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Review

Brief Overview of Specific Features of Cancer in Atherosclerosis Patients and Therapeutic Strategies

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Abstract: Cardiovascular Conditions (CVD) as well as cancer are the main death causes globally. Characteristically, there are numerous interrelations and intersections between these two groups of diseases. So, in particular, cardiovascular disease is one of the main comorbidities and death causes in cancer patients. The development of atherosclerosis is promoted by aggressive anticancer therapy regimens and various risk factors, including hypertension, lipid metabolism disorders, and others. In this review, we considered the features of the treatment of atherosclerosis and cancer in the case of their simultaneous presence.

Keywords: Atherosclerosis, Cardiovascular Disease, Cancer, Breast Cancer, Oncology

Introduction

Incidence and Prognosis of Atherosclerotic Disease in Cancer Patients

Current progress in cancer prevention and management has significantly enhanced survival rates, thus increasing the prevalence of Cancer-Related Complications. CVD is one of the main comorbidities and death causes in oncological patients. For instance, the majority of early-diagnosed breast cancer patients die because of a cardiovascular event, then because of the malignant neoplasm itself (Acevedo *et al*., 2022).

The CVD risk is considerably higher in patients suffering from cancer than in those without a neoplasm. For instance, according to a recent study involving patients who have been diagnosed with cancer within the year before the study, the risk for Acute Myocardial Infarction (AMI) is three times greater Hazard Ratio (HR) = 2.9; 95% CI, 2.8-3.1 in patients who experience a neoplastic process compared to control population (Peng *et al*., 2022). Furthermore, the increase in AMI risk is directly associated with cancer stage. The findings of the study may be particularly important in light of possible strategies aimed at early reduction of CVD risk in cancer patients, such as statin therapy or antithrombotic treatment (Navi *et al*., 2017).

Cancer can contribute to atherogenesis in several different ways, the most common being side effects of chemotherapy and Radiotherapy (RT). In addition to these mechanisms, cancer and atherosclerosis are often linked through a number of well-established factors, such as metabolic and cardiovascular impairments, including hypertension, negative lipoprotein profile, dysfunctional glucose metabolism, and central obesity (Koene *et al*., 2016).

Prior to discussing the increased CVD risk caused by antitumor treatment and RT, it is worth mentioning the increased CVD risk following Hematopoietic Cell Transplantation (HCT) in subjects with hematologic cancer. The proatherogenic consequences of this intervention include endothelial lesions caused by graft-versus-host disease and atherosclerosis acceleration resulting from immunosuppressive treatment (Inamoto *et al*., 2019). Many of the patients also displayed a pro-atherosclerotic lifestyle. In a study involving over 1000 patients who have received HCT, (Chow *et al*., 2011) reported a 300% greater risk for CVD events than in the controls. These results are consistent with earlier studies showing that 20% of patients who have undergone allogeneic HCT have displayed CVD during the following 20 years and presented with cardiac ischemia on average 10-15 years earlier, compared to controls (Rodgers *et al*., 2019).

Cancer in Atherosclerotic Patients: Prevalence and Outcomes

Although there is extensive evidence confirming the common substrate behind cancer and CVD, few contemporary studies have reviewed the incidence of cancer in patients with Acute Coronary Syndrome (ACS). A recent cohort study revealed a 3.1% (95% CI, 2.4-4.0) prevalence of neoplasms in subjects suffering from ACS within 33 months period. The most prevalent cancer types were lung, bladder, pancreatic, and colorectal cancer. The neoplasms appeared during a median time of 25 months (interquartile range, 12.0-56.0) and the main risk factors related to the development of neoplasms were smoking (HR = 2.68; 95% CI, 1.11-6.49; P = .03) and age (HR = 1.03; 95% CI, 1.01-1.06; P = .01) (Lange and Reinecke, 2022). The study revealed the greatest death rates among patients who developed a neoplasm during this period (64.2%), followed by those who already had been diagnosed with cancer by the time they were diagnosed with ACS (40.0%). In addition, over 50% of deaths were directly caused by cancer. As for cardiovascular mortality, the highest rates were reported among subjects with cancer already diagnosed at the time of ACS and not in those with incident neoplasms (Lucà *et al*., 2022). These results can be explained by the unavailability of aggressive treatment methods such as drug-eluting stents or revascularization in individuals with diagnosed cancer. The findings indicate that patients with neoplasms present in ACS or those who develop cancer after ACS diagnosis have an obviously different and more negative prognosis, highlighting that more precise therapy and follow-up strategies are required for such patients (Mohanty *et al*., 2017).

Although higher long-term mortality for noncardiovascular causes than for cardiovascular causes in individuals with ACS or chronic ischemia has been confirmed by a number of prospective and multicenter studies, only a few series have specifically assessed the influence of neoplasms. For instance, the SYNTAX trial reported a 4.3% noncardiovascular mortality rate in subjects with chronic ischemia who received angioplasty with a stent and 5.3% in patients who underwent surgical treatment. The corresponding rates for cancer mortality were 2.2 and 2.4% (Chi *et al*., 2021).

Targeted Therapeutic Strategies for Cancer Treatment in Atherosclerosis

Figure 1 we schematically present the main idea of targeting shared pathways of two diseases. Despite the abovementioned sequelae of some targeted treatment methods, other cancer therapies have been reported to ameliorate experimental atherosclerosis. For instance, Erlotinib, a directly acting Tyrosine Kinase Inhibitor (TKI) that suppresses the membrane-bound protein Epidermal Growth Factor Receptor (EGFR), is primarily used for solid cancer treatment and has also reduced atherosclerosis in Ldlr Knockout (KO) mice (Wang *et al*., 2019a). EGFR is involved in cell division, migration, and survival. Erlotinib prevents T-cell retention and activation in the plaques. The phenotype of mice who received Erlotinib treatment was recapitulated in irradiated Ldlr KO mice reconstituted with bone marrow from Cd4-Cre/EGFR$^{fl/fl}$, suggesting that EGFR in CD4þ T-cell contributed to the development of atherosclerosis. Thus, Erlotinib may be a therapeutic strategy aimed at reducing inflammation in CVD medicine (Brand *et al*., 2011).

In striking contrast to these findings, Erlotinib was observed to increase the prevalence of stroke and Myocardial Infarction (MI) in subjects with cancer in the pancreas. Though this mechanism of action might be partly due to previous platinum-based chemotherapy which could lead to a higher risk of thromboembolic events, further investigation of possible proatherogenic side effects of Erlotinib needs to be carried out in patients with atherosclerosis prior to Erlotinib therapy (Herrmann, 2020).

Bortezomib, ixazomib, and carfilzomib are proteasome inhibitors, widely used for multiple myeloma treatment. Although these drugs have few or no cardiovascular side effects, MI was reported in 0.8% of the subjects (Jayaweera *et al*., 2021). Early atherosclerosis and macrophage accumulation in the plaques, as well as MCP1 and IL6 plasma levels, were decreased in bortezomib-treated Ldlr KO mice, suggesting an improvement in inflammation. However, the drug aggravated the necrotic core and reduced the thickness of the fibrous cap in existing plaques, reducing plaque stability and thus aggravating atherosclerosis in mice (Tabas, 2010). Thus, proteasome inhibitors may have a favorable effect on early lesions, however, the detrimental impact on existing atherosclerosis compromises the feasibility of this approach. Further investigation of the cell-specific mechanisms of action is needed to exploit the full potential of proteasome inhibitors in treating CVD patients (Ramanathan *et al*., 2018).

Cardiotoxicity of Classic Anticancer Agents with a Focus on Atherosclerosis

A number of well-established chemotherapy medications such as methotrexate, paclitaxel, bleomycin, cisplatin, vinblastine, and other cytostatics have been demonstrated to increase the risk of ACS, angina pectoris and peripheral arterial disease (Han *et al*., 2019). The pathophysiology behind ACS includes pro-coagulation status and arterial thrombosis, hypotension, and vasospasms as well as impairments in vasodilation and protective functions of endothelium against thrombosis and inflammation. Cancer patients commonly display atherosclerotic lesions in the aorta and other major arteries. The onset of peripheral artery disease can happen during the first months of chemotherapy or several years after the therapy has been completed (Rajendran *et al*., 2013).

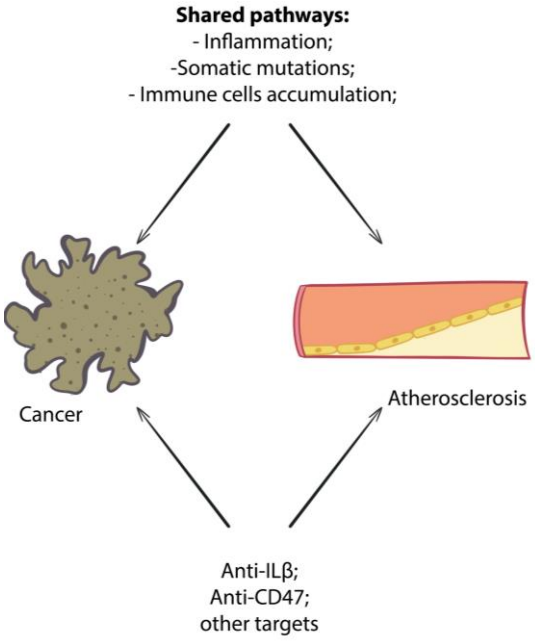

Fig. 1: Strategy of targeting atherosclerosis and cancer at once

Both acute and late proatherosclerotic effects of cisplatin have been extensively reviewed. The drug has been demonstrated to cause several side effects affecting the cardiovascular system, including hypomagnesemia, increased levels of von Willebrand factor, vasospasms, and higher thrombocyte aggregation. Platinum-based medication can have delayed side effects. For instance, cisplatin was still observed in blood 10-20 years after the therapy (Cameron *et al*., 2016). The substance could stimulate endothelium and contribute to the development of atherosclerosis throughout this period. It was also detectable in several different organs.

Cured cancer patients with a more negative cardiovascular profile receive special attention in regard to cisplatin. Patients administered a total dose of 850 mg cisplatin or higher presented with cardiovascular complications three times more often than those who only received surgical treatment (Gugic *et al*., 2017). Meinardi *et al*. (2020) evaluated delayed complications in 50-year-old or younger patients who have completed chemotherapy within the previous 10 years. 79% displayed hypercholesterolaemia while hypertension was observed in 39% of the subjects. Various vascular territories, including capillary beds, can be affected by cisplatin (Meinardi *et al*., 2020).

A Norwegian study by Sagstuen *et al*., estimated cardiovascular complications in approximately 1300 testicular cancer survivors who had received cisplatin treatment (Sagstuen *et al*., 2005). The median follow-up period was 11.2 years. The study reported a significantly higher risk for hypertension in cancer survivors compared with healthy controls following adjustment for age, body mass, and testosterone levels, odds ratio 1.4, 95% CI 1.2-1.7. The odds were highest among individuals administered with a total dose of 850 mg cisplatin or higher (odds ratio = 2.4; 95% CI, 1.4-4.0). Bleomycin and vinblastine have been reported to promote endothelial dysfunction (Morbidelli *et al*., 2016).

Cardiovascular Adverse Effects of Targeted Anticancer Agents with a Focus on Atherosclerosis

In comparison to classical chemotherapy, targeted agents have more specific mechanisms of action and aim at some particular molecules that can be observed on the surface or inside malignant cells. The two main types of such drugs are tyrosine kinase inhibitors (so-called small molecules) and monoclonal antibodies (Bukowski *et al*., 2020). Some of the target molecules and structures affected by this treatment are also involved in the physiological mechanisms of the organism and their suppression outside the tumor may have unfavorable consequences, one of the main side effects being cardiovascular toxicity (Mladěnka *et al*., 2018).

TKIs can contribute to atherogenesis in several different ways, including inhibition of angiogenesis and mitochondrial dysfunction. The latter results in lower Ca2+ and NO levels and higher release of Reactive Oxygen Species (ROS). TKI-related hypertension, dysfunction of endothelium and VSMCs as well as stimulation of inflammatory cytokines can also accelerate atherosclerosis (Hsu *et al*., 2021).

The use of anti-angiogenic therapy such as monoclonal antibodies targeting the Vascular Endothelial Growth Factor (VEGF) and TKI of the VEGF receptor has also been associated with hypertension. For instance, bevacizumab can promote acute coronary thrombosis because of its sequelae affecting endothelium and its pro-coagulative effect (Touyz *et al*., 2018).

A meta-analysis of several prospective studies involving approximately 5,000 patients who have received sunitinib for treatment of renal or other malignant neoplasms demonstrated that 22% of the subjects had hypertension, of which 7% had severe hypertension. At the same time, better treatment response was observed in patients who displayed hypertension during sunitinib therapy (Rini *et al*., 2011). Patients treated with sorafenib presented with slightly lower rates of hypertension and the highest hypertension rate was associated with axitinib in a study involving over 1900 patients. Hypertension was observed in 40% of the subjects, while the rate of severe hypertension was 13% (Rini *et al*., 2015). In addition to hypertension, TKI VEGFR therapy may promote myocardial infarction or ischemic heart disease and affect cardiac function. The long-term consequences of the treatment with VEGF inhibitors remain unknown. Some TKI, such as ponatinib and nilotinib, target Abl and some other proteins. Abl is

important for the functioning of endothelial cells. Thus, its suppression by TKI can result in vascular damage and accelerate atherogenesis (Cortes *et al*., 2016).

Cardiovascular Adverse Effects of Selected Hormonal Anticancer Treatment Methods

Studies assessing cardiovascular side effects of Gonadotropin Releasing Hormone (GnRH) agonists or Luteinizing Hormone Releasing Hormone (LHRH) agonists, such as leuprolide and goserelin, have become more relevant recently in light of Androgen Deprivation Therapy (ADT), predominantly in subjects with concurrent CVD risk factors (Freedland and Abrahamsson 2021). A recent observational study evaluated the cardiotoxicity of ADT in 73 196 prostate cancer patients. The study reported an increase in MI by 11%, cardiac ischemia by 16%, and sudden cardiac arrest by 16% in subjects who received GnRH agonist treatment compared to controls who had no such treatment. Several other studies involving ADT-treated individuals observed an increased rate of such complications as MI, thrombosis, stroke, and others (Boland *et al*., 2021). ADT can affect the cardiovascular system through a variety of mechanisms. The indirect side effects include dyslipidemia, obesity, impaired insulin metabolism, and inflammation. The direct adverse action in the expression of receptors for androgen, GnRH, and Follicle-Stimulating Hormone (FSH) by cardiomyocytes. As of now, the risk of ADT-related coronary artery disease has not been reviewed in any prospective studies (Keating *et al*., 2010).

In a meta-analysis of 13 studies carried out by Carneiro *et al*., ADT treatment of prostate cancer patients was associated with arrhythmias, stroke, thrombosis, and heart failure as well as AMI (Carneiro *et al*., 2017).

Cardiotoxicity of GnRH agonists in comparison with GnRH antagonists is the focus of several ongoing trials. The effects of abiraterone acetate and enzalutamide (androgen-receptor targeted agents) in the therapy of castrate-resistant prostate cancer are also a subject of current research (Challa *et al*., 2021).

Aromatase inhibitors such as exemestan, anastrozole, and letrozole are substances that suppress the conversion of androgens to estrogen and are used in breast cancer treatment. These agents can affect lipids in several different ways. A meta-analysis of several studies involving 30,000 patients in total revealed that long-term exposure to aromatase inhibitors can result in a higher risk of hypercholesterolemia in comparison to treatment with anti-estrogen drug tamoxifen (Tenti *et al*., 2020).

Cardiovascular Adverse Effects of Radiotherapy

Radiotherapy (RT) is a well-known factor contributing to the development of carotid and Coronary Artery Disease (CAD). Radiation doses over 50 Gy have been shown to cause premature atherosclerosis and CAD that can manifest with neurological symptoms. The effects of medium doses (30-50 Gy) on the development of atherosclerosis have not been fully identified yet (Mitchell *et al*., 2021).

Most existing trials investigating the consequences of RT are based on outdated treatment techniques while modern radiation methods allow to minimize the damage of healthy tissues. RT may have proatherogenic effects through various pathways, including lysosome activation, migration of macrophages, lymphocytes, and monocytes into the vessel walls as well as endothelial damage (Sárközy *et al*., 2021). Smoking, diabetes, negative lipid profile, and hypertension can aggravate these effects. Several studies have reviewed long-term CVD-related side effects in patients treated with RT against Hodgkin lymphoma and breast cancer (Mehta *et al*., 2016; Wang *et al*., 2019b).

The cardiotoxic effects of RT are rarely observed during the treatment period and are usually manifested later, following a latent period of over a year. RT-induced cardiologic damage can develop over time after the treatment has been completed. Cardiotoxicity is positively associated with the radiation dose and a significant increase in cardiovascular complications has been predominantly reported after 35 Gy. However, even lower doses below 20 Gy can affect the heart, particularly in individuals with other existing risk factors (Díaz-Gavela *et al*., 2021).

Patients with RT-related Acute Coronary Syndrome (ACS), especially older individuals and childhood cancer survivors often present with silent ischemia. This condition lacks typical symptoms such as chest pain because of RT-related autonomous dysfunction and can be manifested through nausea and vomiting (Costa *et al*., 2021). The risk of MI during the period of 30 years after the completion of RT is 10-13%. Ischemic heart disease can be diagnosed 10-15 years after the treatment (Jacobse *et al*., 2019). In a prospective study Girinsky and Ghalibafian observed 179 Hodgkin lymphoma survivors, including those who received mediastinal RT, during a follow-up period of 0.5-40 years after the completion of the treatment (median 9.5 years) (Girinsky and Ghalibafian, 2007). The authors used coronary angiography and reported a 15% risk of coronary artery dysfunction within the first five years after the therapy and a 34% risk following 10 or more years after the treatment. 5,5% of the patients presented with severe stenosis requiring bypass or stent. Total radiation dose and the presence of cardiologic comorbidities are independent risk factors.

The cohort study carried out in Oxford by Darby *et al*., assessed the occurrence of coronary complications in subjects with breast cancer treated with RT during the period 1958-2001 (Darby *et al*., 2013). The study reported that the radiation dose is directly associated with ischemic

complications, the risk increasing linearly by 7.6% with each Gray of radiation to the cardiac region. Old radiation methods were used in almost all patients. The increased risk was observed starting the first five years after RT and prevailed within 30 years following RT. A recent study involving subjects who survived breast cancer treated with RT between 2005 and 2008 reported a 16.5% increase in the risk of complications for each Gray of radiation delivered to the heart (Simonetto *et al*., 2021).

Higher rates of cardiac ischemia have also been reported in testicular cancer survivors who received mediastinal RT. (Van der Belt-Duseboat *et al*., 2007). revealed a 3.7-fold (95% CI, 2.2-to 6.2-fold) increase in MI risk in patients treated with RT of mediastinum compared to those who only had surgery. However, no correlation between infra-diaphragmatic irradiation and higher MI risk was reported. The Standardized Incidence Ratio (SIR) for MI was markedly higher in nonseminoma patients younger than 45 years (SIR = 2.06) and 45-54 years (SIR = 1.86) (Van der Belt-Duseboat *et al*., 2007).

Higher hyperlipidemia rates were reported in patients who survived testicular cancer, suggesting that RT and/or chemotherapy also affect the lipid profile (de Jesus *et al*., 2022).

Cardiotoxic Consequences of Allogeneic Stem Cell Transplantation (ASCT)

ASCT has been associated with such conditions as dyslipidemia, arterial hypertension, and impaired glucose metabolism. Immunosuppressive therapy and RT can aggravate these effects (deFilipp *et al*., 2017). A retrospective trial by Blaser *et al*., (2011) evaluated adverse effects of ASCT in 761 patients who received the treatment between 1998 and 2008 and survived 100 or more days. Within the first two years following the treatment, hypercholesterolemia was observed in 73% of the patients, and 73% presented with hypertriglyceridemia (Blaser *et al*., 2011).

Considering stem cell-based therapies, it is worth mentioning that besides the regenerative advantages, various actions, such as higher activity of the mTOR pathway promoting autophagy, were observed (Hu and Li, 2018). Moreover, hypoxic pre-cultured MSCs exhibited a pro-senescent cell profile and enhanced activity of superoxide dismutase leading to suppressed apoptosis (Baranovskii *et al*., 2022).

Conclusion

Numerous trials have confirmed the proatherogenic effects of targeted cancer therapies. However, the long-term sequelae of these strategies have not been completely understood yet due to the fact that the majority of them have been used in the past ten years (Pucci *et al*., 2019). Therefore, a more thorough monitoring and examination of potential cardiovascular complications may shed light on the mechanisms of the adverse effects. Although the abovementioned studies in experimental atherosclerosis have definitely provided valuable findings in this field, clinical practice appears to be far more complex due to the interplay between targeted therapy and other factors such as classical cancer treatment, particularly chemotherapy, exhibiting a synergistic proatherogenic effect (Gebbers, 2007). This may explain some discrepancies between clinical and experimental trials. Thus, a combined approach should be used in further experimental studies in order to reveal the precise pathophysiological pathways underlying the cardiovascular toxicity of the agents.

Well-known risk factors, including dyslipidemia, diabetes, and increased blood pressure contribute to atherosclerosis-related side effects, while proper cardiovascular risk management can mitigate the risk of adverse events. The development of new treatment practices and drugs increases the number of long-term cancer survivors, thus increasing the prevalence of delayed cardiovascular complications in these patients (Narayan and Ky, 2018). The clinical decision-making is complicated because the possible side effects of targeted treatment may affect the subject's quality of life, while therapy withdrawal may result in cancer-induced death. The development of optimal preventive and therapeutic strategies requires therefore a close interdisciplinary collaboration and further research.

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Ethics

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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