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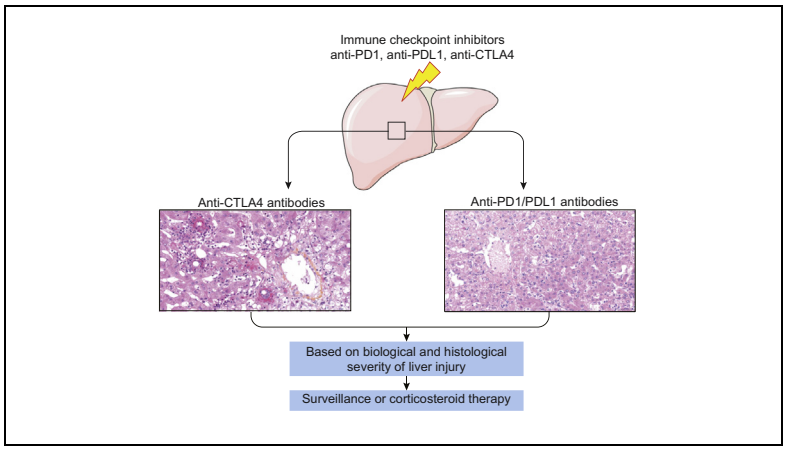
Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors

Graphical abstract



Highlights

- Acute hepatitis resulting from treatment of metastatic cancer with immune checkpoint inhibitors is rare.
- Immune-mediated hepatitis diagnosis requires exclusion of all causes of hepatitis.
- Liver histology is paramount for the diagnosis and severity evaluation of liver damage.
- Management should be based on biological and histological severity of liver injury.
- Immune-mediated hepatitis does not require the systematic use of corticosteroids.

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Lay summary

Immunotherapy for metastatic cancer can be complicated by immune-related adverse events in the liver. In patients receiving immunotherapy for metastatic cancer who develop immune-mediated hepatitis, liver biopsy is helpful for the diagnosis and evaluation of the severity of liver injury. This study demonstrates the need for patient-oriented management, which could eventually avoid unnecessary systemic corticosteroid treatment.

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Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors

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Background & Aims: Immunotherapy for metastatic cancer can be complicated by the onset of hepatic immune-related adverse events (IRAEs). This study compared hepatic IRAEs associated with anti-programmed cell death protein 1 (PD-1)/PD ligand 1 (PD-L1) and anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) monoclonal antibodies (mAbs).

Methods: Among 536 patients treated with anti-PD-1/PD-L1 or CTLA-4 immunotherapies, 19 (3.5%) were referred to the liver unit for grade ≥3 hepatitis. Of these patients, nine had received anti-PD-1/PD-L1 and seven had received anti-CTLA-4 mAbs, in monotherapy or in combination with anti-PD-1. Liver investigations were undertaken in these 16 patients, including viral assays, autoimmune tests and liver biopsy, histological review, and immunostaining of liver specimens.

Results: In the 16 patients included in this study, median age was 63 (range 33-84) years, and nine (56%) were female. Time between therapy initiation and hepatitis was five (range, 1–49) weeks and median number of immunotherapy injections was two (range, 1–36). No patients developed hepatic failure. Histology related to anti-CTLA-4 mAbs demonstrated granulomatous hepatitis including fibrin ring granulomas and central vein endotheliitis. Histology related to anti-PD-1/PD-L1 mAbs was characterised by lobular hepatitis. The management of hepatic IRAEs was tailored according to the severity of both the biology and histology of liver injury: six patients improved spontaneously; seven received oral corticosteroids at 0.5–1 mg/kg/day; two were maintained on 0.2 mg/kg/day corticosteroids; and one patient required pulses and 2.5 mg/kg/day of corticosteroids, and the addition of a second immunosuppressive drug. In three patients, immunotherapy was reintroduced without recurrence of liver dysfunction.

Conclusions: Acute hepatitis resulting from immunotherapy for metastatic cancer is rare (3.5%) and, in most cases, not severe. Histological assessment can distinguish between anti-PD-1/PD-L1 and anti-CTLA-4 mAb toxicity. The severity of liver injury is helpful for tailoring patient management, which does not require systematic corticosteroid administration.

Lay summary: Immunotherapy for metastatic cancer can be complicated by immune-related adverse events in the liver. In patients receiving immunotherapy for metastatic cancer who develop immune-mediated hepatitis, liver biopsy is helpful for the diagnosis and evaluation of the severity of liver injury. This study demonstrates the need for patient-oriented management, which could eventually avoid unnecessary systemic corticosteroid treatment.

Introduction

Immune-modulatory therapies have dramatically improved the survival of patients with metastatic tumours.[1,2] During the development of cancer, the immune system becomes naturally 'tolerant' towards cancer cells, which are seen as part of the 'self'. This tolerance is maintained by immune checkpoint pathways that downregulate immune functions, permitting cancer cells to evade immune attacks.[3,4] Monoclonal antibodies (mAbs) directed against regulatory immune checkpoint molecules that inhibit T cell activation enhance antitumour immunity.[5] Ipilimumab, a human Ig-G1 mAb, blocks cytotoxic T lymphocyte antigen 4 (CTLA-4).[6] Pembrolizumab and nivolumab, humanized IgG4 kappa and human IgG4 mAbs, respectively, block the interaction between programmed cell death protein 1 (PD-1) and the two PD ligands, PD-L1 and PD-L2, by selectively binding the PD-1 receptor.[7,8] Durvalumab, a human IgG1 kappa mAb, targets PD-L1.[9]

By unbalancing the immune system, these new immunotherapies could result in immune-related adverse events (IRAEs), which mimic autoimmune conditions.[10] The incidence of immune-related acute hepatitis of all grades is estimated to affect between 4% and 9% of patients treated with

Keywords: Immunotherapy; Immune-related adverse events; Immune checkpoints inhibitors.
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