Toxicity induced by immunotherapy: management by the medical oncologist

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The development of therapeutic agents that modulate the immune system to induce or potentiate its anti-tumor activity has revolutionized cancer treatment in recent years. Focusing on the immune system of the host rather than the tumor has proven to be an effective strategy in a large number of malignancies. In recent years, the development of antibodies able to inhibit key immune checkpoints has meant a breakthrough in cancer therapy. For decades, efforts were done in directly stimulate the immune system. This approach achieved modest results but when a different strategy was used (the inhibition of inhibitors of the immune system), results have been dramatic. The first checkpoint inhibitor to be granted approval by the Food and Drug Administration (FDA) was the anti-Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) antibody ipilimumab for the treatment of advanced melanoma in 2011. Since then, a number of checkpoint inhibitors and other immunotherapeutic strategies have been assessed in clinical trials with very successful results, mostly inhibitors of the programmed death (PD1) / PD ligand 1 (PD-L1) axis such as pembrolizumab, nivolumab, atezolizumab, durvalumab or avelumab.

But these treatments are not exempt from toxicity. Differently from classic chemotherapy and targeted therapies, with which we are directly attacking tumor cells, with the immunotherapeutic agents we are indirectly attacking the tumor by stimulating the immune system. Therefore, the potential side effects are very different from the ones caused by chemotherapy or targeted therapies since they are derived from an excessive stimulation of the immune system. Thus, a unique profile of toxicities termed immune-related adverse events has been described with immunotherapeutic agents.

The immune system controls infections at any part of the human body so the alteration of its function by the immunotherapy can potentially cause side effects in any organ. The most common immune-related adverse events described with anti-CTLA-4 and anti-PD1/PDL-1 are autoimmune skin phenomena, hepatitis, pneumonitis, colitis and endocrine alterations (hypothyroidism, adrenal insufficiency, autoimmune diabetes…). Fortunately, the incidence of these side effects in severe grades with single agents is low (around 5% of patients). However, when these drugs are combined with other agents, either other immunotherapeutic drug or other antineoplastic compounds, the incidence of immune-related adverse events is usually higher. In recent years, there has been a

large number of immunotherapy drugs approved as single agents in many different tumor types, but it is expected that there will be more new approvals of combinatory regimes in a forthcoming future. Indeed, combinations of immunotherapies with other agents have already been approved in melanoma, renal cell carcinoma or non-small cell lung cancer. Therefore, it is crucial that any healthcare professional involved in the care of cancer patients treated with immunotherapy is aware of these side effects and have enough knowledge to treat them or to refer the patient where appropriate.

The usual first treatment of severe immune-related adverse events is the administration of steroids, initially orally or intravenously in case that the toxicity is not improved or resolved after 48-72 hours of oral treatment. If toxicity persists in spite of several days of intravenous treatment, more potent immunosuppression drugs such as infliximab, mycophenolate or tocilizumab should be considered. Given the complexity of the management of some of these side effects and the potential life-threatening consequences of some of them, the involvement of a wide array of different medical specialities other than medical oncologists is essential in order to provide an optimal care to our cancer patients treated with immunotherapy.