Abstract: P1339

Title: IMPACT OF CLONAL HEMATOPOIESIS AND CANAKINUMAB ON NON-HEMATOLOGICAL MALIGNANCY: ANALYSIS OF THE CANTOS RANDOMIZED CLINICAL TRIAL

Abstract Type: Poster Presentation

Session Title: Hematopoiesis, stem cells and microenvironment

Background:

Canakinumab is a fully human monoclonal antibody that neutralizes interleukin (IL)-1β. In the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) – a randomized, double-blind, placebo-controlled trial that enrolled 10,061 patients with previous myocardial infarction– canakinumab prevented recurrent cardiovascular (CV) events and fewer patients in the canakinumab group developed lung cancer. A CANTOS exploratory genomic substudy revealed that canakinumab treatment reduced more major adverse CV events in patients with *TET2* variants than those without clonal hematopoiesis (CH) mutations. CH is associated with an increased risk of lung cancer and other tumors. CH mutations are associated with higher levels of circulating inflammatory cytokines, which led to the hypothesis that inhibition of IL-1β may provide preferential benefits to patients with CH mutations for the development of non-hematological malignancies.

Aims:

To explore the associations between 1) CH mutations and development of non-hematological malignancies and 2) canakinumab treatment and the development of non-hematological malignancies in patients with or without CH mutations, utilizing the large prospective CANTOS trial

Methods:

To determine the association of IL-1β inhibition and risk of solid tumor for patients with different types of CH mutation, time-to-event analysis and cross-sectional Fisher exact test were performed in a subset (n=3,923) of CANTOS participants with targeted deep sequencing of CH mutations at baseline.

Results:

The baseline characteristics were balanced between treatment groups among patients with the same group of individual CH mutations. Patients with *TET2* mutations in the placebo arm had more frequent non-hematological malignancies (16.1%, 5/31 patients), while patients carrying *TET2* mutations in the canakinumab arm had significantly reduced incidence of non-hematological malignancies (4.2%, 3/71 patients, P=0.05, Figure A). Patients with *DNMT3A* mutations had more frequent lung cancer incidence than other groups in the placebo arm (7.4%, 3.2%, 2.0%, and 2.3% in patients with *DNMT3A*, *TET2*, other CH mutations, and no CH mutations, respectively). However, with canakinumab treatment, a lower lung cancer incidence was observed in patients with *DNMT3A* (0/56 patients) or *TET2* mutations (0/71 patients), while other groups treated with canakinumab had higher lung cancer incidence (2.9%, 1.5% in other CH mutations and no CH mutations, respectively, Figure B). While skin cancers other than melanoma were most frequently diagnosed in patients with *TET2* mutations (9.7%, 3/31 patients, P=0.01) in the placebo arm, a significantly reduced skin cancer incidence was observed in patients with *TET2* mutations treated with canakinumab (0/71 patients, P=0.03, Figure C). The time-to-event analysis of the cumulative incidence of cancers revealed that canakinumab treatment is significantly associated with reduced risk of any non-hematological malignancies (Figure D) and skin cancers other than melanoma in patients with *TET2* mutations, but not in other groups, compared to the placebo (P=0.019 and 0.01, respectively), as well as lung cancers in patients with *TET2* or *DNMT3A* mutations, compared to the placebo (P=0.01).

Summary/Conclusion:

This evaluation of CH mutation and the development of non-hematological malignancies revealed different rates

of cancer incidence in different CH subtypes with and without canakinumab treatment. These data may support the role of IL-1 β inhibition for cancer prevention in patients with specific CH mutation.

Keywords: Inflammation, Clinical outcome, Clonal hematopoiesis of indeterminate potential, Solid tumor