Immunotherapy in cancer: lessons from melanoma

Immunotherapy can now be considered the fourth pillar of cancer treatment, alongside surgery, radiation and chemotherapy. Although sipuleucel-T for prostate cancer was the first immunotherapy to be approved in oncology, it is melanoma where the most progress in immunotherapy has been made with the introduction of checkpoints inhibitors. In 2011, the approval of ipilimumab (an antibody to cytotoxic T-lymphocyte-associated protein 4 [CTLA-4]) was the starting point for the wider introduction of immunotherapy in clinical practice. Now, four years later, other immune checkpoints inhibitors have been developed. These include the anti-programmed-death-1 (PD-1) agents, pembrolizumab and nivolumab, which have been approved by the US Food & Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma and disease progression following therapy with ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor. In addition, very interesting data on the use of immunotherapy in other cancers, including non-small-cell lung cancer (NSCLC), renal cell cancer (RCC), bladder cancer and Hodgkin's lymphoma, have been reported.

The most important aspect of these new drugs is their innovative mechanism of action. Knowledge of the molecular mechanisms involved in the immune response to cancer has allowed the identification of certain key molecules that are important in the immune-escape process of the tumor. These are known as checkpoint molecules and include CTLA-4, B7.1-B7.2 and PD-1/PD-L1, and can be targeted by monoclonal antibodies that enhance the anti-tumor immune response via the inhibition of the different checkpoints.

Most of the current knowledge about immune checkpoint inhibitors comes from research on melanoma. Firstly, we have learnt that immune adaptability and memory offer the potential for long-term survival benefits. A recent meta-analysis of data from 4846 patients treated with ipilimumab in the context of clinical trials and an expanded access program (EAP) showed that 20% of patients was still alive after 10 years' follow-up [1]. On this basis we can state that ipilimumab turns melanoma into a chronic, rather than fatal, disease in two out of every ten patients. This improvement in long-term survival has not only been observed with ipilimumab in melanoma, but also with nivolumab in melanoma as well as other cancers. In patients with melanoma, nivolumab was associated with 1, 2, 3, and 4-year overall survival (OS) rates of 63%, 48%, 42%, and 32%, respectively [2], while 2-year OS rates of 24% in NSCLC [3], and 50% in RCC [4] have been reported.

Surrogate markers may not be useful when assessing immunotherapy

Another characteristic of immunotherapy is that it may have a significant impact on OS but not on surrogate endpoints. Indeed, while results with ipilimumab in terms of OS are incontrovertible, improvements in progression-free survival (PFS) and overall response rate (ORR) appear less transformative. For instance, the ORR achieved in the pivotal study of

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ipilimumab in melanoma was only about 10% [5]. A couple of reasons may explain this phenomenon.

The first is due to the possibility of false disease progression, in which patients are considered to have progressed but then have a response or stable disease for a long time. This pattern resulted in the development of the immune-related response criteria (irRC). These identify unconventional responses not recognized by the WHO or RECIST criteria but which clearly suggest a clinical benefit for patients. These new criteria consider the total tumor mass as important; thus, a small increase in the size or appearance of new lesions in the context of mixed responses is not considered as progression if the total tumor mass does not increase more than defined by the irRC [6]. According to these criteria, cases of progression should be confirmed with another assessment after 4 weeks. The situation appears different with the anti-PD-1 agents (pembrolizumab and nivolumab). These compounds are typically associated with ORRs of 35-40% evaluated according to RECIST 1.1 criteria [7, 8]. However, unconventional responses also occur during treatment with these agents [8], so it is useful to consider the irRC when evaluating patients treated with this class of drugs.

The second reason is that immunotherapy slows disease progression. Indeed, in the pivotal trial of ipilimumab, patients who had progressive disease (PD) in the two ipilimumab arms had a survival advantage of two months compared with control patients who progressed. In melanoma, this is of fundamental importance because with some treatments, such as the BRAF inhibitors, progression after treatment failure is very fast in about 40% of patients, with death often occurring within 1-2 months. This is an important consideration because rapid disease progression may mean these patients do not have the opportunity to be treated with any other potentially beneficial therapy [9, 10].

Importantly, immunotherapy is active regardless of the histology or mutational status of the tumor. Thus, in melanoma, ipilimumab has been shown to be effective regardless of the BRAF or NRAS mutational status [11], while nivolumab was equally effective in NSCLC irrespective of histology or mutational status [3].

Finally, the mechanism of action of immunotherapy results in a typical safety profile of immuno-related adverse events (irAEs). Skin reactions, colitis/diarrhea, autoimmune hepatitis, endocrinopathies, and pneumonitis (typical of anti-PD-1 treatment) represent the most frequent toxicities. However, these irAEs can generally be managed with corticosteroids. Treatment algorithms for the management of the different irAEs have been developed and adherence to these guidelines has shown a reduction in patient hospitalization [11].

Biomarkers needed

Considering that the long-term benefits of current immunotherapies are limited to a subgroup of patients (around 20% in the case of ipilimumab) and given the high costs of these treatments, there is an urgent need for predictive biomarkers to help identify patients who will benefit most. In melanoma, clinical characteristics including performance status, elevated lactate dehydrogenase (LDH), presence of brain metastases and others are not useful in selecting patients for treatment. Indeed, patients with those features can obtain significant benefit from immunotherapy [11].

Several potential biomarkers, such as absolute lymphocyte count, antibody response to tumor antigens (i.e. NY-ISO-1), and change in tumor-infiltrating lymphocytes are being evaluated. However, to date, no predictive biomarkers have been found for melanoma patients. The use of PD-L1 expression as a marker for patient selection has been proposed but is controversial. While preliminary results [3] suggested a possible role, recent data from a prospective phase III trial seem to indicate the possibility of a good response and clinical benefit of anti-PD-L1 therapy even in patients negative for PD-L1 expression [8, 12].

In conclusion, four years of immunotherapy in melanoma have taught us that checkpoint inhibitor antibodies help overcome the mechanisms by which tumors escape immune destruction. Durable, long-term survival across patient groups with various solid or hematological malignancies can be achieved. Both conventional and immune-related response patterns have been observed with immunotherapies and these are associated with a unique but manageable adverse event profile. Predictive biomarkers may help to select those patients most likely to benefit from immunotherapy and various approaches are currently being evaluated. The concept of immune checkpoint inhibition is supported by an increasing amount of clinical evidence, not only in melanoma but also in other cancers. With ipilimumab already established in melanoma, immune checkpoint inhibition is increasingly becoming a therapeutic reality.

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