Immune Checkpoint Inhibitors in Heart or Lung Transplantation: Early Results from a Registry Initiative

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Disclosures

- A. Daud – none
- M. Mehra – personal fees from Abbott, Medtronic, Janssen, Bayer, Portola, FineHeart, NuPulseCV, Leviticus, Mesoblast, Triple Gene, outside the submitted work
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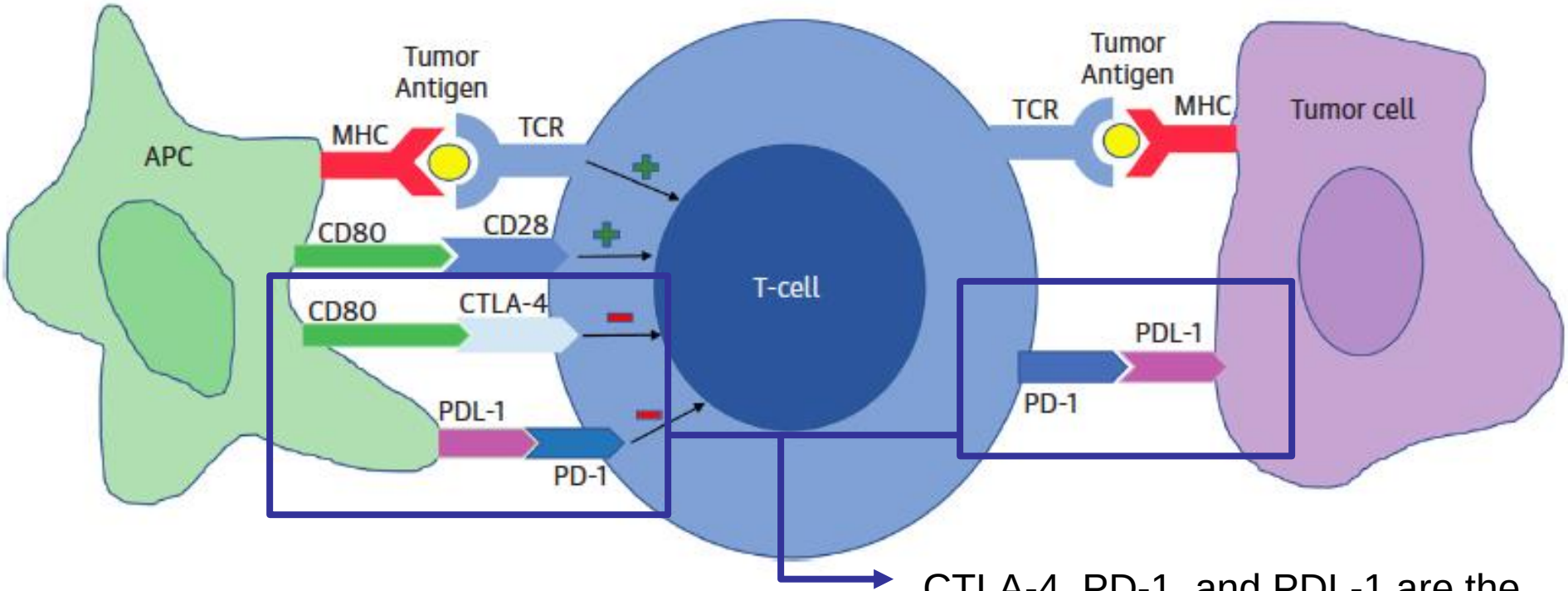
Background

- The immune system uses *checkpoints* to differentiate between self and non-self
  - Checkpoints can activate or suppress immune responses
- Cancer cells use this mechanism to evade the immune system and proliferate
- Advances in immunotherapy have led to development of drugs that inhibit these *checkpoints* and use immune system to target cancer cells
- Immune Checkpoint Inhibitors (ICIs) are therapies for certain cancers that do not respond to traditional chemotherapy
- However, ICIs are associated with immune-related adverse events
  - Myocarditis, endocrinopathies, pneumonitis, enteritis, etc.

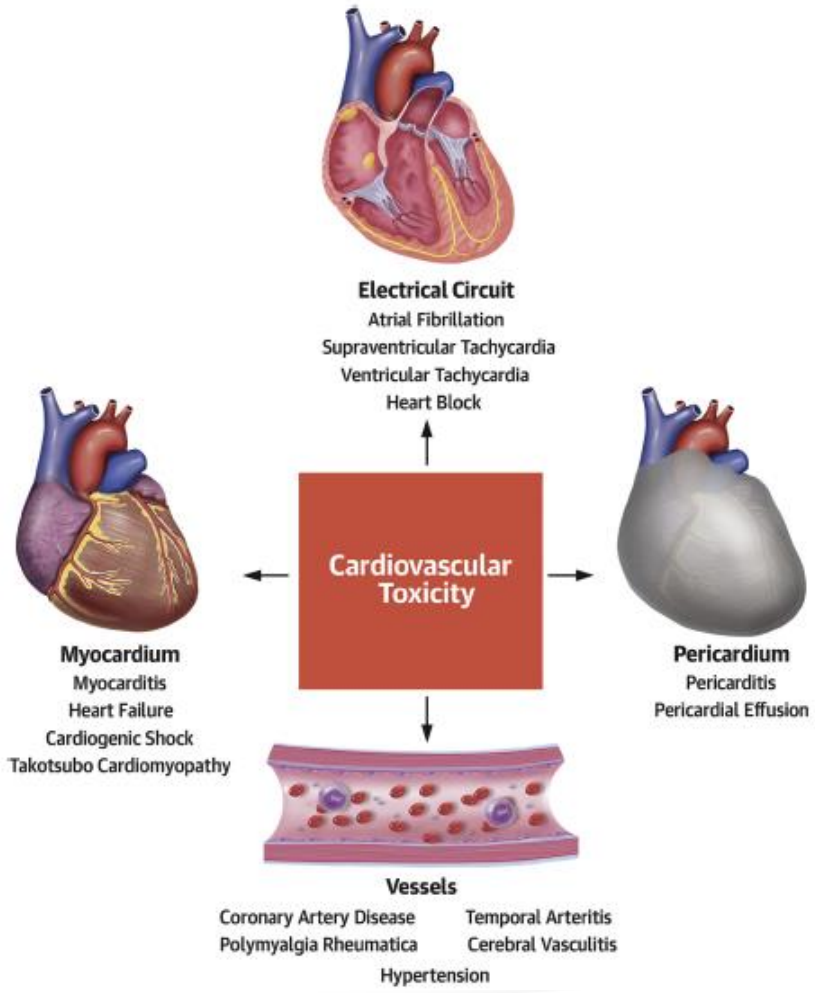
Immune System and Cancer



CTLA-4, PD-1, and PDL-1 are the targets for currently available ICI therapies

Adapted from: Ball S, Ghosh RK, Wongsaengsak S, et al. Cardiovascular Toxicities of Immune Checkpoint Inhibitors: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;74(13):1714-1727.

Cardiovascular Toxicities Associated with ICI Therapy



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Background

- Solid Organ Transplant (SOT) recipients have been excluded from ICI trials
- Chronic immunosuppression in SOT population places these patients at increased risk for malignancy
- Recent reports have shown adverse events affecting the grafts when ICIs have been used in this population
- Experience with ICI use in heart and lung transplant recipients is limited

Aims & Methods

- Characterize adult heart and lung transplant recipients who have received ICI therapy for treatment of their malignancy
- Evaluate clinical course, treatment effects, and outcomes
- Use this information to initiate a global registry to study how to best use ICIs in heart and lung transplant recipients with cancer

Results

- We identified 6 patients with heart or lung transplantation who received ICI therapy
- Metastatic melanoma was the most common malignancy
- Pembrolizumab (PD-1 inhibitor) was the most common ICI

Outcomes

- Heart transplant recipients:
  - 3/4 developed acute graft rejection and graft failure
  - 2 had reductions in LVEF
  - Rejection was treated with steroids +/- plasmapheresis
  - All 3 patients with graft dysfunction were deceased at last follow up (≤3 years since cancer diagnosis)
- Lung transplant recipients
  - Patient 1 developed acute graft dysfunction
    - Treated with steroids
    - Died of respiratory failure within one year of starting ICI therapy
  - Patient 2 had no evidence of acute graft rejection / failure but died within a year of ICI therapy from chronic lung allograft dysfunction or restrictive allograft syndrome
- Data are summarized in Table (next slide)

Patient Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Type of Transplant	Heart	Heart	Heart	Heart	Double Lung	Single Lung
Age (years)	30	78	62	74	35	72
Sex	Male	Male	Female	Male	Female	Male
Immunosuppression Regimen	Tacrolimus, Azathioprine	Cyclosporine, MMF/MPA, Everolimus/Sirolimus, Steroids	Cyclosporine, MMF, Steroids	Tacrolimus	Tacrolimus, MMF/MPA, Steroids	Tacrolimus, Steroids
Reason for Transplant	Congenital Heart Disease	Non-ischemic Cardiomyopathy	Myocarditis	Non-ischemic Cardiomyopathy	Re-transplant	Alpha-1 Anti Trypsin Deficiency
Type of Malignancy	Metastatic melanoma	Lung adenocarcinoma	Metastatic melanoma	Metastatic melanoma	Disseminated squamous cell skin cancer	Metastatic Melanoma
Time From Transplant to Malignancy Diagnosis (Years)	18	16	24	19	4	14
Immune Checkpoint Inhibitor Used	Pembrolizumab	Pembrolizumab	Nivolumab	Pembrolizumab	Pembrolizumab	Ipilimumab
Events After ICI Therapy						
Biopsy-proven Allograft Rejection	Yes	Yes	Yes	No	No	No
Treatment for Rejection	Steroids, Plasmapheresis	Steroids, Cyclosporine	Steroids	--	--	--
Graft Dysfunction	Yes	Yes	Yes	No	No	Yes
LVEF Reduction	Yes	No	Yes	No	--	--
Respiratory Failure	--	--	--	--	No	Yes
Hemodynamic Compromise	Yes	No	No	No	No	No
New Donor Specific Antibodies	Yes	Not Tested	No	No	No	No
New or Accelerated CAV	Yes	Not Tested	Not Tested	No	--	--
Vital Status at Last Follow-up (≤3 years since cancer diagnosis)	Deceased	Deceased	Deceased	Alive	Deceased	Deceased
Cause of Death	Cardiogenic Shock	Metastatic lung adenocarcinoma	Metastatic melanoma	--	Chronic lung allograft dysfunction	Respiratory Failure

Conclusion

- ICIs represent a revolutionary treatment with opportunity to treat malignancy refractory to other forms of therapy
- For SOT recipients, risk of allograft rejection or dysfunction must be balanced with treatment of malignancy
- Our initial results suggest significant risk of graft dysfunction / failure with ICI use
- To address significant gaps in our understanding of ICI use in this population, we started the ***ICI Transplant Registry***
  - https://medicine.utah.edu/internalmedicine/cardiovascular-medicine/research/ici_transplant.php

Daud A, Mehra MR, Siu A, et al. Immune checkpoint inhibitors in heart or lung transplantation: Early results from a registry initiative. *The Journal of Heart and Lung Transplantation*. April 2020.

ICI Transplant Registry Aims

- Identify which patient characteristics predict a favorable or unfavorable response to ICI.
- Gain insights into the mechanism of graft injury.
- Determine immunosuppression adjustments that could minimize adverse outcomes from ICI use.
- Propose optimal transplant-specific testing and surveillance during ICI therapy.
- Assess adjunctive interventions to mitigate the risk associated with ICI treatment.
- Propose optimal treatment strategy for transplant patients that do develop graft dysfunction after ICI therapy.

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