ChinaRxiv

AI translation · View original & related papers at
chinarxiv.org/items/chinaxiv-202212.00093

Incidence and Management of Endocrine Adverse Events Associated with Immune Checkpoint Inhibitors: A Single-Center Real-World Analysis Postprint

Authors: Chang Junpei, Chen Lu, Wu Tong, Zhao Xiaoli, Duan Fangfang, Liu Danna, Kong Tiandong, Kong Tiandong

Date: 2022-12-20T00:00:00+00:00

Abstract

Objective: To investigate the real-world incidence and management protocols of endocrine adverse events associated with immune checkpoint inhibitors (ICIs). Methods: A retrospective analysis was performed on solid tumor patients who received ICI therapy at our hospital from January 2019 to March 2022. Endocrine adverse events occurring during treatment were observed and managed according to standardized severity-graded protocols. Results: Of 204 enrolled patients, 12 developed ICI-related endocrine adverse events. These included 9 cases (4.4%) of hypothyroidism (grade I: 1 case; grade II: 7 cases; grade III: 1 case) with a median onset of 7 weeks after the first ICI administration; 1 case (0.5%) of hyperthyroidism (grade I) occurring 9 weeks after treatment initiation; 1 case (0.5%) of type 1 diabetes mellitus (grade IV) occurring 6 weeks after treatment; and 1 case (0.5%) of adrenal insufficiency (grade III) occurring 7 weeks after treatment. All patients received prompt management per the graded protocol, achieved symptom resolution or normalization, and were able to continue ICI therapy. Conclusion: The risk of endocrine adverse events during ICI therapy is relatively high, particularly thyroid dysfunction. Regular endocrine monitoring is required during treatment, and prompt management does not preclude subsequent ICI therapy.

Full Text

Preamble

Occurrence and Management of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors: A Single-Center Real-World Study

Chang Jun-pei[1], Chen Lu[2], Wu Tong[3], Zhao Xiao-li[2], Duan Fang-fang[2], Liu Dan-na[3], Kong Tian-dong[2]*

[1] Department of Endocrinology, Cancer Hospital of Henan University (The Third People' s Hospital of Zhengzhou)
[2] Department of Medical Oncology, Cancer Hospital of Henan University (The Third People' s Hospital of Zhengzhou)
[3] Department of Pharmacy, Cancer Hospital of Henan University (The Third People' s Hospital of Zhengzhou)

Corresponding author: Kong Tian-dong, Chief Physician; E-mail: kongtian-dong@126.com

Abstract

Objective: To investigate the occurrence and management of endocrine adverse events induced by immune checkpoint inhibitors (ICIs) in a real-world clinical setting. **Methods:** We retrospectively analyzed solid tumor patients treated with ICIs at our hospital from January 2019 to March 2022, observing endocrine system adverse events during treatment and providing standardized management according to severity grading. **Results:** Among 204 enrolled patients, 12 developed ICIs-related endocrine adverse events. Specifically, 9 patients (4.4%) experienced hypothyroidism (1 case grade I, 7 cases grade II, 1 case grade III) at a median onset of 7 weeks after the first immunotherapy dose. One patient (0.5%) developed hyperthyroidism (grade I) at 9 weeks, one (0.5%) developed type 1 diabetes (grade IV) at 6 weeks, and one (0.5%) developed adrenal insufficiency (grade III) at 7 weeks. All patients received timely management according to standardized protocols, with symptoms improving or resolving, and all continued subsequent ICIs treatment. **Conclusion:** Endocrine adverse events represent a relatively common toxicity during ICIs therapy, particularly thyroid dysfunction, necessitating regular endocrine monitoring during treatment. Prompt management does not preclude continuation of ICIs therapy.

Keywords: Immune checkpoint inhibitors; Programmed death receptor-1; Programmed death ligand-1; Immune-related adverse events

Introduction

Immune checkpoint inhibitors (ICIs) represent one of the most significant advances in malignant tumor treatment in recent years, fundamentally transforming oncologic therapeutic strategies. ICIs primarily comprise three categories: cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibodies, programmed death receptor-1 (PD-1) monoclonal antibodies, and programmed death ligand-1 (PD-L1) monoclonal antibodies [1]. These agents work by blocking the interaction between tumor cells expressing immune checkpoints and immune cells, thereby disrupting tumor-mediated immunosuppression [2]. ICIs

have now received regulatory approval for numerous solid tumor indications [3-7].

With expanding clinical use and longer follow-up periods, ICIs have been observed to affect multiple organ systems, leading to immune-related adverse events (irAEs) [8]. Unlike chemotherapy-induced toxicities, irAEs require prompt recognition and management to prevent severe complications. Endocrine irAEs are particularly common, primarily including thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), pituitary dysfunction (central hypothyroidism, central adrenal insufficiency, hypogonadotropic hypogonadism), while primary adrenal insufficiency, hypercalcemia, type 1 diabetes, and hypoparathyroidism are relatively rare [9, 10].

Currently, only one CTLA-4 monoclonal antibody is available in China (ipilimumab from Bristol-Myers Squibb), while three PD-L1 inhibitors have been approved (atezolizumab [Roche], durvalumab [AstraZeneca], and envafolimab [Simcere]). Numerous PD-1 monoclonal antibodies are also available, including pembrolizumab (Merck), nivolumab (Bristol-Myers Squibb), sintilimab (Innovent), camrelizumab (Hengrui), toripalimab (Junshi), tislelizumab (BeiGene), and penpulimab (CTTQ) . Despite the variety of agents and manufacturers, the pathogenesis of endocrine-related irAEs is consistent, involving autoreactive T cells, autoantibodies, and cytokines that collectively target endocrine glands [11]. The rich blood supply of endocrine glands increases their susceptibility to these mechanisms, making them frequent targets of irAEs [12].

Reported incidence rates of endocrine irAEs from randomized controlled trials (RCTs) vary substantially, ranging from 1-20% [13-18], and some adverse events can be challenging to diagnose despite their potentially severe consequences. To characterize the real-world occurrence and management of ICIs-related endocrine adverse events, we retrospectively analyzed patients receiving ICIs therapy at our center over the past three years to provide clinical guidance.

Methods

1.1 Patient Data

This retrospective analysis was approved by our hospital's ethics committee. We identified 204 solid tumor patients treated with ICIs between January 2019 and March 2022. Inclusion criteria were: (1) histologically or cytologically confirmed malignancy; (2) complete medical records or availability for telephone/WeChat follow-up; (3) no pre-existing endocrine disorders (including hyperthyroidism, hypothyroidism, diabetes, hypophysitis) prior to immunotherapy; (4) normal baseline laboratory values for complete blood count, liver and kidney function, thyroid function (T3, T4, TSH), and blood glucose; (5) absence of paraneoplastic syndrome before initial immunotherapy; and (6) completion of at least one cycle of immunotherapy.

ICIs were administered as monotherapy in 20 patients (9.8%), combined with chemotherapy in 67 patients (32.8%), or combined with anti-angiogenic targeted therapy in 117 patients (57.4%). Targeted agents were exclusively anti-angiogenic drugs including anlotinib, lenvatinib, bevacizumab, and axitinib .

1.2 Diagnostic and Grading Criteria for ICIs-Related Endocrine Adverse Events

ICIs-related endocrine adverse events include thyroid dysfunction (hypothyroidism, hyperthyroidism, thyroiditis), acute hypophysitis (resulting in hypopituitarism), primary adrenal insufficiency, type 1 diabetes, hypercalcemia, and hypoparathyroidism [8, 9]. Adverse events were graded according to CTCAE version 5.0 [19] and the 2021 CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicities [20].

(1) Hyperthyroidism: Characterized by excessive thyroid hormone levels [21]. During ICIs therapy, diagnosis is established when patients develop unexplained palpitations, sweating, increased appetite with weight loss, elevated serum FT4 or TT3, and normal or suppressed TSH. Baseline evaluations should include TSH, FT4, TT3, and thyroid antibodies [20, 21].

(2) Hypothyroidism: Resulting from insufficient thyroid hormone production [21]. Diagnosis is confirmed when patients present with unexplained fatigue, weight gain, hair loss, cold intolerance, constipation, or depression, accompanied by elevated TSH and reduced FT4. Baseline assessments should include TSH, FT4, TT3, and thyroid antibodies [20, 21].

(3) Hypophysitis: Patients developing unexplained persistent headache or visual disturbances during ICIs therapy require immediate evaluation for hypophysitis [20]. Brain MRI typically shows pituitary enlargement, thickened stalk, suprasellar convexity, or heterogeneous glandular enhancement. Baseline endocrine workup should include ACTH, TSH, FT4, FT3, thyroid antibodies, LH, FSH, testosterone, and prolactin [21].

(4) Type 1 Diabetes: Also known as autoimmune diabetes, mediated by autoreactive T-cell destruction of pancreatic β-cells. Clinical manifestations include polyuria, polydipsia, weight loss, nausea, vomiting, hyperglycemia, and some patients present with diabetic ketoacidosis [21].

(5) Primary Adrenal Insufficiency: Results from inadequate cortisol production by the adrenal cortex, sometimes with concurrent aldosterone deficiency, and may be caused by Addison' s disease or other adrenal cortical abnormalities [21].

(6) Hypoparathyroidism: A clinical syndrome caused by reduced parathyroid hormone (PTH) secretion and/or activity, characterized by recurrent muscle cramps, tetany, positive Trousseau' s and Chvostek' s signs [21]. Laboratory findings include hypocalcemia, hyperphosphatemia, and markedly low or inappropriately normal PTH levels [21].

(7) Hyperparathyroidism: Excessive PTH production leading to hypercalcemia [21].

1.3 Statistical Analysis

Data were compiled using Excel spreadsheets. Follow-up continued until March 1, 2022, with laboratory and imaging assessments conducted during outpatient visits or hospitalizations, achieving a 100% follow-up rate.

Results

2.1 Incidence of ICIs-Related Endocrine Adverse Events

Among 204 patients, 12 developed ICIs-related endocrine adverse events: 9 cases (4.4%) of hypothyroidism (1 grade I, 7 grade II, 1 grade III) with a median onset of 7 weeks after the first immunotherapy dose; 1 case (0.5%) of hyperthyroidism (grade I) at 9 weeks; 1 case (0.5%) of type 1 diabetes (grade IV) at 6 weeks; and 1 case (0.5%) of adrenal insufficiency (grade III) at 7 weeks.

All 9 hypothyroidism cases were associated with PD-1 monoclonal antibodies: 3 combined with chemotherapy, 4 with targeted therapy, and 2 as monotherapy. The hyperthyroidism case occurred with PD-1 monotherapy at 9 weeks. The type 1 diabetes case developed with PD-1 combined with chemotherapy at 6 weeks. The adrenal insufficiency case occurred with PD-1 combined with targeted therapy at 7 weeks .

2.2 Clinical Manifestations and Management

The 9 hypothyroidism patients presented primarily with fatigue, decreased appetite, nausea, and reduced activity. All showed symptom improvement after thyroid hormone replacement therapy, with normalization of T3 and T4 levels, allowing continuation of immunotherapy without interruption.

The single hyperthyroidism patient was asymptomatic and received no antithyroid medication, continuing ICIs therapy without modification.

Patient 11 (ICIs-related diabetes): A 67-year-old female diagnosed with extensive-stage small cell lung cancer with hepatic, vertebral, and brain metastases in September 2021. She received EP regimen plus anlotinib and penpulimab, achieving partial response after 2 cycles. At week 6 of immunotherapy, she developed nausea, vomiting, weakness, and intermittent altered consciousness. Laboratory evaluation revealed fasting glucose of 31.5 mmol/L, urinary ketones 3+, HbA1c 6.3%, with negative anti-insulin antibodies (AIA), islet cell antibodies (ICA), and glutamic acid decarboxylase antibodies (GAD). With no prior diabetes history, multidisciplinary consultation confirmed ICIs-related diabetic ketoacidosis. Under endocrinology guidance, insulin therapy and supportive management led to symptom resolution. She continues on the original

regimen with insulin support, maintaining stable disease without further severe adverse events.

Patient 12 (ICIs-related adrenal insufficiency): A 62-year-old male diagnosed with advanced left lung squamous cell carcinoma (driver gene negative) in July 2020. After chemoradiotherapy, he received durvalumab maintenance therapy. At week 7 (after 3 cycles), he developed marked fatigue, lethargy, weakness, and arrhythmia. Thyroid function was normal, but morning cortisol was 0.866 g/dl and afternoon cortisol 0.627 g/dl (normal 7-9 g/dl). Multidisciplinary consultation diagnosed secondary adrenal insufficiency, attributed to ICIs after excluding other causes. Prednisone and metoprolol achieved symptom resolution, allowing continuation of ICIs therapy.

2.3 Management Algorithm for ICIs-Related Endocrine Adverse Events

During ICIs therapy, any endocrine-related symptoms warrant careful evaluation for potential ICIs-related toxicity. Initial manifestations are often nonspecific, particularly for hypophysitis and adrenal insufficiency, which can be challenging to diagnose early. Multidisciplinary consultation with endocrinology involvement is essential when indicated. The detailed assessment and management algorithm is presented in [Figure 1: see original paper].

Discussion

Immune checkpoint inhibitors have become a cornerstone of cancer treatment. Immune checkpoints are small molecules expressed on T-lymphocyte surfaces that maintain immune homeostasis and self-tolerance while regulating immune response duration and magnitude [22]. ICIs are inhibitory drugs targeting these checkpoints; these monoclonal antibodies block immune checkpoints to activate T-cell function and eliminate tumor cells [23]. However, this mechanism can disrupt immune tolerance and increase autoantigen-mediated adverse reactions [24], termed immune-related adverse events (irAEs). Besides skin and gastrointestinal systems, the endocrine system is among the most frequently affected. Endocrine irAEs include hypophysitis, thyroid dysfunction, parathyroid dysfunction, type 1 diabetes, and primary adrenal insufficiency [25], which can be life-threatening if not promptly recognized and treated. Understanding their clinical manifestations, diagnosis, and management is therefore essential.

A large meta-analysis reported predicted incidences of 6.6% for ICIs-related hypothyroidism and 2.9% for hyperthyroidism [25], with hypothyroidism being significantly more common. Our single-center real-world analysis similarly identified thyroid dysfunction as the most frequent endocrine adverse event, occurring in 10 patients (4.9% overall). Hypothyroidism predominated with 9 cases (4.4%), while hyperthyroidism occurred in only 1 case (0.5%), consistent with literature reports. Previous studies show that combined PD-1 plus ipilimumab

therapy yields higher thyroid dysfunction rates (13.2%) than monotherapy [15, 25], while single-agent PD-1, PD-L1, and ipilimumab have similar rates of 3-9% without significant differences [26-28]. In our cohort, thyroid dysfunction occurred with PD-1 combined with chemotherapy (3 cases), targeted therapy (4 cases), or as monotherapy (3 cases), though low event numbers precluded statistical comparison. Most thyroid dysfunction cases were grade 1-2, and all 10 patients continued ICIs therapy after adequate thyroid hormone supplementation or adjustment, with none discontinuing treatment due to thyroid adverse events.

We also observed rare endocrine toxicities: one case each of type 1 diabetes and adrenal insufficiency (0.5% each). ICIs-related diabetes is uncommon, with limited large cohort studies and mostly case reports documenting incidence rates of 0.9-1.9% [29, 30]. Nearly all cases are associated with PD-1 inhibitors [31], with only 2 reports linked to CTLA-4 blockade [32]. Median onset ranges from 13-504 days, most frequently within the first 6 months [33]. Our patient developed severe diabetic ketoacidosis (DKA) at week 6 (after 2 doses) of PD-1 inhibitor therapy, aligning with reports that 76% of ICIs-related diabetes presents with DKA [29, 34]. ICIs-related diabetes is typically permanent, as glucocorticoids cannot reverse destroyed islet cells [35], and their use is not recommended [36]. Most patients require lifelong insulin replacement. Whether immunotherapy can be safely resumed after stabilization remains controversial [37]. In our case, multidisciplinary assessment concluded that insulin-supported resumption of immunotherapy posed low DKA risk while providing oncologic benefit. The patient successfully restarted immunotherapy without further severe adverse events and maintains stable disease.

ICIs-related adrenal insufficiency is a rare irAE with reported incidence of 0.8-2% [38], resulting from drug-induced autoimmune adrenalitis. Due to low incidence and limited follow-up, clear risk factors and epidemiological characteristics remain undefined. Monotherapy may cause onset after several months, while combination therapy may accelerate presentation [39]. Our patient developed grade 3 adrenal insufficiency at week 7 after PD-1 inhibitor plus targeted therapy, achieving normal cortisol levels with hormone replacement and continuing ICIs therapy.

ICIs-related hypophysitis is a common endocrine toxicity of ipilimumab but rare with PD-1/PD-L1 inhibitors. The aforementioned meta-analysis [25] of 6,472 ICIs-treated patients reported hypophysitis in 1.3% (85 cases), with 34 cases grade 3 or higher. Stratified analysis showed the highest incidence with PD-1 plus ipilimumab combination (6.4%), followed by ipilimumab monotherapy (3.2%), and lowest with PD-1 inhibitors. This complication typically occurs weeks to months after ICIs initiation [40]. Due to limited ipilimumab availability, our cohort included no patients receiving this agent, and we observed no hypophysitis cases with PD-1/PD-L1 inhibitors.

This study provides real-world, single-center data on endocrine adverse events since ICIs market entry, characterizing their occurrence and management while

summarizing treatment algorithms from literature to guide clinical practice.

Although ICIs-related endocrine toxicity is uncommon, limiting large cohort studies—particularly for diabetes and adrenal insufficiency where evidence derives primarily from case reports—the widespread use of ICIs in oncology necessitates active involvement of oncologists, endocrinologists, and clinical pharmacists. As clinical experience and research data accumulate, management protocols for endocrine adverse events will continue to evolve.

References

[1] Marin-Acevedo JA, Kimbrough EO, Lou Y. Next generation of immune checkpoint inhibitors and beyond[J]. J Hematol Oncol, 2021,14(1):45. DOI: 10.1186/s13045-021-01056-8.

[2] Bagchi S, Yuan R, Engleman EG. Immune Checkpoint Inhibitors for the Treatment of Cancer: Clinical Impact and Mechanisms of Response and Resistance[J]. Annu Rev Pathol, 2021,16:223-249. DOI: 10.1146/annurev-pathol-042020-042741.

[3] Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma[J]. N Engl J Med, 2011,364(26):2517-2526. DOI: 10.1056/NEJMoa1104621.

[4] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer[J]. N Engl J Med, 2015,373(17):1627-1639. DOI: 10.1056/NEJMoa1507643.

[5] Carbone DP, Gandara DR, Antonia SJ, et al. Non-Small-Cell Lung Cancer: Role of the Immune System and Potential for Immunotherapy[J]. J Thorac Oncol, 2015,10(7):974-984. DOI: 10.1097/JTO.0000000000000551.

[6] Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study[J]. Lancet Oncol, 2017,18(9):1182-1191. DOI: 10.1016/S1470-2045(17)30422-9.

[7] Cimino-Mathews A, Thompson E, Taube JM, et al. PD-L1 (B7-H1) expression and the immune tumor microenvironment in primary and metastatic breast carcinomas[J]. Hum Pathol, 2016,47(1):52-63. DOI: 10.1016/j.humpath.2015.09.003.

[8] Geisler AN, Phillips GS, Barrios DM, et al. Immune checkpoint inhibitor-related dermatologic adverse events[J]. J Am Acad Dermatol, 2020,83(5):1255-1268. DOI: 10.1016/j.jaad.2020.03.132.

[9] Elia G, Ferrari SM, Galdiero MR, et al. New insight in endocrine-related adverse events associated to immune checkpoint blockade[J]. Best Pract Res Clin Endocrinol Metab, 2020,34(1):101370. DOI: 10.1016/j.beem.2019.101370.

[10] Chang LS, Barroso-Sousa R, Tolaney SM, et al. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints[J]. Endocr Rev, 2019,40(1):17-65. DOI: 10.1210/er.2018-00006.

[11] Kennedy LB, Salama A. A review of cancer immunotherapy toxicity[J]. CA Cancer J Clin, 2020,70(2):86-104. DOI: 10.3322/caac.21596.

[12] Joshi MN, Whitelaw BC, Palomar MT, et al. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review[J]. Clin Endocrinol (Oxf), 2016,85(3):331-339. DOI: 10.1111/cen.13063.

[13] Corsello SM, Barnabei A, Marchetti P, et al. Endocrine side effects induced by immune checkpoint inhibitors[J]. J Clin Endocrinol Metab, 2013,98(4):1361-1375. DOI: 10.1210/jc.2012-4075.

[14] Torino F, Barnabei A, Paragliola RM, et al. Endocrine side-effects of anti-cancer drugs: mAbs and pituitary dysfunction: clinical evidence and pathogenic hypotheses[J]. Eur J Endocrinol, 2013,169(6):R153-164. DOI: 10.1530/EJE-13-0434.

[15] Barroso-Sousa R, Ott PA, Hodi FS, et al. Endocrine dysfunction induced by immune checkpoint inhibitors: Practical recommendations for diagnosis and clinical management[J]. Cancer, 2018,124(6):1111-1121. DOI: 10.1002/cncr.31200.

[16] Illouz F, Drui D, Caron P, et al. Expert opinion on thyroid complications in immunotherapy[J]. Ann Endocrinol (Paris), 2018,79(5):555-561. DOI: 10.1016/j.ando.2018.07.007.

[17] Byun DJ, Wolchok JD, Rosenberg LM, et al. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies[J]. Nat Rev Endocrinol, 2017,13(4):195-207. DOI: 10.1038/nrendo.2016.205.

[18] Sznol M, Postow MA, Davies MJ, et al. Endocrine-related adverse events associated with immune checkpoint blockade and expert insights on their management[J]. Cancer Treat Rev, 2017,58:70-76. DOI: 10.1016/j.ctrv.2017.06.002.

[19] Freites-Martinez A, Santana N, Arias-Santiago S, et al. Using the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies[J]. Actas Dermosifiliogr (Engl Ed), 2021,112(1):90-92. DOI: 10.1016/j.ad.2019.05.009.

[20] Chinese Society of Clinical Oncology Guidelines Working Committee. CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicity 2021[M]. 1st Edition. Beijing: People' s Medical Publishing House, 2021.

[21] Ge Jun-bo, Xu Yong-jian, Wang Chen. Internal Medicine[M]. 9th Edition. Beijing: People' s Medical Publishing House, 2018.

[22] Brahmer JR, Lacchetti C, Thompson JA. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Ther-

apy: American Society of Clinical Oncology Clinical Practice Guideline Summary[J]. J Oncol Pract, 2018,14(4):247-249. DOI: 10.1200/JOP.18.00005.

[23] Dong M, Yu T, Zhang Z, et al. ICIs-Related Cardiotoxicity in Different Types of Cancer[J]. J Cardiovasc Dev Dis, 2022,9(7)DOI: 10.3390/jcdd9070203.

[24] Haanen J, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[J]. Ann Oncol, 2017,28(suppl_4):iv119-iv142. DOI: 10.1093/annonc/mdx225.

[25] Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis[J]. JAMA Oncol, 2018,4(2):173-182. DOI: 10.1001/jamaoncol.2017.3064.

[26] Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial[J]. Lancet Oncol, 2015,16(5):522-530. DOI: 10.1016/S1470-2045(15)70122-1.

[27] Hersh EM, O' Day SJ, Powderly J, et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma[J]. Invest New Drugs, 2011,29(3):489-498. DOI: 10.1007/s10637-009-9376-8.

[28] Slovin SF, Higano CS, Hamid O, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study[J]. Ann Oncol, 2013,24(7):1813-1821. DOI: 10.1093/annonc/mdt107.

[29] Stamatouli AM, Quandt Z, Perdigoto AL, et al. Collateral Damage: Insulin-Dependent Diabetes Induced With Checkpoint Inhibitors[J]. Diabetes, 2018,67(8):1471-1480. DOI: 10.2337/dbi18-0002.

[30] Tsang V, McGrath RT, Clifton-Bligh RJ, et al. Checkpoint Inhibitor-Associated Autoimmune Diabetes Is Distinct From Type 1 Diabetes[J]. J Clin Endocrinol Metab, 2019,104(11):5499-5506. DOI: 10.1210/jc.2019-00423.

[31] Bai X, Lin X, Zheng K, et al. Mapping endocrine toxicity spectrum of immune checkpoint inhibitors: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase[J]. Endocrine, 2020,69(3):670-681. DOI: 10.1007/s12020-020-02355-9.

[32] Wright JJ, Salem JE, Johnson DB, et al. Increased Reporting of Immune Checkpoint Inhibitor-Associated Diabetes[J]. Diabetes Care, 2018,41(12):e150-e151. DOI: 10.2337/dc18-1465.

[33] Akturk HK, Kahramangil D, Sarwal A, et al. Immune checkpoint inhibitor-induced Type 1 diabetes: a systematic review and meta-analysis[J]. Diabet Med, 2019,36(9):1075-1081. DOI: 10.1111/dme.14050.

[34] Clotman K, Janssens K, Specenier P, et al. Programmed Cell Death-1 Inhibitor-Induced Type 1 Diabetes Mellitus[J]. J Clin Endocrinol Metab, 2018,103(9):3144-3154. DOI: 10.1210/jc.2018-00423.

[35] Aleksova J, Lau PK, Soldatos G, et al. Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma[J]. BMJ Case Rep, 2016,2016DOI: 10.1136/bcr-2016-217454.

[36] Del Rivero J, Cordes LM, Klubo-Gwiezdzinska J, et al. Endocrine-Related Adverse Events Related to Immune Checkpoint Inhibitors: Proposed Algorithms for Management[J]. Oncologist, 2020,25(4):290-300. DOI: 10.1634/theoncologist.2018-0470.

[37] Zhao J, Su CX. Interpretation of the "CSCO Guidelines for Management of Immune Checkpoint Inhibitor-Related Toxicity" : Comparison with NCCN Guidelines for Management of Immunotherapy-Related Toxicity[J]. J Pract Oncol, 2020,35(1):11-15. DOI: 10.13267/j.cnki.syzlzz.2020.01.002.

[38] de Filette J, Andreescu CE, Cools F, et al. A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors[J]. Horm Metab Res, 2019,51(3):145-156. DOI: 10.1055/a-0843-3366.

[39] Chinese Society of Endocrinology, Immunology and Endocrinology Group. Expert consensus on endocrine immune-related adverse events induced by immune checkpoint inhibitors (2020)[J]. Chin J Endocrinol Metab, 2021,37(01):1-16.

[40] Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review[J]. Eur J Cancer, 2016,54:139-148. DOI: 10.1016/j.ejca.2015.11.016.

Note: Figure translations are in progress. See original paper for figures.

Source: ChinaXiv —Machine translation. Verify with original.