CARDIOVASCULAR TOXICITY OF IMMUNE CHECKPOINT INHIBITORS: ANALYZING EMERGING TRENDS WITHIN THE FAERS DATA

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Background

Immune system and cancer

Complex, dynamic and bi-directional relationship of cancer-immune system interface

Health depends critically on well balanced immune system regulated by stimulatory and inhibitory receptors (immune checkpoints)

Immune checkpoint inhibitors (CPI)

Block negative co-stimulation of T-cells → enhanced anti-tumor response

Targets

1. Cytotoxic T-lymphocyte associated protein-4 (CTLA-4)
2. Programmed cell death protein-1 (PD-1)
3. Programmed death ligand-1 (PD-L1)

Approved by the US FDA for several malignancies and under investigation for many others

Immune system consequences

CPIs activate immune system → tissue damage and immune related adverse events (IrAEs)

Nearly all organ systems affected, mild to severe

IrAEs with cardiovascular phenotypes less well described

Methods

FDA Adverse Events Reporting System database (FAERS)

Manually reviewed adverse event data received by FDA from healthcare professionals, drug manufacturers and consumers

Publically available on a quarterly basis

AERSMine

Open access, web-based data mining tool
<https://research.cchmc.org/aers/>

Data recorded through systematic normalization, unification and ontological aggregation of drugs, clinical indications and adverse events

Data analyzed from patients with underlying cancer. Data range: 2004 Q1 to 2017 Q3

Focused analysis of all cardiovascular AEs

Analysis

Well established measures of disproportionality (Used by World Health Organization)

Relative risks

Rates of reports of drug of interest and adverse drug reaction versus reports of all other drugs and adverse drug reaction

Information component (IC)

Observed rate of events/Expected rate of events on the log 2 scale

A robust Bayesian neural network method

Results

We identified **30,939** unique patients with cancer and reports of CPI associated toxicities

Number of unique patients with adverse event reports

1. Ipilimumab (CTLA-4 inhibitor): **7,393**
2. Nivolumab (PD-1 inhibitor): **13,329**
3. Pembrolizumab (PD-1 inhibitor): **6,225**
4. Durvalumab (PD-L1 inhibitor): **467**

Figure 1: Distribution of CPI-IrAE reports

Tables 1: Relative risks and safety signals (IC) of CPI-IrAE reports

IrAE	RR	p value	IC
Nivolumab			
Pericarditis	1.51	0.04	0.59
Pericardial effusion	1.44	0.01	0.53
Cardiac failure	1.62	0.00	0.70
Ipilimumab			
Atrial fibrillation	1.38	0.00	0.47
Ventricular tachycardia	2.22	0.01	1.15
Cardiac arrest	1.97	0.00	0.97
Pembrolizumab			
Congestive cardiac failure	1.72	0.04	0.78
Durvalumab			
Atrial fibrillation	2.21	0.01	1.14

Figure 2: Age and gender distribution of CPI-IrAE reports

Conclusions

Several cardiovascular IrAE safety signals were detected in association with CPIs in the FAERS

Although rare, these toxicities may become more recognizable with expanding use of CPIs

Additional studies are needed to determine whether CPI induced cardiovascular IrAEs represent de novo events or activation of subclinical disease

Take Home Message

A wide spectrum of cardiovascular IrAEs are observed following CPI therapy

Oncologists and cardiologists should be vigilant about these IrAEs

Better understanding of the pathogenesis of these adverse events and how to treat them will benefit patients and could give insight into traditional cardiovascular diseases

References

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