Editorial Commentary

The dark side of immunotherapy: challenges facing the new hope in cancer treatment

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Provenance: This is an invited article commissioned by the Section Editor Dr. Jianrong Zhang, MD, MPH (Master of Public Health Graduate, Clark-Fox Policy Scholar, Brown School at Washington University in St. Louis, MO, USA).

Comment on: Zhao B, Zhao H, Zhao J. Serious adverse events and fatal adverse events associated with nivolumab treatment in cancer patients: Nivolumab-related serious/fatal adverse events. J Immunother Cancer 2018;6:101.

Submitted Jul 05, 2019. Accepted for publication Jul 19, 2019.
doi: 10.21037/atm.2019.07.69
View this article at: http://dx.doi.org/10.21037/atm.2019.07.69

Avoiding immune destruction is an intrinsic cancer characteristic (1). A better understanding of the biological bases underlying this hallmark has allowed a treatment revolution. This new therapeutic option is currently leaving its mark on the cancer treatment strategy for thousands of patients worldwide, and an ever-growing number of clinical trials are increasing its potential future indications in the oncologic setting. Despite these exciting clinical results, immunotherapy treatment has also given rise to new clinical concerns for the future. In this manuscript, we will focus on a recent meta-analysis of the toxicity induced by nivolumab in cancer treatment (2), as well as other issues related to new challenges that immunotherapy implies in the field of oncology.

Among different immunotherapies used in clinical practice, the immune checkpoint inhibitors (ICIs) have become the most extensively used. ICIs are monoclonal antibodies that interact with co-receptors resulting in a reactivation of the immune response against tumor cells. Of note, the 2018 Nobel Prize in Physiology or Medicine has been awarded to James P. Allison and Tasuku Honjo whose discovery of proteins present in immune cells have led to integrating this new principle into cancer therapy. More than 10 co-receptors have been described with a direct relation to tumor recognition (3).

Ipilimumab, the ICI which interacts with CTLA4 protein, was the first approved checkpoint blockade for the treatment of cancer patients. The basic research, explored in this specific pathway by the Nobel laureate James P. Allison, permitted its further use as a line of cancer treatment. Initially tested on melanoma, the good results observed in clinical trials compared to the standard treatment rapidly changed the treatment paradigm for this cancer type. However, despite greater clinical advantages with long-lasting responses, an increased risk of treatment-related mortality compared with control arms, with an incidence of fatal adverse events (FAEs) of 1.13% versus 0.22% was also reported (4).

The programmed cell death protein 1 (PD-1) is primarily expressed on the surface of activated T cells and the interaction with its protein ligand (PD-L1) leads to an anergy phenomenon. PD-1 pathway was identified by the group led by the Nobel laureate Tasuku Honjo, and this discovery has led to the development of antibodies against both PD-1 and PD-L1 of which are now widely used (5). Nivolumab is a fully human IgG4 monoclonal antibody against PD-1 receptor, and was the first drug against this pathway available to cancer patients. By binding PD-1, nivolumab similar to other anti-PD-1/PDL-1 ICIs, interrupts the anergy co-stimulation signals, thus relieving the T-cell inhibition induced by the cancer cells and their microenvironment. As a consequence, anti-PD-1/PD-L1 ICIs can restore the immune response against malignant cells. The clinical indications of nivolumab are growing exponentially and are being applied to multiple cancer types (i.e., non-small cell lung cancer, head and neck squamous

cell cancer, kidney cancer, melanoma, liver cancer, bladder cancer and classical Hodgkin Lymphoma).

With the rise in the use of immunotherapy, a new range of side-effects have impacted the clinical routine. Unlike traditional chemotherapy, immunotherapy adverse events are mostly a consequence of inflammation secondary to immune hyper-activation and are collectively termed as immune related adverse events (irAEs). The pathophysiology underlining these effects is unknown; however, at least four possible mechanisms for irAEs have been described: T-cells cross-reactivity due to similar antigens both in tumor and normal cells, a modulation of humoral immunity enhancing preexisting antibodies level, an increasing number of inflammatory cytokines and an increasing of complement-mediated inflammation (6).

The common factor among the above-mentioned mechanisms is autoimmunity. The irAEs are similar regardless of which ICI antibody was used. However, the rate and the distribution of the affected organs changes. We must take into consideration that the family of ICIs monoclonal antibodies can interact in different protein receptors which affect the immune cancer cycle at different points (7). The incidence of irAEs secondary to the use of PD-1 blockers appears to be of less severity compared to CTLA4 but this could also be, in part, due to the higher doses used in initial clinical trials for melanoma with ipilimumab (10 *vs.* 3 mg/kg).

Previous work has shown that nivolumab has low incidence of overall side effects (8). Zhao *et al.* have performed a systematic review with a meta-analysis focused on the incidence of serious adverse events (SAEs) and FAEs with nivolumab, which are considered of greater clinical significance (2). Overall, the incidence of SAEs were 11.2% and for FAEs were 0.3%, showing no significant increased risk compared with the control arms (standard chemotherapy regimens). Most common SAEs involved the respiratory and gastrointestinal organs being pneumonitis, interstitial lung disease and colitis the most commonly observed (2). Nearly half of the patients (46.9%) included in the SAEs analyses were affected by non-small cell lung carcinoma (NSCLC). The present study reported that the odds ratio of SAEs with nivolumab differs significantly by cancer type ($P<0.01$). For this reason, we present an additional sub-analysis addressing to lung cancer, which is the leading cause of death related to neoplasms (9). Non-small-cell lung cancer is the subclass of epithelial tumors that accounts for about 85% of all lung cancers. Positive results in the pivotal clinical CheckMate 017 and CheckMate 057 trials, which compared docetaxel versus nivolumab as second line treatment of advanced NSCLC patients, allowed for the approval of nivolumab by the regulatory agencies in this setting, becoming the first immunotherapy drug available for one of the most frequent types of cancer (10,11). NSCLC has become the cancer subtype with more currently immunotherapy drug indications and it is an active field of research into the role of immunotherapy and its adverse events in cancer treatment.

Stratifying the subgroup of non-small cell lung cancer, the most representative subset in the meta-analysis of Zhao *et al.*, we find further results of interest (2). The incidence of SAES in NSCLC results of 11.8% compared with 11.2% of global results, and FAEs is of 0.5% versus 0.3% respectively. Although the global incidence of SAEs is maintained, we found that the specific organs affected by nivolumab-related SAEs differ from the global conclusions. The rate of respiratory events doubled from 21.4% to 44.7%, acquiring more distance from the second and the third most affected systems, gastrointestinal and hepatic. One logical explanation to this result could be that the cross-reactivity, due to similar normal and tumor cell antigens, could explain this phenomenon in which using the same drug in different tumor types allow for different incidence of organs affected by irAEs.

Knowing that the use of nivolumab carries a low but attributable rate of severe adverse events and, in some cases, iatrogenic death (2), it is important to advocate for an early detection and prevention of irAEs. In this line some authors are trying to find predictive markers to anticipate them. As an example, it has been demonstrated that the testing of pre-existing antibodies can be significantly correlated with the incidence of some side effects (6,12). Nonetheless, due to cross-reactivity, the adverse events which are directly related to antigen-specific immunity are the consequence of leading the antibodies to attack the tumor and as well as the unaffected organs simultaneously. Consequently, even though toxicity is never desired, this kind of immune-mediated events could also be expected to be linked to tumor response. This hypothesis was first confirmed with the use of ipilimumab in melanoma patients. In this context the vitiligo-like depigmentation was demonstrated to be a result of an accumulation of identical T cells in melanoma and in the vitiligo-like leukoderma (13) and, when it appears during immunotherapy treatment, it has been associated with an improved clinical outcome (12,14). Similarly, some immune-related AEs observed during nivolumab therapy

have also been related with better outcome. For example, it has been reported that hair re-pigmentation (a skin side effect) in patients with NSCLC treated with nivolumab, better oncologic outcomes can also be linked (15). Other retrospective studies analyzing clinical series of patients treated with nivolumab for NSCLC have reported that, in general, irAEs are related to better outcome in terms of overall response rate and progression-free survival, regardless of the organ affected by the adverse event (16,17).

In addition to the specific related toxicity (irAEs), there are other unexpected effects observed as a consequence of immunotherapy in cancer patients. The most feared is the phenomenon of hyper-progression disease (HPD) also known as tumor flare reaction (TFR). HPD is described as an acceleration of tumor growth as a consequence of treatment. Among different criteria, the most frequently accepted definition for this is a progressive disease by response evaluation criteria in solid tumors (RECIST), and a tumor growth rate two folds or more increased compared to the pre-evaluated (18). A recent multicenter retrospective study has compared the incidence of HPD in NSCLC due to antiPD-1/PDL-1 therapy versus that observed with conventional chemotherapy (19). Alarmingly, the finding of HPD occurred in 14% of patients treated with immunotherapy compared to 5% of patients treated with chemotherapy. HPD was associated with a worse outcome and only high metastatic burden seemed significant to predict this phenomenon. What is more, some case reports have suggested that flare reaction can appear later on during treatment with immunotherapy, not only at the first response (or no response) evaluation to the treatment (20).

In conclusion the use of immunotherapy in NSCLC has demonstrated better outcomes and an increase in quality of life compared with standard chemotherapy in advanced NSCLC patients, thereby becoming a new standard of treatment (21). However, immunotherapy has still its own dark side, with potentially severe side effects. In the same fashion as the expedition towards the dark side of the moon led by China at the beginning of 2019, it has been recently shown that the dark side is just an unexplored area in which we still have little data and knowledge. Human curiosity and ingenuity can transform this dark side into a door for new opportunities to improve. The meta-analysis of Zhao *et al.* shows that nivolumab has a lower risk of severe adverse events compared to chemotherapy, but they cannot be ignored because some can be potentially fatal. The relation of the development of irAEs with higher oncologic outcomes (response rates, PFS and/or OS) can increase the interest in improving our knowledge about prediction or early detection of irAEs, in order to increase better outcomes without increasing the risk of SAEs or FAEs. The unexpected hyper-progressive disease due to immunotherapy shows us that we still need a better understanding of the biology of the immune system, reinforcing the need for translational research in this field. On one hand, immunotherapy is a new cornerstone in the treatment of cancer from which a great number of patients are clearly benefiting. On the other hand, more research is urgently required to improve the prevention of toxicity, which would convert this new treatment into a star that brightens the horizon for cancer patients.

Acknowledgments

Funding: Joaquim Bosch-Barrera is the recipient of a Grant from the Health Research and Innovation Strategic Plan (SLT006/17/114; PERIS 2016 2020; Pla estratègic de recerca i innovació en salut; Department de Salut, Generalitat de Catalunya). The authors would like to thank Katie B. Linder for editorial support.

Footnote

Conflicts of Interest: J Bosch-Barrera serves on advisory boards and/or accepted honoraria for giving lectures from Bristol Myers-Squibb (BMS), Roche, Merck Sharp & Dohme (MSD), Astrazeneca, Novartis and Boehringer-Ingelheim. J Bosch-Barrera has also received grants for research from Pfizer and Roche. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Teixidor E, Bosch-Barrera J. The dark side of immunotherapy: challenges facing the new hope in cancer treatment. Ann Transl Med 2019;7(Suppl 6):S183. doi: 10.21037/atm.2019.07.69

