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Use of checkpoint inhibitors in liver transplant recipients

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Abstract

In spite of their major impact in cancer therapy, immune checkpoint inhibitors are considered to be contraindicated in liver transplant recipients due to fear of rejection and fatal liver failure. Nevertheless, an increasing number of instances of liver transplant recipients treated with checkpoint inhibitors is being published. We reviewed the reports on 14 known cases of liver transplant recipients who underwent treatment with checkpoint inhibitors and discuss factors likely to determine susceptibility to organ rejection including the choice of the agent and the immunosuppression employed, the assessment of Programmed cell death 1 ligand 1 (PD-L1) status in liver graft biopsies, and the time of treatment initiation.

Keywords

Checkpoint inhibition, hepatocellular carcinoma, liver transplantation, pembrolizumab, nivolumab, liver transplant recipients, rejection

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The approach to systemic treatment of many malignancies has been changed drastically by the recent advent of immune checkpoint inhibitors (CPIs).[1] These agents are designed to enhance the tumour-specific activity of immune cells and do not possess intrinsic cytotoxicity; their mechanism of action explains the lack of adverse events typically associated with the use of conventional chemotherapy, however it also accounts for the frequent occurrence of autoimmune-related unwanted effects associated with their use as well as the reluctance to use them in transplant recipients.[2]

Owing to long-term immunosuppression, organ transplant recipients are an at-risk population for the development of a wide spectrum of malignancies comprising melanoma and haematological cancers.[3] This risk is further increased in patients who underwent transplantation due to hepatocellular carcinoma (HCC) due to a post-transplant recurrence risk of approximately 10% within five years.[4,5] Despite this increased need for effective cancer treatment options, CPIs are considered as contraindicated in organ transplant recipients for fear of organ rejection.

Nevertheless, due to their potential clinical benefit CPIs have, since their approval, been used as a salvage option in a number of transplanted patients. Accounts of these cases, which at present amount to less than 40 published reports, confirm that organ rejection is a frequent occurrence in this setting.[6–8] However, good tolerability and signs of significant anticancer efficacy were observed in some cases.[6]

As of today, to our knowledge 14 cases of liver transplant recipients who have been treated with immune CPIs have been published (Table 1). Altogether, liver graft rejection was reported in four of 14 reported cases; in three cases with lethal outcome, rejection occurred within three weeks since the initiation of therapy.[9] Overall survival was available in 12 cases and amounted to a median value of 1.2 months. However, in four patients showing a response to treatment, survival ranged between at least four[10] and 18[11] months.

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Table 1. Patients' characteristics and reported outcome of published case reports on treatment with checkpoint inhibitors in liver transplant recipients, listed according to publication date.

Patient	Reference	Malignancy	Compound	Transplant to immunotherapy in years	Response	OS (months)	Graft rejection	PD-L1 status	status	Immunosuppression
1	[17]	Melanoma	Ipilimumab	8	No	>5[a]	No	N/A	N/A	Low dose tacrolimus
2	[10]	Melanoma	Ipilimumab	8	Yes	>4[a]	No	N/A	N/A	Low dose sirolimus
3	[7]	HCC	Nivolumab	1	Yes	10	No	0%	N/A	Low dose tacrolimus
4	[14]	Fibrolamellar HCC	Nivolumab	4	N/A	1	Yes, lethal	Positive	Positive	Sirolimus
5	[14]	Fibrolamellar HCC	Nivolumab	3	N/A	1	Yes, lethal	Positive	Positive	Tacrolimus
6	[9]	Melanoma	Pembrolizumab	N/A	N/A	N/A	Yes, lethal	N/A	N/A	Ciclosporine
7	[19]	HCC	Pembrolizumab	8	No	3	No	N/A	N/A	Low dose tacrolimus
8	[15]	HCC	Nivolumab	2.7	No	1.2	No	N/A	10%	Tacrolimus
9	[15]	Melanoma	Pembrolizumab	5.5	Yes	9.5	No	0%	5%	Everolimus, MMF
10	[15]	HCC	Nivolumab	7.8	No	1.1	No	0%	N/A	Sirolimus, MMF
11	[15]	HCC	Nivolumab	3.7	No	1.3	No	0%	0%	Tacrolimus
12	[15]	HCC	Nivolumab	1.2	N/A	0.3	No	N/A	0%	Tacrolimus
13	[15]	HCC	Nivolumab	1.1	N/A	0.9	Yes	30%	0%	N/A
14	[11]	Melanoma	Ipilimumab/ pembrolizumab	6	Yes/yes	18[a]	No	N/A	N/A	Sirolimus

HCC: hepatocellular carcinoma; OS: overall survival; N/A: not available.
PD-L1 or PD1 - status of the transplant liver; MMF: Mycophenolate Mofetil; PD1: Programmed cell death 1; PD-L1: Programmed cell death 1 ligand 1.
[a]Based on report on response duration.

Data from these reports are scanty and too heterogeneous to draw definitive conclusions on the factors determining graft rejection; they tell us, however, that while some patients experience graft loss upon treatment with CPIs, others do not and that, besides individual host- and donor-related genetic factors, other modifiable factors might determine the susceptibility to organ rejection. We discuss below a possible role of such factors which include the choice of the agent and the immunosuppression employed, the availability of biopsies, and the time of treatment initiation.

Agent used

Out of 14 cases of liver graft recipients treated with CPIs, all but two patients, who received the cytotoxic T-lymphocyte-associated Protein 4 (CTLA-4) inhibitor ipilimumab, underwent treatment with Programmed cell death 1(PD1)/Programmed cell death 1 ligand 1(PD-L1) blocking agents. Organ rejection was reported in four out of 10 patients treated with nivolumab or pembrolizumab but in neither of the two patients treated with ipilimumab, although in these latter cases immunosuppression was tapered at subtherapeutic levels. Data from these reports are insufficient to draw the conclusion that CTLA4 inhibitors are safer than PD-1/PDL-1 inhibitors in liver transplant recipients. However, some authors suggest that the lack of organ rejection during ipilimumab treatment reflects a predominant role of PD-1 in determining graft tolerance.[8,12] Nevertheless, a recent survey reported kidney graft rejection occurring under treatment with either CTLA-4 or PD-1 inhibitors.[8] There is therefore, at this time, no evidence supporting the use of a particular CPI in liver allograft recipients and, until more data become available, it seems reasonable that the choice of the agent should be primarily guided by the data available on effectiveness in the respective tumour entities.

Liver biopsies

Another relevant point regards the issue of whether assessment of immune checkpoint regulators in liver biopsies might serve to predict rejection in the same way their assessment predict response in some tumour entities.[13] Each of the three available biopsies from patients with acute graft rejection showed elevated PD-L1 expression,[9,14,15] whereas none of the four biopsies available from patients without rejection (including

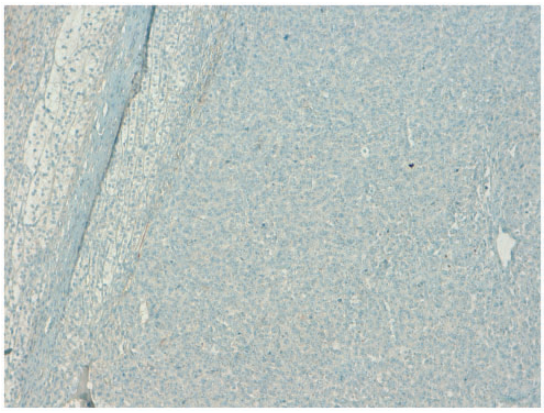

Figure 1. Negative anti-programmed cell death 1 ligand 1 (PD-L1) staining (100x) of a pretherapeutic liver biopsy from a liver graft recipient treated with Nivolumab without signs of organ rejection[7] (Courtesy Prof. Jens Neumann).

a pre-treatment biopsy performed in one of our patients – Figure 1) showed positive PD-L1 staining. It is therefore highly suggestive that PD-L1 expression might predict graft rejection. However, biopsies from patients experiencing rejection were reported to be obtained after initiation of therapy and it cannot be ruled out that positive PD-L1 staining reflects a consequence of organ rejection. It seems therefore reasonable to suggest that graft liver biopsies are preformed routinely prior to therapy with CPI in liver transplant recipients and that staining for PDL-1 is taken into consideration for the choice of whether a PD1/PDL-1- or a CTLA4-blocking agent should be employed.

Immunosuppression

Immunosuppression plays a potentially detrimental role in determining the efficacy of CPIs, since their effect requires an intact T-cell response. Whether concurrent steroid treatment counteracts the efficacy of CPIs in non-transplanted patients is still an issue of debate, a recent survey suggests that concomitant use of steroids does not necessarily influence the efficacy of CPI treatment.[16] In addition, immunosuppression did not prevent response in four patients (cases 1, 3, 8, and 13, Table 1) and a report has recently shown that preventive treatment with high-dose steroids, intended to avoid CPI-mediated rejection, did not prevent a remarkable response in a kidney transplant recipient.[6] Therefore, although reduction of immunosuppression to sub-therapeutic doses was not associated with organ rejection,[7,10,17] pre-treatment with steroids could be attempted in the absence of contraindications and immunosuppression tapered during the course of treatment whenever possible.

Initiation of treatment

Due to the potentially lethal consequences of organ rejection, the decision to employ CPIs is usually delayed until unequivocal signs of therapy failure are observed during treatment with conventional agents. Although response to CPIs are expected to occur soon after treatment initiation (most occurring within three months of initiation of therapy),[18] a delayed onset of treatment might prevent the efficacy of CPIs to become evident before untreatable disease progression or organ dysfunction occur; this might at least in part account for the dismal survival so far reported for liver transplant patients undergoing treatment with CPIs (Table 1). It is therefore advisable that, if CPI treatment is considered as an option, a close follow-up is performed during first-line conventional treatment to recognise signs of disease progression early, and that the decision to initiate treatment with a CPI is taken in a timely manner.

In summary, the decision to initiate CPI treatment in liver transplant patients should be made on an individual basis based on consideration of the patient's performance status, the potential oncological benefits and the tentative nature of this possibility. We suggest that liver biopsies of liver allografts are taken routinely before treatment initiation and that, if staining for PD-L1 is detected, initiation of treatment with a CTL4-blocking agent is considered. Pre-treatment with steroids can be attempted in the absence of obvious contraindications, as recently suggested,[6] and immunosuppression progressively tapered under close surveillance.[7] Close follow-up to detect signs of progression under conventional therapy should trigger a timely choice to begin CPI treatment.

Finally, it cannot be emphasised enough that at the present state of knowledge, the decision to treat transplant recipients with immune CPI is to be considered as *ultima ratio* to be weighed against the possibility of graft loss and fatal organ failure. However, an accurate account of the above factors in future reports will contribute to understanding of the factors determining rejection upon treatment with CPI and possibly guide the design of appropriate prospective studies.

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Declaration of conflicting interests

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