Management of immunotherapy toxicities. Point of view of the intensivist

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Immunotherapy is a biological therapy that boosts the immune system to fight cancer. There are several molecules that are considered immunotherapy that are classified as passive and active. Active immunotherapy enhances the immune system activation through the modulation of endogenous regulatory and/or activatory immune mechanisms, such as the checkpoint inhibitors (CpIs). Passive immunotherapy uses effector cells or molecules of the immune system to directly attack tumor cells. Here, we will focus in some active immunotherapy such as the bi-specific antibodies and the CpIs CTLA-4, PD-1 and PDL-1 and some passive therapies such as chimeric antigen receptor T cells therapy (CAR-T cells).

The CpIs, by removing inhibition of T-cell function, facilitates T cell activity against host tissues causing immune-related adverse events (irAEs). The physiopathology of immune related adverse events is not completely known but there are different proposed mechanisms:

Increase activity of T cells against healthy tissues, higher levels of preexisting antibodies, an increase of inflammatory cytokines after tumor destruction, and by enhancing the complement mediated inflammation to normal tissue in some tissues expressing CTLA-4, between others.

The common terminology for adverse events (CTAE) of the Cancer Institute classifies the adverse events according to their severity, in five grades: Grade 1 or Mild: Grade 2 or Moderate: Grade 3 or severe (or medically significant but not immediately life-threatening); and Grade 4 or life threatening that requires urgent intervention. Grade 5 is death related to AE (4). This classification allows having a common language in the classification of the severity of the adverse events but also to determine the management.

The severity of irAEs are dose dependent in anti-CTLA-4 but not with anti PD1 or PDL1 monotherapies. Monotherapy with CpIs is related with 10 to 20% of grades 3 or 4 side effects. Ipilimumab more frequently induces serious irAEs with 27%, whereas in combination, the presence of grade 3/4 irAEs can be as high as 55%. In average, when the CpIs are used in combination, the irAEs are present in one-third of patients. Higher

doses of checkpoint inhibitors improved survival but the percentage of grade 3 or 4 irAEs in monotherapy with higher doses can reach as much as 50% of cases. Of note, grade 5 irAEs have been reported in 0.38% to 0.6% of the total irAEs. The most frequent organs affected in fatal irAEs are colitis, hepatitis and pneumonitis, whereas myocarditis has the highest fatality rate.

It is important to achieve an adequate diagnosis and implement a prompt therapy with immunosuppressive therapy in order to improve the morbidity and mortality. The general management of grade 4 irAEs should include symptomatic treatment, support therapy, and the CpIs should be stopped. A work-up assessment of diagnosis and differential diagnosis should be started. Immune-suppression with corticosteroids is the cornerstone treatment but alternative drugs should be evaluated if there is not a clinical response to corticoids. Infection has to be ruled out and also because of the use of immunosuppressive drugs the presence of opportunistic infections or some prophylaxis has to be considered. Different specialists should be involved with the evaluation of a patient with irAEs because of the complexity and the multi-systemic affection of the irAEs.

There are also several specific managements according to the organs affected that are going to be discussed in the different topics along the course. Pneumonitis, is one the most frequent reasons for ICU admission and in some cases it requires non-invasive or invasive respiratory support. It is important to follow a diagnostic workup, including imaging (chest X rays or high resolution CT scan) and bronchoalveolar lavage to do the diagnosis or to obtain samples for opportunistic infections. As we mention before, the main treatment is with corticoids, but another immunosuppressive drugs such as infliximab, mychophenolate mofetil, and intravenous immunoglobulin of cyclophosphamyde are alternative therapies if there is no response to corticoids (8, 10) Aside from the previous immunosupressants referred before, different immunosuppressive therapies have been proposed in patients with refractory irAEs. The strategies are as follows: antibodies such as anti-IL-1, -IL-6, -IL-17, anti-TNF, anti-integrin-4, anti IL-23, -IL-12 blockage, the use of intravenous immunoglobulins or some janus-kinase inhibitor. Whenever possible, we should obtain a biopsy of the affected organ in order to direct the suggested treatment.

CAR-T cells have demonstrated their success in hematological malignancies, but until now there is no CAR-T cells treatment for solid tumors, however, there are some clinical trials ongoing and several secondary effects that have been reported. Also, several trials are evaluating different bi-specific antibodies in solid cancer. Two main complications have been desbribe with those treatments: the cytokine release syndrome (CRS) and CART-related encephalopathy syndrome (CRES). The CRS is defined as an uncontrolled systemic inflammatory response that can be produced by external factors mainly secondary to immunotherapy, including bi-specific antibodies and CART cells therapy. There is also a grading scale according to the severity of the signs and symptoms. Grade 1 requires symptomatic therapy: grade 2 can be requires supportive therapy with oxygen or low doses of vaso-active drugs if there is no response to volume. Grade 3 and 4 should be managed in ICU with organ support. Because in CRS there is an

increase in IL-6, tocilizumab should be used in accordance of the specialties involve in the management of the patients. Also, if there is no response to IL-6 antagonists, corticoids should be started. Also, they can produce CRES but it will be explain in the specific presentation in this course.

The survival of cancer patients admitted to ICU is increasing along the years. Immunotherapy is a promising treatment that has demonstrated to improve survival in patients with cancer. This creates a new paradigm in the intensive care. It is difficult to predict cancer mortality in base on new therapeutic options, combination of treatments and new emerging treatments, so the decision of ICU admission should be performed in a multidisciplinary approach involving oncologists, intensivists and other specialists involved in the care of the patients in order to establish the correct goal of care of each cancer patient.

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