News Release

Title

Anti-pituitary antibodies and susceptible human leukocyte antigen alleles as predictive biomarkers for pituitary dysfunction induced by immune checkpoint inhibitors

Key Points

- Immune checkpoint inhibitors (ICIs) have been widely used and improved prognosis in patients with advanced malignancies. In contrast, ICIs cause several immune-related adverse events (irAEs).
- While pituitary-irAEs are life-threatening irAEs, it is not possible to identify patients who may develop pituitary irAEs prior to ICI treatment. The aim of this study was to identify the predictive biomarkers of pituitary irAEs by analyzing anti-pituitary antibodies (APAs) and human leukocyte antigen (HLA).
- We previously reported that there were two different types of pituitary irAEs, i.e., isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) and hypophysitis.
- The prevalence of APAs at baseline was significantly higher in ICI-IAD patients (64.7%) than control patients. Although APAs were negative at baseline in all 5 patients who developed ICI-hypophysitis, they had become positive in 4 of 5 (80.0%) at the onset of ICI-hypophysitis.
- The prevalence of HLA-Cw12, -DR15, -DQ7, and -DPw9 was significantly higher in patients with ICI-IAD, whereas that of HLA-Cw12 and -DR15 was significantly higher in patients with ICI-hypophysitis than in controls.
- Our findings showed that positive APAs at baseline and after treatment, together with susceptible HLA alleles, could become predictive biomarkers for ICI-IAD and ICI- hypophysitis, respectively.

Summary

Immune checkpoint inhibitors (ICIs) activate T cells and show anti-tumor effects through the increased immune responses against cancer cells. ICIs have been shown as an effective treatment for unresectable metastatic melanoma (MM), non-small cell lung cancer (NSCLC), renal cell carcinoma, head and neck cancer, Hodgkin lymphoma, gastric cancer, urothelial cancer, breast cancer and so on. In contrast, ICIs cause several immune-related adverse events (irAEs). Pituitary irAEs are one of the life-threatening irAEs. We previously reported that there were two different types of pituitary irAEs, i.e., isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) and hypophysitis, and that pituitary-irAEs were associated with a better outcome of ICI treatments. However, it is not possible to identify patients who may develop pituitary irAEs prior to ICI treatment.

In this study, APAs and HLA alleles were analyzed in 62 patients (17 who developed ICI-IAD, 5 who developed ICI-hypophysitis, and 40 who did not develop pituitary irAEs) treated with ICIs between November 2, 2015 and March 31, 2020 at Nagoya University Hospital to identify the predictive biomarkers for pituitary irAEs. The prevalence of APAs at baseline was significantly higher in ICI-IAD patients (64.7%) than control patients. Although APAs were negative at baseline in all 5 patients who developed ICI-hypophysitis, they had become positive in 4 of 5 (80.0%) at the onset of ICI-hypophysitis. The

prevalence of HLA-Cw12, -DR15, -DQ7, and -DPw9 was significantly higher in patients with ICI-IAD, whereas that of HLA-Cw12 and -DR15 was significantly higher in patients with ICI- hypophysitis than in controls.

Our findings showed that positive APAs at baseline and after treatment, together with susceptible HLA alleles, could become predictive biomarkers for ICI-IAD and ICI- hypophysitis, respectively.

Research Background

Immune checkpoint inhibitors (ICIs) have recently emerged as promising treatments for advanced malignancies. However, ICIs can cause adverse events, termed immune-related adverse events (irAEs), including pneumonitis, skin toxicities, colitis, and endocrine dysfunction. Endocrine irAEs comprise pituitary dysfunction, adrenal insufficiency, thyroid dysfunction, hypoparathyroidism and type 1 diabetes mellitus (T1DM). Pituitary-irAEs are almost always accompanied by adrenocorticotropic hormone (ACTH) deficiency, a life-threatening disorder. We conducted a prospective study for the development of pituitary irAEs by analyzing all the metastatic melanoma and non-small cell lung cancer patients treated with ICIs at Nagoya University Hospital since November 2, 2015, reporting that there were two different types of pituitary irAEs, i.e., isolated adrenocorticotropic hormone (ACTH) deficiency (IAD) without pituitary enlargement and hypophysitis with deficiency of multiple anterior pituitary hormones accompanied by pituitary enlargement. We also reported that pituitary-irAEs accompanied by ACTH deficiency were associated with a better outcome of ICI treatments. However, it is not possible to identify patients who may develop pituitary irAEs prior to ICI treatment.

To identify the predictive biomarkers for pituitary irAEs, APAs and HLA alleles were analyzed in 62 patients (17 who developed ICI-IAD, 5 who developed ICI-hypophysitis, and 40 who did not develop pituitary irAEs) treated with ICIs between November 2, 2015 and March 31, 2020 at Nagoya University Hospital.

Research Results

Eleven of 17 (64.7%) patients who developed ICI-IAD had APAs at baseline, whereas APAs were positive only in 1 of 40 (2.5%) control patients. Although APAs were negative at baseline in all patients who developed ICI-hypophysitis, they had become positive before the onset of ICI- hypophysitis in 3 of 4 patients several weeks after ipilimumab administration. At the onset of ICI-IAD and ICI- hypophysitis, APAs were positive in 15 of 17 (88.2%) and 4 of 5 (80.0%) patients, respectively. The prevalence of HLA-Cw12, -DR15, -DQ7, and -DPw9 was significantly higher in patients with ICI-IAD, whereas that of HLA-Cw12 and -DR15 was significantly higher in patients with ICI-H than in controls.

Research Summary and Future Perspective

Because pituitary irAEs are almost always accompanied by ACTH deficiency, which is life-threatening, it may be ideal to identify patients with a risk of pituitary irAEs before the initiation of ICI treatment. Our findings showed that positive APAs at baseline and after treatment, together with susceptible HLA alleles, could become predictive biomarkers for ICI-IAD and ICI-hypophysitis, respectively. It would be useful to establish an enzyme-linked immunosorbent assay (ELISA) system to measure APAs quantitatively, which

can be clinically implemented for the future. Based on the findings in this study, establishing prediction system for the development of pituitary irAEs using combination of APAs and HLA can allow oncologists to pay more attentions to the patients who have a high risk of pituitary irAEs.

Publication

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