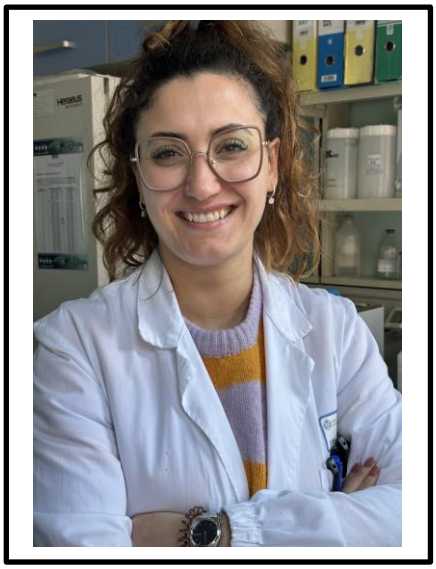
UNIVERSITÀ DI SIENA 1240

DSMCN DIPARTIMENTO DI SCIENZE MEDICHE, CHIRURGICHE E NEUROSCIENZE

Dottorato di Ricerca in Medicina Traslazionale e di Precisione



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Research Project

***Title**: Gene mutations and secondary acute myeloid leukemia: impact on prognosis and classification*

Background

Acute myeloid leukemia (AML) is a biologically heterogeneous disease, characterized by abnormal proliferation and differentiation of clonal hematopoietic stem/progenitor cells. Because of this extreme heterogeneity, proper risk stratification and clear classification are essentials to maximize treatment efficacy. AML can be classified into 3 different categories based on clinical ontogeny: de novo AML (dnAML),secondary AML (s-AML) in patients with a previous diagnosis of myelodysplastic syndrome (MDS) andmtherapy-related AML (t-AML) developed after a prior chemoradiation exposure. Several studies demonstrated a correlation of s-AML and t-AML to worse prognosis, unlike dnAML category, which is associated to a more advantageous prognosis, especially in younger patients [1,2]. However, tAML cases with favorable genetic factors seem to have clinical outcomes comparable to genetically favorable-risk dnAML [3], except for the TP53 mutation which defines poor results regardless of AML ontogeny [4]. Ontogeny provides a readily method to stratify the patients onset of disease; moreover, it is also used to determine eligibility for clinical trials. Based on these evidences, the study of genomic landscape of AML patients, independently of the origin of disease, resulted crucial for classification and consequently for clinical management of these patients.

According the European LeukemiaNet 2022 classification [6] mutations of genes SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR o STAG2 resulted associated to s-AML and implicated in molecular mechanisms and cellular pathways of myeloid maturation aberrancies contributing to dysplasia and leukemogenesis[5]. This group of newly identified mutations plays a dominant role in splicing and epigenetic regulation, with unique opportunities for targeted therapies; in dnAML they are related to poor clinical outcomes [7]. On the other hand, there are limited information about the role of these genetic abnormalities in the context of s-AML..

Aims

The aim of this project is to investigate the presence of gene mutations linked to s-AML, both in a retrospective and prospective study of s-AML cases. The presence of gene mutations will be related to the clinical outcomes and to the specific characteristic of disease, in order to correlate the role of the genomic landscape in the patient's prognosis and response to therapy.

Methods

The study of gene mutations on s-AML will be performed by Next generation sequencing (NGS) technology.
We will select both newly diagnosed and stored samples of AML cases in which the diagnosis of acute leukemia was following a previous myelodysplastic syndrome or developed after prior chemotherapy.
Genomic DNA will be extracted by using automatized tool and then analyzed specifically on Ion Torrent S5 instrument with the Oncomine Myeloid Research Assay which is designed to detect variants across 40 key DNA genes and a broad panel of 29 fusion driver gene targets relevant in major myeloid disorders in a single NGS run. Results obtained will compared with the clinical outcomes of patients, trying to find any possible association between gene mutations and the progress of disease.

Expected results

In the study time frame of 3 years we aim to study prospectively about 30 newly diagnosed s-AML while we will study retrospectively stored samples of all additional s-AML cases of which complete clinical data have been collected in our database. The prognostic role and the clinical relevance of secondary-type mutations

SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, or STAG2 in s-AML patients will be evaluated. The expected results will be aimed at a better classification of s-AML with the purpose of directing patients towards an increasingly precise therapeutic path.

References

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