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CASE REPORT

Atezolizumab plus Bevacizumab as a Bridge for Liver Transplant in Hepatocellular Carcinoma

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ABSTRACT

We report the case of a 68-year-old male with alcohol-related cirrhosis, diagnosed with hepatocellular carcinoma (HCC) not eligible for liver transplant. After immunotherapy with atezolizumab associated with bevacizumab, he underwent a successful living donor liver transplantation (LT), not showing disease evidence or graft injury, maintaining clinically and radiologically stable 14 months after surgery. This is a successful report of combined atezolizumab plus bevacizumab being used as a bridge to LT in a patient with HCC, showing an important finding in therapy in patients with unresectable tumors at diagnosis.

Descriptors: Carcinoma Hepatocellular, Liver Transplantation, Immunotherapy.

Atezolizumabe mais Bevacizumabe como Ponte para Transplante Hepático no Carcinoma Hepatocelular

RESUMO

Relatamos o caso de um homem de 68 anos, com cirrose hepática de etiologia alcoólica, diagnosticado com carcinoma hepatocelular (CHC) não elegível para transplante hepático. Após imunoterapia com atezolizumabe associado ao bevacizumabe, ele foi submetido a um transplante hepático (TH) de doador vivo com sucesso, não mostrando evidencia de doença ou lesão no enxerto, mantendo-se clínica e radiologicamente estável 14 meses após a cirurgia. Esse é um relato de sucesso da combinação atezolizumabe mais bevacizumabe sendo usados como ponte para o TH em um paciente com CHC, mostrando um achado importante na terapia dos pacientes com tumores irresecáveis ao diagnóstico.

Descritores: Carcinoma Hepatocelular, Transplante Hepático, Imunoterapia.

INTRODUCTION

Hepatocellular carcinoma (HCC) is an important cause of cancer-related death worldwide, and liver transplantation (LT) is a potential curative treatment option for patients with HCC in early phases of the disease;[1] however, most diagnosis came with unresectable, local advanced or systemic disease.[2] In these cases, immune checkpoint inhibitors (ICIs) such as atezolizumab associated an anti-vascular endothelial growth factor (anti-VEGF) as the bevacizumab have shown benefit in survival in phase-3 trials and is currently the first line of

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therapy in patients with unresectable HCC.[3,4] Nevertheless, the safety regarding the association of ICI and solid organ transplantation is still unclear, since immune checkpoint molecules and the PD-L1–PD-1 pathway are directly responsible for preventing graft intolerance.[5] Strong evidence is lacking since clinical trials usually exclude patients with prior solid organ transplantation or autoimmune diseases. Our objective is to relate a successful case of association of atezolizumab plus bevacizumab being used as a bridge to a living donor LT (LDLT), progression-free following 14 months after surgery.

CASE REPORT

We present the case of a 68-year-old male, hypertense, active smoker, diagnostic with alcohol-related cirrhosis, last intake in January 2020. Previously decompensated in ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and upper digestive hemorrhage with rubber band ligation. Magnetic resonance imaging (MRI) in April 2020 demonstrating signals of chronic liver disease with portosystemic collateral pathways, splenomegaly, with discreet ascites and three nodules, one sizing 3.8 cm in segment II/IV and another two with 2.5 and 2.1 cm in segment V, with intermediate signal in T1, hypersignal in T2, diffusion restriction, high contrast uptake in arterial phase, no late washout. Computed tomography angiography in June 2020 not showing portal vein thrombosis, *moderate stenosis of right renal artery and important stenosis above iliac artery*, and this exam confirmed the three nodules with sizes and locations similar to April MRI, suggestive for HCC. Bone scintigraphy of May 2020 and chest tomography in October 2020 and January 2021, metastasis free in all exams.

In August 2020, he underwent one session of chemoembolization, after which he decompensated into ascites, jaundice and worsening of liver function, turning into a Child–Pugh C, thus being interrupted the chemoembolization. After compensation, the patient was included in immunotherapy protocol, receiving six cycles of atezolizumab 1,200 mg + bevacizumab 15 mg/kg. MRI after immunotherapy in January 2021 showed regression in the smallest nodule in segment V, with the remaining stable in size, although a necrotic component was found in the greater nodule in segment II/IV, still sizing 3.8 cm.

In February 2021, he underwent a LDLT. In the immediate postoperative period, he evolved with pseudomembranous colitis and pneumonia, with hospital discharge in March 2021 after resolution. Final pathology post-transplant showed HCC in segments I, V and VIII, the greatest measuring 3.2 and 1.5 cm, restricted to liver, with microvascular and perineural invasion present; however, with lymph nodes not evaluated.

In the post-transplantation follow-up, maintenance immunosuppression initiated with prednisone, tacrolimus and mycophenolate mofetil. Six months after the LDLT, he started prednisone and mycophenolate mofetil taping, associating everolimus to the tacrolimus. Fourteen months after the transplant, the patient kept clinically stable with no evidence of diseases (Fig. 1).

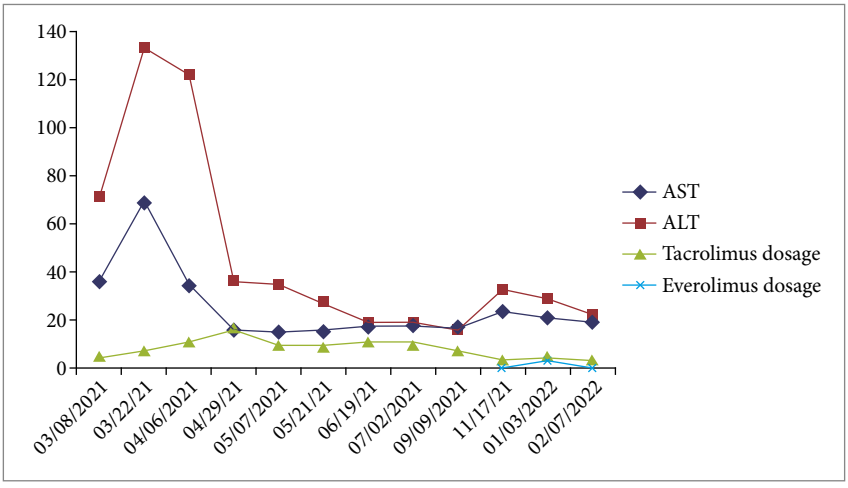

Figure 1. Evolution of transaminases and tacrolimus and everolimus dosage after LT.

DISCUSSION

The HCC is the most common type of primary liver cancer globally and most cases are associated with a known etiology, such as chronic alcohol abuse, chronic viral hepatitis and metabolic diseases, with growing incidence around the world.[6]

Staging, treatment decision and prognosis of HCC is based on disease burden, liver function and patient clinical status.[1] LT is the therapy with the highest chances of curing HCC besides replacing the diseased liver and restoring normal hepatic function.[7]

Indication for cadaveric LT is based on the Milan criteria, developed in 1996, and defined by the presence of a single tumor up to 5 cm or maximum three tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors.[8]

Some limiting factors to the LT is the shortage of apt donors and transplantation, and the waiting time prohibitively prolonged. In this context, an alternative is to perform an LDLT.[1] Although LDLT presents a good alternative in some cases, there is no consensus in literature about its specific indications and no prospective study on indications or transplant benefit advantages have been produced.[1,9]

The selection criteria for cadaveric LT vs. LDLT differs, and, overall, tumor size and number of tumor nodules considered suitable for LT are less restrictive for LDLT. What is already well established in the literature is that mortality rates of children on the waiting list fell to almost zero with a successful pediatric transplant program with LDLT.[9]

HCC has a complex physiopathology, resulting in a challenging treatment. One mechanism is based on programmed cell death protein (PD) which binds to the programmed cell death ligand (PL), known as PD-1/PD-L1 pathway, resisting positive signals and inhibiting the function of T-cell and T-CD28 cells, regulating the adaptive immune response.[10] However, the same mechanism is responsible for graft tolerance, and inhibition of this pathway may lead to graft-versus-host disease.[11] For over 10 years, the multikinase inhibitor sorafenib remained as the first line treatment for unresectable HCC. Only in 2017 the Food and Drug Administration (FDA) approved the first ICIs as treatment for unresectable HCC. To date, FDA approved only five antibody-based inhibitors targeting PD-1/PD-L1 pathway: two anti-PD-1 antibodies—nivolumab and pembrolizumab—and three anti-PD-L1 antibodies—atezolizumab, avelumab, and durvalumab.[12]

Another mechanism is based on superexpression of growth factors, such as the VEGF, resulting in aberrant angiogenesis, contributing to tumor growth and metastasis.[13] The tyrosine kinase inhibitor, sorafenib and the monoclonal antibodies, such as bevacizumab are used to target the VEGF signaling pathway in advanced HCC scenarios.[14]

The IMbrave150, a phase-3 randomized study, compared the association of the ICI atezolizumab plus the anti-VEGF bevacizumab with the multikinase inhibitor sorafenib in patients with unresectable HCC who had not previously received systemic therapy. The study revealed superior progression-free survival and significantly reduced mortality at 6 and 12 months after.[3]

A meta-analysis using indirect results of nine clinical trials also suggests overall survival favoring atezolizumab-bevacizumab combination if compared to therapy with sorafenib, lenvatinib, nivolumab, transarterial chemoembolization (TACE) or placebo in patients with locally advanced or metastatic unresectable HCC.[15] These results lead to the association atezolizumab plus bevacizumab becoming the first line therapy for unresectable HCC.[4] A limiting factor about therapy with bevacizumab is its adverse reaction of causing upper gastrointestinal bleeding, a common and potentially lethal complication.[16] In the IMbrave trial, patients with untreated or incompletely treated esophageal or gastric varices were excluded.[4] Our patient received upper-band ligation prior to inclusion in the immunotherapy scheme.

Following current recommendations, patients with HCC not eligible for LT with preserved liver function are candidates for TACE, a locoregional treatment that aims to prevent cancer progression, reduce tumor burden or even downstage disease in order to allocate in LT criteria.[4] There is conflicting data about the benefit of TACE prior LT in terms of survival and long-term outcomes;[17,18] furthermore, in patients with compromised liver function, TACE does not show benefit and, therefore, should not be used.[1,4] In these cases, the combination of atezolizumab and bevacizumab is currently the first-line treatment.[4] Our patient, initially eligible for TACE, showed worsening of liver function after the first session of the procedure; thus, embolization was suspended and the immunotherapy protocol started.

Some articles report the use of ICI as an adjuvant therapy and in pretransplant settings.[3,15,16] However, severe and fatal allograft injuries with the use of nivolumab have been described, making the safety regarding the association of ICIs and LT still unclear.[19] The reason falls in the role of the PD-1/PL-1 pathway in graft tolerance due regulating the T-cells function.[20] It is remarkable that these cases involve the use of anti-PD-1 antibodies and no report of graft rejection or allograft injury associated with the use of anti-PD-L1 antibodies have been described up to date.

In the post-transplant setting, immunosuppressive therapy is installed in order to prevent allograft rejection. Most centers use a combination of a corticosteroid, a calcineurin inhibitor (CNI) and an antimetabolite, such as mycophenolate mofetil or azathioprine.[21]

Corticosteroids, such as prednisone and hydrocortisone, are used in introduction and maintenance of immunosuppression; however, due to long corticotherapy complications, including diabetes, hypertension, metabolic syndrome, its dosage should be reduced in the following months.[22] A meta-analysis published in 2018 showed that corticoids-free regimen were associated with acute rejection, renal impairment and steroid resistant rejection, compared with corticoids-containing regimen, with no difference in mortality, graft loss or infection rate in the two groups.[23]

CNIs such as tacrolimus and cyclosporine are used in maintenance immunosuppression. In a meta-analysis published involving 16 randomized clinical trials, tacrolimus significantly reduced mortality, graft loss, acute and steroid resistant rejection, but increased de novo diabetes, compared with cyclosporine.[24] Adverse effects are similar between both drugs and include neurotoxicity, electrolyte abnormalities and nephrotoxicity, being dose-related. In these scenarios, mycophenolate mofetil is

associated in a steroid or CNI sparing regimen, due mycophenolate being associated with a lower risk of renal injury. However, mycophenolate mofetil isolated can lead to increased risk of acute rejection.[21],[22] Other option include the use of the mammalian target of rapamycin (mTOR) such as everolimus, alone or associated to the CNI in an attempt to minimize chronic exposure to CNI by decreasing its dose. Both approaches demonstrate an improvement in renal function.[25]

CONCLUSION

We hereby present a successful report of the use of ICI atezolizumab with an anti-VEGF bevacizumab working as a bridge until the LDLT. The LT is the main curative treatment for HCC; however, it is limited by the disease staging and donor availability. The patient survival, absence of graft injury and no disease recurrence in the following months increase the relevancy of this study.

CONFLICT OF INTEREST

Nothing to declare.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: D'Albuquerque LAC, Farias AQ, Pacheco MP and Trindade LZ; **Conception and design**: Pacheco MP and Trindade LZ; **Article writing**: Solino GA and Ferreira RPC; **Critical revision**: Vasconcellos VF, Trindade LZ and Pacheco MP; **Final approval**: Pacheco MP.

AVAILABILITY OF RESEARCH DATA

All data sets were generated or analyzed in the current study.

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