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Letters

RESEARCH LETTER

Myocarditis Associated With Immune Checkpoint Inhibitors in Patients With Thymoma

Myocarditis is associated with thymoma, and is also an uncommon, but potentially lethal, immune-related adverse event (irAE) reported with the use of immune checkpoint inhibitors (ICIs).[1,2]

We hypothesized that among patients treated with ICIs, myocarditis would be more common in those with, as compared to those without, a history or previous treatment for thymoma. A comprehensive search of the Bristol Myers Squibb (BMS) internal databases—clinical trial database and the BMS safety database (including clinical trial and spontaneous postmarketing reports)—was conducted on March 10, 2022, for irAEs in patients with a history or indication for treatment of thymoma or thymic cancer who received nivolumab either as monotherapy or in combination with ipilimumab or relatlimab. All cases reporting myocarditis from both databases were adjudicated by 3 physicians with expertise in ICI therapy and myocarditis.[3]

Background rates of myocarditis per 1,000 person-years at risk for patients with solid tumors were estimated using the Truven Health MarketScan (IBM Watson Health) and PharMetrics (IQVIA) databases. Patients were classified into cohorts based on the first claim for thymoma ≤180 days of the tumor (index date). All patients were followed up for claims for myocarditis until discontinuation in the database (loss of eligibility).

Sixteen cases of myocarditis were identified in patients with a history/treatment indication of thymoma within the clinical trial (n = 2) and safety (n = 14) databases (Table 1). The adjudication panel determined that 8 of these were definite (biopsy/autopsy-proven) or probable (symptomatic with supportive laboratory data and imaging). Adjudication was based on clinical presentation, imaging (including cardiac magnetic resonance imaging and echocardiography), and cardiovascular biomarkers, including troponin and B-type natriuretic peptide.[3]

In the clinical trial database, rates of myocarditis in patients with a history/treatment indication of thymoma (cohort A) were compared with the remaining trial patients without such history/treatment indication (cohort B). Two out of 16 patients (12.5%) from cohort A and 125 out of 44,065 (0.28%) patients in cohort B had myocarditis.

Incidence rates of myocarditis from the claims databases were lower than those from the clinical trial and safety databases in both cohorts. The cohort with evidence of prior thymoma had an incidence rate of 0.57 (95% CI: 0.26-1.23) and 0.83 (95% CI: 0.42-1.63) cases of myocarditis per 1,000 person-years in the MarketScan and PharMetrics databases, respectively. The incidence rate of myocarditis was 0.14 per 1,000 person-years (both databases) in the cohort without evidence of prior thymoma.

Overall, these findings suggest that the rate of myocarditis following nivolumab therapy, alone or in combination with other agents, is more common in patients with current or prior thymoma vs those without a history of thymoma. Results from the claims databases were supportive, indicating higher background rates of myocarditis in patients with a history of thymoma.

Corroborating evidence comes from studies of other ICIs (eg, avelumab and pembrolizumab), which showed similar myocarditis patterns in patients with thymoma and thymic carcinoma.[4-6] Notably, thymoma is associated with higher frequencies of irAEs, including myocarditis, compared with thymic carcinoma.[4,6] Additionally, thymoma and ICI therapy are independently associated with autoimmune diseases, including myasthenia gravis and myocarditis.[2] Thus, the present findings emphasize the clinical relevance of thymoma in the assessment of risk for myocarditis during ICI therapy.

These findings are primarily based on studies from the BMS databases that are limited to nivolumab and its combinations. Eight of the 16 (50%) adjudicated cases had insufficient data to ascertain myocarditis. Thymomas are rare and the small sample size may further limit interpretation of these findings. Finally,

TABLE 1 Cases of Myocarditis in Patients With a History/Treatment Indication of Thymoma

Case #	Sex/ Age (y)	Exposure	Indication	TTO[a] (d)	Concurrent Adverse Events	Cardiovascular Medical History	Action Taken/ Outcome	Decision[b]
1	M/47[c]	NIVO + RELA	Thymoma	35	Anemia; hypothyroidism; skin necrosis; arthritis infective; pneumonia aspiration; MG	HTN, CAD, cardiopulmonary disease, myocardial infarction, stent placement, coronary artery bypass surgery, complete atrioventricular block, AF	WD/death	Definite
2	M/43	NIVO	Thymoma	—	Rhabdomyolysis	Cardiac pacemaker insertion (current)	UNK/death	Definite
3	F/58	NIVO	Renal cell carcinoma	18	MG	HTN, cardiac pacemaker insertion	DI/R	Probable
4	M/58	NIVO + IPI	Malignant melanoma	20	—	None	No change/death	Probable
5	F/55	NIVO	Malignant melanoma	—	Blood CPK increased; immune-mediated myositis; AST increased; ALT increased; MG; rhabdomyolysis; hepatic function abnormal; DVT	None	WD/recovering	Probable
6	UNK/UNK	NIVO	Malignant neoplasm of thymus	—		None	UNK/UNK	Probable
7	F/56[c]	NIVO + IPI	Merkel cell carcinoma	35	Constipation; fatigue; hypocalcemia; myalgia; myositis	None	None/DNR	Probable
8	M/28	NIVO	Malignant thymoma	13	Myositis	None	WD/death	ID
9	M/74	NIVO	Thymoma	—	Muscular weakness; vision blurred; cardiac arrest; pneumonitis	None	UNK/UNK	ID
10	M/43	NIVO	Thymoma	23	Transaminases increased	None	WD/R	ID
11	F/58	NIVO	Thymoma	22	—	AF, superior vena cava syndrome, stent placement	WD/R	ID
12	M/55	NIVO + CT	Recurrent non-small cell lung cancer	17	MG; myositis; cardiac failure acute; AST increased; ALT increased; febrile neutropenia; hepatic function abnormal; neutrophil count decreased; WBC decreased	None	NA/death	Definite
13	F/58	NIVO	Thymoma	22		AF	WD/R	ID
14	F/64	NIVO	Malignant pleural mesothelioma	—	Autoimmune myositis; malignant neoplasm progression	None	DI/death	ID
15	M/33	NIVO	Metastatic thymic cancer	33	MG; hypothyroidism; myositis; pyrexia	None	WD/R	ID
16	F/48	NIVO + IPI	Thymoma	43	—	Viral myocarditis, CAD	DI/NR	ID

[a]From first dose date. [b]Determined by the adjudication panel (Bristol Myers Squibb employees or consultants). [c]Cases identified from the clinical trial database. Other cases are from the Bristol Myers Squibb safety database.

AF = atrial fibrillation; ALT = alanine aminotransferase increased; AST = aspartate aminotransferase; CAD = coronary artery disease; CPK = creatine phosphokinase; CT = chemotherapy; DI = drug interruption; DNR = did not resolve; DVT = deep vein thrombosis; HTN = hypertension; ID = insufficient data; IPI = ipilimumab; MG = myasthenia gravis; NA = not applicable; NIVO = nivolumab; NR = not recovered; R = recovered; RELA = relatlimab; TTO = time to onset; UNK = unknown; WBC = white blood cell count; WD = withdrawn.

the retrospective study design does not allow determination of causality between ICI therapy and myocarditis.

Despite these limitations, this is the first quantitative analysis of myocarditis, attributable to thymoma and ICI therapy. The findings are based on reported cases of myocarditis, and an adjudication committee provided a more complete ascertainment.

In conclusion, these results highlight that heightened awareness of the potential increased risk of myocarditis among patients who have or had thymoma and are receiving ICI therapy may be beneficial.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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