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Nucleophosmin 1 expression in acute myeloid leukemia

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ABSTRACT

Nucleophosmin1 is a multifunctional protein that shuttles between nucleus and cytoplasm in some subtypes of acute myeloid leukemias. Mutated Nucleophosmin1 expresses aberrantly in the cytoplasm of the cell and transports from nucleolus to the cytoplasm. It is diagnosed by immunohistochemical techniques, flow cytometry assay and mutational analysis.

The aim of this study is to evaluate the effects of Nucleophosmin1 mutation on the clinical presentations, prognosis, diagnosis and the treatment of acute myeloid leukemia. Thirteen articles were extracted from PubMed, Google scholar and Scopus in which the Nucleophosmin1 mutation correlated with gingival hyperplasia, high white blood cell count, lymphadenopathy, high platelet count and other signs and symptoms of myelomonocytic and monocytic acute myeloid leukemias.

This mutation is a provisional entity in the classification of acute myeloid leukemia, which influences on the prognosis, clinical course and the treatment of some subtypes of acute myeloid leukemias. Nucleophosmin1 mutation has favorable prognostic value in the absence of other concomitant mutations.

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Introduction

Nucleophosmin 1 (NPM1) is a multifunctional phosphoprotein that contains several functional domains, which the molecule binds partners in different cellular compartments. NPM1 is located in nucleus and constantly shuttles between the nucleus and the cytoplasm (1). NPM1 gene corporates in leukemogenesis as a mutant protein with oncogenic effect, through loss of one functional allele. This mutation translocates the product from nucleus to the cytoplasm of blasts, alters through loss or gain of functions on different proteins (1). NPM1 leukemogenesis is a result of two major mechanisms including the production of a mutated protein and the decreasing level of wild type protein expression. NPM1 gene alterations generates a mutated protein that is associated with hematopoietic malignancies in the case of acute myeloid leukemia (AML) with NPM-cytoplasmic positive (NPMc+) mutant. This loss of one functional allele is stable in AML and NPM1 mutation, represents a founder genetic lesion. Myeloid related protein 8 is the promoter of NPMc+, and controls the overexpression of NPM1c+ in the monocytic progenitors, myeloid progenitors, and mature granulocytes (1). NPM1 affects ribosomal protein transportation and assembly, and prevents protein aggregation in the nucleolus (2). NPM1 binds to alternate-reading-frame protein (ARF) and is used for p53-independent cell cycle regulation; via cyclin E/cyclin dependent kinase 2 phosphorylation. NPM1 initiates

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centrosome duplication (2). Mutations of the NPM1 gene are the most common genetic alteration in AML NK (50-60% of cases) and are about one-third of adult AMLs, usually occurring at exon-12 and more rarely at exon-11. This gene encodes a nucleolar protein (NPM1 or B23) that shuttles between the nucleus and cytoplasm and has multiple functions including ribosomal protein assembly and transport, control of centrosome duplication, and regulation of Arf tumor suppressor gene integrity (2). NPM1 mutations correlate with CD34 and CD133 negative staining, normal karyotyping and reasonable response to induction chemotherapy. In NPM1c+ cases, internal tandem duplication (ITD) of the Fms-like tyrosine kinase 3 (FLT3) gene was twice more frequent than cases negative for cytoplasmic NPM1 (NPM1c–) (2). Favorable prognostic factors are mutant CCAAT/enhancer binding protein-A (CEBPA) and availability of an HLA-compatible family donor, whereas secondary AML and LDH were unfavorable prognostic factors for overall survival (2).

In gastric cancer, NPM1 protein expression is significantly reduced. NPM1 is mainly detected in nucleus and nucleolus compartments. An inverse correlation between protein and mRNA expression is detected. Patients without distant metastasis tumors express NPM1 more than the patients with distant metastasis and these patients present with reduced NPM1 protein levels. NPM1 down-regulation in gastric cancers may have a role in carcinogenesis, which may help in the selection of anticancer treatment strategies (3).

This review article is performed based on the PubMed, Scopus and Google scholar articles. We extracted 13 articles that were relevant to our study purpose from 2005 to 2012. Only English language articles were included. We studied these articles, classified the data systematically in the basis of definition, pathogenicity, clinical presentation, prognosis, diagnosing and the treatment of mutated NPM1 protein in AML.

Literature Review

NPM1 expression in AML

NPM1 mutations delocalized NPM1 from the nucleus into the cytoplasm (NPMc+ in AML samples). NPMc+ AML displays distinctive features such as multilineage involvement, mutual exclusion of recurrent genetic abnormalities, favorable prognosis (in the absence of FLT3-ITD), increased FLT3-ITD positivity and overexpressed Homeobox genes and CD34 negativity (4).

Clinical presentation and prognosis of NPM1 mutation in AML

NPM1 mutations are more frequent in AML French-American-British (FAB) M1 to M6 but are absent in AML FAB M0. No NPM1 mutations are found in AML with recurrent translocations t (8;21), inv (16), and t (15;17) (5). In addition, mutated NPM1 was related with lymphadenopathy, leukocytosis, gingival hyperplasia and female sex. NPM1 mutations are rare in patients younger than 35 years (5). NPM1 mutations has a good prognosis unless older age, leukocytosis, and FLT3-ITD positiveness. NPM1 mutation is more frequent in older children (5). Patients with intermediate cytogenetic risk AML without FLT3-ITD mutations but with NPM1 mutations have a significantly better event free survival and overall survival than those without NPM1 mutations. Finally, NPM1 mutations are independent favorable prognostic factors with regard to overall survival, event free survival and disease-free survival (5). NPM1 mutations are not associated with AML with inv (16) but NRAS mutation is found in AML with inv (16). NRAS mutation has inverse association with NPM1 mutation (5).

AML with mutated NPM1 shows various clinical presentations such as myeloid sarcoma, skin and lymph nodes involvement, concomitant bone marrow and extramedullary involvement, CD34 negativity, no clinical history of myeloproliferative and myelodysplastic syndromes (6).

NPM1 mutations are detected only in 6.5% to 8.4% of pediatric AML; however, they are not seen in children younger than 3 years of age. The most frequent type of mutation in adults is type A NPM1 mutation (4 base TCTG insertion) (75%-80% of cases). NPM1 mutations other than type A are more frequent in children (6). Therapy-induced AMLs show NPM1 mutation in approximately 10% of cases (6).

NPM1 mutation occurs sooner than FLT3-ITD, when NPM1 mutation occurs at the same time with FLT3-ITD (6). Mutations of FLT3 and NRAS in AML correlate with tumor progression (6). Evaluation of the FLT3 status should be performed in all NPM1-mutated AML patients for the identification of the subgroup of cases with NPM1-mutated/FLT3-ITD-negative genotype that has a more favorable prognosis (6). NPM1mutations are used for evaluation of minimal residual disease (6).

Treatment and diagnosis of AML with NPM1 mutation

Response of AML with NPM1 mutation is good after induction therapy. Sixteen days after the treatment, approximately 80% of patients achieve complete remission (6). Bone marrow transplantation is not performed in the first complete remission of AMLs with favorable prognosis such as t (15;17), t (8;21), or inv (16). In NPM1 mutation without FLT3-ITD mutation, allogeneic bone marrow transplantation

is not done at first complete remission. These cases are treated with conventional therapy. Minimal residual disease assessment predicts long-term survey and early relapse (6).

In AML-NK patients of 70 years of age or older, NPM1 mutation is the only factor that influences the prognosis. Overall survival was 5% in nonmutated NPM1gene versus approximately 40% in mutated genes. Taken together, these findings are beneficial for selecting elderly patients for whom the aggressive chemotherapy is indicated (6).

AML results from the multiple genetic alterations that involve the hematopoietic progenitors. By conventional banding analysis, 40–50% of AMLs showed normal karyotype and had a great molecular and clinical heterogeneity. AML specimens with cytoplasmic NPM1gene mutations were predicted to change the protein at its C-terminal; this mutatation caused cytoplasmic localization of NPM1 (7). AML with mutated NPM1 can be diagnosed with immunohistochemistry, which shows aberrant cytoplasmic NPM1, or with flow cytometry, mutational analysis or western blot (8). Multiplex real-time PCR (RT-PCR)followed by capillary electrophoresis was used to analyze the NPM1 and Flt3 gene mutations (NFmPCR assay) at the same time. Because their results showed 100% concordance with NPM1 sequencing and conventional RT-PCR Flt3, this assay may be developed in routine analysis of genetic alterations in AML (9).

Sensitive real-time quantitative-PCR (RQ-PCR) assays are developed for the quantifying and monitoring of minimal residual AML in patients with mutated NPM1 gene and normal karyotyping (10).

Denaturing high performance liquid chromatography method competes with immunohistochemistry and direct sequencing in diagnosis of NPMc+ AML (11).

For rapid screening of NPMI mutation, the fluorescence resonance energy transfer is expanded. Based on individual NPM1 mutations type A and B, mutation specific primers are designed to perform a highly sensitive PCR assay that can be used in the detection of minimal residual disease (12).

NPM1-mutated AMLs express CD123 and CD33 and strong chemotherapy, combined with CD123 AND CD33 immunotherapy, will have a good response. Although many patients with NPM1 mutated AMLs die, NPM1 mutation without FLT3-ITD has a favorable prognosis (13).

Conclusion

NPM1 mutation is a provisional entity in the classification of AML. This mutation has a good prognosis in the absence of a concomitant, presence of normal karyotyping and special clinical presentations. Complementary studies must be done to detect other aspects and additional information about the diagnostic and therapeutic modalities.

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Conflict of Interest

The authors declare no conflict of interest.

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