Scientific Comment

Scientific comment on tumor suppressor p53 protein expression: prognostic significance in patients with low-risk myelodysplastic syndrome

Elvira Deolinda Rodrigues Pereira Velloso*

Universidade de São Paulo (USP), São Paulo, SP, Brazil

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic neoplasms, characterized by dysplastic findings with variable degree of bone marrow failure and proliferation of blast cells. It is the most common neoplastic disease of the bone marrow, with an estimated incidence of 1.3–5 per 100,000 people annually, and reaching 36 per 100,000 in patients aged 80 years or over. Risk factors include: advanced age (MDS de novo, corresponding to 90% of cases), previous exposure to chemotherapy or radiation therapy (therapy-related MDS), aplastic anemia and constitutional diseases, particularly those with abnormal DNA repair, such as Fanconi anemia.

The clinical course is highly variable with survival ranging from several years to a few months and variable risk of progression to acute myeloid leukemia (AML). Because of this heterogeneity, the study of prognostic factors is very important. Factors related to the individual (such as performance status, co-morbidities, age and nutritional status), biological (severity of cytopenias, transfusion need, cytogenetic abnormalities, percentage of blasts, bone marrow fibrosis, primary or secondary disease) and social (access to health care and medications) impact the survival. The models most commonly used in prognostic score for MDS de novo, such as the International Prognostic Scoring System (IPSS), the WHO Prognostic Scoring System (WPSS), and the Revised International Prognostic Scoring System (IPSS-R) basically use biological variables, obtained from the study of blood cell counts (cytopenias), percentage of blasts in bone marrow aspirate and cytogenetic findings. Recently, cytogenetic findings were better defined and cytogenetic abnormalities were divided into 5 risk groups, noting that the higher the complexity observed in the karyotype, the worst the survival is.

Even in patients with normal karyotype, many genetic mutations described by molecular biology techniques have been associated with prognosis. For example, mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 are predictors of poor overall survival, independently of established risk factors. Although a better understanding of the physiopathology of the disease is obtained with these studies, they are not routinely available. In this sense, the study of protein expression altered by dysfunction of these genes, either by flow cytometry or by immunohistochemistry is cheaper and feasible in Brazil and the study of p53 in bone marrow biopsy in MDS has been quite interesting.

The p53 gene (located at 17p13) is a tumor suppressor gene of great importance for genetic stability and integrity of the genome. DNA damage of several types activates the 53 kDa nuclear phosphoprotein p53 protein, resulting in cell cycle arrest at the G1 (post-mitotic phase) and G2 (pre-mitotic) cell cycle checkpoints necessary for DNA repair. If the DNA is not repaired, the p53-dependent apoptotic pathway is activated with cell death. Germline p53 mutations (Li-Fraumeni syndrome) are very rare, but acquired somatic p53 mutations are often detected in solid tumors, leukemias and lymphomas.

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* Correspondence to: Av. Eneas de Carvalho Aguiar, 155 1 andar, Serviço de Hematologia Hospital das Clínicas FMUSP, Laboratório de Citogenética sala 30, 05403-000 São Paulo, SP, Brazil.
E-mail address: elvira.velloso@yahoo.com.br

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The inactivation of the p53 gene in both alleles, loss of heterozygous (LOH), by mutations or deletions have been related to the predisposition to neoplastic transformation. The wild type gene product is a normal protein with a short half-life of only 15 min, while the p53 mutant proteins that form complexes with heat shock protein 70 in the cytoplasm and bind with the wild-type p53 have a longer half-life of several hours,10,11 Rearrangements resulting in loss of 17p (monosomy, deletion, unbalanced translocations involving 17p or isochromosome 17q), usually as part of a complex karyotypes have been observed in 5% of new cases of MDS.12

The p53 mutation is detected in about 5–20% of MDS de novo,13–20 in 18% of patients with low-risk MDS and deletion 5q21 and in 25–70% in adult therapy-related MDS.8,22,23,24 The p53 mutations are associated with complex karyotype with -5/-5q-, short survival, increased risk to transformation to AML and poor response to therapy: patients with MDS de novo often present with excess of blasts, and patients with the 5q deletion have less response to lenalidomide.

Immunohistochemistry and flow cytometry are now described as ideal methods for the detection of the p53 protein in samples from leukemic patients. Although there is a general correlation between the expression of p53 protein and mutation, in some tumors with nonsense mutations in their genetic sequences (less than 20% of human tumors with p53 mutation), the protein expression cannot be detected. On the other hand, rare cases of positive p53 expression were not associated with the p53 mutation.11

Kitagawa detected the expression of p53 by immunohistochemistry in 14% of patients with MDS, with half of them having progressed to AML.11 Also, overexpression of this protein has been shown to be more common in patients in the refractory anemia with excess blasts subgroup. In 22 cases of secondary MDS studied in HCFMUSP, p53 immunoreactivity was observed in 33.3% and was associated in univariate analysis with poor survival (Figure 1).24,25

The work published by Duarte et al. in this issue of the Revista Brasileira de Hematologia e Hemoterapia validates the value of p53 in bone marrow biopsies in low-risk MDS.26 Other studies have also shown its prognostic value in higher risk and secondary MDS. Due to the low cost of immunohistochemistry, reproducibility and availability in various centers of Brazil, we suggest the routine study of p53 expression in bone marrow biopsies of all MDS cases.

Conflicts of interest
The author declares no conflict of interest.

REFERENCES


Figure 1 – Kaplan–Meier survival curve for secondary myeloid neoplasia according to immunoexpression of p53 in bone marrow biopsy.


