RESEARCH TOPIC-MEM1
CDK4/6I TOXICITY PROFILING AND POTENTIAL PROPHYLACTIC -APPLICATION OF A MICROBIOTA-STABILIZER ON GASTROINTESTINAL TOXICITY

Curriculum MEM Clinical

Clinical Unit name and address: Medical Oncology and Hematology Unit, Humanitas Clinical and Research Center-IRCCS

Laboratory name: Mucosal immunology and microbiota Unit, Humanitas University

Clinical Supervisor: Prof. Armando Santoro, armando.santoro@cancercenter.humanitas.it

Pre-clinical Supervisor: Prof. Maria Rescigno, maria.rescigno@hunimed.eu

Abstract

CDK4/6i plus hormone treatment is the standard of care in HR+, HER2- mBC. Compared to other CDK4/6i, abemaciclib presents a higher incidence of gastrointestinal toxicity, with 81.3% of incidence of diarrhea of any grade (9.5% G3).
It could be hypothesized that abemaciclib has a specific activity and interaction with the patient's microbiota of which the gastrointestinal toxicity could represent the consequence.
Postbiotics are a new class of natural molecules released during human microbiome's metabolic activities.
The potential influence of the gut microbiota on CDK4/6i treatment will be studied.
A pilot study will be conducted to obtain preliminary data on the effect of postbiotic use on abemaciclib-induced diarrhea. The underlying hypothesis is that postbiotics should stabilize the microbiota before and during abemaciclib treatment and foster barrier properties, thus avoiding penetrance of bacteria and controlling the mucosal inflammatory response.

Main technical approaches

Microbiota analysis: total bacterial DNA will be extracted using the Meta-G-Nome™ (MGN) DNA Isolation Kit. The hypervariable regions of 16S rDNA will be amplified. The obtained metagenomic libraries will be sequenced with the Illumina MiSeq platform.

Intestinal damage biomarkers: fecal Anti-Microbial Peptides (e.g. defensin), fecal calprotectin, fecal sIgA and plasma Zonulin, plasma LPS, sCD14 and lipopolysaccharide-binding protein (LBP) will be measured by specific Elisa kit.

Untargeted metabolomic analysis: gas chromatography/liquid chromatography with mass spectrometry (GC/LC-MS)-based metabolomic profiling to identify changes in patients' fecal metabolites.

Scientific references

1.Ameratunga M, Kipps E, Okines AFC, Lopez JS. To Cycle or Fight-CDK4/6 Inhibitors at the Crossroads of Anticancer Immunity. Clin Cancer Res. 2019 Jan 1;25(1):21-28.

2.Goez MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. JCO 2017

3.Mileti E, Matteoli G, Iliev ID, Rescigno M. Comparison of the immunomodulatory properties of three probiotic strains of Lactobacilli using complex culture systems: prediction for in vivo efficacy. PLoS One. 2009 Sep 16;4(9):e7056.

4.Tsilingiri K, Barbosa T, Penna G, et al. Probiotic and postbiotic activity in health and disease: comparison on a novel polarised ex-vivo organ culture model. Gut. 2012 Jul;61(7):1007-15.

5.Tsilingiri K, Rescigno M. Postbiotics: what else? Benef Microbes. 2013 Mar 1;4(1):101-7.

Type of contract

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Humanitas University
Via Rita Levi Montalcini 4
20090 Pieve Emanuele (Milano) Italy
Tel +39.02.8224.1 - Fax +39.02.8224.2394
info@hunimed.eu
Website: www.hunimed.eu
C.F. 97692990159