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Effect of NPM1 and FLT3 Mutations on the Outcomes of Elderly Patients With Acute Myeloid Leukemia Receiving Standard Chemotherapy

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Abstract

This study analyzes the clinical impact of NPM1 and FLT3 mutations in AML patients 65 years of age or older treated with cytotoxic chemotherapy at our institution. A total of 557 patients were retrospectively reviewed. No difference in survival was noted for patients with isolated FLT3 or NPM1 mutations. However, elderly AML patients who were NPM1 mutated and FLT3 wild type had significantly improved survival with cytotoxic chemotherapy.

Background—The effect of prognostically important gene mutations (MUTs), nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1) and fms-related tyrosine kinase 3 (FLT3), in elderly patients with acute myeloid leukemia (AML) is not well defined.

Patients and Methods—We analyzed 557 patients, 65 years of age or older with newly diagnosed AML, treated at our institution between 2000 and 2010 with cytotoxic chemotherapy. NPM1 and FLT3 analysis were available in 146 patients (26%) and 388 patients (70%), respectively.

Results—NPM1 and FLT3 MUTs occurred in 16% and 12% of patients, respectively. No difference in median overall survival was observed between FLT3-MUT and NPM1-MUT patients who received cytotoxic chemotherapy. Outcome was significantly better among patients with NPM1-MUT/FLT3-wild type (WT) genotype ($n = 14$) compared with patients carrying FLT3/NPM1 genotypes other than NPM1-MUT/FLT3-WT ($n = 125$). The complete remission rates were 71% and 49%, respectively ($P = .11$). The median survival was 21.5 months vs. 9.0 months and estimated 2-year survival rates were 51% vs. 38%, respectively ($P = .003$). NPM1 and

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Disclosure

The authors have stated that they have no conflicts of interest.

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FLT3 MUTs appear to occur less frequently in elderly AML patients. The prognostic effect of isolated NPM1- or isolated FLT3-MUT is minimal.

Conclusion—Elderly AML patients with NPM1-MUT/FLT3-WT genotype have significantly improved outcomes compared with patients with other NPM1/FLT3 genotypes when treated with cytotoxic chemotherapy.

Keywords

Acute myeloid leukemia; Cytotoxic chemotherapy; Elderly; FLT3; NPM1

Introduction

Acute myeloid leukemia (AML) usually afflicts older people. The median age of patients with AML at presentation is 67 years.¹ The prognosis of patients with AML is determined by a number of factors. Survival is worse in patients with older age, high risk cytogenetic characteristics (ie, -5, -7, monosomal or complex karyotypes), poor performance status, and comorbidities.^{2,3} Advanced age (typically defined as older than 65 years) is also associated with a higher probability of resistant disease, because older patients with de novo AML are more likely to have cytogenetic abnormalities similar to those seen in therapy-related AML.⁴ Induction chemotherapy with standard regimens (ie, cytosine arabinoside in combination with an anthracycline) in elderly patients with AML is associated with complete remission (CR) rates of 35% to 50%, treatment-related mortality of up to 30%, and a median overall survival (OS) of 5 to 6 months.⁵⁻⁹

Frequently recurring molecular mutations (MUTs) add valuable prognostic and predictive information for patients with newly diagnosed AML.¹⁰ This is most helpful for risk stratification of patients whose AML cells have a normal karyotype. In an analysis of 872 adults younger than 60 years of age with cytogenetically normal AML (CN-AML), nucleophosmin (nucleolar phosphoprotein B23, numatrin) (NPM1), fms-related tyrosine kinase 3 (FLT3) internal tandem duplication (FLT3-ITD), and neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS) MUTs were identified in 53%, 31%, and 13% of patients, respectively.¹¹ Patients with mutated NPM1 in the absence of FLT3-ITD MUTs had higher CR rates, approaching those seen in core-binding factor AML. Other favorable risk molecular markers included the presence of biallelic CCAAT/enhancer binding protein (C/EBP), alpha (CEBPA) MUTs. Conversely, several reports have shown that patients harboring FLT3-ITD MUTs had a significantly higher induction death rate, increased relapse risk, inferior event-free survival, and shorter OS.¹²⁻¹⁶

The objective of this study was to analyze the incidence of FLT3 and NPM1 MUTs and better define the prognostic and predictive effect of these gene alterations on outcomes and response to therapy in elderly patients (age 65 years or older) with AML and treated with standard cytotoxic chemotherapy.

Patients and Methods

Patient Population

The medical records of patients older than 65 years of age with newly diagnosed AML treated at M.D. Anderson Cancer Center (MDACC) between January, 2000 and December, 2010 with frontline cytotoxic chemotherapy (including standard dose or high dose cytotoxic chemotherapy) were reviewed. Patients who received epigenetic therapy (ie, azacitidine or decitabine-based therapy) were excluded from the analysis. Patients with core-binding factor AML or acute promyelocytic leukemia (APL) were excluded because such AML subtypes are well established to be associated with significantly better prognosis than other AML subtypes. All clinical trials were approved by the Institutional Review Board, and were conducted in accordance with the Declaration of Helsinki.

Mutational Analysis

Genomic DNA from bone marrow aspirates was isolated using the Autopure extractor (QIAGEN/Gentra). FLT3-ITD and codon 835/836 tyrosine-kinase domain mutational status were determined using DNA from unsorted bone marrow aspirate samples obtained at initial presentation using a polymerase chain reaction (PCR)-based method with an analytical sensitivity of 1% to 2% MUT-bearing cells. FLT3-ITD and codon 835/836 point MUT levels were determined using semiquantitative DNA-based PCR-capillary electrophoresis assay, as described previously.¹⁷ PCR amplifications to detect NPM1 exon 12 MUTs, and exons 1 and 2 MUTs in NRAS and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog genes were carried out as previously described.^{18,19} Conventional cytogenetic analysis (ie, G-banding technique) was also performed on bone marrow aspirate samples and results were reported according to the International System for Human Cytogenetics Nomenclature.²⁰

Therapeutic Regimens

Standard AML induction chemotherapy for most patients at our institution is a combination of cytarabine at a dose of 1.5 g/m² given continuously (intravenous) daily for 3 days and idarubicin 12 mg/m²/d for 3 days (referred to as the “AI regimen” herein). Other cytarabine- and noncytarabine-based regimens were also included. All patients who received frontline cytotoxic chemotherapy regimens (cytarabine-based and otherwise) were included. Patients who received frontline epigenetic therapy with hypomethylating agents (decitabine or azacitidine) were excluded.

Definitions of Outcomes

Acute myeloid leukemia was defined by the presence of ≥ 20% blasts in bone marrow aspirate material or peripheral blood, as previously published in the 2008 revision of the World Health Organization classification of myeloid neoplasms.²¹ Response criteria were based on the revised recommendations of the International Working Group.²² CR was defined as normal bone marrow morphology with < 5% blasts, with recovery of neutrophils to $1 \times 10^9/L$ and platelets to $100 \times 10^9/L$. CR with incomplete platelet recovery (CRp) was defined as CR with platelet count $< 100 \times 10^9/L$. Overall response rate (ORR) included

all patients who achieved CR or CRp. Early mortality was defined as death occurring within 8 weeks of presentation. Cytogenetic risk groups were as follows: poor cytogenetic risk included abnormalities in chromosome 5 or 7, complex karyotype (ie, 3 or more abnormalities), and trisomy 8; good cytogenetic risk included the core-binding factor abnormalities, inv(16) or t(8;21) and APL [t(15;17)]; intermediate cytogenetic risk included diploid karyotype, and abnormalities that did not fall into the poor or good risk categories.

Statistical Considerations

Differences among variables were evaluated using χ^2 for categorical variables and Kruskal-Wallis and Mann-Whitney *U* tests for continuous variables. A Cox proportional hazard regression module was used to determine the independent predictors of survival. Time-to-event analyses were performed using the Kaplan-Meier method, and survival curves were compared using the log-rank test. A 2-sided *P* value < .05 was considered statistically significant.

Results

Patient Characteristics

A total of 671 patients with newly diagnosed AML were older than 65 years of age at the time of presentation to our institution between January, 2000 and December, 2010. Five hundred fifty-seven patients (83%) received frontline cytotoxic chemotherapy and were included for analysis. One hundred fourteen (17%) patients received epigenetic therapy using either decitabine or azacytidine and were excluded from our study. Table 1 shows baseline characteristics for the 557 patients treated with cytotoxic chemotherapy. NPM1- and FLT3-MUT analysis was available in 146 patients (26%) and 388 patients (70%), respectively. The incidence of NPM1- and FLT3-MUT was 16% and 12%, respectively. The discrepancy in the number of patients who had NPM1 and FLT3 mutational analysis (26% vs. 70%) is because of the fact that FLT3 mutational analysis has been available at MDACC since 2003 whereas NPM1 analysis became available in 2005. Also, as part of their research activities, our pathology department has retrospectively performed FLT3 analysis on stored bone marrow samples from 2000 to 2003.

Five hundred fifty-seven patients received standard chemotherapy. Of these, 178 patients (32%) received the AI regimen,²³ 93 (17%) received other high-dose cytarabine-based induction chemotherapy regimens,²⁴⁻²⁶ and 286 (51%) received other chemotherapy combinations, with or without conventional or low-dose cytarabine.

Effect of FLT3-MUT

Table 2 and Figure 1 show outcomes of cytotoxic chemotherapy according to FLT3-MUT status. Among the 388 patients who had FLT3-MUT analysis, 47 patients (12%) had the FLT3-MUT. Among the 47 FLT3-MUT patients receiving cytotoxic chemotherapy, 24 (51%) achieved CR and 2 (4%) achieved CRp, for an ORR of 55%. Median OS, 2-year, and 5-year survival rates were 5.8 months, 4%, and 4%, respectively.

There were a total of 341 elderly AML patients who carried wild type (WT) FLT3 alleles (FLT3-WT) and received cytotoxic chemotherapy. One hundred fifty-four (45%) achieved a CR and 18 (5%) achieved a CRp for an ORR of 50%. Median OS, 2-year, and 5-year survival rates were 8.8 months, 23%, and 8%, respectively. Thus, FLT3-WT patients have a trend toward improved survival with cytotoxic chemotherapy compared with FLT3-MUT patients ($P = .06$).

Effect of NPM1-MUT

Next, we analyzed the response to cytotoxic chemotherapy according to NPM1-MUT status (Table 3 and Figure 2). Overall, 23 (16%) of the 146 patients that underwent NPM1-MUT analysis harbored an NPM1-MUT. The CR, CRp, and ORR rate for NPM1-MUT patients who received cytotoxic chemotherapy were 70%, 9%, and 79%, respectively. The median OS for NPM1-MUT patients who received cytotoxic chemotherapy was 11.8 months with 2-year and 5-year survival rates of 37% and 28%, respectively.

A total of 123 patients carried WT NPM1 alleles (NPM1-WT). CR, CRp, and ORR rates for these patients were 47%, 7%, and 54%, respectively. Median OS, 2-year, and 5-year survival rates were 9.7 months, 22%, and 8%, respectively. Thus, there was no significant difference in survival in patients given cytotoxic chemotherapy for NPM1-MUT vs. NPM1-WT ($P = .13$).

Effect of Combined NPM1- and FLT3-MUT

Although NPM1- and FLT3-MUT status are prognostic when considered independently, combined analysis of both molecular markers further refines risk stratification, particularly among patients with CN-AML. A total of 139 patients had available mutational analysis results for FLT3 and NPM1 (Table 4 and Figure 3). Fourteen patients (10%) had FLT3-WT and NPM1-MUT (FLT3-WT/NPM1-MUT). Chemotherapy resulted in CR in 71%, and CRp in 7% for an ORR rate of 78% with median OS, 2-year, and 5-year survival rates of 21.5 months, 51%, and 20%, respectively.

The remaining 125 patients (90%) who had combined FLT3/NPM1 mutational genotypes that were not FLT3-WT/NPM1-MUT received cytotoxic chemotherapy with a CR rate of 49% and a CRp rate of 7% (ORR rate of 56%). Median OS, 2-year, and 5-year survival rates were 9.0 months, 38%, and 6%, respectively, which were inferior to those achieved by patients with NPM1-MUT/FLT3-WT ($P = .003$). Thus, patients with the NPM1-MUT/FLT3-WT genotype have significantly improved outcomes compared with patients with other NPM1/FLT3 genotypes when treated with cytotoxic chemotherapy.

Discussion

The traditional predictors of poor outcome in AML include age,² high-risk cytogenetic characteristics,²⁷ the presence of an antecedent hematological disorder, and AML arising after chemotherapy or radiation therapy for other malignancies or diseases.²⁸ Advanced age (typically defined as 65 years or older) independently predicts a higher incidence of induction (8-week) mortality, lower CR rates, and shorter OS.²⁹⁻³⁴ Advanced age is more frequently associated with unfavorable cytogenetic characteristics (involving chromosome 5,

7, and 17),^{5,35} antecedent hematological disorders, inferior performance status, and high expression of multidrug resistance transport protein 1.^{32,33} In younger patients, the presence of MUTs in the alleles encoding the NPM1 or CEBPA have been linked to favorable outcomes, particularly among patients with normal karyotypes. The presence of NPM1-MUT represents a very favorable prognostic marker for CR during standard induction chemotherapy.^{11,36} FLT3-ITD MUTs, in contrast, have been associated with lower CR rates and shorter OS.³⁷ The effect of these gene MUTs on the outcomes of elderly patients (age 65 years or older) with AML has not been well established.

In the cohort presented herein, NPM1- and FLT3-MUT status was available in 146 (26%) and 388 (70%) of the patients reviewed, respectively. The incidence of NPM1-MUT and FLT3-MUT were 16% and 12%, respectively. These are markedly lower than the incidence of NPM1-MUT and FLT3-MUT reported in younger AML counterparts (approximately 50% and approximately 35%, respectively).^{11,13} Teleologically, this could be explained by the fact that high-risk cytogenetic characteristics are more prevalent among patients of advanced age, perhaps ameliorating the selection pressure to acquire more virulent genotypes via MUT of genes such as FLT3. Stirewalt et al, however, have reported that FLT3-ITD MUTs occur in 34% of evaluable elderly patients with AML,³⁸ in stark contrast with our patient population. The reason for the difference in incidence rates across our studies remains poorly understood. However, in accord with Stirewalt et al and in contrast with studies in younger patients with AML, we found that FLT3-MUT was not associated with significantly inferior clinical outcomes in our patient cohort, although there was a trend to improved OS in FLT3-WT patients who received cytotoxic chemotherapy ($P = .06$). A possible explanation for the lack of clear prognostic value of FLT3-MUT in elderly AML patients as opposed to their younger counterparts might relate to the fact that elderly AML patients have very poor outcomes because of a much higher frequency of other powerful poor prognostic factors (eg, advanced age, comorbidities, p53 MUTs). The presence of the latter might diminish the negative effect of FLT3-ITD MUTs on survival.

We could not detect significant differences in outcomes among patients treated with cytotoxic chemotherapy according to isolated FLT3 or NPM1 mutational analyses. However, as expected, elderly patients with a FLT3-WT/NPM1-MUT genotype fared significantly better than patients with other FLT3/NPM1 genotypes when treated with cytotoxic chemotherapy. These results are in keeping with series of patients with AML including younger counterparts. The FLT3-WT/NPM1-MUT combination seems to confer a highly favorable prognostic effect with excellent CR rates and OS. In our patient cohort, the median OS for patients with the NPM1-MUT/FLT3-WT genotype was nearly 22 months, which was significantly longer than the OS noted in other genotypic combinations including NPM1-MUT/FLT3-MUT, NPM1-WT/FLT3-WT, or NPM1-WT/FLT3-MUT. Although less of a concern in patients of advanced age compared with younger counterparts, it has been suggested that the NPM1-MUT/FLT3-WT genotype might serve as a predictive marker for prolonged relapse-free survival, and that patients harboring such a genotype might not benefit from an allogeneic stem cell transplant in first CR, especially in elderly patients who have a tendency to do poorly with allogeneic transplantation.³⁶ Thus, elderly AML patients

with the NPM1-MUT/FLT3-WT genotype might benefit from a frontline cytotoxic chemotherapeutic approach.

Conclusion

In contrast to available data in younger patients with AML, NPM1-MUT and FLT3-MUT appear to occur at lower frequencies. The prognostic effect of each individual MUT is minimal for elderly AML patients treated with cytotoxic chemotherapy. Patients with the NPM1-MUT/FLT3-WT genotype have significantly improved outcomes compared with patients with other NPM1/FLT3 genotypes when treated with cytotoxic chemotherapy.

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Clinical Practice Points

- NPM1 and FLT3 mutations appear to occur less frequently in elderly AML patients when compared to their younger counterparts.
- The prognostic effect of isolated FLT3 and NPM1 mutations is minimal for elderly AML patients treated with cytotoxic chemotherapy.
- Elderly AML patients who are NPM1 mutated/FLT3 wild-type have improved outcomes compared with other NPM1/FLT3 genotypes, when treated with cytotoxic chemotherapy.

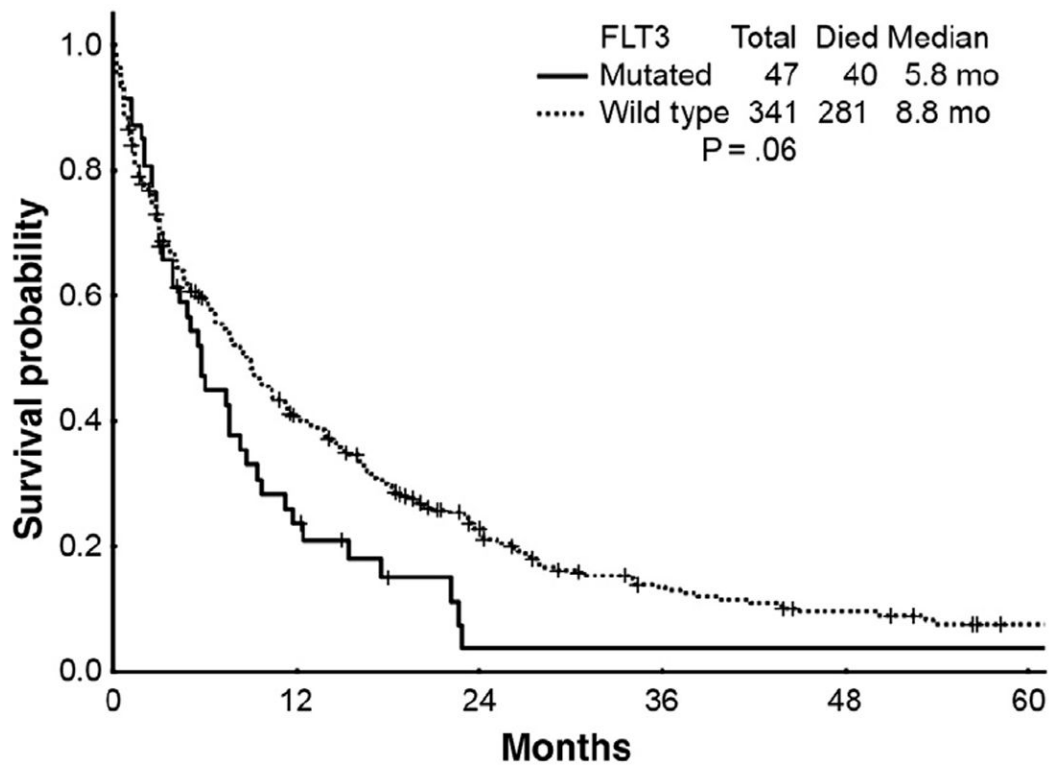


Figure 1. Survival Curves for Patients With Mutated FLT3 (n = 47) Alleles vs. Patients With Wild Type FLT3 (n = 341) Alleles Who Received Cytotoxic Chemotherapy (P = .06)

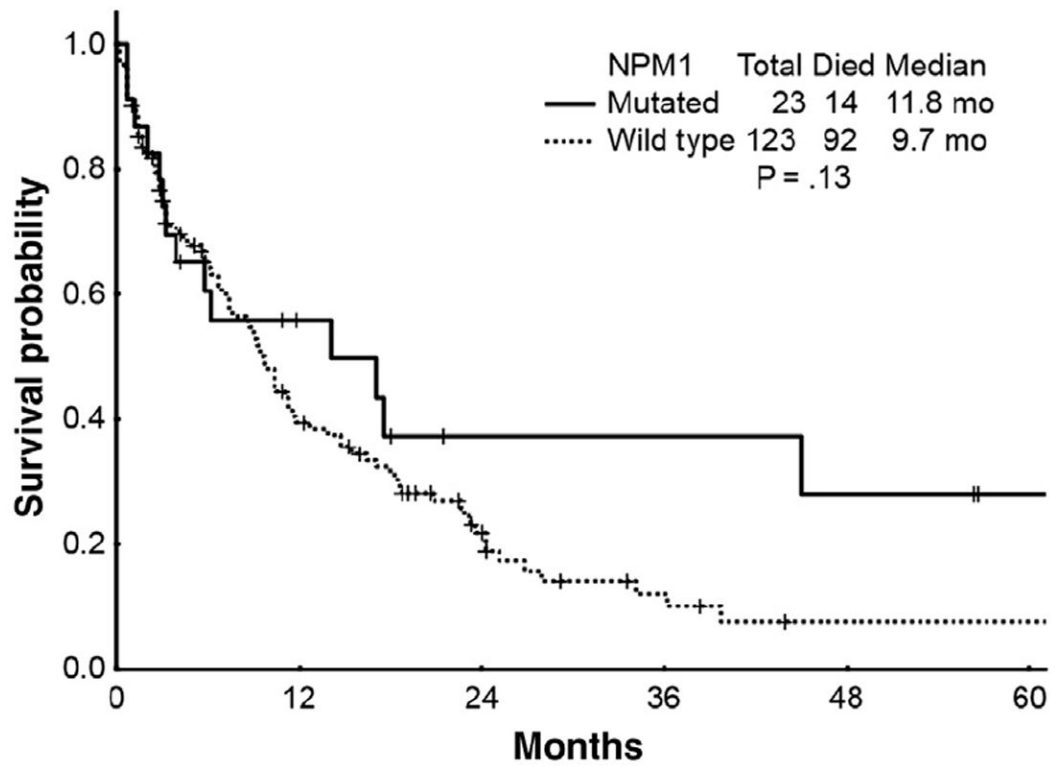


Figure 2.
Survival Curves for Patients With Mutated NPM1 (n = 23) Alleles vs. Patients With Wild Type NPM1 (n = 123) Alleles Who Received Cytotoxic Chemotherapy (P = .13)

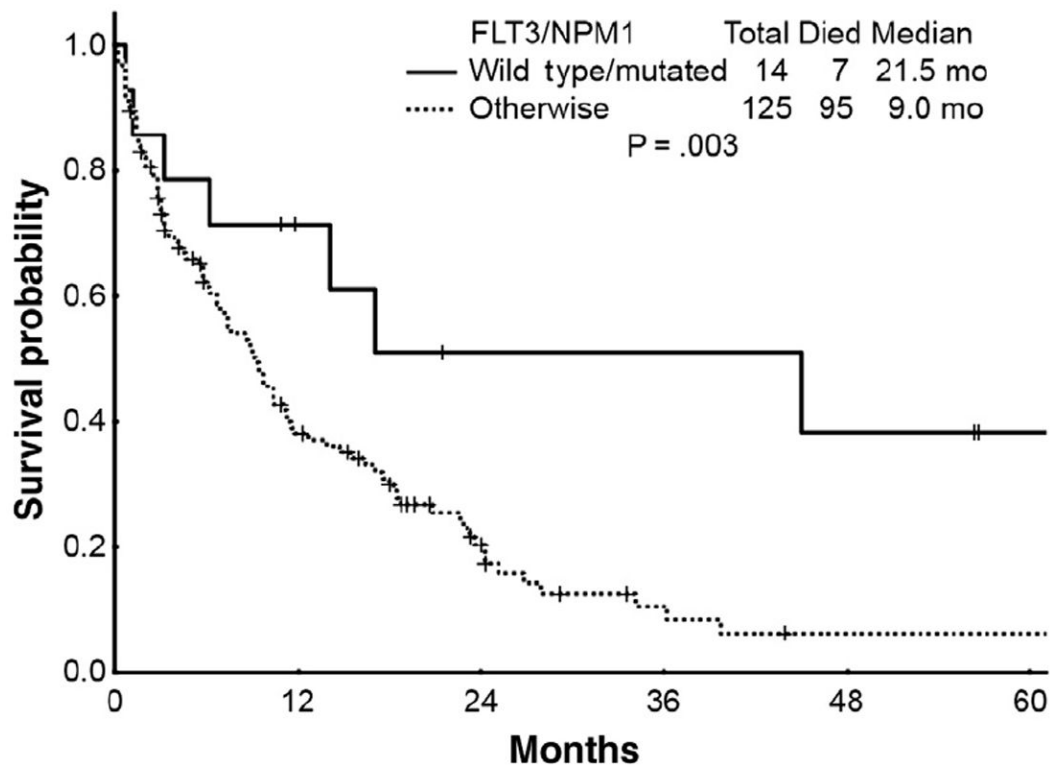


Figure 3. Survival Curves for Patients With Wild Type FLT3 and Mutated NPM1 (n = 14) Genotype vs. Patients With Other FLT3/NPM1 (n = 125) Genotypes ($P = .003$)

Table 1

Baseline Characteristics of Elderly Patients With AML Treated With Standard Cytotoxic Chemotherapy (n = 557)

Patient Characteristics	n (%) or Median [Range]
Male Sex	358 (64)
Age, Years	71 [65-89]
ECOG Performance Status 0 to 2	527 (95)
White Blood Cells × 10⁹/L	5.8 [0.4-433.0]
Hemoglobin, g/dL	8.3 [3.8-14.2]
Platelets × 10⁹/L	51 [3-787]
Bone Marrow Blast, %	43 [0-98]
Peripheral Blast, %	15 [0-99]
Cytogenetic Characteristics	
–5 or –7 alone	15 (3)
–5 or –7 with other abnormalities	127 (23)
Complex (3 abnormalities)	42 (8)
Noncomplex (2 abnormalities)	14 (3)
11q23	98 (18)
Diploid	238 (43)
Not done/insufficient metaphases	23 (4)
MDACC Risk Model for 8-wk Mortality	
Low	192 (34)
Intermediate	334 (60)
High	31 (6)
MDACC Risk Model for Survival	
Low	90 (16)
Intermediate	352 (63)
High	115 (21)
NPM1 Status	
Mutated	23 (16)
Wild Type	123 (84)
FLT3 Status	
Mutated	47 (12)
Wild Type	341 (88)

Abbreviations: AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; MDACC = M.D. Anderson Cancer Center.

Table 2

Outcomes According to FLT3 Mutational Status in Elderly AML Patients Treated With Cytotoxic Chemotherapy (n = 388)

Variable	FLT3-MUT	FLT3-WT
Patients, n	47	341
Response Rates, n (%)		
CR	24 (51)	154 (45)
CRp	2 (4)	18 (5)
Mortality (< 8 wk)	6 (13)	53 (16)
Mortality (> 8 wk)	0	2 (1)
No response	15 (32)	114 (33)
OS		
Median, mo	5.8	8.8
2-y	4%	23%
5-y	4%	8%
<i>P</i>	.06	

Abbreviations: AML = acute myeloid leukemia; CRp = CR with incomplete platelet recovery; MUT = mutation; OS = overall survival; WT = wild type.

Table 3

Outcomes According to NPM1 Mutational Status in Elderly AML Patients Treated With Cytotoxic Chemotherapy (n = 146)

Variable	NPM1-MUT	NPM1-WT
Patients, n	23	123
Response Rates, n (%)		
CR	16 (70)	58 (47)
CRp	2 (9)	8 (7)
Mortality (< 8 wk)	2 (9)	17 (14)
Mortality (> 8 wk)	0	1 (1)
No response	3 (12)	39 (31)
OS		
Median, mo	11.8	9.7
2-y	37%	22%
5-y	28%	8%
P	.13	

Abbreviations: AML = acute myeloid leukemia; CRp = CR with incomplete platelet recovery; MUT = mutation; OS = overall survival; WT = wild type.

Table 4

Outcomes According to Combined FLT3 and NPM1 Mutational Status in Elderly AML Patients Treated With Cytotoxic Chemotherapy (n = 139)

Variable	NPM1-MUT/FLT3-WT	Other Genotypes
Patients, n	14	125
Response Rates, n (%)		
CR	10 (71)	61 (49)
CRp	1 (7)	9 (7)
Mortality (< 8 wk)	1 (7)	18 (14)
Mortality (> 8 wk)	0	1 (1)
No response	2 (15)	36 (29)
OS		
Median, mo	21.5	9.0
2-y	51%	38%
5-y	20%	6%
P	.003	

Abbreviations: AML = acute myeloid leukemia; CRp = CR with incomplete platelet recovery; MUT = mutation; OS = overall survival; WT = wild type.