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Prognostic factors and treatment outcome in 1,516 adult patients with de novo and secondary acute myeloid leukemia in 1999–2009 in 5 hematology intensive care centers in the Czech Republic

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Acute myeloid leukemia (AML) is a severe condition with a high mortality. When making decisions about the optimal tailor-made therapy, numerous prognostic factors are considered. The study represents a detailed analysis of the role of these factors and treatment outcomes based on a long-term follow-up of patients treated in 5 hematology intensive care centers in the Czech Republic.

The studied group comprised 1,188 patients with de novo AML and 328 patients with secondary AML. The latter were significantly older, had more unfavorable cytogenetic changes and less frequently received curative therapy. Curatively treated patients achieved fewer complete remissions and relapsed more often than those with de novo AML. Patients with secondary AML had lower rates of allogeneic transplantation as part of consolidation therapy and a significantly shorter median overall survival. A lower proportion of the patients were alive at the time of analysis.

However, the treatment outcome of de novo AML patients is not satisfactory, the only exception being those with acute promyelocytic leukemia. The analysis, which did not evaluate the intention-to-treat criteria and was without randomization, found allogeneic stem cell transplantation to be the most effective modality of consolidation therapy in both groups of patients.

Key words: Acute myeloid leukemia, prognostic factors, consolidation, stem cell transplantation, treatment outcome, registry

Acute myeloid leukemia (AML), a severe hematopoietic disease, is a relatively rare type of cancer (1). Despite low incidence rates, it has a significant impact on the overall survival of oncological patients. This is due to high overall mortality rates with nearly three quarters of patients dying from the disease (2).

Numerous prognostic factors for AML are known. These include both clinical and laboratory aspects playing a key role in the development of the disease. They help to estimate both treatment response and the chances of cure or relapse of the disease. This contributes to the selection of adequate therapy.

The study is aimed at assessing the value of selected prognostic factors for AML, treatment outcomes and patient survival in a long-term group of 1,516 patients diagnosed with AML between 1999 and 2009. Special attention was focused on the prognostic value of its pathogenesis and assessment of the treatment modalities in order to formulate prognostically valid treatment recommendations.

Materials and methods

The ALERT (Acute LEukemia clinical RegisTry) is a long-term project comprising 5 hematology intensive care centers in the Czech Republic. Since the beginning of 1996, data of patients with acute leukemia are collected and analyzed as a part of the project supervised by the Czech Society of Hematology. Since then, the project has been joined by 4 hematology intensive care centers in the Slovak Republic and 9 Czech regional hematology centers.

Since the registry collects anonymized data from voluntary reports from the collaborating centers, the database is not a completely representative profile of the situation in the catchment

areas of the centers. No registry analysis is used to test and show the differences between the centers or regions. Data are collected according to a registry protocol with a clearly defined structure of parameters and validated prior to analyses.

As of March 30, 2010, the registry contained data of 2,427 AML patients. With respect to the validity of results, the final analysis included "only" 1,516 patients in whom complete data including the current follow-up were available. The excluded data of 911 patients comprised 473 patients treated in a center that terminated its participation in the project in 2006 and refused to consent to the data analysis, and 438 patients with a short follow-up or incomplete data. Using the 2008 WHO classification (3), the AML patients were divided into two groups – de novo and secondary AML. The significance of individual prognostic factors and survival were assessed separately for each of the two groups.

To analyze the impact of age, the patients were divided into 3 age groups: ≤45 years; 46–59 years and ≥60 years. For the analysis of the prognostic value of cytogenetic changes, four prognostic groups were created: patients with very good, good (favorable), intermediate and poor (adverse) prognosis. The criteria are shown in Table 1. The study did not evaluate the role of molecular changes (in patients from the group with intermediate cytogenetic prognosis) as such data were available in only a fraction of patients monitored in the project.

To analyze the prognostic value of white blood cell (WBC) count, the patients were divided into 3 groups: $<4x10^9$/L, 4–$10x10^9$/L and $>10x10^9$/L.

It must be said that the patients were not treated according to a single protocol. The approach to treatment such as the use of high-dose induction and/or consolidation chemotherapy differed among the participating centers and, in some centers, even throughout the time.

In the study, "standard therapy" refers to consolidation chemotherapy based on the 7+3 protocol (7 days of continuous cytarabine and 3 days of an anthracycline antibiotic), and "ID/HD therapy" means chemotherapy based on cytarabine administered in doses of 0.5g/m^2 or more.

Table 1. Distribution of cytogenetic changes in AML into prognostic groups

Very good prognosis
– APL with t(15;17)(q22;q21), PML/RARa +
Good prognosis
– AML with t(8;21) (q22;q22), RUNX1/RUNX1T1+
– AML with inv(16)(p13q22) or t(16;16)(p13;q11), CBFβ/MYH11+
Poor prognosis
– del(5), 5q-
– del(7), 7q-
– MLL gene rearrangement (11q23)
– a complex karyotype (3 or more changes other than those in the good prognosis group)
Intermediate prognosis
– normal karyotype
– changes other than those in the above groups

Patient characteristics were summarized using frequency tables and standard descriptive statistics. Probabilities of overall survival (OS), progression-free survival (PFS) and disease-free survival (DFS) were estimated using the Kaplan-Meier method (4). Univariate analyses to evaluate differences in survival between groups of patients were performed using the log-rank test. The point estimates were accompanied by 95% confidence intervals.

All computations were performed using the SPSS software (5) and STATISTICA software (6). The methods for multivariate analyses are described in the respective sections.

Results

I. De novo AML.

The studied group comprised 1,188 patients (78.4% of all subjects) with de novo AML. Their median age was 58 years (range, 19–92 years) and both the male/female ratio and their age distribution were balanced. The proportions of patients in the age groups were as follows: 22.5% of patients of ≤45 years, 32.4% of patients aged 45–60 years and 45.1% of patients of ≥60 years of age. When the diagnosis was made, 29.1% of patients were with leukopenia, 13.9% with normal WBC count and 55.7% with leukocytosis. In the remaining 1.3% of patients the initial WBC count was not known. Of the patients, 9.4% were diagnosed with acute promyelocytic leukemia (APL), 8.8% had good cytogenetic prognosis (with the exception of APL), 41.1% had intermediate prognosis and 13.9% had poor prognosis. Cytogenetic tests were not performed in 26.8% of patients.

There were significant differences in the prognostic subgroups based on cytogenetics between the individual age categories. The proportion of APL patients was highest (18.0%) in the youngest age group, with 10.9% in the middle age group and only 4.1% in the oldest group. Similarly, the highest proportion of patients with good cytogenetic prognosis was seen in the youngest group (14.2%); in the remaining two age groups, these patients accounted for 13.2% and 2.8%, respectively ($p<0.001$). The number of patients with poor cytogenetic prognosis slightly increased with age (13.1%, 13.2% and 14.8%, respectively). As expected, cytogenetic examinations were most frequently not performed in patients of ≥60 years (in 40.1% of patients from this age group); the proportions were 17.9% and 13.1% of patients aged 45–60 years and ≤45 years, respectively.

Treatment outcome. Patients with completely different treatment and prognosis of APL were excluded from the overall assessment of induction and consolidation therapy. Induction therapy was administered to 75.6% of patients. There were 97.7% and 95.6% of patients aged ≤45 years and 45–60 years, respectively, treated with induction therapy. That is a total of 96.4% of patients younger than 60 years. Elderly patients (≥60 years) were significantly less frequently administered induction therapy – only 52.7% of cases ($p<0.001$).

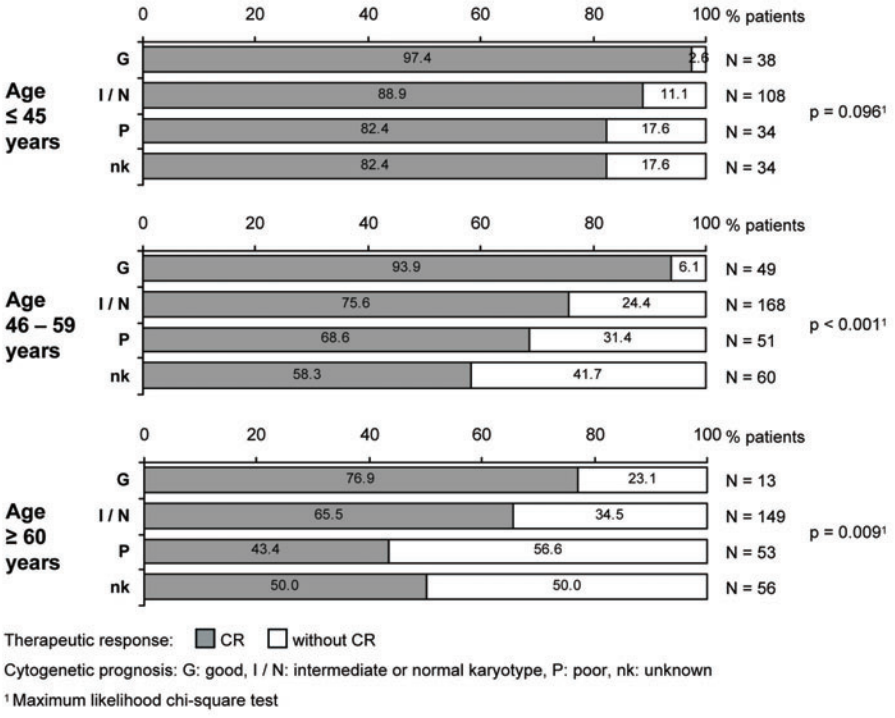


Figure 1 – Cytogenetic prognosis and achievement of CR in de novo AML according to age (except APL)

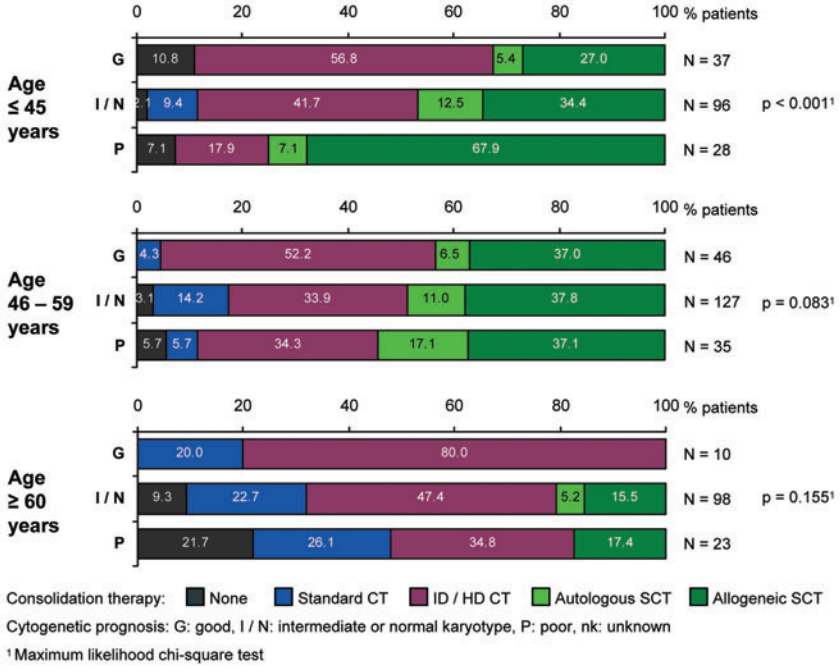
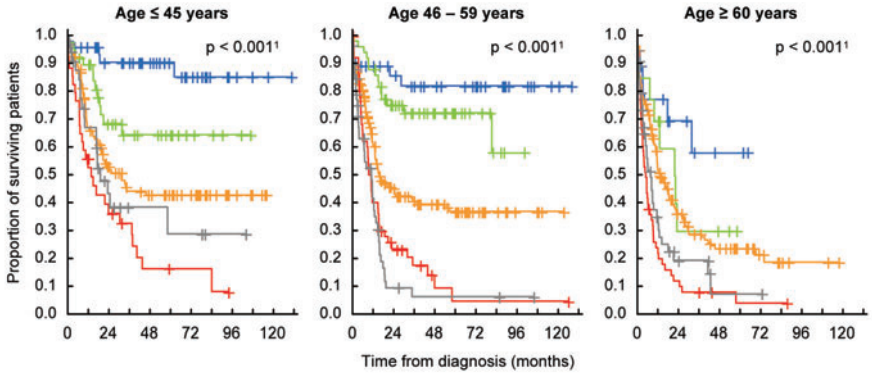


Figure 2 - Cytogenetic prognosis and consolidation in de novo AML according to age (except APL)



Cytogenetic prognosis	Age ≤ 45 years N	Age ≤ 45 years Median OS (95% CI)	Age 46 – 59 years N	Age 46 – 59 years Median OS (95% CI)	Age ≥ 60 years N	Age ≥ 60 years Median OS (95% CI)
Very good (APL²)	47	not achieved	36	not achieved	18	not achieved
Good	38	not achieved	49	not achieved	13	21.8 (8.0 - 35.6)
Intermediate or normal karyotype	108	31.2 (19.0 - 43.4)	168	15.6 (8.3 - 22.8)	148	13.2 (9.1 - 17.3)
Poor	34	13.7 (5.7 - 21.6)	51	9.4 (7.1 - 11.7)	53	4.9 (3.1 - 6.8)
Unknown	34	19.0 (10.2 - 27.9)	60	11.1 (6.3 - 15.9)	56	7.6 (4.1 - 11.1)
Total	261	58.2 (N/A)	364	16.5 (11.6 - 21.4)	288	10.9 (9.2 - 12.7)

¹ Log-rank test; ² APL - acute promyelocytic leukemia

Figure 3 - OS according to age and cytogenetic prognosis in curatively treated de novo AML

Complete remission (CR) was achieved in 88.3%, 74.1% and 58.5% of patients from the youngest, medium and oldest ($p<0.001$) age groups, respectively. Complete remission rates decreased not only with increasing age but also with worsening cytogenetic prognosis in the all three age groups (Fig. 1).

Consolidation therapy was given to 94.2% and 96.3% of patients in CR in the two younger age groups and to 88.6% of patients in CR aged ≥60 years ($p=0.011$). A detailed distribution of patients according to the administered consolidation therapy is shown in Fig.2.

A total of 299 patients underwent hematopoietic stem cell transplantation (HSCT). Of those, 258 transplantations were allogeneic and 41 were autologous. Allogeneic HSCT was performed in 72.5% of patients in the first CR and in 7.4% in the second or other CR. A total of 22.8% of HSCTs from related donors and 18.1% of HSCTs from unrelated donors were performed out of remission. There were 268 patients with a single HSCT, 29 patients with two HSCTs and 2 patients had three HSCTs.

As expected, the numbers of allogeneic HSCTs in the groups based on cytogenetic prognosis significantly decreased with the patients' age. Allogeneic HSCT was performed in 67.9% of patients with poor cytogenetic prognosis in the youngest group, in 37.1% of patients in the middle age group and in only 17.4% of the oldest patients with poor prognosis (Fig. 2).

The median overall survival (OS) rate statistically significantly decreased with increasing age – 25.5 months (95% CI 16.1-34.9) in patients aged ≤45 years, 15 months (95% CI 12.5-17.6) in the age group of 45–60 years, and 9.9 months (95% CI 7.9-11.9) in patients of ≥60 years of age.

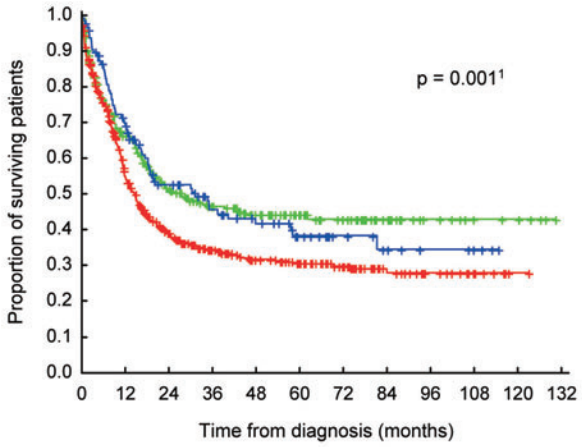
So far, the median OS has been reached neither in any of the age groups of APL patients nor in those with good cytogenetic prognosis under 60 years of age. The older the age group and the worse cytogenetic prognosis are, the statistically significantly shorter the patient survival is (Fig. 3). Very similar results were found when assessing PFS as well as OS in patients with CR.

Poorer OS was observed in patients with higher WBC count at diagnosis (Fig. 4). The median OS in patients with WBC count of $>10x10^9$/L was 14.6 months, as compared with 27.5 and 31.2 months in the $<4x10^9$/L and $4–10x10^9$/L groups, respectively.

When assessing the results of individual consolidation therapy modalities, the highest survival rates (both OS and PFS) were seen in transplanted patients (Fig. 5). The median OS was 53.3 and 26.1 months and the PFS was 34.2 and 19.1 months in patients <60 and ≥60 years, respectively.

Subsequently, multivariate survival analysis was used to specify the role of individual prognostic factors in assessing the OS of patients with de novo AML who achieved CR (with the exception of APL). In the model, the following variables were considered: consolidation therapy, age and cytogenetic prognosis. The hazard ratios and 95% confidence intervals corresponding to the Cox regression model (6, 7) for the OS from the date of CR are shown in Table 2.

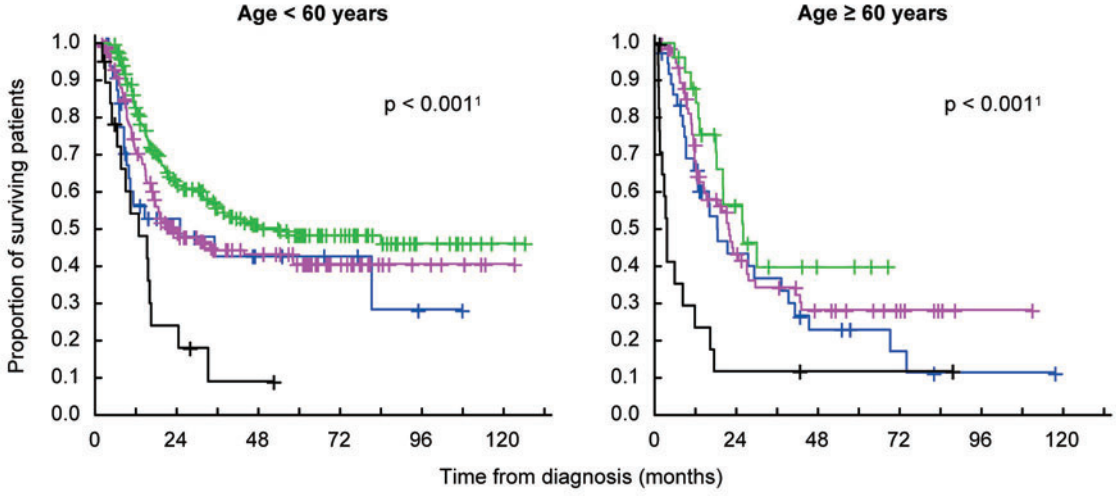
At the time of assessment, 431 patients (36.3%) were alive, with the median OS of 32.6 months. In the age groups, the rates were as follows: 53.9% of the youngest patients were alive (median OS of 42.9 months) and so were 42.9% of patients in the middle age group (median OS 38.4 months) and 22.7% in the oldest age group (median OS of 12.6 months).



WBC count	N	Median OS (95% CI)
< 4 × 10^9/l	274	27.5 (13.6 - 41.4)
4 - 10 × 10^9/l	127	31.2 (15.6 - 46.8)
> 10 × 10^9/l	511	14.6 (12.2 - 17.0)

[1] Log-rank test

Figure 4 - OS according to WBC count at diagnosis in curatively treated de novo AML



Consolidation therapy	Age < 60 years N	Age < 60 years Median OS (95% CI)	Age ≥ 60 years N	Age ≥ 60 years Median OS (95% CI)
Transplantation	202	53.3 (N/A)	26	26.1 (13.7 - 38.4)
ID/HD CT	174	22.8 (11.5 - 34.0)	78	21.8 (17.3 - 26.2)
Standard CT	36	25.0 (0.0 - 57.2)	37	18.5 (11.5 - 25.5)
No consolidation therapy	20	12.9 (4.6 - 21.1)	18	3.6 (2.5 - 4.8)
Total	432	33.8 (21.1 - 46.4)	159	20.1 (15.8 - 24.3)

[1] Log-rank test

Figure 5 - OS according to consolidation therapy in de novo AML (except APL)

II. Secondary AML

Secondary AMLs are cancers arising from a previous myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN) and AMLs developing as late complications of cytotoxic or radiation therapy.

In the studied group, secondary AML (sAML) accounted for 21.6% of all cases (328 patients). The basic prognostic factors were compared between the groups of patients with curatively treated de novo AML (N=915) and sAML (N=176).

The median age of sAML patients was five years higher than the median age in patients with de novo AML (p<0.001). The proportion of patients aged 60 or more was significantly higher (41.5% vs 31.5%, p=0.011). The WBC count at diagnosis was significantly lower than in de novo AML (a median of $4.7x10^9$/L vs $13.1x10^9$/L; p<0.001). Cytogenetic examinations confirmed APL in only 3.4% of patients, good prognosis in 1.7% of patients, intermediate prognosis in 38.6% and poor prognosis in 23.9% of patients. The remaining 32.4% of patients were not cytogenetically tested (Table 3).

Curative therapy was administered to 53.7% of sAML patients, as compared with 77.0% of cases with de novo AML (p<0.001).

Treatment outcome. Complete remission was achieved in 48.9% of patients, as compared with 74.6% of de novo AML patients (p<0.001). However, 59.3% of them relapsed (vs 41,3% de novo AML; p=0.001).

There were no statistically significant differences between the types of consolidation therapy (standard chemotherapy, ID/HD chemotherapy, allogeneic/autologous HSCT) given to de novo AML and sAML subjects. Curatively treated patients with sAML had a significantly worse OS when compared with de novo AML patients (a median of 8.2 months (95% CI 5.7-10.7) vs 18.2 months (95% CI 15.6-20.8). The difference was not statistically significant in patients with palliative/supportive treatment.

Table 2. Prognostic factor analysis for the OS after the achievement of CR in 553 curatively treated de novo AML patients (without APL) who underwent subsequent consolidation therapy.

Prognostic factor	Risk category / Basal category	Hazard ratio	95% CI	p-value
Consolidation therapy	CT1 + Auto-HSCT / Allo-HSCT	1.58	1.20 - 2.09	0.001
Age	45–60 years / <45 years	1.20	0.90 - 1.59	0.219
	≥60 years / <45 years	1.38	1.01 - 1.89	0.043
Cytogenetic prognosis	Intermediate / Good	2.01	1.32 - 3.07	0.001
	Poor / Good	4.92	3.09 - 7.85	<0.001
	Not available / Good	3.23	1.98 - 5.24	<0.001

[1] CT - chemotherapy

Table 3. Risk factors in curatively treated patients with de novo AML and sAML

	De novo AML	Secondary AML	P
	N = 915	N = 176	
Age at diagnosis			
Median	54 years	59 years	< 0.001
60 years and older	31.5 %	41.5 %	0.011
Leukocytes at diagnosis			
Median	13.1 × 109/l	4.7 × 109/l	< 0.001
< 4 × 109/l	30.0 %	45.7 %	
4 - 10 × 109/l	13.9 %	18.9 %	< 0.001
> 10 × 109/l	56.0 %	35.4 %	
Cytogenetic prognosis			
Very good (APL)	11.1 %	3.4 %	
Good	10.9 %	1.7 %	
Intermediate	46.4 %	38.6 %	< 0.001
Poor	15.1 %	23.9 %	
Unknown	16.4 %	32.4 %	

Significant differences in both the OS and DFS were also found when comparing the groups of patients who achieved complete remission after induction (a median OS of 14.1 months (95% CI 11.5-16.7) in secondary AMLs and 37.4 months (95% CI 20.6-54.3) in de novo AML patients).

The prognostic value of cytogenetic testing was confirmed in sAML patients as well. Those with good cytogenetic prognosis (in this case including APL due to a small number of cases) survived longer (a median OS of 28 months; 95% CI 12.2-43.8) than patients with intermediate or poor prognosis (a median OS of 12.3 (95% CI 7.7-16.8) and 5.8 months (95% CI 4.9-6.8), respectively). In addition, statistically significant differences were found when comparing the individual cytogenetic prognostic subgroups of de novo AML and sAML (Fig. 6).

The age at diagnosis was also of a prognostic value. Whereas curatively treated patients under 60 years had a median OS of 9.2 months, those aged 60 or more had a median OS of 6.5 months. A significantly shorter OS was noted in sAML patients (as compared with de novo AML) in all age groups (Fig. 7). Similarly, the OS rates in categories based on WBC count at diagnosis were significantly higher in de novo AML patients (Fig. 8).

As a part of consolidation therapy, 28.4% of patients underwent allogeneic HSCT. These patients had a median OS of 19.2 months (95% CI 10.5-27.9) and tended to survive longer than those treated with both ID/HD consolidation chemotherapy (a median OS of 13.8 months; 95% CI 10.8-16.8) and standard chemotherapy (a median OS of 12.6; 95% CI 6.1-19.0). However, the difference was not statistically significant, possibly also due to small numbers of patients in individual treatment groups, i.e. small statistical power.

At the time of analysis, 48 patients (14.6%) with secondary AML were alive, with a median survival of 12.1 months (range, 0–78.9) months.

III. Multivariate modeling in the entire group

1. A multivariate survival analysis of the impact of individual prognostic factors on the OS was performed in the entire group of curatively treated patients, i.e. those with both de novo AML and sAML.

In the model, the following variables were considered: age, sex, AML type, WBC count at diagnosis, cytogenetic prognosis and time period.

The Cox proportional hazards model with both fixed and random effects was considered for the survival modeling. The interactions between variables were also analyzed, however, no statistically significant interactions between the considered variables were identified. Regression diagnostics was performed to find out whether the final model adequately describes the data, proportionality of hazards was assessed using a test based on weighted Schoenfeld residuals, whereas the scaled score residuals and the deviance residuals were used to assess the overall model fit.

All statistical computations were performed with the R software for statistical computing and graphics (9). The resulting hazard ratios and 95% CIs corresponding to the Cox model for the OS from the date of diagnosis are shown in Table 4.

2. A multivariate analysis of the impact of individual prognostic factors on achieving CR was performed in the entire group of 1,091 curatively treated patients, i.e. those with both de novo AML and sAML.

In the model, the following variables were considered: age, sex, AML type, WBC count at diagnosis, cytogenetic prognosis and time period.

A multiple logistic regression model with stepwise variable selection was used for identification of the significant prognostic factors. Clinically relevant interactions were considered in the model selection process, however, none of them was statistically significant.

The odds ratios estimated with the final model accompanied with the 95% CIs are presented in Table 5. The odds ratios represent the increased chance of complete remission achievement in patients with the more favorable variant of the risk factor considered.

Discussion

Age. Age is one of the most important prognostic factors in AML. The disease is seen in all age groups and its incidence increases with age (10). The arbitrary age limit, above which the patients' ability to undergo curative therapy and their chances to achieve treatment response are significantly decreased, with the risk of relapse being much higher, is set at 60–65 years (11). These patients have more frequent and severe associated diseases and poorer overall health status at the time of diagnosis as compared with their younger counterparts (12–14). As a result of fatty changes in the bone marrow, a damaged metabolism and impaired removal of toxins, AML patients have problems tolerating intensive chemotherapy (15, 16). Last but not least, they are often characterized by other negative prognostic factors such as adverse cytogenetic changes (17), development of secondary leukemia (18) and frequent overexpression of the multi-drug resistance glycoprotein 1 (19). In our study, patients over 60 years of age accounted for as much as 45.1% of the entire group. The reported median age of patients in the population ranges from 64 to 72 years (2, 20–25). The median age of patients in the ALERT registry is lower (60 years; 58 years in de novo AML; 63 years in sAML). The difference is associated with lower numbers of patients in older age groups of the registry. This is in contradiction with the literature data suggesting an increasing incidence of AML in patients over 60 years of age. The discrepancy may be explained by the fact that due to their poor health status, older AML patients are often treated in regional hematology outpatient clinics instead of the centers, or they die even before they are diagnosed with AML. The differences between the age distribution of patients referred to hematology intensive care centers and the incidence reported in the literature are shown in Figure 9. It compares

Table 4. Prognostic factor analysis for the OS in 1,091 curatively treated AML patients diagnosed in 1999–2009.

Prognostic factor	Risk category / Basal category	Hazard ratio	95% CI	p-value
AML type	Secondary / De novo	1.61	1.32 - 1.96	<0.001
WBC count	>10×109/L / <10×109/L	1.40	1.19 - 1.65	<0.001
Age	45-60 years / <45 years	1.55	1.26 - 1.92	<0.001
	≥60 years / <45 years	2.04	1.65 - 2.52	<0.001
Cytogenetic prognosis	Intermediate / Good (including APL)1	2.66	1.98 - 3.56	<0.001
	Poor / Good (including APL)1	5.82	4.25 - 7.96	<0.001
	Not available / Good (including APL)1	4.77	3.47 - 6.57	<0.001

[1] Patients with good and very good prognosis (APL) were considered together due to non-proportional hazards in the group with very good prognosis (APL).

Table 5. Prognostic factor analysis for the achievement of CR in 1,091 curatively treated AML patients diagnosed in 1999–2009.

Prognostic factor	Basal category / Risk category	Odds ratio	95% CI	p-value
AML type	De novo / Secondary	2.17	1.52 - 3.13	<0.001
Age	<45 years / 45-60 years	2.56	1.69 - 4.00	<0.001
	<45 years / ≥60 years	4.55	3.03 - 7.14	<0.001
Cytogenetic prognosis	Good (including APL)1 / Intermediate	2.94	1.72 - 5.00	<0.001
	Good (including APL)1 / Poor	5.26	2.94 - 10.00	<0.001
	Good (including APL)1 / Not available	6.25	3.57 - 11.11	<0.001

[1] Patients with good and very good prognosis (APL) were considered together due to no difference in the proportion of patients who achieved CR in both groups.

the age distribution of AML patients in the Czech National Cancer Registry (NCR), i.e. including those with post-mortem diagnosis since pathologists and all physicians are obliged by law to report them, with patients diagnosed in most Czech hematology intensive care centers and voluntarily reported to the ALERT acute leukemia clinical registry.

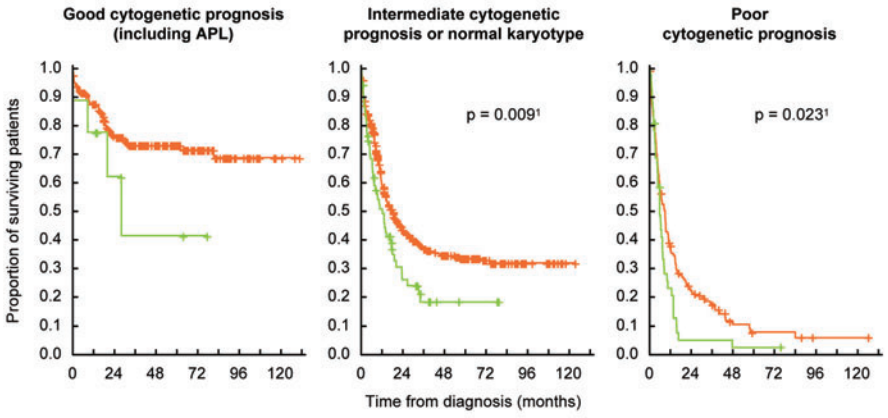
The data on cytogenetic changes in the individual age groups suggest that the elderly patients have lower rates of favorable cytogenetic changes and a slight increase in changes associated with poor prognosis. The data are consistent with the aforementioned literature reports and have a significant impact on the elderly patients' prognosis.

The effect of age on treatment outcomes – both the achievement of CR and OS – was confirmed by the multivariate analyses (Tables 2, 4 and 5).

Cytogenetics. Currently, cytogenetic assays are indispensable for making the diagnosis of AML (according to the WHO classification) and determining its prognosis (26). They are one of the most important prognostic factors predicting the patient's treatment response and survival (27, 28). A relatively high percentage of cytogenetically tested patients indicated for curative therapy (83.6% in de novo AML and 67.6% in sAML) suggests very good availability of the methods in Czech centers.

Due to their completely different therapy and prognosis, patients with APL were not included in some of the analyses. Their survival curves (Fig. 3) demonstrate a very good prognosis of this AML subtype when compared with the other AMLs. This is true for all age groups, with slightly decreased OS rates in patients aged 60 or more. Similar results may be seen in AML groups based on disease genesis. Long-term remission is observed in more than 80% of APL patients younger than 60 years of age and even more than 90% of those who achieved complete remission after induction.

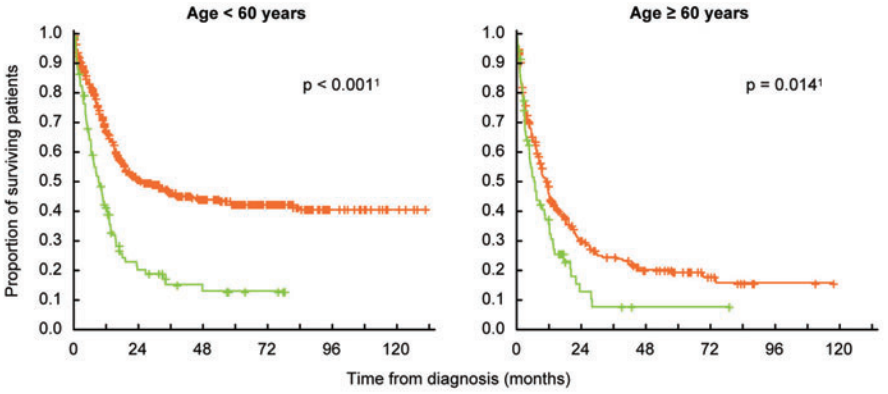
When compared with APL patients, those with the other two favorable cytogenetic changes have significantly worse survival curves despite the fact that even in this group, patients



AML type	Cytogenetic prognosis: Good (including APL) N	Median OS (95% CI)	Intermediate / normal karyotype N	Median OS (95% CI)	Poor N	Median OS (95% CI)
De novo AML	202	not reached	425	17.6 (13.7 - 21.6)	138	8.9 (6.9 - 10.9)
Secondary AML	9	28.0 (12.2 - 43.8)	68	12.3 (7.7 - 16.8)	42	5.8 (4.9 - 6.8)

[1] Log-rank test

Figure 6 – OS of patients with curatively treated AML according to AML type and cytogenetic prognosis



AML type	Age < 60 years N	Median OS (95% CI)	Age ≥ 60 years N	Median OS (95% CI)
De novo AML	627	24.6 (14.4 - 34.8)	288	10.9 (9.2 - 12.7)
Secondary AML	103	9.2 (6.4 - 12.1)	73	6.5 (4.1 - 8.9)

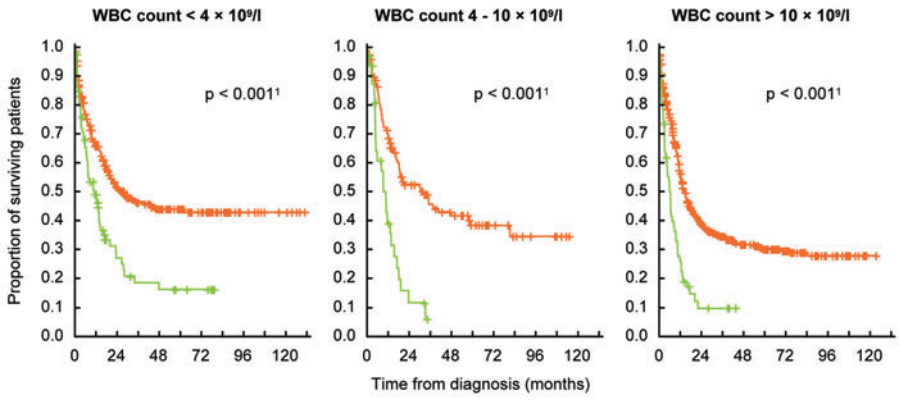
[1] Log-rank test

Figure 7 – OS of patients with curatively treated AML according to AML type and age

under 60 years of age have not reached the median survival. It must be stressed that in this prognostic group of patients, HSCT in consolidation was the least frequent. Moreover, no patient aged 60 or more underwent transplantation. The most frequent form of consolidation treatment is based on chemotherapy with moderate- or high-dose cytarabine (Fig. 2). This is fully consistent with the published data on the effectiveness of these regimens in this prognostic group (29), with allogeneic HSCT being indicated only after a relapse (or the second CR, respectively).

The largest group was made up of patients with intermediate cytogenetic prognosis. The survival analysis found that nearly half of patients under 60 years of age with de novo AML and intermediate cytogenetic prognosis are in long-term remission. In this cytogenetic category, significantly worse survival is reported in patients older than 60 years of age and those with sAML, with less than a fifth of them achieving long-term survival. HSCT is not a dominant approach to consolidation therapy in this group of patients, not even those with sAML.

The least satisfactory treatment outcomes were in the group with poor cytogenetic prognosis. Only less than a tenth of the patients survive for a long time, regardless of age, genesis of leukemia and the fact that in patients under



	WBC count < 4 × 10⁹/l		WBC count 4 - 10 × 10⁹/l		WBC count > 10 × 10⁹/l	
AML type	N	Median OS (95% CI)	N	Median OS (95% CI)	N	Median OS (95% CI)
De novo AML	274	27.5 (13.6 - 41.4)	127	31.2 (15.6 - 46.8)	511	14.6 (12.2 - 17.0)
Secondary AML	80	11.1 (5.8 - 16.4)	33	9.2 (5.8 - 12.7)	62	6.4 (4.4 - 8.4)

¹ Log-rank test

Figure 8 – OS of patients with curatively treated sAML according to WBC count at diagnosis

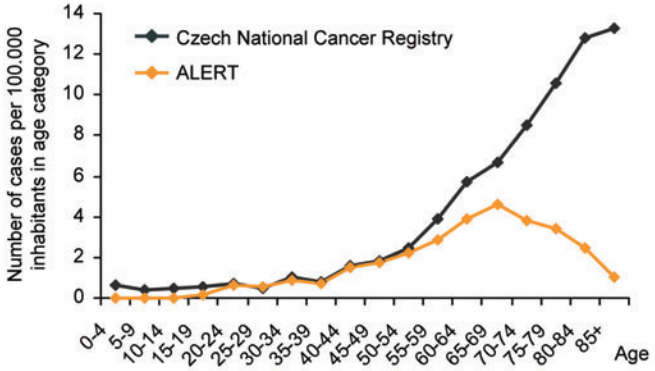


Figure 9 – Age-specific incidence of AML in the NCR and ALERT registries

60 years from this group, HSCT is the most frequent type of consolidation therapy.

The multivariate analysis found cytogenetic tests to be the most important prognostic factor affecting both CR and OS of the patients.

WBC count at diagnosis. This factor has a clear prognostic value in two groups of patients. Firstly, patients with APL in whom WBC count at diagnosis is part of a scoring system assessing the risks of both early mortality and relapse (30). Secondly, patients with hyperleukocytosis (>100x10^9/L), have a higher risk of early death, leukostasis, tumor lysis syndrome, infection and the leukemic CNS involvement (31-35). The results of the other analyses of the prognostic value of the initial WBC count in AML patients are inconsistent.

Our group was numerically dominated by a group of patients with initial leukocytosis of >10x10^9/L. The analyses (including multivariate modeling) showed its negative prognostic value (Figs. 4 and 8; Table 4). The median OS of these patients is statistically significantly shorter than that of patients with normal or low WBC count at diagnosis. The adverse effect of leukocytosis is apparent in both de novo AML and sAML.

Pathogenesis of AML. Secondary AML accounts for 10–30% of all AMLs (36). In this respect, our results are consistent with the reported data. Secondary AML is more frequent in older patients. This is probably related to a higher incidence of the MDS and other malignancies in the older population (37). Also in our group, sAML patients were significantly older than those with de novo AML. They were also found to have significantly higher rates of unfavorable and lower rates of favorable cytogenetic changes.

Patients with sAML are significantly less frequently curatively treated and less often achieve CR. On the other hand, they more often relapse.

All the above factors contribute to a significantly worse OS of sAML patients, including those who achieved CR.

As in de novo AML, the OS of patients with sAML statistically significantly reflects the cytogenetic prognosis.

However, the treatment outcomes are significantly worse in sAML patients than in those with de novo AML and identical cytogenetic abnormalities.

The role of the secondary nature of AML as a statistically highly significant prognostic factor adversely affecting both the achievement of CR and OS was in our group confirmed by multivariate analyses.

In our relatively small group of patients with sAML, a higher chance of being cured (statistically insignificant, probably due to the small number of patients) was observed in those undergoing HSCT.

However, the overall treatment outcome is not satisfactory. With the exception of APL in which secondary genesis has no significant influence on survival, there is no effective treatment for sAML patients as yet.

Therefore, patients with HLA-matched donors and meeting the criteria for allogeneic HSCT should be offered allogeneic HSCT. The other sAML patients able to undergo curative treatment should be offered participation in clinical trials.

Consolidation therapy. In the first CR, allogeneic HSCT is normally indicated for all patients who are not in the group with good cytogenetic prognosis, have matched donors and have a health status that enables them to undergo such a demanding therapeutic approach (38). There are no standard indications for autologous HSCT in AML. Usually, it is performed in patients indicated for allogeneic HSCT who do not have matched donors.

As part of consolidation, allogeneic HSCT was performed in 46.7% of de novo AML patients but in only 28.4% of those with sAML. We can only speculate about the reasons for such low rates of transplantations since in most patients, data are unavailable on donor availability, comorbidities and how consolidation therapy modalities were selected. Almost certainly, it was due to the higher age of sAML patients and possibly also due to their poorer general condition related to their earlier (primary) disease and its treatment.

Yet in both de novo AML and sAML patients, the analysis of our group found allogeneic HSCT as part of consolidation therapy in the first CR to have better outcomes demonstrated by a longer median OS as compared with the other approaches. In de novo AML, the difference from the other modalities is statistically highly significant and it was also confirmed by a multivariate analysis (Table 2).

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