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Case Report **Hepatology and Gastroenterology**

Pembrolizumab as a Second-Line Therapy: About a Case Report with Literature Review

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Abstract

Hepatocellular carcinoma (HCC) remains a major cause of cancer-related mortality worldwide, most often arising in the setting of chronic liver disease and cirrhosis. Although tyrosine kinase inhibitors have long represented the cornerstone of systemic therapy in advanced stages, therapeutic resistance and disease progression are frequent. Recent advances in immunotherapy, particularly immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway, have reshaped the therapeutic landscape of HCC. Pembrolizumab has demonstrated clinically meaningful antitumor activity and an acceptable safety profile in patients previously treated with sorafenib, as reported in pivotal clinical trials. This article highlights the therapeutic role of pembrolizumab as a second-line option in advanced HCC and discusses its place within current evidence-based treatment strategies, emphasizing the growing importance of immunotherapy in the multidisciplinary management of this disease.

Keyword: Hepatocellular Carcinoma, Immunotherapy, Cirrhosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. It is a major complication of most chronic liver diseases, most often occurring at the stage of cirrhosis.

Management is necessarily multidisciplinary and expert. The treatment of HCC has seen profound changes, with the introduction of new therapeutic methods.

Immunotherapy, designed to correct the immunosuppressive context frequently associated with this tumor, has shown promising results and could challenge the therapeutic algorithm for hepatocellular carcinoma.

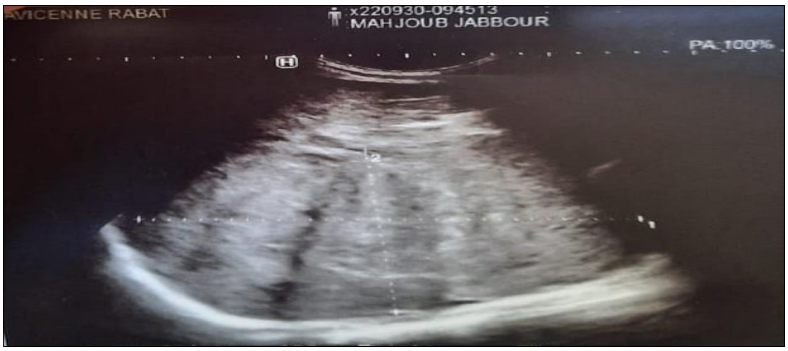
We report the case of a 60-year-old patient diagnosed with HCC who received second-line treatment with pembrolizumab, achieving a favorable therapeutic response.

OBSERVATION

This is a 60-year-old male patient with history of: Hypothyroidism managed with Levothyrox, diet-controlled type 2 diabetes, hypertensive receiving medical treatment, viral hepatitis C treated and declared cured in 2008, chronic smoker weaned 18 months ago.

Follow-up for post-viral cirrhosis, Child A5 and Meld 12, ascitic decompensation on diuretic and hemorrhagic on protocol for eradication of esophageal varices.

In the context of HCC screening during the follow-up of a cirrhotic patient, the diagnosis of HCC was based on both biological and radiological criteria. Serum alpha-fetoprotein (AFP) was elevated at 948 ng/mL. Screening abdominal ultrasonography revealed a large hepatic mass measuring 9.15 × 7.5 cm, located across segments VI and VII.



Ultrasond Image: HCC measuring 9.15*7.5cm.

We completed by an abdominal angioscan which confirmed this lesion, it has objectived: Liver of chronic hepatopathy, site of a 9x8cm mass straddling segments VI and VII isodense in spontaneous contrast heterogeneously enhanced at arterial time with Wash out at portal and late time. Tumour thrombosis of the right posterior portal branch with early enhancement at arterial time. Peri-splenic and peri-gastric porto-systemic shunts.

The patient was initially treated with: Sorafenib for 11 months with a good initial response to treatment marked by a decrease in AFP values. In view of the progressive rise in AFP and the size of the HCC, Sorafenib was stopped and replaced initially by Regorafenib for 3 months and then Lenvatinib for 2 months, with therapeutic failure of both classes.

Pembrolizumab was administered as a second line treatment with a favorable therapeutic response: clinically, the patient was in good general condition (WHO 0), with no neurological or hemorrhagic or ascitic decompensation; biologically, the AFP level fell from 60359 to 59; on ultrasound, the size of the HCC was reduced from 17cm to 2cm after 11 months' treatment.

DISCUSSION

Hepatocellular carcinoma is a primary tumor developed from hepatocytes, most often on a cirrhotic liver [1], more rarely on chronic non-cirrhotic liver disease, and exceptionally on a healthy liver. In cases of HCC developed on cirrhosis, the prognosis and therapeutic approach are conditioned by both the stage of the cancer and liver function [2]. This was exemplified in our patient, who developed HCC on a background of post-hepatitis C cirrhosis.

Management is necessarily multidisciplinary and expert. For more than a decade, Sorafenib, an antiangiogenic multikinase inhibitor, was the only systemic agent available with a survival benefit for the treatment of advanced HCC. Over the past 2 years, a number of new agents have demonstrated activity in advanced HCC in phase III studies. All of these are antiangiogenic agents, including tyrosine kinase inhibitors Lenvatinib in the first-line setting and Regorafenib, Cabozantinib, and the monoclonal antibody Ramucirumab in the second-line setting after prior Sorafenib therapy [3, 4]. In our case, disease progression under sorafenib prompted sequential use of regorafenib and lenvatinib; however, both treatments failed to control tumor progression, mirroring the known variability in response to TKIs.

Pembrolizumab prevents PD-1 from interacting with its two known ligands PDL-1 and PDL-2, which are present on tumor cells and dendritic cells. PD-1 / PDL-1 interaction sends repressive signals to the T lymphocyte, which becomes unable to control tumor cell expansion [5].

In the field of immunotherapy, KEYNOTE-224 cohort 1 is a non-randomised, multicentre, open-label, phase 2 trial that is set in 47 medical centres and hospitals across ten countries, Between June 2016, and Feb 2017. Eligible patients had pathologically confirmed hepatocellular carcinoma; had previously been treated with Sorafenib and were either intolerant to this treatment or showed radiographic progression of their disease after treatment [6, 7], such is also the case of our patient. Pembrolizumab was effective and tolerable in patients with advanced hepatocellular carcinoma who had previously been treated with Sorafenib. These results indicate that Pembrolizumab might be a treatment option for these patients. This drug is undergoing further assessment in two phase 3, randomised trials as a second-line treatment in patients with hepatocellular carcinoma [8, 6].

After~2.5 years of additional follow-up in the KEYNOTE-224 study, Pembrolizumab continued to provide durable anti-tumour activity and improvement in best overall response BOR in patients with advanced HCC previously treated with sorafenib. The proportion of patients who achieved a CR increased compared with the primary analysis (3.8% versus 1.0%). The median DOR was 21 months, and 77% of patients had response lasting ≥12 months [9]. In our patient, pembrolizumab was introduced as a second-line treatment following failure of two TKIs. Remarkably, he demonstrated a significant clinical and radiological response: AFP decreased from 60,359 ng/mL to 59 ng/mL, and the tumor size was reduced from 17 cm to 2 cm after 11 months of therapy. This degree of tumor shrinkage surpasses the average DOR reported in KEYNOTE-224

and highlights the potential for profound response in selected individuals.

Furthermore, the KEYNOTE-240 phase III trial, although not meeting its co-primary endpoints for statistical significance, showed a trend toward improved overall survival and progression-free survival compared to best supportive care alone. Our patient's clinical stability (WHO 0 performance status) throughout pembrolizumab treatment, in the absence of major adverse events or hepatic decompensation, reinforces the tolerability and favorable risk-benefit profile described in both trials.

Extended follow-up from KEYNOTE-224 demonstrated that Pembrolizumab provides robust and durable efficacy in patients with advanced HCC who were previously treated with Sorafenib. Taken together with the consistent safety profile for Pembrolizumab, this report confirms the favourable benefit-risk of Pembrolizumab in this population [9].

These results are comparable to the magnitude of benefit observed in the double-blind, randomised phase III KEYNOTE-240 study, which evaluated Pembrolizumab plus best supportive care (BSC) compared with placebo plus BSC in patients with advanced HCC who experienced progression during or after treatment with Sorafenib or were intolerant to Sorafenib [10, 11].

KEYNOTE-224 cohort 2 was an open-label, multicountry phase II trial. Eligible patients in cohort 2 had advanced HCC not amenable or refractory to locoregional therapy and not previously treated with systemic therapy [12].

Between September 2018, and February 2019, 51 patients were allocated in cohort 2. The median time from the first dose to data cutoff (January 19, 2021) was 27 months (23-29). Objective response rate ORR was 16% [95% confidence interval (CI), 7-29] and was similar across key subgroups. Median duration of response DOR was 16 months (3,24), and disease control rate DCR was 57%. The median progression-free survival PFS was 4 months (2-8), and median time to progression TTP was 4 months (3-9). Median overall survival OS was 17 months (8-23) [12, 13].

Taken together, the clinical course of our patient illustrates the potential of pembrolizumab to induce meaningful and lasting tumor control in advanced HCC, particularly following failure of multiple systemic therapies. Our experience supports the integration of pembrolizumab as a second-line option in eligible patients, consistent with the evolving international guidelines and trial evidence.

CONCLUSION

Progress in the therapeutic management of HCC are indisputable. They result from a better understanding of tumor biology, optimized treatments and of treatments and their indications, as well as a recent and rapid expansion of treatment options, particularly immunotherapy. Despite these advancements, clinical decision-making remains complex and must be individualized, relying on multidisciplinary expertise. The integration of evidence-based algorithms and updated international guidelines plays a crucial role in standardizing and improving patient care.

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