Diseases and Treatments as Aging Accelerators

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Disclosures

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Increasing Cancer Survivorship

CV Disease is the Leading Cause of Non-Cancer Related Death in Cancer Survivors
Cancer Treatment Associated Cardiotoxicity

- **Hypertension**
  - Tyrosine kinase inhibitors (VEGFi), proteosome inhibitors

- **Ischemia**
  - 5-FU/capecitabine, nilotinib, ponatanib, radiation, immunomodulators

- **Ventricular Dysfunction**
  - Anthracyclines, HER-2 blockers, MEK inhibitors, osimertinib, immunotherapy

- **Arrhythmias**
  - Bruton tyrosine kinase inhibitors, cisplatin, crizotinib, immunotherapy, radiation

- **Venous Thrombosis**
  - Tyrosine Kinase Inhibitors, immunomodulators, endocrine therapy
Outline

• Pathophysiology of vascular aging

• Potential mechanisms by which cancer therapies may accelerate vascular aging

• Potential therapeutic targets to mitigate cancer-therapy associated vascular aging
Characteristics of Vascular Aging

• Increased arterial stiffness
  • ↑SBP and pulse pressure
  • LV hypertrophy
  • End-organ damage via ↑ pulsatile flow

• Endothelial dysfunction
  • Impaired vasodilation
  • Thrombosis
  • Inflammation
  • Abnormal mitochondrial function and cellular energy metabolism
Mechanisms of Anthracycline Cardiotoxicity
Doxorubicin Increases Vascular Stiffness
Doxorubicin Promotes Endothelial Dysfunction

Aging and Cancer 2021;2:45-69.
Characteristics of Vascular Aging

- Decreased responsiveness to angiogenic stimuli
- Altered expression of genes regulating angiogenesis
- Microvascular rarefaction → ↓tissue oxygenation → ↓mitochondrial activity → metabolic perturbations → multi-organ dysfunction

VEGF and VEGF Inhibitors in Cancer

Decreased VEGF Signaling Contributes to Vascular Aging
Restoration of VEGF Signaling Promotes Healthy Aging and Longevity

Science 2020; 373:533
Inflammation as Mediator of Cancer and CVD

CANTOS Trial: MI + CRP ≥ 2 mg/L; IL-1β antagonist; Recurrent CV Events

Non-fatal MI, non-fatal stroke or CV death

Incident Lung Cancer

Damage Associated Molecular Patterns and Inflammation

<table>
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<th>DAMP</th>
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<th>Treatment</th>
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### Potential Therapeutic Targets To Reduce Negative Impact of Oxidative Stress

#### Therapeutics | Description
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**Mitochondria-targeted compounds**
MitoQ | Mitochondria-targeted antioxidant
SS-31 | Mitochondria-targeted peptide
Urollithin-A | Gut microbiome-derived mitophagy activator
Dexrazoxane | Mitochondria DNA damage inhibitor

**NAD⁺ boosting compounds**
Nicotinamide mononucleotide | NAD⁺ salvage pathway activator
Nicotinamide riboside | NAD⁺ salvage pathway activator

**CD-38 inhibitors**
Apigenin | Food-derived (flavonoid) CD-38 inhibitor
Daratumumab | Synthetic CD-38 inhibitor
Thiazologuin(az)olin(on)e | Synthetic CD-38 inhibitor

**Sirtuin activators**
Resveratrol | Food-derived (plant polyphenol) sirtuin activator
SRT1720 | Synthetic sirtuin activator

**PARP inhibitors**
Nicotinamide | Inhibits PARP and increases NAD⁺ bioavailability
Rucaparib | Inhibits PARP and increases NAD⁺ bioavailability

**AMPK activator**
AICAR | AMP analog (Increases circulating AMP)

**mTOR inhibitor**
Rapamycin | Immunosuppressive compounds that inhibit mTOR

**PRRI agonists**
Calorie restriction, aerobic exercise

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Summary

• Cardiovascular disease is a significant cause of morbidity and mortality in cancer survivors
• Many cancer therapies are associated with cardiotoxicity
• Cancer therapies can lead to increased oxidative stress and inflammation that may promote vascular aging
• A better understanding of these mechanisms is needed to identify therapeutic targets to reduce cancer therapy associated cardiotoxicity and potentially reduce adverse impact on vascular aging