Do statins ameliorate radiation-induced cardiovascular toxicity?

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Abstract

Introduction

Radiation therapy has for long been implicated as a cause of cardiovascular morbidity and mortality with early reports of vessel injury dating back to the late 1800s. On the other hand, statins are a class of drugs used to lower cholesterol levels. We aimed to evaluate whether statins ameliorate radiation-induced vessel injury by decreasing the atherosclerotic plaque formation or not.

Hypothesis

We hypothesize that statins may be able to decrease the radiation-induced atherosclerotic plaques in the coronary arteries by protecting vascular endothelium and decreasing oxidative stress.

Evaluation of hypothesis

The pathology and pathophysiology of coronary artery disease after radiotherapy appear to differ, however, only slightly from those of coronary artery disease in the general population. Numerous studies of radiation injury show that the injury of endothelial cells is the key point in most tissues. Radiation also causes a loss of endothelial thromboreistance through the loss of thrombomodulin and increased expression of tissue factor, which promote inflammatory processes. The morphologic changes associated with radiation-induced arterial disease are identical to those found in spontaneous atherosclerosis. On the other hand, statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase that plays a central role in the production of cholesterol in the liver. Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. The commonly used lipid-lowering compounds, statins, in addition to their effect on cholesterol, have many cholesterol-independent, vasculoprotective, so-called pleiotropic effects, many of which counteract the effects of radiation on endothelial cells. The non-lipid related effects of inhibitors of statins counteract many of the radiation-induced changes in vascular endothelium.

Conclusion

We would use 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors to decrease radiation-induced atherosclerotic plaques in the coronary vessels. This idea would be important and has implication for future use.

Introduction

Radiation-induced cardiovascular diseases are major dose-limiting factors during mediastinal irradiation. The estimates of relative risk of fatal cardiovascular events after mediastinal irradiation for Hodgkin’s disease range between 2.2 and 7.2 and those after irradiation for left-sided breast cancer range from 1.0 to 2.2. Risk is life long, and absolute risk appears to increase with length of time since exposure. Radiation-induced cardiovascular disease may in fact be progressive.

Radiation-induced changes in blood vessels have been known since Gassmann1 described the histologic picture of X-ray damage in small blood vessels of the skin. A common pathophysiologic pathway of damage to the blood vessels appears to be microcirculatory damage. There are many studies showing that the injury of endothelial cells is the key point in most tissues, which ultimately leads to fibrosis or necrosis. The sequence of endothelial injury, cell detachment, thrombosis and fibrosis results in significant tissue injury that often limits radiation oncologists in attempting to deliver curative doses to a nearby tumour. Increased permeability, blood flow and perfusion pressure eventually end with oedema. Further injury results in the detachment of the basement membrane and formation of microthrombi, which leads to further reduction in the blood flow.

The endothelial injury activates the coagulation cascade and fibrocytes, which eventually cause oxidative stress. At the end of this process, atherosclerotic plaques are morphologically the same as spontaneous plaques of hyperlipidemic patients.

The commonly used lipid-lowering compounds, statins, are well established as a long-term strategy to reduce death and ischaemic cardiovascular events in patients with stable coronary artery disease.10-12 Major mechanisms by which lipid lowering is thought to improve outcome include prevention of the development of new atherosclerotic lesions and stabilization of existing atherosclerotic plaques. In addition to their effect on cholesterol, statins...
have many cholesterol-independent, vasculoprotective, so-called pleiotropic effects; many of which counteract the effects of radiation on endothelial cells. One of the most prominent pleiotropic effects is upregulation of trombomodulin (TM), and endothelial cell glycoprotein that, as one of its effects, activates the natural anticoagulant protein C. This paper discusses whether statins ameliorate radiation-induced cardiovascular toxicity.

**Hypothesis**

We hypothesize that statins may be able to influence the adverse effects of radiation in the coronary arteries by decreasing atherosclerotic plaque formation and oxidative stress.

**Evaluation of hypothesis**

Numerous studies on radiation-induced toxicity show that endothelial cell injury is the key point in most tissues. The sequence of physiological events, including endothelial injury, cell detachment, thrombosis and fibrosis results in significant tissue injury that often limits radiation oncologists in attempting to deliver curative doses to a nearby tumour. Fajardo and Stewart have demonstrated that damage to the myocardium develops through three phases of injury. The acute inflammation phase occurs about 6 hours after radiotherapy, and a neutrophilic infiltrate develops involving all layers of the vessel. During the second phase, also known as the latent phase, a slight progressive fibrosis begins about 2 days after exposure. However, electron microscopy of the myocardial capillary endothelial cells demonstrates progressive damage leading to the obstruction of the lumen and thrombi of fibrin and platelets. Although healthy endothelial cell replication occurs in the vicinity, it is generally inadequate and an inevitable ischaemia leads to progressive fibrosis. Animals begin to die at approximately the 70th day due to extensive fibrosis. The hallmark of this late stage is extensive fibrosis.

Atherosclerosis is an inflammatory and degenerative disease of arterial walls and the pathogenesis of early atherosclerosis involves the accumulation of lipoprotein aggregates in the subendothelial space, upregulation of specific endothelial adhesion molecules and chemokines, monocyte recruitment and subsequent foam cell formation. Inflammation has an important role in all stages of atherosclerosis. Deficiencies of P-selectin, E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) have been shown to decrease atherosclerosis in hypercholesterolemic mice.

On the other hand, radiation has been shown to upregulate endothelial cell adhesion molecules, such as ICAM-1, VCAM-1, P-selectin and platelet endothelial cell adhesion molecule-1 (PECAM-1), leading to increased leukocyte-endothelial cell interactions and leukocyte transmigration. Radiation also causes a loss of endothelial thromboresistance through the loss of TM and increased expression of tissue factor, which promote inflammatory processes. TM controls the balance between the procoagulant activities of thrombin (fibrin generation and platelet activation) and anticoagulant activity. Radiation has been shown to increase permeability of endothelial cells by induction of inflammatory response and thrombotic pathways, including increased production and release of von Willebrand factor (vWF). The increase in vWF deposition in the irradiated endothelium is also indicative of thrombotic endothelial cell damage. This could increase vascular permeability and, combined with hypercholesterolemia, lead to lipid accumulation, thus stimulating atherogenesis.

Statins [or 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) inhibitors] are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase that has a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases, and statins are therefore used in the prevention of these diseases. Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. The commonly used lipid-lowering compounds, statins, in addition to their effect on cholesterol, have many cholesterol-independent, vasculoprotective, so-called pleiotropic effects, many of which counteract the effects of radiation on endothelial cells. The non-lipid related effects of inhibitors of statins counteract many of the radiation-induced changes in vascular endothelium. Statins reduce isoprenylation of small guanosine-5’-triphosphate (GTP)-binding proteins (e.g. Rho, Ras, Rac) and influence many metabolic and physiological processes, including cell proliferation, apoptosis, immune function, inflammation, coagulation and fibrinolysis. The endothelium is a major effector cell compartment for the pleiotropic effects of statins. Statins increase endothelial NOS (eNOS) activity, decrease oxidative stress, down-regulate expression of tissue factor (TF), endothelin-1 and plasminogen activator inhibitor-1 (PAI-1), and upregulate prostacyclin, tissue-type plasminogen activator (TPA) and endothelial TM. Statins exert anti-inflammatory and anti-thrombotic effects on irradiated endothelial cells in vitro and reduce lung injury in mice after irradiation of the chest.

**Empirical data**

Radiation has been shown to increase vascular permeability by induction of inflammatory response and thrombotic pathways which may eventually lead to lipid accumulation, thus stimulating atherogenesis. On the other
hand, statins have anti-inflammatory and anti-thrombotic effects on the irradiated endothelial cells\textsuperscript{14}.

**Consequences of hypothesis**

The primary basic mechanism behind the radiation-induced cardiovascular injury seems to be the endothelial damage. Radiation causes endothelial damage by increasing vascular permeability and fibrin formation. Therefore, radiation induces thrombotic pathways. It is well known that statins also have pleiotropic effects, many of which counteract the effects of radiation on endothelial cells. Statins reduce isoprenylation of small GTP-binding proteins (e.g. Rho, Ras, and Rac) and influence many metabolic and physiological processes, including cell proliferation, apoptosis, immune function, inflammation, coagulation and fibrinolysis. The non-lipid related effects of inhibitors of statins counteract many of the radiation-induced changes in vascular endothelium. Therefore, statins may reverse radiation-induced atherosclerotic plaque formation in the coronary arteries.

**Discussion**

As the number of cancer survivors grows because of advances in cancer treatments, it has become increasingly important to assess cardiovascular complications of mediastinal irradiation. The majority of radiation-induced cardiovascular disease has been reported in patients previously treated for Hodgkin's disease. As these patients tend to be young, they generally live long enough to develop delayed sequelae, and thus the potential loss of productive life years is large. On the other hand, during the treatment of lung cancer, we usually hesitate to escalate radiation dosage because of tolerance of nearby tissues although higher doses were found to be more effective in some patients. Radiation-induced vascular injury including coronary arteries is the major dose-limiting factor for radiation oncologists in an attempt to deliver curative doses to a nearby tumour.

The pathophysiological manifestations of radiation toxicity in the blood vessels and other normal tissues are a result of a complex interaction among different components and cell types, in which endothelial injury seems to have a crucial role. We hypothesized that statins due to their vasculo-protective properties may ameliorate radiation-induced vascular injury. The toxic effects of radiotherapy and vasculoprotective effects of statins use the same molecules in some parts of their mechanisms.

The pathology and pathophysiology of coronary artery disease after radiotherapy appears to differ only slightly from that of coronary artery disease in the general population. This is demonstrated by the location of lesions and their morphology. An autopsy study of 16 subjects with radiation-associated heart disease and 10 controls demonstrated that smooth muscle in the media tended to be greatly decreased in those treated with radiotherapy, but not in those with typical coronary artery disease\textsuperscript{32}. Media and adventitia were also more densely thickened with fibrous tissue compared to the generic coronary lesion\textsuperscript{32}. These same investigators, as well as others, found intimal plaques to be largely composed of fibrous tissues with little lipid present\textsuperscript{32,33}; however, others have found them to be quite lipid-laden as well as fibrotic\textsuperscript{34}. Therefore, although certain features, such as plaque location and replacement of smooth muscle with extensive fibrosis, are suggestive of disease caused by irradiation, definitive histological discrimination of a radiation-induced lesion from typical atherosclerosis may be difficult in any one particular case.

Blaha and Martin\textsuperscript{25} studied the mechanism of action of the statins, and they divided statin mechanisms into three non-mutually exclusive paradigms. The first paradigm also called “lipoprotein load hypothesis” states that statins work primarily by reducing the circulatory burden of all apolipoprotein B-containing lipoproteins. The second paradigm, “systemic inflammatory hypothesis” states that statins preferentially work by reducing systemic subclinical inflammation, such as that seen in rheumatoid arthritis, which promotes the propagation of early atherosclerosis. It is also well known that radiation induces inflammatory processes that begin after approximately 6 hours of radiotherapy. The second paradigm supports our hypothesis. The third paradigm is known as “plaque modulation hypotheses” and it suggests that statins work predominantly by changing the characteristics of early atherosclerotic plaque, including delipidation, regression, reducing plaque-level inflammation and plaque stabilization. This paradigm also supports our hypothesis.

In a preclinical study, Wang et al.\textsuperscript{14} examined whether administration of simvastatin ameliorates radiation-induced intestinal injury via a protein C-independent mechanism. They demonstrated that simvastatin ameliorated radiation-induced intestinal injury. The authors suggested that statins should undergo clinical testing as a strategy to minimize side effects of radiotherapy on the normal tissues. It is clear that the intestine has an endothelial structure just like vascular structure. The mechanism of the radiation-induced intestinal injury was explained as the increased expression of adhesion molecules and chemokines and loss of endothelial thromboreistance through the loss of TM and increased expression of tissue factor and WF and upregulation of the thrombin receptor, proteinase-activated receptor 1 (PAR 1). This mechanism is similar to the mechanism of radiation on the vascular structure which uses the vasculo-protective properties of the statins.
Conclusion

The available data shows that the mechanisms of action of radiotherapy and statins on the vascular structure are just opposite to each other. On the other hand, the molecular mechanisms of their effects use similar molecules. Therefore, statins may have radioprotective effects on the vascular structure. In summary, according to the hypothesis mentioned above, we may use HMG-CoA reductase inhibitors to ameliorate radiation-induced atherosclerotic plaques in the coronary arteries. This idea may be important and has implication for future use.

Abbreviations list

eNOS, endothelial NOS; GTP, guanosine-5’-triphosphate; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-CoA reductase; ICAM-1, intercellular adhesion molecule-1; PAI-1, plasminogen activator inhibitor-1; PAR-1, proteinase-activated receptor-1; PECAM-1, platelet endothelial cell adhesion molecule-1; TF, tissue factor; TM, thrombomodulin; tPA, tissue-type plasminogen activator; VCAM-1, vascular cell adhesion molecule-1; vWF, Von Willebrand factor.

References


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Hypothesis

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