Clinical Implications of Clonal Hematopoiesis Mutations in Patients with Solid Tumors

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Background

Clonal hematopoiesis (CH) is a frequent, age-related premalignant condition and represents the acquisition of somatic mutations in hematopoietic stem cells, leading to clonal expansion.

In cancer setting, recent data suggest that CH confers a greater risk for developing therapy-related myeloid neoplasms and appears to contribute to adverse cancer-related survival.

However, the clinical implications of CH in patients with solid tumors have not been extensively studied and there is no clear understanding of which CH mutations have prognostic significance.

Furthermore, the detection of CH mutations has been increasingly reported as a source of biological "noise" of blood liquid biopsy. Incorrect classification of CH mutations as tumor-derived mutations could lead to inappropriate clinical management of cancer patients.

Only a few studies have addressed the practical clinical implications of these alterations in solid-tumor sequencing.

Trial design

Part I - Retrospective study

The hypothesis of the current proposal came from a previous research project (PANCNGS):

- study group: 28 PDAC patients
- genomic DNA and cfDNA have been sequenced using the Illumina NextSeq500 platform and a custom targeted NGS panel optimized for cfDNA templates

In 23 somatic variants clonal hematopoiesis could be suspected, based on low variant frequency, similarity of variant read frequency between positive samples, and high concordance between gDNA and cfDNA sequencing results.

15 out of the 23 respective variants have not been previously described.

- first study to assess the presence and clinical relevance of CH in patients with locally advanced/metastatic PDAC

- to evaluate the presence of CH-related mutations in genes relevant for PDAC in plasma cfDNA and tumor tissues (EUS-FNA samples)

- to evaluate the clinical significance of CH-related mutations on the interpretation of liquid biopsy/tumor sequencing results

Could CH be confirmed for the 23 variants mentioned above?

Do these variants have a functional significance or they represent biological "noise captured during the NGS protocol?

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Part II – Prospective study

- evaluate the prevalence and type of CH-mutations in patients with solid tumors and the impact of CH on survival
- investigate the relationship between CH and external exposures such as age, cancer treatment or smoking
- evaluate the impact of identifying CH-related mutations on the interpretation of liquid biopsy in clinical setting

Matched tumor tissues, peripheral blood cells (PBCs), and multiple time-point cell free DNA(cfDNA) samples for longitudinal monitoring will be collected from patients diagnosed with solid malignant tumors at Fundeni Clinical Institute, Bucharest.

The clinical information will be obtained from the electronic medical record for each patient.

The matched surgically resected tumor tissues, PBCs and plasma cfDNA samples will be sequenced using a targeted pan-cancer DNA panel.

Mutations detected from PBCs will be categorized as CH-related mutations.

This study will provide a better insight into the clinical implications of CH in the cancer setting and the contribution of CH to the mutations detected by cfDNA analysis.