Immune-related adverse events in patients treated with immune checkpointsinhibitors: Management in the emergency room

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Immune checkpoints inhibitors (ICIs) are a novel class of drugs used in cancer immunotherapy that are becoming more commonly used among advanced-stage cancers. These ICIs, targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and the programmed death-1 receptor (PD-1) and its ligand (PD-L1), have revolutionized the treatment of many different types of cancers and have increased the life expectancy of many patients. However, the inhibition of immune checkpoints may lead to unintended tissue damage which manifests into immune-related adverse effects (irAEs) that seem to arise from increase activity in the immune system.

Emergency physicians are encountering increasing number of patients on these medications as well as the associated side effects and it is important that they have the knowledge to recognize these new averages of complications and how to treat them. Early recognition and treatment of these irAEs may prevent severe complications, inappropriate discharges from emergency room and ICIs discontinuation.

The irAEs can affect nearly every organ system, normally only one but in some special cases the toxicity may present affecting more than one system. The most common irAEs are dermatological, gastrointestinal, endocrine, hepatical and pulmonary; being the cardiological, neurological, ophthalmologic, renal and haematological infrequently reported. Emergency physicians face the challenge of differentiating these irAEs from any other pathology related or not with the underlying cancer. Differential diagnosis in the emergency room may embrace from pathology not related with the underlying cancer, complications of the underlying cancer, cancer progression, opportunistic infections (as long term -> 6 weeks- treatment with immunosupressive drugs increases the chance of opportunistic infections), irAEs affecting one system to irAEs multisystem. The incidence of the irAEs will depend on the ICIs administered and the basal substrate of the patient. In general, irAEs occurs quite early, mostly within weeks to 3 months being

dermatological and gastrointestinal the earliest to manifest. However, physicians must be aware that risk is still present for weeks to months after termination of treatment and that recent history of ICI administration should keep irAE on differential diagnosis. The principle of clinical management of irAEs includes a proacting monitoring, the differential diagnosis, the determination of severity, the management and the follow-up. Both proacting monitoring and follow-up are normally exclusively carried out by oncologist in their specific consultation while the differential diagnosis, determination of severity and acute management may be carried out in the emergency room by more than one specialist. It is important to distinguish the severity of each irAE and quantify by using the Common Terminology Criteria for Adverse Events v4.03 in order to standardize treatment and follow-up of these patients. In general, low-grade irAEs (grade 1-2) are mild to moderate while grades 3-4 are severe or even life-threatening. Grade 1 irAEs should be treated symptomatically and on an outpatient basis and do not need to interrupt ICI treatment while grade 2 or persistent grade 1 should consider oral corticosteroids (0.5-1mg/kg/day) and may need to temporary interrupt ICI treatment. Grade 3 and 4 are considered severe forms of presentation, with hospitalization needs and use of high-dose IV corticosteroids (1-2mg/kg/day). In grade 4 toxicities physicians must consider other immunosuppressive agents such as infliximab or micofenolate, permanent interrupt of ICIs and intensive care unit (ICU) admission. As grade 1-2 toxicities are usually seen and treated in the oncologist consultation, the emergency physicians normally encounter grade 3 and 4 toxicities. Eventhough these toxicities are infrequent, they are much more severe and their management, much more challenging. The most feared irAEs in the emergency room are pneumonitis, severe enterocolitis with colonic perforation, autoimmune type I diabetes mellitus presented as diabetic ketoacidosis, toxic epidermal necrolysis, miocarditis with reduced ejection fraction, encephalitis and myelitis.

We should not forget that emergency room is a stressful scenario where physicians must make difficult decisions, such as limit the treatment, decide the ceiling of care or indicate the ICU admission. So that, they must have the knowledge and the tools for early detection and management of the irAEs as much as advanced information related with the underlying cancer. They usually find problems with organizational constraints and disagreements between different specialists. A multidisciplinary approach should help to better attend these patients, with the emergency physician, the consulting oncologist and the organ-specific physician teams.

In conclusion, we should remember that early recognition and treatment of the irAEs can help to decrease the associated morbidity and mortality and also take into account that emergency physicians are seeing an increasing number of these irAEs and should have the knowledge and the tools to early recognize and treat them. We should not forget that risk is still present for weeks to months after termination of treatment and that multidisciplinary approach should be taken with these patients.

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