Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype

Susanne Schnittger, Claudia Schoch, Wolfgang Kern, Cristina Mecucci, Claudia Tschulik, Massimo F. Martelli, Torsten Haferlach, Wolfgang Hiddemann, and Brunangelo Falini

Nucleophosmin (NPM1) exon-12 gene mutations are the hallmark of a large acute myelogenous leukemia (AML) subgroup with normal karyotype, but their prognostic value in this AML subset has not yet been determined. We screened 401 AML patients with normal karyotype treated within the German AML Cooperative Group Protocol 99 (AMLCG99) study for NPM1 mutations. Results were related with partial tandem duplications within the MLL gene (MLL-PTD), Fms-like tyrosine kinase 3–length mutations (FLT3-LM), the tyrosine kinase domain of FLT3 (FLT3-TKD), NRAS, KIT, and CEBPA mutations and with clinical characteristics and outcome. NPM1 mutations were detected in 212 (52.9%) of 401 patients. Fourteen mutations, including 8 new variants, were identified. NPM1-mutated cases associated frequently with FLT3 mutations but rarely with other mutations. The NPM1-mutated group had a higher complete remission (CR) rate (70.5% vs 54.7%, P = .003), a trend to a longer overall survival (OS; median 1012 vs 549 days, P = .076), and significantly longer event-free survival (EFS; median 428 vs 336 days; P = .012). The favorable impact of NPM1 mutations on OS and EFS clearly emerged in the large group (264 [66.8%] of 395 cases) of normal-karyotype AML without FLT3-LM. This positive effect was lost in the presence of a concomitant FLT3-LM, since survival of the NPM1/FLT3-LM+ double positive was similar to NPM1+/FLT3-LM+ cases. In conclusion, this study demonstrates that NPM1+/FLT3-LM+ mutations are an independent predictor for a favorable outcome in AML with normal karyotype. (Blood. 2005;106:3733-3739) © 2005 by The American Society of Hematology

Introduction

Acute myelogenous leukemia (AML) is a clinically and molecularly heterogeneous disease.1 The World Health Organization (WHO) classification2 subdivides AMLs predominantly according to karyotype since recurrent chromosomal abnormalities identify distinct leukemia entities and have a major impact on prognosis.3,4 Almost 45% of AMLs show a normal karyotype by conventional cytogenetics, and the clinical and biologic features of this large cytogenetic subgroup are still poorly understood. Accordingly, most of these cases are presently classified in the WHO scheme2 under the term “acute myeloid leukemia not otherwise characterized.”

Molecular analyses indicate that AML with normal karyotype are a heterogeneous subgroup, as a number of distinct mutations have been identified. They include mutations affecting genes encoding for transcription factors (AML1, CEBPA; 2%-3% and 15%-20% of cases, respectively),5-9 receptor tyrosine kinases (FLT3, KIT; 25%-30% and 1% of cases, respectively),10-12 and the RAS genes (10% of cases).13,14 and a partial tandem duplication within the MLL gene (MLL-PTD; 5%-10% of cases).15-19 Mutations at the exon-12 of the NPM1 gene have been recently identified as the underlying genetic lesion of a distinct, large subgroup of adult AML20 characterized by normal karyotype, aberrant cytoplasmic expression of the mutated nucleophosmin (NPM1) proteins (NPM1-cytoplasmic–positive [NPM1c+] AML), wide morphologic spectrum, multilineage involvement, increased frequency of FLT3 mutations, and CD34+ negativity. NPM1c+ AML also shows a distinctive gene expression profile.21

Mutational analysis for NPM1 was restricted to a small cohort of patients, and no information on the impact of NPM1 mutations on outcome was available. The present study analyzed the type, prevalence, association with other mutations, and prognostic impact of NPM1 exon-12 mutations in 401 AML patients with normal karyotype that were treated within protocol 99 of the German AML Cooperative Group (AMLCG99).

Patients, materials, and methods

Patient samples

The study was focused on 401 AML patients with normal karyotype (age, 16.8-81.9 years; median, 60.3 years) who entered the AMLCG99 between 1999 and 2004.

Patient characteristics are given in Table 1. All samples of bone marrow or peripheral blood (with at least 70% circulating blast cells) were obtained at diagnosis and were sent to the AMLCG reference laboratory (Munich, Germany).

All patients gave informed consent before entering the AMLCG99 study. The study design adhered to the principles of the Helsinki
continuous detection with channel F2/F1. A typical result is shown in Figure 1.

All cases that revealed an aberrant melting curve were subjected to nucleotide sequence analyses. Approximately 100 ng purified PCR products were directly sequenced with 3.3 pmol each of forward and reverse primer using the Big Dye Terminator Cycle Sequencing Kit (Appliedera, Darmstadt, Germany). After initial denaturation at 95°C for 5 minutes, 25 cycles at 94°C for 15 seconds and 60°C for 4 minutes were performed. Sequence analysis was performed on a 3100 Avant sequence detection system (Applied Biosystems, Foster City, CA).

Mutation analysis of MLL-PTD, FLT3-length mutations (LM), the tyrosine kinase domain of FLT3 (FLT3-TKD), NRAS, KIT, and CEBPA was performed as previously described.8,10,16,25

Statistical analysis
Survival curves were calculated for overall survival (OS), event-free survival (EFS), and relapse-free survival (RFS) according to Kaplan-Meier and compared using the 2-sided log-rank test. OS was calculated from time of diagnosis to death and EFS was calculated from time of diagnosis to death, documentation of persistent leukemia, or relapse. Cox regression analysis related OS and EFS with analyzed parameters. Fisher exact test compared NPM1 mutation status and dichotomous variables and Student t test compared NPM1 mutation status and continuous variables. For all analyses, results were significant at a P level less than .05 at both sides. SPSS version 12.1.4 software (Chicago, IL) was used for statistical analysis.

Results

Frequency and type of NPM1 mutations

NPM1 gene mutations were detected in 212 (52.9%) of 401 AML patients. All cases were heterozygous for the mutation and retained a wild-type allele. Fourteen different mutations were characterized (Table 2). Type A, a tcgt insertion between position nucleotide (nt) 960 and 961, was detected in 166 (78.3%) of 212 AML patients, followed by type D in 21 (9.9%) cases, and type B mutations in 13 (6.1%) cases. All other mutations were rare and were detected in only 1 to 3 individuals. One hundred sixty-two (97.6%) of 166 individuals had 4-base pair (bp) insertions of 10 different types between position nt 960 and 961. Two cases had 9-bp insertions between nt 965 and 966 (types E and F), 1 case had a 4-bp insertion between nt 964 and 965 (type M), and 1 case had 2 2-bp insertions between nt 960 and 961 and nt 962 and 963, respectively (type L; Table 2). All mutant proteins contained at their C-terminus mutations of at least 1 of the 2 tryptophans at position nt 288 and
Table 2. *NPM1* mutation variants in 401 AML patients with normal karyotype

<table>
<thead>
<tr>
<th>Type</th>
<th>n</th>
<th>Wt</th>
<th>Insertion</th>
<th>Wt</th>
<th>Insertion</th>
<th>Wt</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>A'</td>
<td>166</td>
<td>gatctcttg</td>
<td>tctg</td>
<td>gcaagttctcttt</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>B'</td>
<td>13</td>
<td>gatctcttg</td>
<td>cctg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>C'</td>
<td>—</td>
<td>gatctcttg</td>
<td>cttg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>D'</td>
<td>21</td>
<td>gatctcttg</td>
<td>—</td>
<td>gcagct</td>
<td>ctctctcgeccctt</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>E'</td>
<td>—</td>
<td>gatctcttg</td>
<td>—</td>
<td>gcagct</td>
<td>ctctctcgeccctt</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>F'</td>
<td>—</td>
<td>gatctcttg</td>
<td>gcagct</td>
<td>—</td>
<td>ctctctcgeccctt</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Qu</td>
<td>1</td>
<td>gatctcttg</td>
<td>caggg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Kw</td>
<td>3</td>
<td>gatctcttg</td>
<td>cccctg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Lg</td>
<td>1</td>
<td>gatctcttg</td>
<td>ccgggg</td>
<td>aqgt</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Mu</td>
<td>1</td>
<td>gatctcttg</td>
<td>—</td>
<td>gcagct</td>
<td>agga</td>
<td>tggagagactctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Nu</td>
<td>2</td>
<td>gatctcttg</td>
<td>ccaggg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Qu</td>
<td>1</td>
<td>gatctcttg</td>
<td>ttgg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Pu</td>
<td>2</td>
<td>gatctcttg</td>
<td>cttgg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
<tr>
<td>Qd</td>
<td>1</td>
<td>gatctcttg</td>
<td>tcggg</td>
<td>gcagct</td>
<td>—</td>
<td>ggaagagcttctcttt</td>
<td>DLINCAVEVSLSRK</td>
</tr>
</tbody>
</table>

— indicates no cases detected.
*According to Falini et al; 
mutations H, I, and J are not listed since they have been recently detected in AML pediatric patients. Wt indicates wild type; tryptophans 288 and 290 are expressed as underlined letters; NES motif, italics.

NPM1 mutations and other gene mutations

All NPM1-mutated cases were also analyzed for FLT3-LM, mutations in FLT3-TKD, NRAS- and KIT-mutations, as well as MLL-PTD. In addition, 83 cases were analyzed for CEBPA mutations in parallel. The results are shown in Figure 2. The NPM1-mutated group showed a significantly higher incidence of FLT3 mutations than the unmutated group (FLT3-LM: 40.6% vs 24.5%, \(P = .001\); FLT3-TKD: 9.5% vs 3.8%, \(P = .040\)). MLL-PTD was detected in only 1 (0.5%) NPM1-mutated case compared with 16.4% MLL-PTD in the unmutated NPM1 group (\(P < .001\)). Thus NPM1 mutations and MLL-PTD are almost exclusive. Frequency of KIT, NRAS, and CEBPA mutations did not differ in mutated and unmutated NPM1 AML.

NPM1 mutations, morphology, and immunophenotype

Frequencies of NPM1 gene mutations among French-American-British (FAB) subgroups were heterogeneous. They were significantly lower in FAB M2 (34%) and higher in M4 (77%), M5a (71%), and especially in M5b (90%) compared with the total group (\(P < .001\) for each comparison) (Figure 3).

The NPM1-mutated cases had higher expression of monocytic differentiation-associated antigens and a lower expression of CD34 (\(P < .001\)) and CD133 (\(P < .001\)) as well as of myeloperoxidase (\(P < .001\)) (Table 3).

NPM1 mutations and other biologic parameters

NPM1 mutations occurred at higher frequency in women (men, \(n = 89\) [42%]; women, \(n = 123\) [58%]; \(P = .04\)). There was no significant difference with regard to age (NPM1-mutated: median, 55.8 years; NPM1-unmutated: median, 58.1 years; \(P = .126\)).

In the NPM1-mutated group the peripheral leukocyte count was significantly higher (mean, 61.1 \(\times 10^9/L\); median, 38.7 \(\times 10^9/L\); range, 0.2-486.0 \(\times 10^9/L\)) than in the unmutated group (mean, 39.1 \(\times 10^9/L\); median, 10.0 \(\times 10^9/L\); range, \(\times 10^9/L\) 0.1-361.0 \(\times 10^9/L\); \(P < .001\)).

Prognostic impact of NPM1 mutations

All 401 patients were evaluated for the prognostic impact of NPM1 gene mutations. The median follow-up time was 484 days. In NPM1-mutated cases, CR rates were significantly higher (70.5% vs 54.7%, \(P = .04\)) and especially in M5b (90%) compared with the total. Median OS did not yet show significant difference (median, 428 vs 336 days; \(P = .012\)) (Figure 4B). RFS also did not show significant difference (median, 473 vs 473 days; \(P = .126\)).
However the curves split after 1 year and after longer follow-up a significant difference may come out. All of these differences were not related to different treatment modalities assigned by randomization. Other factors impacting on EFS were leukocyte count (P = 0.001), platelets (P = 0.007), age (P < 0.001), and FLT3-LM (P = 0.006). Multivariate analysis showed that the prognostic impact of NPM1 mutations on EFS is independent of all these other factors (Table 4).

Prognostic relevance of additional mutations

NPM1 and FLT3-LM mutations. As there was a high coincidence of NPM1 mutations with FLT3-LM, survival data were evaluated for the 4 groups, NPM1- /FLT3-LM- (n = 138), NPM1- /FLT3-LM+ (n = 45), NPM1+/FLT3-LM- (n = 126), and NPM1+/FLT3-LM+ (n = 86). Median OS was 601, 405, 1183, and 321 days, respectively (P = .041). OS was significantly longer in NPM1+/FLT3-LM- than in both NPM1-/FLT3-LM- (P = .022) and NPM1+/FLT3-LM+ (P = .014) and especially in NPM1+/FLT3-LM- versus all others (P = .005) (Figure 5A). Thus, when FLT3-LM is associated with mutated NPM1 it shifts NPM1+ cases into the poor prognosis group. No difference in OS emerged...
between \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} and \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} cases ($P = .644$).

The same pattern was found for EFS. Median EFS was 773 days (\textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM}), 365 days (\textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM}), 279 days (\textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM}), and 234 days (\textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM}), respectively ($P < .001$). EFS was longer in \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} compared with \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} ($P = .001$) and \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} ($P = .001$) as well as to \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} versus all others ($P = .001$). No difference in EFS emerged between \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} and \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} cases ($P = .885$) (Figure 5B). The RFS was significantly better for the \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-LM} group compared with all other groups ($P < .001$).

\textbf{NPM1 and FLT3-TKD mutations.} We analyzed the combination of NPM1 and FLT3-TKD mutations: \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD}$^*$ (n = 153), \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD}$^*$ (n = 6), \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD}$^*$ (n = 192), and \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD}$^*$ (n = 20). Median OS was 676 days, not reached, 992 days, and not reached, respectively. There was a trend to a longer OS in the double-mutated \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD}$^*$ than in the double-negative \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD} ($P = .076$) (Figure 6A). Median EFS was 336 days, 385 days, 373 days, and median not reached, respectively ($P = .051$). EFS of the double-mutated \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD}$^*$ was significantly longer than the double-negative \textit{NPM1}\textsuperscript{mut}/\textit{FLT3-TKD} ($P = .014$) (Figure 6B).

\textbf{NPM1 and other mutations (NRAS, AML1, MLL-PTD, KIT, and CEBPA).} Additional NRAS mutations (n = 18) did not have any prognostic impact in cases with mutated NPM1 (data not shown). AML1, MLL-PTD, KIT, or CEBPA mutations were rarely found in combination with NPM1, and thus prognostic relevance could not be analyzed.

**Discussion**

In this study, we determined the frequency and type of exon-12 NPM1 gene mutations in 401 AML patients with normal karyotype treated within study 99 of the AMLCG, determined their association with other gene mutations, and demonstrated the impact of NPM1 mutations on prognosis.

Point mutations at exon-12 of the NPM1 gene occurred more frequently than any other gene mutations (52.9% of all normal karyotype AMLs). Fourteen different NPM1 mutations were identified, including 8 previously unreported variants. All 14 mutations were heterozygous and resulted in frame shifts in the region encoding the C-terminus of the NPM1 protein that led to replacement of the last 7 amino acids with 11 different residues (the last 5 amino acids, VSLRK, being common to all variants) and substitution of at least one of 2 tryptophan residues at positions 288 and 290. Recently, Nakagawa et al\textsuperscript{27} reported a nuclear export signal (NES) motif in the first 6 described NPM1 mutants (A to F) and hypothesized that this motif might be responsible for the aberrant NPM1 cytoplasmic expression. This assumption is supported by the fact that all 8 newly detected NPM1 mutant proteins also all bear an NES motif at the protein C-terminus. Thus, despite genetic variations, all mutations result in distinct changes at the extreme C-terminus of the NPM1 mutant proteins.

Within the group of AML patients with normal karyotype, NPM1-mutated cases had a significantly higher rate of CR compared with wild-type NPM1 cases (70.5% vs 54.7%; $P = .003$). This finding confirms, at mutation level, previous findings mainly based on the aberrant cytoplasmic expression of the NPM1 protein.\textsuperscript{20}

Most importantly, however, this study demonstrates a favorable impact of NPM1 mutations on outcome. In fact, NPM1-mutated AML patients with normal karyotype had a significantly longer EFS (median, 428 vs 336 days; $P = .012$) and a strong trend to a long OS (median, 1012 vs 549 days; $P = .076$) as compared with NPM1 wild-type cases. This finding is of major clinical importance since it strongly suggests that NPM1 mutations may allow dissection of the heterogenous group of AML with normal karyotype into prognostically different subgroups. This thesis is supported by multivariate analysis revealing NPM1 mutations as an independent prognostic factor.

![Figure 4. Kaplan-Meier analysis of AML with normal karyotype bearing mutated or unmutated NPM1. (A) OS. (B) EFS. (C) RFS. Red lines indicate mutated NPM1; blue lines, unmutated NPM1. Results were significant at a level of $P < .05$ at both sides.](image-url)
Further analyses were performed to assess the impact of NPM1 mutations in the context of other molecular aberrations. The prognostic value of NPM1 mutations clearly emerged in the large group of AML patients with normal karyotype (about 70%) that lacked FLT3-LM. Analysis for NPM1 clearly identified patients with mutated NPM1 and FLT3-LM as having the better prognosis. This subgroup accounted for 31.4% of all AML cases with normal karyotype. In the group of NPM1+/FLT3-LM category, NPM1 mutations are presently the only identifiable genetic lesions that also promise to serve as a marker for monitoring minimal residual disease. The favorable impact of NPM1 mutations on prognosis was lost in the presence of a concomitant FLT3-LM, a recognized predictor of poor prognosis in AML with normal karyotype.10,11,14,25 Thus, prognosis of NPM1/FLT3-LM double-mutated cases was as unfavorable as the cases bearing NPM1 wild type and an FLT3-LM. The prognostically favorable effect of NPM1 mutations on RFS was especially strong when the FLT3-LM was taken into account. FLT3-LM has formerly been shown to be associated with a high relapse rate.10-12 In contrast, our data show that NPM1c+/FLT3-LM cases have a remarkably low relapse rate.

The overall prognostic significance of FLT3-TKD mutations is still unclear. However, in cases with mutated NPM1, FLT3-TKD mutations seem to be associated with further improvements in OS and EFS when compared with NPM1-mutated cases without FLT3-TKD mutations.

Partial tandem duplications within the MLL gene (MLL-PTD) and CEBPA mutations had a very low probability for coincidence with NPM1 mutations. In contrast, both FLT3-LM and mutations in the FLT3 tyrosine kinase domain (FLT3-TKD) occurred more frequently in cases with mutated genes than with unmutated NPM1 gene. This finding is in keeping with the hypothetical model that at least 2 hints of different mutation types are needed to induce AML26,29 (ie, type I mutations, such as in FLT3, KIT, or RAS genes that increase proliferation, and type II mutations such as AML1-ETO or PML-RARA fusion genes, which block differentiation).

So far, it is unclear why NPM1 mutations are associated with better response to induction therapy and outcome. Since the mutated NPM1 proteins maintain the dimerization domain and are therefore able to form heterodimers with the wild-type NPM1, it is likely that this may result in subcellular dislocation of the wild-type protein by the mutated NPM1. Altered distribution in cell compartments may possibly interfere with the normal functions of NPM1, a nucleocytoplasmic shuttling protein30 mainly found in the nucleolus,31,32 which plays a key role in the regulation of the adenosine diphosphate ribosylation factor–tumor protein 53 (ARF-p53) pathway33,34 and centrosome duplication.36 As daunorubicin was shown to induce nucleoloplasia dislocation of NPM1, which was associated with increased apoptosis,37 the subcellular relocation of wild-type NPM1 in NPM1c+ AML may possibly lead to increased sensitivity to chemotherapeutic agents.

The prevalence of NPM1 mutations in females (58% vs 42%; P = .04) detected in this study appears to be the first genetic aberration in AML with a sex prevalence. Sex-prevalent mutations have been found only for the 5q− syndrome in females,38 and hypereosinophilic syndrome (HES) in males.39

Gene expression profiling identified 2 prognostically relevant subgroups (named I and II) in AML with normal karyotype in a recent analysis.40 However, they clearly differ from our subgroups of mutated and unmutated NPM1 in terms of survival, FAB subtypes, frequency of FLT3-LM, sex, and white blood cell count. In the future, gene expression profiling and mutational analysis for NPM1 and FLT3 may be combined to build up a new prognostic model for AML with normal karyotype.

In conclusion, detection of NPM1 mutations by molecular techniques and/or looking at the aberrant cytoplasmic expression of the NPM1 protein by immunohistochemistry20 should be included in the diagnostic work-up of AML patients with normal karyotype, since it helps dissecting this heterogenous cytogenetic category into prognostically different subgroups.

Acknowledgments

The authors are indebted to all participating centers of the AMLCG. We are grateful to Madlen Fuchs, Theresa Förster, Nina Leopold, and Gudrun Mellert for excellent technical assistance. We thank Claudia Tibidò for helpful secretarial assistance.
clinical and biologic features of the disease, including AML1 gene mutations: a report of 59 cases by the Groupe Français d'Hématologie Cellulaire (GFHC) and the Groupe Français de Cytogenétique Hématologique (GFCH). Blood. 2003;101:1277-1283.
17. Christiansen DH, Pedersen-Bjergaard J. Internal tandem duplications of the FLT3 and MLL genes are mainly observed in atypical cases of therapy-related acute myeloid leukemia with a normal karyotype and are unrelated to type of previous therapy. Leukemia. 2001;15:1848-1851.

From www.bloodjournal.org by guest on April 15, 2017. For personal use only.
Nucleophosmin gene mutations are predictors of favorable prognosis in acute myelogenous leukemia with a normal karyotype

Susanne Schnittger, Claudia Schoch, Wolfgang Kern, Cristina Mecucci, Claudia Tschulik, Massimo F. Martelli, Torsten Haferlach, Wolfgang Hiddemann and Brunangelo Falini