The Oncologist®

Editorial

Canakinumab and Lung Cancer: Intriguing, but Is It Real?

Bruce A. Chabner,[a] Christopher S. Nabel[a,b]

[a]Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA; [b]Dana-Farber Cancer Institute, Boston, Massachusetts, USA

A recent report in Lancet [1] disclosed a startling finding. In a large, randomized trial (Canakinumab Anti-inflammatory Thrombosis Outcomes Study [CANTOS]) of canakinumab, an interleukin (IL)-1β inhibitory antibody, in patients with prior myocardial infarction, the authors noted a dramatic reduction in the number of incident cases of lung cancer. The trial was designed to test the hypothesis that an anti-inflammatory intervention could reduce the secondary incidence of heart attack, stroke, or cardiovascular death in patients with elevated C-reactive protein, a biomarker for inflammation and cardiovascular risk. Although the primary and secondary endpoints of reducing cardiovascular-related outcomes were only realized in the intermediate dosing cohort (150 mg) [2], in a retrospective analysis, the investigators found a marked reduction in the hazard ratio (HR) of lung cancer incidence in two of the three treatment groups (150 and 300 mg) compared with placebo controls. Results in the 300-mg group were particularly impressive: There were no incident cases of lung cancer in the 2,263 patients at risk during the first 6 months of the trial, and a hazard ratio of 0.33 after 3.7 years of follow-up. Paradoxically, the incidence rate for all nonlung cancers was not statistically significant (HR = 1.10) for the 300-mg dose arm, as compared with placebo, and the rate was similar (HR 1.08 and 0.99) for the other two dose levels, 50 and 150 mg, respectively. As an immunosuppressant, canakinumab significantly increased the rate of fatal infections and sepsis, but the striking difference in lung cancer rates drew immediate attention and set in motion plans by Novartis for a follow-up phase I study of the combination of canakinumab and a programmed cell death protein 1 (PD-1) inhibitor in patients with non-small cell lung cancer (www.clinicaltrials.gov).

The relationship between inflammation and cancer is complicated, with features of inflammation that range from adaptive to maladaptive. It was Coley's observation of cancer regression in the face of active infection that gave rise to the concept of immunotherapy. On the other hand, there is certainly background information to suggest that this anti-inflammatory antibody might have anticancer activity. In general, chronic inflammation has long been implicated in the genesis and promotion of tumors following inflammatory lung, bowel, and liver disease. A specific role for IL-1β is suggested by preclinical studies. In mice, IL-1β decreases tumor invasion, growth, and metastases [3]. IL-1β also stimulates production of IL-6, a well-established mediator of tumor growth in experimental systems. The anti-IL-6 antibody siltuximab has not produced benefit in multiple myeloma (4) but is U.S. Food and Drug Administration approved for the treatment of idiopathic multicentric Castleman disease [5]. Anti-inflammatory drugs might have the opposite effect of dampening the immune response to tumors, and this consideration, in fact, prompted the investigators in the CANTOS trial to record data on cancer incidence and death as a secondary aim of the trial.

As prior experience has taught us in the cancer field, retrospective analysis can be misleading. Results such as these are hypothesis generating and need further verification. There are reasons to have reservations about the findings. The participants in the study, approximately 70% of whom were current or former smokers, did not undergo computed tomography screening for lung cancer before entering the trial; thus, there might have been an imbalance in the number of pre-existing lung cancers among the arms of the trial. The actual incidence of all cancers in the treated and placebo patients were very nearly equal (7.7 cases per 100 patients accrued in the placebo arm vs. 7% in the treated arms, combined). Whether case histories, histopathology, and imaging were available to the authors to verify the tissue of origin, staging, molecular subtyping, or programmed death-ligand 1 status of the cancers is not noted in the publication. A final observation of particular concern is the marked separation of the incidence curves for lung cancer and lung cancer-specific mortality, as reflected in the 300-mg versus placebo arms, during the first few months of the trial, implying that the antibody had an immediate therapeutic effect on established lung tumors.

The CANTOS trial has opened the door to testing the hypothesis that blocking inflammation can affect cancer-related outcomes in addition to cardiovascular ones. There are many avenues by which to test this hypothesis prospectively. The use of canakinumab as a single agent in non-small cell lung cancer may have therapeutic potential; in addition, canakinumab may provide paradigm-changing evidence in establishing an important role of inflammation in lung cancer progression and opening an entirely new avenue for drug development for lung cancer prevention. The design of appropriate follow-up clinical trials is therefore critical.

The recently initiated phase I trial in which canakinumab is combined with anti-PD-1 therapy may not provide a clear answer as to the single-agent activity of the IL-1β antagonist. One can envision that these two agents may synergize or just as easily antagonize one another. Suppression of an

Correspondence: Bruce A. Chabner, M.D., Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, USA. Telephone: 617-724-3200; e-mail: bchabner@partners.org Received February 27, 2018; accepted for publication March 2, 2018; published Online First on April 17, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0116

inflammatory response by canakinumab could either promote or inhibit the activity of T-cell antitumor responses to PD-1 inhibition. A straightforward single-agent trial of canakinumab in patients with lung cancer would have been preferable in our opinion.

Ultimately, it remains to be proven whether there is a role for anti-inflammatory therapy in cancer, particularly while immune checkpoint blockade continues to gain traction. Meanwhile, let us just say that the results from the CANTOS trial are positively intriguing.

References

1. Ridker PM, MacFadyen JG, Thuren T et al. Effect of interleukin-1βB inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: Exploratory results from a randomized, double-blind, placebo-controlled trial. Lancet 2017;390:1833–1841.

2. Ridker PM, Everett BM, Thuren T et al. Anti-inflammatory therapy with canakinumab for atherosclerotic disease. New Engl J Med 2017;377:1119–1131.

3. Voronov E, Shouval DS, Krelin Y et al. IL-1 is required for tumor invasiveness and angiogenesis. Proc Natl Acad Sci U S A 2003;100:2645–2650.

4. San-Miguel J, Blade J, Shpilberg O et al. Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti-IL-6) in multiple myeloma. Blood 2014;123:4136–4142.

5. van Rhee F, Wong RS, Munshi N et al. Siltuximab for multicentric Castleman's disease: A randomized, double blind, placebo-controlled trial. Lancet Oncol 2014;9:966–974.

For Further Reading:

Attila Feher, Polydoros N. Kampaktsis, Rekha Parameswaran et al. Aspirin Is Associated with Improved Survival in Severely Thrombocytopenic Cancer Patients with Acute Myocardial Infarction. ***The Oncologist*** 2017;22:213–221.

Implications for Practice:

In patients with hematologic malignancies and acute myocardial infarction with severe thrombocytopenia (platelet count $<$50,000 cells/μL), guideline-recommended medical therapy is often withheld because of the fear of major bleeding. In this study, aspirin therapy was associated with improved survival without an increase in major bleeding in this high-risk patient cohort.