Clinical relevance of mutant *NPM1* and *CEBPA* in patients with acute myeloid leukaemia – preliminary report

Grzegorz Helbig, Krzysztof Wozniczka, Agnieszka Wieclawek, Anna Soja, Aleksandra Bartkowska-Chrobok, Slawomira Kyrcz-Krzemien

Department of Haematology and Bone Marrow Transplantation, Silesian Medical University, Katowice, Poland

Aim of the study: Mutant *NPM1* and *CEBPA* have been reported in patients with acute myeloid leukaemia (AML) and intermediate cytogenetic risk, and they appear to be associated with characteristic demographic and laboratory data, as well as clinical outcome. The objective of the study was to assess the clinical relevance of *NPM1* and *CEBPA* mutations in AML.

Material and methods: This retrospective analysis was based on 60 newly diagnosed patients with AML and normal/no metaphases karyotype and known mutation status, who were treated in our centre between 2008 and 2011 according to the PALG (Polish Adult Leukaemia Group) study protocol. Pretreatment bone marrow samples were studied by G-banding analysis, and *NPM1*, *CEBPA*, and *FLT3-ITD* mutations were detected by polymerase chain reaction (PCR).

Results: *NPM1* mutations were detected in 21 AML patients (35%). In the *NPM1*-positive subgroup, the *FLT3-ITD* mutation was observed in 3 cases (14%), which was significantly less frequent than in the *NPM1*-negative patients, where *FLT3-ITD* was detected in 16 cases (41%; $p = 0.04$). Among the *CEBPA*-positive population ($n = 11$; 18%), none of the studied patients had *FLT3-ITD* mutation, whereas it was detected in 19 *CEBPA*-negative patients (0% vs. 38%; $p = 0.01$). The highest complete remission rate was reported for the *NPM1*-positive/*FLT3-ITD*-negative group ($n = 18$; 88%) and the *CEBPA*-positive/*FLT3-ITD*-negative group ($n = 8$; 73%). For OS, multivariable analysis revealed *NPM1*-positive/*FLT3-ITD*-negative (HR: 0.18, 95% CI: 0.19–0.63) and *CEBPA*-positive/*FLT3-ITD*-negative (HR: 0.35, 95% CI: 0.19–0.63) as favourable prognostic factors. The presence of the *NPM1*-negative/*FLT3-ITD*-positivecombination predicted adverse overall survival (HR: 2.03, 95% CI: 1.13–3.66).

Conclusions: *NPM1* and *CEBPA* mutations are associated with clinical outcome in AML patients.

Key words: acute myeloid leukaemia, *NPM1*, *CEBPA*, *FLT3-ITD*, complete remission, overall survival.

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Introduction

Nucleophosmin (*NPM*) gene mutation is the most frequent gene lesion in acute myeloid leukaemia (AML) and it accounts for about 40–50% of patients with a normal karyotype [1]. Nucleophosmin functions as a nucleus-cytoplasm shuttling protein, and it was found to be involved in the pathogenesis of leukaemia and lymphoma [2, 3]. It was demonstrated that the presence of the *NPM1* mutation is associated with an increased white blood cell (WBC) count, monocytic blast cell morphology, female gender, and the absence of CD34 and CD133 markers [1, 4]. Mutant *NPM1* predicts better response to induction therapy and favourable overall survival (OS), but only in the absence of *FLT3-ITD* [5].

The *CEBPA* gene encodes a transcription factor that is expressed in myelomonocytic cells [6]. *CEBPA* mutation is thought to be involved in leukaemogenesis by blocking granulocytic differentiation [7]. Acquired point mutations of the *CEBPA* gene have been detected in about 10–20% of patients with AML and normal karyotype [7, 8]. The correlations between *CEBPA* mutations and age, gender, WBC, and platelet count of AML patients have not been demonstrated. However, *CEBPA* gene mutations have been preferentially observed in M1, M2, and M4 subtypes [8, 9], and they are associated with the co-expression of the following markers: CD7, CD34, HLA-DR, and CD15 [10]. The presence of mutant *CEBPA* genotype appears to be associated with a favourable outcome in terms of relapse-free and overall survival [11].

The objective of our study was to assess the prevalence of *NPM1* and *CEBPA* mutations in AML as well as describe the clinical profile and prognosis of this patient subgroup.

Material and methods

This retrospective analysis was based on 60 newly diagnosed patients with AML and normal/no metaphases karyotype and known mutation status, who were treated in our centre between 2008 and 2011 according to the PALG (Polish Adult Leukaemia Group) study protocol. The details of the study have been published previously [12]. Shortly, patients were randomised to receive one of the two following induction regimens: arm 1: DAC-7 (60 mg/m^2 daunorubicin for 3 days, 200 mg/m^2 cytarabine as continuous infusion for 7 days and 5 mg/m^2 cladribine for 5 days) and arm 2: DA-7 with daunorubicin and cytarabine at previously mentioned doses. Twenty-five patients were transplanted from matched sibling or unrelated donors. Eighteen patients had a prior history of myelodysplastic syndrome. Patients with AML-M3 were not included in this study. All blood and marrow tests necessary to establish the diagnosis of AML as well as response criteria for AML were

implemented according to European Leukaemia Net (ELN) recommendations [13]. Pretreatment bone marrow samples of all patients were studied by G-banding analysis and fluorescence in-situ hybridisation if required. Chromosomal abnormalities were described according to the International System for Human Cytogenetic Nomenclature [14]. The *NPM1*, *CEBPA*, and *FLT3-ITD* mutations were detected in bone marrow aspirates or peripheral blood cells as previously described [1, 7, 15].

Statistical analysis

Nonparametric comparisons of group means were performed by using the Mann-Whitney *U* test. Proportions were compared by Fisher's exact test. The distribution for overall survival (OS) was estimated using the method of Kaplan and Meier and compared using the log-rank test. All variables that were found to have a p value < 0.1 in univariate analysis were considered to be candidates for the stepwise Cox regression model. The following variables were included: age, gender, leukocyte count, haemoglobin concentration, platelet count, peripheral blood and bone marrow myeloblasts, the presence of organomegaly/lymphadenopathy, mutation status, and the type and response to induction treatment. A p value < 0.05 was considered significant in the multivariate model. For all outcome estimations, the 25 patients who underwent allogeneic stem cell transplantation in first complete remission were censored at transplantation date. All calculations were performed using StatSoft software, version 10.0. Due to an interaction observed between *NPM1*, *CEBPA*, and *FLT3-ITD* mutations, the patients were categorised into four subgroups: 1) *NPM1/FLT3-ITD*-double positive, 2) *NPM/FLT3-ITD*-double negative, 3) *NPM1*-positive/*FLT3-ITD*-negative, and 4) *NPM1*-negative/*FLT3-ITD*-positive. The same was created for the combinations of *CEBPA/FLT3-ITD* mutations.

Results

Cytogenetic results

Diploid karyotype was detected in 47 studied patients whereas metaphases were not demonstrated in 13 cases. No other cytogenetic abnormalities were found.

Incidence of NPM1, CEBPA, and FLT3-ITD mutations

NPM1 mutations were detected in 21 AML patients (35%). In the *NPM1*-positive subgroup, the simultaneous occurrence of the *FLT3-ITD* tyrosine kinase mutation was observed in just 3 cases (14%), which was significantly

Table 1. Patient characteristics

Parameter	NPMmut	NPMwt	*p*	CEBPAmut	CEBPAwt	*p*
no. of patients	21	39		11	49	
median age, yr (range)	50 (20–60)	52 (22–60)	0.72	42 (24–52)	53 (20–60)	**0.02**
gender, M/F	11/10	16/23	0.42	6/5	21/28	0.52
WBC (×10^9/l); median, range	25 (0.9–227)	22.8 (1.9–264)	0.56	10.5 (2.4–264)	23 (0.9–242)	0.88
PLT (×10^9/l); median, range	56 (16–270)	41 (6–244)	0.24	44 (6–199)	41 (7–270)	0.92
Hgb (g/dl); median, range	9.3 (6.8–12)	9.4 (4.3–12.8)	0.74	9.4 (8.6–12.8)	9.4 (4.3–12)	0.18
blast cells in PB (%); median, range	74 (0–100)	70 (0–100)	0.76	52 (0–100)	74 (0–100)	0.60
blast cells in BM (%); median, range	80 (20–100)	80 (18–100)	0.61	55 (19–100)	80 (18–100)	0.18
LDH activity (IU), median, range	252 (85–1137)	422 (134–1694)	0.11	479 (143–1650)	305 (85–1664)	0.14
splenomegaly, no. (%)	4 (19)	8 (21)	0.4	3 (27)	4 (8)	0.10
hepatomegaly, no. (%)	1 (5)	6 (15)	0.21	3 (27)	4 (8)	0.10
lymphadenopathy, no. (%)	4 (19)	8 (21)	0.58	4 (36)	8 (16)	0.20
prior MDS, no. (%)	3 (14)	6 (15)	0.61	1 (9)	8 (16)	0.47
diploid karyotype	19 (90)	28 (71)	0.38	10 (91)	37 (75)	0.42
FLT3-ITD, no. (%)	3 (14)	16 (41)	**0.04**	0 (0)	19 (38)	**0.01**
DAC7, no. (%)	15 (71)	29 (74)	0.75	10 (48)	34 (69)	0.25
CR, no. (%)	18 (86)	16 (41)	**0.001**	8 (73)	26 (53)	0.32
AlloSCT, no. (%)	15 (71)	10 (26)	**0.001**	8 (72)	17 (43)	**0.03**

AlloSCT – allogeneic stem cell transplantation; CR – complete remission; DAC – daunorubicin, cytarabine, cladribine; F – female; FLT3-ITD – FLT3 internal tandem duplication; Hgb – haemoglobin; M – male; MDS – myelodysplastic syndrome; mut – mutation; PLT – platelets; WBC – white blood count; wt – wild type

less frequent than in the *NPM1*-negative patients (n = 16; 41%; p = 0.04). Among *CEBPA*-positive population (n = 11; 18%), none of the studied patients had *FLT3-ITD* mutation, whereas it was detected in 19 *CEBPA*-negative patients (0% vs. 38%; p = 0.01).

Patient characteristics

There was no difference in demographic and clinical data between *NPM1*-mutated and *NPM1*-negative groups. The CD38 expression was seen more frequently in patients with *NPM1* mutation than in those without this abnormality (57% vs. 28%; p = 0.04) (data not shown).

There was also no significant difference between *CEBPA*-positive and *CEBPA*-negative patients except for age at diagnosis: 42 years vs. 53 years, respectively (p = 0.02). Characteristics of AML patients at diagnosis are presented in Table 1.

Response to induction treatment

There were three early deaths in this study group including *NPM1*-negative/*FLT3-ITD*-negative (n = 1) and *NPM1*-negative/*FLT3-ITD*-positive patients (n = 2).

The DAC-7 regimen was administered for 44 patients, whereas 16 received DA-7. There was a trend towards better CR rate in patients receiving DAC-7 regimen (64% vs. 37%; p = 0.08).

There was a statistically significant difference in complete response (CR) rates after induction treatment according to *NPM1/FLT3-ITD* mutation status. The highest CR was reported for *NPM1*-positive/*FLT3-ITD*-negative group (n = 18; 88%), followed by double-positive *NPM1/FLT3-ITD* groups (n = 3; 66%) and the double-negative *NPM1/FLT3-ITD* (n = 23; 56%). The lowest CR was achieved for the *NPM1*-negative/*FLT3*-ITD-positive patients (n = 16; 37%); p = 0.002.

There were no patients with double-positive *CEBPA/FLT3-ITD* mutations. Among the remaining three groups we found no significant difference in CR rates, and the highest CR rate was reported for the *CEBPA*-positive/*FLT3-ITD*-negative group (n = 11; 73%), followed by the double-negative *CEBPA/FLT3-ITD* group (n = 30; 60%). The lowest CR was observed for the *CEBPA*-negative/*FLT3-ITD*-positive patients (n = 19; 42%), p = 0.49.

Survival rates

The median survival was 13.3 months (range 0.03–58.6). In total, 14 out of the 34 CR patients relapsed (41%). The relapse-free survival (RFS) was not assessed due to the small number of patients in each subgroup according to the mutation status. Median time to relapse for the CR cohort was 7.1 months (range 2.3–19.1).

We found statistically significant difference in OS rates between AML patients according to the *NPM1/FLT3-ITD* mutations. The highest OS at 12 months was demonstrated in the *NPM1*-positive/*FLT3-ITD*-negative group (82%), and the lowest OS in the *NPM1*-negative/*FLT3-ITD*-positive subgroup (37%). Regarding the *CEBPA/FLT3-ITD* mutation status, the patients with *CEBPA*-positive/*FLT3-ITD*-negative mutations had the highest OS at 12 months (91%), whereas the lowest OS was observed in double-negative

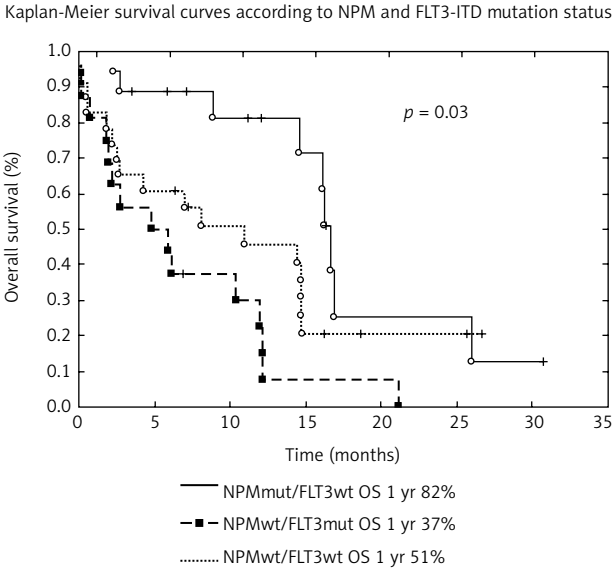

Fig. 1. Overall survival according to NPM1 and FLT3-ITD mutation status

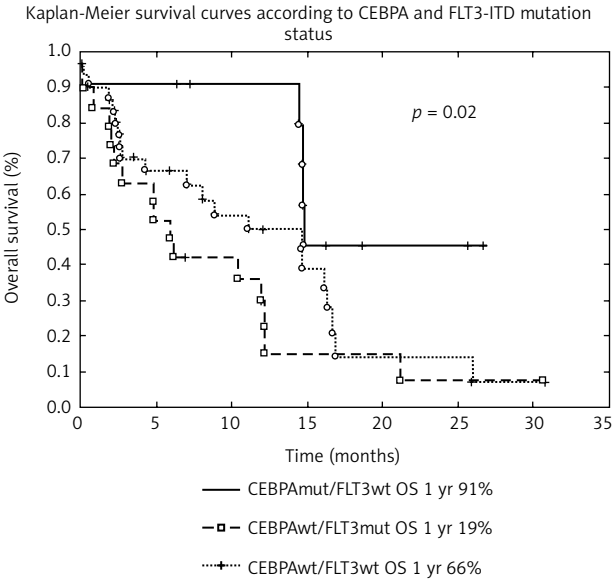

Fig. 2. Overall survival according to CEBPA and FLT3-ITD mutation status

combinations (30%). Due to the low number of patients with double-positive *NPM/FLT3-ITD* mutations, they were not included in the OS analysis (see Figs. 1–2).

For OS, multivariable analysis revealed *NPM1*-positive/*FLT3-ITD*-negative (p < 0.017; HR: 0.18, 95% CI: 0.19–0.63) and *CEBPA*-positive/*FLT3-ITD*-negative (p < 0.001; HR: 0.35, 95% CI: 0.19–0.63) as favourable prognostic factors. The presence of the *NPM1*-negative/*FLT3-ITD*-positive combination predicted adverse overall survival (p < 0.001; HR: 2.03; 95% CI: 1.13–3.66).

An allogeneic matched sibling or unrelated stem cell transplantation in CR was performed in 25 patients (74%), and their referral for transplantation was based on cytogenetic but not mutation risk groups. Mutant *NPM1* and *CEBPA*

patients were transplanted statistically more frequently. However, there was no difference in death rate after transplant at the last contact between *NPM1*-positive and *NPM1*-negative patients ($p = 0.53$; 50% vs. 66%) as well as between *CEBPA*-positive and *CEBPA*-negative patients ($p = 0.62$; 37% vs. 35%).

Discussion

The *NPM1* mutation is the most frequent molecular abnormality seen in patients with AML and normal karyotype. It should be emphasised that to date this mutation has not been reported in patients with t(15;17), t(8;21), inv(16)/t(16;16), and 11q23 rearrangements [1, 4]. The same was also the case in our cohort; however, cytogenetic studies were unsuccessful in 13 patients (22%). The frequency of *NPM1* mutation was slightly lower than that reported by other groups [1, 4]. Demographic and laboratory data did not differ between *NPM1*-mutated and *NPM*-wild type patients except for the CD38 expression, which was more frequently reported in the former group. The association of *NPM1* mutation with female gender, M4/M5 FAB types, high WBC count, and marrow blast cells was not found in our analysis. The *FLT3-ITD* mutation was significantly more frequent in the *NPM1*-negative group (41% vs. 14%; $p = 0.04$).

One of the first retrospective studies included 106 AML patients, and it did not show any association between *NPM1* mutation status, CR rate, and long-term overall survival [4]. However, further studies with a larger patient population have shown that the presence of *NPM1* mutation was strongly associated with achievement of CR and a longer OS, but only in the absence of *FLT3-ITD*. The above-mentioned combined mutations have been found to be a favourable prognostic factor in multivariable analysis for OS [5]. The same was revealed in our study; patients with this combination had the highest CR rate (88%) and OS at 12 months (82%; $p < 0.017$; HR: 0.18, 95% CI: 0.19–0.63). It should be mentioned that these results refer to patients < 60 years old. However, *NPM1* mutation also has a favourable prognostic impact in patients over 70 years old [16]. Moreover, it was demonstrated that *NPM1*, but not *FLT3-ITD*, was associated with an early blast clearance and with the achievement of CR in AML patients with a normal karyotype [17]. A beneficial impact of mutant *NPM1* without *FLT3-ITD* was finally confirmed in the largest study to date of the German-Austrian AML Study Group. A significant association between the risk of relapse or the risk of death while in CR and the above-mentioned mutant combination was demonstrated in a study on 872 AML patients < 60 years old with a normal karyotype (HR: 0.44, 95% CI: 0.30–0.75 and HR: 0.51, 95% CI: 0.37–0.70, respectively). Moreover, the *NPM1*-positive/*FLT3-ITD*-negative AML patients did not benefit from allogeneic stem cell transplantation. The opposite conclusions have been drawn for patients with mutant *FLT3-ITD* and wild-type *NPM1* and *CEBPA* without *FLT3-ITD* [11]. It was also found that AML patients with the presence of *NPM1* mutation at diagnosis still had this abnormality at relapse. This demonstrates the stability of *NPM* mutation throughout the disease course, and this mutation may serve as a sensitive marker of disease relapse. Quantitative assessment of *NPM1*-mutant was found to be helpful in monitoring disease remission and relapse [18, 19].

The frequency of *CEBPA* mutation in previous studies was found to be between 10% and 20% of cytogenetically normal AML patients [7, 8, 11, 20], and this finding was also confirmed in our study. The presence of *CEBPA* mutation was associated with younger age at diagnosis. No other differences have been observed between *CEBPA*-positive and *CEBPA*-negative patients. The *FLT3-ITD* mutation was significantly more frequently seen in the latter mutation (38% vs. 0%; $p = 0.01$).

The clinical outcome differs between *CEBPA*-positive and *CEBPA*-negative AML patients. Although CR rates after induction treatment seem to be similar, the *CEBPA*-mutated patients were found to have an increased OS and RFS [21]. It was demonstrated that *CEBPA* mutation significantly decreased the relapse risk (HR: 0.48; 95% CI: 0.30–0.75) and the risk of death (HR: 0.50; 95% CI: 0.30–0.83) in AML patients, but only in the absence of *FLT3-ITD* mutation or associated cytogenetic abnormalities. Moreover, this all seems to be true only for AML with double-*CEBPA* gene mutation [22, 23]. It should be mentioned that only single *CEBPA* mutations have been detected in our study. On the other hand, the presence of *CEBPA* mutation was found to be an independent, favourable prognostic factor in patients with a normal karyotype and molecular features of high disease risk including *FLT3-ITD* mutation [24]. A single *CEBPA* mutation may be associated with favourable clinical outcome in *NPM1/FLT3-ITD* wild-type AML patients [25].

Our study did not demonstrate the statistical difference in CR rate between patients with positive and negative *CEBPA* gene (73% vs. 53%, $p = 0.32$). However, the presence of *CEBPA* mutation without *FLT3-ITD* had a favourable prognostic impact on OS ($p < 0.001$; HR: 0.35; 95% CI: 0.19–0.63). These patients seem to have a prognosis similar to that with inv16 or t(8;21), and they do not require transplant in first CR [26]. The prognostic value of autologous (AHSCT) and allogeneic stem cell transplantation (AlloHSCT) for AML patients with biallelic *CEBPA* mutation has recently been evaluated. It was concluded that double-mutant *CEBPA* patients may benefit from transplants in terms of RFS, but not OS, when compared to conventional chemotherapy [27].

Conclusions

Despite the low statistical power of this study due to the small number of included patients, our preliminary results suggest that the presence of mutant *NPM1* and *CEBPA* without *FLT3-ITD* may have a favourable prognostic impact on overall survival. Based on similar conclusions provided by other study groups, two new provisional entities were introduced to the revised 2008 WHO classification. Namely, cases with *NPM1* and *CEBPA* mutations were added to the "AML with recurrent genetic abnormalities" subgroup; however, the term "provisional" means that more studies are still needed to better characterise these AML patients [28].

The authors declare no conflict of interest.

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Address for correspondence

Grzegorz Helbig MD, PhD
Department of Haematology and Bone Marrow Transplantation
Silesian Medical University
Dąbrowskiego 25
40-032 Katowice
tel. +48 32 259 13 10
fax +48 32 255 49 85
e-mail: ghelbig@o2.pl

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