# INFLUENCE OF TP53 MUTATIONS ON HEMATOPOIETIC STEM CELL TRANSPLANTATION OUTCOMES FOR ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROME

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## INTRODUCTION

Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS) are clonal diseases of the myeloid hematopoietic lineage. The recent advance in the molecular knowledge of these two diseases reveals that the great heterogeneity in clinical behavior and therapeutic response is directly related to the genetic background. Genetic profiles in these patients desribes TP53 mutations in 10-20% of the cases. TP53 is one of the most important tumor suppressor gene. It plays a crucial role in genomic stability in response to cellular stress, regulates DNA repair, induces cell cycle arrest and apoptosis. Studies have shown that TP53 mutation correlates with resistance to chemotherapy and with negative outcomes after allogeneic hematopoietic stem cell transplantation (aloTCTH).

## HYPOTHESIS

The presence of TP53 mutations negatively impacts the prognosis after aloTCTH for AML and MDS patients.

## OBJECTIVES

(1) To analyze the frequency of TP53 mutations in patients with AML or MDS undergoing aloTCTH;

(2) To correlate clinical outcomes (relapse and death) after transplantation with pretransplant mutational status (TP53mut versus TP53wt);

(3) To determine the prognostic impact of TP53 mutations in the therapeutic response to alloTCTH and

(4) To identify a subset of patients with unmet needs for whom new strategies need to be offered in order to mitigate the high risk of therapeutic failure.

## LOCATION

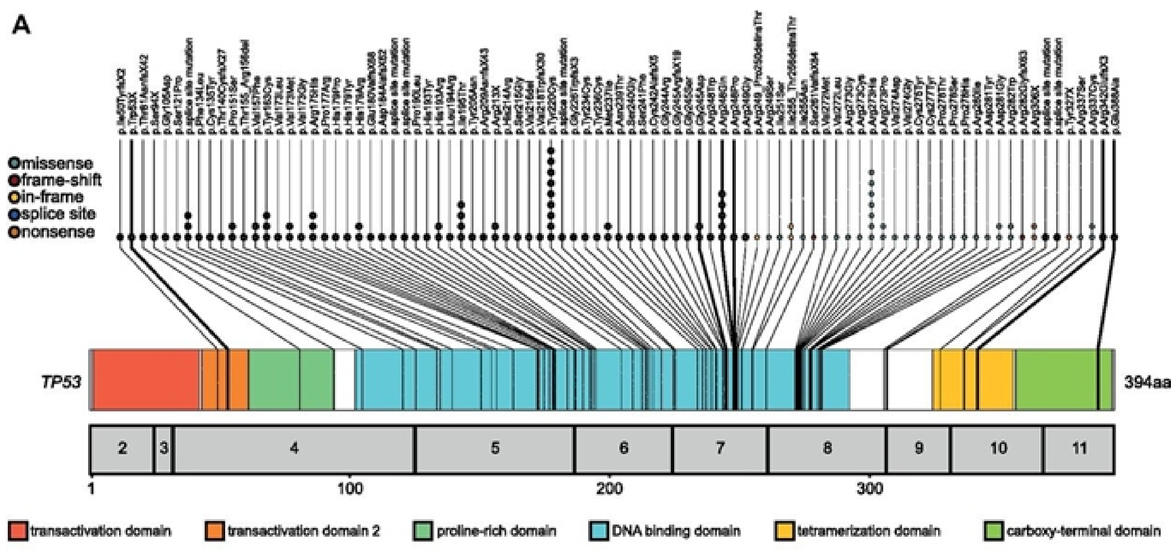
Laboratory of Molecular Biology of CEMO/ INCA.

## PATIENTS

All patients with AML and MDS submitted to aloTCTH at CEMO/INCA since January 2010. Inclusion criteria: (1) 18 years or older;(2) Stored DNA sample. Exclusion criteria: (1) Acute Promyelocytic Leukemia;(2) Umbilical cord stem cells; (3) Refusal to sign an informed consent.

## METHODS

The clinical data will be obtained from the hospital records. For the molecular tests, DNA samples obtained from the peripheral blood or bone marrow before transplantation and stored in the lab as a routine practice for characterization of allogeneic transplant recipients will be used. Mutations in TP53 gene hotspots, exons 2-11 (Fig.1), will be evaluated by Sanger sequencing. The statistical analysis will be done with the SPSS program.




Vera Grossmann et al. Blood 2012;120:2963-297

Figure 1: TP53 mutations: localization and association with cytogenetics and other molecular mutations.

## RESULTS

The study was approved by the research ethics committee. So far, 85 patients have been identified and about 45 samples have already been collected.Laboratory tests will be started in the second semester.

## REFERENCES

1- Dohner, H.; Weisdorf, D.J.; Bloomfield, C.D. Acute myeloid leucemia. N Engl J Med., n. 373, p.1136-1152, 2015.
2- Papaemmanuil, E. et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. N Engl J Med., n. 23, Vol. 374 2209-2222, 2016.
3- Malcovati L, et al. Driver somatic mutations identify distinct disease entities within myeloid neoplasm with myelodysplasia. Blood 28: 124(9): p-1513-1521, 2014.
4- Arber, D. A. et al. The 2016 revision to the World health organization classification of myeloid neoplasms and acute leucemia. Blood, vol 127 (20): 2391-2405, 2016.
5- Döhner, H. et al. Diagnosis and Management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood, vol 129 (4): p424-447, 2017.
6- Bejar, R. et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem cell transplantation. JCO 32, p-2691-2698, 2014.
7- Seifert et al. The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leucemia. Leukemia, 23:656-663, 2009.
8- Middeke et al. TP53 mutation in patients with high-risk myeloid leukaemia treated with allogeneic haematopoietic stem cell transplantation. BJH 172, p-914-922, 2016.
9- Luskin et al. Clinical utility of Next-Generation Sequencing for oncogenic mutations in patients with acute myeloid leucemia undergoing allogeneic stem cell transplantation. BBMT 22, p-1961-1967, 2016.
10- Lindsley et al. Prognostic mutations in Myelodisplastic Syndrome after stem-cell transplantation. NEJM 376 (6), p- 536-547, 2017.
11- Yoshizato et al. Genetic abnormalities in Myelodisplasia and secondary acute myeloid leucemia: impact on outcome of stem cell transplantation. Blood 129: 2347-2358, 2017.
12- Vera Grossmann et al. A novel hierarchical prognostic model of AML solely based on molecular

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