wjpmr, 2020,6(11), 14-16

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Case Report

ISSN 2455-3301

WJPMR

IMMUNE CHECKPOINT INHIBITORS IN THE TREATMENT OF PATIENTS WITH CANCER AND PREEXISTING AUTOIMMUNE DISEASE: CASE REPORT

EL. Mouhtadi S.,*[1] Filali N.,[1] Abahssain H.,[2] Harrak S.,[1] Mrabti H.,[3] Boutayeb S.[3] and Errihani H.[4]

[1]Resident in Medical Oncology, National Oncology Institute of Rabat Morocco.
[2]Doctor Specialist Medical Oncology Department, National Oncology Institute of Rabat Morocco.
[3]Professor of Medical Oncology Department, National Oncology Institute of Rabat Morocco.
[4]Head of Medical Oncology Department, National Oncology Institute of Rabat Morocco.

***Corresponding Author: EL. Mouhtadi S.**

Resident in Medical Oncology, National Oncology Institute of Rabat Morocco.

Article Received on 07/09/2020 **Article Revised on 28/09/2020** **Article Accepted on 18/10/2020**

INTRODUCTION

The anti-tumour immune response involves a cycle of complex immunological events, in which T lymphocytes play a major role. Cytotoxic T cells lysis tumour cells in collaboration with T lymphocytes with auxiliary functions.

The immune system is therefore able to eliminate neoplastic cells through a complex and finely regulated response.[1-2]

Immunological checkpoints play a major role in maintaining self-tolerance, and in regulating the duration and extent of the physiological immune response in order to reduce its impact on healthy tissues.

Tumour cells, which are the most genetically unstable, are able to hijack these regulatory mechanisms to evade the immune system.

In front of these cells, the immune system becomes tolerant and the tumour progresses. This is how immune checkpoint inhibitors are born, in order to block this escape mechanism.[3]

Immune checkpoint inhibitors represent a revolution in cancer management, with a considerable change in therapeutic standards.

The cancer cell is no longer the direct target, now it is the immune cells that are the target of these new molecules in order to boost anti-tumour immunity. By targeting the signaling pathways that allow the cancer cell to escape.

Their use exposes them to a wide spectrum of autoimmune toxicities.

This balance of efficacy versus toxicity is evidenced by checkpoint inhibitor toxicities such as enterocolitis, hypophysitis, thyroiditis, pneumonitis, and others.[4]

Immune related adverse events (irAEs) are common and depending on the severity, can require cessation of therapy as well as glucocorticoids, anti-tumor necrosis factor antibodies or other forms of immunosuppression.

This spectrum of toxicities raises the question of whether patients with pre-existing autoimmune diseases should be treated with this class of therapy.

Clinical trials demonstrating the immune checkpoints inhibitors efficiency, have excluded patients with autoimmune diseases. Although there are retrospective studies that assess whether these agents can be used safely in patients with autoimmune diseases, this has not been evaluated in many clinically relevant scenarios.[4]

We present a clinical case of a patient with metastatic melanoma treated with Pembrolizumab, who also has ulcerative colitis (UC) and has developed a fatal disease flare-up.

CASE REPORT

Mrs T.F, 58 years old, from Morocco, with ulcerative colitis (UC) diagnosed in 2001, stable on Salazopyrine.

The patient presented to the dermatology department in May 2019 with a tumour in the heel of the right foot, a wide excision with sentinel node in June 2019 showed an acrolentiginous invasive malignant melanoma (Clark Mihm level IV, Breslow thickness 4.9 mm, mitotic index 20 mitosis/10 fields) and a positive sentinel lymph node.

In July 2019, the patient presented at the National Institute of Oncology in Rabat for an initial consultation on the diagnosis of melanoma after resection. The post-operative radiological extension showed bone and lymph node metastases. The BRAF V600E mutation was positive.

A chemotherapy Dacarbazine (DTIC) was initiated due to financial problems. After 3 cycles, the patient presented a clinical and radiological progression.

The medical decision was to start Pembrolizumab, an initial rectoscopy was requested showing a stable aspect of UC.

Fifteen days after the first cycle of Pembrolizumab, the patient presented to the emergencies with a deteriorating general condition, fever of 39°C, bloody diarrhoea and severe abdominal pain, the rectoscopy showed a significant flare-up of UC.

The patient was hospitalised in the medical oncology department and treated with high dose corticosteroid therapy, but without improvement after 48 hours. The patient was then admitted to the intensive care unit, an immunosuppressive treatment with Infliximab was initiated but the patient had died within hours.

DISCUSSION

Checkpoint inhibitors have been shown to be effective in many cancers, however they may be accompanied by the untoward effects of immune-activation beyond the tumor, and inflammatory- mediated destruction in many organs.

Their use in patients with pre-existing autoimmune diseases has been limited due to their exclusion from registration trials.[1,5,8]

The few retrospective studies carried out show that about 25% of patients develop an exacerbation of their autoimmune diseases.

A retrospective study published by Johnson *et al.* included six patients with autoimmune diseases who received Ipilimumab for the treatment of advanced melanoma.[6] Two out of six had treatment- associated enterocolitis, successfully managed with infliximab or methylprednisolone, while the remaining four had no flare-ups or side effects.

In another retrospective study,[7] Menzies *et al.* included 119 patients with underlying autoimmune disease or major prior toxicity to Ipilimumab who were treated with anti-PD1 (Pembrolizumab or Nivolumab).

Of the 52 patients with autoimmune diseases in total, 38% developed a disease flare-up, and there was a trend for increased number of flares in patients who required immunosuppressive therapy at baseline for the management of their autoimmune disease.

Leonardi *et al* conducted a retrospective study of 56 patients with non-small cell lung cancer and concomitant autoimmune disease who received monotherapy with a PD-1 / PD-L1 inhibitor,[8] 13% of the patients developed an exacerbation of their underlying disease, but none required permanent cessation of immunotherapy.

The presence of active symptoms of autoimmune diseases has been previously evaluated, although with conflicting results.

It seems reasonable to assume that patients with active symptoms at baseline were more likely to experience a disease flare on checkpoint inhibitors, the retrospective study by Menzies et al. confirms this hypothesis with a statistically significant increase in the number of disease flare-ups in patients with active symptoms compared to clinically inactive disease.

However, a study by Abdel-Wahab *et al*. found no difference in the frequency of adverse events in patients with active pre-existing autoimmune disease.[9]

For our patient, her autoimmune disease was clinically inactive and yet she developed a fatal flare-up, so it is clear that further studies are needed in this group of patients to better elucidate these events.

CONCLUSION

Checkpoint inhibitors represent a revolution in cancer treatment, whose efficacy is demonstrated in the literature and confirmed in daily practice, with a globally acceptable tolerance.

Patients with cancer who have personal or family history of autoimmune pathologies, and are candidates for treatment with checkpoint inhibitors, are more exposed to the risk of their appearance or reactivation, which can be fatal, as in the case of our patient.

So the prescription in these cases must be particularly careful with close monitoring.

REFERENCES

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with Ipilimumab in patients with metastatic melanoma. N Engl J Med, 2010; 363: 711–23.
2. Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nat Rev Clin Oncol, 2016; 13: 473–86.
3. E. Ileana, S. Champiat, et J.-C. Soria, « Immune-Checkpoints: les nouvelles immunothérapies anticancéreuses », Bull. Cancer (Paris), 2013; 100(6): 601-610.
4. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med, 2018; 378: 158–68.
5. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med, 2015; 372: 320–30.
6. Johnson DB, Sullivan RJ, Ott PA, et al. Ipilimumab

therapy in patients with advanced melanoma and preexisting autoimmune disorders. JAMA Oncol, 2016; 2(2): 234–40.
7. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol, 2017; 28(2): 368–76.
8. Leonardi GC, Gainor JF, Altan M, et al. Safety of programmed Death-1 pathway inhibitors among patients with non-small-cell lung Cancer and preexisting autoimmune disorders. J Clin Oncol, 2017; 77: 0305.
9. Abdel-Wahab N, Shah M, Lopez-Olivo MA, et al. Use of immune checkpoint inhibitors in the treatment of patients with Cancer and preexisting autoimmune disease. Ann Intern Med, 2018; 168: 121–30.