Follow-up Care for Patients Receiving Immune Checkpoint Inhibitors

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ABSTRACT

The rapid advances in cancer immunotherapy using immune checkpoint inhibitors (ICIs) have led to significantly improved survival of patients. But at the same time, it also associates with multiple immune-related adverse events (irAEs). The irAEs can affect a wide range of organs, and induce nonspecific symptoms with delayed onset and prolonged duration that is easily neglected, which may lead to life-threatening disorders. Therefore, follow-up care for patients receiving ICIs for irAEs management has become an essential competency in cancer nursing. There are several guidelines about the management of irAEs, which focused on diagnosis, grading, and treatment. However, studies on relevant follow-up care are rare. Nurses play an important role in follow-up care, whose relevant knowledge and skills are indispensable. Combined with domestic and foreign guidelines and related studies, this paper reviewed the occurrence and characteristics of irAEs and highlighted the contents, timing, models, and effects of follow-up care for patients receiving ICIs, to provide a reference for clinical nursing practice and improve the safety of immunotherapy for patients.

Key words: Follow-up, immune checkpoint inhibitors, immune-related adverse events

Introduction

In recent years, immunotherapy, represented by immune checkpoint inhibitors (ICIs), has become an important means of cancer therapy following surgery, chemotherapy, radiation, and targeted therapy.[1] Common ICIs include cytotoxic T lymphocyte-associated antigen 4 (CTLA4), programmed death-1 receptor (PD-1), and protein programmed death-ligand 1 (PD-L1). It is currently approved by the FDA for the treatment of lung cancer, melanoma, kidney cancer, head-and-neck cancer, colorectal cancer, and other malignant cancers.[2] However, at the same time, ICIs also lead to extensive immune-related adverse events (irAEs).[3]

To promote efficient management of irAEs, several major oncology organizations including the Society for Immunotherapy of Cancer,[4] European Society of Medical Oncology,[3,5] American Society of Clinical Oncology,[3] and National Comprehensive Cancer Network,[6] as well as two nursing organizations concluding Oncology Nursing Society[7] and Melanoma Nursing Initiative,[8] have published guidelines for diagnosis, grading, treatment, and care in hospitals. However, follow-up care has not been systematically studied.

Identification and occurrence of immune-related adverse events

The adverse events caused by immunotherapy represented by ICIs were named irAEs, which can affect almost the entire body system.[3] The most frequently occurring irAEs affect the skin, colon, endocrine organs, liver, and lungs. The incidence for any-grade irAEs due to single-agent ICI therapy is as high as 90%.[9,10] Among them, ≥Grade 3 irAEs occur in about 20%–43% of the patients[11] and 2% die.[12] Moreover, the incidence of irAEs is significantly increased when ICIs are used in combination. Specifically, the incidence of irAEs is higher when CTLA-4 agent is used. The most common irAEs induced by CTLA-4 monotherapy are colitis, followed by hypophysitis and rashes. However, pneumonia, hypothyroidism, arthralgia, and vitiligo are more commonly induced by anti-PD-1 therapy.[13] The relationship between irAEs and clinical outcome is one of the hot research topics. Several irAEs have been reported to be associated with progression-free survival or overall survival, though it is still controversial.[14-18]

Characteristics and mechanisms of immune-related adverse events

ICIs enhance immune functions of the body against cancer by specifically binding to the corresponding immune checkpoints, clearing the immunosuppressive effect, and restoring the proliferation and effect of T cells. However, immune checkpoints are key proteins for maintaining immune balance, and interrupting their functions by ICIs can lead to immune tolerance disorders and immune damage on normal tissues or organs.[3] Moreover, the symptom and mechanism of irAEs caused by chemotherapy, targeted therapy, or other traditional cancer therapies are very different. Therefore, fundamental knowledge of irAEs characteristics is essential for providing optimal care of the patients receiving such therapies.

The irAEs may even cause lethal consequences such as neurological disorders and myocarditis, and the symptom is usually nonspecific (e.g., fatigue, diarrhea, and rash), which is easily to be confused with the symptom of other diseases. Meanwhile, they share similar abnormal imaging or laboratory results with cancer progression or the side effects of chemotherapy, which are easily neglected by the patients or the health providers.[19] In addition, irAEs typically have a delayed onset and prolonged duration compared to the adverse events caused by chemotherapy, most of which appear within weeks to 3 months following the initiation of immunotherapy, while they also show up after months or even years following withdrawal of the agents.[20]

Treatment Principles

According to the relevant guidelines,[3-6] irAEs are graded by the Common Terminology Criteria for Adverse Events (CTCAE) from 1 (mild) to 4 (life threatening). Most irAEs are either Grade 1 (mild; asymptomatic or mildly symptomatic) or Grade 2 (moderate; moderately symptomatic, with some impact on daily living activities). For Grade 1 irAEs, frequent monitoring is needed, and maintenance or conservative ICIs therapy is considered based on the symptom and involved organs. For Grade 2 irAEs, ICIs are generally withheld and oral corticosteroids are given. For some Grade 3 (severely symptomatic or having a large impact on daily living activities) or Grade 4 (life threatening) irAEs, ICIs are usually permanently discontinued, and high doses of corticosteroids are given. For those who do not respond to 72-h high-dose corticosteroids, infliximab may be considered. However, due to the hepatic toxicity of infliximab, mycophenolate is preferred. Restoring ICIs therapy is not considered, especially in the case of Grade 4 or fatal irAEs, until the irAEs have turned into the first grade.

Follow-up Care for Immune-Related Adverse Events

Heath providers are required to follow up and recognize the onset of irAEs in time, because early identification and treatment are essential to minimize the severity. Any worsened toxic sequelae from previous treatments are considered as suspected irAEs. As suggested by relevant guidelines,[3-6] symptom assessment, laboratory tests, physical examination, and imaging performed at baseline (before initiating immunotherapy) are used as the references for clinical, biological, or imaging abnormality observed following treatment. Patients need to be closely monitored at the beginning of treatment, during treatment, or even after the discontinuation of the treatment. We recommend that such surveillance to be continued for 12 months following the discontinuation of immunotherapy.

Contents and Timing

Symptom assessment

Nurses and patients need to learn about the full range of performance and the timeline of potential irAEs. It is important for the patients to report any unusual signs or symptom at the first occurrence, even appearing months after the completion or discontinuation of the treatment.[21] They should be aware of the importance of carrying an immunotherapy wallet card all the time even after discontinuing therapy,[7] which helps inform

the emergency department (ED) or other health providers about the immunotherapy regimen they are receiving or have received as well as the associated irAEs.

Dermatologic irAEs are developing in 30%–50% of the patients, which typically occurs within the first two cycles of ICI therapy.[22] The symptom includes pruritus, burning sensation, erythematous rash, alopecia, stomatitis, vitiligo, and bullous dermatitis.[23] Bullous dermatitis and Stevens–Johnson syndrome/toxic epidermal necrolysis are rare, but serious, and potentially life-threatening complications of ICIs, and the patients require inpatient care and pain/palliative consultations from the aspects of urgent dermatology, ophthalmology, urology, and infectious diseases.[5,6]

As the second common form of irAE, gastrointestinal irAEs include diarrhea and colitis.[24] A systematic review of CTLA-4 therapy[9] shows that 27%–54% of the patients had diarrhea and 8%–22% had colitis, most of which occurred within 5–8 weeks following the initial therapy, whereas several occurred after 1 month of drug withdrawal. The recovery process is relatively slow. Diarrhea and colitis can be recurrent even after the stoppage of ICIs.[25] Some of the common clinical manifestations are bloating, gas, fever, abdominal pain, diarrhea, bloody stool and mucus, fever, etc.[26] Significant hepatotoxicity is a less common manifestation of checkpoint inhibition, manifested as asymptomatic elevation of transaminases and rare elevations of bilirubin. It is associated with 3%–9% of CTLA-4 and 1%–2% of PD-1/PD-L1 therapies, usually at 6–14 weeks after the initiation of the immunotherapy.[27] Occasionally, patients present with abdominal pain, ascites, jaundice, somnolence, and mental status change.

Endocrine toxicity is a very common type of irAE, which includes hypophysitis and thyroid dysfunction (the most common[28,29]), as well as primary adrenal insufficiency, hypoparathyroidism, and Type 1 diabetes mellitus. The incidence of endocrine toxicity is up to 20%, which usually occurs at 9–10 weeks following ICI treatment.[30] The symptom is usually nonspecific, which includes nausea, vomiting, appetite loss, weight loss, general weakness, fatigue, mild cognitive dysfunction, hypotension, and headache. The occurrence of hypophysitis is commonly observed in patients following treatment with anti-CTLA-4 agents than PD-1/PD-L1 inhibitors,[31] and it occurs more frequently in males and older patients.[32] On the contrary, the occurrence of thyroid dysfunction is commonly observed in patients following treatment with PD-1/PD-L1 inhibitors than those with anti-CTLA-4 agents, and ICI-related thyroid dysfunctions occur more frequently in females.[30] Adrenal insufficiency caused by hypophysitis[33] and diabetic ketoacidosis caused by Type 1 diabetes mellitus[34,35] are

two potentially fatal endocrine toxicities, which need to be noticed though rarely occur. Unlike the other irAEs, endocrine toxicity is treated based on the replacement of the deficient hormone.

Pneumonitis occurs in about 3%–5% of the patients with ICI therapy,[36] usually at 2.5–21 months (median of 2.8 months) following the therapy. Compared with anti-CTLA-4 agents, PD-1/PD-L1 inhibitors confer a higher incidence of pneumonitis at any grade and severity,[37] while the highest incidence is found in patients with lung or renal cancer,[38] especially those previously had lung irradiation.[39] Other risk factors include preexisting fibrotic lung disease, comorbidities such as chronic obstructive pulmonary disease,[40] a history of current or prior tobacco use,[41] and combinations of ICI therapy.[42,43] The symptom includes dyspnea, dry cough, wheezing, tachycardia, and severe dyspnea, which rapidly progresses to fulminant respiratory failure.[3,4] However, around one-third of the patients are asymptomatic, and can only be diagnosed with routine restaging imaging.[3,4]

Cardiac irAEs are rare, with an incidence of about 1%, while they are associated with the highest death rate. Recent studies[44] have found that although cardiac irAEs can be rapidly diagnosed and treated, the fatality rate is still as high as 23%. Patients may be asymptomatic, experiencing fatigue and weakness or develop chest pain, shortness of breath, heart failure, or arrhythmia. Hematological toxicity refers to the decreased numbers of various types of blood cells, inducing autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, hemolytic urine toxin syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia, and acquired hemophilia.[10]

Renal toxicity mainly refers to nephritis and the subsequently induced acute kidney insufficiency. The patients are usually asymptomatic, while oliguria, hematuria, peripheral edema, and anorexia have also been occasionally reported.[45]

Rheumatologic/musculoskeletal irAEs include arthralgias (more specifically, arthritis), myositis vasculitis, new-onset fractures, resorptive bone lesions, sicca syndrome, and sarcoidosis,[46,47] whose onset may occur at 2.1–17.1 weeks (median of 5.4 weeks) following the therapy. A systematic review[48] demonstrated that arthralgia is the most commonly reported (1%–43%), followed by myalgia (2%–21%). Musculoskeletal complications are commonly found in general populations, such as individuals with joint pain or swelling and muscle soreness, which are easily ignored.

Neurological irAEs mainly include myasthenia gravis, Guillain–Barre syndrome, peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis,

and transmyelitis.[49] The patients usually experience mental status alteration, headache, and epilepsy.

The most common types of eye toxicities are uveitis, orbital inflammation, scleral blepharitis, blepharitis, optic edema, ulcerative keratitis, and Vogt–Koyanagi–Harada syndrome.[50] Patients usually present with blurred vision, floaters, flash, altered color vision, red eye, photophobia or light sensitivity, distorted vision, altered visual field, blind spots, soft or painful eyeballs, eyelid edema or protrusion, and diplopia.[51]

Overall, nurses need to be familiar with and aware of the above-mentioned relevant symptom of irAEs, especially cardiac and neurological irAEs, which require immediate evaluation and treatment once being suspected. On the other hand, patients need to be informed of the common irAEs and encouraged to report any discomfort in time.

Laboratory tests

Laboratory tests are also the baseline assessments of follow-up care, as multiple irAEs may present as laboratory abnormalities rather than clinical changes.[3-6] Baseline laboratory tests should include (1) general blood tests – complete blood count (CBC) differential and a comprehensive metabolic panel (CMP), fasting lipid profile, glycosylated hemoglobin, and glycated hemoglobin; (2) infectious disease screening – hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis C antibody, *Cytomegalovirus* antibody, T-spot test (tuberculosis), human immunodeficiency virus (HIV) antibody, and HIV antigen (p24); (3) baseline serum creatinine cardiac tests –total creatinine kinase, troponin 1, brain natriuretic peptide (BNP), and N-terminal pro b-type natriuretic peptide; (4) endocrine tests – thyroid-stimulating hormone, free thyroxin4 (T4), total T3, 8-am cortisol, and 8-am adrenocorticotropic hormone (ACTH).

During treatment, the following items need to be monitored periodically: CBC differential and a CMP before each infusion; thyroid functional studies need to be performed every 6–8 weeks; ACTH and morning cortisol monitoring need to be performed at regular intervals during therapy and after the termination of the therapy;[6] and other blood index tests need to be performed as clinically indicated, as irAEs might be detected early before the appearance of symptom based on laboratory results.[6]

Physical examination

Physical examination needs to be conducted at baseline and before each infusion or potential irAEs.[3-6] The examinations include: (1) full skin and mucosal examination (record the present extent and type of lesions); (2) baseline oxygen saturation in room air and during ambulation, pulmonary functional tests, and 6-min walk test; (3) electrocardiogram; (4) joint examination/ functional assessment; and (5) brain and neurologic examination.

Imaging

Patients need to be scanned with computed tomography (CT) or brain magnetic resonance imaging (MRI) at baseline. Moreover, periodic CT during treatment to detect pneumonitis and MRI when headache was reported or hypophysitis was suspected are suggested as well.[3-6]

Side effect intervention

The management of irAEs is largely relied on corticosteroids and other immunomodulatory agents. For Grade 3/Grade 4 irAEs, the initiating dose of corticosteroids is usually 1 mg/kg to 2 mg/kg or plus prednisone, and the total course of the treatment is usually 4–6 weeks or longer.[52] However, several potential long-term complications have been noticed, which may affect multiple systems throughout the body, including: musculoskeletal side effects such as osteoporosis, osteonecrosis, and steroid myopathy; digestive side effects such as peptic ulcer, bleeding, pancreatitis, and fatty liver; cardiovascular side effects including hypertension, early onset of arteriosclerosis, and arrhythmias; endocrine side effects of metabolism such as glucose and lipid metabolism disorders, water and sodium reservoir disorder, electrolyte disorders, hypothalamic–pituitary–adrenal axis inhibition[53], gonad inhibition, excessive appetite, and body weight increase; mental behavioral side effects such as insomnia, emotional instability, and cognitive impairment; opportunistic infections caused by fungi, tuberculosis, etc.; and others such as cataract, glaucoma, acne, purple lines, brittle skin, ecchymosis, hairy skin, and nonhealing wounds.[5]

Therefore, attention needs to be paid on monitoring blood pressure, blood glucose, electrolyte, and output during medication to detect potential infections. Large doses of corticosteroids can be used with proton pump inhibitors or H2 receptor antagonists to prevent gastric injury. Furthermore, patients need to be educated to take corticosteroids with food to avoid potential infection or contact with infectious sources, control diet, avoid significant weight gain, monitor blood glucose, etc.[51] Once undercontrolled, corticosteroids need to be slowly tapered (over at least a month) to avoid rebound symptoms.[5]

Models and Effects

Traditional models conduct face-to-face visits in clinics or at the patients' home, or evaluate through mail, telephone call, telemedicine, and web-based patient portals for remote follow-ups. Considering that the follow-up for

patients under ICIs requires a heavy workload and long time duration, an efficient, labor- or time-saving follow-up model is necessary. However, relevant studies, especially based on nursing, are limited.

Telephone triage

Follow-up via telephone is a common model of continuing nursing, while it is associated with more uncertainties and difficulties compared with face-to-face visits, especially because of the various presentations of irAEs. Hoffner et al.[54] emphasized the importance of improving telephone triage and the implementation of dedicated oncology acute care services, which can largely reduce the burden of irAEs' management. The Immuno-Oncology Essentials materials developed by Melanoma Nursing Initiative[7] are used as the principles for triaging irAEs via telephone. Meanwhile, the patients and their caregivers are educated to recognize and report early symptom suggestive of an irAE, which can efficiently improve the effectiveness of telephone triage as well.

Multidisciplinary cooperation

Le et al.[55] evaluated the impact of a pharmacist-led and managed irAEs of 17 patients at the University of Wisconsin Carbone Cancer from October 2019 to February 2020. In that study, nurses in the ED received in-person education and obtained a printed educational document that summarized updated practice guidance and included a list of ICIs. This was also posted at ED triage nurse stations and uploaded electronically to the Sarasota Memorial Hospital intranet. Nurses identified the symptom of irAEs and referred the patients to an oncology pharmacist. The pharmacists determined the presence of a potential irAE and recommended guideline-based treatments. Furthermore, the pharmacists followed up the patients with active consults every day during their inpatient admission, and monitored the treatment response to the diagnosed irAEs and any sign or symptom of new irAEs. Nine out of the 17 patients were managed and monitored under the pharmacists' protocol until toxicity resolution, followed by two additional cycles. Thirty-three separate recommendations were made by the pharmacists for these 17 patients. Such a practice reduced physician hours per month required for managing irAEs and promoted the confidence of the physician in irAE management.

Electronic patient report outcome

As a new follow-up model, electronic patient report outcome (ePRO) consists of health-related questionnaires completed by the patients, which can capture both the symptom and the severity of irAEs. Previous studies showed that ePRO enables the timely and continuous information collection in a cost-effective manner.[56,57] Meanwhile, studies also showed that ePROs can improve the quality of life (QoL), decrease emergency clinic visits, improve Eastern Cooperative Oncology Group performance status, and reduce the number of patients receiving active cancer treatments at disease progression.[58] Furthermore, Basch et al.[59] found that ePRO used in the management of cancer patients lead to a better QoL, fewer emergency room visits and hospitalizations, a longer duration of palliative chemotherapy, and superior quality-adjusted survival in the patients.

However, only few studies investigated ePRO follow-up approach for cancer patients treated with ICIs. Iivanainen et al.[60] recruited 37 adult cancer patients whose advanced cancer was treated with anti-PD-L1 agents. The ePRO consisted of a weekly questionnaire evaluating the presence of typical side effects, with an algorithm assessing the severity of the symptom according to the CTCAE and an urgency algorithm sending alerts to the care team. An additional patient experience survey was conducted monthly. The patients were followed for up to 6 months or until disease progression. A total of 889 symptom questionnaires were completed, and the findings demonstrated the feasibility of ePRO follow-up of cancer patients receiving ICIs. ePROs capture a wide range of symptoms, some of which correlate with treatment benefits, suggesting that individual prediction models could be generated.

Tolstrup et al.[52] provided an eHealth intervention based on 57 malignant melanoma patients under immunotherapy. This eHealth intervention based on questions from the PRO-CTCAE library was used and tested in a randomized clinical trial for patients receiving immunotherapy and clinicians at Odense University Hospital in Denmark. On a weekly basis, the patients reported their symptom during the treatment via a provided tablet. Meanwhile, mixed approaches were applied to investigate the patients' and clinicians' experiences with the intervention. Data were collected from the patients via a short survey, and a subset of the patients and clinicians were also interviewed about their experience. Satisfaction with the eHealth intervention was high among the patients and the clinicians, indicating that the tool is easy to use and contributes to enhancing symptom awareness and promoting patient involvement.

Wang et al.[61] provided continuous follow-up care for 72 patients with digestive system cancer under immunotherapy, in which the nurses provided one-to-one health education as well as regular lectures about the treatment and the importance of supervision on the patients. In addition, they provided follow-up via telephone and home visits, kept good records, recognized abnormal signs, and provided timely treatments for the patients. The

results showed that the scores of Hamilton Depression Scale and Hamilton Anxiety Scale were lower, whereas the QoL and satisfaction were higher in the experimental group than that of the control group. Zhang *et al*.[62] investigated the patients who received immunotherapy, including 242 patients in the control group that were followed up manually and 294 patients in the experimental group that were followed up by a web-based system. The functional modules of the follow-up system included user management, patient management, system information management, follow-up work management, follow-up results management, and consultation platform. The results showed that compared with the control group, the experimental group was associated with a significantly lower lost rate of follow-up (7.1% vs. 20.3%), higher rate of treatment in time (96.9% vs. 94.9%), and higher satisfaction rate (94.6% vs. 88.8%). These evidence revealed that the follow-up system can effectively improve the compliance and satisfaction of the patients.

Suggestions and barriers

Health-care providers need to select appropriate follow-up methods according to the number of patients and available medical resources. For developed regions, community health resources and hospital community cooperation can be adopted. For young patients who can use mobile phones or computers, electronic follow-up platforms, such as smartphones, E-mail, and Tencent QQ could be applied. For regions covered by e-health system, online medical visit can be used. For medical institutions with a small number of follow-ups or a sufficient number of follow-up nurses, home visit or telephone follow-ups can be selected. On the contrary, models with the less work burden such as ePRO can be used.

However, the current follow-up care of immunotherapy patients is unsatisfied. Potential barriers of providing adequate follow-up care are: firstly, immunotherapy is a new treatment method, so nurses lack the relative training, knowledge, and awareness for the follow-up of special patients. Secondly, the insufficient number of nurses leads to heavy daily workload, and the traditional follow-up methods such as through telephone are overburdened. Thirdly, ePRO and other methods require a special electronic follow-up platform, for which the initial cost is high.

Conclusions

To the best of our knowledge, this is the most updated review to provide references of follow-up care for patients receiving ICIs. The occurrence of irAEs is frequent due to the wide use of immunotherapy, which require long-term close follow-up to avoid further inducing life-threatening events. This article reviews the guidelines and research papers to provide the latest knowledge and comprehensive

nursing strategies for the occurrence, characteristics, and treating principles, highlighting the models and effectiveness of follow-up for managing irAEs. Further studies need to be conducted focusing on exploring efficient and labor-saving nursing follow-up models, in order to improve the competency of nurses and ensure the safety of the patients who are treated with ICIs.

Conflicts of interest

The corresponding author, Prof. Yuhan Lu, is an editorial board member of *Asia-Pacific Journal of Oncology Nursing.* The article was subject to the journal's standard procedures, with peer review handled independently of Prof. Lu and their research groups.

References

1. Smyth MJ, Teng MW. The 2018 Nobel prize in physiology or medicine. Clin Transl Immunology 2018;7:e1041.
2. Seidel JA, Otsuka A, Kabashima K. Anti-PD-1 and anti-CTLA-4 therapies in cancer: Mechanisms of action, efficacy, and limitations. Front Oncol 2018;8:86.
3. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714-68.
4. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, *et al.* Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95.
5. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, *et al.* Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28 Suppl 4:iv119-42.
6. Thompson JA. New NCCN Guidelines: Recognition and Management of Immunotherapy-Related Toxicity. J Natl Compr Canc Netw 2018;16:594-6.
7. Rubin KM. Managing immune-related adverse events to ipilimumab: A nurse's guide. Clin J Oncol Nurs 2012;16:E69-75.
8. McGettigan S, Rubin KM. PD-1 inhibitor therapy: Consensus statement from the faculty of the melanoma nursing initiative on managing adverse events. Clin J Oncol Nurs 2017;21:42-51.
9. Eggermont AM, Chiarion-Sileni V, Grob JJ, Dummer R, Wolchok JD, Schmidt H, *et al.* Prolonged survival in stage III melanoma with Ipilimum abadjuvant therapy. N Engl J Med 2016;375:1845-55.
10. Kennedy LB, Salama AK. A review of cancer immunotherapy toxicity. CA Cancer J Clin 2020;70:86-104.
11. Kumar V. Current diagnosis and management of immune related adverse events (irAEs) induced by immune

checkpoint inhibitor therapy. Front Pharmacol 2017;8:49.

12. Pennock GK, Chow LQ. The evolving role of immune checkpoint inhibitors in cancer treatment. Oncologist 2015;20:812-22.

13. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: A systematic review. Ann Oncol 2017;28:2377-85.

14. Rogado J, Sánchez-Torres JM, Romero-Laorden N, Ballesteros AI, Pacheco-Barcia V, Ramos-Leví A, et al. Immune-related adverse events predict the therapeutic efficacy of anti-PD-1 antibodies in cancer patients. Eur J Cancer 2019;109:21-7.

15. Elias R, Yan N, Singla N, Fabiana Perrone, Roberta Minari, Melissa Bersanelli, et al. Immune related adverse events are associated with improved outcomes in ICI-treated renal cell carcinoma patients. J Clin Oncol 2019;37 Suppl 7:645A.

16. Grangeon M, Tomasini P, Chaleat S, Jeanson A, Maxime Souquet-Bressand M, Khobta N, et al. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non-small-cell lung cancer. Clin Lung Cancer 2019;20:201-7.

17. Greally M, Chou JF, Chatila WK, Margolis M, Capanu M, Hechtman JF, et al. Clinical and molecular predictors of response to immune checkpoint inhibitors in patients with advanced esophagogastric cancer. Clin Cancer Res 2019;25:6160-9.

18. Okada N, Kawazoe H, Takechi K, Matsudate Y, Utsunomiya R, Zamami Y, et al. Association between immune-related adverse events and clinical efficacy in patients with melanoma treated with nivolumab: A multicenter retrospective study. Clin Ther 2019;41:59-67.

19. Daly B, Nicholas K, Gorenshteyn D, Sokolowski S, Gazit L, Adams L, et al. Misery loves company: Resenting symptoms clusters to urgent care by patients receiving antineoplastic therapy. J Oncol Pract 2018;14:e492-5.

20. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158-68.

21. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of immune checkpoint blockade dysimmune toxicities: A collaborative position paper. Ann Oncol 2016;27:559-74.

22. Belum VR, Benhuri B, Postow MA, Hellmann MD, Lesokhin AM, Segal NH, et al. Characterisation and management of dermatologic adverse events to agents targeting the PD-1 receptor. Eur J Cancer 2016;60:12-25.

23. Sibaud V. Dermatologic reactions to immune checkpoint inhibitors: Skin toxicities and immunotherapy. Am J Clin Dermatol 2018;19:345-61.

24. Gupta A, Defelice KM, Lofeus EV, Khanna S. Systematic review: Colitis associated with anti-CTLA-4 therapy. Aliment Pharmacol Ther 2015;42:406-17.

25. Wang Y, Abu-Sbeih H, Mao E, Ali N, Qiao W, Trinh VA, et al. Endoscopic and histologic features of immune checkpoint inhibitor-related colitis. Inflamm Bowel Dis 2018;24:1695-705.

26. Abdel-Rahman O, ElHalawani H, Fouad M. Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: A meta-analysis. Immunotherapy 2015;7:1213-27.

27. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68:1181-90.

28. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. JAMA Oncol 2018;4:173-82.

29. Caturegli P, Di Dalmazi G, Lombardi M, Grosso F, Larman HB, Larman T, et al. Hypophysitis secondary to cytotoxic T-lymphocyte-associated protein 4 blockade: Insights into pathogenesis from an autopsy series. Am J Pathol 2016;186:3225-35.

30. Chang LS, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. Endocr Rev 2019;40:17-65.

31. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. Horm Metab Res 2019;51:145-56.

32. Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, et al. Ipilimumab-induced hypophysitis: A detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab 2014;99:4078-85.

33. Ariyasu H, Inaba H, Ota T, Yamaoka H, Furukawa Y, Iwakura H, et al. Thyrotoxicosis and adrenocortical hormone deficiency during immune checkpoint inhibitor treatment for malignant melanoma. In Vivo 2018;32:345-51.

34. Hughes J, Vudattu N, Sznol M, Gettinger S, Kluger H, Lupsa B, et al. Precipitation of autoimmune diabetes with anti-PD-1 immunotherapy. Diabetes Care 2015;38:e55-7.

35. Stamatouli AM, Quandt Z, Perdigoto AL, Clark PL, Kluger H, Weiss SA, et al. Collateral damage: Insulin-dependent diabetes induced with checkpoint inhibitors. Diabetes 2018;67:1471-80.

36. Hu YB, Zhang Q, Li HJ, Michot JM, Liu HB, Zhan P, et al. Evaluation of rare but severe immune related adverse effects in PD-1 and PD-L1 inhibitors in non-small cell lung cancer: A meta-analysis. Transl Lung Cancer Res 2017;6:S8-20.

37. Suresh K, Voong KR, Shankar B, Forde PM, Ettinger DS, Marrone KA, et al. Pneumonitis in non-small cell lung cancer patients receiving immune checkpoint immunotherapy: Incidence and risk factors. J Thorac Oncol 2018;13:1930-9.

38. Ma K, Lu Y, Jiang S, Tang J, Li X, Zhang Y. The relative risk and incidence of immune checkpoint inhibitors related pneumonitis in patients with advanced cancer: A meta-analysis. Front Pharmacol 2018;9:1430.

39. Shaverdian N, Lisberg AE, Bornazyan K, Veruttipong D, Goldman JW, Formenti SC, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase 1 trial. Lancet Oncol 2017;18:895-903.

40. Voong KR, Hazell SZ, Fu W, Hu C, Lin CT, Ding K, et al. Relationship between prior radiotherapy and checkpoint-inhibitor pneumonitis in patients with advanced nonsmall-cell lung cancer. Clin Lung Cancer 2019;20:e470-9.

41. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol 2017;35:709-17.

42. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, *et al.* Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: A systematic review and meta-analysis of trials. Chest 2017;152:271-81.

43. Delaunay M, Cadranel J, Lusque A, Nicolas Meyer N, Gounant V, Moro-Sibilot D, *et al.* Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J 2017;50:170-85.

44. Grawal N, Khunger A, Vachhani P, Colvin TA, Alexander Hattoum A, Spangenthal E, *et al.* Cardiac toxicity associated with immune checkpoint inhibitors case series and review of the literature. Case Rep Oncol 2019;12:260-76.

45. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, *et al.* Adverse renal effects of immune checkpoint inhibitors: A narrative review. Am J Nephrol 2017;45:160-9.

46. Cappelli LC, Gutierrez A, Bingham CO, Shah A A. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: A systematic review of the literature. Arthritis Care Res 2017;69:1751-63.

47. Suarez-Almazor ME, Kim ST, Abdel-Wahab N, Diab A. Review: Immune-related adverse events with use of checkpoint inhibitors for immunotherapy of cancer. Arthritis Rheumatol 2017;69:687-99.

48. Moseley KF, Naidoo J, Bingham CO, Carducci MA, Forde PM, Gibney GT, *et al.* Immune-related adverse events with immune checkpoint inhibitors affecting the skeleton: A seminal case series. J Immunother Cancer 2018;6:104.

49. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, *et al.* Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer 2017;73:1-8.

50. Bricout M, Petre A, Amini-Adle M, Bezza W, Seve P, Kodjikian L, *et al.* Vogt-Koyanagi-Harada-like syndrome complicating pembrolizumab treatment for metastatic melanoma. J Immunother 2017;40:77-82.

51. Matsuo T, Yamasaki O. Vogt-Koyanagi-Harada disease-like posterior uveitis in the course of nivolumab (anti-PD-1 antibody), interposed by vemurafenib (BRAF inhibitor), for metastatic cutaneous malignant melanoma. Clin Case Rep 2017;5:694-700.

52. Tolstrup LK, Pappot H, Bastholt L, Zwisler AD, Dieperink KB. Patient-reported outcomes during immunotherapy for metastatic melanoma: Mixed methods study of Patients' and Clinicians' experiences. J Med Internet Res 2020;22:e14896.

53. Williams KJ, Grauer DW, Henry DW, Rockey ML. Corticosteroids for the management of immune-related adverse events in patients receiving checkpoint inhibitors. J Oncol Pharm Pract 2019;25:544-50.

54. Hoffner B, Rubin KM. Meeting the challenge of immune related adverse events with optimized telephone triage and dedicated oncology acute care. J Adv Pract Oncol 2019;10 Suppl 1:9-20.

55. Le S, Chang B, Pham A, Chan A. Impact of pharmacist-managed immune checkpoint inhibitor toxicities. J Oncol Pharm Pract 2021;27:596-600.

56. Holch P, Warrington L, Bamforth LC, Keding A, Ziegler LE, Absolom K, *et al.* Development of an integrated electronic platform for patient self-report and management of adverse events during cancer treatment. Ann Oncol 2017;28:2305-11.

57. Jensen RE, Snyder CF, Abernethy AP, Basch E, Potosky AL, Roberts AC, *et al.* Review of electronic patient-reported outcomes systems used in cancer clinical care. J Oncol Pract 2014;10:e215-22.

58. Basch E, Deal AM, Dueck AC, Scher HI, Kris MG, Hudis C, *et al.* Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA 2017;318:197-8.

59. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, *et al.* Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial. J Clin Oncol 2016;34:557-65.

60. Iivanainen S, Alanko T, Vihinen P, Konkola T, Ekstrom J, Virtanen H, *et al.* Follow-up of cancer patients receiving anti-PD-(L) 1 therapy using an electronic patient-reported outcomes tool (KISS): Prospective feasibility cohort study. JMIR Form Res 2020;4:1-16.

61. Peipei Wang. Study on the application effect of continuous care in patients with digestive system tumor after immunization or targeted therapy. Fam Med 2020;1:334-5.

62. Zhang S, Wang Y, Wang XL, Hu LT, Xia Q, Shi CC, *et al.* Application of follow-up system in patients with specific immunotherapy. China Digit Med 2020;15:78-81.