The good and the bad sides of immunotherapy

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The Nobel Prize for medicine and physiology was awarded last Monday to Drs. James Allison and Tasuku Honjo for their discoveries which led to the development of immunotherapy, a new anticancer strategy based on the destruction of tumors by stimulation of the immune system. Let's take a look at the good and the less-good sides of this new class of therapeutic agents.

IMMUNE PARALYSIS

Each day, the killer T lymphocytes of the immune system eliminate millions of abnormal (and potentially cancerous) cells which form spontaneously within us. In order to progress, a cancer must necessarily play hide and seek with these cells, i.e. by developing the capacity to remain incognito and thus avoid being destroyed once they appear.

The work by Drs. Allison and Honjo enabled the identification of some of the mechanisms used by the cancer cells to stupefy the immune system. To recognize normal cells and avoid uselessly attacking them, the killer immune cells have a sort of antenna (called PD-1) which specifically interacts with a protein present on the surface of body cells. This interaction then sends a signal to the killer cells that it is in the presence of a friendly cell, which inhibits the immune response and prevents the destruction of the other cell. The cancer cells have managed to take advantage of this braking system to become invisible: by overexpressing at their cell surfaces the protein recognized by the PD-1 antenna of the killer cells, they succeed in putting the immune system "to sleep" and thus avoid being attacked. This discovery provides an explanation for one of the greatest enigmas in cancer, i.e. why the tumors are so often infested with white blood cells ready to attack but which remain somehow somnolent, as if they had been hypnotized by the cancer cells.

SHOCKING SUCCESSES

The basis of immunotherapy is thus to destroy this interaction between the immune cells and tumors in such a way as to allow the immune system "to wake up" and eliminate the cancer cells.

Several antibodies capable of preventing this interaction have been developed in recent years and the results obtained are quite remarkable. For example, clinical studies have shown that this class of medications extraordinarily increased the survival of some patients suffering from incurable metastatic melanoma (3 years and more compared to several months with standard treatments)[1]. This was notably seen with former American president Jimmy Carter, diagnosed at age 91 with an incurable metastatic melanoma, who is still in complete remission 3 years after being treated with one of these antibodies. These remarkable results have also been observed in some patients suffering from Hodgkin's lymphoma or with cancers of the bladder, lung, kidney and head and neck. This is certainly a revolutionary form of treatment, endowed with an enormous therapeutic power.

LIMITATIONS OF IMMUNOTHERAPY

The spectacular successes of immunotherapy seen in some patients are, however, shadowed by the total absence of a therapeutic response in others. This is a serious limitation of this approach, and we do not always know why this occurs. As well, certain types of cancers (most notably cancers of the brain) contain few if any resident immune cells, which makes impossible the use of this type of immunotherapy. Thus, despite the great potential of this approach, it is certain that immunotherapy has intrinsic limitations and does not represent a universal treatment for cancer.

Another aspect to consider is the occurrence of secondary effects. By activating the immune system, these antibodies can thereby also unleash an autoimmune response with side effects that are potentially serious and even, in some cases, fatal. For example, a recent analysis revealed that the incidence of mortality varied between 0.6 and 1.23% according to the type of antibody used, principally due to side effects concerning the heart (myocarditis) and the nervous system[2].

Finally, it is impossible to ignore the exorbitant cost of these treatments, around $100,000 per patient, which means that including them in the list of medications covered by public health systems is quite problematic. Even worse, the current trend is to combine two or more different antibodies to improve the therapeutic response and thus to double or triple the cost of treatment. There is thus a risk that treatment of certain cancers will be reserved for the most prosperous patients.

In summary, even though we must celebrate the immense scientific progress made by immunotherapy, it must be borne in mind that these medications cannot by themselves take on all cancers. A cancer which reaches an advanced stage is a disease of incredible complexity and the best way to reduce the mortality levels associated with this disease remains to prevent its occurrence at the beginning, by adopting a healthy lifestyle which can prevent cancer from growing and expressing its immense destructive potential.

(1) Schadendorf D et al. Pooled analysis of long-term survival data from Phase II and Phase III trials of Ipilimumab in unresectable or metastatic melanoma. J Clin Oncol. 2015; 33: 1889-1894.
(2) Wang DY et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol., published online September 13 2018.

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