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Advances and effectiveness of the immunotherapy after liver transplantation

Vulasala SSR *et al*. Immunotherapy after liver transplantation

Abstract

Transplant recipients usually have increased chances of graft rejection and graft *vs* host disease, requiring chronic immunosuppressive therapy. Nonetheless, long-term immunosuppression risks malignancies such as skin cancer, lymphoma, and Kaposi sarcoma. However, there are very few studies that included solid organ transplant recipients while studying the efficacy of immunotherapy. "Immunotherapy after liver transplantation: Where are we now?" is a study, where the authors described the mechanism of action and outcomes of immune checkpoint inhibitors specific to liver transplant recipients. The authors reported the graft rejection rates and the factors contributing to the rejection in the liver transplant recipients.

Key Words: Immunotherapy; Hepatocellular carcinoma; Immune checkpoint inhibitors; Liver transplantation; Solid organ transplant; Graft rejection

Vulasala SSR, Onteddu NK, Kumar SP, Lall C, Bhosale P, Virarkar MK. Advances and effectiveness of the immunotherapy after liver transplantation. *World J Gastrointest Surg* 2022; In press

Core Tip: There is an increased risk of cancer among transplant recipients receiving chronic immunosuppression. Immunotherapy has a beneficiary effect over immunosuppressors in reducing the overall cancer risk. However, there are very few studies that included solid organ transplant recipients while studying the efficacy of immunotherapy. "Immunotherapy after liver transplantation: Where are we now?" is a study, where the authors described the mechanism of action and outcomes of immune checkpoint inhibitors specific to liver transplant recipients.

TO THE EDITOR

Au *et al*[1] studied the consequences of immunotherapy in patients who underwent liver transplantation (LT) for hepatocellular carcinoma (HCC). We are writing to thank the

authors after reading their article conscientiously. Many trials were conducted in the literature studying the efficacy of immunotherapy. However, they excluded organ transplant recipients due to the higher risk of fatal graft rejection.

Transplant recipients usually have increased chances of graft rejection and graft *vs* host disease (GVHD), requiring chronic immunosuppressive therapy. Nonetheless, long-term immunosuppression risks malignancies such as skin cancer, lymphoma, and Kaposi sarcoma. These malignancies constitute the second most common cause of death in organ transplant recipients[2]. Immunotherapy is a breakthrough in managing transplant recipients and acts through interruption of the cancer-immunity cycle. Immune checkpoints, cytotoxic T-lymphocyte antigen 4 (CTLA-4), and programmed cell death 1 (PD-1) are physiologically responsible for preventing effector T cell overactivation.

Immunotherapy includes antibodies against CTLA-4 and PD-1, thereby upregulating the T-cell immune response to the cancer antigen[3]. Although the host immunity against tumor antigens is restored, on the other hand, T-cell stimulation is one of the significant components of graft rejection. The overall rejection rates following immunotherapy are 29%-54% and 25%, respectively, in patients who underwent solid organ transplantation and LT[4-6]. Kidney (40%) is associated with higher rates of graft rejection than liver (35%) and heart (20%)[3]. Au *et al*[1] studied that the graft rejection rates were seen in 32% of patients who specifically underwent an LT. The rejection rates among individuals who received immunotherapy within 2.9 years of transplant were increased compared to 5.3 years of transplant. They also noticed a higher mortality rate of 56% among graft rejected patients.

Compared with CTLA-4 inhibitors, PD-1 inhibitors are associated with higher rates of graft rejection and graft loss in LT recipients[7,8]. Kittai *et al*[9] reported graft rejection in 4 of 8 patients treated with anti-PD-1, whereas no rejections were detected in patients receiving anti-CTLA-4 therapy. Programmed death-ligand 1 (PD-L1) expression on the graft lymphocytes aids as a marker of rejection after immunotherapy[2]. Tacrolimus-based or combination agents (corticosteroids, antimetabolites, calcineurin inhibitors,

and mechanistic target of rapamycin inhibitors) immunosuppression is shown to reduce graft rejection and improve the response to immunotherapy[2]. A 10%-20% of post-transplant patients encounter recurrence of HCC[10]. In such cases, immunotherapy is effective only in 11% of patients.

A higher dose of immunotherapy medication, a shorter interval between LT and immunotherapy initiation, expression of PD-L1 on the graft lymphocytes, and a previous GVHD history are positively related with the risk of and response to graft rejection[4]. Studies on patient characteristics such as gender, age, pathological type of primary tumor, donor type, type, and duration of ischemia during LT and post-operative hepatitis virus status of the patient are necessary to learn the factors associated with favorable outcomes after immunotherapy. Proper patient selection is quintessential to preventing lethal graft rejection. Hence, a close collaboration among oncologists and transplant specialists is encouraged when handling patients who require immunotherapy. However, prospective studies focusing on: (1) Although the PD-1 pathway is dominant in establishing immune tolerance, whether anti-PD-1 and anti-CTLA-4 antibodies are associated with graft rejection[9]; (2) The treatment of immunotherapy related graft rejection; and (3) Its efficacy is there any difference in treatment modality between immunotherapy related graft rejection and isolated graft rejection, are required beforehand to recommend immune checkpoint inhibitors in transplant recipients.

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