Immune-Mediated Hepatitis: A Single Drug or a Class Effect?

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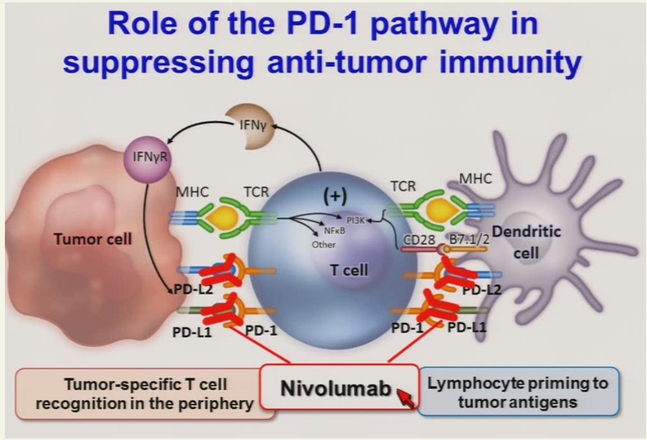
Abstract

- Non Small Cell Lung cancer (NSCLC) is the most common type of lung cancer in the United States, accounting for 82% of all lung cancer diagnoses.
- Checkpoint inhibitors have drastically changed the landscape in the treatment of metastatic NSCLC.
- Patients can develop liver toxicity from this class of drugs. The mechanism of liver injury is thought to be immunologically mediated.
- Generally, liver toxicity leads to discontinuation of the drug and eliminates the entire drug category as the toxicity is thought to be seen with the drug class itself, not individual agents.
- Here, we present a case of a patient who was transitioned from one PD-1 inhibitor to another due to immune mediated liver injury for the treatment of metastatic NSCLC.

Case Presentation

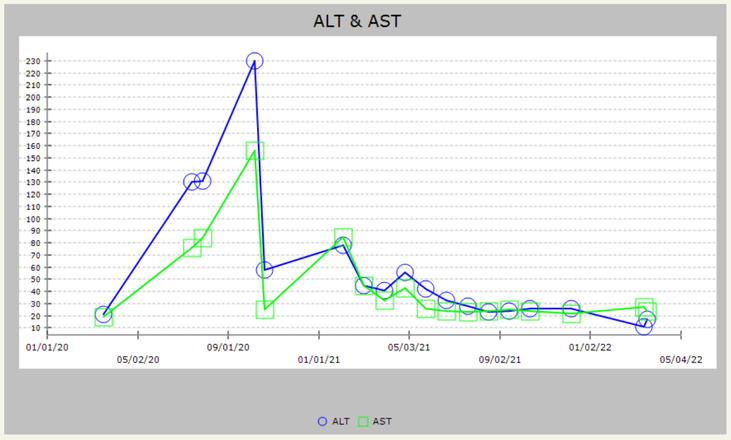
- 84 year old woman with remote history of squamous cell carcinoma of the lung treated with lobectomy and adjuvant chemotherapy.
- 15 years later, she developed recurrence of her lung cancer with metastasis to the lymph nodes and the liver.
- Somatic tumor mutation testing revealed no actionable driver mutations, but she did have PD-1 expression of 100%.
- She started palliative combination chemotherapy, but only completed 2 cycles due to significant toxicity from chemo.
- She was switched to single agent immunotherapy, IV pembrolizumab 200mg every 21 days to be continued until progression or unacceptable toxicity.
- She completed five cycles, then developed elevated liver enzymes. Drug was held and she was treated with a high dose steroid taper.
- Drug was resumed at 28 day interval dosing, but she developed elevated liver enzymes again. A liver US (unremarkable) was ordered and she was referred to GI for evaluation, who agreed that the liver enzyme elevation was likely secondary to DILI.
- Given her age, comorbidities, and repeated DILI the decision was made to discontinue pembrolizumab permanently. She had no other actionable mutations and because of her age and ECOG performance status, chemotherapy was not a safe treatment option for her. She was switched to switch to IV Nivolumab (PD-1 Inhibitor) 480mg every 28 days.
- This is not conventional as the presumption is these immune mediated toxicities are consistent with drugs of the same class so one would expect her to develop DILI with Nivolumab as well.
- She has been on Nivolumab for over one year without any immune mediated toxicities or any signs of progression of her disease.

Figure 1



- The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body .
- Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells.

Figure 2



- Trends of AST and ALT since initiation of Pembrolizumab including periods of drug discontinuation.
- Hepatocellular pattern of liver injury can be seen in approximately 10% of patients who receive Pembrolizumab. Usually, the degree of enzyme elevation is mild to moderate, self-limited, and resolve even with continuing cyclic therapy.

Discussion

- While the rates of diagnosis and death due to non small cell lung cancer are decreasing, the five year relative survival rate is still only around 20%.
- Treatment of lung cancer is rapidly evolving, particularly in the metastatic setting. Immunotherapies, most notably PD-1 inhibitors, have drastically changed the landscape in the treatment of metastatic non small cell lung cancer.
- Currently, single agent check point inhibitors are approved in the metastatic setting for patients whose tumor has greater than 50% PD-1 expression. Examples of PD-1/PD-L1 inhibitors are pembrolizumab, nivolumab, atezolizumab.
- Toxicities can, unfortunately, be a reason for interruption and sometimes discontinuation of the drugs. In our patient, liver toxicity led to discontinuation of pembrolizumab.
- The mechanism of liver injury due to pembrolizumab is likely to be immunologically mediated and some cases have appeared to respond to corticosteroid or immunosuppressive therapy, allowing for continuation or restarting of pembrolizumab therapy. In this patient's case the drug was restarted with noted re-injury of the liver.
- The general practice is to consider this hepatotoxicity as an entire drug class effect, not limited to single agents. Her tolerance to Nivolumab without evidence of drug induced liver injury challenges this concept.

Conclusion

- Our case challenges the concept of drug induced liver injury in PD-1 inhibitors applying to an entire drug class versus a single agent.
- In patients with limited treatment options, transition to a different agent of the same drug class can be considered despite documented history of liver injury.

References and Acknowledgements

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