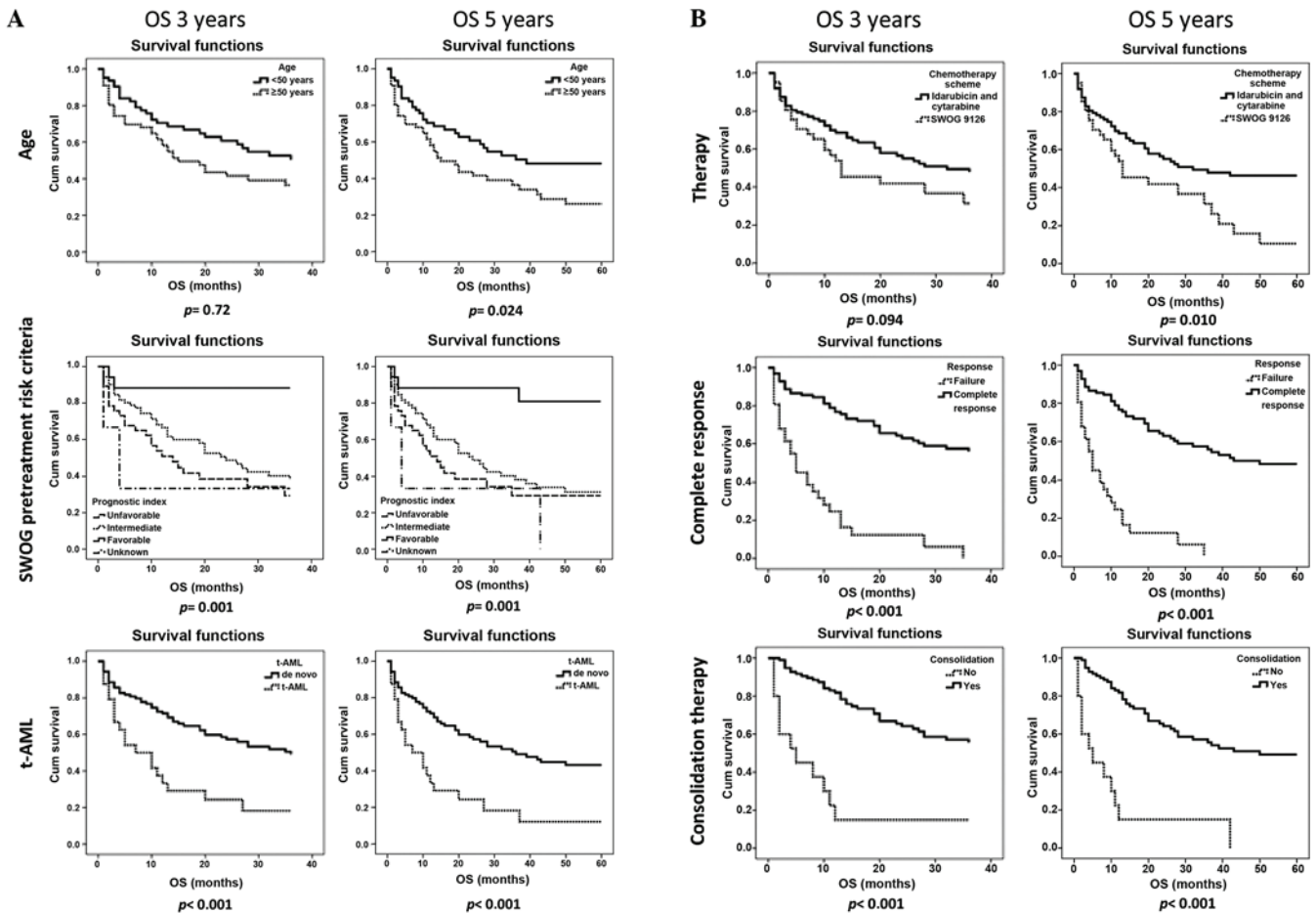
Figure 1. (A) Overall survival (OS) at 3 and 5 years according to age, Southwest Oncology Group (SWOG) pretreatment risk criteria and therapy-related acute myeloid leukemia (t-AML). (B) OS at 3 and 5 years according to complete response achievement, induction therapy and consolidation therapy performed.

In our study, there were more therapy-related AML cases compared with other published series (25). As our hospital is an oncology centre, it admits a high number of cancer patients. When patients develop AML as a secondary malignancy, they are referred to our department.

The most frequent cytogenetic finding was a normal karyotype (26,27). Data on molecular findings were not available for this study. NPM1 and FLT3 gene mutations are now relevant for prognosis assessment (28-32). However, when the patients of this cohort were diagnosed, this molecular analysis was not widely available.

Using the SWOG pretreatment risk criteria, three different groups may be defined, with different survivals. Male gender, failure of complete response achievement, risk of relapse and indication for allogeneic bone marrow transplantation are significantly associated with an unfavourable cytogenetic group. Analysing the effect of age, response to induction, treatment administered, consolidation therapy and t-AML on OS at 3 and 5 years, we observed that all these factors affect outcome. Cytogenetic risk, defined by the SWOG pretreatment risk criteria, also affects OS. However, when analysing this score in association with other factors also related to outcome, such as complete response achievement, cytogenetics does not statistically significantly affect OS. This suggests that cytogenetic groups previously defined and related to disease prognosis (7,12,33,34) may be factors predictive of response,

being statistically relevant for complete response to induction therapy, but not prognostic factors, having no statistical significance in OS when associated with other entities.

Predictive and prognostic factor are definitions frequently confused and overlapping. As defined in the literature, a prognostic factor is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy that patients are likely to receive; a predictive factor is a measurement that is associated with response or lack of response to a particular therapy (23,24). In conclusion, SWOG pretreatment risk groups may not be consistent as prognostic markers, but may be more reliable as predictive markers for response to standard therapy, while complete response achievement is a prognostic markers as it affects outcome.

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