

An Interleukin-1 Signature in Breast Cancer Treated with Interleukin-1 Receptor Blockade: Implications for Treating Cytokine Release Syndrome of Checkpoint Inhibitors

Charles Anthony Dinarello^{1,2}



In this issue of *Cancer Research*, Wu and colleagues show that IL1 β orchestrates tumor-promoting inflammation in breast cancer and can be targeted in patients

using an IL1 receptor antagonist. *Cancer Res*; 78(18); 5200–2. ©2018 AACR.

See related article by Wu et al., p. 5243

The study reported in this issue of *Cancer Research* makes a significant contribution to the concept that inflammation in cancer is driven by IL1 β and identified an "IL1 signature" in women with HER2-negative breast cancer (1). The study represents several years of dedicated research on cancer by Palucka and colleagues. Although there are several advantages of knowing a transcriptional signature, including risk and prognosis, a real benefit is the exploitation of the signature to develop specific, targeted therapies. In the case of patients with cancer with IL1 signature genes, one could simply block IL1. In fact, this is exactly what the Wu and colleagues' study accomplished.

The study linked mechanistic preclinical and mouse experiments with transcriptional signatures from patients with HER2-negative breast cancer. *In vitro*, cocultures of human myeloid cells with breast cancer cells revealed that direct contact with tumor cells was necessary for caspase-1-dependent release of IL1 β from myeloid cells. In addition, treatment with a naturally occurring IL1 receptor antagonist, anakinra, was found to be highly effective in reducing breast tumor growth in mice. At the peripheral blood transcriptional level, as well as the cytokine protein levels from primary breast cancer tissue, the authors identified IL1 β rather than IL1 α in breast cancer. Of 579 selected immune-related genes in the study, 288 were identified as differentially expressed genes (DEG) between healthy controls and the patients. Several IL1-related DEGs were abundant and consistent with an IL1 transcriptional signature in the patients. An IL1 transcriptional signature was also present in two large breast cancer databases and correlated with poor survival. In comparison, patients with systemic juvenile idiopathic arthritis, an IL1-mediated inflammatory disease, have a similar IL1 signature. Thus, an IL1-driven inflammatory signature is present in patients with breast

cancer with a poor prognosis and in patients with noncancer systemic inflammation.

Of the many biologics now in use to treat autoimmune and autoinflammatory diseases, anakinra has an excellent safety record. In fact, due to its short half-life, anakinra is ideal for treating patients who are also receiving chemotherapy. There are three approved IL1-blocking biologics and several ongoing clinical trials. Of the approved IL1-blocking strategies, anakinra has been used for over 15 years to treat thousands of patients with an expanding number of systemic inflammatory diseases (2). Anakinra is increasingly used as adjunct therapy to reduce the inflammation of metastatic cancer. A trial in metastatic colorectal cancer showed significant survival benefit when anakinra was added to standard-of-care chemotherapy for colorectal cancer (3) and patients with pancreatic cancer also benefit when anakinra is added to chemotherapy (4). Moreover, in these trials, the patients report improved quality-of-life scores with the use of anakinra.

There are two IL1 genes, *IL1 α* and *IL1 β* ; both bind to the IL1 receptor type-1 (IL1R1) and initiate identical proinflammatory signals. Because anakinra blocks IL1R1, the activities of both IL1 α and IL1 β are prevented. A study using daily anakinra in combination with low-dose weekly dexamethasone in 47 patients with smoldering or indolent myeloma for over 10 years reported a significant increase ($P < 0.001$) in overall survival compared with historic controls and a subset of patients are still alive without advancing to full-blown multiple myeloma (5).

On the basis of these and other preclinical data, anakinra was used to block IL1 in the pilot trial. Eleven women with metastatic HER2-negative breast cancer were treated with anakinra for a median duration of 4 months (11–179 days) in combination with one of the standard chemotherapeutics for breast cancer. The trial began with a 2-week run-in treatment of only anakinra, during which time gene expression in peripheral blood leukocytes was evaluated. After only two weeks of daily anakinra, gene expression for IL1 β , IL1R1, IL1R2, and IL1R3 were decreased as well as IL1 signaling kinases MyD88 and SYK compared with baseline levels. The downregulation of IL1R3 is particularly relevant because IL1R3 is the coreceptor for IL1 α , IL1 β , IL33, IL36 α , IL36 β , and IL36 γ , all members of the IL1

¹Department of Medicine, University of Colorado, Aurora, Colorado. ²Department of Medicine, Radboud University Medical Center, Nijmegen, the Netherlands.

Corresponding Author: Charles Anthony Dinarello, University of Colorado Denver Anschutz Medical Campus, 12700 19th Avenue B168, Aurora, CO 80045. Phone: 303-724-6174; E-mail: cdinare333@aol.com

doi: 10.1158/0008-5472.CAN-18-2225

©2018 American Association for Cancer Research.

family. A significant role for IL1 in the pathogenesis of acute myeloid leukemia has been known for decades and recent studies demonstrate that IL1R3 is a target for this leukemia. During the pilot trial, anakinra treatment at any timepoint also resulted in decreased expression of five members of the Toll-Like Receptor (TLR) family. In contrast to the suppression of the TLR and IL1 β families by anakinra, increased expression of several natural killer cell and cytotoxic T-cell genes that favor immune-mediated tumor destruction was observed (1). The take home message from the comprehensive Wu and colleagues' study is the identification of high-risk HER2-negative patients who would benefit from reducing IL1 β .

Are there other cancers that would benefit from reducing IL1? On the basis of clinical data using IL1 blocking therapeutics, an IL1 signature is likely in other cancers. In the case of smoldering myeloma, IL1 β from the bone marrow plasma cells induces IL6, which is a growth factor for myeloma cells. Anakinra treatment suppresses IL1 β -driven IL6 and accounts for the lack of progression to active myeloma (5). Canakinumab is an approved anti-IL1 β neutralizing mAb, which significantly reduced the incidence of cancer, deaths from all cancers, and a 77% reduction in deaths from lung cancer (6). These data come from the world-wide randomized, placebo controlled trial in 10,000 high-risk atherosclerotic patients treated with canakinumab to prevent a second myocardial infarction. Many patients were smokers. Although none of the patients had past or known cancer upon entry, some developed cancer during the trial while others had small, undetected malignancies, which developed during the 4 years of the trial. Because the trial was designed to reduce atherosclerosis, as soon as a cancer was detected, those patients were dropped from the trial and there was no further canakinumab treatment. Yet, despite receiving no further canakinumab, overall survival was greater in canakinumab-treated patients (6). The reduction in cancer incidence and deaths by solely neutralizing IL1 β are impressive and are consistent with an IL1 β signature also in lung cancer. In fact, a benefit in treating human cancer with IL1-blocking strategies was predicted (7). There are many mechanisms by which IL1 promotes cancer progression including IL1 as a growth and proangiogenic factor, a suppressor of dendritic and immune cell function, and a promoter of metastasis (8).

Although the Palucka trial focused on IL1 β as a target for treating breast cancer, why block IL1 β when you can block both IL1 β and IL1 α with anakinra? There is no dearth of preclinical data to support a role for IL1 α in human cancer. Increased survival was reported in a randomized, placebo controlled trial of a neutralizing natural antibody to IL1 α in patients with advanced, metastatic colorectal cancer (9). The IL1 α precursor is constitutively present in healthy breast cells, and several studies have identified polymorphisms in the IL1 α promoter as risk factors in breast cancer. However, unlike IL1 β , the IL1 α precursor is biologically active either when expressed as an integral membrane protein or when released upon cell death. IL1 α was present in the supernatants of 149 primary cultured breast cancer tissues stimulated with PMA and ionomycin (1). Using coculture of breast cancer cells with myeloid cells, membrane TGF β was identified as an inducer of the caspase-1-dependent secretion of IL1 β . However, in my opinion, membrane IL1 α in the cocultures was also inducing IL1 β . Indeed, the breast cancer tumor microenvironment is comprised of IL1 α expressing tumor cells and infiltrating mye-

loid-derived suppressor cells, which are the source of IL1 β . In reducing IL1 α and IL1 β , anakinra will reduce the immunosuppression from myeloid-derived suppressor cells (8). IL1 α induction of IL1 β is an example of autoinflammation and, as reported in the study, patients with autoinflammatory diseases exhibit the same IL1 β signature as patients with breast cancer (1). Myeloid cells in the tumor microenvironment are also a source of growth factors for tumors. For example, IL1 α from breast cancer cells induce infiltrating myeloid cells to produce thymic stromal lymphopoietin (TSLP; ref. 10) and TSLP then contributes to the survival of the tumor cells by increasing Bcl-2 that restricts apoptosis in tumor cells. In that regard, compared with placebo-treated patients, anti-IL1 α improved quality of life as well as increased survival (9).

In the Palucka trial, following the 2-week run-in course of anakinra only at the approved dose of 100 mg subcutaneously each day, patients then continued the trial receiving the combination of anakinra plus one of the standard chemotherapy regimens for HER2-negative breast cancer. Because chemotherapy often results in bone marrow suppression and because IL1-blocking therapies can also suppresses peripheral neutrophils, the risk of infection increases with the combination. The daily subcutaneous anakinra has a short plasma half-life of less than 12 hours, although IL1R1 receptor occupancy is likely 24 hours. Nevertheless, a short half-life is a clear advantage because it allows the oncologist to stop anakinra therapy with the first indication of infection. This is not possible with long-lasting antibodies such as canakinumab. The combination of anakinra plus chemotherapy was not associated with any adverse events such as serious infection. Similar to the trial of anti-IL1 α in patients with metastatic colorectal cancer (9), some patients with breast cancer reported reduced pain and increased quality of life on anakinra plus chemotherapy and in other studies, anakinra reduced the "sickness syndromes" of chemotherapy used to treat metastatic colorectal cancer but also increased overall survival (3). Three of the 11 patients in the Palucka trial are still alive (1).

What else can we learn from the Wu and colleagues' study? Anakinra treatment accomplished a sustained reduction in expression of the IL1 signature inflammatory genes in the IL1 family but also in the TLR family and in inflammatory kinases. With the use of anti-CTLA-4, anti-PD-1, or anti-PD1 ligand as checkpoint inhibitors to reverse the immunosuppression of cancer, systemic inflammation, which can be lethal, is a drawback for these therapies. To increase the efficacy of checkpoint inhibitors, some trials add chemotherapy which increases the toxicity. Because anakinra is administered as an adjunct with chemotherapy (1, 3, 4), can anakinra be considered a safe checkpoint inhibitor? The concept that IL1 blockade itself provides for checkpoint inhibition is supported by the canakinumab trial data (6). The mechanisms that account for the reduction in cancer and cancer-related deaths in patients treated with canakinumab likely include increased immune-mediated tumor cell destruction. Why not add anakinra to checkpoint inhibitor therapeutics? Anakinra will reduce IL1-driven inflammation and IL1-driven immunosuppression, but also reduce the cytokine storm associated with checkpoint inhibitors. Cytokine release syndrome is a form of macrophage activation syndrome and anakinra is the standard of treatment for macrophage activation syndrome (2).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The author thanks Dr. Owen Wilson for his helpful comments. These studies are supported by NIH grant AI-15614 and the Colorado Cancer Center. This

work was also supported by grants GM046883, GM113943, HD076125, HL131182, and HD090637 from the NIH.

Received July 19, 2018; accepted July 19, 2018; published first September 14, 2018.

References

1. Wu T-C, Xu K, Martinek J, Young RR, Banchereau R, George J, et al. IL1 receptor antagonist controls transcriptional signature of inflammation in patients with metastatic breast cancer. *Cancer Res* 2018;78:5243–58.
2. Dinarello CA, Simon A, van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nat Rev Drug Discov* 2012;11:633–52.
3. Isambert N, Hervieu A, Rébé C, Hennequin A, Borg C, Zanetta S, et al. Fluorouracil and bevacizumab plus anakinra for patients with metastatic colorectal cancer refractory to standard therapies (IRAFU): a single-arm phase 2 study. *OncoImmunol* 2018 In press.
4. Becerra C, Paulson AS, Cavaness K, Hoof PD, Celinski S. Gemcitabine, nab-paclitaxel, cisplatin, and anakinra (AGAP) treatment in patients with non-metastatic pancreatic ductal adenocarcinoma (PDAC). *J Clin Oncol* 2018;36. Suppl 4, abstract 449. NCT02550327.
5. Lust JA, Lacy MQ, Zeldenrust SR, Witzig TE, Moon-Tasson LL, Dinarello CA, et al. Reduction in C-reactive protein indicates successful targeting of the IL-1/IL-6 axis resulting in improved survival in early stage multiple myeloma. *Am J Hematol* 2016;91:571–4.
6. Ridker PM, MacFadyen JG, Thuren T, Everett BM, Libby P, Glynn RJ, et al. Effect of interleukin-1beta inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1833–42.
7. Dinarello CA. Why not treat human cancer with interleukin-1 blockade? *Cancer Metastasis Rev* 2010;29:317–29.
8. Mantovani A, Barajon I, Garlanda C. IL-1 and IL-1 regulatory pathways in cancer progression and therapy. *Immunol Rev* 2018;281:57–61.
9. Hickish T, Andre T, Wyrwicz L, Saunders M, Sarosiek T, Kocsis J, et al. MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2017;18:192–201.
10. Kuan EL, Ziegler SF. A tumor-myeloid cell axis, mediated via the cytokines IL-1alpha and TSLP, promotes the progression of breast cancer. *Nat Immunol* 2018;19:366–74.

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

An Interleukin-1 Signature in Breast Cancer Treated with Interleukin-1 Receptor Blockade: Implications for Treating Cytokine Release Syndrome of Checkpoint Inhibitors

Charles Anthony Dinarello

Cancer Res 2018;78:5200-5202.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/78/18/5200>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/78/18/5200>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.