Cardiovascular Complications of Novel Anticancer Agents

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3000 B.C. - 1890
Surgical Treatments
Surgical treatment or cauterization of tumors as the only therapeutic option

1900
Radiotherapy
Marie and Pierre Curie started to treat tumors by using X-Rays

1940
Chemotherapy
Development of antitumor drugs for the treatment of hematological and solid tumors

1980
Targeted Therapy
Tyrosine Kinase Inhibitors and Monoclonal Antibodies directed to specific tumors and molecular alteration

2010
Checkpoint Inhibitors
Use of Monoclonal Antibodies able to stimulate the immune system against cancers

Oncology Patient Webinar
VALENCIA CORDOVA (CNS) 2019
A Retailers Consultancy
ANTINEOPLASTIC DRUGS

CHEMOTHERAPY

Cytotoxic agents which destroy or inhibit the growth and division of malignant cells in the treatment of cancer.

IMMUNOTHERAPY

Treatment of disease by inducing, enhancing, or suppressing an immune response.

TARGETTED THERAPY

A form of molecular medicine, targeted therapy blocks the growth of cancer cells by interfering with specific targeted molecules needed for carcinogenesis and tumor growth.

How Does Immunotherapy Work?

Tumor cells bind to T-cells to deactivate them.

Immunotherapy drugs can block tumor cells from deactivating T-cells.
G1 - Growth
S - DNA synthesis
G2 - Growth and preparation for mitosis
M - Mitosis (cell division)
1. Epipodophyllotoxin Derivatives
   - etoposide
   - teniposide
2. Miscellaneous
   - bleomycin

Topoisomerase-1 inhibitors
   - topotecan
   - irinotecan

1. Antimetabolites
   a. Folate Analogs
      - methotrexate
   b. Purine Analogs
      - cladribine
      - fludarabine
      - mercaptopurine
      - pentostatin
      - thioguanine
   c. Pyrimidine Analogs
      - capecitabine
      - cytarabine
      - gemcitabine
      - floxuridine
      - fluorouracil
2. Miscellaneous
   - hydroxyurea

1. Hormonal Drugs
2. Antineoplastic Enzymes
   - asparaginase
   - pegasparagase

Taxanes
   - docetaxel
   - paclitaxel

Vinca Alkaloids
   - vinblastine
   - vincristine
   - vinorelbine
PATHOPHYSIOLOGY

- increases the vasoconstriction mediated by endothelins resulting in **hypertension and increased cardiac afterload**.
- Reduced myocardial perfusion can reduce myocardial contractility and lead to both **ischemia and heart failure**.
- induces **myocyte necrosis**, with surviving myocytes undergoing hypertrophy.
- Acceleration of **atherosclerosis** potentially disruption of endothelial cell homeostasis by increase in mitochondrial superoxide generation, resulting in **reduced nitric oxide** availability and decreased proliferation.
- **Downstream endothelial cell apoptosis, plaque erosions, and acute arterial thrombotic events.**
Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF) that inhibits binding of the normal VEGF ligand to its receptor.

The approval of bevacizumab for:
- metastatic colorectal cancer (mCRC)
- metastatic non-squamous non-small cell lung cancer (NSCLC)
- renal cell carcinoma (RCC)
- ovarian cancer
- cervical cancer
- and glioblastoma multiforme (GBM).
Multiple orally active tyrosine kinase inhibitors (TKIs) that block angiogenesis by inhibiting the actions of VEGF and other growth factors (eg, platelet-derived growth factor) including:

- sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib, axitinib, ponatinib, lenvatinib, and regorafenib.

Approval for:
- RCC, hepatocellular cancer (HCC), gastrointestinal stromal tumors (GIST), thyroid cancer, pancreatic neuroendocrine tumors (PNET), soft tissue sarcomas (STS), refractory chronic myelogenous leukemia (CML), and refractory mCRC both in the United States and Europe.
CLASS SIDE EFFECTS OF ALL VEGF INHIBITORS

- Hypertension
- Arterial and venous thromboembolism
- Left ventricular dysfunction and myocardial ischemia
- Aortic dissections and aneurysms

VEGF TYROSINE KINASE INHIBITORS:
- Prolongation of the QTc interval and cardiac arrhythmias
Non-chemotherapeutic factors
1. Prior underlying substrate for arrhythmias
2. Post cancer surgery arrhythmias
3. Radiation induced pericarditis/atherosclerosis
4. Adjuvant medications – e.g. Antiemetics

Direct cardiac involvement
1. Primary cancer
2. Metastasis to heart
3. Cardiac amyloidosis

Electrolyte disturbances
1. Vomiting
2. Diarrhea from colitis
3. Drug induced imbalance (amsacrine, cetuximab, cisplatin and necitumumab)

Myocardial ischemia
- 5-FU/Capecitabine
- Cisplatin
- Bevacizumab
- PKI

Myopericarditis
- Cisplatin
- Checkpoint inhibitors

HA release causing SB
- Paclitaxel

Systolic dysfunction
- Anthracyclines
- Her2/ner inhibitors
- Proteosome inhibitors

Effects on cardiac myocytes
1. hERG blockade - ATO, PKI
2. Abnormal calcium homeostasis – Taxanes, ATO, AC
3. Mitochondrial injury - Sunitinib, AC
4. Cardiac apoptosis – Sorafenib, antimetabolites, AC
5. Inhibition of PI3K - PKI
Cancer immunotherapy

Active
- Antigen dependent
  - Therapeutic vaccines
    - Cellular onco-vaccines
    - Dendritic cells vaccines
    - Protein/Peptide based vaccines
    - DNA vaccines
    - Vaccines targeting TAAs

- Antigen independent
  - Modulating T cell function
    - Immune checkpoint inhibitors:
      - Anti-CTLA-4 Ab
      - Anti-PD-1 Ab
      - Anti-PD-L1 Ab

Passive
- Anti-tumor monoclonal antibody
- Adoptive cell transfer
  - TCR engineering
  - CAR T cells
  - TILs infusion
- Enhancing immune cell function
  - Cytokines:
    - IL-2
    - IFN-α
Application of immune checkpoint inhibitors (ICIs)

T-Cell activation/cytotoxic factors

Immune-related adverse events (IRAEs) or immune-related adverse reactions (IMARs)
Any organ in the gastrointestinal, hepatic, endocrine, pulmonary, cardiac, renal, ophthalmological, and nervous systems

Clinical and subclinical signs/symptoms
Myocarditis/myocyte damage
Systolic and diastolic dysfunction and HFpEF
Heart failure and sudden cardiac death
Ipilimumab; Myocardial fibrosis, Pericarditis, Cardiomyopathy with takotsubo-like syndrome, Myocarditis, Heart failure, Myocarditis/CHF

Nivolumab; Myocarditis

Pembrolizumab; Myocarditis, Cardiovascular toxicities, Acute heart failure

Atezolizumab; Cardiac failure, Myocarditis

Durvalumab; Myocarditis

Avelumab; Autoimmune myocarditis

Anti-LAG-3; Tachycardia, Hypotension
- Myocarditis
- pericarditis
- arrhythmias
- impaired ventricular function with heart failure and vasculitis.
- VTE?

ESPECIALLY COMBINATION THERAPY
TROPONIN?
### Conventional Chemotherapies

<table>
<thead>
<tr>
<th>Arhythmia</th>
<th>Cardiomyopathy</th>
<th>Arterial vascular disease</th>
<th>Venous thromboembolism</th>
<th>Pulmonary hypertension</th>
<th>Systemic hypertension</th>
<th>Pericardial disease</th>
<th>Valvular heart disease</th>
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- **Anticancer drugs** (taxol, doxorubicin, vinblastine)
- **Alkylating agents** (cyclophosphamide, melphalan)
- **Antimetabolites** (5-fluorouracil, capecitabine, cytarabine)
- **Microtubule-binding agents** (paclitaxel)
- **Platinum-based therapy** (cisplatin)
- **Antibiotics** (bleomycin)
- **Immunomodulatory drugs** (thalidomide)

### Targeted Agents

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<tr>
<th>Proteasome inhibitors</th>
<th>HDAC inhibitors</th>
<th>CDK4/CDK6 inhibitors</th>
<th>PI3K inhibitors</th>
<th>mTOR inhibitors</th>
<th>c-RAF inhibitors</th>
<th>HER2 inhibitors</th>
<th>VEGF inhibitors</th>
<th>BCR-ABL1 inhibitors</th>
<th>BTK inhibitors</th>
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- **HDAC inhibitors** (vernonstat)
- **CDK4/CDK6 inhibitors** (palbociclib)
- **mTOR inhibitors** (Everolimus)
- **HER2 inhibitors** (pertuzumab, trastuzumab)
- **VEGF inhibitors** (bevacizumab, sunitinib)
- **BCR-ABL1 inhibitors** (dasatinib, nilotinib, ponatinib)
- **BTK inhibitors** (ibrutinib)
- **ALK inhibitors** (crizotinib, ceritinib, crizotinib)
- **BRAF inhibitors** (vemurafenib)
- **MEK inhibitors** (binimetinib, cobimetinib, trametinib)

### Immunotherapies

- **Immune checkpoint inhibitors**
- **CAR-T cell therapy**

### Other Therapies

- **Radiation therapy**

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**Fig. 1** Outline of cardiovascular toxic effects associated with cancer therapies. Numerous cancer therapies have
Thank you