A prospective observational study of cardiotoxicity associated with immune checkpoint and/or angiogenesis inhibitors

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Introduction

- ✓ The number of cancer survivors is increasing due to improved cancer treatment outcomes[1]. However, as survival times increase, cancer therapeutics-related cardiac dysfunction (CTRCD) has become an increasing problem[2,3].
- ✓ To establish early diagnosis and intervention strategies for CTRCD, information on the incidence and risk factors is needed. In particular, there is a lack of information on the cardiotoxicity of recently developed immune checkpoint inhibitors (ICIs) and angiogenesis inhibitors (AIs).
- ✓ We designed this study to explore the frequency and risk factors of cardiac dysfunction associated with ICIs and AIs.

1. Mayer DK, et al. Lancet Oncol 2017.
2. Carver JR, et al. J Clin Oncol 2007.
3. Plana JC, et al. Eur Heart J Cardiovasc Imaging 2014.

Patients and Methods

- ✓ This was a multicenter, prospective observational study.

Planned enrollment N = 200

Registration

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Evaluation prior to initiation of ICIs and/or AIs*

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Start of systemic treatment with ICIs and/or AIs

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Evaluation after 12 weeks*

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Evaluation after 24 weeks*

Primary endpoint

- ✓ **Left ventricular dysfunction (LVD)** frequency on echocardiography**

Secondary endpoints

- ✓ Frequency of cardiotoxicities other than LVD (other cardiotoxicities)
- ✓ Risk factors associated with LVD and other cardiotoxicities
- ✓ Frequency of symptomatic LVD
- ✓ Treatment for LVD

***Factors to be evaluated**

- Left ventricular ejection fraction (LVEF) by echocardiography
- Electrocardiogram
- Blood test (cardiac muscle troponin T and NT-pro BNP)

****Definition of LVD**

- Echocardiographic evaluation showing a decrease in LVEF of at least 10% from baseline and a decrease in LVEF to less than 53%.

Key eligibility criteria

- ✓ Patients with solid tumors with no prior systemic therapy of less than two regimens
- ✓ Plans to start treatment with an ICI- and/or AI-containing regimen within 28 days
- ✓ The patient is at least 20 years old and provided written consent

Key exclusion criteria

- ✓ Previous treatment with ICI and/or AI
- ✓ With emergent cardiac disease

Sample size

- ✓ Assuming a 10% incidence of cardiac dysfunction, a power analysis indicated that 189 participants are needed to achieve a 95% confidence interval width of ≤10% with ≥90% probability using the Clopper–Pearson method. Accounting for ineligible cases, 200 participants were targeted for enrollment.

Results

Table 1. Patient characteristics (**N = 199***)

Age (years)	
Median	71
Range	37-88
Sex, n (%)	
Female	51 (26%)
Male	148 (74%)
Primary tumor sites, n (%)	
Lung	99 (50%)
Bowel	32 (16%)
Stomach	25 (13%)
Esophageal	19 (10%)
Liver	12 (6%)
Head and neck	5 (3%)
Other	7 (3%)
Complications, n (%)	
Hypertension	88 (44%)
Dyslipidemia	50 (25%)
Diabetes	39 (20%)
Arrhythmia	16 (8%)
LVEF (%)	
Median	65
Range	27-78
Troponin T, (mg/mL)	
Median	0.009
Range	0.003-0.140
NT-pro BNP, (pg/mL)	
Median	108
Range	5-3120

***One ineligible patient was excluded from this analysis**

Patients receiving ICIs and/or AIs: n = 194

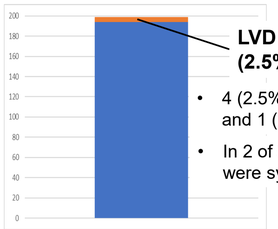
- Immune checkpoint inhibitors (ICIs): n = 158
- Angiogenesis inhibitors (AIs): n = 53
- Both drugs: n = 17

Table 2. ICIs and/or AIs administered (n = 194)

AIs, n (%)	
Bevacizumab	46 (23%)
Ramucirumab	6 (3%)
Lenvatinib	1 (1%)
ICIs, n (%)**	
Pembrolizumab	65 (32%)
Nivolumab	48 (24%)
Atezolizumab	33 (16%)
Ipilimumab	18 (9%)
Durvalumab	12 (6%)
Tremelimumab	1 (1%)

**In 19 cases, multiple ICIs were administered

Figure 1. Incidence of LVD in all eligible patients (N = 199)



LVD occurred in 5 patients. (2.5%, 95%CI; 0.8-5.8%)

- 4 (2.5%) treated with ICI (n = 158) and 1 (1.9%) treated with AI (n = 53)
- In 2 of 5 patients, LVDs were symptomatic.

Table 3. Univariate analysis of the incidence of LVD in all eligible patients (N = 199)

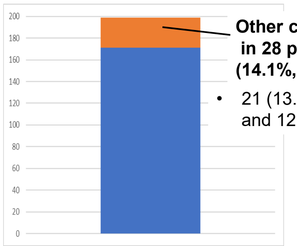
Variables	n	LVD	Odds ratio	95% CI	*p*
Age					
< 71 years old	99	0 (0%)	Reference		
≥ 71 years old	100	5 (5%)	Inf	0.925-Inf	0.059
Other anticancer drugs					
Without	52	0 (0%)	Reference		
With	142	4 (2.8%)	Inf	0.241-Inf	0.575
LVEF*** (baseline)					
< 53%	10	0 (0%)	Reference		
≥ 53%	188	5 (2.7%)	Inf	0.044-Inf	1.000
Troponin T*** (baseline)					
< 0.015 ng/mL	157	2 (1.3%)	Reference		
≥ 0.015 ng/mL	42	3 (7.1%)	5.889	0.651-72.602	0.064
NT-proBNP*** (baseline)					
< 126 pg/mL	114	1 (0.9%)	Reference		
≥ 126 pg/mL	85	4 (4.7%)	5.536	0.535-276.788	0.166
Concomitant arrhythmias					
Without	183	4 (2.2%)	Reference		
With	16	1 (6.2%)	2.959	0.057-32.510	0.345

*** Cutoff values were set in accordance with Japanese reference values

Summary and conclusion

- ✓ In this cohort, LVDs were observed in 5 patients (2.5%) treated with ICIs and/or AIs (4 [2.5%] treated with ICIs and 1 [1.9%] treated with AIs). No significant risk factors were observed, although there was a trend toward a higher incidence of LVDs in cases over 70 years old and in cases of high baseline troponin T levels.
- ✓ Other cardiotoxicities occurred in 28 patients (14.1%) treated using ICIs and/or AIs (ICI group: 21 [13.3%]; AI group: 12 [22.6%]). Common cardiotoxicities were hypertension and arrhythmia. Concomitant arrhythmias (p = 0.002) and high baseline NT-pro BNP levels (p = 0.007) were significantly associated with the incidence of other cardiotoxicities. In addition, other cardiotoxicities tended to be more frequent in patients over 70 years old.
- ✓ More careful follow-up may be necessary in patients with concomitant arrhythmias or higher baseline NT-pro BNP levels. In addition, age and baseline troponin T levels may be related to the frequency of cardiotoxicity.

Figure 2. Incidence of other cardiotoxicities in all eligible patients (N = 199)



Other cardiotoxicities occurred in 28 patients. (14.1%, 95%CI; 9.6-19.7%)

- 21 (13.3%) treated with ICI (n = 158) and 12 (22.6%) treated with AI (n = 53)

Table 4. Breakdown of other cardiotoxicities**** (n = 28)

Events	n
Hypertension	12
Arrhythmia	10
Valve disease	1
Coronary artery disease	1
Other	8

**** Patients with multiple events were included

Table 5. Univariate analysis of the incidence of other cardiotoxicities in all eligible patients (N = 199)

Variables	n	Other cardiotoxicities	Odds ratio	95% CI	*p*
Age					
< 71 years old	99	9 (9.1%)	Reference		
≥ 71 years old	100	19 (19.0%)	2.336	0.943-6.213	0.065
Other anticancer drugs					
Without	52	8 (15.4%)	Reference		
With	142	19 (13.4%)	0.850	0.326-2.412	0.815
LVEF*** (baseline)					
< 53%	10	1 (10.0%)	Reference		
≥ 53%	188	27 (14.4%)	1.507	0.195-68.556	1.000
Troponin T*** (baseline)					
< 0.015 ng/mL	157	19 (12.1%)	Reference		
≥ 0.015 ng/mL	42	9 (21.4%)	1.973	0.719-5.092	0.137
NT-proBNP*** (baseline)					
< 126 pg/mL	114	9 (7.9%)	Reference		
≥ 126 pg/mL	85	19 (22.4%)	3.338	1.344-8.905	0.007
Concomitant arrhythmias					
Without	183	21 (11.5%)	Reference		
With	16	7 (43.8%)	5.815	1.686-20.093	0.002