ejpmr, 2025, 12(5), 08-10

SJIF Impact Factor 7.065

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Case Study

ISSN 2394-3211

EJPMR

IMMUNE RELATED ADVERSE EVENTS INDUCED BY NIVOLUMAB/IPILIMUMAB COMBINATION THERAPY NOT OBSERVED WITH NIVOLUMAB MONOTHERAPY- A STUDY OF 2 CASE REPORTS

Shrushti Dalal* and Aditya Parekh

[1]PGY2 Internal Medicine, Western Reserve Health Education/NEOMED, Warren, Ohio, USA.
[2]MD Internal Medicine, Summa Health, Akron, Ohio, USA.

***Corresponding Author: Shrushti Dalal**

PGY2 Internal Medicine, Western Reserve Health Education/NEOMED, Warren, Ohio, USA.

Article Received on 04/03/2025 **Article Revised on 24/03/2025** **Article Accepted on 14/04/2025**

ABSTRACT

Immune checkpoint inhibitors (ICIs) have significantly advanced cancer immunotherapy, producing substantial antitumor responses across a variety of cancer types. Combination immune checkpoint inhibitor (ICI) therapy using anti-CTLA-4 and anti-PD-1 antibodies has demonstrated superior clinical efficacy compared to monotherapy with either antibody alone.[1] However, the combination therapy is seen to be associated with an increased manifestation of autoimmune adverse effects. We present two separate patient cases in which combination therapy with Nivolumab/Ipilimumab resulted in autoimmune side effects which were not evident with Nivolumab monotherapy in the same patients.

KEYWORD:- Immune checkpoint inhibitors, Autoimmune colitis, Autoimmune hepatitis, Monoclonal antibodies.

CASE REPORT

Case 1

A 79 year old male presented to his primary care doctor with a chief complaint of unintentional weight loss of 40 pounds over 2 months. His past medical history included osteoarthritis, hyperlipidemia, prostate cancer diagnosed 20 years ago, status post prostatectomy, chronic lymphocytic leukemia diagnosed 5 years ago and GERD. Due to his personal history of cancers, he was referred to an oncologist for further work-up. He underwent total body CT imagining which revealed multiple metastasis in liver, bilateral lungs, bone and peritoneal area. He underwent liver biopsy and was diagnosed with stage IV malignant melanoma (BRAF V600E negative). He was then started on combination immunotherapy with nivolumab/ipilimumab. After the first cycle, he developed extensive diarrhea, with about 10 episodes/day of liquidy stools. The episodes continued throughout his course of 4 cycles of immunotherapy. He underwent colonoscopy and was diagnosed to have autoimmune colitis. Immunotherapy was discontinued and he was started on PO prednisone 40mg which was gradually tapered over the course of a few weeks per his clinical response. He was then started on nivolumab monotherapy a year later and he continues to tolerate the treatment without any further complications.

Case 2

A 61 year old male presented to an ER with a chief complaint of hematuria and right sided non-radiating, sharp shooting abdominal pain. He was hemodynamically stable on presentation. His past medical history included hypertension and hyperlipidemia. His CBC was unremarkable except anemia with Hgb 7.8 gm/dL, CMP was within normal limits except for Cr of 1.67 mg/dl (baseline 0.9). Urinalysis was positive for RBCs. He underwent CT abdomen and pelvis with contrast which demonstrated a right sided renal mass and multiple enlarged abdominal and retroperitoneal lymph nodes. His PET scan revealed multiple bilateral lung nodules. He then underwent a right total nephrectomy. He was diagnosed with stage IV metastatic right kidney clear cell carcinoma with metastasis to abdominal, peritoneal nodes and bilateral lungs. He was started on combination immunotherapy with nivolumab/ipilimumab therapy and underwent 4 cycles of therapy. A month after completion of immunotherapy, he developed autoimmune hepatitis as was noted on his routine lab work. His AST was elevated at 1105 U/L, ALT 1050 U/L, Alkaline phosphatase 225 U/L. He was immediately started on high dose PO prednisone which was gradually tapered off over the course of next few weeks. His LFTs were closely monitored during this time and they gradually trended down to the current normal levels. 3 months later, he was restarted on nivolumab monotherapy and he continues to

show response to treatment without any further complications.

DISCUSSION

Before the breakthrough with immune checkpoint inhibitors, the mainstay of cancer treatment was directly targeting the tumor cells with surgical modalities, chemotherapy, and radiotherapy. These treatments had significant side effects and toxicities associated with them. The advent of immunotherapy came with a better understanding of the pathogenesis of tumor cells. The host immune system was identified as a crucial endogenous agent against the development of tumors. During tumor progression, cancer cells acquire the ability to evade immunosurveillance and suppress adaptive immunity by stimulating immunosuppressive co-signals or immune checkpoints on T cells, such as cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4 or CD152) and programmed cell death-1 (PD-1 or CD279).[2],[3] Immune checkpoint inhibitors (ICIs), which are monoclonal antibodies (mAb), target these immune checkpoint molecules, thereby reversing T-cell inhibition and enhancing anti-tumor immunity.[4],[5]

Monotherapy with immune checkpoint inhibitors was initially approved for the treatment of cancers like metastatic melanoma, renal cell carcinoma, non-small cell lung cancer, Hodgkin's lymphoma and squamous cell cancer of head and neck, which did not demonstrate any response in some cancers and resistance was seen to be developing during or after treatment resulting in tumor relapse. These findings led to the usage of combination immunotherapy as a proposed more therapeutic strategy to create a synergistic antitumor effect. Dual checkpoint blockade, has since then shown a more durable response in decreasing the tumor burden especially in advanced malignancies as compared to monotherapy.[6][7][8] One of the extensively studied combination immunotherapy is with nivolumab (IgG4 anti-PD-1 MAb) and ipilimumab (totally humanized IgG1 antiCTLA-4 MAb). PD-1 contributes to T-cell exhaustion in peripheral tissues primarily and within the tumor milieu while CTLA-4 causes T-cell inhibition in the early stages of its activation. Thus, combination immunotherapy acts synergistically to inhibit T-cell activation as they act at different points in the T-cell activation pathway.

The enhanced immune activity induced by these immunotherapeutic agents is linked to inflammatory side effects, commonly referred to as immune-related adverse events (irAEs). The exact pathophysiological mechanisms underlying these adverse events, which can sometimes be severe, remain unclear, and no prospective studies have been published on their effective management. While virtually any organ may be affected, irAEs most commonly involve the gastrointestinal tract, endocrine glands, skin, and liver, with less frequent involvement of the pulmonary, musculoskeletal, and central nervous systems.[9] Hence, regular treatment surveillance with biomarkers to distinguish responders from non-responders is warranted in order to deliver better treatment outcomes and to avoid serious immune toxicities.

CONCLUSION

As outlined in the aforementioned cases, combination immunotherapy with nivolumab and ipilimumab resulted in autoimmune side effects that were not observed with nivolumab monotherapy. Further research is required to elucidate the underlying causes of these effects. Additionally, the question of whether combination immunotherapy remains as beneficial as previously demonstrated warrants further investigation.

REFERENCES

1. Nikoo M, Rabiee F, Mohebbi H, et al. Nivolumab plus ipilimumab combination therapy in cancer: Current evidence to date. *Int Immunopharmacol*, 2023; 117: 109881. doi:10.1016/j.intimp.2023.109881
2. Padmanee Sharma, Siwen Hu-Lieskovan, Jennifer A. Wargo, Antoni Ribas, Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy, Cell, 2017; 168, 4: 707-723, ISSN 0092-8674
3. A. Rotte, J.Y. Jin, V. Lemaire, Mechanistic overview of immune checkpoints to support the rational design of their combinations in cancer immunotherapy, Annals of Oncology, 2018; 29, 1: 71-83. ISSN 0923-7534
4. Ronald H. Schwartz, Costimulation of T lymphocytes: the role of CD28, CTLA-4, and B7/BB1 in interleukin-2 production and immunotherapy, Cell, 1992; 71, 7: 1065-1068, ISSN 0092-8674
5. Theresa L. Walunas, Deborah J. Lenschow, Christina Y. Bakker, Peter S. Linsley, Gordon J. Freeman, Jonathan M. Green, Craig B. Thompson, Jeffrey A. Bluestone, CTLA-4 can function as a negative regulator of T cell activation, Immunity, 1994; 1, 5: 405-413, ISSN 1074-7613
6. D.M. Pardoll The blockade of immune checkpoints in cancer immunotherapy Nat. Rev. Cancer, 2012.
7. S. Bagchi *et al.* Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. Annu. Rev. Pathol, 2021.
8. S. Qin *et al.* Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. Mol. Cancer, 2019.
9. Michael A. Postow and Jason Chesney and Anna C. Pavlick and Caroline Robert and Kenneth Grossmann and David McDermott and Gerald P. Linette and Nicolas Meyer and Jeffrey K. Giguere and Sanjiv S. Agarwala and Montaser Shaheen and Marc S. Ernstoff and David Minor and April K. Salama and Matthew Taylor and Patrick A. Ott and Linda M. Rollin and Christine Horak and Paul Gagnier and Jedd D. Wolchok and F. Stephen Hodi. Nivolumab and Ipilimumab versus Ipilimumab in

Untreated Melanoma. New England Journal of Medicine, 2015; 372, 21: 2006-2017. doi 10.1056/NEJMoa1414428