References

[1] De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68:1181–1190.
[2] Bhave P, Buckle A, Sandhu S, Sood S. Mortality due to immunotherapy related hepatitis. J Hepatol 2018;69:976–978.
[3] Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28: iv119–iv142.
[4] Reeves HM, Winters JL. The mechanisms of action of plasma exchange. Br J Haematol 2014;164:342–351.
[5] Larsen FS, Schmidt LE, Bernsmeier C, Rasmussen A, Isoniemi H, Patel VC, et al. High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial. J Hepatol 2016;64:69–78.

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Reply to: "Acute liver failure due to immune-mediated hepatitis successfully managed with plasma exchange: New settings call for new treatment strategies?"

To the Editor:

We thank Riveiro-Barciela *et al.* for their interest in our paper "Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors".[1] They reported the case of a patient who developed grade 2 hepatitis under first line treatment with nivolumab (anti-PD-1) and dioxygenasel inhibitor for a metastatic melanoma. The hepatitis improved with corticosteroid therapy. Because of tumor progression a second line treatment with ipilimumab (anti-CTLA4) was administered. She developed fulminant hepatitis induced by ipilimumab and she was treated with corticosteroids and mycophenolate mofetil, since no improvement was seen she underwent plasma exchange with hepatitis resolution.

Retreatment of a patient who developed acute hepatitis induced by immune checkpoint inhibitors is a crucial issue. Compared to other drug-induced liver disease, in which the drug re-administration is not possible, the re-challenge with immune checkpoint inhibitors is feasible as it is not always associated with acute hepatitis recurrence. The choice of the monoclonal antibody and the time of therapy re-introduction are relevant points and there are no data in the literature that can help in taking the decision.

In our experience 2 patients who developed acute hepatitis on ipilimumab were previously exposed to nivolumab.[1] We hypothesized that the activation of the immune system by a first treatment might have enhanced the immune response to the second line therapy and induced the immune related adverse event (irAE). While ipilimumab front-line followed by nivolumab is well tolerated, the nivolumab front-line followed by ipilimumab has been associated with severe adverse events.[2] In the clinical case the patient was first exposed to the anti-PD-1 and secondly to the anti-CTLA4. Considering our experience and the data reported in the literature, we think that retreatment with ipilimumab might be avoided.

Of course the re-challenge with immunotherapy can be associated with hepatitis recurrence but also with the development of another irAE. We followed a 64-year-old woman who was treated with the combination of nivolumab and ipilimumab for a metastatic melanoma. After the first injection she developed an acute hepatitis characterized by aspartate aminotransferase 2,048 IU/L, alanine aminotransferase 2,122 IU/L and total bilirubin 87 μmol/L. Immunotherapy was discontinued. The liver biopsy showed sub-acute hepatitis with lobular inflammatory infiltration made by lymphocytes and eosinophils associated with a cholangiolitis. She was treated with corticosteroids 1 mg/kg/day and her liver tests normalized. Three months later she presented with tumor progression. After multidisciplinary discussion the patient was retreated with pembrolizumab (anti-PD-1) and concomitant corticosteroids prophylaxis (20 mg/day). After 8 courses of immunotherapy she had no hepatitis but presented with diarrhea and was diagnosed with immune-related colitis. The immunotherapy was stopped and the corticosteroid dose was increased to 40 mg/day and then to 60 mg/day. The diarrhea improved but it recurred after corticosteroid discontinuation. The patient was treated with anti-TNFα. The corticosteroid-dependent colitis responded to anti-TNFα therapy.

Fatal events induced by immune checkpoint inhibitors remain a rare complication of cancer immunotherapy. A recent published paper based on Vigilyze-Vigibase, the World Health Organization pharmacovigilance database, identified 613 (2%) fatal irAEs among 31,059 individuals who received cancer immunotherapy. Overall they noted an increase of fatal toxic effects over time. Fulminant hepatitis related death was reported in 124 (0.4%) patients, 31 on ipilimumab, 74 on anti-PD-1/PD-L1 and 19 on combination therapy. The study authors also reported on a multicenter analysis, which included 7 academic centers. The incidence of fatal irAEs was 0.6%. Of 3,545

treated patients, fulminant hepatitis was described in 5 (0.14%), all patients received high doses of corticosteroids at a median of 5 days after the onset of symptoms.[3]

Fulminant hepatitis due to cancer immunotherapy seems to be refractory to a first and even to a second line treatment with immunosuppressive drugs and liver transplantation cannot be proposed in a patient with an active cancer. A case report described the use of antithymocyte globulin therapy in a corticosteroid non-responder with clinical and biological improvement.[4] The use of plasma exchange, as described by Riveiro-Barciela and colleagues, is an interesting therapeutic option but further studies are required before it can be recommended.

In conclusion, retreatment with immune checkpoint inhibitors after immune-mediated acute hepatitis should not be denied. The patient has to be informed that there is a risk of hepatitis recurrence possibly characterized by a more severe phenotype, or of an irAE involving another organ. The oncological benefit needs of course to outweigh the risk. The interest of a corticosteroid prophylaxis is not known.

Fulminant hepatitis can complicate cancer immunotherapy, but it is still a rare irAE. The use of plasma exchange in non-responders to immunosuppressive therapy deserves further exploration.

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Conflict of interest

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Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

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References

[1] De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 2018;68:1181–1190.
[2] Weber JS, Gibney G, Sullivan RJ, Sosman JA, Slingluff Jr CL, Lawrence DP, et al. Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. Lancet Oncol 2016;17:943–955.
[3] Wang Y, Farmer M, Izaguirre EW, Schwartz DL, Somer B, Tillmanns T, et al. Association of definitive pelvic radiation therapy with survival among patients with newly diagnosed metastatic cervical cancer. JAMA Oncol 2018;4:1288–1291.
[4] Chmiel KD, Suan D, Liddle C, Nankivell B, Ibrahim R, Bautista C, et al. Resolution of severe ipilimumab-induced hepatitis after antithymocyte globulin therapy. J Clin Oncol 2011;29:e237–e240.

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Predicting early hepatocellular carcinoma recurrence after resection: A comment for moving forward

To the Editor:

Tumour recurrence, which occurs in 70% of patients with hepatocellular carcinoma (HCC) within 5 years after hepatic resection, is a major cause of post-resection death.[1] This recurrence can be true recurrence (intrahepatic metastases), which occurs sooner than 2 years later, or it can be due to the development of *de novo* tumours at least 2 years later. Despite this high rate of tumour recurrence, no anti-recurrence adjuvant therapies are currently recommended by the European Association for the Study of the Liver (EASL)[1] or the American Association for the Study of Liver Diseases (AASLD).[2] Therefore, identifying patients with HCC at high risk of post-resection recurrence is important to enhance surveillance and to detect recurrence as early as possible.

Toward this goal, Chan and coworkers[3] have described two statistical models that may allow clinicians to estimate the risk of tumour recurrence in patients with HCC. Their retrospective study included 3,903 patients who underwent curative hepatic