A Potential New Use for Tocilizumab: Refractory Checkpoint Inhibitor Hepatitis

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Introduction

- Immune checkpoint inhibitors (CPI) are becoming increasingly common treatment options for several types of cancers (*1*).
- Typically, checkpoint proteins deactivate T-cells to prevent the immune system from harming the body's own cells
- CPIs work by preventing this deactivation so the immune system can better destroy the cancer cells *(Figure 1)*
- Many side effects, including a frequent association with hepatitis *(2)*
- Current mainstay of treatment for CPI-induced hepatitis includes high dose steroids and immunomodulators if needed (3)
- However, it's not well-established how to proceed if typical treatments fail

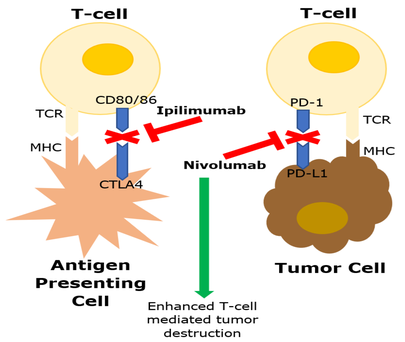

Figure 1. Overview of the function of CPIs.
Major Histocompatibility Complex (MHC), T-cell Receptor (TCR), Cytotoxic T-lymphocyte Antigen-4 (CTLA-4), Programmed death-ligand 1 (PDL-1)

Case Description

35 y.o. female with recurrent right kidney renal cell carcinoma, status-post resection with nephrectomy, on palliative treatment with nivolumab/ipilimumab.

Presentation:

- Referred to the ED for elevated liver function tests (LFTs) and an MRI concerning for hepatitis
- 3 weeks prior, had been started on steroids with concern for CPI-induced hepatitis

Hospital Course:

- At admission, started on IV steroids and mycophenolic acid
- On hospital day 4, LFT and bilirubin continued to rise, so was given a dose of rituximab
- Liver biopsy was obtained and was consistent with CPI-induced hepatitis *(image 2)*
- On hospital day 8, LFTs and total bilirubin were still rising so tocilizumab was given based on a prior case report showing improvement following tocilizumab treatment (4)
- The following day, LFTs had decreased
- 4 days after tocilizumab was given, AST and ALT were nearly half their pretreatment values and bilirubin began downtrending
- Discharged on hospital day 12

	HD1	HD2	HD3	HD4	HD5	HD6	HD7	HD8	HD9	HD10	HD11	HD12
AST	582	599	592	640	886	637	720	660	576	531	404	333
ALT	2838	2920	2950	3342	3603	4002	4084	4091	3429	3304	2731	2573
tBilli	7.7	7.2	8.4	10.6	12.9	14.8	17.2	20.5	20.8	23.2	22.7	22.2
Tx given				Ritux				Toci				

Table 1. The trend of the patient's liver function tests and total bilirubin over her hospital course.
Hospital Day (HD), Aspartate transaminase (AST), Alanine transaminase (ALT), total bilirubin (tbili), rituximab (ritux), tocilizumab (toci)

Pathology

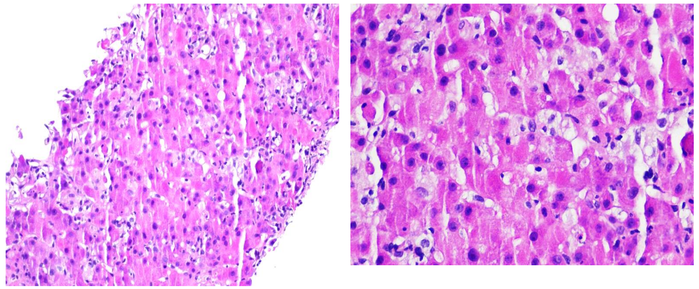

Figure 2. Patient's livery biopsy showing CPI-induced hepatitis.

Conclusion

- As CPI treatment becomes more common, so will the incidence of these well-established side effects, like autoimmune hepatitis.
- It will be necessary to find efficacious treatment options for these side effects.
- Tocilizumab appears to be a potential option for refractory cases of CPI-induced autoimmune hepatitis

References

1. K. M. Hargadon, C. E. Johnson, C. J. Williams, Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. *International Immunopharmacology* 62, 29-39 (2018).
2. N. Sengul Samanci *et al.*, Immune-related adverse events associated with immune checkpoint inhibitors in patients with cancer.
3. M. Dougan, Y. Wang, A. Rubio-Tapia, J. K. Lim, AGA Clinical Practice Update on Diagnosis and Management of Immune Checkpoint Inhibitor Colitis and Hepatitis: Expert Review. *Gastroenterology* 160, 1384-1393 (2021).
4. C. R. Stroud *et al.*, Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade. *J Oncol Pharm Pract* 25, 551-557 (2019).