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Cardiovascular risks of chemo-immunotherapy for lung cancer: A population-based cohort study

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ABSTRACT

Objectives: Despite their proven efficacy for treating lung cancer, the cardiovascular risks associated with programmed cell death protein 1 (PD-1) inhibitors and their combinations with chemotherapy (chemo-immunotherapy) are unclear. This study aimed to investigate these associations.
Materials and methods: This retrospective cohort study included Hong Kong patients with lung cancer receiving PD-1 inhibitors during 2013–2021. Patients with non-concurrent use of PD-1 inhibitors and chemotherapy, any use of tyrosine kinase inhibitors or other immunotherapy agents, and those with prior stroke, heart failure, or myocardial infarction were excluded. PD-1 inhibitors and chemo-immunotherapy were compared for major adverse cardiovascular events (MACE), a composite of cardiovascular mortality, heart failure, stroke, and myocardial infarction. All patients were followed up until the end of 2021. Inverse probability of treatment weighting was used to balance covariates between the two treatment groups.
Results: In total, 713 patients (333 PD-1 inhibitors users and 380 chemo-immunotherapy users) were analysed. Over a mean follow-up of 1.4 ± 1.3 years, 24 had MACE, with an observed incidence of 2.8 [1.6–4.8] events per 100 person-year for patients on PD-1 inhibitors, and 2.1 [1.2–3.8] per 100 person-year for patients on chemo-immunotherapy. No significant between-group difference in MACE incidence was observed (log-rank p = 0.641).
Conclusion: The cardiovascular risks associated with PD-1 inhibitors and chemo-immunotherapy may not be significantly different amongst patients with lung cancer. Cardiovascular events associated with either regimen may be uncommon.

1. Introduction

Immune checkpoint inhibitors (ICIs[1]), such as programmed cell death protein 1 (PD-1) inhibitors, and chemo-immunotherapy combinations have been shown to result in better survival outcomes than conventional platinum-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) [1,2]. Nevertheless, immune checkpoint inhibitors and platinum-based chemotherapy are both

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[1] Abbreviations: CDARS, Clinical Data Analysis and Reporting System; HF, heart failure; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; ICI, immune checkpoint inhibitor; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; SMD, standardized mean difference.

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independently associated with elevated cardiovascular risks, with as much as 40–60 % of the cases of ICI-related cardiotoxicity being fatal [3]. Nonetheless, cardiotoxicity of chemo-immunotherapy were not specifically compared against immunotherapy nor reported by the landmark KEYNOTE-024 and KEYNOTE-189 trials [1,2]. There has also been a scarcity of reports on the utilisation and toxicity profiles of these agents within an Asian population. This population-based study thus aimed to compare the cardiovascular risks between PD-1 inhibitors and combination chemo-immunotherapy in Asian patients with lung cancer.

2. Materials and methods

This retrospective cohort study was conducted in accordance with the Declaration of Helsinki, and was approved by the local institutional review board. Individual consent was not required as deidentified data were used. The Strengthening the Reporting of Observational Studies in Epidemiology guideline was followed. All underlying data are available upon reasonable request to the corresponding authors. Data were obtained from the Clinical Data Analysis and Reporting System (CDARS), a population-based electronic database of all patients attending Hong Kong public healthcare institutions which serve an estimated 90 % of Hong Kong's population. Diagnoses were recorded using *International Classification of Diseases, Ninth Revision* (ICD-9) codes (**Supplemental** Table 1) regardless of the time of data entry, as ICD-10 has not been implemented in CDARS to date. Mortality data were obtained from the linked Hong Kong Death Registry, a governmental registry of all Hong Kong citizens' death records; causes of death were encoded by either ICD-9 or ICD-10 codes (**Supplemental Table 2**). Both CDARS and the Hong Kong Death Registry have been used in previous studies and shown to have good coding accuracy [4,5].

Patients aged at least 18 years old with lung cancer receiving any PD-1 inhibitor (pembrolizumab or nivolumab, as other PD-1 inhibitors are not available in Hong Kong to date) in Hong Kong between 1st January 2013 and 31st December 2021 were included. Patients with non-concurrent (i.e. sequential) use of PD-1 inhibitor and chemotherapy, any use of tyrosine kinase inhibitors, any use of other immunotherapy agents, and those with prior stroke, heart failure (HF), or myocardial infarction (MI) were excluded. The treatment groups were defined as PD-1 inhibitor only, and concurrent use of chemotherapy and PD-1 inhibitor (chemo-immunotherapy). The endpoint was major adverse cardiovascular events (MACE), defined as the first occurrence of cardiovascular mortality, HF, stroke, or MI. All patients were followed up until 31st December 2021.

Continuous variables were expressed as mean ± standard deviation or median and interquartile range. As all diagnoses were identified by ICD codes and since CDARS captures all prescriptions automatically, there was no missing record. Due to the non-randomized, observational nature of this study, the treatment groups may have important differences in covariates. To reduce bias, inverse probability of treatment weighting (IPTW) was performed to minimize differences in covariates (demographics, comorbid conditions, and use of other medications; Table 1) using a generalized boosted model, a machine learning approach, with a maximum of 10,000 regression trees and an iteration stopping point minimizing the absolute standardized mean difference of the effect size. Between-group covariate balance was assessed by the absolute standardized mean difference (SMD), with SMD < 0.2 considered to reflect good balance. Observed incidence rates of MACE with 95 % confidence intervals were calculated for each treatment group. Kaplan-Meier curves with IPTW were used to visualize the cumulative incidence of MACE. As the proportional hazards assumption was violated on visual inspection of the log–log plot and the Kaplan-Meier curve, the log-rank test was used to compare between groups. Restricted cubic spline with three knots was used to visualize the variation of hazard ratio throughout the study period. As this approach does not rely on a single hazard ratio, it provides more quantitative information about how the two treatment groups compared at each timepoint without requiring the proportional hazards assumption. Three to five knots were considered, with the model minimizing the Akaike's information criterion being selected as the final model. As some studies have suggested a difference in the risk of thromboembolism between adenocarcinoma and squamous cell carcinoma of the lung [6], and as patients with the former were more likely to have received pemetrexed [7], a sensitivity analysis was performed in which only patients who never received pemetrexed were analysed. Two-sided P-values < 0.05 were considered statistically significant. All analyses were performed using Stata (version 16.1, StataCorp LLC, USA).

Table 1
Summary of baseline characteristics of included patients, with between-group balance summarized by the absolute standardized mean difference (SMD).

	PD-1 inhibitor only (N = 333)	Both PD-1 and chemotherapy (N = 380)	Unweighted SMD	Weighted SMD
Age, years	70.6 ± 10.3	62.3 ± 9.3	0.789	0.129
Males, N (%)	267 (80.2)	271 (71.3)	0.206	0.053
Duration of therapy, days [IQR]	97 (21–275)	106 (51–215)	0.167	0.172
Hypertension, N (%)	139 (41.7)	132 (34.7)	0.144	0.004
Ischaemic heart disease, N (%)	22 (6.6)	9 (2.4)	0.208	0.115
Atrial fibrillation, N (%)	7 (2.1)	10 (2.6)	0.035	0.054
Diabetes mellitus, N (%)	56 (16.8)	52 (13.7)	0.087	0.050
Hyperlipidaemia, N (%)	118 (35.4)	90 (23.7)	0.258	0.108
Chronic kidney disease, N (%)	4 (1.2)	0 (0)	0.161	0.124
Valvular heart disease, N (%)	2 (0.6)	1 (0.3)	0.052	0.033
Cardiomyopathy, N (%)	0 (0)	1 (0.3)	0.070	0.054
Peripheral vascular disease, N (%)	1 (0.3)	1 (0.3)	0.007	0.007
ACEI/ARB, N (%)	71 (21.3)	59 (15.5)	0.150	0.010
Metformin, N (%)	40 (12.0)	40 (10.5)	0.047	0.005
Sulfonylurea, N (%)	24 (7.2)	24 (6.3)	0.036	0.027
Insulin, N (%)	22 (6.6)	25 (6.6)	0.001	0.004
DPP4 inhibitor, N (%)	13 (3.9)	10 (2.6)	0.072	0.019
Thiazolidinediones, N (%)	3 (0.9)	3 (0.8)	0.012	0.009
Dihydropyridine CCB, N (%)	106 (31.8)	105 (27.6)	0.092	0.049
Beta-blocker, N (%)	41 (12.3)	46 (12.1)	0.006	0.004
Statin, N (%)	109 (32.7)	82 (21.6)	0.252	0.096
Fibrate, N (%)	5 (1.5)	4 (1.1)	0.040	0.052
Radiotherapy, N (%)	3 (0.9)	1 (0.3)	0.167	0.106

ACEI, angiotensin-converting enzyme inhibitor. ARB, angiotensin receptor blocker. CCB, calcium channel blocker. DPP4, Dipeptidyl peptidase-4. IQR, interquartile range. PD-1, programmed cell death protein 1. SMD, standardized mean difference.

3. Results

Initially, 1508 patients were identified. After applying the exclusion criteria (Fig. 1), 713 patients were included in the analysis (538 (75.5 %) male, mean age 66.2 ± 10.6 years old), of which 333 patients received PD-1 inhibitors only, and 380 received chemo-immunotherapy. Of the 380 patients on chemo-immunotherapy, 369 (97.1 %) received platinum compounds (36 received cisplatin, 361 received carboplatin, and 29 ever received both agents), 302 (79.5 %) received folate antimetabolites, and 175 (46.1 %) received taxanes; 317 (83.4 %) received

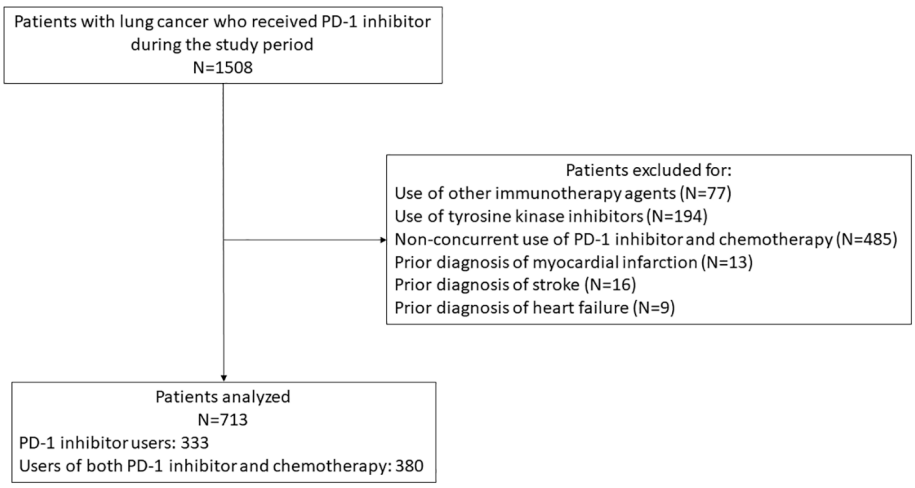

Fig. 1. Study flowchart. PD-1, programmed cell death protein 1.

platinum compounds, PD-1 inhibitors, and taxanes or folate antimetabolites concurrently. IPTW achieved good balance for all covariates (SMD < 0.2; Table 1).

Over a mean follow-up duration of 1.4 ± 1.3 years, 24 patients (3.4 %) had MACE, with ten cases of stroke, eight cases of MI, three cases of cardiovascular mortality, and three cases of HF. The observed incidence rate of MACE was 2.8 [1.6–4.8] events per 100 person-year for patients on PD-1 inhibitors, and 2.1 [1.2–3.8] per 100 person-year for patients on chemo-immunotherapy. The log-rank test with IPTW showed no statistically significant difference in cumulative incidence of MACE between groups ($p = 0.641$; Fig. 2**A**). The restricted cubic spline showed that despite considerable variation of the hazard ratio over time, there was never any significant difference between the two groups (Fig. 2**B**). Consistently, no significant differences in the cumulative incidence of MACE were observed between the treatment groups in the sensitivity analysis restricted to patients who never received pemetrexed (log-rank $p = 0.745$).

4. Discussion

In this population-based retrospective cohort study, we observed that cardiovascular risks of PD-1 inhibitors and chemo-immunotherapy may not be significantly different amongst patients with lung cancer, and cardiovascular events may be uncommon amongst these patients. To the best of the authors' knowledge, this was one of the first studies that specifically investigated the cardiovascular risk associated with chemo-immunotherapy and compared it with immunotherapy.

Little is known about the relative cardiovascular risks among immunotherapy and chemo-immunotherapy: a 2021 network *meta*-analysis did not identify any study that directly compared immunotherapy with chemo-immunotherapy in terms of cardiovascular risks [8]. Additionally, most studies of immunotherapy and chemo-immunotherapy were conducted on Caucasians. With the known racial differences in the risk of cancer therapy-induced cardiotoxicity [9], the cardiovascular safety profiles of these regimens as described in Caucasian patients may not be assumed to be extrapolatable to Asian patients. Our results suggested that MACE is uncommon amongst recipients of immunotherapy and chemo-immunotherapy with lung cancer, and these therapies may not differ significantly in their associated cardiovascular risks. Using a population-based database, our results may be generalizable and reflect real-life practice in an Asian setting. Larger prospective studies are needed to further delineate the relative cardiovascular toxicity of these therapies, as well as the risk factors for MACE amongst recipients of immunotherapy and chemoimmunotherapy.

With landmark trials having demonstrated the efficacy of chemo-

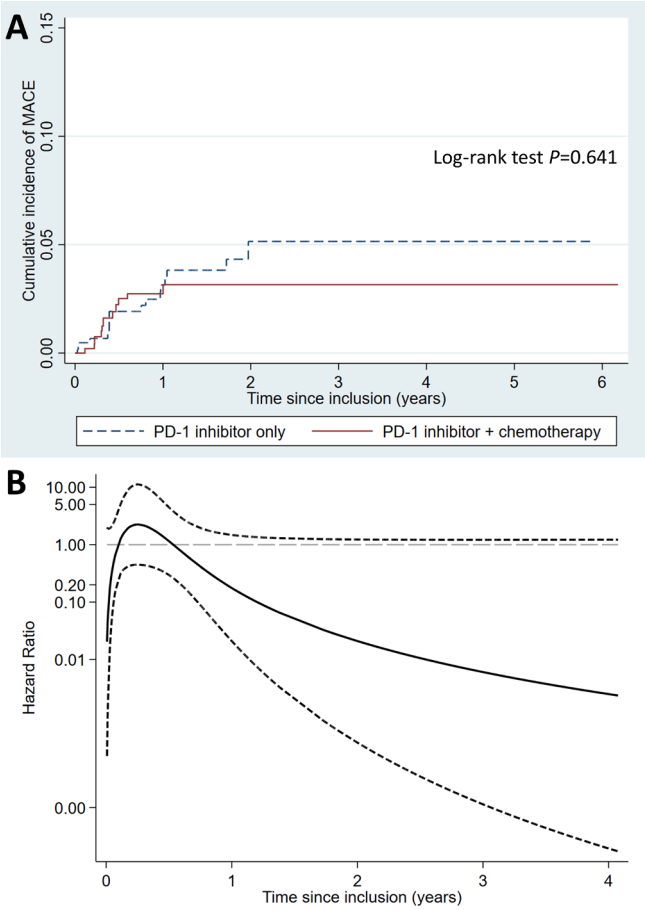

Fig. 2. (A) Kaplan-Meier curve of the cumulative incidence of major adverse cardiovascular events (MACE). **(B)** Restricted cubic spline showing the variation of estimated hazard ratio over the study period. Dash lines indicate the 95% confidence interval. PD-1, programmed cell death protein 1.

immunotherapy, both immunotherapy and chemo-immunotherapy have become established in the treatment of advanced lung cancer [7]. Nonetheless, many patients with lung cancer in real life have different body compositions, increased affliction of comorbidities, poorer performance status, and higher risk for toxicities than those reflected in clinical trials [10]. When determining an optimal treatment strategy for patients with advanced NSCLC, especially those who are

older and with more co-morbidities, clinicians are faced with the challenge of not having dedicated clinical trials on this subgroup and being forced to extrapolate findings derived from trial patients who are often younger and physically fitter. Therefore, considerations need to be made on the impact on quality of life to steer discussions about risk–benefit balance, and our findings should facilitate these discussions and offer at least some reassurance to clinicians when weighing between these treatment options in clinical practice.

This study was limited by its observational nature which predisposes to residual confounding. Some cardiovascular risk factors, such as smoking status, were not available from the database used. Nonetheless, IPTW has included numerous key cardiovascular risk factors which should reasonably reflect the cardiovascular risk of the included patients. Also, lung cancer subtypes and staging were unavailable, both of which are potential confounders. Additionally, data from CDARS could not be individually adjudicated. Nevertheless, diagnostic codes were entered by treating clinicians independent of the authors. Previous studies have also demonstrated good accuracy for CDARS data [4].

5. Conclusion

The associated risks of MACE may not be significantly different between PD-1 inhibitors and chemo-immunotherapy amongst patients with lung cancer, and MACE may be uncommon amongst patients receiving either regimen. Despite the limitations associated with retrospective studies, these findings may facilitate risk–benefit discussions in clinical practice.

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CRediT authorship contribution statement

Jeffrey Shi Kai Chan: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Pias Tang:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Kenrick Ng:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Edward Christopher Dee:** Conceptualization, Supervision, Writing – review & editing. **Teddy Tai Loy Lee:** Investigation, Writing – review & editing. **Oscar Hou In Chou:** Investigation, Writing – review & editing. **Yan Hiu Athena Lee:** Investigation, Writing – review & editing. **Dawnie Ho Hei Lau:** Investigation, Writing – review & editing. **Tong Liu:** Supervision, Writing – review & editing. **Gary Tse:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.10.010.

References

[1] L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, M.C. Garassino, Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer, N. Engl. J. Med. 378 (22) (2018) 2078–2092.

[2] M. Reck, D. Rodríguez-Abreu, A.G. Robinson, R. Hui, T. Csőszi, A. Fülöp, M. Gottfried, N. Peled, A. Tafreshi, S. Cuffe, M. O'Brien, S. Rao, K. Hotta, M. A. Leiby, G.M. Lubiniecki, Y. Shentu, R. Rangwala, J.R. Brahmer, Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer, N. Engl. J. Med. 375 (2016) 1823–1833, https://doi.org/10.1056/NEJMOA1606774/SUPPL_FILE/NEJMOA1606774_DISCLOSURES.PDF.

[3] K.J. Ruddy, S.R. Patel, A.S. Higgins, S.H. Armenian, J. Herrmann, Cardiovascular Health during and after Cancer Therapy, Cancers 2020 (12) (2020) 3737, https://doi.org/10.3390/CANCERS12123737.

[4] M.F. Tsoi, M.H. Chung, B.M.Y. Cheung, C.S. Lau, T.T. Cheung, Epidemiology of gout in Hong Kong: A population-based study from 2006 to 2016, Arthritis Res. Ther. 22 (2020) 1–9. doi: 10.1186/S13075-020-02299-5/FIGURES/5.

[5] J.S.K. Chan, I. Lakhani, T.T.L. Lee, O.H.I. Chou, Y.H.A. Lee, Y.M. Cheung, H. W. Yeung, P. Tang, K. Ng, E.C. Dee, T. Liu, W.T. Wong, G. Tse, F.P. Leung, Cardiovascular outcomes and hospitalizations in Asian patients receiving immune checkpoint inhibitors: a population-based study, Curr. Probl. Cardiol. 48 (1) (2023) 101380.

[6] J.W. Blom, S. Osanto, F.R. Rosendaal, The risk of a venous thrombotic event in lung cancer patients: higher risk for adenocarcinoma than squamous cell carcinoma, J. Thromb. Haemost. 2 (2004) 1760–1765, https://doi.org/10.1111/J.1538-7836.2004.00928.X.

[7] D. Planchard, S. Popat, K. Kerr, S. Novello, E.F. Smit, C. Faivre-Finn, T.S. Mok, M. Reck, P.E. Van Schil, M.D. Hellmann, S. Peters, ESMO Guidelines Committee, Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up., Ann. Oncol. Off. J. Eur. Soc. Med. Oncol. 29 Suppl 4 (2018) iv192–iv237. doi: 10.1093/annonc/mdy275.

[8] Y.D. Yan, J.J. Cui, J. Fu, Y.J. Su, X.Y. Chen, Z.C. Gu, H.W. Lin, A Network Comparison on Safety Profiling of Immune Checkpoint Inhibitors in Advanced Lung Cancer, Front. Immunol. 12 (2021), 760737, https://doi.org/10.3389/FIMMU.2021.760737/FULL.

[9] R.E. Ohman, E.H. Yang, M.L. Abel, Inequity in Cardio-Oncology: Identifying Disparities in Cardiotoxicity and Links to Cardiac and Cancer Outcomes, J. Am. Heart Assoc. 10 (2021), https://doi.org/10.1161/JAHA.121.023852.

[10] J. Clarey, S.C. Kao, S.J. Clarke, J. Vardy, The eligibility of advanced non-small-cell lung cancer patients for targeted therapy clinical trials, Ann. Oncol. 23 (2012) 1229–1233, https://doi.org/10.1093/ANNONC/MDR443.