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Interleukin-1 blocking agents as promising strategy for prevention of anticancer drug-induced cardiotoxicities: possible implications in cancer patients with COVID-19

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Abstract. – Cytokines in cardiac tissue plays a key role in progression of cardiometabolic diseases and cardiotoxicity induced by several anticancer drugs. Interleukin-1β is one on the most studied regulator of cancer progression, survival and resistance to anticancer treatments. Recent findings indicate that interleukin1-β exacerbates myocardial damages in cancer patients treated with chemotherapies and immune check-point inhibitors. Interleukin1-β blocking agent canakinumab reduces major adverse cardiovascular events and cardiovascular death in recent cardiovascular trials. We focalized on the main biological functions of interleukin1-β in cancer and cardiovascular diseases, summarizing the main clinical evidence available to date in literature. Especially in the era of SARS-CoV-2 infection, associated to coagulopathies, myocarditis and heart failure, cancer patients have an increased risk of cardiovascular complications compared to general population, therefore, the pharmacological inhibition of interleukin1-β should be discussed and considered.

Key Words:
Cardiomyopathy, Prevention, Cancer, Covid-19, Canakinumab, Interleukin-1.

Introduction

Pro-inflammatory cytokines play a key role in progression of several cardiovascular diseases, like myocarditis, heart failure and atherosclerosis[1,2]. Interleukin-1 (IL-1) is a cytokine well associated to acute and chronic inflammation and other chronic diseases like cancer and cardiomyopathy[3]. Among the members of the IL-1 family, IL-1β has been proven to be a therapeutic target for many auto-inflammatory diseases, including rheumatoid arthritis, acute gout and psoriasis [4].

A chronic inflammation plays a central role in heart failure[5], acute myocardial infarction[6], pericarditis, myocarditis[7] and sepsis-induced cardiomyopathy[8]. Preclinical studies correlate high levels of IL-1β to a greater risk of cardiovascular diseases; the underlying mechanism of cardiotoxicity involves the induction of lipid peroxidation[9], rising levels of intracellular calcium[10] and dysfunction of mitochondrial metabolism[11]. Moreover, IL-1 activates pathways of cancer progression and resistance to chemotherapy and radiotherapy[12]; high levels of IL-1 were seen in patients with melanoma, colon, lung, head, neck or breast cancer compared to non-cancer patients[13,14]; therefore, pharmacological inhibition of IL-1β could be a promising approach for the treatment of cardiovascular diseases and cancer.

From December 2019, the management of cancer patients changed radically due to the extraordinary progression worldwide of coronavirus disease-2019 (named COVID-19 or SARS-CoV-2 infection)[15]. It is clear that virus of COVID-19 interacts with angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2

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(named TMPRSS2), a serine protease expressed in cardiomyocytes and vascular cells[16,17]. SARS-CoV-2 infection exposed cancer patients to a high risk of recurrence and cardiovascular complications due to significant delays in medical checks and follow-ups[18]. SARS-CoV-2 infection induces secondary hemophagocytic lymphohistiocytosis, a multi organ hyper-inflammatory disease associated to immune-mediated myocarditis and coagulation dysfunctions[19]. A storm of scientific works is available on this topic, with more and more detailed information on the pathophysiology of COVID-19 and therapeutic strategies[20]. One of the key factors involved in SARS-CoV-2-induced secondary hemophagocytic lymphohistiocytosis is the overexpression of IL-1[21]; in fact, here we highlight the pharmacological inhibition of IL-1 *via* canakinumab in cancer patients at high risk of cardiovascular complications.

This review focalized on three major points: (1) the biochemical effects of IL-1β in pathogenesis of heart diseases, cancer cell growth and survival; (2) cardiovascular benefits of canakinumab, an IL-1β-blocking antibody in cardiovascular outcomes trials;(3) the rationale for the administration of canakinumab in cancer patients at high risk of developing heart dysfunctions and affected by SARS-CoV-2 infection.

Biology of IL-1: Role and Molecular Pathways

The IL-1 is composed by several units with different properties, called IL-33, IL-1α and -β (able to activate their receptors) and antagonists of IL-1 receptors (characterized by inhibitory activities)[22]. Among IL-1 members, all are able to bind the type 1 receptor IL-1R1 with the exception of IL-33. IL-1α and IL-1β are encoded by two different genes, able to produce pro-IL-1α (involved in pro-inflammatory pathways) and pro-IL-1β in inactive form[23]. IL-1α, activated from calpain, is a pro-inflammatory transcription factor with key roles in the activation of metabolism, cell survival and metastasis, whereas IL-1β is produced and secreted by immune cells, endothelial cells, cardiomyocytes and cancer cells[24,25]. Notably, the production of IL-1β involves two phases: priming and cleavage. Priming is led by activators of toll-like receptors, such as lipopolysaccharides LPS, cytokines, growth factors, insulin, advanced glycation end products and chemotherapies[26]. IL-1β activates the nucleotide-binding oligomerization domain-containing protein NOD-like receptors called also NLRs; the most known receptor is called NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) able to regulate the secretion of cytokines/chemokines involved in cancer cell growth and cardiac injuries[27]. IL-1 β acts in autocrine and paracrine manner and is secreted by human cells through vesicles autophagolysosomes, microvesicles and exosomes, as well as through gasdermin D pores[28]. Pathways activated by IL-1 involves also Myd88, also called myddosome complex, a protein complex involved in pathogenesis of viral myocarditis, colitis, rheumatoid arthritis and heart failure[29]; MyD88 interacts with IRAK and TRAF6. The association of Myd88/IRAK/TRAF6 pathways activates the nuclear translocation of nuclear factor k B (NF-κB) units, i.e., p50/p65, thus increasing the inflammatory state, angiogenesis, heart fibrosis and myocarditis[29]. Moreover, several interleukins, like IL-1, IL-18, IL-33, IL-36, IL-37, and IL-38 regulates innate and adaptive immune system[30]; in fact, IL-1 family members activates both differentiation and polarization of myeloid cells and lymphoid cells. Notably, IL-18 is involved in the activation of natural killer cells and Th1 cells[31] instead IL-33 is involved in type 2 innate and adaptive immunity and inflammation, therefore regulating the immune response to bacterial and viral infections as well as the allergic responses[32]. A complex interaction between IL-1 and immune cells should be deeply studied, especially in cancer patients treated with immune check-point inhibitors.

Interleukin-1β and Cardiovascular Diseases

The heart microenvironment involves multiple pathways derived from interleukins, cytokines, chemokines, small interfering RNA and hormones that are able to manage cardiac metabolism[33-37]. Cardiac tissue is composed by cardiomyocytes, fibroblasts, immune and endothelial cells that are strictly responsive to interleukins and chemokines[38]. Inflammatory cytokines are small proteins that exert negative ionotropic effects on left ventricular remodeling in several heart diseases[39].

IL-1β is associated to atherosclerosis, heart failure, myocarditis and doxorubicin-induced cardiotoxicity[40]. As shown in Figure 1, IL-1β activates inflammatory pathways of crucial interest in cardiology. It activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), the type I myeloid differentiation factor 88 (MyD88) and cryopyrin[41] in cardiac cells.

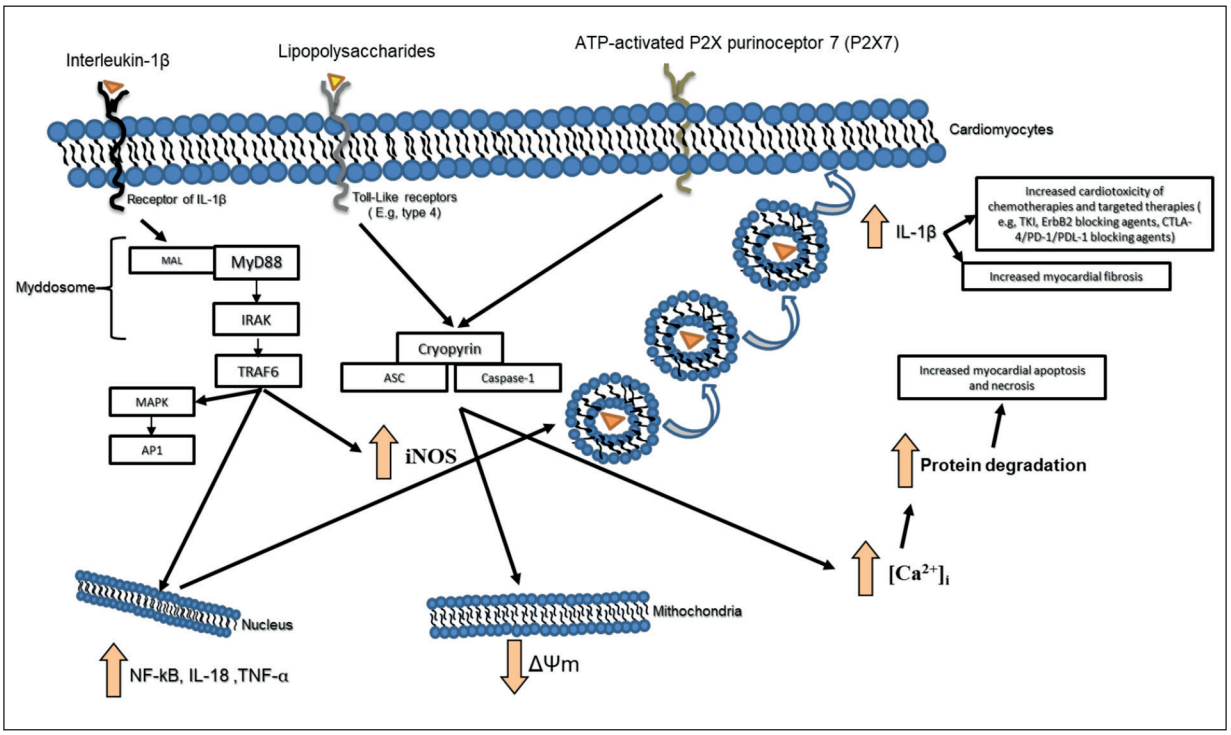

Figure 1. Interleukin-1β binds to its receptor expressed in cardiomyocytes leading to the activation of myddosome complex, composed by myddosome, MyD88 and IRAK. Myddosome complex activates TRAF6 able to increase the expression of NF-kB, IL-18 and TNFα involved in cardiac fibrosis and necrosis; TRAF6 activates also iNOS expression and MAPK/AP1 pathway involved in cell apoptosis and cardiac inflammation. IL-1 exerts a cross-talk with ATP-activated P2X purinoreceptor 7 and LPS. LPS binds to Toll-like receptor type 4, expressed on cardiomyocytes, thus activating the association of Cryopirin/ASC/Caspase1 leading to apoptosis by reducing mitochondrial potential of cardiac cells. LPS increases intracellular calcium content in cardiac cells leading to protein degradation and dysfunction of calcium/calmodulin. IL-1 and the intracellular cross-talk with LPS-mediated signaling leading to autocrine and paracrine signals involved in the exacerbation of cardiotoxicity induced by chemotherapies and targeted therapies e.g, TKI, ErbB2 blocking agents, CTLA-4/PD-1/PDL-1 blocking agents. AP1=Activator protein type-1; ASC= Apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain: IRAK1= IL-1R-associated kinase MAL= Myddosome; MAPK= mitogen-activated protein kinase; TNF= Tumor Necrosis Factor; TRAF6= TNF Receptor Associated Factor 6; LPS: lipopolysaccharide; TKI: tyrosine kinases inhibitors; ErbB2: v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2; CTLA4: Cytotoxic T-Lymphocyte Antigen 4; PD-1: Programmed cell death protein 1; PDL-1: Programmed cell death protein ligand 1.

MyD88 and cryopyrin work in synergy and lead to activation of IL-6 and IL-8 involved in several cardiovascular diseases[42]. IL-6 binds to two types of receptors thereby stimulating the production of high-sensitivity C-reactive protein and other mediators of atherosclerosis[43]. Both MyD88 and cryopyrin, activated by IL-1β, activates apoptosis in cardiac cells and their expression is associated to high risk of heart failure[44]. Another pathway of IL-1β involves the activation of p38-MAPK and nitric oxide that dysregulates metabolism in sarcoplasmic reticulum and calcium homeostasis in cardiomyocytes[45,46]. The identification of the pleiotropic effects of interleukins in cardiac tissue opened a new era in cardiology. As shown in Figure 1, the Myddosome complex activated by IL-1β exerts both epigenetic and cytoplasmic effects on cardiomyocytes[47-49]. In fact, IL-1β increases NF-kB activation thereby stimulating the production and vesicular translocation of IL-1β[50] and of IL-18[51] thereby increasing TNF-α levels[52].

Dynamic crosstalk among TLR4 and IL-1 receptors signaling is involved cancer, diabetes, metabolic syndrome and cardiovascular diseases[53-56]. LPS exerts a crosstalk with TLR4 which contributes to angiogenesis and fibrosis[57]. For example, IL-1 and TLR4 downstream signaling activates pro-apoptotic factors, like the ATP-activated P2X purinoceptor 7 (P2RX7) (Figure 1).

It activates the Cryopyrin-Caspase-1 axis, thereby resulting in cardiotoxic effects[58]. The P2X7 purinergic receptor, a calcium permeable cationic channel, is activated by extracellular ATP and it is considered a "cardiac danger sen-

sor" able to initiate vascular and cardiac inflammation processes. P2X7 receptors are expressed in cardiac and endothelial cells and their pharmacological targeting could be a new treatment approach to hypertension and thrombosis[59]. Notably, the P2X7 receptor increases the intracellular calcium concentration in cardiomyocytes, as occurs during exposure to doxorubicin[60], and alters mitochondrial potential[61], which in turn leads to cardiac cell necrosis[62]. Moreover, there is increasing evidence that the pro-inflammatory cytokine IL-1β may play a key role in the cardiac damage induced by doxorubicin or daunorubicin[63]. In fact, anthracycline-related cardiotoxicity is, at least in part, induced by the cryopyrin-caspase 1 axis and increases intracellular calcium content[64]. Given the involvement of the IL-1β pathway in DOXO-induced cardiotoxicity, treatment with IL-1β inhibitors during anthracyclines could reduce cardiovascular risk in this setting of cancer patients.

Interleukin-1β and Cancer

IL-1β is a pluripotent cytokine that is required for many normal physiological processes like induction of vascular permeability, fever during sepsis and increased secretion of other cytokines involved in autoimmune diseases[65]. IL-1β is also involved in the production and release of prostaglandins, pituitary hormones, and collagenases, and stimulates the immune system to boost lymphocyte production. Therefore, an important balance exists between the beneficial and harmful effects of IL-1β[66]. In fact, overexpression of IL-1β is associated to endothelitis, vasculitis, diseases affecting the central nervous system and bone marrow[67-69]. Moreover, overexpression of IL-1β is associated to rheumatoid arthritis[70], atherosclerosis[71], diabetes mellitus[72] and several solid tumors[73]. As shown in Figure 2, cancer cells directly produce IL-1β, which can affect their nuclear and mitochondrial metabolism. IL-1β is also correlated to a poor prognosis of lung cancer[74]. The bio-

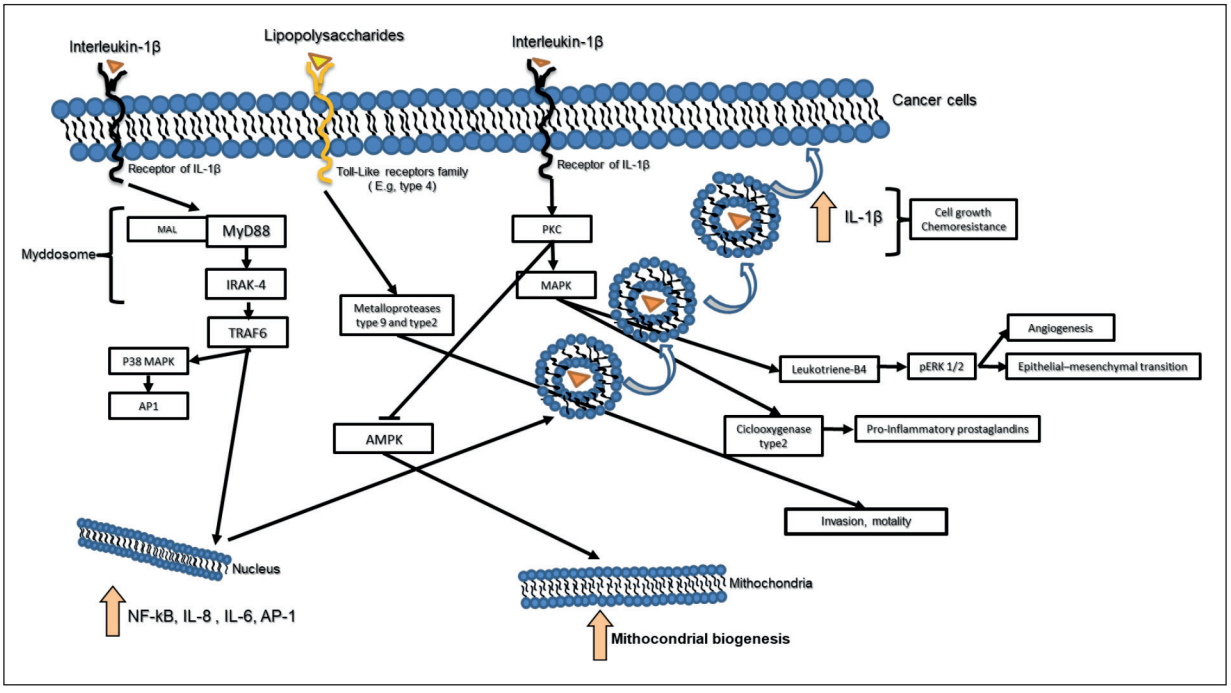

Figure 2. Interleukin-1β exerts pro-inflammatory and pro-tumorigenic effects through the activation of myddosome and inhibition of AMPK. IL-1 binds to its receptor overexpressed in cancer cells leading to the activation of myddosome complex, composed by myddosome, MyD88 and IRAK-4. Myddosome complex activates TRAF6 able to increase the expression of NF-kB, IL-8, IL-6 and AP-1 involved in cancer cell survival and resistance to chemotherapy and radiotherapy. Notably, IL-1 activates PKC that inhibits AMPK and regulates MAPK. Inhibition of AMPK leading to cancer cell survival and mitochondrial biogenesis in cancer cells. Activation of MAPK increases the expression of COX2 and pro-inflammatory prostaglandins, like leukotriene B4 that are the key activators of pERK1/2 involved in angiogenesis and EMT. Intracellular cross-talk between IL-1 and LPS leads to the activation of MMP2 and MMP9 involved in cell invasion and motility. AMPK= 5' AMP-activated protein kinase; IRAK4= IL-1R-associated kinase; pERK= protein kinase R-like endoplasmic reticulum kinase; PKC= Protein kinase C. MAPK: Mitogen-activated protein kinase; COX2: Cyclooxygenase type2 ; pERK1/2: phospho extracellular signal-regulated kinases; MMP2: Matrix Metallopeptidase 2; MMP9: Matrix Metallopeptidase 9 ; EMT: Epithelial-Mesenchymal Transition.

chemical mechanisms by which IL-1β promotes tumor growth are mainly based on the induction of the expression of MMP-9, VEGF, TNFα and several interleukins[75]. Specifically, stimulation of IL-1β receptor activates MyD88-MAL, inducing IRAK4 and TRAF6 that, in cancer cells, activate p38MAPK, that enhances the expression of AP-1/NF-kB pathways[76]. Moreover, IL-1β induces PKC-MAPK that overexpress COX-2 that has been implicated in the promotion of angiogenesis, invasion of tumor tissue and resistance to apoptosis and chemotherapy[77]. In addition, COX-inhibitors can inhibit tumor immune evasion[78].

Through the PKC-MAPK axis, IL-1β stimulates the expression of leukotriene B4[79], which is a driver of the epithelial-mesenchymal transition and of cancer cell angiogenesis[80]. Specifically, LTB4 is a leukocyte chemoattractant and plays a major role pathogenesis of pancreatitis[81]. LTB4 is correlated with cancer progression and induces keratin phosphorylation and reorganization by activating ERK[82]. Moreover, it was recently demonstrated that the IL-1β-PKC axis is able to inactivate AMPK phosphorylation in cancer cells[72], thereby reducing mitochondrial functions and mitophagy[83,84]. Mitophagy positively regulates cancer cell survival by targeting the removal of damaged mitochondria, thereby eliminating the source of apoptogenic signals[84].

Anthracycline-Induced Cardiotoxicity and IL-1

A special attention should be made on the association between anthracycline-induced cardiotoxicities and IL-1[85]. Doxorubicin is a potent antineoplastic drug used to treat breast cancer, leukemias and lymphomas. However, its clinical use is characterized by specific cardiotoxicity exposing patients to high risk of heart failure[86-88].

Doxorubicin-induced cardiotoxicity is due to the production of ROS, lipid peroxidation, calcium overload, activation of ferroptosis and mitochondrial dysfunctions[88]. Recently, a key role of IL-1 in doxorubicin-mediated cardiac injury was found. High systemic and cardiac expression of IL-1 were found in preclinical models exposed to doxorubicin[89]. Notably, histological studies of cardiac tissues confirmed a high expression of IL-1β and IL-1Ra, indicating a potential role in doxorubicin-induced inflammation.

IL-1 Blocking Agents in Clinical Trials

The most studied IL-1 blocking agents are anakinra, canakinumab, gevokizumab, rilonacept[90] (Figure 3). Anakinra is a recombinant human IL-1R antagonist that reduces systemic levels of IL-1α and IL-1β[90]. Anakinra has a half-life of 4-6 h after subcutaneous administration and is currently suggested for treatment of rheumatoid arthritis

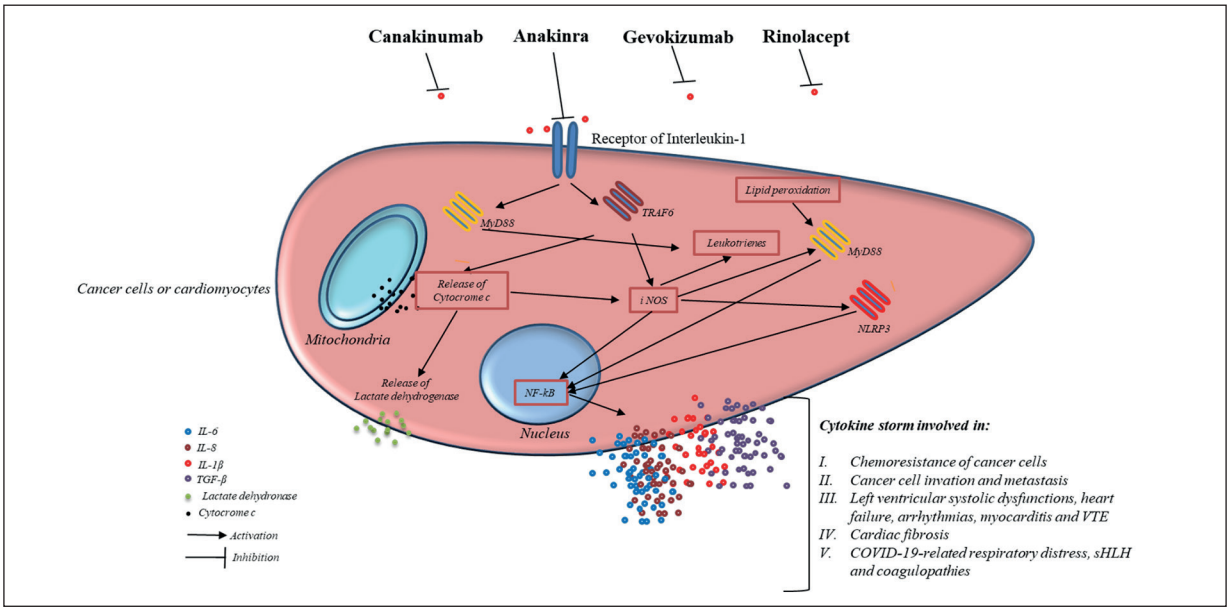

Figure 3. Selective IL-1 inhibitors and their metabolic effects in cancer cells and cardiomyocytes. IL: interleukin; TGF: Transforming Growth Factor; VTE: venous thromboembolism; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; MyD88: myddosome type 88; iNOS: inducible nitric oxide synthesis; TRAF-6: TNF Receptor Associated Factor 6.

and juvenile arthritis[91]. Anakinra has approved for cryopyrin-associated period syndromes, a genetic disease associated to high systemic levels of NLRP3 inflammasome and IL-1β[92]. Considered its half-life, anakinra may be preferred for acute treatment indications compared to other IL-1 antagonists. Canakinumab is a humanized monoclonal antibody inhibitor of IL-1β. Canakinumab, approved for the treatment of juvenile arthritis and CAPS, is generally administrated every month, and therefore, it is more suitable for chronic uses[93].

Rilonacept is a chimeric recombinant form of IL-1 receptor able to bind IL-1α, IL-1β, and IL-1 receptor α[94]. Rilonacept is currently approved for the treatment of CAPS and is subcutaneously administered every 2 weeks[94]. Gevokizumab is a monoclonal antibody able to block the binding of IL-1β to their receptors[95]; clinical trials on Gevokizumab are currently underway[96].

Selective Inhibition of Interleukin-1 β Through Canakinumab: a Focus on CANTOS trial

In the field of cardiology, it is now established that atherosclerosis is a chronic progressive inflammatory disease[97]. In this context, Russell Ross[97] proposed "the response to injury" theory according to which inflammation is the mechanism mediated by several cardiovascular risk factors, e.g., high-sensitivity C-reactive protein and interleukins that leads to the formation of atherosclerotic plaques. Subsequently, it was established that inflammation and several cytokines play a role in the atherosclerosis process[98].

Given the increasing pathophysiological relevance of IL-1β in the pathogenesis of a wide variety of diseases, new biologic agents have recently been introduced to restrict the effects of inflammatory cytokines. Canakinumab, an IgG1k monoclonal antibody that neutralizes soluble IL-1β, is one such IL-1β-targeting drug that has been approved for clinical use in cryopyrin-associated periodic syndromes, gout, Behçet's syndrome and rheumatoid arthritis[99]. Promising results in the fields of cardiology and oncology were obtained with this agent in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study (named CANTOS trial)[100]. A total of 10,061 patients with previously diagnosed myocardial infarction were enrolled in the trial that evaluated the effects of canakinumab at three doses (50, 150 or 300 mg) all administered subcutaneously every 3 months *vs.* untreated patients. After 4 years of administration, the plasma levels of high sensitivity C-reactive protein were around 26%, 37% and 41% lower in patients treated with 50, 150 and 300 mg of canakinumab, respectively, *vs.* the placebo group[101]. Moreover, canakinumab at 150 mg, after approximately 4 years of follow-up, significantly reduced the incidence of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, which was the primary endpoints of the CANTOS trial. Canakinumab reduces both high sensitivity C-reactive protein and IL-6 in a dose-dependent manner, without modifying the initial lipid homeostasis. The CANTOS trial demonstrated that modulation of the systemic inflammatory state results in clinical benefits in terms of reduction of cardiovascular events. Currently, the clinical evidence available is limited to aspirin and statins and drugs that, in addition to their anti-inflammatory activity, exert anti-platelet and anti-cholesterolemic effects. Despite the clinical results, the use in clinical practice of canakinumab is limited by the significant increase in fatal infections in treated patients[101]. Another limitation is the cost of the drug. Given the impending use of anti-inflammatory therapies in cardiovascular disease, clinicians need to learn how to evaluate the safety profile of this agent beyond the risk of infection. First, canakinumab in CANTOS and other IL-1 blockers in other studies did not increase the risk of opportunistic infections[102], which argues against the immunosuppressive effects seen with corticosteroids, TNF blockers and IL-6 antagonists[102]. Second, the absolute increased risk of fatal infection or sepsis in CANTOS trial was low: 0.31 *vs.* 0.18 per 100-person years for all three doses *vs.* placebo. Most infections were cellulitis[101], which occurred infrequently, and there was no difference in pneumonia or infections in genito urinary tract. It is important to remember that IL-1 is the primary mediator of fever[104]. In fact, IL-1 acts in the preoptic hypothalamic nuclei by increasing the body temperature and the production of arachidonate involved in thermogenesis[105]. The slight increase in cases of infection during CANTOS trial should be explainable because IL-1 blockade prevents fever, infection awareness is decreased, and patients present later after the infection has worsened. This implies that heightened monitoring can mitigate the risk of infection in routine practice. Of course, the risk of infection will be heightened in people with cancer and more specific trials are needed to quantify and characterize this risk of infection in relation to the benefits of treatment with canakinumab and other IL-1 inhibitors.

IL-1 and Cardiac/Vascular Diseases

Inflammation contributes to all phases of the atherothrombosis. Patients with high levels of inflammatory biomarkers have an increased cardiovascular risk and recent studies associated atherogenesis to IL-1 and IL-6[106]. IL-1β is secreted by endothelial cells and cardiomyocytes[107]. High levels of IL-1 are produced by vascular endothelial and smooth muscle cells, and macrophages during atherosclerosis. In CANTOS, canakinumab reduced significantly matrix metalloproteinase 2 type IV and collagenase that are involved in metastasis, as well as in the backbone of extracellular matrix in several organs[108]. However, IL-1β represents only one of multiple targets involved in atherosclerosis. In CANTOS trial, there was no significant difference in all-cause mortality hazard ratio for all canakinumab doses compared to untreated patients. However, as well described in an exploratory analysis of the CANTOS study, cancer mortality was significantly lower with canakinumab than with placebo[109], a finding that is consistent with experimental data relating IL-1 and IL-6 to the progression and invasiveness of certain tumors.

Other studies in patients with acute coronary syndrome indicated a significant reduction of mortality in patients treated with selective inhibitors of IL-1. In a more recent perspective analysis[110] authors concluded that canakinumab could be used in therapy of acute coronary syndrome[111].

Other small trials demonstrated protective role of IL-1 blocking agents in patients with acute myocardial infarction and heart failure. Harouki concluded that gevokizumab initiated shortly after reperfusion significantly improved cardiac remodeling and systolic function in mice with acute myocardial infarction[112]. Other two small trials tested the effects of anakinra in patients with acute myocardial infarction or heart failure: in a study, the incidence of death or rehospitalization for heart failure at 24 weeks from anakinra administration was 6%, 31%, and 30%, in the anakinra 12-week, anakinra 2-week, and placebo groups, respectively, indicating that a significant improvement should be obtained only after 12 weeks of treatment with IL-1 blocking agent[113]. In another study[114] anakinra improved the median peak oxygen consumption and median ventilator efficiency *vs.* placebo in patients with heart failure. Other two pilot studies, called CU-ART and VCU-ART2 pilot studies, demonstrated that treatment with anakinra for two weeks was associated with a hazard ratio of 1.08 for death, recurrent acute myocardial infarction or stroke, and an hazard ratio of 0.16 for death or heart failure in patients after ST-segment elevation myocardial infarction[115].

Following the success of CANTOS, other studies tried to target inflammation in high-risk patients through selective inhibitors. Colchicine is another inhibitor of IL-1, clinically used to mitigate inflammatory diseases as well as to reduce cardiovascular events in two trials called LoDoCo and LoDoCo2[116,117]. Colchicine Cardiovascular Outcomes Trial (COLCOT) indicated that colchicine reduces heart failure, stroke and mortality of 1.6% compared to placebo[118].

IL-1 Inhibitors and Risk of Infection

After CANTOS trial, there is some confusion on the mechanism of infection and the role of IL-1[100]. Clinicians evidenced that canakinumab causes infection through neutropenia, but the difference is not statistically significant: incidence rates per 100 person-years was 0.06, and 0.10 for placebo and all doses of canakinumab, respectively; p=0.17 for combined dose groups *vs.* placebo[100]. Notably, anakinra (daily injected) reduces both IL-1β and IL-1α that are involved in immune-mediated responses to virus and bacteria; in contrast, canakinumab (injected every 3 months) did not increase significantly the risk of infection compared to anakinra. However, some cases of fatal infections were seen in CANTOS trial, that was not related to neutropenia but to a delayed clinical recognition of the infection by clinicians during the trial.

Selective Inhibition of IL-1 Through Canakinumab for Cancer Treatment: What are the Evidence and Perspectives?

Inflammation in the tumor microenvironment mediated by IL-1 plays a major role in cancer invasiveness, survival and resistance to chemotherapy[119,120]. The promotion of the angiogenic phenotype increases cancer cell survival[110]. Cancer cells directly produce IL-1 and stimulate other cells to secrete it[122]. The ability of IL-1 to induce the expression of growth factors, including vascular endothelial growth factor and IL-8 has been implicated in tumor growth and metastasis[123].

The production of IL-1β in human cancer cells and tissue has been observed also in sarcoma and ovarian cancer[124]. Increased concentrations of IL-1 have been identified in numerous solid tumors[122], and patients with IL-1β-produc-

ing cancers have a poor prognosis[122,123]. In fact, changes in the tumor microenvironment promote the growth and metastasis of cancer tissue. The CANTOS trial documented an additive clinical benefit in patients taking 300 mg of canakinumab, i.e., a statistically significant reduction in the incidence of lung cancer (67%, $p = 0.00008$, death from lung cancer 77%, $p = 0.0002$ and death from any type of tumor 51%, $p = 0.0009$)[100].

However, the baseline concentrations of hs-CRP and IL-6 were significantly higher in lung cancer patients than in non-cancer patients (6 mg/L *vs.* 4.2 mg/L for high sensitivity-C reactive protein and 3.2 *vs.* 2.6 ng/L for IL-6, respectively; $p<0,0001$ for all). The latter findings corroborate the relationship between pro-inflammatory interleukins and neoplastic diseases. During treatment with canakinumab for three years, high-sensitivity C-reactive protein and IL-6 levels were 26-41% and 25-43%, respectively, lower compared to untreated patients for all comparisons.

These preliminary results are of clinical interest, providing the key role of IL-1β in the genesis and progression of lung cancer. Effectively, the CANTOS trial showed a strong signal in cancer mortality, but that was almost entirely limited to lung cancer incidence and mortality, without deeper analysis on patients with other cancers. Based on this, an exploratory analysis of the CANTOS trial indicated the key role of IL-1 in lung cancer cell survival and chemoresistance and the beneficial properties of canakinumab in patients with lung cancer[125]. An ongoing trial (CANOPY-N) associates pembrolizumab to canakinumab in patients with lung cancer (Clinical Trial Registration: NCT03968419 ClinicalTrials.gov)[126] in order to evaluate differences in Major Pathological Response rate compared to patients treated with pembrolizumab.

Selective Inhibition of IL-1 Through Canakinumab for Patients with Cancer, Cardiovascular Diseases and COVID-19: a Clinical Perspective

In the era of COVID-19[127] cancer patients were exposed to high risk of cancer recurrence and heart failure induced by anticancer therapies, due to slips in cardiac and oncological checks[128]. In summary, SARS-CoV-2 induces secondary hemophagocytic lymphohistiocytosis[129] that causes fulminant myocarditis, vasculitis[130] and heart failure[131]. The overexpression of IL-1 β[132] increases the liver production of IL-6 and high-sensitivity C-reactive protein[133] that are associated to myocarditis, myocardial infarction, venous thromboembolism and bleeding[134]. Clinical trials designed to target IL-1 in COVID-19 patients are currently underway. One blinded randomized controlled trial demonstrated that IL-1 antagonism can reduce myocardial injury and inflammation in patients with COVID-19[135]. In another recent trial, ten patients with COVID-19 with severe pneumonia and inflammation were treated with 300 mg of canakinumab; after 45 days of follow-up, patients treated with canakinumab showed a rapid reduction in the systemic inflammatory response and an improvement in oxygenation[136]. Cavalli et al[137] treated COVID-19 affected patents with intravenous anakinra at 5 mg/kg twice daily; after treatments, a fast reduction in serum C-reactive protein, significant improvements in oxygenation and consequently in survival were seen in anakinra-treated patients compared to placebo. Other small trials in patients with COVID-19 evaluated the beneficial effects of colchicine on cardiovascular events. A recent meta-analysis[138] concluded that colchicine reduces the overall mortality: a pooled odds ratio for mortality was 0.35; however, more detailed and randomized clinical trials are needed in order to confirm the benefits of colchicine administration in COVID-19 patients. To date, no studies investigate the effects of colchicine in cancer patients with COVID-19.

A case report in a patient affected by COVID-19 with acute respiratory distress syndrome and cardiac and renal failure hospitalized for less than 1 month described the beneficial effects of canakinumab. After 24 h from canakinumab administration, a significant reduction in IL-6 levels and natural killer cells were seen; however, patient died after less than 2 months for pulmonary bacterial superinfection[139]. From October 2020, a randomized interventional trial was started with the recruitment of patients with COVID-19 and type 2 diabetes allowed to receive canakinumab over 2 hours vs. placebo[140]. Another trial (named Phase 3 Multicenter, Randomized, Double-blind, Placebo-controlled Study) is still recruiting to assess the efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia[141]. Moreover, the Cleveland Clinic USA started a prospective, phase 2, single center, blinded, randomized controlled study aimed at preventing the progressive heart and respiratory failure in patients with COVID-19 infection treated with canakinumab. In conclusion, canakinumab could be studied in patients with COVID-19 in order to

improve cardio-pulmonary functions. To date, no trials have been started or proposed to reduce cardiovascular complications in patients with cancer and COVID-19. Long-term cancer survivors, as well as cancer patients treated with radiotherapy or anticancer therapies with estimated cardiotoxic and vasculotoxic properties, have high risk of venous thromboembolism, bleeding, heart failure, arrhythmia and myocarditis[142,143]. Cardiotoxic events of anticancer drugs often involve pro-inflammatory mediators; cancer patients have poor prognosis after SARS-CoV-2 infection compared to patients without cancer[144-146]. Based on this, we propose a randomized, placebo-controlled trial aimed to reduce cardiovascular complications in cancer patients with high risk of cardiotoxic events through i.v. administration of canakinumab in a single dose (Figure 4). To this aim, an algorithm for treatment is described for patients with cancer and COVID-19 with a positive reverse transcription polymerase chain reaction nasopharyngeal swab. Trial involves the recruitment of patients with cancer at high risk of cardiac dysfunctions, in line with recent guidelines in cardio-oncology[147], specifically:

1. cancer patients treated with high dose of anthracyclines or radiotherapy or anthracyclines (at low doses) associated to low dose of radiotherapy;
2. cancer patients treated with low doses of anthracyclines or trastuzumab alone associated to cardiovascular risk factors (listed in Figure 4)
3. cancer patients treated with low doses of anthracyclines and trastuzumab (as sequential treatment).

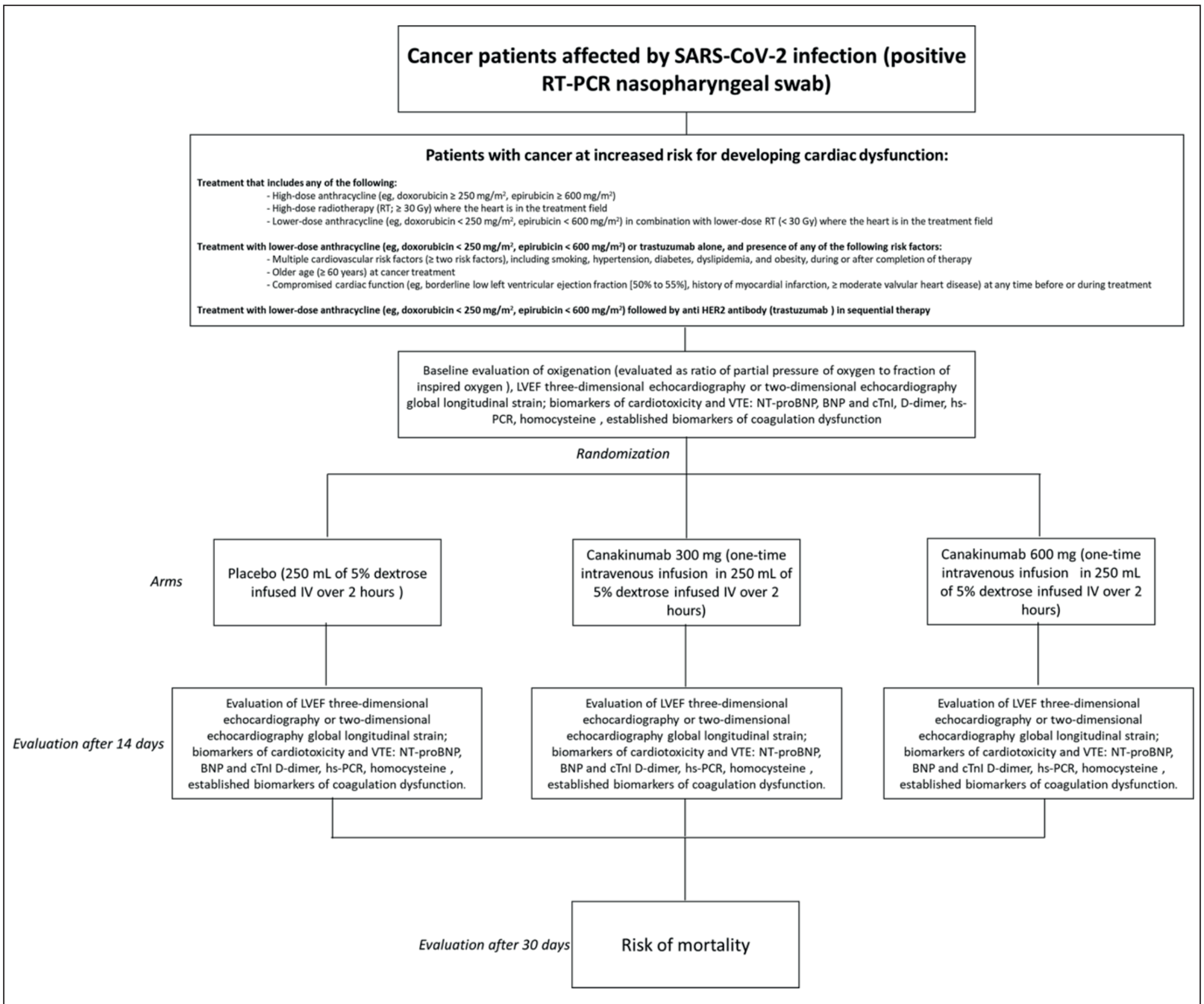

Figure 4. Proposal of treatment algorithm for reduction of heart failure, coagulation dysfunction and mortality in cancer patients, with SARS-CoV-2 infection, at high risk for developing cardiovascular diseases.

A baseline evaluation of oxygenation evaluated as ratio of partial pressure of oxygen to fraction of inspired oxygen, left ventricular ejection fraction through three-dimensional echocardiography or two-dimensional echocardiography global longitudinal strain or diastolic function through PW method should be analyzed. Moreover, quantification of plasma biomarkers of cardiotoxicity and VTE should be performed: N-terminal pro b-type natriuretic peptide, BNP and cardiac troponin I, D-Dimer, C-reactive protein and homocysteine. Patients with active cancer, cardiovascular disease and COVID-19 will be divided in three arms: placebo (intravenous administration of 250 mL of 5% dextrose solution over 2 hours); canakinumab at 300 mg or 600 mg (one-time intravenous infusion in 250 mL of 5% dextrose infused IV over 2 hours). After 14 days, as primary outcome of the trial, cardio-pulmonary function studies will be performed and putative differences with basal values could be analyzed; as secondary outcome, overall mortality will be evaluated after one month. From this trial, we expect that cancer patients treated with canakinumab on top of standard of care will reduces pro-inflammatory biomarkers and will improve oxygenation and cardiac functions compared to placebo.

Conclusions

Beneficial effects of the IL-1β blocking agent canakinumab are seen in recent cardiovascular trials. In line with the expected outcomes, canakinumab reduced significantly both mortality rate and cardiovascular diseases in patients at high risk of mortality. Considering the key role of IL-1 in cancer and chemoresistance, it is expected that canakinumab may reduce cancer incidence or mortality. Considering that IL-1 is involved in pathophysiology of chemotherapy-induced cardiotoxicity, we strongly suggest further trials aimed to study if canakinumab could reduce MACE in cancer patients with high risk of developing heart failure or cardiomyopathies. Moreover, in the era of COVID-19 characterized by a broad spectrum of clinical manifestations[148-152], cancer patients are particularly vulnerable, and we hypothesize that canakinumab treatment in this patient cohort could reduce the risk of mortality and improve cardio-pulmonary functions.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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